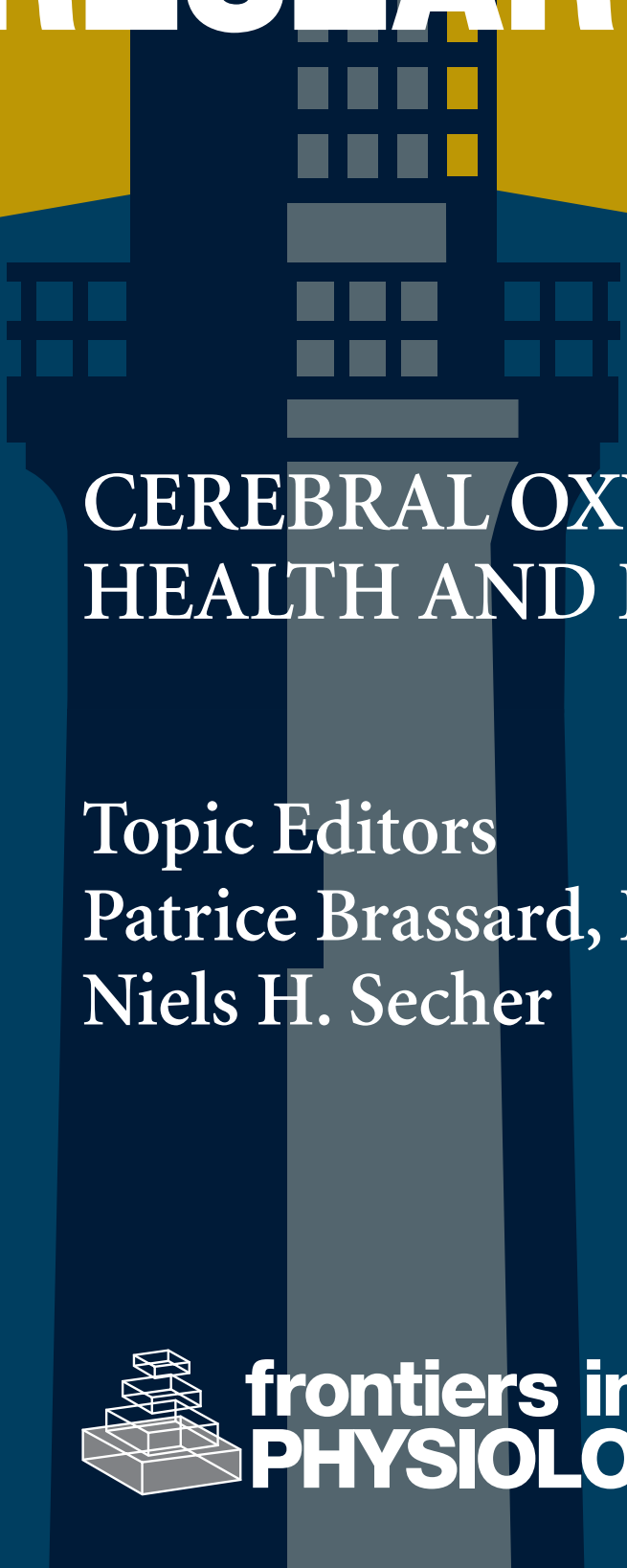
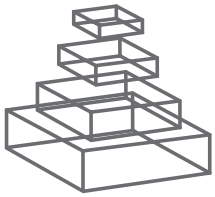
frontiers
RESEARCH TOPICS



CEREBRAL OXYGENATION IN HEALTH AND DISEASE

Topic Editors
Patrice Brassard, Phil N. Ainslie and
Niels H. Secher

frontiers in
PHYSIOLOGY



frontiers

Cover image provided by Ibbl sarl, Lausanne CH

ISSN 1664-8714
ISBN 978-2-88919-453-7
DOI 10.3389/978-2-88919-453-7

ABOUT FRONTIERS

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

FRONTIERS JOURNAL SERIES

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing.
All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

DEDICATION TO QUALITY

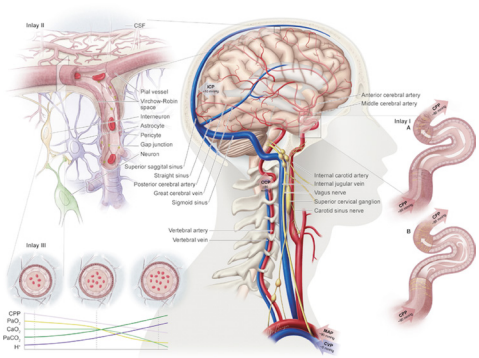
Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view.
By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

WHAT ARE FRONTIERS RESEARCH TOPICS?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area!
Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

CEREBRAL OXYGENATION IN HEALTH AND DISEASE

Topic Editors:
Patrice Brassard, Université Laval, Canada
Phil N. Ainslie, University of British Columbia, Canada
Niels H. Secher, University of Copenhagen, Denmark



Willie CK, Tzeng YC, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow J Physiol. 2014 Mar 1;592(Pt 5):841-59. doi: 10.1113/jphysiol.2013.268953. Epub 2014 Jan 6.

Scientists and clinicians interested in cerebrovascular physiology in humans now have numerous possibilities to monitor, invasively or non-invasively, the oxygenation status of cerebral tissue. Monitoring cerebral oxygenation has several utilities; to improve patient outcome, to better understand the mechanisms underlying orthostatic hypotension; to provide insight into functional neurovascular coupling; to evaluate the influence of vasopressors on cerebral oxygen levels in patients under anesthesia; and to study the limitations of exercise tolerance. This themed research topic, through theoretical and experimental papers, covers new and exciting issues related to the study of cerebral oxygenation in health and disease. This e-book includes manuscripts inclusive of original research, methodologies and reviews in the field of integrative physiology, cognitive testing, orthostatic stress, exercise physiology and anesthesia.

Table of Contents

frontiers in PHYSIOLOGY

EDITORIAL
published: 24 November 2014
doi: 10.3389/fphys.2014.00458

Cerebral oxygenation in health and disease

Patrice Brassard[1]*, Philip N. Ainslie[2] and Niels H. Secher[3]

[1] *Department of Kinesiology, Faculty of Medicine, Université Laval, Québec, QC, Canada*
[2] *Centre for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia-Okanagan, Kelowna, BC, Canada*
[3] *The Copenhagen Muscle Research Center, Department of Anesthesia, University of Copenhagen, Copenhagen, Denmark*
**Correspondence: patrice.brassard@kin.ulaval.ca*

Edited and reviewed by:
Geoffrey A. Head, Baker IDI Heart and Diabetes Institute, Australia

Keywords: cerebral oxygenation, cerebral blood flow, near-infrared spectroscopy

Monitoring cerebral blood flow (CBF) and oxygenation has implications for both clinical practice and research interests; e.g., to provide insight into functional neurovascular coupling, to better understand orthostatic hypotension, and to evaluate the influence of vasopressors on cerebral oxygenation during anesthesia and/or surgery. These topics, and others, are addressed in this e-book by presenting original research, reviews, and opinion papers covering new, exciting but also controversial issues related to cerebral oxygenation in health and disease as evaluated by near-infrared spectroscopy (NIRS).

There is interest in the impact of vasopressors on the NIRS-determined frontal lobe oxygenation (S_cO_2). For example, a reduction in S_cO_2 is reported with use of phenylephrine and noradrenaline at rest in healthy subjects, during anesthesia in non-cardiac and cardiac patients and during cardiopulmonary bypass in diabetics. However, possible extracranial contamination of the NIRS signal, especially with the utilization of vasopressors, challenges these conclusions. Keeping this limitation in mind, Foss et al. (2014) explored the influence of phenylephrine and ephedrine, on S_cO_2 during cesarean section with spinal anesthesia. Both vasopressors were effective at maintaining mean arterial pressure (MAP). Still, phenylephrine was the agent associated with a reduction in S_cO_2. In addition, Kitchen et al. (2014) studied the effect of calcium chloride compared to α- and β-adrenergic receptor agonists (ephedrine, phenylephrine, adrenaline, or noradrenaline) following anesthesia-induced hypotension in patients scheduled for major abdominal surgery. This case series suggested that S_cO_2 was preserved in patients who received calcium chloride, as well as β-adrenergic receptor agonists, but slightly reduced (2%) in those who received α-adrenergic drugs.

Also, ventilation, O_2 supplementation and body position have the potential to affect NIRS-derived S_cO_2 during surgery. Larsen et al. (2014) explored whether induction of anesthesia in the reclining, compared to sitting beach-chair position, secures cerebrovascular hemodynamics, including S_cO_2. S_cO_2 was found to be higher, combined with more stable hemodynamics, characterized by a reduced utilization of ephedrine, following induction of anesthesia in the reclining beach-chair vs. the sitting position. In their retrospective analyses of patients undergoing liver transplantation, Sørensen et al. (2014) report that S_cO_2 changes during surgery were closely related to those in end-tidal carbon dioxide tension. In order to ensure stability in S_cO_2 during the different phases of a liver transplantation, a varying ventilatory strategy may be needed to reduce the incidence of postoperative complications. Rokamp et al. (2014a) examined whether O_2 supplementation could maintain S_cO_2 and skeletal muscle oxygenation in vascular surgical patients. These authors conclude that O_2 supplementation indeed elevates S_cO_2 and skeletal muscle oxygenation in these patients during surgery but does not seem to sufficiently prevent a critical reduction in S_cO_2. Nielsen (2014) reviewed the impact of different surgeries on S_cO_2. His report indicates that the impact of non-cardiac surgery on S_cO_2 is highly variable and in some types of surgery, cerebral desaturation may be related to postoperative cognitive dysfunction.

Arterial pressure influences CBF. However, the role of arterial pressure variability on clinical outcome is not clear. Bronzwaer et al. (2014) explored the relationship between arterial pressure variations, stroke volume index and regional cerebral perfusion during transient central blood volume depletion and repletion in healthy volunteers and found that middle cerebral artery flow velocity (MCA Vmean) is related linearly to arterial pressure variability in subjects under these conditions. In their review, Rickards and Tzeng (2014) tried to reconcile two apparently discrepant views regarding variability in arterial pressure and CBF (negative vs. positive impact on clinical outcome), and suggest that the time scale of hemodynamic variability, that is short time variability vs. longer term fluctuations, may be the key to merge these divergent views.

To better understand the integrative components of cerebrovascular control, and thus oxygenation, during hyperthermia, Bain et al. (2014) discuss the mechanisms related to CBF and oxygenation changes during moderate to severe levels of hyperthermia. On the opposite spectrum, a reduction in cerebral temperature (hypothermia) may be important, for example to prevent cerebral ischemia during anesthesia or to improve neurological outcome and survival after cardiac arrest. Nybo et al. (2014) explored the impact of different means of brain cooling on cerebral temperature balance and oxygenation, namely intranasal cooling, percutaneous cooling of the carotid arteries and nasal ventilation.

Other physiological challenges influence CBF and oxygenation. Rokamp et al. (2014b) explored whether cholinergic vasodilatation is of importance for the elevation in regional CBF, measured by arterial spin labeling and blood O_2 level dependent functional magnetic resonance imaging during a handgrip

motor task and visual light stimulation in healthy subjects. By using blockade of acetylcholine receptors, known to abolish the exercise-induced increase in MCA Vmean, they observed that the elevation in regional CBF does not seem to be affected by glycopyrrolate. Also, since associations between arterial stiffness and cerebrovascular pulsatility have only been cross-sectional, and that resistance exercise increases arterial stiffness, Lefferts et al. (2014) explored whether increases in arterial stiffness induced by acute resistance exercise elevates CBF velocity pulsatility. While resistance exercise increased carotid artery stiffness and pressure pulsatility, this type of acute exercise did not affect CBF pulsatility. The impact of the Valsalva maneuver (VM) on different physiological functions is well documented but its influence on cerebrovascular function, including beat-to-beat measures of CBF velocity and oxygenation, have not been reported. Perry et al. (2014) studied the impact of 30 and 90% of subjects' maximal VM mouth pressure on MCA velocity and S_cO_2. They observed greater reductions in CBF velocity and oxygenation during phase II and III of the VM with the more intense maneuver. The latter was associated with a larger overshoot of CBF velocity and oxygenation after release of the strain (phase IV).

Aging influences cerebrovascular function. Flück et al. (2014) examined the relationship between CBF responses to a visual stimulus and a hypercapnic challenge with cerebral augmentation index, i.e., a measure of arterial stiffening. They conclude that MCA Vmean responses to both challenges were reduced with advancing age, with a parallel elevation in cerebrovascular stiffness. In their review, Tarumi and Zhang (2014) present the current evidence in regards to how vascular health affects the aging brain, and how improvements in vascular health, especially through regular aerobic exercise, may benefit cognitive function.

While different methodologies exist to monitor neural control of gait in humans, Perrey (2014) focused on the utilization of functional NIRS to perform brain imaging during walking, with emphasize on the sensitivity and pitfalls of this methodology in an opinion paper. Even if NIRS represents an interesting non-invasive tool to assess cerebral oxygenation, Grocott and Davie (2013) highlight the uncertainties, which could prevent this methodology from reaching its full potential. Finally, Sørensen et al. (2013) provide some insight to improve algorithms used in NIRS devices.

This research topic covers a wide range of exciting but at the same time unsettled issues related to cerebrovascular physiology with a focus on cerebral oxygenation. We hope that this e-book represents an opportunity to improve understanding in this field, as well as provide directions for further research.

REFERENCES

Bain, A. R., Morrison, S. A., and Ainslie, P. N. (2014). Cerebral oxygenation and hyperthermia. *Front. Physiol.* 5:92. doi: 10.3389/fphys.2014.00092

Bronzwaer, A. S., Stok, W. J., Westerhof, B. E., and van Lieshout, J. J. (2014). Arterial pressure variations as parameters of brain perfusion in response to central blood volume depletion and repletion. *Front. Physiol.* 5:157. doi: 10.3389/fphys.2014.00157

Flück, D., Beaudin, A. E., Steinback, C. D., Kumarpillai, G., Shobha, N., McCreary, C. R., et al. (2014). Effects of aging on the association between cerebrovascular responses to visual stimulation, hypercapnia and arterial stiffness. *Front. Physiol.* 5:49. doi: 10.3389/fphys.2014.00049

Foss, V. T., Christensen, R., Rokamp, K. Z., Nissen, P., Secher, N. H., and Nielsen, H. B. (2014). Effect of phenylephrine vs. ephedrine on frontal lobe oxygenation during caesarean section with spinal anesthesia: an open label randomized controlled trial. *Front. Physiol.* 5:81. doi: 10.3389/fphys.2014.00081

Grocott, H. P., and Davie, S. N. (2013). Future uncertainties in the development of clinical cerebral oximetry. *Front. Physiol.* 4:360. doi: 10.3389/fphys.2013.00360

Kitchen, C. C., Nissen, P., Secher, N. H., and Nielsen, H. B. (2014). Preserved frontal lobe oxygenation following cacium chloride for treatment of anesthesia-induced hypotension. *Front. Physiol.* 5:407. doi: 10.3389/fphys.2014.00407

Larsen, S. L., Lyngeraa, T. S., Maschmann, C. P., Van Lieshout, J. J., and Pott, F. C. (2014). Cardiovascular consequence of reclining vs. sitting beach-chair body position for induction of anesthesia. *Front. Physiol.* 5:187. doi: 10.3389/fphys.2014.00187

Lefferts, W. K., Augustine, J. A., and Heffernan, K. S. (2014). Effect of acute resistance exercise on carotid artery stiffness and cerebral blood flow pulsatility. *Front. Physiol.* 5:101. doi: 10.3389/fphys.2014.00101

Nielsen, H. B. (2014). Systematic review of near-infrared spectroscopy determined cerebral oxygenation during non-cardiac surgery. *Front. Physiol.* 5:93. doi: 10.3389/fphys.2014.00093

Nybo, L., Wanscher, M., and Secher, N. H. (2014). Influence of intranasal and carotid cooling on cerebral temperature balance and oxygenation. *Front. Physiol.* 5:79. doi: 10.3389/fphys.2014.00079

Perrey, S. (2014). Possibilities for examining the neural control of gait in humans with fNIRS. *Front. Physiol.* 5:204. doi: 10.3389/fphys.2014.00204

Perry, B. G., Cotter, J. D., Mejuto, G., Mundel, T., and Lucas, S. J. (2014). Cerebral hemodynamics during graded Valsalva maneuvers. *Front. Physiol.* 5:349. doi: 10.3389/fphys.2014.00349

Rickards, C. A., and Tzeng, Y. C. (2014). Arterial pressure and cerebral blood flow variability: friend or foe? A review. *Front. Physiol.* 5:120. doi: 10.3389/fphys.2014.00120

Rokamp, K. Z., Olesen, N. D., Larsson, H. B., Hansen, A. E., Seifert, T., Nielsen, H. B., et al. (2014b). Glycopyrrolate does not influence the visual or motor-induced increase in regional cerebral perfusion. *Front. Physiol.* 5:45. doi: 10.3389/fphys.2014.00045

Rokamp, K. Z., Secher, N. H., Eiberg, J., Lonn, L., and Nielsen, H. B. (2014a). O2 supplementation to secure the near-infrared spectroscopy determined brain and muscle oxygenation in vascular surgical patients: a presentation of 100 cases. *Front. Physiol.* 5:66. doi: 10.3389/fphys.2014.00066

Sørensen, H., Grocott, H. P., Niemann, M., Rasmussen, A., Hillingso, J. G., Frederiksen, H. J., et al. (2014). Ventilatory strategy during liver transplantation: implications for near-infrared spectroscopy-determined frontal lobe oxygenation. *Front. Physiol.* 5:321. doi: 10.3389/fphys.2014.00321

Sørensen, H., Secher, N. H., and Rasmussen, P. (2013). A note on arterial to venous oxygen saturation as reference for NIRS-determined frontal lobe oxygen saturation in healthy humans. *Front. Physiol.* 4:403. doi: 10.3389/fphys.2013.00403

Tarumi, T., and Zhang, R. (2014). Cerebral hemodynamics of the aging brain: risk of Alzheimer disease and benefit of aerobic exercise. *Front. Physiol.* 5:6. doi: 10.3389/fphys.2014.00006

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 28 October 2014; accepted: 07 November 2014; published online: 24 November 2014.

*Citation: Brassard P, Ainslie PN and Secher NH (2014) Cerebral oxygenation in health and disease. Front. Physiol. **5**:458. doi: 10.3389/fphys.2014.00458*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 03 March 2014
doi: 10.3389/fphys.2014.00081

Effect of phenylephrine vs. ephedrine on frontal lobe oxygenation during caesarean section with spinal anesthesia: an open label randomized controlled trial

Visti T. Foss[1]*, Robin Christensen[2], Kim Z. Rokamp[1], Peter Nissen[3], Niels H. Secher[3] and Henning B. Nielsen[3]

[1] *Department of Anaesthesia, Næstved Hospital, Næstved, Denmark*
[2] *Musculoskeletal Statistics Unit, Department of Rheumatology, The Parker Institute, Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark*
[3] *Department of Anaesthesia, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Ashraf Habib, Duke University, USA
Samuel J. E. Lucas, University of Birmingham, UK

****Correspondence:***
Visti T. Foss, Department of Anaesthesia, Næstved Hospital, Ringstedgade 61, 4700 Næstved, Denmark
e-mail: vistifoss@gmail.com

Background: During caesarean section spinal anesthesia may provoke maternal hypotension that we prevent by administration of phenylephrine and/or ephedrine. Phenylephrine is however reported to reduce the near infrared spectroscopy-determined frontal lobe oxygenation (ScO_2) but whether that is the case for patients exposed to spinal anesthesia is not known.

Objectives: To evaluate the impact of phenylephrine vs. ephedrine on ScO_2during caesarean section with spinal anesthesia in a single center, open-label parallel-group study with balanced randomization of 24 women (1:1). Secondary aims were to compare the effect of the two drugs on maternal hemodynamics and fetal heart rate.

Intervention: Ephedrine (0.8–3.3 mg/min) *vs.* phenylephrine infusion (0.02–0.07 mg/min).

Results: For the duration of surgery, administration of ephedrine maintained ScO_2 (compared to baseline $+2.1 \pm 2.8\%$; mean ± SE, while phenylephrine reduced ScO_2 ($-8.6 \pm 2.8\%$; $p = 0.005$) with a 10.7% difference in ScO_2between groups ($p = 0.0106$). Also maternal heart rate was maintained with ephedrine ($+3 \pm 3$ bpm) but decreased with phenylephrine (-11 ± 3 bpm); difference 14 bpm ($p = 0.0053$), but no significant difference in mean arterial pressure ($p = 0.1904$) or CO ($p = 0.0683$) was observed between groups. The two drugs also elicited an equal increase in fetal heart rate (by 19 ± 3 vs. 18 ± 3 bpm; $p = 0.744$).

Conclusion: In the choice between phenylephrine and ephedrine for maintenance of blood pressure during caesarean section with spinal anesthesia, ephedrine maintains frontal lobe oxygenation and maternal heart rate with a similar increase in fetal heart rate as elicited by phenylephrine.

Trial registration: Clinical trials NCT 01509521 and EudraCT 2001 006103 35.

Keywords: cerebral autoregulation, drug effect, heart rate, fetal, near infrared spectroscopy, vasoconstrictor agents

INTRODUCTION

Spinal anesthesia is used for caesarean section although it is commonly associated with hypotension. In addition to tilting patient to the left and providing i.v. fluids, we use ephedrine and/or phenylephrine to prevent or correct hypotension that could result in, e.g., dizziness, nausea, and vomiting and also hinder adequate perfusion of the child (Berlac and Rasmussen, 2005; Cyna et al., 2006; Saravanan et al., 2006; Ngan Kee et al., 2008a).

The effect of ephedrine and phenylephrine on maternal and fetal hemodynamics has been investigated extensively (Mercier et al., 2001; Saravanan et al., 2006; Langesaeter et al., 2008; Ngan Kee et al., 2008a) There seems to be no difference between the two drugs in regards to preventing hypotension following spinal anesthesia for caesarean section (Cyna et al., 2006) However, fetal tachycardia appears to be more frequent with the use of ephedrine, or combined ephedrine and phenylephrine than with the use of phenylephrine (Wang et al., 2011) Furthermore, the effect of phenylephrine on fetal acid base status seems to be more favorable than manifested with the use of ephedrine (Vesser et al., 2012).

On the other hand, near infrared spectroscopy (NIRS) determined cerebral (frontal lobe) oxygenation (ScO_2) decreases when hypotension is supported by phenylephrine (Nissen et al., 2009a, 2010; Ogoh et al., 2011; Meng et al., 2011a) while it is maintained with the use of ephedrine (Nissen et al., 2010; Meng et al., 2011a; Ogoh et al., 2011) We investigated how phenylephrine and ephedrine influence ScO_2 when used to prevent maternal hypotension during caesarean section performed under spinal anesthesia where phenylephrine may hinder accumulation of blood in the blocked area of the body and thereby support

cardiac output (CO)(Cannesson et al., 2012) and in turn ScO_2. Thus, we hypothesized that administration of both ephedrine and phenylephrine would maintain ScO_2 in patients undergoing caesarean section with spinal anesthesia since an increase in vascular tone can enhance venous return and thereby support cardiac preload and CO during hypovolemia as demonstrated in anesthetized pigs (Cannesson et al., 2012) In this randomized clinical trial the primary outcome was to evaluate the ScO_2 response to administration of ephedrine vs. phenylephrine. Secondary aims were to evaluate changes in maternal hemodynamics and in fetal heart rate. Umbilical cord blood gas variables were also determined.

METHODS

For this single center, open label, parallel-group study with balanced randomization (1:1), written informed consent was obtained from healthy women undergoing elective caesarean section during spinal anesthesia after approval by the local ethics committee (SJ—271) and the Danish medicine agency (NCT 01509521; EudraCT 2001 006103 35). The Good Clinical Practice (GCP) unit at the University of Copenhagen monitored the trial conducted from April 2012 to July 2012 at Næstved Hospital. Eligible participants were older than 18 years in ASA group I or II, 160–180 cm and with a single pregnancy. Patients with either preeclampsia, non-singleton pregnancy, HELLP-syndrome (hemolysis, elevated liver enzyme, low platelet count), elevated serum bilirubin, or reported allergy to ephedrine or phenylephrine were excluded from the study.

PREPARATION

Upon arrival to the operating theater, the patient was provided with 500 mL isotonic saline, tilted 15° to the left and nasal supplementation of oxygen (2 L/min) was established. A cuff was applied to the third finger of the left hand and heart rate (HR), systolic (SBP), diastolic (DBP) and mean arterial (MAP) blood pressures were determined by Nexfin (BMEYE, The Netherlands, Amsterdam). Thus stroke volume (SV) was determined from the pressure curve using Modelflow (Bogert and van Lieshout, 2005) that takes sex, age, and weight into account. CO (SV times HR) and total peripheral resistance (TPR; MAP divided by CO) were calculated. Nexfin data were obtained on a beat to beat basis and averaged over 15 s every 2.5 min. Fetal HR was obtained by Doppler (Sonicaid Dopplers, Luton, Huntleigh, UK) and averaged over 15 s from before spinal anesthesia (baseline) and after spinal anesthesia (2.5–5 min), during surgery (7.5–17.5 min), and after delivery (13–28 min).

SPINAL ANESTHESIA

With 2.4 mL bupivacaine 0.5% (12 mg) and 10 μg fentanyl spinal anesthesia was established using a 27 or 25 G pencil point needle at the L2–L3 or L3–L4 intervertebral space. Spinal anesthesia was administered in the right lateral position in 21 patients and in three patients spinal anesthesia was provided in a seated position. Surgery started when the sensory block included the T5 dermatome as indicated by the loss of sensation to application of cold to the skin.

FRONTAL LOBE OXYGENATION

ScO_2 was monitored by NIRS (INVOS 3100 Cerebral Oxymeter, Somanetics, Troy, USA). Optodes were placed on both sides of the forehead immediately below the hairline and secured with a headband that also served to seal ambient light. The NIRS-determined mean ScO_2 is based on optodes that emit and detect near-infrared light at two wavelengths (730 and 810 nm) and ScO_2 is calculated as the ratio between oxyhemoglobin and total hemoglobin. The signal detector closest to the light source (3 cm) is considered the "shallow detector" and used to attenuate influence from superficial tissue, while the detector 4 cm from the light source is considered to detect light from "deep tissue." The distance between the source and detectors is considered sufficient for light to reach the brain (Choi et al., 2004) Thus it was assumed that values are accounted for predominantly by hemoglobin in the frontal lobe cortex, although a contribution from the skin is acknowledged (Davie and Grocott, 2012).

INTERVENTIONS AND RANDOMIZATION

The patients were allocated randomly into two groups (ephedrine or phenylephrine) of 12 using sequentially numbered, opaque, sealed envelopes prepared by an individual not involved in the study. Dose equivalence between phenylephrine (0.1 mg/mL) and ephedrine (5 mg/mL) was chosen in according to previous trials and recommendations (Saravanan et al., 2006; Ngan Kee et al., 2008b; Das et al., 2011).

After spinal anesthesia, the infusion was started (20 ml/h; 1.6 mg/min for ephedrine and 0.03 mg/min for phenylephrine) and adjusted to maintain SBP. If SBP increased from baseline by 10–20%, the infusion was reduced to 10 mL/h and paused if SBP increased more than 20%. Conversely, if SBP decreased by 10–20%, the infusion was increased to 40 mL/h. A bolus of either 10 mg ephedrine or 0.2 mg phenylephrine was to be administered if SBP decreased by more than 20%, or if the patient complained of symptoms of hypotension (dizziness, vomiting, faintness, nausea). At delivery the infusion was reduced to 10 mL/h and terminated 5–15 min thereafter. Data collected included Apgar score, and umbilical arterial and venous blood gas variables from a double-clamped cord segment. Further, data pertaining to the duration of surgery, volume of saline administered and the vasopressor dosages used are mentioned.

OUTCOME MEASURES

The primary outcome is expressed as the percentage ScO_2 change from baseline, with baseline defined as rest prior to spinal anesthesia (time 0 min). The secondary outcomes variables (maternal hemodynamics and fetal heart rate) were also expressed as the change from baseline and all observations were continued until the end of surgery.

STATISTICAL ANALYSIS

Power calculations based on former studies (Nissen et al., 2010; Kim et al., 2000) revealed that in order to detect a statistically significant difference between means of 57 and 67% in ScO_2, assuming a common standard deviation of 7%, a sample size of $n = 9$ per group was required to obtain a power of a least 0.8 ($\beta = 20\%$; two-tailed $\alpha = 5\%$). To compensate for

potential dropouts and missing data (25%) the sample size was increased to 12 participants per group. Data analyses were according to a pre-established plan using SAS software (v. 9.2; SAS Institute Inc., Cary, NC, USA). Descriptive statistics and tests are reported in accordance with the "Enhancing the QUAlity and Transparency Of health Research" (EQUATOR) network: the CONSORT Statement (Schulz et al., 2010). In order to evaluate data distribution of the outcome and statistical models, inspection was used to suggest whether the assumption of normality was reasonable. The PROC UNIVARIATE statement was used to summarize descriptive data. If the assumption of normality was not reasonable, we analyzed the data with the nonparametric Wilcoxon Rank Sum test using PROC NPAR1WAY; and the median difference was reported. The 95% confidence limit was estimated from an approximated standard error, based on the Wilcoxon p-value from a Wald-Z-test.

To analyse the longitudinal element of the study objectives, a linear approach was used for repeated measurements, using the procedure PROC MIXED based on restricted maximum likelihood (REML) estimates of the variables (Littell et al., 2000). The factor *Subject* was applied as a random effect factor. Assessment of the treatment and time effects tested possible interaction and both treatment and time were included as systematic factors using the baseline value as co-variate to reduce random variation and increase power. Unless stated otherwise, results are expressed as the difference between the group means and 95% CI with the associated p-values, based on the mixed linear model. The average change from the baseline during the study in each group was analyzed based on the mixed model with only the main effects of group and time without taking interaction into account. All comparisons were two tailed and $p < 0.05$ was considered statistically significant.

RESULTS

PATIENTS

Written informed consent to participate in the study was obtained from 33 patients; 24 of whom were subsequently randomized (**Figure 1**) and the randomized patients had a body mass index of 30.1 (5.4) mean (SD), range 21.6–41.6 kg/m^2 (**Table 1**).

FRONTAL LOBE OXYGENATION

In patients allocated to administration of phenylephrine ScO_2 decreased by $-8.6 \pm 2.8\%$ while in patients randomized to infusion of ephedrine, ScO_2 was not affected ($+2.1 \pm 2.8\%$). Comparing the values determined in the two groups, the difference in ScO_2 was 10.7% (95% CI 2.8–18.7%, $p = 0.0106$: **Table 2**, **Figure 2**). Whereas ScO_2 was reduced from baseline in the phenylephrine group ($p = 0.005$), this was not the case with the administration of ephedrine ($p = 0.4657$).

CARDIOVASCULAR EFFECTS

Phenylephrine (-14 ± 3 mmHg) and ephedrine (-20 ± 3 mmHg) were equally effective in maintaining MAP (**Figure 3**) with a group mean difference of 6 mmHg (95% CI -15 to 3, $p = 0.1904$). Similar results were obtained for DBP and SBP (**Table 2**). The maternal HR was maintained with ephedrine ($+3 \pm 3$ bpm) but decreased with phenylephrine (-11 ± 3 bpm); difference 14 (95% CI 5–23, $p = 0.0053$) bpm. SV appeared to increase both with phenylephrine (9.7 ± 4.8 ml) and with ephedrine (4.4 ± 5.0 ml), but this difference was not significant: -5.3 ml (95% CI -18.9 to 8.3, $p = 0.4299$). In the ephedrine group CO increased by 0.9 ± 0.4 l/min, while in the phenylephrine group CO was stable (-0.1 ± 0.4 l/min); 95% CI -0.08 to 2.02, $p = 0.0683$). There was a tendency for TPR to be lower in the ephedrine group compared with the phenylephrine group (-232 ± 42 vs. -129 ± 41) dyn s cm^{-5} ($p = 0.0684$).

FETAL VARIABLES

The difference in fetal heart rate between the ephedrine and phenylephrine group was 1 bpm (95% CI -6 to 9, $p = 0.7441$); for ephedrine $+19 \pm 3$ vs. $+18 \pm 3$ bpm for phenylephrine (**Table 2**, **Figure 4**). When compared to baseline both ephedrine ($p < 0.005$) and phenylephrine ($p < 0.005$) increased fetal heart rate. All Apgar scores were = 8 one minute after delivery and increased to 10 after 5 min in both groups. There was a difference ($p = 0.0223$) in regard to the umbilical venous base excess: -1.0 (95% CI -0.86 to -0.14) mM and arterial umbilical lactate was higher in the ephedrine than in the phenylephrine group: 0.50 (95% CI 0.09–0.91) mM, $p = 0.017$, while no differences were observed in any of the other umbilical cord blood variables assessed (**Table 3**).

OPERATIVE RESULTS

The time between intra-thecal injection and start of surgery [difference 0.0 (95% CI -2.8 to 2.8) min, $p = 0.9976$)] and between intra-thecal injection and delivery [difference 0.2 (95% CI 0.2 to 3.2) min, $p = 0.9106$)] were similar for the ephedrine and the phenylephrine groups (**Table 4**). The amount of i.v. saline was also equal between the two groups: 63 ml (95% CI -259 to 134, $p = 0.0515$) and there was no difference in the blood loss (100 ml (95% CI of difference -275 to 475), $p = 0.601$).

VASOPRESSOR DOSE

The ephedrine dose per minute was 1.7 mg (1.3–2) range 0.7–5.9 mg and of phenylephrine 1.38 mg (0.91–1.55) range 0.57–1.82 mg. No patient was treated with both phenylephrine and ephedrine.

Further monitoring (not reported) included pulse oximetry, ECG, non-invasive blood pressure on the right arm after initiation of saline administration and continued until the patient was transferred to the postoperative observation unit (no abnormal values were noted).

DISCUSSION

The present study confirmed that phenylephrine and ephedrine are equally effective in maintaining MAP in patients undergoing caesarean section with spinal anesthesia. The new finding is that in patients undergoing spinal anesthesia, the use of the ephedrine, capable of activating both α and β adrenergic receptors, preserves the near infrared-determined frontal lobe oxygenation (ScO_2) while ScO_2 was reduced in patients allocated to administration of phenylephrine, a selective α-adrenergic receptor agonist. We considered that women going through caesarean section during

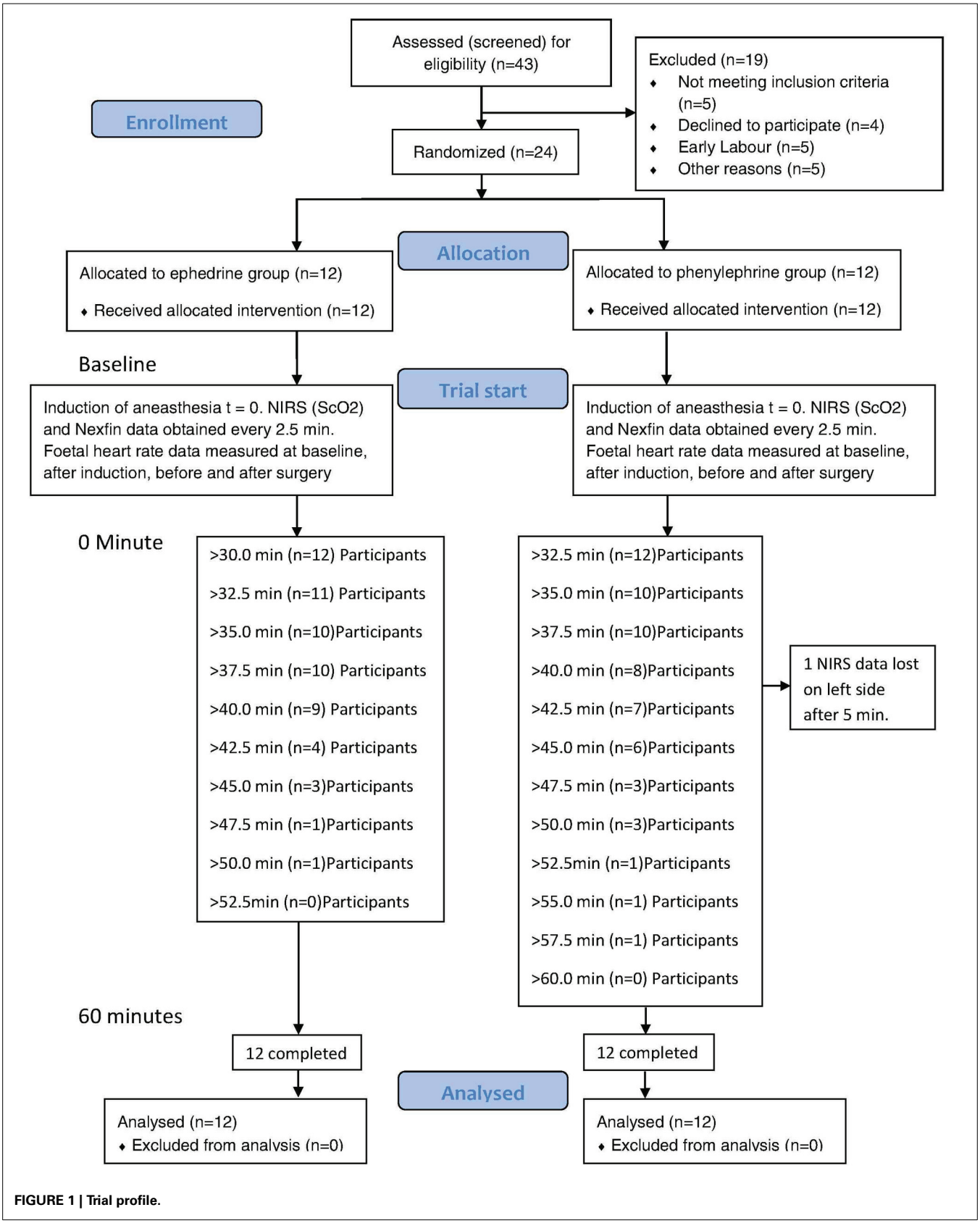


FIGURE 1 | Trial profile.

Table 1 | Patient characteristics, cardiovascular values, fetal heart rate, and frontal lobe oxygenation at baseline.

	Ephedrine *N* = 12	Phenylephrine *N* = 12	Total *N* = 24
Age (years)	30.8 ± 5.5	33.0 ± 3.7	31.9 ± 4.7 (21–39)
Height (cm)	166 ± 6	168 ± 7	167 ± 6 (160–180)
Weight (kg)	89 ± 20	81 ± 8	85 ± 15.5 (67–125)
Body mass index (kg/m2)	32.2 ± 6.3	28.1 ± 3.2	30.1 ± 5.4 (21.6–41.6)
Systolic pressure (mmHg)	135 ± 20	137 ± 14	136 ± 17 (104–168)
Diastolic pressure (mmHg)	83 ± 9	80 ± 13	81 ± 11 (62–105)
Mean arterial pressure (mmHg)	102 ± 11	101 ± 12	101 ± 11 (82–122)
Heart rate (bpm)	95 ± 18	89 ± 21	92 ± 19 (59–132)
Stroke volume (ml)	97 ± 21	105 ± 20	101 ± 20 (59–149)
Cardiac output (L/min)	8.9 ± 1.1	9.0 ± 2.1	8.9 ± 1.6 (5.7–13.2)
Total peripheral resistance (dyn s cm^{-5})	933 ± 162	946 ± 262	940 ± 213 (570–1530)
Fetal heart rate (bpm)	138 ± 9	137 ± 9	138 ± 9 (120–150)
Frontal lobe oxygenation (%)	67 ± 10	64 ± 7	66 ± 8 (56–91)

Values are means ± SD. (range: minimum and maximum).

Table 2 | Change in outcomes from baseline on average during 60 min trial period, in patients randomized to either ephedrine or phenylephrine.

	(*n* = 12) Ephedrine	(*n* = 12) Phenylephrine	Difference (95% CI)	*p*-Value
Frontal lobe oxygenation (%)	2.1 ± 2.8	−8.6 ± 2.8	10.7 (2.8–18.7)	0.0106
Systolic pressure (mmHg)	−19 ± 5	−16 ± 5	−3 (−17 to 11)	0.6329
Diastolic pressure (mmHg)	−17 ± 3	−14 ± 2	−3 (−10 to 3)	0.3093
MAP (mmHg)	−20 ± 3	−14 ± 3	−6 (−15 to 3)	0.1904
Heart rate (bpm)	3 ± 3	−11 ± 3	14 (5–23)	0.0053
Stroke volume (ml)	4.4 ± 5.0	9.7 ± 4.8	−5.3 (−18.9 to 8.3)	0.4299
Cardiac output (L/min)	0.85 ± 0.39	−0.12 ± 0.38	0.97 (−0.08 to 2.02)	0.0683
TPR (dyn s cm^{-5})	−232 ± 42	−129 ± 41	−103 (214 to 8)	0.0684
Fetal heart rate (bpm)	19 ± 3	18 ± 3	1 (−6 to 9)	0.7441

Presented are the ephedrine and phenylephrine group with values in means ± SE (standard error) and differences in mean changes (95% CI). Values for frontal lobe oxygenation (ScO_2) are changes in percent.

spinal anesthesia might be hypovolemic because of compromised venous return and that phenylephrine therefore could support cardiac output and in turn cerebral oxygenation as expressed by ScO_2. In contrast to our hypothesis, however, phenylephrine did not increase CO and maybe therefore reduced ScO_2. In other word, with the established routine for maintaining the circulation during caesarean section during spinal anesthesia, CO in response to administration of phenylephrine indicated that the patients were maintained "normovolemic." Furthermore, only ephedrine maintained HR and the two drugs elicited an equal almost 20 bpm increase in fetal heart rate.

Spinal anesthesia influences MAP because of sympathetic blockade and during caesarean section inferior caval compression may reduce venous return to the heart and thus CO (Cyna et al., 2006) During caesarean section hypotension is considered when maternal SBP decreases by 20–30% or decreases to less than 90–100 mmHg (Saravanan et al., 2006; Ngan Kee et al., 2008a) although we acknowledge that the lower limit of cerebral autoregulation has been challenged (Lucas et al., 2010; Tan, 2012). Thus, MAP did not fall to what is considered to be the lower limit of cerebral autoregulation (Paulson et al., 1990) and the patients were not expected to be exposed to cerebral hypoperfusion and a reduction in ScO_2. However, administration of phenylephrine led to a ∼9% reduction in ScO_2 (**Figure 2**, **Table 2**). A decrease in MAP to below ∼80 mmHg, as provoked for example during head-up tilt, reduces cerebral blood flow and ScO_2 because of a reduced central blood volume and CO (Madsen et al., 1998) However, whether or not a balance exists between cerebral oxygen supply and demand during anesthesia-induced hypotension remains unknown (Meng et al., 2013).

A 10–15% reduction in ScO_2 and a 50% reduction in middle cerebral artery mean flow velocity are associated with presyncopal symptoms (Kurihara et al., 2007) The 9% reduction in ScO_2 in response to administration of phenylephrine during spinal anesthesia for elective caesarean section approaches that level and could thus represent clinically important cerebral hypoperfusion (Hunt et al., 2006; Suzuki et al., 2008; Nissen et al., 2009b). On the other hand, the patients were awake and able to report hypotension-associated symptoms (nausea, vomiting or dizziness), but no complaints were expressed regardless

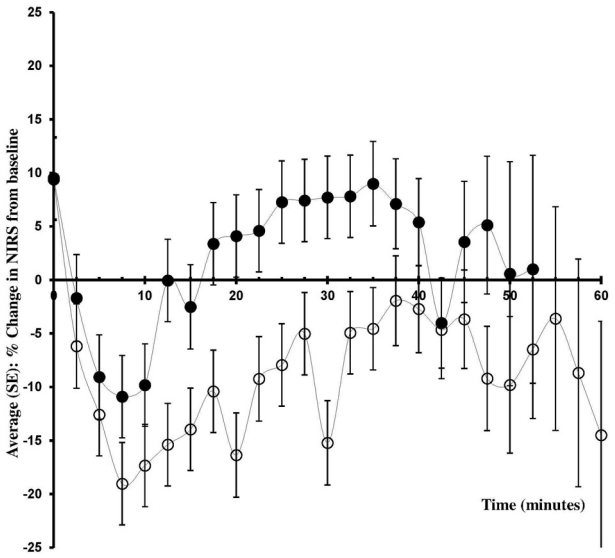


FIGURE 2 | Change in ScO_2 from baseline. Changes in frontal lobe oxygenation (ScO2; % from baseline) during caesarean section with spinal anesthesia. Patients received either phenylephrine ($n = 12$; open circles) or ephedrine ($n = 12$; black circles).

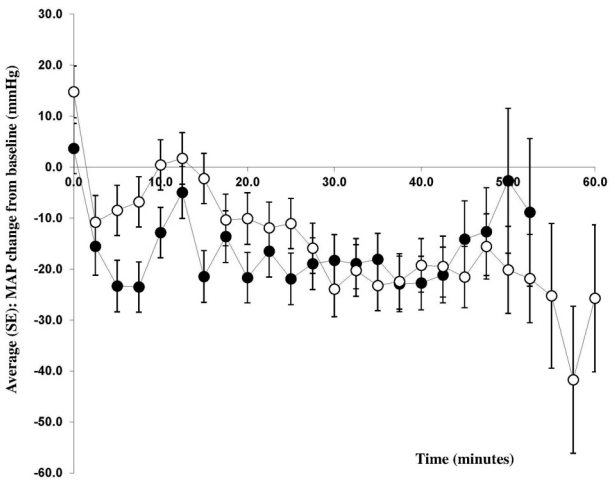


FIGURE 3 | Change in mean arterial pressure from baseline. Changes in mean arterial blood pressure (MAP) from baseline (mmHg) during caesarean section with spinal anesthesia. Patients received either phenylephrine ($n = 12$; open circles) or ephedrine ($n = 12$; black circles).

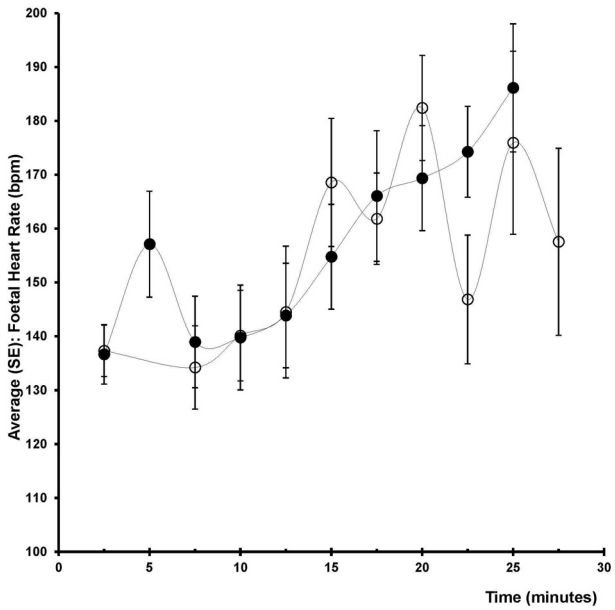


FIGURE 4 | Foetal heart rate. Change in fetal heart rate (bpm) after induction (2.5–5 min), before surgery (7.5–17.5 min), after delivery (12.5–27.5 min) in two groups of 12 patients undergoing spinal anesthesia for caesarean section and receiving either phenylephrine (open circles) or ephedrine (black circles).

of the NIRS value. It is possible that the 9% reduction in ScO_2 following the administration of phenylephrine reflects contamination of the NIRS signal from extracranial tissue (Davie and Grocott, 2012).

There was no difference in fetal HR among groups of patients and neonatal outcome was similar, although there were small but probably clinically unimportant differences in regard to umbilical arterial lactate and venous base excess. Ephedrine could increase fetal HR due to β-adrenergic stimulation, when or if it crosses placenta inducing fetal acidaemia (LaPorta et al., 1995) The impact of ephedrine on arterial lactate and venous base excess could be related to an effect on uteroplacental or feto-placental circulation (McGrath et al., 1994; LaPorta et al., 1995).

We recognize that this evaluation is not a blinded randomized controlled trial and further that it is a limitation to the study that both physicians and nurses expected that ephedrine would increase maternal heart rate and therefore potentially influenced by that expectation.We estimated blood pressure 2.5 min after initiation of anesthesia and with the use of vasopressor this considered as a long time and could represent a limitation of the study.

There were some difficulties in using Nexfin to estimate cardiovascular variables during caesarean section when the patients moved due to anxiety. Also, Modelflow may not be provide an accurate CO (Remmen et al., 2002) and calibration by thermodilution (Jansen et al., 2001) or by the Fick method (van Lieshout et al., 2001) may be in need. However, for tracking changes in CO the Nexfin has been successfully validated against a thermodilution estimate during a deliberate reduction in central blood volume induced by standing up in healthy subjects (Harms et al., 1999) during cardiac surgery (Jansen et al., 2001) in intensive care medicine (Jellema et al., 1999) and during liver transplantation (Nissen et al., 2009c).

Phenylephrine preserved MAP and reduced HR and maintained CO with a slight increase in SV that was 5 ml higher than the increase in the subjects receiving ephedrine. Phenylephrine may increase cardiac afterload to an extent that SV and CO decrease. On the other hand, an increase in vascular tone can increase venous return and thereby cardiac preload, SV and CO during hypovolemia as demonstrated in anesthetized pigs (Cannesson et al., 2012) Meng et al. found an increase in SV

Table 3 | Umbilical cord blood analysis.

Variable	Ephedrine	Phenylephrine	Difference between groups (95% CI)	*p*-Value
UMBILICAL ARTERIAL				
pH	7.29 ± 0.08	7.31 ± 0.05	−0.02 (−0.07 to 0.04)	0.4699
Pco2; kPa	7.36 ± 1.63	6.98 ± 0.77	0.38 (−0.72 to 1.48)	0.4793
Base excess (mM)**	−0.3 ± 2.8	0.6 ± 1.6	0.9 (−3.0 to 1.1)	0.3414
Lactate (mM)	2.4 [2.2 to 3.4]	1.9 [1.5–2.2]	0.50 (0,09–0.91)*	0.0170
UMBILICAL VENOUS				
pH	7.37 ± 0.06	7.37 ± 0.04	0.00 (−0.04 to 0.04)	0.9350
Pco2; kPa	5.58 ± 1.00	5.95 ± 0.60	−0.37 (−1.10 to 0.37)	0.3083
Base excess (mM)	−1.0 [−2.6 to −0.5]	0.0 [−0.1 to 0.3]	−1.0 (−0.86 to −0.14)*	0.0223
Lactate (mM)	2.1 [1.4–2.6]	1.9 [1.5–2.2]	0.20 (−0,09 to 0.49)*	0.1738

Values are mean ± SD and differences in mean changes (95% CI). Exceptions are arterial and venous blood lactate, venous base excess which is shown as median with interquartile range (IQR) in square brackets.

**Median difference.*

Table 4 | Surgical times and intravenous fluid.

Variable	Ephedrine	Phenylephrine	Difference between groups (95% CI)	*p*-value
Induction to incision (min)	13.3 ± 3.3	13.3 ± 3.3	0.0 (−2.8 to 2.8)	0.9976
Induction to delivery (min)	17.5 ± 3.2	17.3 ± 3.9	0.2 (−2.8 to 3.2)	0.9106
Total intravenous fluid (ml)	904 ± 254	967 ± 206	−63 (−259 to 134)	0.5153

Values are mean ± SD and differences in mean changes (95% CI).

and CO after administration of phenylephrine using pulsewave analysis by Vigileo-FloTrac in non-pregnant patients, but the increases were not confirmed with the use of a trans-esophageal Doppler apparatus (Meng et al., 2011b). Also an increase in SV in response to administration of phenylephrine is supported by Doherty et al. who used a CO monitor based on bi-reactance technology (Doherty et al., 2012) and by Dyer et al. using a LiDCOplus monitor (Dyer et al., 2009).

Another limitation of this trial was that we measured ScO_2 and not cerebral blood flow, but parallel variation between middle cerebral artery mean flow velocity in basal cerebral arteries and ScO_2 is reported (Ide et al., 1999; Yoshitani et al., 2007; Steiner et al., 2009) Furthermore, determination of internal jugular venous oxygen saturation could validate if the data obtained by NIRS are representative for the whole brain (Kim et al., 2000).

Three different NIRS approaches can be implemented: (1) Continuous wave (CW), (2) Frequency-domain (FD), and (3) time domain technology (TD). An approximate 3–4% decrease in ScO_2 is reported after treatment with phenylephrine with the use of FD (Meng et al., 2011a), compared with the 9% decrease in this evaluation while others (Nissen et al., 2010; Ogoh et al., 2011) find an approximate decrease by 14% using CW. With commercial CW monitors there is a variation in the ability to estimate ScO_2 (Davie and Grocott, 2012).

CONCLUSION

This study confirmed that infusion of phenylephrine and ephedrine are equally effective for sustaining blood pressure during elective caesarean section with spinal anesthesia. Phenylephrine, however, reduced ScO_2 and maternal heart rate when compared to ephedrine but the two drugs induced an equal increase in fetal heart rate.

AUTHOR'S CONTRIBUTION

Peter Nissen, Niels H. Secher, Henning B. Nielsen, Kim Z. Rokamp, and Visti T. Foss conceived and designed the trial protocol. Visti T. Foss procured the project funding in cooperation with Department of Anaesthesia, Næstved Hospital, Denmark. Visti T. Foss and Kim Z. Rokamp contributed to clinical screening and recruitment of patients. Visti T. Fossand Kim Z. Rokamp handled the cooperation with the Good Clinical Practice (GCP) unit at the University of Copenhagen with VF as primary investigator and Kim Z. Rokamp as sponsor. Visti T. Foss and Robin Christensen did the statistical analyses. Visti T. Foss, Robin Christensen, Niels H. Secher and Kim Z. Rokamp drafted the manuscript, and Peter Nissen and Henning B. Nielsen contributed to the manuscript. All authors read and approved the final manuscript. Visti T. Foss and Kim Z. Rokamp accept full responsibility for this work and act as guarantors for the study.

ACKNOWLEDGMENTS

The authors wish to thank Malene L. Pedersen M.D. for the recruitment of patients. In addition the authors thank the midwives of Næstved Hospital, Denmark for their assistance and cooperation. For the use of INVOS 3100 cerebral oxymeter we

thank Malene Brorsen, Covidien, Denmark. For proofreading the manuscript, we thank James Fisher, School of Sport and Exercise Sciences, University of Birmingham, UK.

FUNDING

This work was supported by Department of Anaesthesia, Næstved Hospital, Denmark and by the Copenhagen Muscle Research Center. The Musculoskeletal Statistics Unit, The Parker Institute, is supported by the Oak Foundation. The Rigshospitalet research foundation supported Henning B. Nielsen.

REFERENCES

Berlac, P. A., and Rasmussen, Y. H. (2005). Per-operative cerebral near-infrared spectroscopy (NIRS) predicts maternal hypotension during elective caesarean delivery in spinal anaesthesia. *Int. J. Obstet. Anesth.* 14, 26–31. doi: 10.1016/j.ijoa.2004.06.003

Bogert, L. W., and van Lieshout, J. J. (2005). Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Exp. Physiol.* 90, 437–446. doi: 10.1113/expphysiol.2005.030262

Cannesson, M., Zhongping, J., Chen, G., Vu, T. Q., and Hatib, F. (2012). Effects of phenylephrine on cardiac output and venous return depend on the position of the heart on the Frank-Starling relationship. *J. Appl. Physiol.* 113, 281–289. doi: 10.1152/japplphysiol.00126.2012

Choi, J., Wolf, M., Toronov, V., Wolf, U., Polzonetti, C., Hueber, D., et al. (2004). Noninvasive determination of the optical properties of adult brain: near-infrared spectroscopy approach. *J. Biomed. Opt.* 9, 221–229. doi: 10.1117/1.1628242

Cyna, A. M., Andrew, M., Emmett, R. S., Middleton, P., and Simmons, S. W. (2006). Techniques for preventing hypotension during spinal anaesthesia for caesarean section. *Cochrane Database Syst. Rev.* 4:CD002251. doi: 10.1002/14651858.CD002251.pub2

Das, S., Mukhopadhyay, S., Mandal, M., Mandal, S., and Basu, S. R. (2011). A comparative study of infusions of phenylephrine, ephedrine and phenylephrine plus ephedrine on maternal haemodynamics in elective caesarean section. *Indian J. Anaesth.* 55, 578–583. doi: 10.4103/0019-5049.90612

Davie, S. N., and Grocott, H. P. (2012). Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology* 116, 834–840. doi: 10.1097/ALN.0b013e31824c00d7

Doherty, A., Ohashi, Y., Downey, K., and Carvalho, J. C. (2012). Phenylephrine infusion versus bolus regimens during cesarean delivery under spinal anesthesia: a double-blind randomized clinical trial to assess hemodynamic changes. *Anesth. Analg.* 115, 1343–1350. doi: 10.1213/ANE.0b013e31826ac3db

Dyer, R. A., Reed, A. R., van Dyk, D., Arcache, M. J., Hodges, O., Lombard, C. J., et al. (2009). Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. *Anesthesiology* 111, 753–765. doi: 10.1097/ALN.0b013e3181b437e0

Harms, M. P., Wesseling, K. H., Pott, F., Jenstrup, M., Van Goudoever, J., Secher, N. H., et al. (1999). Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. *Clin. Sci.* 97, 291–301. doi: 10.1042/CS19990061

Hunt, K., Tachtsidis, I., Bleasdale-Barr, K., Elwell, C., Mathias, C., and Smith, M. (2006). Changes in cerebral oxygenation and haemodynamics during postural blood pressure changes in patients with autonomic failure. *Physiol. Meas.* 27, 777–785. doi: 10.1088/0967-3334/27/9/002

Ide, K., Horn, A., and Secher, N. H. (1999). Cerebral metabolic response to submaximal exercise. *J. Appl. Physiol.* 87, 1604–1608.

Jansen, J. R., Schreuder, J. J., Mulier, J. P., Smith, N. T., Settels, J. J., and Wesseling, K. H. (2001). A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth.* 87, 212–222. doi: 10.1093/bja/87.2.212

Jellema, W. T., Wesseling, K. H., Groeneveld, A. B., Stoutenbeek, C. P., Thijs, L. G., and van Lieshout J. J. (1999). Continuous cardiac output in septic shock by simulating a model of the aortic input impedance: a comparison with bolus injection thermodilution. *Anesthesiology* 90, 1317–1328. doi: 10.1097/00000542-199905000-00016

Kim, M. B., Ward, D. S., Cartwright, C. R., Kolano, J., Chlebowski, S., and Henson, L. C. (2000). Estimation of jugular venous O2 saturation from cerebral oximetry or arterial O2 saturation during isocapnic hypoxia. *J. Clin. Monit. Comput.* 16, 191–199. doi: 10.1023/A:1009940031063

Kurihara, K., Kikukawa, A., Kobayashi, A., and Nakadate, T. (2007). Frontal cortical oxygenation changes during gravity-induced loss of consciousness in humans: a near-infrared spatially resolved spectroscopic study. *J. Appl. Physiol.* 103, 1326–1331. doi: 10.1152/japplphysiol.01191.2006

Langesaeter, E., Rosseland, L. A., and Stubhaug, A. (2008). Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery: a randomized, double-blind comparison of low-dose versus high-dose spinal anesthesia with intravenous phenylephrine or placebo infusion. *Anesthesiology* 109, 856–863. doi: 10.1097/ALN.0b013e31818a401f

LaPorta, R. F., Arthur, G. R., and Datta, S. (1995). Phenylephrine in treating maternal hypotension due to spinal anaesthesia for caesarean delivery: effects on neonatal catecholamine concentrations, acid base status and Apgar scores. *Acta Anaesthesiol. Scand.* 39, 901–915. doi: 10.1111/j.1399-6576.1995.tb04195.x

Littell, R. C., Pendergast, J., and Natarajan, R. (2000). Modelling covariance structure in the analysis of repeated measures data. *Stat. Med.* 19, 1793–1819. doi: 10.1002/1097-0258(20000715)19:13<1793::AID-SIM482>3.3.CO;2-H

Lucas, S. J., Tzeng, Y. C., Galvin, S. D., Thomas, K. N., Ogoh, S., and Ainslie, P. N. (2010). Influence of changes in blood pressure on cerebral perfusion and oxygenation. *Hypertension* 55, 698–705. doi: 10.1161/HYPERTENSIONAHA.109.146290

Madsen, P., Olsen, S. B., Nielsen, H. B., Burcev, I., and Secher, N. H. (1998). Near-infrared spectrophotometry determined brain oxygenation during fainting. *Acta Physiol. Scand.* 162, 501–517. doi: 10.1046/j.1365-201X.1998.0308f.x

McGrath, J. M., Chestnut, D. H., Vincent, R. D., DeBruyn, C. S., Atkins, B. L., and Poduska, D. J. (1994). Ephedrine remains the vasopressor of choice for treatment of hypotension during ritodrine infusion and epidural anesthesia. *Anesthesiology* 80, 1073–1081. doi: 10.1097/00000542-199405000-00016

Meng, L., Cannesson, M., Alexander, B. S., Yu, Z., Kain, Z. N., Cerussi, A. E., et al. (2011a). Effects of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. *Br. J. Anaesth.* 107, 209–217. doi: 10.1093/bja/aer150

Meng, L., Gelb, A. W., and McDonagh, D. L. (2013). Changes in cerebral tissue oxygen saturation during anaesthetic-induced hypotension: an interpretation based on neurovascular coupling and cerebral autoregulation. *Anaesthesia* 68, 736–441. doi: 10.1111/anae.12254

Meng, L., Tran, N. P., Alexander, B. S., Laning, K., Chen, G., Kain, Z. N., et al. (2011b). The impact of phenylephrine, ephedrine, and increased preload on third-generation Vigileo-FloTrac and esophageal doppler cardiac output measurements. *Anesth. Analg.* 113, 751–757. doi: 10.1213/ANE.0b013e31822649fb

Mercier, F. J., Riley, E. T., Frederickson, W. L., Roger-Christoph, S., Benhamou, D., and Cohen, S. E. (2001). Phenylephrine added to prophylactic ephedrine infusion during spinal anesthesia for elective cesarean section. *Anesthesiology* 95, 668–674. doi: 10.1097/00000542-200109000-00020

Ngan Kee, W. D., Khaw, K. S., Lau, T. K., Ng, F. F., Chui, K., and Ng, K. L. (2008a). Randomised double-blinded comparison of phenylephrine vs ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective caesarean section. *Anaesthesia* 63, 1319–1326. doi: 10.1111/j.1365-2044.2008.05635.x

Ngan Kee, W. D., Lee, A., Khaw, K. S., Ng, F. F., Karmakar, M. K., and Gin, T. (2008b). A randomized double-blinded comparison of phenylephrine and ephedrine infusion combinations to maintain blood pressure during spinal anesthesia for cesarean delivery: the effects on fetal acid-base status and hemodynamic control. *Anesth. Analg.* 107, 1295–1302. doi: 10.1213/ane.0b013e31818065bc

Nissen, P., Brassard, P., Jørgensen, T. B., and Secher, N. H. (2010). Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. *Neurocrit. Care* 12, 17–23. doi: 10.1007/s12028-009-9313-x

Nissen, P., Nielsen, H. B., van Lieshout, J. J., and Secher, N. H. (2009a). Frontal lobe oxygenation is maintained during hypotension following propofol-phentanyl anesthesia. *AANAJ.* 77, 271–276.

Nissen, P., Pacino, H., Frederiksen, H. J., Novovic, S., and Secher, N. H. (2009b). Near-infrared spectroscopy for evaluation of cerebral autoregulation during orthotropic liver transplantation. *Neurocrit. Care* 11, 235–241. doi: 10.1007/s12028-009-9226-8

Nissen, P., Van Lieshout, J. J., Novovic, S., Bundgaard-Nielsen, M., and Secher, N. H. (2009c). Techniques of cardiac output measurement during liver transplantation: arterial pulse wave versus thermodilution. *Liver Transplant*. 15, 287–291. doi: 10.1002/lt.21689

Ogoh, S., Sato, K., Fisher, J. P., Seifert, T., Overgaard, M., and Secher, N. H. (2011). The effect of phenylephrine on arterial and venous cerebral blood flow in healthy subjects. *Clin. Physiol. Funct. Imaging* 31, 445–451. doi: 10.1111/j.1475-097X.2011.01040.x

Paulson, O. B., Strandgaard, S., and Edvinsson, L. (1990). Cerebral autoregulation. *Cerebrovasc. Brain Metab. Rev*. 2, 161–192.

Remmen, J. J., Aengevaeren, W. R., Verheugt, F. W., van ver Werf, T., Luijten, H. E., Bos, A., et al. (2002). Finapres arterial pulse wave analysis with model flow is not a reliable non-invasive method for assessment of cardiac output. *Clin. Sci*. 103, 143–149. doi: 10.1042/CS20010357

Saravanan, S., Kocarev, M., Wilson, R. C., Watkins, E., Columb, M. O., and Lyons, G. (2006). Equivalent dose of ephedrine and phenylephrine in the prevention of post-spinal hypotension in Caesarean section. *Br. J. Anaesth*. 96, 95–99. doi: 10.1093/bja/aei265

Schulz, K. F., Altman, D. G., and Moher, D. (2010). for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *J. Clin. Epi.* 63, 834–840. doi: 10.1016/j.jclinepi.2010.02.005

Steiner, L. A., Pfister, D., Strebel, S. P., Radolovich, D., Smielewski, P., and Czosnyka, M. (2009). Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. *Neurocrit. Care* 10, 122–128. doi: 10.1007/s12028-008-9140-5

Suzuki, K., Asahina, M., Suzuki, A., and Hattori, T. (2008). Cerebral oxygenation monitoring for detecting critical cerebral hypoperfusion in patients with multiple system atrophy during the head-up tilt test. *Intern. Med*. 47, 1681–1687. doi: 10.2169/internalmedicine.47.1094

Tan, C. O. (2012). Defining the characteristic relationship between arterial pressure and cerebral flow. *J. Appl. Physiol*. 15, 1194–1200. doi: 10.1152/japplphysiol.00783.2012

van Lieshout, J. J., Pott, F., Madsen, P. L., van Goudoever, J., and Secher, N. H. (2001). Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. *Stroke* 32, 1546–1551. doi: 10.1161/01.STR.32.7.1546

Vesser, M., Hofmann, T., Roth, R., Klöhr, S., Rossaint, R., and Hessen, M. (2012). Vasopressors for management of hypotension after spinal anesthesia for elective caesarean section. Systematic review and cumulative meta-analysis. *Acta Anaesthesiol. Scand*. 56, 810–816. doi: 10.1111/j.1399-6576.2011.02646.x

Wang, M., Han, C. B., and Qian, Y. N. (2011). Comparison of effects in puerpera and fetus with ephedrine and phenylephrine during a cesarean delivery. *J. Chin. Med. Assoc*. 91, 2195–2198.

Yoshitani, K., Kawaguchi, M., Miura, N., Okuno, T., Kanoda, T., Ohnishi, Y., et al. (2007). Effects of hemoglobin concentration, skull thickness, and the area of the cerebrospinal fluid layer on near-infrared spectroscopy measurements. *Anesthesiology* 106, 458–462. doi: 10.1097/00000542-200703000-00009

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 22 November 2013; accepted: 08 February 2014; published online: 03 March 2014.

*Citation: Foss VT, Christensen R, Rokamp KZ, Nissen P, Secher NH and Nielsen HB (2014) Effect of phenylephrine vs. ephedrine on frontal lobe oxygenation during caesarean section with spinal anesthesia: an open label randomized controlled trial. Front. Physiol. **5**:81. doi: 10.3389/fphys.2014.00081*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 22 October 2014
doi: 10.3389/fphys.2014.00407

Preserved frontal lobe oxygenation following calcium chloride for treatment of anesthesia-induced hypotension

Carl-Christian Kitchen, Peter Nissen, Niels H. Secher and Henning B. Nielsen*

Department of Anesthesia, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Yu-Chieh Tzeng, University of Otago, Wellington, New Zealand
Samuel J. E. Lucas, University of Birmingham, UK

***Correspondence:**
Henning B. Nielsen, Department of Anesthesia 2043, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark
e-mail: henningbay@hotmail.com

Vasopressor agents may affect cerebral oxygenation ($rScO_2$) as determined by near-infrared spectroscopy on the forehead. This case series evaluated the effect of calcium chloride vs. α and β-adrenergic receptor agonists on $rScO_2$ in patients ($n = 47$) undergoing surgery during i.v. anesthesia. Mean arterial pressure (MAP) and cardiac output (CO) were assessed by Model-flow® and ephedrine (55 ± 3 vs. 74 ± 9 mmHg; 10 mg, $n = 9$), phenylephrine (51 ± 5 vs. 78 ± 9 mmHg, 0.1 mg, $n = 11$), adrenaline (53 ± 3 vs. 72 ± 11 mmHg; 1–2 μg, $n = 6$), noradrenaline (53 ± 5 vs. 72 ± 12 mmHg; 2–4 μg, $n = 11$), and calcium chloride (49 ± 7 vs. 57 ± 16 mmHg; 5 mmol, $n = 10$) increased MAP (all $P < 0.05$). CO increased with ephedrine (4.3 ± 0.9 vs. 5.3 ± 1.2, $P < 0.05$) and adrenaline (4.7 ± 1.2 vs. 5.9 ± 1.1 l/min; $P = 0.07$) but was not significantly affected by phenylephrine (3.9 ± 0.7 vs. 3.6 ± 1.0 l/min), noradrenaline (3.8 ± 1.2 vs. 3.7 ± 0.7 l/min), or calcium chloride (4.0 ± 1.4 vs. 4.1 ± 1.5 l/min). Following administration of β-adrenergic agents and calcium chloride $rScO_2$ was preserved while after administration of α-adrenergic drugs $rScO_2$ was reduced by app. 2% ($P < 0.05$). Following α-adrenergic drugs to treat anesthesia-induced hypotension tissue oxygenation is reduced while the use of β-adrenergic agonists and calcium chloride preserve tissue oxygenation.

Keywords: brain, blood pressure, cardiac output, NIRS, cerebral oxygenation, cerebral oximetry

INTRODUCTION

Cerebral autoregulation has a lower limit (Paulson et al., 1990) and following induction of anesthesia blood pressure may decrease to what is considered to be below that level. Accordingly, patients receive intravenous administration of vasopressor agents such as phenylephrine (an α-adrenergic receptor agonist) or ephedrine that stimulates both α- and β-adrenergic receptors. Bolus calcium chloride could also increase blood pressure (Ellender and Skinner, 2008) by an increase in intracellular calcium to increase cardiac stroke volume via an effect on myocytes and vascular resistance via increased contraction of smooth muscles. Also calcium chloride may increase venous return by unloading the splanchnic reservoir. Thus, with administration of calcium chloride cardiac output (CO) increases without affecting heart rate (HR) (Ellender and Skinner, 2008) contrasting ephedrine that has the potential to increase both HR and CO.

Phenylephrine decreases the near infrared spectroscopy (NIRS) determined frontal lobe oxygenation ($rScO_2$) (Brassard et al., 2010, 2014; Nissen et al., 2010; Meng et al., 2011; Foss et al., 2014) related to vasoconstriction in extracranial vasculature rather than to a decrease in cerebral oxygenation (Ogoh et al., 2011, 2014; Sørensen et al., 2012). In this study patients undergoing major abdominal surgery were recruited to evaluate $rScO_2$ following routine administration of vasoactive drugs to treat a drop in blood pressure by induction of anesthesia. We used bolus calcium chloride along with the vasopressor agents phenylephrine, ephedrine, adrenaline or noradrenaline depending on the choice of the anesthesiologist. We tested the hypothesis that administration of ephedrine, adrenaline and calcium chloride to treat anesthesia-induced hypotension would preserve $rScO_2$, while $rScO_2$ would be reduced following administration of drugs that stimulate α-adrenergic receptors (phenylephrine and noradrenaline).

METHODS

In a pilot-like prospective study-design as approved by the regional ethical committee (H-1-2009-107) we included predominantly patients planned for major abdominal surgery. In 47 patients (age 63 ± 7 yrs, height 176 ± 7 cm, weight 78 ± 16 kg; 28 males; mean ± SD) this selection of cases tested the effect of different vasopressor agents on anesthesia-induced hypotension and $rScO_2$. Most patients were admitted for planned surgery including the liver, pancreas, esophagus, ventricle, or colon. In one case the spleen was the target for surgery and an other patient suffered from a retroperitoneal tumor. Three patients underwent vascular surgery and one patient was in surgery for hydronephrosis. Diabetes requiring insulin and the use of anti-hypertensive medication were considered to contradict inclusion in the evaluated series of patients. An increase in bilirubin was also an exclusion criterion due to the influence of bilirubin on near-infrared light absorption (Madsen et al., 2000).

The patients were exposed to at least 6 h of fast and orally intake of clear fluids was stopped 2 h before surgery. Three-lead electrocardiography monitored HR and pulse oximetry assessed arterial hemoglobin O_2 saturation (SpO_2). A hand vein was used for administration of fluid and anesthetics. According to

local guidelines, a radial artery catheter (20 gage; 1.1 mm) was, after local anesthesia, inserted in the arm with the highest non-invasively determined systolic blood pressure and the catheter was kept patent by isotonic saline (3 ml/h) through to a transducer (Edwards Life Sciences, Irving, CA, USA) positioned at the level of the heart. For surgery an epidural catheter was placed at Th. 8–10 in the lateral decubitus position and under local anesthesia, lidocaine (3 ml, 10 mg/ml) with adrenaline (5 μg/ml) was administered to test for intravascular or intrathecal placement.

A two channel cerebral oximeter (INVOS 5100C, Somanetics, Troy, MI, USA) detected $rScO_2$ that represents hemoglobin oxygen saturation in the tissue beneath the sensor as the ratio between oxygenated and total hemoglobin. As approved by the US Food and Drug Administration (510k-080769), the INVOS 5100C-determined $rScO_2$ is considered a trend monitor of the hemoglobin O_2 saturation for skin, scalp, and cortical tissue. With the NIRS-probe applied on the forehead it is assumed that capillaries within the frontal lobe contribute to light absorbance (Madsen and Secher, 1999) but skin, subcutaneous tissue and the scalp blood flow also influences the INVOS-determined $rScO_2$ (Davie and Grocott, 2012). $rScO_2$ was determined at least 2 cm above the eyebrows to limit an influence from the frontal sinus on $rScO_2$ (Tubbs et al., 2002). Cardiovascular variables including mean arterial pressure (MAP), HR, cardiac stroke volume (SV) and thus CO were assessed invasively by Model-flow® (Nexfin, B.V, Amsterdam, The Netherlands; Bogert and van Lieshout, 2005).

Anesthesia was induced with propofol (2 mg/kg) and maintained with propofol (0.08 mg/kg/min) and remifentanil (0.3–0.4 μg/kg/min). For ventilation a Dräger CATO (M32040, Lübeck, Germany) in volume-controlled mode was adjusted to an end-tidal CO_2 tension of 4–4.5 kPa and a positive end-expiratory pressure of 5 cm H_2O was used. When the patient was orally intubated, the inspiratory O_2 fraction was set to 0.7 to preserve $rScO_2$ (Rokamp et al., 2014). From induction of anesthesia, including tracheal intubation and until surgical incision, a reduction in MAP to below 60 mmHg was treated with administration calcium chloride (5 mmol) or α- and β adrenergic receptors: ephedrine (10 mg), phenylephrine (0.1–0.2 mg), adrenaline (1–2 μg), or noradrenaline (2–4 μg). No patient received more than one vasoactive agent.

It was estimated that to demonstrate a 10 ± 1.5% change in $rScO_2$ (from 70% to 63%) as compared to the level before administration of the drug (alpha 0.05, power >90%) 17 patients was needed in each group. The goal was set to 20 patients to take drop-outs into account, but due to slow enrolment in study it was terminated. The study was conducted as open-label as the drug used depended on the choice of the anesthesiologist.

For comparison of values before and after drug administration a paired *t*-test (two tailed) was used and for comparison between groups and a *t*-test for unpaired data. For evaluation of differences in age, height and weight between groups we used ANOVA with unpaired data and a Tukey-test for *post-hoc* analysis. Analysis was performed by statistical software (PRISM 6.0 for MacOS; GraphPad software, San Diego, CA, USA) and a $P < 0.05$ was considered statistically significant.

RESULTS

Nine patients were provided with ephedrine to correct anesthesia-induced hypotension, phenylephrine was administered to eleven patients, noradrenaline to eleven patients, six patients received adrenaline, and calcium chloride was administered to ten patients. The five groups of patients were comparable in terms of height and weight but the patients in the adrenaline group were younger than those in the other groups (**Table 1**).

Bolus calcium chloride maintained HR, SV, and CO and, as intended MAP increased (from 49 ± 7 to 57 ± 16 mmHg, $P < 0.05$) (**Table 2**, **Figure 1**). The other vasoactive agents also influenced cardiovascular variables: following administration of adrenaline SV tended to increase ($P = 0.08$) and as HR was maintained ($P = 0.71$) also CO tended to increase (by 25%, $P = 0.07$). Similarly, administration of ephedrine increased CO ($P < 0.05$) due to a non-significant change in HR ($P = 0.26$) and SV ($P = 0.10$). Both adrenaline and ephedrine increased MAP by 19 mmHg. Phenylephrine and noradrenaline maintained HR, SV, and CO with an increase in MAP by 27 and 20 mmHg, respectively.

The effect of vasoactive therapy on the NIRS determined $rScO_2$ are shown in **Table 2** and **Figure 1**. In patients treated with adrenaline and ephedrine $rScO_2$ was not affected significantly and when these data were pooled into one group of patients treated with β-adrenergic drugs, $rScO_2$ remained statistical unaffected: there was an increase in $rScO_2$ for five patients and for seven patients $rScO_2$ decreased without relation to changes in MAP or CO. After noradrenaline and phenylephrine a small but non-significant reduction in $rScO_2$ was noted for each vasoactive agent. However, with data evaluated as one group (α-adrenergic receptor agonists; noradrenaline and phenylephrine), seven patients with noradrenaline and seven patients with phenylephrine demonstrated lowered $rScO_2$ after drug administration while for only six patients $rScO_2$ increased (**Figure 2**). For two of these patients $rScO_2$ decreased almost 10%

Table 1 | Patient characteristics in five groups of patients who received vasoactive therapy to treat anesthesia-induced hypotension.

	Ephedrine ($n = 9$)	Adrenaline ($n = 6$)	Phenylephrine ($n = 11$)	Noradrenaline ($n = 11$)	Calcium chloride ($n = 10$)
Age (yrs)	67 ± 3	56 ± 11*	64 ± 7	64 ± 3	60 ± 9
Weight (kg)	84 ± 18	76 ± 13	76 ± 9	76 ± 16	80 ± 22
Height (cm)	178 ± 5	174 ± 6	179 ± 7	177 ± 7	172 ± 7

*Variable are mean ± SD. *Difference between Ephedrine and Adrenaline; $P < 0.05$.*

Table 2 | Cardiovascular variables in five groups of vasoactive therapy to treat anesthesia-induced hypotension.

	Adrenaline before	After	Ephedrine before	After	Noradrenaline before	After	Phenylephrine before	After	Calcium before	After
HR (beat/min)	65 ± 5	63 ± 9	60 ± 9	64 ± 18	57 ± 18	58 ± 19	56 ± 11	55 ± 12	61 ± 14	58 ± 15
SV (ml)	72 ± 17	89 ± 10*	76 ± 14	82 ± 15*	64 ± 14	70 ± 12	66 ± 9	67 ± 11	65 ± 21	67 ± 17
CO (L/min)	4.7 ± 1.1	5.9 ± 1.1*	4.3 ± 0.9	5.3 ± 1.2*	3.8 ± 1.2	3.7 ± 0.7	3.9 ± 0.7	3.6 ± 1.0	4.0 ± 1.4	4.1 ± 1.5
MAP (mmHg)	53 ± 3	72 ± 11*	55 ± 3	74 ± 9*	53 ± 5	72 ± 12*	51 ± 5	78 ± 9*	49 ± 7	57 ± 16*
$rScO_2$ (%)	58 ± 13	58 ± 12	73 ± 10	73 ± 11	70 ± 12	68 ± 11	67 ± 8	66 ± 7	68 ± 12	68 ± 11

*Variables are mean ± SD. HR, heart rate; SV, cardiac stroke volume; CO, cardiac output; MAP, mean arterial pressure; $rScO_2$, frontal lobe oxygenation. *Different between before and after in each group; $P < 0.05$. In calcium group determination of CO and SV was successful in six patients. After adrenaline SV and CO changed with P-values at 0.08 and 0.07, respectively. Epedrine affected SV at $P = 0.10$.*

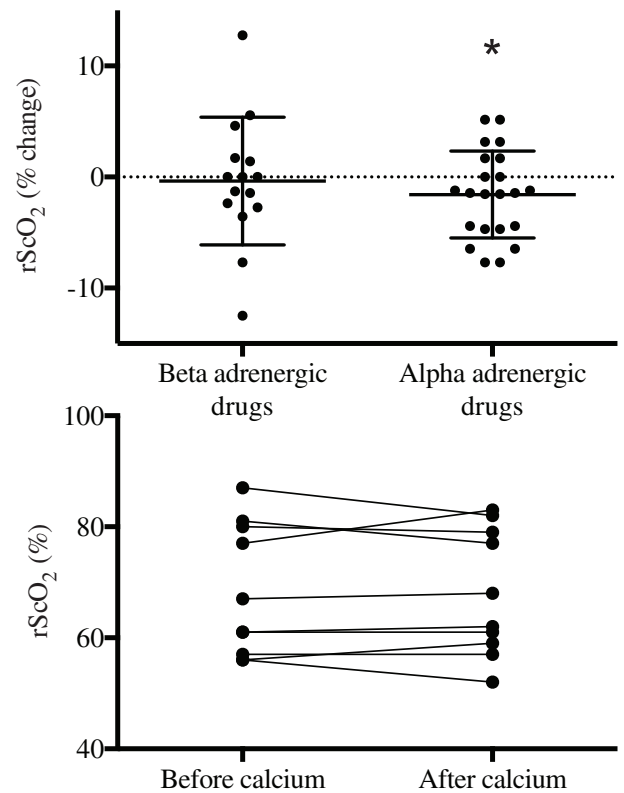


FIGURE 1 | Frontal lobe oxygenation ($rScO_2$) in response to α- or β-adrenergic agents or to calcium chloride (lower panel) to treat anesthesia-induced hypotension in surgical patients. *Different from baseline; $P < 0.05$.

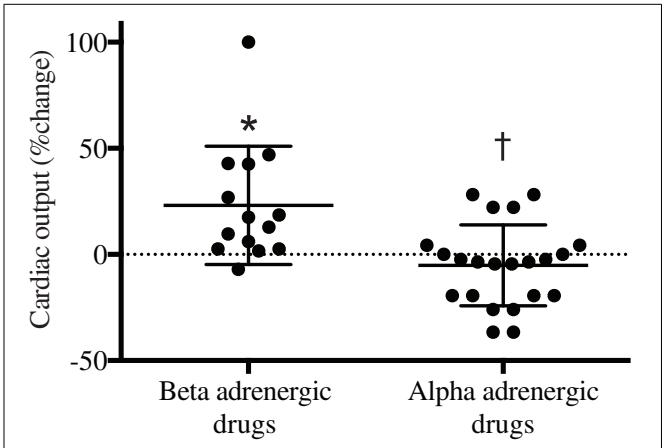


FIGURE 2 | Effects of α- or β-adrenergic agents on cardiac output following anesthesia in surgical patients. *Different from baseline; †, difference between groups. $P < 0.05$.

while CO increased (0.5 and 2.3 L/min) and for the whole group of patients (α-adrenergic receptor agonists) $rScO_2$ decreased 2%. After calcium chloride in four patients $rScO_2$ decreased (1–5%) and while $rScO_2$ was unchanged ($n = 2$) or increased (up to 6%) in the other eight patients, $rScO_2$ was not statistical affected by calcium chloride. Correlations between $rScO_2$ and MAP or CO were not observed.

DISCUSSION

This case series of 47 patients confirms that following anesthesia-induced hypotension in elective surgical patients, a vasopressor agent including calcium chloride increases MAP. The new finding is that frontal lobe oxygenation ($rScO_2$), as determined by near-infrared spectroscopy was not significantly affected following the use of calcium chloride for treatment of anesthesia-induced hypotension. A similar finding was observed with the use of ephedrine, phenylephrine, adrenaline, and noradrenaline as $rScO_2$ remained at levels similar to those established before drug administration. However, when data from patients treated with α-adrenergic receptor agonists (phenylephrine and noradrenaline) were pooled into one group and patients treated with β-adrenergic drugs (adrenaline or ephedrine) were sampled in an other group, $rScO_2$ decreased 2% after α-adrenergic drug administration but remained unaffected with administration of β-adrenergic stimulating drugs. This observation supports results obtained in patients (Nissen et al., 2010; Meng et al., 2011; Brassard et al., 2014) and healthy awake subjects (Brassard et al., 2010). Although a 2% reduction in $rScO_2$ seems small, the change is in the magnitude as induced by hyperventilation that lowers arterial CO_2 partial pressure with development of presyncopal symptoms (Madsen and Secher, 1999). Also Thomas et al. (2009) report ∼6% drop in cerebral oxygenation at presyncope.

Why $rScO_2$ is reduced after α-adrenergic drugs and not after administration of β-adrenergic-therapy and calcium chloride

remains unclear. In patients with intact cerebral autoregulation, the decrease in $rScO_2$ after phenylephrine and noradrenalin administration is associated with concordant reduction in CO, whereas $rScO_2$ remains unchanged when CO was maintained with ephedrine (Meng et al., 2011). This observation supports that changes in CO, independently of arterial pressure, affect cerebral hemodynamics (Ogoh et al., 2005). Cerebral arteries are abundantly innervated by sympathetic fibers (Sandor, 1999) and the decrease in $rScO_2$ after administration of α-adrenergic drugs could be by direct α-receptor-mediated cerebral vasoconstriction. An influence of cutaneous vasoconstriction beneath the NIRS optode, however has to be considered (Davie and Grocott, 2012; Sørensen et al., 2012).

The increase in MAP by vasoactive therapy was expected and the use of bolus calcium chloride also increased MAP even in patients without a suspected reduction in plasma ionized calcium. Indication for the use of calcium chloride is more clear after the use of blood products containing citrate that may lead to hypocalcemia (Jawan et al., 2003) and hemodynamic instability (Marquez et al., 1986). Thus, calcium chloride restores the levels of ionized calcium in blood and in turn also MAP.

Despite the effect of vasoactive agents on MAP was similar with the use of different drugs, the rise in pressure was achieved differently. Both ephedrine and adrenaline increased CO but such an effect was absent after administration of phenylephrine or noradrenaline. When data from patients treated with noradrenaline and phenylephrine were pooled into one group, CO was reduced in several patients (**Figure 2**): the eight lowest points with a decrease in CO by up to app. 50% represent four patients treated with phenylephrine and four patients treated with noradrenaline. After calcium chloride CO was unchanged and there was a trend towards a reduced HR ($P = 0.16$). For most of the patients treated with β-adrenergic agonists, CO increases by unloading of the splanchnic reservoir (Cannesson et al., 2012). An increase in CO may be important to override potential vasoconstriction in cutaneous and subcutaneous vessels following the use of vasoactive therapy. Considering that microvascular circulation influences wound healing, we consider that vasoactive drugs with significant vasoconstrictive capacity should be avoided both during and after surgery.

The use of calcium chloride to restore MAP is safe and in terms of the effect on $rScO_2$ this study is unable to promote one vasoactive drug over an other. The data do suggest that the use of a vasopressor agent with combined α- and β-adrenergic agonistic capacity appears to be favorable to restore MAP following anesthesia-induced hypotension. Results from a randomized double-blinded clinical trial are needed before a general recommendation to use combined α- and β-adrenergic drugs or calcium chloride for treatment of anesthesia-induced hypotension is substantiated.

ACKNOWLEDGMENTS

Henning Bay Nielsen was funded by Rigshospitalet Research fund and the Danish Agency for Science Technology and Innovation (271-08-0857).

REFERENCES

Bogert, L. W., and van Lieshout, J. J. (2005). Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Exp. Physiol.* 90, 437–446. doi: 10.1113/expphysiol.2005.030262

Brassard, P., Pelletier, C., Martin, M., Gagné, N., Poirier, P., Ainslie, P. N., et al. (2014). Influence of norepinephrine and phenylephrine on frontal lobe oxygenation during cardiopulmonary bypass in patients with diabetes. *J. Cardiothorac. Vasc. Anesth.* 28, 608–617. doi: 10.1053/j.jvca.2013.09.006

Brassard, P., Seifert, T., Wissenbrg, M., Jensen, P. M., Hansen, C. K., and Secher, N. H. (2010). Phenylephrine decreases frontal lobe oxygenation at rest but not during moderately intense exercise. *J. Appl. Physiol.* 108, 1472–1478. doi: 10.1152/japplphysiol.01206.2009

Cannesson, M., Jian, Z., Chen, G., Vu, T. Q., and Hatib, F. (2012). Effects of phenylephrine on cardiac output and venous return depend on the position of the heart on the Frank-Starling relationship. *J. Appl. Physiol.* 113, 281–289. doi: 10.1152/japplphysiol.00126.2012

Davie, S. N., and Grocott, H. P. (2012). Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology* 116, 834–840. doi: 10.1097/ALN.0b013e31824c00d7

Ellender, T. J., and Skinner, J. C. (2008). The use of vasopressors and inotropes in the emergency medical treatment of shock. *Emerg. Med. Clin. North Am.* 26, 759–786. doi: 10.1016/j.emc.2008.04.001

Foss, V. T., Christensen, R., Rokamp, K. Z., Nissen, P., Secher, N. H., and Nielsen, H. B. (2014). Effect of phenylephrine vs. ephedrine on frontal lobe oxygenation during caesarean section with spinal anesthesia: an open label randomized controlled trial. *Front. Physiol.* 5:81. doi: 10.3389/fphys.2014.00081

Jawan, B., de Villa, V., Luk, H. N., Chen, Y. S., Chiang, Y. C., Wang, C. C., et al. (2003). Ionized calcium changes during living-donor liver transplantation in patients with and without administration of blood-bank products. *Trans. Int.* 16, 510–514. doi: 10.1111/j.1432-2277.2003.tb00340.x

Madsen, P. L., and Secher, N. H. (1999). Near-infrared oximetry of the brain. *Prog. Neurobiol.* 58, 541–560.

Madsen, P. L., Skak, C., Rasmussen, A., and Secher, N. H. (2000). Interference of cerebral near-infrared oximetry in patients with icterus. *Anesth. Analg.* 90, 489–493. doi: 10.1097/00000539-200002000-00046

Marquez, J., Martin, D., Virji, M. A., Kang, Y. G., Warty, V. S., Shaw, B. Jr., et al. (1986). Cardiovascular depression secondary to ionic hypocalcemia during hepatic transplantation in humans. *Anesthesiology* 65, 457–461.

Meng, L., Cannesson, M., Alexander, B. S., Yu, Z., Kain, Z. N., Cerussi, A. E., et al. (2011). Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. *Br. J. Anaesth.* 107, 209–217. doi: 10.1093/bja/aer150

Nissen, P., Brassard, P., Jorgensen, T. B., and Secher, N. H. (2010). Phenylephrine but not Ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. *Neurocrit. Care* 12, 17–23. doi: 10.1007/s12028-009-9313-x

Ogoh, S., Brothers, R. M., Barnes, Q., Eubank, W. L., Hawkins, M. N., Purkayastha, S., et al. (2005). The effect of changes in cardiac output on middle cerebral artery mean blood velocity at rest and during exercise. *J. Physiol.* 569, 697–704. doi: 10.1113/jphysiol.2005.095836

Ogoh, S., Sato, K., Fisher, J. P., Seifert, T., Overgaard, M., and Secher, N. H. (2011). The effect of phenylephrine on arterial and venous cerebral blood flow in healthy subjects. *Clin. Physiol. Funct. Imaging* 31, 445–451. doi: 10.1111/j.1475-097X.2011.01040.x

Ogoh, S., Sato, K., Okazaki, K., Miyamoto, T., Secher, F., Sørensen, H., et al. (2014). A decrease in spatially resolved near-infrared spectroscopy-determined frontal lobe tissue oxygenation by phenylephrine reflects reduced skin blood flow. *Anesth. Analg.* 118, 823–829. doi: 10.1213/ANE.0000000000000145

Paulson, O. B., Strandgaard, S., and Edvinsson, L. (1990). Cerebral autoregulation. *Cerebrovasc. Brain Metab. Rev.* 2, 161–192.

Rokamp, K. Z., Secher, N. H., Eiberg, J., Lønn, L., and Nielsen, H. B. (2014). O2 supplementation to secure the near-infrared spectroscopy determined brain and

muscle oxygenation in vascular surgical patients: a presentation of 100 cases. *Front. Physiol.* 5:66. doi: 10.3389/fphys.2014.00066

Sandor, P. (1999). Nervous control of the cerebrovascular system: doubts and facts. *Neurochem. Int*. 35, 237–259.

Sørensen, H., Secher, N. H., Siebenmann, C., Nielsen, H. B., Kohl-Bareis, M., Lundby, C., et al. (2012). Cutaneous vasoconstriction affects spectroscopy-determined cerebral oxygen saturation during administration of norepinephrine. *Anesthesiology* 117, 263–270. doi: 10.1097/ALN.0b013e3182605afe

Thomas, K. N., Cotter, J. D., Galvin, S. D., Williams, M. J., Willie, C. K., and Ainslie, P. N. (2009). Initial orthostatic hypotension is unrelated to orthostatic tolerance in healthy young subjects. *J. Appl. Physiol.* 107, 506–517. doi: 10.1152/japplphysiol.91650.2008

Tubbs, R. S., Elton, S., Salter, G., Blount, J. P., Grabb, P. A., and Oakes, W. J. (2002). Superficial surgical landmarks for the frontal sinus. *J. Neurosurg.* 96, 320–322. doi: 10.3171/jns.2002.96.2.0320

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 04 July 2014; accepted: 01 October 2014; published online: 22 October 2014.
*Citation: Kitchen C-C, Nissen P, Secher NH and Nielsen HB (2014) Preserved frontal lobe oxygenation following calcium chloride for treatment of anesthesia-induced hypotension. Front. Physiol. **5**:407. doi: 10.3389/fphys.2014.00407*
This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 19 May 2014
doi: 10.3389/fphys.2014.00187

Cardiovascular consequence of reclining vs. sitting beach-chair body position for induction of anesthesia

Søren L. Larsen[1]*, Tobias S. Lyngeraa[1], Christian P. Maschmann[1], Johannes J. Van Lieshout[2,3] and Frank C. Pott[1]

[1] Department of Anesthesiology, Bispebjerg Hospital, University of Copenhagen, Denmark
[2] Acute Admissions Unit, Laboratory for Clinical Cardiovascular Physiology, Department of Internal Medicine, AMC Center for Heart Failure, University of Amsterdam, Netherlands
[3] Queen's Medical Centre, School of Life Sciences, University of Nottingham Medical School, Nottingham, UK

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Mildred Audrey Pointer, North Carolina Central University, USA
Henrik Sørensen, University of Copenhagen, Denmark

***Correspondence:**
Søren L. Larsen, Department of Anesthesiology, Bispebjerg Hospital, University of Copenhagen, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark
e-mail: soerenll@gmail.com

The sitting beach-chair position is regularly used for shoulder surgery and anesthesia may be induced in that position. We tested the hypothesis that the cardiovascular challenge induced by induction of anesthesia is attenuated if the patient is placed in a reclining beach-chair position. Anesthesia was induced with propofol in the sitting beach-chair ($n = 15$) or with the beach-chair tilted backwards to a reclining beach-chair position ($n = 15$). The last group was stepwise tilted to the sitting beach-chair position prior to surgery. Hypotension was treated with ephedrine. Continuous hemodynamic variables were recorded by photoplethysmography and frontal cerebral oxygenation (ScO_2) by near infrared spectroscopy. Significant differences were only observed immediately after the induction when patients induced in a reclining beach-chair position had higher mean arterial pressure (MAP) (35 ± 12 vs. 45 ± 15 % reduction from baseline, $p = 0.04$) and ScO_2 (7 ± 6 vs. 1 ± 8% increase from baseline, $p = 0.02$) and received less ephedrine (mean: 4 vs. 13 mg, $p = 0.048$). The higher blood pressure and lower need of vasopressor following induction of anesthesia in the reclining compared to the sitting beach-chair position indicate more stable hemodynamics with the clinical implication that anesthesia should not be induced with the patient in the sitting position.

Keywords: anesthesia, hemodynamics, patient positioning, shoulder, near-infrared spectroscopy

INTRODUCTION

During endoscopic shoulder surgery the patient is preferably placed in the sitting beach-chair position (Skyhar et al., 1988; Pohl and Cullen, 2005). This position facilitates surgical access (Papadonikolakis et al., 2008; Tange et al., 2010) and limits the blood loss since the shoulder is above heart level (Papadonikolakis et al., 2008).

On the other hand, the sitting position is associated with pooling of blood in the legs. The resulting postural reduction in stroke volume (SV) and cardiac output (CO) impacts the circulation (Dalrymple et al., 1979; Porter et al., 1999; Buhre et al., 2000; Truijen et al., 2012). In healthy awake humans, baroreceptor reflex-mediated sympathetic activation with an increase in heart rate (HR) and vascular tone maintains mean arterial pressure (MAP), but induction of anesthesia with propofol attenuates this adaptive response. The circulatory challenge of being positioned in a sitting position during induction of anesthesia may jeopardize maintenance of MAP leading to bradycardic hypotensive events (Kinsella and Tuckey, 2001; Jeong et al., 2012). Against this background we questioned whether under these circumstances the hemodynamic challenge of anesthesia in the sitting beach-chair position compromises cerebral perfusion and oxygenation (McCulloch et al., 2010; Lee et al., 2011; Moerman et al., 2012).

In a survey among 26 anesthesiology departments in Denmark, ~40% preferred induction of anesthesia for shoulder surgery with the patient positioned in the sitting beach-chair position to reduce the risk of nerve injury by repositioning an anesthetized patient, and to minimize the setup time. Nerve injury is extremely rare in the beach-chair position (Peruto et al., 2009). However, transient or permanent loss of neural conductivity, so-called neurapraxia, may occur due to nerve fiber compression or inadvertent stretch especially when repositioning the head (Rains et al., 2011).

While several studies focused on the perioperative hemodynamic challenge of the beach-chair position (Dalrymple et al., 1979; Porter et al., 1999; Buhre et al., 2000; Jeong et al., 2012; Moerman et al., 2012), no attention has been paid to the position of the patient during induction of anesthesia. It remains unsettled whether induction of anesthesia in the reclining vs. sitting beach-chair position secures cerebrovascular hemodynamics. To that purpose we investigated the effects of induction of anesthesia in the reclining beach-chair position with subsequent stepwise rise to the sitting beach-chair position vs. induction of anesthesia in the sitting beach-chair position on MAP and cerebral oxygenation.

MATERIALS AND METHODS

PATIENTS

This quality control study was performed to assess a change in clinical practice after the departments' advisory board had

discouraged induction of anesthesia in the sitting beach-chair position, and it was approved by the Ethical Committee of Copenhagen (H-3-2013-FSP15). Data were recorded in 15 consecutive patients in whom anesthesia was induced in the reclining beach-chair position and results compared to those from a historical control group of 15 patients induced in the sitting beach-chair position. These patients had participated in a trial on the effect of a sequential leg compression device on hemodynamic stability during anesthesia in the sitting beach-chair position (ethical approval: H-1-2009-070; registered in Clinical Trials NCT01680393). Apart from the position of the patient during induction of anesthesia, inclusion procedures, the setup, and the investigators were the same for both groups. All patients signed written informed consent prior to the investigation.

Patients undergoing elective shoulder arthroscopy in general anesthesia were eligible for inclusion when >18 years and in ASA physical status I–II. All patients received an interscalene block (ropivacaine 7.5 mg/ml, 10–20 ml) and wore TED compression stockings throughout the surgical procedure. On the day of surgery, patients were allowed to take clear fluids freely until 2 h before the induction of anesthesia. Hemodynamic variables (MAP, HR, SV, and CO), frontal cerebral oxygenation (ScO_2), and lower leg oxygenation (SmO_2) were recorded continuously. Primary endpoint was the decrease in MAP, whereas the amount of ephedrine administered, ScO_2, SmO_2, HR, SV, and CO were secondary endpoints.

STUDY PROTOCOL

Baseline

For both groups signal recording started with the patients sitting comfortably in the sitting beach-chair. After ∼5 min rest, baseline values were registered as 1 min averages.

Reclining beach-chair position

After baseline monitoring patients in the reclining beach-chair group were tilted backwards so that the toes were at the same height as the forehead. Following pre-oxygenation anesthesia was induced. When the hemodynamic condition was judged stable (approximately 5–10 min after induction), the patients were tilted ∼ 30° to halfway sitting position prior to sterile draping and remained in that position for approximately 5 min. Prior to the surgical procedure the patients were tilted further up (∼ 60° sitting beach-chair position), and remained in that position throughout the surgical procedure.

Sitting beach-chair position

The body position of the sitting group was maintained during baseline signal recording, induction of anesthesia and throughout the surgical procedure.

Positioning of beach-chair (sitting)

The surgical table was set into the sitting beach-chair position with the upper body section raised to ∼ 60°, the mid-section in ∼ 10° Trendelenburg position, and the leg section flexed ∼ 20° at the level of the knees. The head was stabilized in a head rest to prevent head rotation which interferes with cerebral blood flow and cerebrovenous drainage (Højlund et al., 2012). The shoulder panel on the operated side was removed, and an arm support was placed on both sides. Straps were fastened around the torso and the legs to fasten the patient.

Anesthesia

After the patient was placed, pre-oxygenation started through a loose fitting facial mask and propofol (∼0.5 mg kg^{-1} h^{-1}) and remifentanil (∼0.5 μg kg^{-1} h^{-1}) infusions were initiated. Propofol (2.0–2.5 mg kg^{-1} i.v. in a bolus injection) as inductive agent was administered when the patient felt first signs of anesthesia, and a laryngeal mask was placed after loss of eyelid reflexes. Anesthesia was maintained by continued infusion of propofol and remifentanil. Hypotension (MAP<60 mmHg) was treated with ephedrine 5–10 mg. Ventilation was maintained by a respirator with a tidal volume ∼8 ml kg^{-1}, an inspiratory oxygen fraction of 0.4, and a respiratory frequency ∼12 min^{-1}. Isotonic saline was administered at ∼500 ml h^{-1}. Hemodynamic stability was assessed by (1) the maximal decline in MAP, SV and ScO_2 during the first 4 min following induction of anesthesia and position change; (2) the total dosage of ephedrine administered during anesthesia; and (3) the average change in MAP, HR, SV, and CO under steady state (during surgery, 15 and 30 min following induction of anesthesia) compared with baseline.

MEASUREMENTS

Oxygenation

ScO_2 and SmO_2 were recorded by near-infrared spectroscopy (NIRS, INVOS® System technology, model 5100C, Somanetics Corporation, Troy, MI) (Moritz et al., 2007; Smith and Elwell, 2009). One probe was placed high on the lateral forehead ipsilateral to the arm being operated. A second probe was placed over the left gastrocnemius muscle.

Circulatory measurements and data analysis

SV was obtained from continuously measured arterial pressure by the pulse contour method (BMEYE Nexfin® monitor, Amsterdam, The Netherlands) (Martina et al., 2012). A cuff was applied to the midphalanx of the middle finger of the arm not being operated. A "heart reference system" with a transducer at both the finger and the heart level corrected for the hydrostatic difference between the finger cuff and the heart. Compared with Doppler-measured changes in CO, pulse contour analysis provides reliable estimates, especially in regard to changes (Bogert et al., 2010; Van Geldorp et al., 2011; Van der Spoel et al., 2012).

Data from the near-infrared and photoplethysmographic devices were not disclosed to the anesthesiologist who relied on standard intra-operative monitors, including sphygmomanometric blood pressure as measured on the arm opposite to the operated shoulder every second minute following induction and later every fifth minute.

Post-hoc analysis included visual judgment of blood pressure tracings for obvious artifacts that were removed using MATLAB 7.12 analysis software (MathWorks, Natick, MA, USA). Signals of ScO_2, MAP, HR, SV, CO, and SmO_2 were resampled at 1 Hz and expressed as averages of 15-s intervals.

Blood pressure tracings were inspected for instances of 15-s intervals with hypotension (MAP < 60 mmHg), as were NIRS-tracings for cerebral deoxygenation defined as a 20% decrease in ScO_2 compared to baseline (Moritz et al., 2007).

STATISTICAL ANALYSIS

Data are expressed as mean ±*SD* unless otherwise indicated. A sample size of 14 patients in each group gave 80% power to detect a 15% difference in MAP at a significance level of 0.05. Comparison between groups was analyzed using Student's unpaired *t*-test when data were normally distributed; otherwise Mann-Whitney Rank sum test was used. One-Way repeated measurements analysis (ANOVA) was used to test for changes in hemodynamics after shift in body position. Paired Student's *t*-test was used to compare values before and after induction. $P < 0.05$ was considered statistically significant and all statistical procedures were performed using the SigmaPlot version 11.0.

RESULTS

In two patients (one in each group) photoplethysmographic measurements were of insufficient quality, leaving data from 28 patients for analysis. Patient characteristics were comparable between the two groups (**Table 1**).

PRIOR TO INDUCTION

Baseline values were similar among the groups (**Table 2**).

In the reclining beach-chair position pre-oxygenation increased ScO_2 more than in the sitting beach-chair group.

AFTER INDUCTION

Induction of anesthesia resulted in the largest drops in ScO_2 and MAP in patients induced in the sitting beach-chair position while their SmO_2 was higher (**Table 2**). However, due to the pre-oxygenation induced offset, ScO_2 remained higher than baseline in both groups during the first 4 min after induction of anesthesia. CO tended to be lower (**Figure 1**), but minimum values for CO, SV, and HR were not different between the groups.

TILTING TO THE SITTING BEACH-CHAIR POSITION

When patients from the reclining beach-chair group were tilted to the sitting beach-chair position, MAP, SV, and CO remained stable, whereas HR and ScO_2 decreased (**Table 2**). At the same time SmO_2 increased.

CHANGES FROM BASELINE TO A STEADY-STATE CONDITION (15 AND 30 MIN AFTER INDUCTION)

In both groups, MAP, HR, SV, and CO were lower 15–30 min after induction of anesthesia without significant differences between the groups (**Figure 1**).

Table 1 | Clinical characteristics of the study population.

	Sitting beach-chair ($n = 14$)	Reclining beach-chair ($n = 14$)
Age (years)	40 ± 17	42 ± 15
Gender (m/f)	9/5	9/5
Height (cm)	175 ± 8	177 ± 8
Weight (kg)	76 ± 11	83 ± 11
BMI (kg/m^2)	25 ± 3	27 ± 4
Operated side (left/right)	6/8	7/7
Per-operative saline IV (ml)	690 ± 160	660 ± 230
Propofol infusions (mg/kg/h)	0.50 ± 0.11	0.45 ± 0.09
Remifentanil infusions (μg/kg/h)	0.49 ± 0.16	0.44 ± 0.07
Induction bolus of propofol (mg/kg)	2.24 ± 0.39	2.12 ± 0.51

Table 2 | Circulatory and oxygenation parameters at baseline, following induction of anesthesia in either the sitting or reclining position, and during subsequent elevation to the sitting position in the patients in whom anesthesia was induced in the reclining position.

	Position during induction	Baseline	Prior to induction (15 s)	After induction (minimum 0–4 min)	Inclination 30° (minimum 0–4 min)	Inclination 60° (minimum 0–4 min)	15–30 min following induction
ScO_2	Sitting	72 ± 7(%)	+7 ± 5*	+1 ± 8*			−4 ± 10
	Reclining	68 ± 6 (%)	+12 ± 4	+7 ± 6	+3 ± 15	−5 ± 12#	−1 ± 10
SmO_2	Sitting	70 ± 12 (%)	+2 ± 7	+11 ± 6* (Max)			+8 ± 5
	Reclining	76 ± 8 (%)	+1 ± 4	+5 ± 5 (Max)	+5 ± 7 (Max)	+8 ± 6# (Max)	+4 ± 5
MAP	Sitting	104 ± 10 (mmHg)	+3 ± 8	−45 ± 15*			−37 ± 11
	Reclining	102 ± 17 (mmHg)	−2 ± 13	−35 ± 12	−35 ± 17	−36 ± 12	−31 ± 11
HR	Sitting	73 ± 16 (beats/min)	+11 ± 20	−21 ± 11			−12 ± 15
	Reclining	71 ± 16 (beats/min)	+6 ± 14	−18 ± 11	−27 ± 7#	−24 ± 9#	−21 ± 10
SV	Sitting	91 ± 20 (ml)	0 ± 6	−24 ± 14			−10 ± 15
	Reclining	101 ± 29 (ml)	0 ± 15	−20 ± 19	−10 ± 27	−18 ± 26	−9 ± 30
CO	Sitting	6.5 ± 1.1 (l/min)	+12 ± 17	−36 ± 16			−23 ± 11
	Reclining	6.9 ± 1.7 (l/min)	+5 ± 16	−29 ± 17	−33 ± 18	−36 ± 16	−29 ± 18

*All values are mean ± SD. For both groups, absolute baseline values represent a 60 s average in the sitting position. Other values are percent changes compared to baseline; averages of the 15 s interval prior to induction, and the 15–30th min after induction. Between 0 and 4 min after the induction and inclination, values represent the minimum (SmO_2: maximum) of 15 s averages. *Sitting vs. reclining; $p < 0.05$. # Different from the minimum value after induction; $p < 0.05$.*

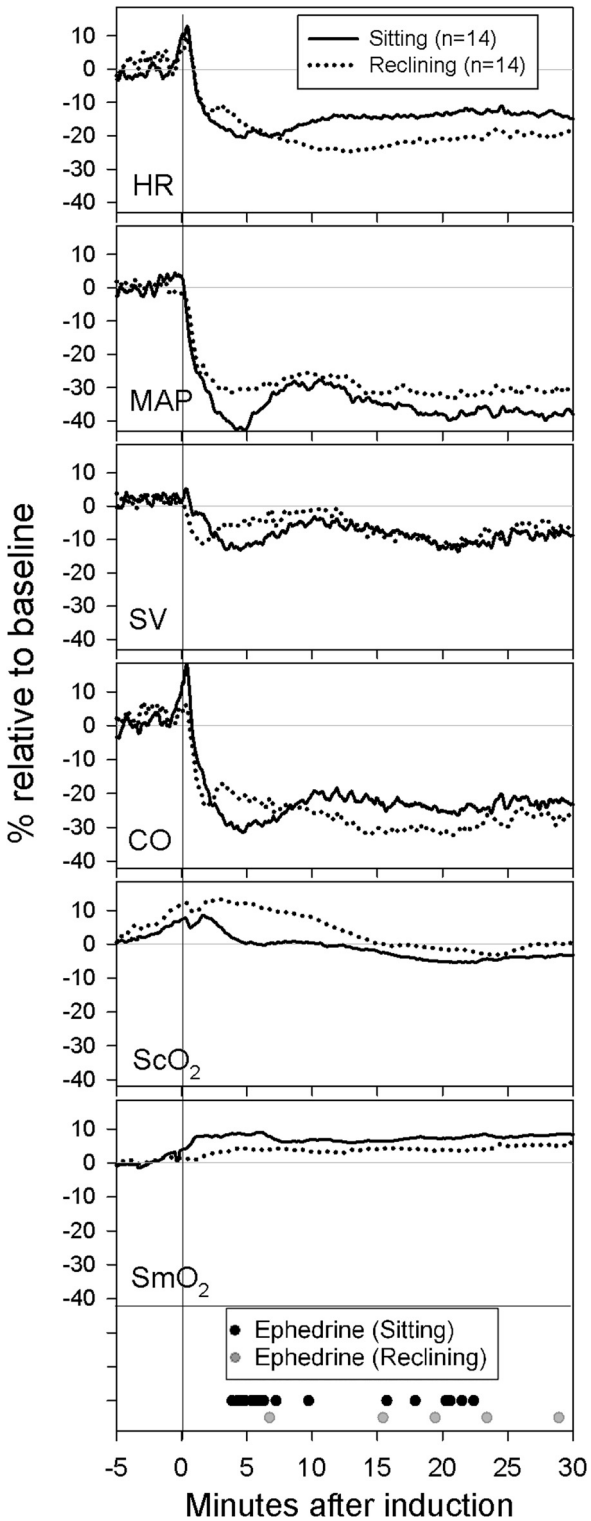


FIGURE 1 | Mean-values for all patients from 5 min prior to induction until 30 min after induction. Baseline was recorded in the sitting beach-chair position approximately 5 min prior to induction. During the 5 min prior to induction the patient was placed in the induction position (either sitting or reclining) with start of propofol and remifentanil infusions and preoxygenation. Instances of individual ephedrine-administrations are shown.

Table 3 | Number of 15 s periods per patient with MAP <60 mmHg, (median and range); and the number of ephedrine (Eph) administrations during three consecutive 10 min intervals.

	0–10 min after induction	10–20 min after induction	20–30 min after induction
Sitting	13 (0–29); Eph × 11	3 (0–37); Eph × 2	8 (0–34); Eph × 4
Reclining	0 (0–31); Eph × 1	0 (0–40); Eph × 2	2 (0–40); Eph × 2

BLOOD PRESSURE AND EPHEDRINE TREATMENT

The incidence of hypotensive events was not statistically different between the two groups (**Table 3**). However, during surgery the group induced in the sitting beach-chair position received more ephedrine (mean: 13 vs. 4 mg, $p = 0.048$), especially during the first 10 min after induction [10 (0–20 mg); median (range) vs. 0 (0–5 mg); $p < 0.001$].

CEREBRAL DEOXYGENATION

Two patients induced in the sitting beach-chair position and three patients in the reclining beach-chair position had episodes with cerebral deoxygenation, defined as a 20% decrease compared to baseline. Cerebral deoxygenations were detected following 10–30 min after induction. In these patients deoxygenations coincided with hypotensive events where MAP decreased by 40–70%.

DISCUSSION

The main new finding is that induction of anesthesia in the reclining beach-chair position resulted in higher MAP, fewer requirements for ephedrine, and higher ScO_2 as compared to induction in the sitting beach-chair position.

The observed differences between the two modes of induction are small but may become clinically significant for patients with less effective cerebrovascular autoregulatory capacity associated with microvascular disease in whom any reduction in MAP is translated into a fall in cerebral blood flow (Kim et al., 2011). Following induction of anesthesia ScO_2 was slightly higher in the reclining compared with the sitting beach-chair group whereas the opposite occurred for SmO_2. This might be due to caudal accumulation of blood in the sitting position and suggesting that anesthesia induction in the reclining vs. the sitting beach-chair position secures central hemodynamics more efficiently. NIRS recordings might have been different with use of vasopressors other than ephedrine. With phenylephrine and norepinephrine reductions in NIRS signals have been observed concomitant with elevated MAP and were taken to reflect either cerebral vasoconstriction or reduced cardiac stroke volume (Brassard et al., 2009; Nissen et al., 2009). However, recent studies suggest that such reduction is explained by a major contribution of (reduced) skin perfusion to the NIRS signal rather than actual changes in cerebral blood flow (Sørensen et al., 2012, 2014; Ogoh et al., 2014).

No study has addressed the cardio- and cerebrovascular effects of the postural reduction in central blood volume (Buhre et al., 2000; Tange et al., 2010) associated with the sitting position for

induction of anesthesia. We can only speculate whether patients induced in the sitting position are imposed to a higher risk of adverse neurologic events, but no such events were reported in >5000 patients who were anesthetized in the supine position and subsequently tilted to the sitting beach-chair position (Pin-On et al., 2013).

In our small number of patients no incidents of post-operative neural dysfunction were observed and the risk of neurapraxia is not expected to be higher by reclining the operation table since the conscious patients place themselves comfortable in the beach-chair including the head-rest. Thus, no major repositioning is performed in anesthetized patients. Although not assessed in this study setup time is expected to be slightly higher (∼5 min) when inducing the patient in the reclining position since the subsequent tilting to the sitting position is performed slowly.

We adopted a threshold for cerebral ischemia of 20% change from baseline and during surgery in only five patients desaturations were observed. This may reflect that following induction of anesthesia arterial blood pressure was not reduced below the lower limit of the cerebral autoregulation (Joshi et al., 2012). However, the evolving concept of the brain as a index organ is ambiguous, so it is relevant preventing hypotension because other organs, e.g., the kidneys, may suffer from comprised perfusion before the brain becomes affected due to the hierarchy of blood flow (Ono et al., 2013). As even brief hypotensive episodes may predispose patients to postoperative complications (Fischer et al., 2011) prompt reversal of ScO_2 in those patients is crucial to improve clinical outcome (Casati et al., 2005).

During induction in the sitting vs. reclining beach-chair group the hemodynamic challenge is larger by the caudal accumulation of blood and in turn reduced cardiac preload. However, in our small group of patients changes in SV and CO were not consistent albeit there was a tendency for lower values following induction of anesthesia with the upper body elevated. Of interest, HR tended to be higher, which may equally reflect the more frequent use of ephedrine as well as strain on the circulation.

Following induction of anesthesia ScO_2 was higher in the reclining compared with the sitting beach-chair group whereas the opposite occurred for SmO_2 indicating caudal accumulation of blood in the sitting position. Such gravitational influence is supported by similar changes in SmO_2 when patients induced in the reclining beach-chair subsequently were tilted to the sitting position. These results are in line with those observed in conscious volunteers during head up tilt, where a rapid increase in the concentration of oxygenated hemoglobin (HbO_2) of the calf reflects an initially rapid arterial inflow into the leg (Truijen et al., 2012). A subsequent postural reduction in HbO_2 may represent reflex vasoconstriction, as a decrease in HbO_2 correlates with leg blood flow and inversely with sympathetic activity (Hachiya et al., 2010). However, following induction of anesthesia more pronounced and opposite changes in both muscle oxygenation and blood pressure in the sitting group suggest that anesthesia attenuates counter-regulatory mechanisms to orthostasis. Of interest, during beach-chair surgery intermittent pneumatic sequential compression of the lower extremities stabilizes hemodynamics (Kwak et al., 2010).

LIMITATIONS

The reclining beach-chair group received less ephedrine although the incidence of significant hypotension was similar in the two groups. Apparently, the anesthetists might have had a lower threshold for the use of ephedrine in the sitting beach-chair group. However, even with less ephedrine treatment, the patients induced in the reclining beach-chair position had higher MAP than the patients induced in the sitting beach-chair position.

Following an interscalene block, local anesthetics may spread to the stellate ganglion (Song and Roh, 2012), and especially a right stellate ganglion block may suppress cardiac sympathetic function (Koyama et al., 2002). Since the side of blockade was evenly distributed within each group we consider this effect unlikely to explain the hemodynamic differences.

CONCLUSIONS

Induction of anesthesia in the reclining compared with the sitting beach-chair position resulted in higher MAP and ScO_2 as well as less frequent use of ephedrine indicating more stable hemodynamics. We propose that for surgery in the beach-chair position, induction of anesthesia is performed in the reclining position with the chair tilted backward.

FUNDING

This work was supported by the Lundbeck-foundation Denmark, (grant number R83-A8124).

REFERENCES

Bogert, L. W. J., Wesseling, K. H., Schraa, O., Van Lieshout, E. J., De Mol, B. A. J. M., Van Goudoever, J., et al. (2010). Pulse contour cardiac output derived from non−invasive arterial pressure in cardiovascular disease. *Anaesthesia* 65, 1119–1125. doi: 10.1111/j.1365-2044.2010.06511.x

Brassard, P., Seifert, T., and Secher, N. H. (2009). Is cerebral oxygenation negatively affected by infusion of norepinephrine in healthy subjects? *Br. J. Anaesth.* 102, 800–805. doi: 10.1093/bja/aep065

Buhre, W., Weyland, A., Buhre, K., Kazmaier, S., Mursch, K., Schmidt, M., et al. (2000). Effects of the sitting position on the distribution of blood volume in patients undergoing neurosurgical procedures. *Br. J. Anaesth.* 84, 354–357. doi: 10.1093/oxfordjournals.bja.a013439

Casati, A., Fanelli, G., Pietropaoli, P., Proietti, R., Tufano, R., Danelli, G., et al. (2005). Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth. Analg.* 101, 740–747. doi: 10.1213/01.ane.0000166974.96219.cd

Dalrymple, D. G., Macgowan, S. W., and Macleod, G. F. (1979). Cardiorespiratory effects of the sitting position in neurosurgery. *Br. J. Anaesth.* 51, 1079–1082. doi: 10.1093/bja/51.11.1079

Fischer, G. W., Lin, H.-M., Krol, M., Galati, M. F., Di Luozzo, G., Griepp, R. B., et al. (2011). Noninvasive cerebral oxygenation may predict outcome in patients undergoing aortic arch surgery. *J. Thorac. Cardiovasc. Surg.* 141, 815–821. doi: 10.1016/j.jtcvs.2010.05.017

Hachiya, T., Walsh, M. L., Saito, M., and Blaber, A. P. (2010). Delayed vasoconstrictor response to venous pooling in the calf is associated with high orthostatic tolerance to LBNP. *J. Appl. Physiol.* 109, 996–1001. doi: 10.1152/japplphysiol.00593.2009

Højlund, J., Sandmand, M., Sonne, M., Mantoni, T., Jørgensen, H. L., Belhage, B., et al. (2012). Effect of head rotation on cerebral blood velocity in the prone position. *Anesthesiol. Res. Pract.* 2012, 647258. doi: 10.1155/2012/647258

Jeong, H., Jeong, S., Lim, H. J., Lee, J., and Yoo, K. Y. (2012). Cerebral oxygen saturation measured by near-infrared spectroscopy and jugular venous bulb oxygen saturation during arthroscopic shoulder surgery in beach chair position under sevoflurane-nitrous oxide or propofol-remifentanil anesthesia. *Anesthesiology* 116, 1047–1056. doi: 10.1097/ALN.0b013e31825154d2

Joshi, B., Ono, M., Brown, C., Brady, K., Easley, R. B., Yenokyan, G., et al. (2012). Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. *Anesth. Analg.* 114, 503–510. doi: 10.1213/ANE.0b013e31823d292a

Kim, Y.-S., Davis, S. C. A. T., Truijen, J., Stok, W. J., Secher, N. H., and van Lieshout, J. J. (2011). Intensive blood pressure control affects cerebral blood flow in type 2 diabetes mellitus patients. *Hypertension* 57, 738–745. doi: 10.1161/HYPERTENSIONAHA.110.160523

Kinsella, S. M., and Tuckey, J. P. (2001). Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold–Jarisch reflex. *Br. J. Anaesth.* 86, 859–868. doi: 10.1093/bja/86.6.859

Koyama, S., Sato, N., Nagashima, K., Aizawa, H., Kawamura, Y., Hasebe, N., et al. (2002). Effects of right stellate ganglion block on the autonomic nervous function of the heart: a study using the head-up tilt test. *Circ. J.* 66, 645–648. doi: 10.1253/circj.66.645

Kwak, H. J., Lee, J. S., Lee, D. C., Kim, H. S., and Kim, J. Y. (2010). The effect of a sequential compression device on hemodynamics in arthroscopic shoulder surgery using beach-chair position. *Arthrosc. J. Arthrosc. Relat. Surg.* 26, 729–733. doi: 10.1016/j.arthro.2009.10.001

Lee, J. H., Min, K. T., Chun, Y.-M., Kim, E. J., and Choi, S. H. (2011). Effects of beach-chair position and induced hypotension on cerebral oxygen saturation in patients undergoing arthroscopic shoulder surgery. *Arthroscopy* 27, 889–894. doi: 10.1016/j.arthro.2011.02.027

Martina, J. R., Westerhof, B. E., van Goudoever, J., de Beaumont, E. M. F. H., Truijen, J., Kim, Y.-S., et al. (2012). Noninvasive continuous arterial blood pressure monitoring with Nexfin®. *Anesthesiology* 116, 1092–1103. doi: 10.1097/ALN.0b013e31824f94ed

McCulloch, T. J., Liyanagama, K., and Petchell, J. (2010). Relative hypotension in the beach-chair position: effects on middle cerebral artery blood velocity. *Anaesth. Intensive Care* 38, 486–491.

Moerman, A. T., De Hert, S. G., Jacobs, T. F., De Wilde, L. F., and Wouters, P. F. (2012). Cerebral oxygen desaturation during beach chair position. *Eur. J. Anaesthesiol.* 29, 82–87. doi: 10.1097/EJA.0b013e328348ca18

Moritz, S., Kasprzak, P., Arlt, M., Taeger, K., and Metz, C. (2007). Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy. *Anesthesiology* 107, 563–569. doi: 10.1097/01.anes.0000281894.69422.ff

Nissen, P., Brassard, P., Jørgensen, T. B., and Secher, N. H. (2009). Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. *Neurocrit. Care* 12, 17–23. doi: 10.1007/s12028-009-9313-x

Ogoh, S., Sato, K., Okazaki, K., Miyamoto, T., Secher, F., Sorensen, H., et al. (2014). A decrease in spatially resolved near-infrared spectroscopy-determined frontal lobe tissue oxygenation by phenylephrine reflects reduced skin blood flow. *Anesth. Analg.* 118, 823–829. doi: 10.1213/ANE.0000000000000145

Ono, M., Arnaoutakis, G. J., Fine, D. M., Brady, K., Easley, R. B., Zheng, Y., et al. (2013). Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. *Crit. Care Med.* 41, 464–471. doi: 10.1097/CCM.0b013e31826ab3a1

Papadonikolakis, A., Wiesler, E. R., Olympio, M. A., and Poehling, G. G. (2008). Avoiding catastrophic complications of stroke and death related to shoulder surgery in the sitting position. *Arthroscopy* 24, 481–482. doi: 10.1016/j.arthro.2008.02.005

Peruto, C. M., Ciccotti, M. G., and Cohen, S. B. (2009). Shoulder arthroscopy positioning: lateral decubitus versus beach chair. *Arthroscopy* 25, 891–896. doi: 10.1016/j.arthro.2008.10.003

Pin-On, P., Schroeder, D., and Munis, J. (2013). The hemodynamic management of 5177 neurosurgical and orthopedic patients who underwent surgery in the sitting or "beach chair" position without incidence of adverse neurologic events. *Anesth. Analg.* 116, 1317–1324. doi: 10.1213/ANE.0b013e31828446bb

Pohl, A., and Cullen, D. J. (2005). Cerebral ischemia during shoulder surgery in the upright position: a case series. *J. Clin. Anesth.* 17, 463–469. doi: 10.1016/j.jclinane.2004.09.012

Porter, J. M., Pidgeon, C., and Cunningham, A. J. (1999). The sitting position in neurosurgery: a critical appraisal. *Br. J. Anaesth.* 82, 117–128. doi: 10.1093/bja/82.1.117

Rains, D. D., Rooke, G. A., and Wahl, C. J. (2011). Pathomechanisms and complications related to patient positioning and anesthesia during shoulder arthroscopy. *Arthroscopy* 27, 532–541. doi: 10.1016/j.arthro.2010.09.008

Skyhar, M. J., Altchek, D. W., Warren, R. F., Wickiewicz, T. L., and O'Brien, S. J. (1988). Shoulder arthroscopy with the patient in the beach-chair position. *Arthroscopy* 4, 256–259.

Smith, M., and Elwell, C. (2009). Near-infrared spectroscopy: Shedding light on the injured brain. *Anesth. Analg.* 108, 1055–1057. doi: 10.1213/ane.0b013e31819a0301

Song, S. Y., and Roh, W. S. (2012). Hypotensive bradycardic events during shoulder arthroscopic surgery under interscalene brachial plexus blocks. *Korean J. Anesthesiol.* 62, 209–219. doi: 10.4097/kjae.2012.62.3.209

Sørensen, H. M. S., Secher, N. H. M. D., Siebenmann, C. M. S., Nielsen, H. B. M. D., Kohl-Bareis, M. P. D., Lundby, C. P. D., et al. (2012). Cutaneous vasoconstriction affects near-infrared spectroscopy determined cerebral oxygen saturation during administration of norepinephrine. *Anesthesiology* 117, 263–270. doi: 10.1097/ALN.0b013e3182605afe

Sørensen, H., Rasmussen, P., Sato, K., Persson, S., Olesen, N. D., Nielsen, H. B., et al. (2014). External carotid artery flow maintains near infrared spectroscopy-determined frontal lobe oxygenation during ephedrine administration. *Br. J. Anaesth.* doi: 10.1093/bja/aet481. [Epub ahead of print].

Tange, K., Kinoshita, H., Minonishi, T., Hatakeyama, N., Matsuda, N., Yamazaki, M., et al. (2010). Cerebral oxygenation in the beach chair position before and during general anesthesia. *Minerva Anestesiol.* 76, 485–490.

Truijen, J., Kim, Y. S., Krediet, C. T. P., Stok, W. J., Kölgen, R. S., Colier, W. N., et al. (2012). Orthostatic leg blood volume changes assessed by near-infrared spectroscopy. *Exp. Physiol.* 97, 353–361. doi: 10.1113/expphysiol.2011.061051

Van der Spoel, A. G. E., Voogel, A. J., Folkers, A., Boer, C., and Bouwman, R. A. (2012). Comparison of noninvasive continuous arterial waveform analysis (Nexfin) with transthoracic Doppler echocardiography for monitoring of cardiac output. *J. Clin. Anesth.* 24, 304–309. doi: 10.1016/j.jclinane.2011.09.008

Van Geldorp, I. E., Delhaas, T., Hermans, B., Vernooy, K., Broers, B., Klimusina, J., et al. (2011). Comparison of a non-invasive arterial pulse contour technique and echo Doppler aorta velocity-time integral on stroke volume changes in optimization of cardiac resynchronization therapy. *Europace* 13, 87–95. doi: 10.1093/europace/euq348

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 19 February 2014; accepted: 26 April 2014; published online: 19 May 2014.
Citation: Larsen SL, Lyngeraa TS, Maschmann CP, Van Lieshout JJ and Pott FC (2014) Cardiovascular consequence of reclining vs. sitting beach-chair body position for induction of anesthesia. Front. Physiol. ***5****:187. doi: 10.3389/fphys.2014.00187*
This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 25 August 2014
doi: 10.3389/fphys.2014.00321

Ventilatory strategy during liver transplantation: implications for near-infrared spectroscopy-determined frontal lobe oxygenation

Henrik Sørensen[1]*, Hilary P. Grocott[2], Mads Niemann[1], Allan Rasmussen[3], Jens G. Hillingsø[3], Hans J. Frederiksen[1] and Niels H. Secher[1]

[1] *Department of Anesthesia, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*
[2] *Department of Anesthesia and Perioperative Medicine, St. Boniface Hospital, University of Manitoba, Winnipeg, MB, Canada*
[3] *Department of Surgery and Transplantation, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Stephane Perrey, Montpellier I University, France
Phil Neil Ainslie, University of British Columbia, Canada

****Correspondence:***
Henrik Sørensen, Department of Anesthesia, Rigshospitalet 2041, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
e-mail: hs770@hotmail.com

Background: As measured by near infrared spectroscopy (NIRS), cerebral oxygenation (S_cO_2) may be reduced by hyperventilation in the anhepatic phase of liver transplantation surgery (LTx). Conversely, the brain may be subjected to hyperperfusion during reperfusion of the grafted liver. We investigated the relationship between S_cO_2 and end-tidal CO_2 tension ($EtCO_2$) during the various phases of LTx.

Methods: In this retrospective study, 49 patients undergoing LTx were studied. Forehead S_cO_2, $EtCO_2$, minute ventilation (VE), and hemodynamic variables were recorded from the beginning of surgery through to the anhepatic and reperfusion phases during LTx.

Results: In the anhepatic phase, S_cO_2 was reduced by 4.3% (95% confidence interval: 2.5–6.0%; $P < 0.0001$), $EtCO_2$ by 0.3 kPa (0.2–0.4 kPa; $P < 0.0001$), and VE by 0.4 L/min (0.1–0.7 L/min; $P = 0.0018$). Conversely, during reperfusion of the donated liver, S_cO_2 increased by 5.5% (3.8–7.3%), $EtCO_2$ by 0.7 kPa (0.5–0.8 kPa), and VE by 0.6 L/min (0.3–0.9 L/min; all $P < 0.0001$). Changes in S_cO_2 were correlated to those in $EtCO_2$ (Pearson $r = 0.74$; $P < 0.0001$).

Conclusion: During LTx, changes in S_cO_2 are closely correlated to those of $EtCO_2$. Thus, this retrospective analysis suggests that attention to maintain a targeted $EtCO_2$ would result in a more stable S_cO_2 during the operation.

Keywords: cerebral oxygenation, cerebral oximetry, end-tidal carbon dioxide, liver transplantation, monitoring, ventilation

INTRODUCTION

Autoregulation ensures that cerebral blood flow (CBF) is sufficient to meet the metabolic requirements of the brain, but may be challenged by a low arterial pressure, hypoxia and/or hypocapnia (Kety and Schmidt, 1948; Lassen, 1959). Maintaining mean arterial pressure (MAP) within the cerebral autoregulatory range during surgery has been suggested to result in improved patient outcome (Ono et al., 2013). An evolving strategy for control of the circulation during surgery is to maintain cerebral oxygenation (S_cO_2), a real-time surrogate for CBF measured using near infrared spectroscopy (NIRS). S_cO_2 not only has the ability to identify whether patients demonstrate intact cerebral autoregulation, but also determines its lower limit threshold (Nissen et al., 2009).

Impaired cerebral autoregulation (Larsen et al., 1995), cerebral hyperemia, and increased intracranial pressure (Aggarwal et al., 1994) are all associated with end-stage liver disease and may predispose to either ischemic or hyperemic cerebral injury. Cerebral perfusion and thereby S_cO_2, is challenged by the hemodynamic events that can occur during liver transplantation (LTx) (Adams et al., 1987; Larsen et al., 1999; Pere et al., 2000; Van Mook et al., 2005; Nissen et al., 2010; Zheng et al., 2012). In the hepatic dissection phase, there is a risk for hemorrhage. In the anhepatic phase inadequate venous return to the heart and a low arterial carbon dioxide tension (P_aCO_2) can occur. This contrasts with the reperfusion phase where increases in P_aCO_2 may occur (Pere et al., 2000; Panzera et al., 2006). With clamping of the inferior vena cava (IVC), cardiac output (CO) is reduced by as much as 50%, and this can result in compromised perfusion to vital organs including the brain (Pere et al., 2000). Thus, to facilitate hemodynamic stability and to optimize organ perfusion, veno-venous bypass may be utilized (Shaw et al., 1985). Alternatively, venous return to the heart may be assisted by only partially clamping the IVC (so-called piggyback technique) (Panzera et al., 2006). However, even with the piggyback technique, S_cO_2 is likely to decrease by about 15% (Panzera et al., 2006) increasing the risk of cerebral ischemia (Al-Rawi and Kirkpatrick, 2006).

In the anhepatic phase of LTx, the systemic metabolic rate is reduced by ∼30% and there is therefore a reduced need for minute ventilation (VE) in order to preserve CBF and S_cO_2. Conversely, with reperfusion of the grafted liver, metabolism is restored and the brain may be subjected to hyperperfusion due to enhanced CO_2 and/or liberation of vasodilating substances (Ejlersen et al., 1994; Skak et al., 1997) that could lead to brain

edema, hemorrhage and even death (Van Mook et al., 2005). S_cO_2 follows changes in CBF with hyper- and hypo-capnia (Rasmussen et al., 2007) and therefore to maintain S_cO_2 during the operation potentially minimizes incidence of post-operative neurological complications (Madsen and Secher, 2000; Pere et al., 2000; Zheng et al., 2012).

In this retrospective observational study, we reviewed S_cO_2, end-tidal CO_2 tension ($EtCO_2$), and VE for LTx patients and hypothesized that S_cO_2 would decrease in the anhepatic phase of the operation and increase again with reperfusion of the grafted liver. We considered that the data would provide an indication as to what extent VE should be adjusted to maintain S_cO_2 and potentially contribute to brain protection during LTx.

MATERIALS AND METHODS

Data were collected retrospectively for patients undergoing LTx at Rigshospitalet (Copenhagen) from 1997 to 2001. The study was performed in accordance with guidelines provided by The National Committee on Health Research and approved by the Local Ethical Committee (H-2-2014-FSP27) who waived the need for patient consent.

The liver transplantation technique involved clamping of the IVC with lower body venous return supported by a veno-venous bypass from the left femoral vein to one or two arm veins (Rasmussen et al., 1994). Reperfusion of the grafted liver was established by opening the IVC above the hepatic vein, followed by the IVC below the hepatic vein, and lastly the hepatic artery. Reported hemodynamic variables include heart rate (HR) and femoral MAP measured via an arterial catheter (Becton Dickinson and Company, New Jersey, NY, USA) cardiac output (CO) by thermodilution (7.5F; Baxter, Uden, Holland), thoracic electrical impedance index (THI) ($n = 30$) (TI; Caspersen and Nielsen, Copenhagen, Denmark) as an indication of the central blood volume (Cai et al., 2000), and S_cO_2 (Invos 3100 Cerebral Oximeter, Somanetics, Troy, MI, USA) along with VE and $EtCO_2$. P_aCO_2 was not continuously monitored, however, it was assumed that $EtCO_2$ reflects changes in P_aCO_2 as expressed by the ratio between CO_2 and the alveolar ventilation. All values were noted every 10 min as recorded in the anesthetic chart. Hematocrit was monitored (ABL 700 Radiometer, Copenhagen) and any administration of packed red blood cells and plasma was performed through a rapid infusion system (Haemonetics, Braintree, MA, USA) to maintain a hematocrit of 30%.

Data from the last 60 min of the dissection phase, first and last 30 min of the anhepatic phase, and the first 40 min of the reperfusion phase of the operation were included in the analysis. Hemodynamic changes from dissection to early anhepatic phase were calculated as the difference between an average over 60 min in the dissection phase and 30 min in the early anhepatic phase. Changes from late anhepatic to reperfusion phase were identified as the difference in average from the last 30 min of the anhepatic phase, and the first 20 min of the reperfusion phase.

Distribution of data including variance and probability plots were assessed independently for each patient and the whole population using *Proc Univariate* in SAS 9.2 (SAS Institute, Cary NC, USA). All variables exhibited normal distribution, however, CO and THI were skewed to the right. Thus, we performed a logarithmic transformation ($\log_{10}$) on CO and THI-data and relative changes are reported as $\log(x) - \log(y) = \log(x/y)$ (Bland and Altman, 1996a). In **Figure 1**, CO and THI are presented as geometric means ±95% confidence interval (Bland and Altman, 1996b). We applied an analysis of variance followed by a Tukey–Kramer *post-hoc* test to evaluate changes between conditions and a P-value < 0.05 was considered as statistically significant. Association between S_cO_2, VE, and $EtCO_2$ was evaluated by Pearson's correlation. Since S_cO_2 has been reported to decrease with increasing plasma bilirubin (Madsen et al., 2000; Song et al., 2011) that relation was also evaluated with Spearman rank order correlation.

RESULTS

Forty nine patients, [21 women, 28 men, 53±10 (mean ± SD) years] were admitted for LTx. Twenty six patients had cirrhosis, 5 primary biliary cirrhosis, 4 primary sclerosing cholangitis, 3 acute liver failure, 3 hepatocellular carcinoma, and the remaining 8 patients had other liver diseases. The duration of surgery was 368 min (range; 240–675), representing 141 min (60–465) for the dissection phase of the operation, 83 min (50–250) for the anhepatic phase, and 145 min (70–230) for completion of the operation.

ANHEPATIC PHASE

From the initial dissection to the anhepatic phase of the operation, S_cO_2 and $EtCO_2$ decreased by 4.3% [(95% confidence intervals: 2.5–6.0%) and by 0.3 kPa (0.2–0.4 kPa; both $P < 0.0001$)] as VE was reduced by 0.4 L/min (0.1–0.7 L/min; $P = 0.0018$). HR, MAP, and THI remained stable (**Figure 1**). CO was reduced by 15% (6–24%; $P = 0.0003$).

Changes in S_cO_2 was correlated to those in $EtCO_2$ (Pearson $r = 0.74$; $P < 0.0001$), however, no correlation between S_cO_2 and VE was observed (Pearson $r = 0.06$; $P = 0.7$) (**Figure 2**). In 11 patients, S_cO_2 was reduced by more than 15%. We observed an inverse relationship between S_cO_2 with plasma bilirubin (Spearman $r = -0.49$; $P = 0.008$) ranging from 9 to 565 μmol/L ($n = 28$).

REPERFUSION PHASE

During reperfusion of the grafted liver, S_cO_2 and $EtCO_2$ increased 5.5% (3.8–7.3%) and 0.7 kPa (0.5–0.8 kPa; $P < 0.0001$) as VE was increased by 0.6 L/min (−0.5–3.1 L/min; all $P < 0.0001$) (**Figure 1**). No changes were observed in HR and THI, but CO increased by 90% (71–110%; $P < 0.0001$). Conversely, MAP decreased by 5 mmHg (1–9 mmHg; $P = 0.007$). No significant correlation between S_cO_2 and VE was identify (Pearson $r = -0.18$; $P = 0.21$) (**Figure 2**), but 13 patients S_cO_2 increased >15% compared to the late anhepatic phase.

DISCUSSION

In this retrospective study of measurements during LTx in 49 patients, cerebral oxygenation (S_cO_2), as determined by NIRS, was shown to decrease in the anhepatic phase of the operation and to increase during reperfusion of the grafted liver. Changes in S_cO_2 were directly related to the end-tidal CO_2 tension. Therefore, a ventilatory strategy directed to a maintain

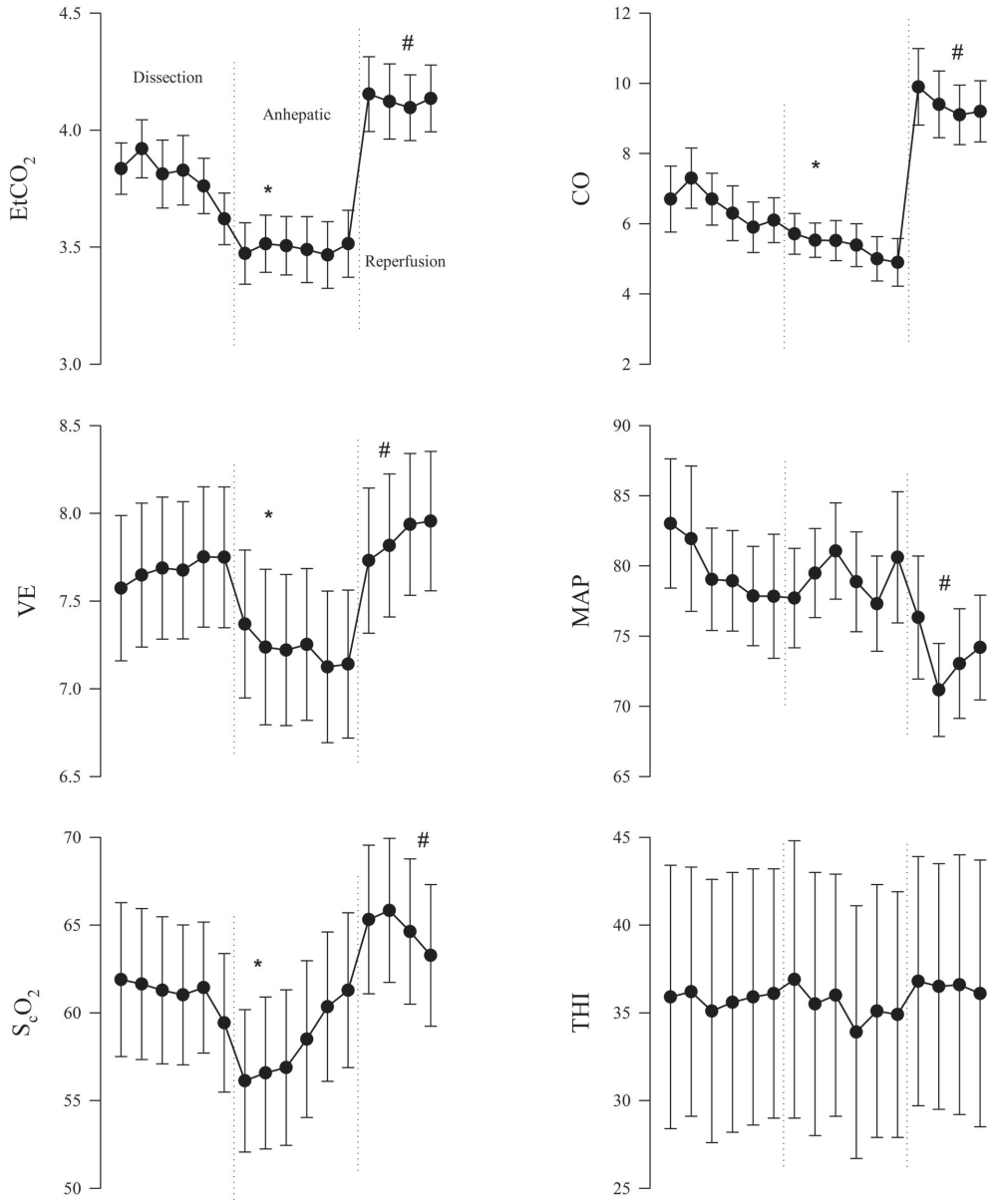


FIGURE 1 | Mean (±95% confidence interval) for 10th min in the dissection, anhepatic and reperfusion phases of liver transplantation surgery for end-tidal CO_2 tension ($EtCO_2$); ventilation (VE); near infrared spectroscopy-determined frontal lobe oxygenation (S_cO_2); cardiac output (CO); mean arterial pressure (MAP); and thoracic electrical impedance index (THI). CO and THI reported as geometric means. $^{*}P < 0.05$ compared to the dissection phase of the operation. $^{\#}P < 0.05$ compared to the anhepatic phase.

$EtCO_2$ could ensure stability of S_cO_2 during the operation and may, at least potentially, minimize the incidence of post-operative seizures, confusion, and stroke (Madsen and Secher, 2000; Pere et al., 2000; Zheng et al., 2012). Despite bilirubin absorption of infrared light resulting in a low S_cO_2, NIRS detected changes in cerebral oxygenation even in patients who were significantly jaundiced (Madsen et al., 2000).

Patients with liver disease are susceptible to alterations in MAP that can frequently result in pressure below the limits of cerebral autoregulation and then may lead to cerebral ischemia. Cerebral oxygenation might further be aggravated by increases in intracranial pressure that reduce cerebral perfusion pressure according to the Monro–Kellie doctrine (Larsen and Wendon, 2008). Thus, it seems to be an advantage if handling of the circulation during LTx involves continuous monitoring of the brain circulation to reduce adverse neurological outcome. NIRS represents a real-time, though indirect, monitor of CBF and indicates its autoregulatory capacity (Nissen et al., 2009; Zheng et al., 2012). In this cohort of LTx patients, S_cO_2 was reduced by 4.3% (2.5–6.0%) with IVC clamping (**Figure 1**), which is likely induced

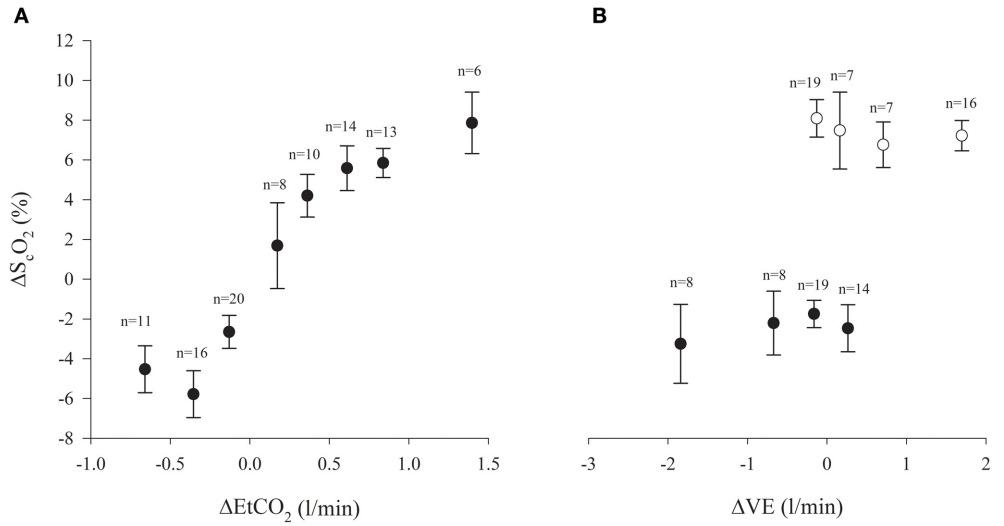


FIGURE 2 | (A) Frontal lobe oxygenation (S_cO_2) and end-tidal CO2 tension ($EtCO_2$) in the anhepatic and reperfusion phases of liver transplantation surgery (% changes from baseline; ± s.e.m.) (Pearson $r = 0.74$; $P < 0.0001$). Number of subjects indicated. **(B)** Changes from baseline (± s.e.m.) for S_cO_2 and ventilation (VE). Black symbols: anhepatic phase (Pearson $r = 0.06$; $P = 0.7$). Open symbols: reperfusion phase (Pearson $r = -0.18$; $P = 0.21$). Number of subjects is indicated.

by hyperventilation as indicated by a reduction in $EtCO_2$ by 0.3 kPa, albeit VE was diminished by 0.4 l/min. Thus, with the central blood volume maintained as indicated by THI (Cai et al., 2000), a ventilatory strategy guided by $EtCO_2$ may avoid cerebral ischemia in the anhepatic phase (Pott et al., 1995), e.g., by keeping $EtCO_2$ between 4.7 and 6.0 kPa, arterial CO_2, CBF, and S_cO_2 were maintained (Pott et al., 1995; Zheng et al., 2012). In contrast, no ventilatory adjustment in the anhepathic phase of the operation has been reported to lead to pronounced reductions in P_aCO_2, and yet maintained CBF as indicated by transcranial Doppler (Pere et al., 2000). In that study (Pere et al., 2000), cardiac preload was not supported by a venous-venous bypass, while we registered an 15% reduction in CO when the shunt was established. Although we cannot rule out that this reduction in CO may affect CBF and S_cO_2, we find it more likely that changes in S_cO_2 relate to alterations in $EtCO_2$ than to the reduction in CO with the hierarchy of blood flow in the anhepatic phase (**Figure 2**) (Rhee et al., 2012; Ono et al., 2013; Mahal et al., 2014). In 22% of the patients, S_cO_2 was reduced by >15% (relative to the value in the dissection phase) thus lowering the threshold for cerebral ischemia (Al-Rawi and Kirkpatrick, 2006). Similar significant cerebral deoxygenation is reported in up to 50% of patients undergoing LTx (Plachky et al., 2004), and also seen with the use of the piggy-back technique (Panzera et al., 2006).

Postoperative biomarkers of brain damage include neuron-specific enolase and S-100β and they may increase three-fold in patients who demonstrate cerebral deoxygenation (Plachky et al., 2004). S-100β levels are high in patients who develope post-operative cognitive dysfunction (POCD) (Linstedt et al., 2002) and cerebral deoxygenation (>15% relative to baseline) is related to POCD and longer hospital stay (Casati et al., 2005; Ballard et al., 2012; Colak et al., 2014). Moreover, inherent to prolonged cerebral deoxygenation, confusion, somnolence and transient hemiparesis manifest post-operatively (Madsen and Secher, 2000) or permanent neurological damage develops (Philips et al., 1998). Also in patients with acute liver failure, cerebral infarction after LTx can led to long-term hospital care, however, perioperative cerebral oxygenation was not reported for that patient (Pere et al., 2000). In general, patients with encephalopathy have been reported with a 15% higher S_cO_2 (Panzera et al., 2006), may be as a result of cerebral hyperemia because of lack of cerebral autoregulation (Ejlersen et al., 1994). However, similar reductions of ∼30% relative to the pre-operative S_cO_2 were seen with IVC clamping in patients with and without encephalopathy (Panzera et al., 2006).

When the transplanted liver is reperfused, the brain can be subjected to hyperemia due to enhanced CO_2 reactivity and/or liberation of vasodilating substances (Ejlersen et al., 1994) as we demonstrated by the 0.7 kPa increase in $EtCO_2$ and if untreated can have adverse effects and affect even mortality (Skak et al., 1997). With impaired cerebral autoregulation, the risk of hyperperfusion is even larger due to missing cerebral vasoconstriction in response a 90% increase in CO and be aggravated by the vasodilatory effect of CO_2 (**Figure 1**). Accordingly, S_cO_2 may guide to what extent VE should be increased in order to protect the brain. We observed an increase in S_cO_2 by 5.5% (3.8–7.3%) during reperfusion although VE was increased by 0.6 l/min. We, therefore, suggest a more meticulous control of VE is in need, as guided by $EtCO_2$, until the end of LTx (Nissen et al., 2010). Although $EtCO_2$ was kept within 4.6–6.0 kPa (Pott et al., 1995; Zheng et al., 2012) or VE increased by 15% (Pere et al., 2000), CBF becomes elevated (by more than 80% in some patients) with reperfusion of the liver, which emphasizes that attempts to maintain $EtCO_2$ toward the end of the operation could attenuate

cerebral hyperperfusion (Pott et al., 1995; Philips et al., 1998; Zheng et al., 2012).

The P_aCO_2 relates to hydrogen ion concentration and is a potent modulator of cerebrovascular resistance and, thus, CBF (Lassen, 1959). Hypercapnia leads to cerebral vasodilation while the opposite occurs with hypocapnia through a serial of endogenous mediators (Eriksson et al., 1983). In healthy humans, CBF increases 2–8% per mmHg CO_2 as determined by Fick's principle (Kety and Schmidt, 1946) or transcranial Doppler (Madsen and Secher, 1999), however, CO_2-reactivity has not yet been describe for NIRS despite S_cO_2 does follow CBF induced by hypercapnia and hypocapnia (Rasmussen et al., 2007). As evaluated by ^{133}Xenon clearance in patients undergoing LTx, CBF increases by 25% and may be more than can be explained by the increase in P_aCO_2 (Larsen et al., 1999). Increasing P_aCO_2 may mitigate the CO_2-reactivity because of near-maximal cerebral vasodilatation or may be attributable to other vasodilating substances interfering with the effect of CO_2 on the cerebral vasculature (Philips et al., 1998).

As this was a retrospective study, we did not evaluate neurological outcome. In related studies, neurological complications range from mild seizures to hemorrhage and stroke after LTx (Adams et al., 1987; Stein et al., 1992; Madsen and Secher, 2000; Pere et al., 2000; Zheng et al., 2012) and cerebral hemorrhage and anoxic-ischemic lesions are common at brain autopsy after LTx (Ferreiro et al., 1992). However, the evidence for improved neurological outcome by maintaining S_cO_2 during LTx remains sparse, although improved outcome is seen in cardiac (Slater et al., 2009; Ono et al., 2013; Colak et al., 2014; Harilall et al., 2014), abdominal (Casati et al., 2005), and orthopedic surgery (Ballard et al., 2012). An observational cohort study is underway investigating the relationship between perioperative desaturation during hepatic surgery or LTx and adverse postoperative events and length of ICU stay, but optimization of S_cO_2 in the anhepatic and reperfusion phase is not included (clinicaltrials.gov: NCT01458262). Although the adequacy of cerebral autoregulation and oxygenation can be monitored in the operating room, impaired CBF regulation may persist into the early postoperative phase (Larsen et al., 1999), but no study describes the efficacy of maintaining cerebral monitoring in the ICU after LTx (Ejlersen et al., 1994; Van Mook et al., 2005).

From this retrospective study, we conclude that despite adjustments of VE in the anhepatic and reperfusion phases of LTx, S_cO_2 changes occur that have the potential to expose patients to cerebral ischemia and/or hyperemia. We suggest that a ventilatory strategy guided by $EtCO_2$ would keep S_cO_2 more stable during LTx.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the design, data analysis and interpretation, drafting the manuscript and critical revision. All authors approved the final version before submission.

ACKNOWLEDGMENTS

Assistance with the article: We thank Carol A. Cooke, MLIS (Neil John Maclean Health Sciences Library) for developing the literature search strategies and John McVagh, Study Coordinator, Department of Anesthesia, University of Manitoba, for invaluable help and encouragement. *Financial support and sponsorship:* The author (Henrik Sørensen) received a grant from *Dansk Medicinsk Selskab i København* to visit Department of Anesthesia & Perioperative Medicine, St. Boniface Hospital, University of Manitoba, Winnipeg, Canada.

REFERENCES

Adams, D. H., Ponsford, S., Gunson, B., Boon, A., Honigsberger, L., Williams, A., et al. (1987). Neurological complications following liver transplantation. *Lancet* 1, 949–951. doi: 10.1016/S0140-6736(87)90294-7

Aggarwal, S., Kramer, D., Yonas, H., Obrist, W., Kang, Y., Martin, M., et al. (1994). Cerebral hemodynamic and metabolic changes in fulminant hepatic failure: a retrospective study. *Hepatology* 19, 80–87. doi: 10.1002/hep.1840190114

Al-Rawi, P. G., and Kirkpatrick, P. J. (2006). Tissue oxygen index: thresholds for cerebral ischemia using near-infrared spectroscopy. *Stroke* 37, 2720–2725. doi: 10.1161/01.STR.0000244807.99073.ae

Ballard, C., Jones, E., Gauge, N., Aarsland, D., Nilsen, O. B., Saxby, B. K., et al. (2012). Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomised controlled trial. *PLoS ONE* 7:e37410. doi: 10.1371/journal.pone.0037410

Bland, J. M., and Altman, D. G. (1996a). Statistics notes. Logarithms. *BMJ* 312, 700. doi: 10.1136/bmj.312.7032.700

Bland, J. M., and Altman, D. G. (1996b). Transformations, means, and confidence intervals. *BMJ* 312, 1079. doi: 10.1136/bmj.312.7038.1079

Cai, Y., Holm, S., Jenstrup, M., Stromstad, M., Eigtved, A., Warberg, J., et al. (2000). Electrical admittance for filling of the heart during lower body negative pressure in humans. *J. Appl. Physiol. (1985)* 89, 1569–1576.

Casati, A., Fanelli, G., Pietropaoli, P., Proietti, R., Tufano, R., Danelli, G., et al. (2005). Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth. Analg.* 101, 740–747. doi: 10.1213/01.ane.0000166974.96219.cd

Colak, Z., Borojevic, M., Bogovic, A., Ivancan, V., Biocina, B., and Majeric-Kogler, V. (2014). Influence of intraoperative cerebral oximetry monitoring on neurocognitive function after coronary artery bypass surgery: a randomized, prospective study. *Eur. J. Cardiothorac. Surg.* doi: 10.1093/ejcts/ezu193. [Epub ahead of print].

Ejlersen, E., Larsen, F. S., Pott, F., Gyrtrup, H. J., Kirkegaard, P., and Secher, N. H. (1994). Hepatectomy corrects cerebral hyperperfusion in fulminant hepatic failure. *Transplant. Proc.* 26, 1794–1795.

Eriksson, S., Hagenfeldt, L., Law, D., Patrono, C., Pinca, E., and Wennmalm, A. (1983). Effect of prostaglandin synthesis inhibitors on basal and carbon dioxide stimulated cerebral blood flow in man. *Acta Physiol. Scand.* 117, 203–211. doi: 10.1111/j.1748-1716.1983.tb07198.x

Ferreiro, J. A., Robert, M. A., Townsend, J., and Vinters, H. V. (1992). Neuropathologic findings after liver transplantation. *Acta Neuropathol.* 84, 1–14. doi: 10.1007/BF00427209

Harilall, Y., Adam, J. K., Biccard, B. M., and Reddi, A. (2014). The effect of optimising cerebral tissue oxygen saturation on markers of neurological injury during coronary artery bypass graft surgery. *Heart Lung Circ.* 23, 68–74. doi: 10.1016/j.hlc.2013.07.002

Kety, S. S., and Schmidt, C. F. (1946). The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men. *J. Clin. Invest.* 25, 107–119. doi: 10.1172/JCI101680

Kety, S. S., and Schmidt, C. F. (1948). The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood floow and cerebral oxygen consumption of normal young men. *J. Clin. Invest.* 27, 484–492. doi: 10.1172/JCI101995

Larsen, F. S., Ejlersen, E., Hansen, B. A., Knudsen, G. M., Tygstrup, N., and Secher, N. H. (1995). Functional loss of cerebral blood flow autoregulation in patients with fulminant hepatic failure. *J. Hepatol.* 23, 212–217. doi: 10.1016/0168-8278(95)80338-6

Larsen, F. S., Ejlersen, E., Strauss, G., Rasmussen, A., Kirkegaard, P., Hansen, B. A., et al. (1999). Cerebrovascular metabolic autoregulation is impaired during liver transplantation. *Transplantation* 68, 1472–1476. doi: 10.1097/00007890-199911270-00007

Larsen, F. S., and Wendon, J. (2008). Prevention and management of brain edema in patients with acute liver failure. *Liver Transpl.* 14(Suppl. 2), S90–S96. doi: 10.1002/lt.21643

Lassen, N. A. (1959). Cerebral blood flow and oxygen consumption in man. *Physiol. Rev.* 39, 183–238.

Linstedt, U., Meyer, O., Kropp, P., Berkau, A., Tapp, E., and Zenz, M. (2002). Serum concentration of S-100 protein in assessment of cognitive dysfunction after general anesthesia in different types of surgery. *Acta Anaesthesiol. Scand.* 46, 384–389. doi: 10.1034/j.1399-6576.2002.460409.x

Madsen, P. L., and Secher, N. H. (1999). Near-infrared oximetry of the brain. *Prog. Neurobiol.* 58, 541–560. doi: 10.1016/S0301-0082(98)00093-8

Madsen, P. L., and Secher, N. H. (2000). Postoperative confusion preceded by decreased frontal lobe haemoglobin oxygen saturation. *Anaesth. Intensive Care* 28, 308–310.

Madsen, P. L., Skak, C., Rasmussen, A., and Secher, N. H. (2000). Interference of cerebral near-infrared oximetry in patients with icterus. *Anesth. Analg.* 90, 489–493. doi: 10.1213/00000539-200002000-00046

Mahal, I., Davie, S. N., and Grocott, H. P. (2014). Cerebral oximetry and thoracic surgery. *Curr. Opin. Anaesthesiol.* 27, 21–27. doi: 10.1097/ACO.0000000000000027

Nissen, P., Frederiksen, H. J., and Secher, N. H. (2010). Intraoperative hemodynamic monitoring during liver transplantation: goals and devices. *Minerva Gastroenterol. Dietol.* 56, 261–277.

Nissen, P., Pacino, H., Frederiksen, H. J., Novovic, S., and Secher, N. H. (2009). Near-infrared spectroscopy for evaluation of cerebral autoregulation during orthotopic liver transplantation. *Neurocrit. Care* 11, 235–241. doi: 10.1007/s12028-009-9226-8

Ono, M., Arnaoutakis, G. J., Fine, D. M., Brady, K., Easley, R. B., Zheng, Y., et al. (2013). Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. *Crit. Care Med.* 41, 464–471. doi: 10.1097/CCM.0b013e31826ab3a1

Panzera, P., Greco, L., Carravetta, G., Gentile, A., Catalano, G., Cicco, G., et al. (2006). Alteration of brain oxygenation during "piggy back" liver transplantation. *Adv. Exp. Med. Biol.* 578, 269–275. doi: 10.1007/0-387-29540-2_43

Pere, P., Hockerstedt, K., Isoniemi, H., and Lindgren, L. (2000). Cerebral blood flow and oxygenation in liver transplantation for acute or chronic hepatic disease without venovenous bypass. *Liver Transpl.* 6, 471–479. doi: 10.1053/jlts.2000.8186

Philips, B. J., Armstrong, I. R., Pollock, A., and Lee, A. (1998). Cerebral blood flow and metabolism in patients with chronic liver disease undergoing orthotopic liver transplantation. *Hepatology* 27, 369–376. doi: 10.1002/hep.510270209

Plachky, J., Hofer, S., Volkmann, M., Martin, E., Bardenheuer, H. J., and Weigand, M. A. (2004). Regional cerebral oxygen saturation is a sensitive marker of cerebral hypoperfusion during orthotopic liver transplantation. *Anesth. Analg.* 99, 344–349, doi: 10.1213/01.ANE.0000124032.31843.61

Pott, F., Larsen, F. S., Ejlersen, E., Linkis, P., Jorgensen, L. G., and Secher, N. H. (1995). Cerebral perfusion during human liver transplantation. *Clin. Physiol.* 15, 119–130. doi: 10.1111/j.1475-097X.1995.tb00436.x

Rasmussen, L. S., Ejlersen, E., Hjortrup, A., Kirkegaard, P., and Secher, N. H. (1994). Veno-venous bypass during human liver transplantation. *Transplant. Proc.* 26, 1791.

Rasmussen, P., Dawson, E. A., Nybo, L., Van Lieshout, J. J., Secher, N. H., and Gjedde, A. (2007). Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. *J. Cereb. Blood Flow Metab.* 27, 1082–1093. doi: 10.1038/sj.jcbfm.9600416

Rhee, C. J., Kibler, K. K., Easley, R. B., Andropoulos, D. B., Czosnyka, M., Smielewski, P., et al. (2012). Renovascular reactivity measured by near-infrared spectroscopy. *J. Appl. Physiol.* 113, 307–314. doi: 10.1152/japplphysiol.00024.2012

Shaw, B. W. Jr., Martin, D. J., Marquez, J. M., Kang, Y. G., Bugbee, A. C. Jr., Iwatsuki, S., et al. (1985). Advantages of venous bypass during orthotopic transplantation of the liver. *Semin. Liver Dis.* 5, 344–348. doi: 10.1055/s-2008-1040631

Skak, C., Rasmussen, A., Kirkegaard, P., and Secher, N. H. (1997). Cerebral oxygen saturation and blood flow during liver transplantation. *Anesth. Analg.* 84, 730–733.

Slater, J. P., Guarino, T., Stack, J., Vinod, K., Bustami, R. T., Brown, J. M. 3rd., et al. (2009). Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. *Ann. Thorac. Surg.* 87, 36–44. discussion: 44–45. doi: 10.1016/j.athoracsur.2008.08.070

Song, J. G., Jeong, S. M., Shin, W. J., Jun, I. G., Shin, K., Huh, I. Y., et al. (2011). Laboratory variables associated with low near-infrared cerebral oxygen saturation in icteric patients before liver transplantation surgery. *Anesth. Analg.* 112, 1347–1352. doi: 10.1213/ANE.0b013e318214b2b0

Stein, D. P., Lederman, R. J., Vogt, D. P., Carey, W. D., and Broughan, T. A. (1992). Neurological complications following liver transplantation. *Ann. Neurol.* 31, 644–649. doi: 10.1002/ana.410310612

Van Mook, W. N., Rennenberg, R. J., Schurink, G. W., Van Oostenbrugge, R. J., Mess, W. H., Hofman, P. A., et al. (2005). Cerebral hyperperfusion syndrome. *Lancet Neurol.* 4, 877–888. doi: 10.1016/S1474-4422(05)70251-9

Zheng, Y., Villamayor, A. J., Merritt, W., Pustavoitau, A., Latif, A., Bhambhani, R., et al. (2012). Continuous cerebral blood flow autoregulation monitoring in patients undergoing liver transplantation. *Neurocrit. Care* 17, 77–84. doi: 10.1007/s12028-012-9721-1

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 31 May 2014; accepted: 04 August 2014; published online: 25 August 2014.
*Citation: Sørensen H, Grocott HP, Niemann M, Rasmussen A, Hillingsø JG, Frederiksen HJ and Secher NH (2014) Ventilatory strategy during liver transplantation: implications for near-infrared spectroscopy-determined frontal lobe oxygenation. Front. Physiol. **5**:321. doi: 10.3389/fphys.2014.00321*
This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 25 February 2014
doi: 10.3389/fphys.2014.00066

O_2 supplementation to secure the near-infrared spectroscopy determined brain and muscle oxygenation in vascular surgical patients: a presentation of 100 cases

Kim Z. Rokamp[1], Niels H. Secher[1], Jonas Eiberg[2], Lars Lønn[3] and Henning B. Nielsen[1]*

[1] *Departments of Anesthesia, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*
[2] *Vascular Surgery, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*
[3] *Interventional Radiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Kurt J. Smith, Centre for Heart Lung and Vascular Health, Canada
Migue Arango, LHSC University Hospital, Canada

****Correspondence:***
Henning B. Nielsen, Departments of Anesthesia, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 København Ø, Denmark
e-mail: henning.bay@rh.regionh.dk

This study addresses three questions for securing tissue oxygenation in brain ($rScO_2$) and muscle (SmO_2) for 100 patients (age 71 ± 6 years; mean ± SD) undergoing vascular surgery: (i) Does preoxygenation (inhaling 100% oxygen before anesthesia) increase tissue oxygenation, (ii) Does inhalation of 70% oxygen during surgery prevent a critical reduction in $rScO_2$ (<50%), and (iii) is a decrease in $rScO_2$ and/or SmO_2 related to reduced blood pressure and/or cardiac output? Intravenous anesthesia was provided to all patients and the intraoperative inspired oxygen fraction was set to 0.70 while tissue oxygenation was determined by INVOS 5100C. Preoxygenation increased $rScO_2$(from 65 ± 8 to 72 ± 9%; $P < 0.05$) and SmO_2 (from 75 ± 9 to 78 ± 9%; $P < 0.05$) and during surgery $rScO_2$ and SmO_2 were maintained at the baseline level in most patients. Following anesthesia and tracheal intubation an eventual change in $rScO_2$ correlated to cardiac output and cardiac stroke volume (coefficient of contingence = 0.36; $P = 0.0003$) rather to a change in mean arterial pressure and for five patients $rScO_2$was reduced to below 50%. We conclude that (i) increased oxygen delivery enhances tissue oxygenation, (ii) oxygen supports tissue oxygenation but does not prevent a critical reduction in cerebral oxygenation sufficiently, and (iii) an eventual decrease in tissue oxygenation seems related to a reduction in cardiac output rather than to hypotension.

Keywords: blood pressure, cardiac output, cerebral oxygenation, muscle oxygenation

INTRODUCTION

Monitoring regional cerebral oxygenation ($rScO_2$) by near infrared spectroscopy (NIRS) is used for both cardiac and non-cardiac surgery (Casati et al., 2005; Murkin and Arango, 2009) and suggested as an index for how well the circulation is managed (Murkin, 2011). A decrease in intraoperative $rScO_2$ to less than 80% of the preoperative value, or to a level lower than 50% have been associated with postoperative complications such as cognitive dysfunction (Casati et al., 2005; Slater et al., 2009), stroke (Olsson and Thelin, 2006) and increased length of stay in hospital (Casati et al., 2005). Furthermore, patients with a preoperative $rScO_2$ below 50% demonstrate increased probability for 1-year postoperative mortality (Heringlake et al., 2011). Thus, it appears to be an advantage to maintain $rScO_2$ during surgery but with induction of general anesthesia subsequent reduction in blood pressure may affect regional blood flow and in turn tissue oxygenation (Petrozza, 1990). Yet, in patients undergoing minor surgery such as mastectomy, thyroidectomy or parathyroidectomy, a low blood pressure does not appear to affect $rScO_2$ as determined by NIRS (Nissen et al., 2009). During surgery mean arterial pressure (MAP) is maintained often above 60 mmHg that is considered to represent the level that secures cerebral autoregulation (Paulson et al., 1990). On the other hand, during certain types of surgery deliberate reduction of MAP to below 60 mmHg may be initiated to limit hemorrhage (Martin and Galliano, 1965; Beaussier et al., 2000; Boonmak et al., 2013).

Patients undergoing vascular surgery are supplemented with O_2 to prevent arterial desaturation (Dixon et al., 2005) and a high intraoperative inspired O_2 fraction has the potential to improve postoperative outcome (Niinikoski, 1969; Hunt and Pai, 1972; Greif et al., 2000; Fries et al., 2005; Turtiainen et al., 2011). Raised inspired O_2 fraction might affect regional blood flow to the brain (Nielsen et al., 1999; Smith et al., 2012) and skeletal muscle (Welch et al., 1977; Pedersen et al., 1999) and we aimed to assess influence of O_2 supplementation on $rScO_2$ and muscle oxygenation (SmO_2) in a cohort of vascular surgical patients. It was addressed whether (i) preoxygenation (inhaling 100% oxygen before anesthesia) increases tissue oxygenation, (ii) inhalation of 70% oxygen during surgery prevents a critical reduction in ScO_2 to below 50%, and (iii) a decrease in $rScO_2$ and/or SmO_2 is related to reduced blood pressure or cardiac output (CO).

MATERIALS AND METHODS

Using a non-randomized single-center retrospective study-design we included vascular surgical patients enrolled in a cohort as approved by the Danish Data Protection Agency (2009-41-3617) and by the local ethical committee (H-4-2012-FSP). The evaluation included, arbitrarily, 100 patients (71 males; age 71 ± 6 years,

height 171 ± 12 cm, weight 75 ± 16 kg; mean ± SD) in whom vascular surgery was performed between March 2009 and August 2011. Patients were planned for open ($n = 23$) or endovascular aortic repair (EVAR) ($n = 56$) of an abdominal aortic aneurysm, lower limb by-pass surgery ($n = 6$), an iliaco-femoral ($n = 9$) or axillo-femoral bypass ($n = 1$), open surgery for arterial mesenteric stenosis ($n = 2$), or EVAR of a thoracic aortic aneurysm ($n = 3$). Fifty-nine patients were in treatment for arterial hypertension and medication included an ACE antagonist ($n = 36$), adrenergic β-receptor blockade ($n = 23$), a calcium channel inhibitor ($n = 18$), and diuretics ($n = 25$). Ten patients were diabetics and for 14 patients suffered from chronic obstructive lung disease.

The patients were exposed to at least 6 h of fast and orally intake of clear fluids was stopped 2 h before surgery. Three-lead electrocardiography monitored heart rate (HR) and pulse oximetry assessed arterial hemoglobin O_2 saturation (SpO_2). A peripheral vein was used for administration of fluid and anesthetics. In accordance to local guidelines, a radial artery catheter (20 gauge; 1.1 mm) was, after local anesthesia, inserted in the arm with the highest non-invasively determined systolic blood pressure. The catheter was kept patent by isotonic saline (3 ml/h) through to a transducer (Edwards Life Sciences, Irving, CA, USA) positioned at the level of the heart. A two channel cerebral oximeter (INVOS 5100C, Somanetics, Troy, MI, USA) was used to detect $rScO_2$ and SmO_2. The reported values are taken to represent hemoglobin oxygen saturation in the tissue beneath the sensor as the ratio between deoxygenated hemoglobin and the sum of deoxygenated and oxygenated hemoglobin. Thus, as approved by the US Food and Drug Administration (510k-080769), the INVOS 5100C- determined $rScO_2$ is considered a trend monitor of the hemoglobin O_2 saturation for skin, scalp, and cortical tissue. With the NIRS-probe applied to the forehead it is assumed that capillaries within the frontal lobe contribute most to light absorbance (Madsen and Secher, 1999) but the skin, subcutaneous tissue and the scalp also contribute to change the INVOS-determined $rScO_2$ (Davie and Grocott, 2012; Soerensen et al., 2012). The $rScO_2$ was determined with a sensor attached to the forehead as least 2 cm above the eyebrows and that position is considered to limit an influence from the frontal sinus on $rScO_2$ (Tubbs et al., 2002). Monitoring a change in NIRS-determined SmO_2 indicates an early warning of an acute blood loss (Madsen et al., 1995) but the decision to apply a NIRS sensor to the middle part of the right biceps muscle was made by the anesthesiologist in charge and SmO_2 is therefore reported for only 61 patients. The SmO_2 value reflects both hemoglobin/oxyhemoglobin and myoglobin (Madsen and Secher, 1999).

Modelflow methodology (Nexfin, bmeye B.V, Amsterdam, The Netherlands) (Bogert and van Lieshout, 2005) was used to assess CO and cardiac stroke volume (SV) from the pressure curve and heart rate (HR) and MAP were monitored through the arterial line. Neuromuscular blockade was evaluated with "train of four" (Organon Dublin, Ireland). Lactated Ringer and Macrodex (Fresenius Kabi, Bad Homburg, Germany) were administered to support the central blood volume according to a goal-directed strategy (Bundgaard-Nielsen et al., 2007) as guided by SV and CO and by central venous O_2 hemoglobin saturation in patients instrumented with a central venous catheter (via the internal jugular vein as guided by an ultrasound image). Administration of red blood cells was initiated in bleeding patients when hemoglobin was below 6 mmol/L.

The patients received no sedating drugs and in accordance to local guidelines inhalation of O_2 was introduced using a bilateral nasal catheter. Thereafter a facial mask was applied for continued O_2 breathing until anesthesia was induced with propofol (1 mg/kg) and fentanyl (1 μg/kg). Cisatracurium (0.1–0.15 mg/kg) facilitated oral tracheal intubation and anesthesia was maintained with propofol (0.08 mg/kg/min) and remifentanil (0.3–0.4 μg/kg/min). For ventilation a Dräger CATO (M32040, Lübeck, Germany) in volume-controlled mode was adjusted to an end-tidal CO_2 tension of 4–4.5 kPa and a positive end-expiratory pressure of 5 cm H_2O was used. When the patient was intubated, the inspiratory O_2 fraction was set to 0.7 for maintenance of tissue oxygenation whereby the incidence of surgical site infections may decrease (Greif et al., 2000; Turtiainen et al., 2011). In 16 patients arterial blood was obtained for immediate blood gas analysis (ABL 725; Radiometer, Copenhagen, Denmark) to secure that changes in SpO_2 reflected those in SaO_2.

Values were recorded: (a) with the patient breathing room air, (b) after breathing O_2 enriched air, (c) following induction of anesthesia, and finally (d) after tracheal intubation. Reported values during surgery represent the lowest noted $rScO_2$ with the associated values for SmO_2, HR, SV, CO, and MAP.

STATISTICS

For normally distributed data, One-Way analysis of variance (ANOVA) with repeated measures was used. In the case of a significant main effect, a Tukey-test based *post-hoc* evaluation was applied. Correlations among variables were evaluated by Spearman's test. A GLM matrix analysis was use to locate the factor that had the statistically strongest influence on $rScO_2$. A P-value < 0.05 was considered statistical significant.

RESULTS

Breathing O_2 enriched air increased arterial O_2 tension (from 10 ± 2 to 34 ± 12 kPa), SpO_2 (95.3 ± 2.4 to 99.7 ± 1.1%), arterial hemoglobin O_2 saturation (from 96.2 ± 2.0 to 99.7 ± 0.2%), and the arterial CO_2 tension (from 5.1 ± 0.6 to 5.4 ± 0.7 kPa; all $P < 0.05$). In all patients O_2 breathing increased $rScO_2$ (**Figure 1**) and SmO_2 while there was no effect on cardiovascular variables (**Table 1**). Statistically, SpO_2 contributed most to $rScO_2$ ($P < 0.0001$): changes in tissue oxygenation correlated to those in SpO_2 ($rScO_2$, $r = 0.50$; SmO_2, $r = 43$. $P < 0.05$) as provoked by breathing O_2 enriched air before anesthesia.

Following induction of anesthesia, MAP, HR, and CO lowered, while $rScO_2$ and SmO_2 remained elevated. For three patients $rScO_2$ was reduced by more than 10% indicative of a potentially critical reduction in regional cerebral O_2 supply. During surgery with an end-tidal CO_2 pressure of 4.4 ± 0.4 kPa, SV, and CO were at the levels before anesthesia, SmO_2 remained elevated and $rScO_2$ was not significantly changed as compared to the preoperative level. In seven patients, however, $rScO_2$ decreased by more than 10% and for five of these patients $rScO_2$ was below 50%. In the patients demonstrating a significant drop in $rScO_2$, CO

was reduced by 1.6 ± 1.2 L/min but $rScO_2$ appeared independent of MAP when CO was maintained or increased (**Figure 2**). Thus, there was no statistical significant relation between $rScO_2$ and MAP but ScO_2 was correlated to SV and CO (**Table 2**). Also $rScO_2$ correlated to age, while SmO_2 correlated only to SV and CO before but not after induction of anesthesia ($P = 0.0025$).

DISCUSSION

This study aimed to answer three questions: (i) Does preoxygenation (inhaling 100% oxygen before anesthesia) increase tissue oxygenation? (ii) Does inhalation of 70% oxygen during surgery prevent a reported critical reduction in ScO_2 to 50%? and (iii) When ScO_2 and/or SmO_2 decrease, is the decrease then related to reduced blood pressure and/or cardiac output? In vascular surgical patients, administration of elevated inspiratory O_2 fraction increased oxygenation of both the cerebral frontal lobe ($rScO_2$) and skeletal muscle (SmO_2) (by 10 and 3%, respectively). Importantly, this increase in tissue oxygenation appeared protective for development of tissue hypoxemia following induction of anesthesia, although the incidence of critical reduction in $rScO_2$ remained 5%. The third important observation was that during anesthesia a correlation between tissue oxygenation and a decrease in MAP was not observed indicating

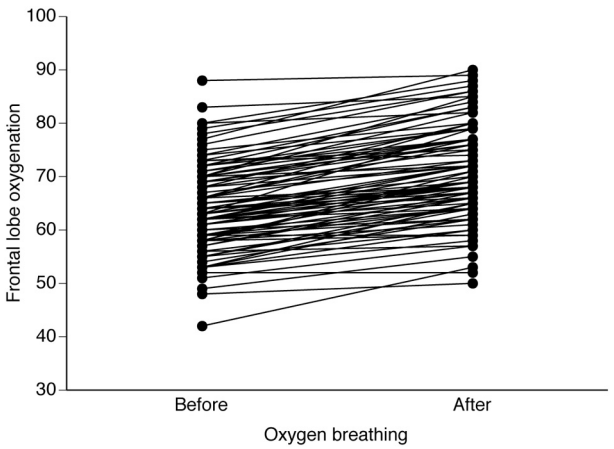


FIGURE 1 | Effects of O_2 breathing on NIRS determined frontal lobe oxygenation. Data are individual responses from vascular surgical patients exposed to preoperative facial mask breathing with 100% O_2.

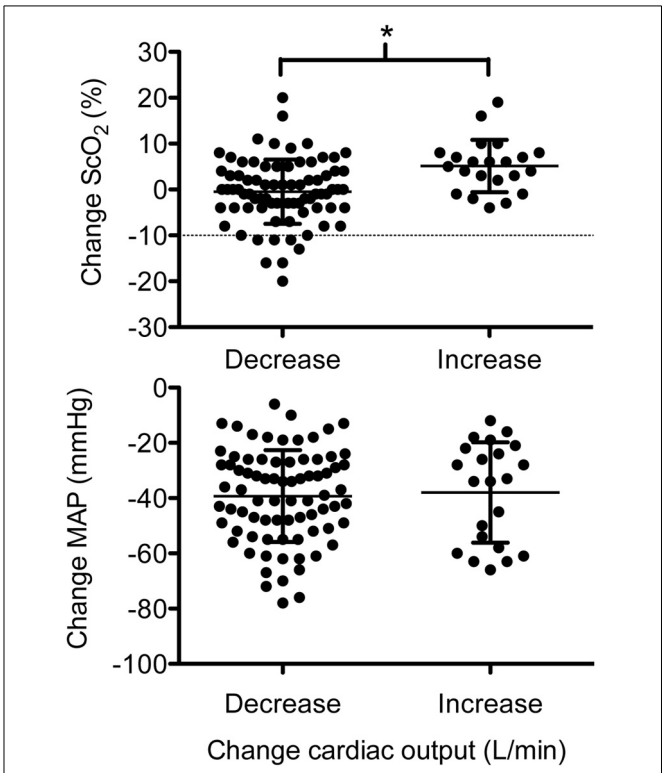


FIGURE 2 | The surgical changes in frontal lobe oxygenation (ScO_2) and mean arterial pressure (MAP) related to cardiac output (CO; decrease is CO below the preoperative level and increase is CO above the preoperative level). The dotted line straight line (upper panel) at −10% represents the change in ScO_2 considered to be critical. *Different value; $P < 0.05$.

Table 1 | Cardiovascular and blood gas variables for vascular surgical patients.

	Before anesthesia		During anesthesia		
	$-O_2$	$+O_2$	Induction	Intubation	Surgery
SpO_2 (%)	95.3 ± 2.4	99.7 ± 1.1*	99.8 ± 1.1*	99.8 ± 0.9*	99.9 ± 0.2*
ScO_2(%)	65 ± 8	72 ± 9*	70 ± 10*	75 ± 8*	66 ± 7†
SmO_2(%)	75 ± 9	78 ± 9*	80 ± 7*	79 ± 7*	80 ± 8*
HR (b min^{-1})	73 ± 13	72 ± 14	65 ± 13*	72 ± 16	61 ± 11*†
MAP (mmHg)	103 ± 18	102 ± 18	69 ± 18*	86 ± 25*	64 ± 11*†
SV (ml)	67 ± 16	66 ± 16	60 ± 17*	59 ± 17*	69 ± 15†
CO (L min^{-1})	4.9 ± 1.3	4.8 ± 1.3	4.1 ± 1.2*	4.3 ± 1.3*	4.1 ± 1.1*

Values are means ± SD with ($+O_2$) and without ($-O_2$) preoxygenation and following induction of anesthesia, immediately after the patient was intubated, and during surgery 47 ± 24 min after intubation. CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; SV, cardiac stroke volume; SpO_2, puls oximetry determined hemoglobin O_2 saturation in arterial blood; SmO_2 and ScO_2, near infrared determined muscle and frontal lobe oxygenation, respectively.

**Different from before anesthesia without O_2 supplementation.*

†Different between intubation and surgery; $P < 0.05$.

Table 2 | Relationship between frontal lobe oxygenation and cardiovascular variables.

	Breathing atm	Breathing O_2	Anesthesia	Intubation	Surgery
HR	$-0.02/P = 0.8529$	$0.01/P = 0.9451$	$0.02/P = 0.8689$	$0.01/P = 0.8987$	$-0.06/P = 0.5814$
MAP	$-0.01/P = 0.9258$	$-0.01/P = 0.9532$	$0.21/P = 0.8689$	$0.11/P = 0.2565$	$0.11/P = 0.2917$
SV	$0.36/P = 0.0002$*	$0.34/P = 0.0006$*	$0.23/P = 0.0392$*	$0.29/P = 0.0032$*	$0.30/P = 0.0724$
CO	$0.40/P < 0.0001$*	$0.40/P < 0.0001$*	$0.32/P = 0.0013$*	$0.36/P = 0.0003$*	$0.20/P = 0.0513$
SpO_2	$0.10/P = 0.3433$	$0.07/P = 0.5195$	$0.02/P = 0.8116$	$0.04/P = 0.7232$	$0.04/P = 0.7262$
Age	$-0.20/P = 0.0415$*	$-0.19/P = 0.0599$	$-0.18/P = 0.0697$	$-0.20/P = 0.0420$*	$0.09/P = 0.3985$
FiO_2					$0.16/P = 0.1133$
CO_2					$-0.16/P = 0.1183$

Correlations are evaluated by Spearmans Rank Test and the included numbers are the coefficient of contingence with its level of statistical significance as determined by two-tailed t-test. CO, cardiac output; FiO_2, inspired O_2 fraction; HR, heart rate; MAP, mean arterial pressure; SV, cardiac stroke volume; SpO_2, pulse oximetry determined hemoglobin O_2 saturation in arterial blood.

**Marks the variable with statistical significance at $P < 0.05$.*

that for vascular surgical patients, as for patients scheduled for other types of surgery (Nissen et al., 2009), a transient drop in blood pressure to below what is often considered the lower limit of cerebral autoregulation does not affect $rScO_2$. On the other hand, $rScO_2$ correlated to a reduction in CO and SV.

It has not been evaluated whether it is profitable to control flow-related variables (SV, CO, or SvO_2) in conjunction with an effort to maintain $rScO_2$ during surgery. With fluid administration according to an "individualized goal-directed regime," SV and hence CO is optimized to a level considered to represent normovolemia (Bundgaard-Nielsen et al., 2010). In the present study, the cardiovascular variables reported during surgery represent situations where $rScO_2$ reached a minimum and the associated CO may reflect that fluid resuscitation was about to be initiated.

A correlation between $rScO_2$ and CO supports a link to blood flow (Ide et al., 1999) and as cardiovascular capacity decline with advancing age (Proctor and Joyner, 1997), this view is further supported by a correlation between $rScO_2$ and age. Seven patients suffered a critical reduction in $rScO_2$ when CO dropped (**Figure 2**) and if O_2 supplementation had not induced a 10% increase in $rScO_2$, it is likely that $rScO_2$ would have been reduced to a critical level in more patients. We did not find indication for that a low MAP affected $rScO_2$ and in ASA class I patients, a 30% reduction in MAP with a minimum MAP of 50 mmHg, is considered acceptable (Yamada et al., 1988; Petrozza, 1990). In this evaluation 32 of 100 patients undergoing vascular surgery at one stage of the operation developed a MAP < 60 mmHg, apparently without affecting $rScO_2$. Even when MAP was below 50 mmHg ($n = 12$), $rScO_2$ was maintained.

Administration of an O_2 enriched atmosphere was introduced to reduce the incidence of complications after colorectal surgery (Greif et al., 2000) and vascular surgery (Turtiainen et al., 2011). Yet, not all follow-up studies support that a high O_2 fraction reduces surgical site infections (Pryor et al., 2004; Belda et al., 2005; Meyhoff et al., 2009; Bustamante et al., 2011) and O_2 supplementation may provoke formation of O_2 free radicals (García-de-la-Asunción et al., 2011). Furthermore, surgical site infection, atelectasis, pneumonia, and respiratory failure occur at similar frequencies in patients with an inspired O_2 fraction of 0.80 compared to 30% O_2 (Meyhoff et al., 2009). The tendency for O_2 breathing to provoke pulmonary atelectasis (Hedenstierna, 2012) suggests the use of positive end expiratory pressure as applied in this evaluation. Also the relevance for using O_2 supplementation is likely to vary among groups of patients. For vulnerable patients a reduction in tissue oxygenation may provoke ischemic stroke after surgery (Waggoner et al., 2001; Cheng-Ching et al., 2010). Importantly, vascular surgical patients often present with coronary artery or cerebrovascular disease (Hertzer et al., 1984) and hypotension may become critical for maintained tissue oxygenation. We suggest that O_2 supplementation is important for perioperative preservation of tissue oxygenation.

This study is limited by several factors: a retrospective design often fails to extract dynamic cardiovascular variables in patients exposed to surgery. Furthermore, for the patients included in the present cohort, the recommendation to use NIRS to guide the circulation during surgery may not have been followed and a placebo-controlled randomized design is in need. A third reservation relates to the NIRS used for interpretation of changes in tissue oxygenation as the INVOS cerebral oximeter appears to be sensitive to changes in skin blood flow (Davie and Grocott, 2012).

From this retrospective evaluation of tissue oxygenation including 100 patients undergoing vascular surgical procedures, it is concluded that O_2 supplementation increases the NIRS-determined oxygenation of the cerebral frontal lobe and skeletal muscles. Furthermore, the data suggest that an elevated inspired oxygen fraction is not efficient to prevent a critical reduction in cerebral oxygenation since a decrease seems to be related to a reduced cardiac output.

ACKNOWLEDGMENTS

Peter Rasmussen, MSci PhD is thanked for statistical work and valuable discussions. Henning Bay Nielsen was funded by Rigshospitalet Research fund and the Danish Agency for Science Technology and Innovation (271-08-0857).

REFERENCES

Beaussier, M., Paugam, C., Deriaz, H., Mestari, M., Chandon, M., Sautet, A., et al. (2000). Haemodynamic stability during moderate hypotensive anaesthesia for spinal surgery. A comparison between desflurane and isoflurane. *Acta Anaesthesiol. Scand.* 44, 1154–1159. doi: 10.1034/j.1399-6576.2000.440921.x

Belda, F. J., Aguilera, L., García de la Asunción, J., Alberti, J., Vicente, R., Ferrándiz, L., et al. (2005). Spanish Reduccion de la Tasa de Infeccion Quirurgica Group. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. *JAMA* 294, 2035–2042. doi: 10.1001/jama.294.16.2035

Bogert, L. W., and van Lieshout, J. J. (2005). Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Exp. Physiol.* 90, 437–446. doi: 10.1113/expphysiol.2005.030262

Boonmak, S., Boonmak, P., and Laopaiboon, M. (2013). Deliberate hypotension with propofol under anaesthesia for functional endoscopic sinus surgery (FESS). *Cochrane Database Syst. Rev.* 6, CD006623. doi: 10.1002/14651858.CD006623.pub2

Bundgaard-Nielsen, M., Holte, K., Secher, N. H., and Kehlet, H. (2007). Monitoring of peri-operative fluid administration by individualized goal-directed therapy. *Acta Anaesthesiol. Scand.* 51, 331–340. doi: 10.1111/j.1399-6576.2006.01221.x

Bundgaard-Nielsen, M., Jørgensen, C. C., Kehlet, H., and Secher, N. H. (2010). Normovolemia defined according to cardiac stroke volume in healthy supine humans. *Clin. Physiol. Funct. Imaging* 30, 318–322. doi: 10.1111/j.1475-097X.2010.00944.x

Bustamante, J., Tamayo, E., Alvarez, F. J., García-Cuenca, I., Flórez, S., Fierro, I., et al. (2011). Intraoperative PaO_2 is not related to the development of surgical site infections after major cardiac surgery. *J. Cardiothorac. Surg.* 6, 4. doi: 10.1186/1749-8090-6-4

Casati, A., Fanelli, G., Pietropaoli, P., Proietti. R., Tufano, R., Danelli, G., et al. (2005). Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth. Analg.* 101, 740–747. doi: 10.1213/01.ane.0000166974.96219.cd

Cheng-Ching, E., Fong, J., Ontaneda, D., Hussain, M. S., Katzan, I., and Gupta, R. (2010). Intracranial atherosclerosis as a risk factor for ischemic stroke during open heart surgery. *J. Stroke Cerebrovasc. Dis.* 19, 257–260. doi: 10.1016/j.jstrokecerebrovasdis.2009.04.011

Davie, S. N., and Grocott, H. P. (2012). Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology* 116, 834–840. doi: 10.1097/ALN.0b013e31824c00d7

Dixon, B. J., Dixon, J. B., Carden, J. R., Burn, A. J., Schachter, L. M., Playfair, J. M., et al. (2005). Preoxygenation is more effective in the 25 degrees head-up position than in the supine position in severely obese patients: a randomized controlled study. *Anesthesiology* 102, 1110–1115. doi: 10.1097/00000542-200506000-00009

Fries, R. B., Wallace, W. A., Roy, S., Kuppusamy, P., Bergdall, V., Gordillo, G. M., et al. (2005). Dermal excisional wound healing in pigs following treatment with topically applied pure oxygen. *Mutat. Res.* 579, 172–181. doi: 10.1016/j.mrfmmm.2005.02.023

García-de-la-Asunción, J., Barber, G., Rus, D., Perez-Griera, J., Belda, F. J., Martí, F., et al. (2011). Hyperoxia during colon surgery is associated with a reduction of xanthine oxidase activity and oxidative stress in colonic mucosa. *Redox Rep.* 16, 121–128. doi: 10.1179/174329211X13049558293632

Greif, R., Akça, O., Horn, E. P., Kurz, A., Sessler, D. I., and Outcomes Research Group. (2000). Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N. Engl. J. Med.* 342, 161–167. doi: 10.1056/NEJM200001203420303

Hedenstierna, G. (2012). Oxygen and anesthesia: what lung do we deliver to the post-operative ward? *Acta Anaesthesiol. Scand.* 56, 675–685. doi: 10.1111/j.1399-6576.2012.02689.x

Heringlake, M., Garbers, C., Käbler, J. H., Anderson, I., Heinze, H., Schön, J., et al. (2011). Preoperative cerebral oxygen saturation and clinical outcomes in cardiac surgery. *Anesthesiology* 114, 58–69. doi: 10.1097/ALN.0b013e3181fef34e

Hertzer, N. R., Beven, E. G., Young, J. R., O'Hara, P. J., Ruschhaupt, W. F. 3rd., Graor, R. A., et al. (1984). Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann. Surg.* 199, 223–233. doi: 10.1097/00000658-198402000-00016

Hunt, T. K., and Pai, M. P. (1972). The effect of varying ambient oxygen tension on wound metabolism and collagen synthesis. *Surg. Gynecol. Obstet.* 135, 561–567.

Ide, K., Gulløv, A. L., Pott, F., Van Lieshout, J. J., Koefoed, B. G., Petersen, P., et al. (1999). Middle cerebral artery blood velocity during exercise in patients with atrial fibrillation. *Clin. Physiol.* 19, 284–289. doi: 10.1046/j.1365-2281.1999.00178.x

Madsen, P., Lyck, F., Pedersen, M., Olesen H. L., Nielsen, H. B., and Secher, N. H. (1995). Brain and muscle oxygen saturation during head-up-tilt-induced central hypovolaemia in humans. *Clin. Physiol.* 15, 523–533. doi: 10.1111/j.1475-097X.1995.tb00541.x

Madsen, P. L., and Secher, N. H. (1999). Near-infrared oximetry of the brain. *Prog. Neurobiol.* 58, 541–560. doi: 10.1016/S0301-0082(98)00093-8

Martin, D. S., and Galliano, R. (1965). Bloodless liver resection under hypotensive hypothermia. *Am. J. Surg.* 109, 625–628.

Meyhoff, C. S., Wetterslev, J., Jorgensen, L. N., Henneberg, S. W., Høgdall, C., Lundvall, L., et al. (2009). PROXI Trial Group. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. *JAMA* 302, 1543–1550. doi: 10.1001/jama.2009.1452

Murkin, J. M. (2011). Cerebral oximetry: monitoring the brain as the index organ. *Anesthesiology* 114, 12–13. doi: 10.1097/ALN.0b013e3181fef5d2

Murkin, J. M., and Arango, M. (2009). Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br. J. Anaesth.* 103, i3–i13. doi: 10.1093/bja/aep299

Nielsen, H. B., Boushel, R., Madsen, P., and Secher, N. H. (1999). Cerebral desaturation during exercise reversed by O_2 supplementation. *Am. J. Physiol.* 277, H1045–H1052.

Niinikoski, J. (1969). Effect of oxygen supply on wound healing and formation of experimental granulation tissue. *Acta Physiol. Scand. (Suppl.)* 334, 1–72.

Nissen, P., van Lieshout, J. J., Nielsen, H. B., and Secher, N. H. (2009). Frontal lobe oxygenation is maintained during hypotension following propofol-fentanyl anesthesia. *AANA J.* 77, 271–276.

Olsson, C., and Thelin, S. (2006). Regional cerebral saturation monitoring with near-infrared spectroscopy during selective antegrade cerebral perfusion: diagnostic performance and relationship to postoperative stroke. *J. Thorac. Cardiovasc. Surg.* 131, 371–379. doi: 10.1016/j.jtcvs.2005.08.068

Paulson, O. B., Strandgaard, S., and Edvinsson, L. (1990). Cerebral autoregulation. *Cerebrovasc. Brain Metab. Rev.* 2, 161–192.

Pedersen, P. K., Kiens, B., and Saltin, B. (1999). Hyperoxia does not increase peak muscle oxygen uptake in small muscle group exercise. *Acta Physiol. Scand.* 166, 309–318. doi: 10.1046/j.1365-201x.1999.00575.x

Petrozza, P. H. (1990). Induced hypotension. *Int. Anesthesiol. Clin.* 28, 223–229. doi: 10.1097/00004311-199002840-00008

Proctor, D. N., and Joyner, M. J. (1997). Skeletal muscle mass and the reduction of VO_2max in trained older subjects. *J. Appl. Physiol.* 82, 1411–1415.

Pryor, K. O., Fahey, T. J. 3rd., Lien, C. A., and Goldstein, P. A. (2004). Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population: a randomized controlled trial. *JAMA* 291, 79–87. doi: 10.1001/jama.291.1.79

Slater, J. P., Guarino, T., Stack, J., Vinod, K., Bustami, R. T., Brown, J. M. 3rd., et al. (2009). Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. *Ann. Thorac. Surg.* 87, 36–44. doi: 10.1016/j.athoracsur.2008.08.070

Smith, K. J., Wong, L. E., Eves, N. D., Koelwyn, G. J., Smirl, J. D., Willie, C. K., et al. (2012). Regional cerebral blood flow distribution during exercise: influence of oxygen. *Respir. Physiol. Neurobiol.* 184, 97–105. doi: 10.1016/j.resp.2012.07.014

Soerensen, H., Secher, N. H., Siebenmann, C., Nielsen, H. B., Kohl-Bareis, M., Lundby, C., et al. (2012). Cutaneous vasoconstriction affects spectroscopy-determined cerebral oxygen saturation during administration of norepinephrine. *Anesthesiology* 117, 263–270. doi: 10.1097/ALN.0b013e3182605afe

Tubbs, R. S., Elton, S., Salter, G., Blount, J. P., Grabb, P. A., and Oakes, W. J. (2002). Superficial surgical landmarks for the frontal sinus. *J. Neurosurg.* 96, 320–322. doi: 10.3171/jns.2002.96.2.0320

Turtiainen, J., Saimanen, E. I., Partio, T. J., Mäkinen, K. T., Reinikainen, M. T., Virkkunen, J. J., et al. (2011). Supplemental postoperative oxygen in the prevention of surgical wound infection after lower limb vascular surgery: a randomized controlled trial. *World J. Surg.* 35, 1387–1395. doi: 10.1007/s00268-011-1090-y

Waggoner, J. R. 3rd., Wass, C. T., Polis, T. Z., Faust, R. J., Schroeder, D. R., Offord, K. P., et al. (2001). The effect of changing transfusion practice on rates of perioperative stroke and myocardial infarction in patients undergoing carotid endarterectomy: a retrospective analysis of 1114 Mayo Clinic patients. Mayo Perioperative Outcomes Group. *Mayo Clin. Proc.* 76, 376–383.

Welch, H. G., Bonde-Petersen, F., Graham, T., Klausen, K., and Secher, N. H. (1977). Effects of hyperoxia on leg blood flow and metabolism during exercise. *J. Appl. Physiol.* 42, 385–390.

Yamada, S., Brauer, F., Knierim, D., Purtzer, T., Fuse, T., Hayward, W., et al. (1988). Safety limits of controlled hypotension in humans. *Acta Neurochir.* 42, 14–17. doi: 10.1007/978-3-7091-8975-7_3

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 13 November 2013; accepted: 03 February 2014; published online: 25 February 2014.

Citation: Rokamp KZ, Secher NH, Eiberg J, Lønn L and Nielsen HB (2014) O_2 supplementation to secure the near-infrared spectroscopy determined brain and muscle oxygenation in vascular surgical patients: a presentation of 100 cases. Front. Physiol. ***5****:66. doi: 10.3389/fphys.2014.00066*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in
PHYSIOLOGY

REVIEW ARTICLE
published: 17 March 2014
doi: 10.3389/fphys.2014.00093

Systematic review of near-infrared spectroscopy determined cerebral oxygenation during non-cardiac surgery

Henning B. Nielsen*

Department of Anesthesia, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Shawnda A. Morrison, Acadia University, Canada
Hilary P. Grocott, University of Manitoba, Canada

****Correspondence:***
Henning B. Nielsen, Department of Anesthesia, Rigshospitalet, University of Copenhagen, Rigshospitalet 2041, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark
e-mail: henning.bay@rh.regionh.dk

Near-infrared spectroscopy (NIRS) is used to monitor regional cerebral oxygenation ($rScO_2$) during cardiac surgery but is less established during non-cardiac surgery. This systematic review aimed (i) to determine the non-cardiac surgical procedures that provoke a reduction in $rScO_2$ and (ii) to evaluate whether an intraoperative reduction in $rScO_2$ influences postoperative outcome. The PubMed and Embase database were searched from inception until April 30, 2013 and inclusion criteria were intraoperative NIRS determined $rScO_2$ in adult patients undergoing non-cardiac surgery. The type of surgery and number of patients included were recorded. There was included 113 articles and evidence suggests that $rScO_2$ is reduced during thoracic surgery involving single lung ventilation, major abdominal surgery, hip surgery, and laparoscopic surgery with the patient placed in anti-Tredelenburg's position. Shoulder arthroscopy in the beach chair and carotid endarterectomy with clamped internal carotid artery (ICA) also cause pronounced cerebral desaturation. A >20% reduction in $rScO_2$ coincides with indices of regional and global cerebral ischemia during carotid endarterectomy. Following thoracic surgery, major orthopedic, and abdominal surgery the occurrence of postoperative cognitive dysfunction (POCD) might be related to intraoperative cerebral desaturation. In conclusion, certain non-cardiac surgical procedures is associated with an increased risk for the occurrence of $rScO_2$. Evidence for an association between cerebral desaturation and postoperative outcome parameters other than cognitive dysfunction needs to be established.

Keywords: tissue oxygenation, brain, muscle, cerebral cortex, intraoperative monitoring

With the introduction of near infrared spectroscopy (NIRS) for intraoperative evaluation of regional cerebral oxygenation ($rScO_2$), focus on maintaining cerebral blood flow (CBF) has lead to intervention algorithms to support cardiac stroke volume and central venous oxygen saturation in addition to mean arterial pressure (MAP), arterial hemoglobin O_2 saturation, and arterial carbon dioxide pressure (Bundgaard-Nielsen et al., 2007a). Several commercial NIRS-devices provide for a cerebral oximetry evaluation of $rScO_2$ reflecting changes in CBF (Madsen and Secher, 1999). During cardiac surgery NIRS is used for anesthetic management of the circulation (Murkin and Arango, 2009) while, as indicated by the number of review papers there is no standard recommendation for the use of NIRS in non-cardiac surgical procedures other than in carotid endarterectomy (CEA; ref. Pennekamp et al., 2009, 2011). In non-cardiac surgery hypotension and in turn a decrease in $rScO_2$ may arise when the blood loss challenges the central blood volume or when it is compromised during head-up tilt (Madsen et al., 1995) as used for both abdominal and orthopedic surgery. Thus $rScO_2$ may decrease when pressure is reduced below the lower limit of cerebral autoregulation as during cardiac surgery requiring cardiopulmonary by-pass (Ono et al., 2013). Maintained regional tissue blood flow is, however, important for limiting postoperative complications such as acute kidney failure (Chenitz and Lane-Fall, 2012), wound infection (Sørensen, 2012), and cognitive dysfunction (Murkin et al., 2007; Slater et al., 2009) both in cardiac and non-cardiac surgery.

A systematic review was undertaken (i) to determine the non-cardiac surgical procedures that provoke a reduction in $rScO_2$ and (ii) to evaluate whether an intraoperative reduction in $rScO_2$ influences postoperative outcome such as cognitive dysfunction. Publications included for the review are presented in a table with inclusion of the surgical speciality, the number of patients included in each article, the NIRS device used, and whether cerebral oxygenation was changed intraoperatively.

METHODS

Relevant publications were found by searching the PubMed and Embase database from inception through April 30, 2013. The search strategy combined the following MeSH (medical subject headings) terms and keywords: (NIRS or NIS or near infrared spectroscopy or oximetry), (oximetry or saturation or oxygenation or desaturation or oxygen), (brain or cerebral or muscle), and (surgery or surgical or perioperative).

Publications were included in the review if they addressed monitoring of tissue oxygenation by NIRS for intraoperative monitoring during non-cardiac and non-head-trauma surgery in adult patients (**Figure 1**). Each title and/or abstract identified was

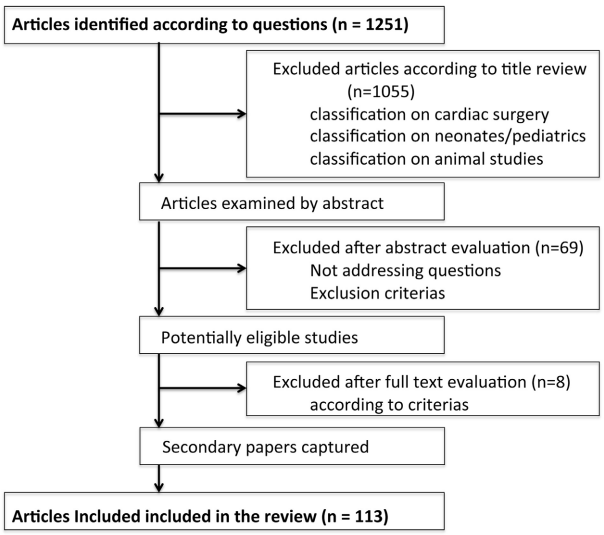


FIGURE 1 | Flow chart for study selection.

screened for eligibility. Publications were excluded if they did not include original data (e.g., review, commentary), or if they were not published as a full-length article in a peer-reviewed journal. Non-English articles were also excluded and articles evaluating non-brain tissue only were excluded as well. If articles included animals, pediatric patients or cardiac surgical patients they did not fulfill inclusion criteria and they were therefore not considered eligible for inclusion in the study. Articles reporting changes in $rScO_2$ before or after surgery were also excluded. Data regarding the number of patients, type of surgery, and type of NIRS for determination of cerebral oxygenation were noted. The articles were grouped according to the predominant surgical procedure.

RESULTS

Figure 1 is a summary of the search with the initial strategy resulting in 1251 citations. According to title review, 1055 papers did not met the inclusion criteria: 321 papers were on cardiacthoracic and/or pediatric/fetal issues, 54 articles addressed studies in animals, and 99 papers were reviews and/or comments predominantly addressing cardiac surgical patients, 67 articles included head-trauma or neurological patients, 149 articles were in non-English language and 145 papers did not address intraoperative issues. In total 196 articles were included for abstract review. Additional 69 abstracts were excluded for not meeting the main inclusion criteria of this review. After full review additional papers were excluded. NIRS results from 113 papers are presented (**Table 1**).

NEUROSURGERY AND SURGERY ON THE SPINE

During neurovascular procedures (aneurysm clipping, bypass procedures, or balloon occlusion testing), $rScO_2$, and the NIRS-determined concentration of oxygenated hemoglobin (HbO_2) decrease (Calderon-Arnulphi et al., 2007) and $rScO_2$ reflects the success of surgical resection of a cerebral arterio-venous malformation (Asgari et al., 2003). While induction of anesthesia does not change brain oxygenation tracheal intubation increases HbO_2 (Paisansathan et al., 2007). In contrast the head up tilted position provokes a decrease in $rScO_2$ (69 vs. 71%) (Fuchs et al., 2000) and also the NIRS-determined total Hb becomes reduced (Lovell et al., 2000).

MAXILLO-FACIAL-EYE SURGERY AND BREAST SURGERY

Minor reduction in $rScO_2$ is observed immediately after peribulbar block for eye surgery (Fodale et al., 2006) and with MAP reduced to 60 mmHg during orthognathic surgery $rScO_2$ decreases 5% (Choi et al., 2008). Such changes do not provoke postoperative cognitive dysfunction (POCD) as determined by a decrease in the minimal mental state examination (MMSE) score =2 points from baseline (Choi et al., 2008).

In patients scheduled for mastectomy induction of anesthesia with subsequent hypotension, $rScO_2$ increases (from 67 to 72%) to remain stable during surgery (Nissen et al., 2009a, 2010). While ephedrine preserves $rScO_2$, phenylephrine is reported to decrease $rScO_2$ 14% (Nissen et al., 2010).

THORACIC SURGERY

During open thoracotomy or thorascopy, about half of the patients present at least one $rScO_2$ value that is lower than 80% of the baseline value (Tobias et al., 2008) and during surgery with single lung ventilation up to 75% of the patients suffer from a more than a 20% decrease in $rScO_2$ (Hemmerling et al., 2008; Kazan et al., 2009; Tang et al., 2012). Risk factors for a reduction in $rScO_2$ are age, weight, and ASA class III (Tobias et al., 2008) and the minimum $rScO_2$ value predicts postoperative complications as evaluated by the Clavien and SOFA scoring systems (Kazan et al., 2009). The exposure time to $rScO_2$ values below <65% correlates with occurrence of POCD (Tang et al., 2012). This study used MMSE for evaluation of cognitive function before surgery and several days after surgery. A decrease >2 points from baseline was defined as POCD.

SHOULDER SURGERY

During arthroscopic shoulder surgery in the lateral decubitus position, $rScO_2$ is maintained (Murphy et al., 2010) but when the patient is placed in the beach chair position $rScO_2$ may decrease (Fischer et al., 2009; Dippmann et al., 2010; Tange et al., 2010; Lee et al., 2011; Yadeau et al., 2011; Jeong et al., 2012; Ko et al., 2012; Moerman et al., 2012; Salazar et al., 2013a,b) with different incidence of intraoperative cerebral desaturation (0 vs. 27%) (Tange et al., 2010; Jeong et al., 2012). The duration of cerebral desaturation episodes range from 1 min to 1 h or longer (Jeong et al., 2012). In the recent study by Salazar et al. (2013a), it is stated that mean maximal desaturation is 32% with each desaturation event lasting an average of 3 min 3 s. Lowered $rScO_2$ coincides with low MAP (<70 mmHg; 30, 33, 36) and raised MAP restores $rScO_2$ (Lee et al., 2011). In a case report including one patient it is noted that the α_1-agonist phenylephrine increases both MAP and $rScO_2$ (Fischer et al., 2009). Large body mass index is reported to be associated with a reduction in $rScO_2$ (Salazar et al., 2013a).

The influence of intravenous (propofol) anesthesia vs. inhalational (sevoflurane) anesthesia on $rScO_2$ has also been evaluated

Table 1 | Studies included in the systematic review grouped in accordance to surgical procedures.

Paper	Patients	Apparatus	Intended tissue	Change in oxygenation
NEUROSURGERY AND SPINE SURGERY				
Asgari et al., 2003	*N* = 20 Cerebral arteriovenous malformations	Multiscan OS 30	Cortical surface	∧
Calderon-Arnulphi et al., 2007	*N* = 25 Neurovascular procedures	Oxiplex	Brain	∨
Fuchs et al., 2000	*N* = 74 Lumbar discectomy Healthy volunteers CEA	INVOS 4100	Frontal lobe	∨
Lovell et al., 2000	*N* = 20 Micro discectomy Healthy volunteers	NIRO 500	Frontal lobe	∨
Paisansathan et al., 2007	*N* = 13 Spinal or peripheral nerve surgery	Oxiplex	Frontal lobe	∧
MAXILLO-FACIAL-EYE SURGERY				
Choi et al., 2008	*N* = 60 Orthognathic surgery	INVOS 5100	Frontal lobe	∨
Fodale	*N* = 66 Ophthalmic procedures	INVOS 5100B	Frontal lobe	∨
BREAST SURGERY				
Nissen et al., 2009a	*N* = 71 mastectomy, thyroidectomy or parathyroidectomy	INVOS	Frontal lobe* Skeletal muscle	∧
Nissen et al., 2010	*N* = 78 Mastectomy, thyroidectomy or parathyroidectomy	INVOS	Frontal lobe*	∨
THORACIC SURGERY				
Tobias et al., 2008	*N* = 40 Open thoracotomy and thorascopy	INVOS 3100A	Frontal lobe	∨
Hemmerling et al., 2008	*N* = 20 Open thoracotomy	FORE-SIGHT	Frontal lobe	∨
Kazan et al., 2009	*N* = 50 Thoracic surgery	FORE-SIGHT	Frontal lobe	∨
Tang et al., 2012	*N* = 76 Thoracic surgery	FORE-SIGHT	Frontal lobe	∨
ORTHOPEDIC SURGERY				
Dippmann et al., 2010	*N* = 2 Arthroscopic shoulder surgery	INVOS 5100	Frontal lobe	∨
Fischer et al., 2009	*N* = 1 Arthroscopic shoulder surgery	FORESIGHT	Frontal lobe	∨
Jeong et al., 2012	*N* = 56 Arthroscopic shoulder surgery	INVOS 5100B	Frontal lobe	∨
Han et al., 2006	*N* = 56 Major orthopedic surgery	INVOS 4100	Frontal lobe	∨
Lee et al., 2011	*N* = 28 Arthroscopic shoulder surgery	INVOS 5100	Frontal lobe	∨
Lin et al., 2013	*N* = 46 Total hip arthroplasty	INVOS 5100B	Frontal lobe	∨
Ko et al., 2012	*N* = 50 Arthroscopic shoulder surgery	INVOS 5100	Frontal lobe	∨
Moerman et al., 2012	*N* = 20 Arthroscopic shoulder surgery	INVOS 5100	Frontal lobe	∨
Murphy et al., 2010	*N* = 124 Arthroscopic shoulder surgery in beach chair and LDP	FORE-SIGHT	Frontal lobe	∨
Papadopoulos et al., 2012	*N* = 69 Hip fracture repair	INVOS 5100C	Frontal lobe	∨

(Continued)

Table 1 | Continued

Paper	Patients	Apparatus	Intended tissue	Change in oxygenation
Salazar et al., 2013a	$N = 51$ Arthroscopic shoulder surgery	INVOS 5100	Frontal lobe	∨
Salazar et al., 2013b	$N = 50$ Arthroscopic shoulder surgery	INVOS 5100	Frontal lobe	∨
Song et al., 2012	$N = 28$ Total knee replacement	INVOS 5100	Frontal lobe	–
Tange et al., 2010	$N = 30$ Arthroscopic shoulder surgery	NIRO-200	Frontal lobe	–
Tzimas et al., 2010	$N = 1$ Hip fracture repair	INVOS 5100	Frontal lobe	∧
Yadeau et al., 2011	$N = 99$ Arthroscopic shoulder surgery	INVOS 5100C	Frontal lobe	∨
Yoshitani et al., 2005	$N = 42$ Total hip arthroplasty	INVOS 4100	Frontal lobe	∨
UROLOGY				
Bundgaard-Nielsen et al., 2007b	$N = 12$ Open prostatectomy	INVOS	Frontal lobe Biceps muscle	–
Burkhart et al., 2011	$N = 104$ Non-epidural major surgery	NIRO-200	Frontal lobe	∨
Kalmar et al., 2012	$N = 31$ Robot prostatectomy	FORE-SIGHT	Frontal lobe	–
Meng et al., 2012	$N = 29$ Predominant patients for robot prostatectomy	Oxiplex	Frontal lobe	∨
Meng et al., 2011	$N = 14$ Predominant patients for robot prostatectomy	Oxiplex	Frontal lobe	∨
Park et al., 2009	$N = 32$ Robot prostatectomy	INVOS 5100	Frontal lobe	–
GYNECOLOGY				
Berlac and Rasmussen, 2005	$N = 38$ Caesarean section	INVOS 3100	Frontal lobe	∨
Fassoulaki et al., 2006	$N = 44$ Hysterectomy	INVOS 3100	Frontal lobe	∨
Kondo et al., 2013	$N = 42$ Caesarean section	NIRO pulse	Brain	∨
Lee et al., 2006	$N = 24$ Laparoscopic gynecology	INVOS 4100	Frontal lobe	∨
Morimoto et al., 2000	$N = 45$ Gynecologic surgery	NIRO-500	Frontal lobe	∧
GASTRO-INTESTINAL SURGERY				
Casati et al., 2005	$N = 122$ Major abdominal surgery	INVOS 4100	Frontal lobe	∨
Casati et al., 2007	$N = 60$ Major abdominal surgery	INVOS 4100	Frontal lobe	∨
Gipson et al., 2006	$N = 70$ Laparoscopic herniorrhaphy, cholecystectomy, gastric bypass	INVOS 3100A	Frontal lobe	∨
Green, 2007	$N = 46$ Major abdominal surgery: whipple, hepatectomy, prostatectomy, cystectomy, aortic aneurysm repair	INVOS	Frontal lobe	∨
Harrison, 2001	$N = 13$ Surgery for gastrointestinal or gynecological malignancy	INVOS 3100	Frontal lobe	∨
Kitajima et al., 1998	$N = 12$ Laparoscopic cholecystectomy	NIRO-500	Brain	∨

(Continued)

Table 1 | Continued

Paper	Patients	Apparatus	Intended tissue	Change in oxygenation
Kurukahvecioglu et al., 2008	$N = 60$ Laparoscopic cholecystectomy	INVOS 5100	Frontal lobe	∨
Madsen et al., 2000	$N = 48$ Liver transplantation	INVOS 3100	Frontal lobe	∨
Madsen and Secher, 2000	$N = 1$ Liver transplantation	INVOS 3100	Frontal lobe	∨
Morimoto et al., 2009	$N = 20$ Laparotomy or laparoscopic surgery	INVOS 3100	Frontal lobe	∨
Nissen et al., 2009b	$N = 33$ Liver transplantation	INVOS	Frontal lobe	∨
Plachky et al., 2004	$N = 16$ Liver transplantation	INVOS 3100A	Frontal lobe	∨
Zheng et al., 2012	$N = 9$ Liver transplantation	INVOS (Somanetics)	Frontal lobe	∨
VASCULAR SURGERY				
Liu et al., 1999††	$N = 12$ AAA patients	INVOS-3100	Frontal lobe	∨
Kuroda et al., 1996a	$N = 5$ Balloon occlusion test of ICA	OM-100 (Shimadzu Co.)	Frontal lobe	∨
Torella et al., 2002**	$N = 30$ Aortic surgery	INVOS-4100	Frontal lobe Calf muscle	∨
Torella et al., 2003***	$N = 29$ Aortic surgery ($n = 21$)	INVOS-4100	Frontal lobe Calf muscle	∧
Torella and McCollum, 2004****	Spinal surgery ($n = 8$)	INVOS-4100	Frontal lobe Calf muscle	
CAROTID SURGERY				
Ali et al., 2011	$N = 10$ Aortic surgery	INVOS	Frontal lobe	∨
Beese et al., 1998	$N = 49$ CEA, LA	INVOS-3100	Frontal lobe	∨
Carlin et al., 1998	$N = 137$ CEA, GA	INVOS-3100	Frontal lobe	∨
Cho et al., 1998	$N = 16$ CEA, LA	INVOS-3100A NIRO500 ($n = 20$)	Frontal lobe	∨
Cuadra et al., 2003	$N = 29$ CEA, GA	INVOS-4100	Frontal lobe	∨
Duncan et al., 1995	$N = 40$ CEA, GA	–	Frontal lobe	∨
Duffy et al., 1997	$N = 22$	INVOS-3100	Frontal lobe	∨
Espenell et al., 2010	$N = 72$ CEA, GA	FORE-SIGHT	Frontal lobe	∨
Fassiadis et al., 2006	$N = 35$ CEA, GA	INVOS	Frontal lobe	∨
Fearn et al., 2000	$N = 40$ CEA, LA	INVOS-3100A	Frontal lobe	∨
Friedell et al., 2008	$N = 100$ CEA	INVOS	Frontal lobe	∨
Giustiniano et al., 2010	$N = 323$ CEA, GA	INVOS-5100B	Frontal lobe	∨
Grubhofer et al., 1997	$N = 104$ CEA, GA	INVOS-3100A	Frontal lobe	∨
Grubhofer et al., 2000	$N = 12$ CEA, GA	INVOS-3100	Frontal lobe	∨

(Continued)

Table 1 | Continued

Paper	Patients	Apparatus	Intended tissue	Change in oxygenation
Ishigaki et al., 2008	$N = 59$ CEA, GA	TOS96	Frontal lobe	∨
Kacprzak et al., 2012	$N = 41$ CEA, GA	Selfconstruct	Frontal lobe	∨
Kawada et al., 2002	$N = 16$ CEA	TOS	Frontal lobe	∨
Kobayashi et al., 2009	$N = 3$ Extracranial ICA Aneurysm	TOS96	Frontal lobe	∨
Komoribayashi et al., 2006	$N = 171$ CEA, GA	TOS96	Frontal lobe	∨
Kragsterman et al., 2004	$N = 89$ CEA, GA	INVOS4100	Frontal lobe	∨
Kuroda et al., 1996b	$N = 62$ CEA, GA	OM100/110	Frontal lobe	∨
Laffey et al., 2000	$N = 22$ CEA, GA	INVOS3100	Frontal lobe	∨
Lee et al., 2008	$N = 1$ CEA, GA	INVOS4100	Frontal lobe	∨
de Letter et al., 1998	$N = 37$ CEA, GA	–	Frontal lobe	∨
McCleary et al., 1996	$N = 102$ CEA, GA	Critikon	Frontal lobe	∨
Manwaring et al., 2010	$N = 65$ CEA, LA/GA	INVOS	Frontal lobe	∨
Mason et al., 1994	$N = 104$ CEA, GA	NIRO500	Frontal lobe	∨
Mead et al., 1996	$N = 11$ CEA, GA	INVOS	Frontal lobe	∨
Matsumoto et al., 2009	$N = 16$ CEA	INVOS5100	Frontal lobe	∨
Mille et al., 2004	$N = 64$ CAS, LA	INVOS 3100/4100	Frontal lobe	∨
Moritz et al., 2007	$N = 594$ CEA, GA	INVOS3100	Frontal lobe	∨
Moritz et al., 2010	$N = 48$ CEA, LA	INVOS3100	Frontal lobe	∨
Nakamura et al., 2009	$N = 96$ CEA, LA/GA	INVOS3110A/ OMM2000	Frontal lobe/Global brain	∨
Ogasawara et al., 2003	$N = 1$ CEA	TOS96	Frontal lobe	∨
Pedrini et al., 2012	$N = 50$ CEA, GA	INVOS4100	Frontal lobe	∨
Pennekamp et al., 2012a	$N = 473$ CEA, GA	INVOS	Frontal lobe	∨
Pennekamp et al., 2012b	$N = 11$ CEA, GA	INVOS	Frontal lobe	∨
Pugliese et al., 2009	$N = 151$ CEA, GA	INVOS	Frontal lobe	∨
Rigamonti et al., 2005	$N = 40$ CEA, LA	INVOS4100	Frontal lobe	∨
Ritter et al., 2011	$N = 50$ CEA, LA	INVOS4100	Frontal lobe	∨

(Continued)

Table 1 | Continued

Paper	Patients	Apparatus	Intended tissue	Change in oxygenation
Samra et al., 1996	$N = 83$ CEA, LA	INVOS3100	Frontal lobe	∨
Samra et al., 2000	$N = 38$ CEA, LA	INVOS3100	Frontal lobe	∨
Samra et al., 1999	$N = 99$ CEA, LA	INVOS3100	Frontal lobe	∨
Sehic and Thomas, 2000	$N = 34$ CEA, LA	INVOS3100A	Frontal lobe	∨
Shang et al., 2011	$N = 1$ CEA, GA	DCS flow-oximeter	Frontal lobe	∨
Stilo et al., 2012	$N = 11$ CEA, GA	INVOS4100	Frontal lobe	∨
Stoneham et al., 2008	$N = 100$ CEA, LA	INVOS4100	Frontal lobe	∨
Takeda et al., 2000	$N = 16$ CEA, LA	INVOS3100	Frontal lobe	∨
Tambakis et al., 2011	$N = 24$ CEA	INVOS4100	Frontal lobe	∨
Uchino et al., 2012	$N = 56$ CEA, GA	INVOS5100C	Frontal lobe	∨
Vets et al., 2004	$N = 20$ CEA, GA	NIRS	Frontal lobe	∨
Williams et al., 1999	$N = 14$ CEA	Critikon2020	Frontal lobe	∨
Yamamoto et al., 2007	$N = 45$ CEA, LA	OM-220	Frontal lobe	∨
Zogogiannis et al., 2011	$N = 43$ CEA, GA	INVOS4100	Frontal lobe	∨

For changes in oxygenation during vascular surgical procedures see text for specific results. LA, local anesthesia; GA, general anesthesia. The full papers by Williams et al. (1994a,b,c) could not be retrieved. As these papers are among the first to report $rScO_2$ in patients undergoing CEA the papers are cited in the text but not in the table.

***Following 30 min acute normovolemic hemodilution decreased tissue oxygenation that reduced the hemoglobin concentration from 14.5 to 10.8 g/dl.*

****Increased tissue oxygenation following blood transfusion.*

*****Reduced tissue oxygenation following blood loss equivalent to 650 ml or 16% of the patients' blood volume.*

††Decreased cerebral oxygenation with aortic cross-clamping and following declamping increased oxygenation.

(Jeong et al., 2012). During surgery in the beach chair patients in sevoflurane anesthesia have higher internal jugular venous O_2 saturation ($SjvO_2$) than patients in propofol anesthesia (minimum $SjvO_2$ 63 vs. 42%), $rScO_2$ is similar in the two groups and $rScO_2$ and $SjvO_2$ correlate. As MAP also is higher with sevoflurane anesthesia, despite a less frequent use of vasopressors, the authors conclude that sevoflurane anesthesia may be a better choice in patients undergoing surgery in beach chair position (Jeong et al., 2012).

An influence of cerebral desaturation on the occurrence of POCD after shoulder surgery in the beach chair is evaluated by Salazar et al. (2013b). Based on a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score the authors conclude that POCD is almost identical in subjects with intraoperative cerebral desaturation compared to those in the cohort who did not (Salazar et al., 2013b). The findings are supported by Moerman et al. (2012) who report that neurological or cognitive dysfunction does not occur after surgery in the beach chair.

OTHER TYPES OF ORTHOPEDIC SURGERY

Major orthopedic surgery (hip surgery) reduces $rScO_2$ ≈10% below baseline, with esmolol induced hypotension, $rScO_2$ becomes even lower (Han et al., 2006) and also the NIRS-determined deoxygenated hemoglobin (Hb) concentration decreases (Yoshitani et al., 2005). During hip fracture repair $rScO_2$ <50 or 75% of baseline occurs in 38% of patients (Papadopoulos et al., 2012) and $rScO_2$ decreases independently of the anesthesia used (propofol vs. sevoflurane; ref. Yoshitani et al., 2005). During knee surgery $rScO_2$ remains stable (Song et al., 2012).

Before surgery neurocognitive dysfunction is associated to low $rScO_2$ (44%) (Tzimas et al., 2010) and in patients with cerebral desaturation during major orthopedic surgery the occurrence of

POCD is reported to increase (Papadopoulos et al., 2012; Lin et al., 2013). Following surgery for hip fracture, patients with POCD have lower intraoperative $rScO_2$ (55 vs. 65%) compared to non-POCD patients (Papadopoulos et al., 2012). In this study cognitive function was assessed by the MMSE preoperatively and on the 7th postoperative day and compared to baseline, a reduction of MMSE score by >2 points indicated POCD. Lin et al. (2013) used MMSE, digit span test, digit symbol substitution test, trail making test, verbal fluency test, and word recognition tests and it was noted that in patients with POCD the intraoperative $rScO_2$ drop (14 vs. 8%) was more marked compared to non-POCD patients (Lin et al., 2013). The authors suggest that an intraoperative decrease in $rScO_2$ max >11% is to be considered a warning signal for development of POCD (Lin et al., 2013).

UROLOGY

In patients undergoing robotic assisted prostactomy in the Trendelenburg position $rScO_2$ is reported to increase (Park et al., 2009; Kalmar et al., 2012). However, the elderly patient may demonstrate profound intraoperative desaturation (to 20% or more below baseline) (Burkhart et al., 2011). Also hemodilution may lower $rScO_2$ (Bundgaard-Nielsen et al., 2007b) and a reduction in $rScO_2$ correlates to development of hypotension (Burkhart et al., 2011). The use of phenylephrine to preserve MAP reduces $rScO_2$ and this effect is intensified by hypocapnia and blunted by hypercapnia (Meng et al., 2012). Importantly, $rScO_2$ remains unchanged after bolus ephedrine (Meng et al., 2011).

GYNAECOLOGICAL AND OBSTETRIC PROCEDURES

During gynecological laparoscopic procedures in the Trendelenburg position $rScO_2$ decreases from 66 to 57% with MAP at 80 mmHg (Lee et al., 2006). Different gas anesthesia (desflurane vs. sevoflurane) results in similar $rScO_2$ values and larger anesthetic depth increases $rScO_2$ (66 vs. 72%) (Fassoulaki et al., 2006). Also spinal anesthesia reduces $rScO_2$ (>5%) related to development of hypotension (Berlac and Rasmussen, 2005). The use of hyperbaric rather than isobaric bupivacaine for spinal anesthesia decreases HbO_2 (6 vs. 3 mmol/L) as also hypotension is more severe (Kondo et al., 2013). In contrast, tracheal extubation increases HbO_2 (Morimoto et al., 2000). The authors also demonstrate that compared with a control nicardipine and diltiazem inhibited an increase in MAP and further enhanced the increase in HbO_2 (Morimoto et al., 2000).

In a patient with an intraoperative reduction in $rScO_2$ to below 50% is reported to be the likely explanation for postoperative headache (Lee et al., 2006).

GASTRO-ABDOMINAL SURGERY

Laparoscopic cholecystectomy in the head-up position is reported to decrease HbO_2 even when MAP is maintained above 80 mmHg (Kitajima et al., 1998) and up to one-fifth of the patients present at least one $rScO_2$ value of less than 80% of baseline (Gipson et al., 2006). Even in the supine position, $rScO_2$ tends to be reduced while the head-down position maintains $rScO_2$ (Harrison, 2001). A lowered $rScO_2$ can be restored by intermittent sequential compression of the lower extremities (Kurukahvecioglu et al., 2008).

A 15% decrease in $rScO_2$ correlates with the blood loss (Green, 2007) and in the elderly patient minimum $rScO_2$ (49 vs. 55%), mean $rScO_2$ (61 vs. 66%) and area under curve $rScO_2$ are higher with interventions that improve $rScO_2$ (Casati et al., 2005). In liver patients high bilirubin (icterus) interfere with NIRS measurements (Madsen et al., 2000), however, an intraoperative decrease in $rScO_2$ by up to 13% correlates to release of neuron-specific enolase (Plachky et al., 2004). NIRS is also used for investigation of cerebral autoregulation during a liver transplantation (Nissen et al., 2009b; Zheng et al., 2012) and $rScO_2$ decreases markedly after clamping the caval vein (Plachky et al., 2004).

A possible relationship between intraoperative cerebral desaturation and development of POCD was first described in a case report (Madsen and Secher, 2000). In randomized clinical trial Casati et al. (2005) included a total of 122 patients from 5 participating hospitals randomly allocated to an intervention group (with a NIRS visible and $rScO_2$ maintained at =75% of preinduction values) or a control group. No differences in MMSE score were observed. However, at the seventh postoperative day those patients of the control group who had intraoperative desaturation showed lower value of MMSE (26 vs. 28) as compared with patients of the treatment group. Patients of the control group who had intraoperative desaturation also showed a longer hospital stay as compared with patients of the treatment group. These findings were confirmed by another study by Casati et al. (2007) and the authors further report that up to one in every four patients demonstrate cerebral desaturation. Furthermore, in patients with postoperative delirium intraoperative $rScO_2$ is lower compared to patients with no delirium (57 vs. 60%; ref. Morimoto et al., 2009).

VASCULAR SURGERY

Open aortic repair of an abdominal aortic aneurysm affects $rScO_2$ (Liu et al., 1999) with a reduction in proportion to the blood loss (Torella and McCollum, 2004) and hemodilution (Torella et al., 2002) while blood transfusions increase $rScO_2$ (Torella et al., 2003). Several report $rScO_2$ during carotid surgery (Williams et al., 1994a,b,c, 1999; Duncan et al., 1995; Kuroda et al., 1996a; Mead et al., 1996; Samra et al., 1996; Duffy et al., 1997; Beese et al., 1998; Carlin et al., 1998; de Letter et al., 1998; Fearn et al., 2000; Takeda et al., 2000; Kawada et al., 2002; Cuadra et al., 2003; Ogasawara et al., 2003; Vets et al., 2004; Komoribayashi et al., 2006; Yamamoto et al., 2007; Ishigaki et al., 2008; Lee et al., 2008; Stoneham et al., 2008; Kobayashi et al., 2009; Giustiniano et al., 2010; Moritz et al., 2010; Ali et al., 2011; Ritter et al., 2011; Pedrini et al., 2012; Uchino et al., 2012).

During CEA clamping the internal carotid artery (ICA) decreases ipsilateral $rScO_2$ (Williams et al., 1994a,b,c, 1999; Duncan et al., 1995; Mead et al., 1996; Samra et al., 1996; Duffy et al., 1997; Beese et al., 1998; Carlin et al., 1998; de Letter et al., 1998; Fearn et al., 2000; Takeda et al., 2000; Cuadra et al., 2003; Ogasawara et al., 2003; Vets et al., 2004; Komoribayashi et al., 2006; Yamamoto et al., 2007; Ishigaki et al., 2008; Lee et al., 2008; Stoneham et al., 2008; Kobayashi et al., 2009; Giustiniano et al., 2010; Moritz et al., 2010; Ali et al., 2011; Ritter et al., 2011; Pedrini et al., 2012; Uchino et al., 2012) corresponding to a drop in HbO_2 (Kuroda et al., 1996b; Cho et al., 1998; Shang et al., 2011) and

the contralateral $rScO_2$ remains largely unchanged (Samra et al., 1999). Clamping the external carotid artery may decrease $rScO_2$ 1–3% (Kuroda et al., 1996b; Samra et al., 1999; Fearn et al., 2000) and after ICA clamp a decrease in $rScO_2$ often exceeds 20% (Pedrini et al., 2012). An influence of anatomic irregularities in skull shape and cerebral venous drainage needs to be considered. In a case report it is described that inability to obtain a monitorable signal may be attributed to abnormal frontal sinus ipsilateral to the endarterectomy site (Sehic and Thomas, 2000). Another factor of importance is that diabetic patients are more likely to demonstrate a drop in $rScO_2$ >20% (Stilo et al., 2012).

With clamped ICA a change in $rScO_2$ also reflects a change in the transcranial doppler determined cerebral perfusion (Mason et al., 1994; Fearn et al., 2000; Grubhofer et al., 2000; Vets et al., 2004; Fassiadis et al., 2006; Pugliese et al., 2009; Shang et al., 2011) and also in the reperfusion phase changes in $rScO_2$ correlate to measures of CBF (Ogasawara et al., 2003; Matsumoto et al., 2009). Similarly, $rScO_2$ correlates to $SjvO_2$ (Williams et al., 1994b; Grubhofer et al., 1997; Espenell et al., 2010) and a correlation to stump pressure is also reported (Kragsterman et al., 2004; Yamamoto et al., 2007; Lee et al., 2008; Manwaring et al., 2010; Tambakis et al., 2011) so that a low stump (<40 mmHg) results in a large change in $rScO_2$ (Tambakis et al., 2011) but the relationship might be absent in a large series of patients (Pedrini et al., 2012). $rScO_2$ and systemic blood pressure correlate, with higher pressures leading to better oxygenation values (Williams et al., 1994c; Ritter et al., 2011). The use of multichannel NIRS with 8 lightsource fibers and 8 detectors providing 24 source-detector pairs supports that following application of ICA cross clamp, HbO_2, and Hb change in the border region between the right middle and posterior cerebral supply areas (Nakamura et al., 2009) with distinct changes in Hb and HbO_2 of the ipsilateral brain cortex (Kacprzak et al., 2012).

Oxygen breathing (Stoneham et al., 2008) and the use of ephedrine (Pennekamp et al., 2012a) increase $rScO_2$ while it declines following administration of phenylephrine (Pennekamp et al., 2012a). The most effective approach to increase $rScO_2$ during CEA, however, is to use a shunt (Cuadra et al., 2003; Ali et al., 2011; Ritter et al., 2011; Pedrini et al., 2012). Especially patients with $rScO_2$ drop >20% require shunting (Ritter et al., 2011; Stilo et al., 2012) and NIRS has a sensitivity of ≈75% and specificity ≈98% of the need for shunting (Ali et al., 2011; Ritter et al., 2011). The criterion for establishing a shunt is (i) a 20% drop in ipsilateral $rScO_2$ from baseline (Zogogiannis et al., 2011) or (ii) a change in $rScO_2$greater than 25% or a delta $rScO_2$ greater than 20% that is not improved within 3 min by increasing blood pressure (Pedrini et al., 2012), or (iii) a cut-off of 21 or 10% reduction from the baseline (Tambakis et al., 2011). In patients operated under cover of local anesthesia (LA), it is the awake testing procedure that determines when a shunt is needed (Stilo et al., 2012).

Neurological deterioration relates to a decrease in $rScO_2$ (Williams et al., 1999; Samra et al., 2000; Moritz et al., 2007) and the anesthetic approach might be important (McCleary et al., 1996; Moritz et al., 2010). In symptomatic patients $rScO_2$ decreases from 63 to 51% compared to a $rScO_2$ drop from 66 to 61% in non-symptomatic patients (Williams et al., 1999; Samra et al., 2000). About 10% of patients have neurologic changes after carotid clamping (Moritz et al., 2007). Indices of cerebral ischemia (amplitude transcranial motor evoked potentials, electroencephalographic evaluation, cortical somatosensory evoked potentials) correlate to $rScO_2$ (Beese et al., 1998; Rigamonti et al., 2005; Uchino et al., 2012) and $rScO_2$ needs to decrease >10% for cerebral ischemia to be detected by somatosensory evoked potentials (Duffy et al., 1997) or electroencephalography (Friedell et al., 2008).

Importantly, in patients with focal cerebral ischemia with an embolic event in the territory of the middle cerebral artery ipsilateral frontal lobe $rScO_2$ is unchanged (Laffey et al., 2000). However, a reduction in an ischemic ratio (the lowest $rScO_2$ value during clamping of the ICA divided by the mean $rScO_2$ value in the last 2 min before ICA clamping) predicts new neurological deficit following CEA (Kobayashi et al., 2009) and a large decrease in intraoperative $rScO_2$ reflects a change in cerebral metabolism (Espenell et al., 2010). The cerebral release of matrix metalloproteinase correlates to development of cerebral ischemia as determined by NIRS (Ishigaki et al., 2008). $rScO_2$ criteria for cerebral ischemia is (i) a $rScO_2$ drop of 10 index points from a stable baseline (ii) a $rScO_2$ decrease below an absolute value of 50%, (iii) a relative $rScO_2$ decrease by 20–25%, and (iv) an interhemispheric $rScO_2$ difference of >25% (Friedell et al., 2008). Using NIRS during CEA neurologica deficit is predicted 5–10 s before the clinical observation of neurological complications (Pugliese et al., 2009).

Postoperative neurological complications may rise following an early drop in $rScO_2$ by more than 20% (Mille et al., 2004) and $rScO_2$ reduction of at least 15% relates to neurologic, cardiac or renal postoperative complications (Rigamonti et al., 2005; Giustiniano et al., 2010). Thus a fall of larger than 10% from baseline $rScO_2$ is dangerous but less than 5% is safe (Takeda et al., 2000). The postoperative cerebral hyperperfusion syndrome (CHS) can also be predicted by the intraoperative change in $rScO_2$ during clamping and unclamping ICA (Cho et al., 1998; Komoribayashi et al., 2006). After declamping a change in $rScO_2$ >20% predicts CHS (Pennekamp et al., 2012b) and patients with CHS exhibit a larger increase in $rScO_2$ (Matsumoto et al., 2009).

DISCUSSION

The present study aimed (i) to determine the non-cardiac surgical procedures that provoke a reduction in $rScO_2$ and (ii) to evaluate whether an intraoperative reduction in $rScO_2$ influences postoperative outcome. A literature search was conducted and several articles were reviewed. The Results section provides an overview of different non-cardiac surgical procedures affecting $rScO_2$ and the included articles representing case reports, observational studies, interventional studies, and randomized clinical trials with inclusion of single patients up to a population of 594 patients. The studies also differ in terms of patient categories, interventions applied and the NIRS device used for the evaluation of $rScO_2$. Taken the heterogeneous material into consideration the included articles provide answer to the primary aim of the present study. Based on the Results section it is concluded that some but not all non-cardiac surgical procedures may decrease $rScO_2$. While $rScO_2$ appears to be maintained in

patients undergoing minor non-cardiac surgery such as mastectomy, $rScO_2$ is reported to decrease during surgery involving procedures such as the anti-Trendelenburg body position often used for shoulder surgery and laparoscopic surgery. Hip surgery, single lung ventilation in thoracic surgery, and clamped ICA also appear to be associated with a reduction of $rScO_2$.

Concerning the second aim of the present review, only a limited number of studies report that the occurrence of cerebral desaturation is linked to bad postoperative outcome: (i) a randomized clinical trial including elderly patients for major abdominal surgery suggests that in patients with intraoperative optimization of $rScO_2$ the occurrence of POCD and length of stay in hospital become reduced, (ii) a study on patients undergoing thoracic surgery reports an association between low $rScO_2$ and scores of postoperative complications, and (iii) low $rScO_2$ may predict POCD in patients undergoing thoracic surgery, major orthopedic surgery, and major abdominal surgery. Also in patients undergoing carotid endarterectomy low $rScO_2$coincides with measures of bad outcome: indices of cerebral ischemia during surgery and the occurrence of the CHS after surgery. However, pronounced intraoperative cerebral desaturation does not lead to POCD after shoulder surgery in the beach chair. Furthermore, an association between cerebral desaturation and outcome parameters such as acute kidney failure, postoperative wound infection, myocardial infarction remains to be established. So the overall conclusion is that the available evidence points toward an increase in the occurrence of POCD in patients with severe cerebral desaturation under certain types of non-cardiac surgery but more studies are needed to demonstrate a clear association between low $rScO_2$ and bad postoperative outcome.

In the studies supporting a potential association between $rScO_2$ and bad postoperative outcome, a 20–25% decline in $rScO_2$ appears to predict POCD and in accordance to the reviewed articles the recommendation is that in order to prevent reaching this potentially injurious level, a less extreme threshold of perhaps 10% should be an indicator for therapeutic intervention to raise cerebral O_2 saturation. Thus, with a NIRS probe attached to the forehead enables the anesthetist to follow changes in regional CBF changes both in local and global cerebral oxygenation can be monitored. The obtained value for tissue oxygenation reflects a balance between O_2 delivery and extraction measurements. Therefore factors influencing regional blood flow (Madsen and Secher, 1999; Boushel et al., 2001) such as hemoglobin concentration, blood volume, cardiac output, arterial hemoglobin O_2 saturation, and for the brain arterial carbon dioxide pressure ($PaCO_2$) need to be considered when NIRS is incorporated for clinical evaluations. For most of the studies included in the present review it is not obvious how such factors were controlled.

Importantly, an influence from the skin to the NIRS signal is not trivial. The NIRS devices used for clinical purposes provide light absorption into a depth of 3–4 cm. Extra-cranial tissue as indicated by dermal tissue flow, however, appears to contribute as much as 20% to $rScO_2$, at least with the use of two commonly applied NIRS systems (Sørensen, pers. commun.). For estimation of muscle oxygenation light only needs to traverse skin and subcutaneous tissue that may be 2–3 mm thick (Kjeld et al., 2014) but subcutaneous tissue may, obviously be vast in obese patients. The penetration depth for light is proportional to the emitter-detector distance (Germon et al., 1999) of importance for light to reach brain tissue. Forehead skin is relatively thin in both adipose and lean patients, but the frontal sinuses in addition to the superior sagittal veins need to be considered (Sehic and Thomas, 2000). Also forehead skin blood flow is supplied with blood from both the internal and external carotid arteries (Hove et al., 2006) and with a headband preventing blood to enter the scalp, the $rScO_2$ decreases (Davie and Grocott, 2012). This study clearly showed that three different NIRS devices weighed changes in skin flow differently of importance when NIRS is used to guide clinical interventions.

Vasopressor medication and its influence on NIRS deserve attention. Depending on the NIRS device used up to 1/3 of changes in $rScO_2$ e.g., in response to administration of noradrenaline can be accounted for by change in skin blood flow (Sørensen et al., 2012). Thus, the INVOS cerebral oximeter appears more sensitive to changes in skin blood flow compared to the Foresight cerebral oximeter (Davie and Grocott, 2012). This could explain why ephedrine does not change $rScO_2$ while strict α-adrenergic receptor stimulation such as treatment with norepinephrine (Brassard et al., 2009) or phenylephrine may decrease $rScO_2$. In the case with hypotension causing cerebral deoxygenation, however, raised pressure with vasopressor medication may result in increased $rScO_2$. When a low $rScO_2$ is the combined effect of hypotension and lowered central blood volume, the use of α_1-agonists such as phenylephrine may result in further cerebral desaturation due to a possible increase in cardiac afterload. Thus, a low cardiac output appears to influence CBF (van Lieshout et al., 2003) and phenylephrine might exert a different impact on cardiac output depending on preload to the heart (Cannesson et al., 2012). Furthermore, individual α- and β-adrenergic receptor sensitivity might be of importance and related to a genetic polymorphism (Snyder et al., 2006; Rokamp et al., 2013). When a vasopressor is administered the effect on $rScO_2$ depends on individual factors and the NIRS technology used.

It remains that $rScO_2$ responds to CO_2 (Madsen and Secher, 1999) implying a contribution from the cerebrum since skin (and muscle) blood flow does not demonstrate "CO_2 reactivity." For clinical interventions directed to protect $rScO_2$ it may, however, be less relevant whether the intervention is directed to address flow to the skin or the brain or both as long as the intervention improves postoperative outcome (Casati et al., 2005, 2007; Kazan et al., 2009; Slater et al., 2009; Papadopoulos et al., 2012; Stilo et al., 2012; Tang et al., 2012; Lin et al., 2013) including renal complications (Murkin et al., 2007) and wound infections (Ives et al., 2007). In addition, intraoperative severe cerebral desaturation may provoke postoperative vision loss (Pohl and Cullen, 2005; Roth, 2009). Thus, intraoperative $rScO_2$ is an index for the systemic circulation reflecting changes in blood flow to other organs than the brain as the skin and kidney (Murkin and Arango, 2009).

Obviously, MAP should not be allowed to decrease to a level below the lower limit of cerebral autoregulation (60 mmHg). However, vasodilatation and reduction in intravascular volume challenge $rScO_2$. While the spinal anesthesia induced vasodilatation causes only minor cerebral desaturation (Berlac and

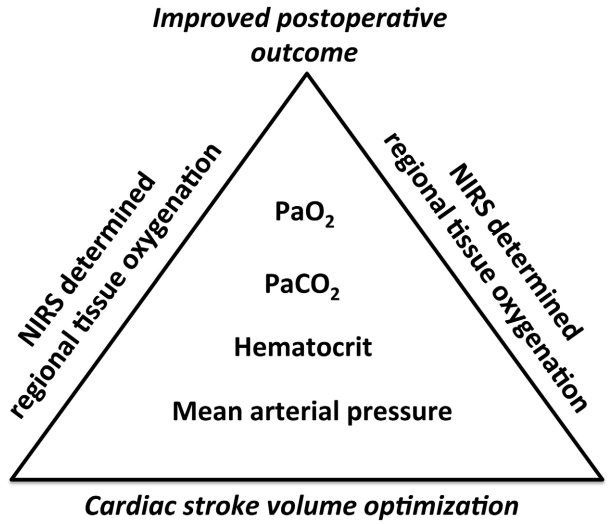


FIGURE 2 | A proposal for incorporation of near-infrared spectroscopy (NIRS) determined tissue in algorithms to maintain both central and peripheral blood flow in anesthesized patients. Cardiac stroke volume is optimized by fluid administration and according to individual adjusted levels for mean arterial pressure (MAP), hematocrit, arterial carbon dioxide pressure ($PaCO_2$), and arterial oxygen pressure (PaO_2) it is secured that rScO2 does not change >11% considered the warning signal for postoperative complications (Kondo et al., 2013).

Rasmussen, 2005), the decrease in $rScO_2$ is aggravated when hypotension is pronounced by the use of, e.g., hyperbaric bupivacaine (Kondo et al., 2013). On the other hand, the vasodilatation provoked by GA to minor surgery does not seem to affect $rScO_2$ (Nissen et al., 2009a) may be because an effect on CBF is outweighed by a reduction in cerebral metabolism. In contrast, when GA is combined with procedures reducing cardiac output such as the anti-Trendelenburg body positions or the use of β-receptor antagonists, $rScO_2$ decreases even at MAP at 80 mmHg (Lee et al., 2006).

The majority of papers included in this review did not include a measurement of cardiac output but one study did find that $rScO_2$ decreased 10% as cardiac output was reduced from 5 to 4 L/min (Lee et al., 2006). In addition, the use of phenylephrine reduces $rScO_2$ secondary to a drop in cardiac output while ephedrine raises MAP without an effect on cardiac output (Meng et al., 2011). Thus, as mentioned vasopressors appear to affect $rScO_2$ differently and before a vasopressor is used, it seems an advantage that the central blood volume is secured by optimization of, e.g., stroke volume or cardiac output by administration of fluid (Bundgaard-Nielsen et al., 2007b). Such so-called individualized goal directed fluid therapy reduces postoperative complications (Bundgaard-Nielsen et al., 2007a) as is the case for algorithms directed to maintain $rScO_2$ (Casati et al., 2005; Murkin et al., 2007; Slater et al., 2009). Which of the two recommendations to manage circulation during anesthesia is most profitable remains to be evaluated, but the algorithms used to support the circulation could be combined as illustrated in **Figure 2**. Here it is recommended that management of a patients under GA includes not only NIRS monitoring of the brain but also a determination of cardiac output that can be derived easily, both non-invasively and invasively from the use of, e.g., model flow technology (van Lieshout et al., 2003).

In conclusion, this review on the use of NIRS to monitor changes in cerebral oxygenation of patients scheduled for non-cardiac surgery indicates that while $rScO_2$ appears to be maintained in patients undergoing minor non-cardiac surgery such as mastectomy, $rScO_2$ may decrease during surgery involving procedures such as the anti-Trendelenburg body position often used for shoulder surgery and laparoscopic surgery. Hip surgery, single lung ventilation in thoracic surgery, and clamped ICA also appear to be associated with a reduction of $rScO_2$. An association of cerebral desaturation to postoperative outcome parameters such as acute kidney failure, postoperative wound infection, and myocardial infarction remains to be evaluated. After certain types of non-cardiac surgery severe cerebral desaturation might be associated with an increase in the occurrence of POCD.

ACKNOWLEDGMENTS

Henning B. Nielsen was funded by Rigshospitalet Research fund and Danish Agency for Science Technology and Innovation (271-08-0857).

REFERENCES

Ali, A. M., Green, D., Zayed, H., Halawa, M., El-Sakka, K., and Rashid, H. I. (2011). Cerebral monitoring in patients undergoing carotid endarterectomy using a triple assessment technique. *Interact. Cardiovasc. Thorac. Surg.* 12, 454–457. doi: 10.1510/icvts.2010.235598

Asgari, S., Röhrborn, H. J., Engelhorn, T., Fauser, B., and Stolke, D. (2003). Intraoperative measurement of cortical oxygen saturation and blood volume adjacent to cerebral arteriovenous malformations using near-infrared spectroscopy. *Neurosurgery* 52, 1298–1304. doi: 10.1227/01.NEU.0000064801.78895.86

Beese, U., Langer, H., Lang, W., and Dinkel, M. (1998). Comparison of near-infrared spectroscopy and somatosensory evoked potentials for the detection of cerebral ischemia during carotid endarterectomy. *Stroke* 29, 2032–2037. doi: 10.1161/01.STR.29.10.2032

Berlac, P. A., and Rasmussen, Y. H. (2005). Per-operative cerebral near-infrared spectroscopy (NIRS) predicts maternal hypotension during elective caesarean delivery in spinal anaesthesia. *Int. J. Obstet. Anesth.* 14, 26–31. doi: 10.1016/j.ijoa.2004.06.003

Boushel, R., Langberg, H., Olesen, J., Gonzales-Alonzo, J., Bülow, J., and Kjaer, M. (2001). Monitoring tissue oxygen availability with near infrared spectroscopy (NIRS) in health and disease. *Scand. J. Med. Sci. Sports* 11, 213–222. doi: 10.1034/j.1600-0838.2001.110404.x

Brassard, P., Seifert, T., and Secher, N. H. (2009). Is cerebral oxygenation negatively affected by infusion of norepinephrine in healthy subjects? *Br. J. Anaesth.* 102, 800–805. doi: 10.1093/bja/aep065

Bundgaard-Nielsen, M., Holte, K., Secher, N. H., and Kehlet, H. (2007a). Monitoring of peri-operative fluid administration by individualized goal-directed therapy. *Acta Anaesthesiol. Scand.* 51, 331–340. doi: 10.1111/j.1399-6576.2006.01221.x

Bundgaard-Nielsen, M., Ruhnau, B., Secher, N. H., and Kehlet, H. (2007b). Flow-related techniques for preoperative goal-directed fluid optimization. *Br. J. Anaesth.* 98, 38–44. doi: 10.1093/bja/ael287

Burkhart, C. S., Rossi, A., Dell-Kuster, S., Gamberini, M., Möckli, A., Siegemund, M., et al. (2011). Effect of age on intraoperative cerebrovascular autoregulation and near-infrared spectroscopy-derived cerebral oxygenation. *Br. J. Anaesth.* 107, 742–748. doi: 10.1093/bja/aer252

Calderon-Arnulphi, M., Alaraj, A., Amin-Hanjani, S., Mantulin, W. W., Polzonetti, C. M., Gratton, E., et al. (2007). Detection of cerebral ischemia in neurovascular surgery using quantitative frequency-domain near-infrared spectroscopy. *J. Neurosurg.* 106, 283–290. doi: 10.3171/jns.2007.106.2.283

Cannesson, M., Jian, Z., Chen, G., Vu, T. Q., and Hatib, F. (2012). Effects of phenylephrine on cardiac output and venous return depend on the position of the heart on the Frank-Starling relationship. *J. Appl. Physiol.* 113, 281–289. doi: 10.1152/japplphysiol.00126.2012

Carlin, R. E., McGraw, D. J., Calimlim, J. R., and Mascia, M. F. (1998). The use of near-infrared cerebral oximetry in awake carotid endarterectomy. *J. Clin. Anesth.* 10, 109–113. doi: 10.1016/S0952-8180(97)00252-3

Casati, A., Fanelli, G., Pietropaoli, P., Proietti, R., Tufano, R., Danelli, G., et al. (2005). Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth. Analg.* 101, 740–747. doi: 10.1213/01.ane.0000166974.96219.cd

Casati, A., Fanelli, G., Pietropaoli, P., Proietti, R., Tufano, R., and Montanini, S. (2007). Monitoring cerebral oxygen saturation in elderly patients undergoing general abdominal surgery: a prospective cohort study. *Eur. J. Anaesthesiol.* 24, 59–65. doi: 10.1017/S0265021506001025

Chenitz, K. B., and Lane-Fall, M. B. (2012). Decreased urine output and acute kidney injury in the postanesthesia care unit. *Anesthesiol. Clin.* 30, 513–526. doi: 10.1016/j.anclin.2012.07.004

Cho, H., Nemoto, E. M., Yonas, H., Balzer, J., and Sclabassi, R. J. (1998). Cerebral monitoring by means of oximetry and somatosensory evoked potentials during carotid endarterectomy. *J. Neurosurg.* 89, 533–538. doi: 10.3171/jns.1998.89.4.0533

Choi, S. H., Lee, S. J., Jung, Y. S., Shin, Y. S., Jun, D. B., Hwang, K. H., et al. (2008). Nitroglycerin- and nicardipine-induced hypotension does not affect cerebral oxygen saturation and postoperative cognitive function in patients undergoing orthognathic surgery. *J. Oral Maxillofac. Surg.* 66, 2104–2109. doi: 10.1016/j.joms.2008.06.041

Cuadra, S. A., Zwerling, J. S., Feuerman, M., Gasparis, A. P., and Hines, G. L. (2003). Cerebral oximetry monitoring during carotid endarterectomy: effect of carotid clamping and shunting. *Vasc. Endovascular Surg.* 37, 407–413. doi: 10.1177/153857440303700604

Davie, S. N., and Grocott, H. P. (2012). Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology* 116, 834–840. doi: 10.1097/ALN.0b013e31824c00d7

de Letter, J. A., Sie, H. T., Thomas, B. M., Moll, F. L., Algra, A., Eikelboom, B. C., et al. (1998). Near-infrared reflected spectroscopy and electroencephalography during carotid endarterectomy–in search of a new shunt criterion. *Neurol. Res.* 20, S23–S27.

Dippmann, C., Winge, S., and Nielsen, H. B. (2010). Severe cerebral desaturation during shoulder arthroscopy in the beach-chair position. *Arthroscopy* 26, S148–S150. doi: 10.1016/j.arthro.2010.03.012

Duffy, C. M., Manninen, P. H., Chan, A., and Kearns, C. F. (1997). Comparison of cerebral oximeter and evoked potential monitoring in carotid endarterectomy. *Can. J. Anaesth.* 44, 1077–1081. doi: 10.1007/BF03019229

Duncan, L. A., Ruckley, C. V., and Wildsmith, J. A. (1995). Cerebral oximetry: a useful monitor during carotid artery surgery. *Anaesthesia* 50, 1041–1045. doi: 10.1111/j.1365-2044.1995.tb05947.x

Espenell, A. E., McIntyre, I. W., Gulati, H., Girling, L. G., Wilkinson, M. F., Silvaggio, J. A., et al. (2010). Lactate flux during carotid endarterectomy under general anesthesia: correlation with various point-of-care monitors. *Can. J. Anaesth.* 57, 903–912. doi: 10.1007/s12630-010-9356-7

Fassiadis, N., Zayed, H., Rashid, H., and Green, D. W. (2006). Invos Cerebral Oximeter compared with the transcranial Doppler for monitoring adequacy of cerebral perfusion in patients undergoing carotid endarterectomy. *Int. Angiol.* 25, 401–406.

Fassoulaki, A., Kaliontzi, H., Petropoulos, G., and Tsaroucha, A. (2006). The effect of desflurane and sevoflurane on cerebral oximetry under steady-state conditions. *Anesth. Analg.* 102, 1830–1835. doi: 10.1213/01.ane.0000205739.37190.14

Fearn, S. J., Picton, A. J., Mortimer, A. J., Parry, A. D., and McCollum, C. N. (2000). The contribution of the external carotid artery to cerebral perfusion in carotid disease. *J. Vasc. Surg.* 31, 989–993. doi: 10.1067/mva.2000.104598

Fischer, G. W., Torrillo, T. M., Weiner, M. M., and Rosenblatt, M. A. (2009). The use of cerebral oximetry as a monitor of the adequacy of cerebral perfusion in a patient undergoing shoulder surgery in the beach chair position. *Pain Pract.* 9, 304–307. doi: 10.1111/j.1533-2500.2009.00282.x

Fodale, V., Di Pietro, R., Ferreri, F., Tescione, M., Russo, G., Santamaria, S., et al. (2006). The effect of peribulbar block with ropivacaine on bi-hemispheric cerebral oxygen saturation in aged patients. *Anaesthesia* 61, 764–767. doi: 10.1111/j.1365-2044.2006.04710.x

Friedell, M. L., Clark, J. M., Graham, D. A., Isley, M. R., and Zhang, X. F. (2008). Cerebral oximetry does not correlate with electroencephalography and somatosensory evoked potentials in determining the need for shunting during carotid endarterectomy. *J. Vasc. Surg.* 48, 601–606. doi: 10.1016/j.jvs.2008.04.065

Fuchs, G., Schwarz, G., Kulier, A., and Litscher, G. (2000). The influence of positioning on spectroscopic measurements of brain oxygenation. *J. Neurosurg. Anesthesiol.* 12, 75–80. doi: 10.1097/00008506-200004000-00001

Germon, T. J., Evans, P. D., Barnett, N. J., Wall, P., Manara, A. R., and Nelson, R. J. (1999). Cerebral near infrared spectroscopy: emitter-detector separation must be increased. *Br. J. Anaesth.* 82, 831–837. doi: 10.1093/bja/82.6.831

Gipson, C. L., Johnson, G. A., Fisher, R., Stewart, A., Giles, G., Johnson, J. O., et al. (2006). Changes in cerebral oximetry during peritoneal insufflation for laparoscopic procedures. *J. Minim. Access Surg.* 2, 67–72. doi: 10.4103/0972-9941.26651

Giustiniano, E., Alfano, A., Battistini, G. M., Gavazzeni, V., Spoto, M. R., and Cancellieri, F. (2010). Cerebral oximetry during carotid clamping: is blood pressure raising necessary? *J. Cardiovasc. Med. (Hagerstown)* 11, 522–528. doi: 10.2459/JCM.0b013e32833246e7

Green, D. W. (2007). A retrospective study of changes in cerebral oxygenation using a cerebral oximeter in older patients undergoing prolonged major abdominal surgery. *Eur. J. Anaesthesiol.* 24, 230–234. doi: 10.1017/S0265021506001645

Grubhofer, G., Lassnigg, A., Manlik, F., Marx, E., Trubel, W., and Hiesmayr, M. (1997). The contribution of extracranial blood oxygenation on near-infrared spectroscopy during carotid thrombendarterectomy. *Anaesthesia* 52, 116–120. doi: 10.1111/j.1365-2044.1997.20-az020.x

Grubhofer, G., Plöchl, W., Skolka, M., Czerny, M., Ehrlich, M., and Lassnigg, A. (2000). Comparing Doppler ultrasonography and cerebral oximetry as indicators for shunting in carotid endarterectomy. *Anesth. Analg.* 91, 1339–1344. doi: 10.1097/00000539-200012000-00006

Han, S. H., Bahk, J. H., Kim, J. H., Lim, Y. J., Park, C. D., Do, S. H., et al. (2006). The effect of esmolol-induced controlled hypotension in combination with acute normovolemic hemodilution on cerebral oxygenation. *Acta Anaesthesiol. Scand.* 50, 863–868. doi: 10.1111/j.1399-6576.2006.01048.x

Harrison, G. R. (2001). The effect of posture on cerebral oxygenation during abdominal surgery. *Anaesthesia* 56, 1181–1184. doi: 10.1046/j.1365-2044.2001.02084.x

Hemmerling, T. M., Bluteau, M. C., Kazan, R., and Bracco, D. (2008). Significant decrease of cerebral oxygen saturation during single-lung ventilation measured using absolute oximetry. *Br. J. Anaesth.* 101, 870–875. doi: 10.1093/bja/aen275

Hove, J. D., Rosenberg, I., Sejrsen, P., Hove, K. D., and Secher, N. H. (2006). Supraorbital cutaneous blood flow rate during carotid endarterectomy. *Clin. Physiol. Funct. Imaging* 26, 323–327. doi: 10.1111/j.1475-097X.2006.00697.x

Ishigaki, D., Ogasawara, K., Suga, Y., Saito, H., Chida, K., Kobayashi, M., et al. (2008). Concentration of matrix metalloproteinase-9 in the jugular bulb during carotid endarterectomy correlates with severity of intraoperative cerebral ischemia. *Cerebrovasc. Dis.* 25, 587–592. doi: 10.1159/000134375

Ives, C. L., Harrison, D. K., and Stansby, G. S. (2007). Prediction of surgical site infections after major surgery using visible and near-infrared spectroscopy. *Adv. Exp. Med. Biol.* 599, 37–44. doi: 10.1007/978-0-387-71764-7_6

Jeong, H., Jeong, S., Lim, H. J., Lee, J., and Yoo, K. Y. (2012). Cerebral oxygen saturation measured by near-infrared spectroscopy and jugular venous bulb oxygen saturation during arthroscopic shoulder surgery in beach chair position under sevoflurane-nitrous oxide or propofol-remifentanil anesthesia. *Anesthesiology* 116, 1047–1056. doi: 10.1097/ALN.0b013e31825154d2

Kacprzak, M., Liebert, A., Staszkiewicz, W., Gabrusiewicz, A., Sawosz, P., Madycki, G., et al. (2012). Application of a time-resolved optical brain imager for monitoring cerebral oxygenation during carotid surgery. *J. Biomed. Opt.* 17, 016002. doi: 10.1117/1.JBO.17.1.016002

Kalmar, A. F., Dewaele, F., Foubert, L., Hendrickx, J. F., Heeremans, E. H., Struys, M. M., et al. (2012). Cerebral haemodynamic physiology during steep Trendelenburg position and CO_2 pneumoperitoneum. *Br. J. Anaesth.* 108, 478–484. doi: 10.1093/bja/aer448

Kawada, T., Oki, A., Iyano, K., Bitou, A., Okada, Y., Matsuo, Y., et al. (2002). Surgical treatment of atherosclerotic and dysplastic aneurysms of the extracranial internal carotid artery. *Ann. Thorac. Cardiovasc. Surg.* 8, 183–187.

Kazan, R., Bracco, D., and Hemmerling, T. M. (2009). Reduced cerebral oxygen saturation measured by absolute cerebral oximetry during thoracic surgery correlates with postoperative complications. *Br. J. Anaesth.* 103, 811–816. doi: 10.1093/bja/aep309

Kitajima, T., Okuda, Y., Yamaguchi, S., Takanishi, T., Kumagai, M., and Ido, K. (1998). Response of cerebral oxygen metabolism in the head-up position during laparoscopic cholecystectomy. *Surg. Laparosc. Endosc.* 8, 449–452. doi: 10.1097/00019509-199812000-00010

Kjeld, T., Rasmussen, M. R., Jattu, T., Nielsen, H. B., and Secher, N. H. (2014). Ischemic preconditioning of one forearm enhances static and dynamic apnea. *Med. Sci. Sports Exerc.* 46, 151–155. doi: 10.1249/MSS.0b013e3182a4090a

Ko, S. H., Cho, Y. W., Park, S. H., Jeong, J. G., Shin, S. M., and Kang, G. (2012). Cerebral oxygenation monitoring of patients during arthroscopic shoulder surgery in the sitting position. *Korean J. Anesthesiol.* 63, 297–301. doi: 10.4097/kjae.2012.63.4.297

Kobayashi, M., Ogasawara, K., Suga, Y., Chida, K., Yoshida, K., Otawara, Y., et al. (2009). Early post-ischemic hyperemia on transcranial cerebral oxygen saturation monitoring in carotid endarterectomy is associated with severity of cerebral ischemic insult during carotid artery clamping. *Neurol. Res.* 31, 728–733. doi: 10.1179/174313209X382269

Komoribayashi, N., Ogasawara, K., Kobayashi, M., Saitoh, H., Terasaki, K., Inoue, T., et al. (2006). Cerebral hyperperfusion after carotid endarterectomy is associated with preoperative hemodynamic impairment and intraoperative cerebral ischemia. *J. Cereb. Blood Flow Metab.* 26, 878–884. doi: 10.1038/sj.jcbfm.9600244

Kondo, Y., Sakatani, K., Hirose, N., Maeda, T., Kato, J., Ogawa, S., et al. (2013). Effect of spinal anesthesia for elective cesarean section on cerebral blood oxygenation changes: comparison of hyperbaric and isobaric bupivacaine. *Adv. Exp. Med. Biol.* 765, 109–114. doi: 10.1007/978-1-4614-4989-8_16

Kragsterman, B., Pärsson, H., and Bergqvist, D. (2004). Local haemodynamic changes during carotid endarterectomy–the influence on cerebral oxygenation. *Eur. J. Vasc. Endovasc. Surg.* 27, 398–402. doi: 10.1016/j.ejvs.2004.01.024

Kuroda, S., Houkin, K., Abe, H., Hoshi, Y., and Tamura, M. (1996b). Near-infrared monitoring of cerebral oxygenation state during carotid endarterectomy. *Surg. Neurol.* 45, 450–458. doi: 10.1016/0090-3019(95)00463-7

Kuroda, S., Houkin, K., Abe, H., and Tamura, M. (1996a). Cerebral hemodynamic changes during carotid artery balloon occlusion monitored by near-infrared spectroscopy. *Neurol. Med. Chir. (Tokyo)* 36, 78–86. doi: 10.2176/nmc.36.78

Kurukahvecioglu, O., Sare, M., Karamercan, A., Gunaydin, B., Anadol, Z., and Tezel, E. (2008). Intermittent pneumatic sequential compression of the lower extremities restores the cerebral oxygen saturation during laparoscopic cholecystectomy. *Surg. Endosc.* 22, 907–911. doi: 10.1007/s00464-007-9505-4

Laffey, J. G., Mehigan, D., and Boylan, J. F. (2000). Postoperative neurologic deficit despite normal cerebral oximetry during carotid endarterectomy. *J. Clin. Anesth.* 12, 573–574. doi: 10.1016/S0952-8180(00)00208-7

Lee, J. H., Min, K. T., Chun, Y. M., Kim, E. J., and Choi, S. H. (2011). Effects of beach-chair position and induced hypotension on cerebral oxygen saturation in patients undergoing arthroscopic shoulder surgery. *Arthroscopy* 27, 889–894. doi: 10.1016/j.arthro.2011.02.027

Lee, J. R., Lee, P. B., Do, S. H., Jeon, Y. T., Lee, J. M., Hwang, J. Y., et al. (2006). The effect of gynaecological laparoscopic surgery on cerebral oxygenation. *J. Int. Med. Res.* 34, 531–536. doi: 10.1177/147323000603400511

Lee, T. S., Hines, G. L., and Feuerman, M. (2008). Significant correlation between cerebral oximetry and carotid stump pressure during carotid endarterectomy. *Ann. Vasc. Surg.* 22, 58–62. doi: 10.1016/j.avsg.2007.07.022

Lin, R., Zhang, F., Xue, Q., and Yu, B. (2013). Accuracy of regional cerebral oxygen saturation in predicting postoperative cognitive dysfunction after total hip arthroplasty: regional cerebral oxygen saturation predicts POCD. *J. Arthroplasty* 28, 494–497. doi: 10.1016/j.arth.2012.06.041

Liu, G., Burcev, I., Pott, F., Ide, K., Horn, A., and Secher, N. H. (1999). Middle cerebral artery flow velocity and cerebral oxygenation during abdominal aortic surgery. *Anaesth. Intensive Care* 27, 148–153.

Lovell, A. T., Marshall, A. C., Elwell, C. E., Smith, M., and Goldstone, J. C. (2000). Changes in cerebral blood volume with changes in position in awake and anesthetized subjects. *Anesth. Analg.* 90, 372–376. doi: 10.1097/00000539-200002000-00025

Madsen, P., Lyck, F., Pedersen, M., Olesen, H. L., Nielsen, H. B., and Secher, N. H. (1995). Brain and muscle oxygen saturation during head-up-tilt-induced central hypovolaemia in humans. *Clin. Physiol.* 15, 523–533. doi: 10.1111/j.1475-097X.1995.tb00541.x

Madsen, P. L., and Secher, N. H. (1999). Near-infrared oximetry of the brain. *Prog. Neurobiol.* 58, 541–560. doi: 10.1016/S0301-0082(98)00093-8

Madsen, P. L., and Secher, N. H. (2000). Postoperative confusion preceded by decreased frontal lobe haemoglobin oxygen saturation. *Anaesth. Intensive Care* 28, 308–310.

Madsen, P. L., Skak, C., Rasmussen, A., and Secher, N. H. (2000). Interference of cerebral near-infrared oximetry in patients with icterus. *Anesth. Analg.* 90, 489–493. doi: 10.1097/00000539-200002000-00046

Manwaring, M. L., Durham, C. A., McNally, M. M., Agle, S. C., Parker, F. M., and Stoner, M. C. (2010). Correlation of cerebral oximetry with internal carotid artery stump pressures in carotid endarterectomy. *Vasc. Endovascular Surg.* 44, 252–256. doi: 10.1177/1538574410361785

Mason, P. F., Dyson, E. H., Sellars, V., and Beard, J. D. (1994). The assessment of cerebral oxygenation during carotid endarterectomy utilising near infrared spectroscopy. *Eur. J. Vasc. Surg.* 8, 590–594. doi: 10.1016/S0950-821X(05)80596-1

Matsumoto, S., Nakahara, I., Higashi, T., Iwamuro, Y., Watanabe, Y., Takahashi, K., et al. (2009). Near-infrared spectroscopy in carotid artery stenting predicts cerebral hyperperfusion syndrome. *Neurology* 72, 1512–1518. doi: 10.1212/WNL.0b013e3181a2e846

McCleary, A. J., Dearden, N. M., Dickson, D. H., Watson, A., and Gough, M. J. (1996). The differing effects of regional and general anaesthesia on cerebral metabolism during carotid endarterectomy. *Eur. J. Vasc. Endovasc. Surg.* 12, 173–181. doi: 10.1016/S1078-5884(96)80103-1

Mead, G. E., Lardi, A. M., Bonner, J. A., Williams, I. M., Hardy, S. C., and McCollum, C. N. (1996). Neutrophil activation in jugular venous blood during carotid endarterectomy. *Eur. J. Vasc. Endovasc. Surg.* 11, 210–213. doi: 10.1016/S1078-5884(96)80054-2

Meng, L., Cannesson, M., Alexander, B. S., Yu, Z., Kain, Z. N., Cerussi, A. E., et al. (2011). Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. *Br. J. Anaesth.* 107, 209–217. doi: 10.1093/bja/aer150

Meng, L., Gelb, A. W., Alexander, B. S., Cerussi, A. E., Tromberg, B. J., Yu, Z., et al. (2012). Impact of phenylephrine administration on cerebral tissue oxygen saturation and blood volume is modulated by carbon dioxide in anaesthetized patients. *Br. J. Anaesth.* 108, 815–822. doi: 10.1093/bja/aes023

Mille, T., Tachimiri, M. E., Klersy, C., Ticozzelli, G., Bellinzona, G., Blangetti, I., et al. (2004). Near infrared spectroscopy monitoring during carotid endarterectomy: which threshold value is critical? *Eur. J. Vasc. Endovasc. Surg.* 27, 646–650. doi: 10.1016/j.ejvs.2004.02.012

Moerman, A. T., De Hert, S. G., Jacobs, T. F., De Wilde, L. F., and Wouters, P. F. (2012). Cerebral oxygen desaturation during beach chair position. *Eur. J. Anaesthesiol.* 29, 82–87. doi: 10.1097/EJA.0b013e328348ca18

Morimoto, Y., Kemmotsu, O., Gando, S., Shibano, T., and Shikama, H. (2000). The effect of calcium channel blockers on cerebral oxygenation during tracheal extubation. *Anesth. Analg.* 91, 347–352. doi: 10.1097/00000539-200008000-00021

Morimoto, Y., Yoshimura, M., Utada, K., Setoyama, K., Matsumoto, M., and Sakabe, T. (2009). Prediction of postoperative delirium after abdominal surgery in the elderly. *J. Anesth.* 23, 51–56. doi: 10.1007/s00540-008-0688-1

Moritz, S., Kasprzak, P., Arlt, M., Taeger, K., and Metz, C. (2007). Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy: a comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. *Anesthesiology* 107, 563–569. doi: 10.1097/01.anes.0000281894.69422.ff

Moritz, S., Schmidt, C., Bucher, M., Wiesenack, C., Zimmermann, M., Schebesch, K. M., et al. (2010). Neuromonitoring in carotid surgery: are the results obtained in awake patients transferable to patients under sevoflurane/fentanyl anesthesia? *J. Neurosurg. Anesthesiol.* 22, 288–295. doi: 10.1097/ANA.0b013e3181e16e14

Murkin, J. M., Adams, S. J., Novick, R. J., Quantz, M., Bainbridge, D., Iglesias, I., et al. (2007). Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesth. Analg.* 104, 51–58. doi: 10.1213/01.ane.0000246814.29362.f4

Murkin, J. M., and Arango, M. (2009). Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br. J. Anaesth.* 103, i3–i13. doi: 10.1093/bja/aep299

Murphy, G. S., Szokol, J. W., Marymont, J. H., Greenberg, S. B., Avram, M. J., Vender, J. S., et al. (2010). Cerebral oxygen desaturation events assessed by near-infrared spectroscopy during shoulder arthroscopy in the beach

chair and lateral decubitus positions. *Anesth. Analg.* 111, 496–505. doi: 10.1213/ANE.0b013e3181e33bd9

Nakamura, S., Kano, T., Sakatani, K., Hoshino, T., Fujiwara, N., Murata, Y., et al. (2009). Optical topography can predict occurrence of watershed infarction during carotid endarterectomy: technical case report. *Surg. Neurol.* 71, 540–542. doi: 10.1016/j.surneu.2007.11.012

Nissen, P., Brassard, P., Jørgensen, T. B., and Secher, N. H. (2010). Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. *Neurocrit. Care* 12, 17–23. doi: 10.1007/s12028-009-9313-x

Nissen, P., Pacino, H., Frederiksen, H. J., Novovic, S., and Secher, N. H. (2009b). Near-infrared spectroscopy for evaluation of cerebral autoregulation during orthotopic liver transplantation. *Neurocrit. Care* 11, 235–241. doi: 10.1007/s12028-009-9226-8

Nissen, P., van Lieshout, J. J., Nielsen, H. B., and Secher, N. H. (2009a). Frontal lobe oxygenation is maintained during hypotension following propofol-fentanyl anesthesia. *AANA J.* 77, 271–276.

Ogasawara, K., Konno, H., Yukawa, H., Endo, H., Inoue, T., and Ogawa, A. (2003). Transcranial regional cerebral oxygen saturation monitoring during carotid endarterectomy as a predictor of postoperative hyperperfusion. *Neurosurgery* 53, 309–314. doi: 10.1227/01.NEU.0000073547.86747.F3

Ono, M., Zheng, Y., Joshi, B., Sigl, J. C., and Hogue, C. W. (2013). Validation of a stand-alone near-infrared spectroscopy system for monitoring cerebral autoregulation during cardiac surgery. *Anesth. Analg.* 116, 198–204. doi: 10.1213/ANE.0b013e318271fb10

Paisansathan, C., Hoffman, W. E., Gatto, R. G., Baughman, V. L., Mueller, M., and Charbel, F. T. (2007). Increased brain oxygenation during intubation-related stress. *Eur. J. Anaesthesiol.* 24, 1016–1020. doi: 10.1017/S0265021507000567

Papadopoulos, G., Karanikolas, M., Liarmakopoulou, A., Papathanakos, G., Korre, M., and Beris, A. (2012). Cerebral oximetry and cognitive dysfunction in elderly patients undergoing surgery for hip fractures: a prospective observational study. *Open Orthop. J.* 6, 400–405. doi: 10.2174/1874325001206010400

Park, E. Y., Koo, B. N., Min, K. T., and Nam, S. H. (2009). The effect of pneumoperitoneum in the steep Trendelenburg position on cerebral oxygenation. *Acta Anaesthesiol. Scand.* 53, 895–899. doi: 10.1111/j.1399-6576.2009.01991.x

Pedrini, L., Magnoni, F., Sensi, L., Pisano, E., Ballestrazzi, M. S., Cirelli, M. R., et al. (2012). Is near-infrared spectroscopy a reliable method to evaluate clamping ischemia during carotid surgery? *Stroke Res. Treat.* 2012, 156975. doi: 10.1155/2012/156975

Pennekamp, C. W., Bots, M. L., Kappelle, L. J., Moll, F. L., and de Borst, G. J. (2009). The value of near-infrared spectroscopy measured cerebral oximetry during carotid endarterectomy in perioperative stroke prevention. A review. *Eur. J. Vasc. Endovasc. Surg.* 38, 539–545. doi: 10.1016/j.ejvs.2009.07.008

Pennekamp, C. W., Immink, R. V., den Ruijter, H. M., Kappelle, L. J., Ferrier, C. M., Bots, M. L., et al. (2012b). Near-infrared spectroscopy can predict the onset of cerebral hyperperfusion syndrome after carotid endarterectomy. *Cerebrovasc. Dis.* 34, 314–321. doi: 10.1159/000343229

Pennekamp, C. W., Immink, R. V., Moll, F. L., Buhre, W. F., and de Borst, G. J. (2012a). Differential effect of phenylephrine and ephedrine on cerebral haemodynamics before carotid cross-clamping during carotid endarterectomy. *Br. J. Anaesth.* 109, 831–833. doi: 10.1093/bja/aes370

Pennekamp, C. W., Moll, F. L., and de Borst, G. J. (2011). The potential benefits and the role of cerebral monitoring in carotid endarterectomy. *Curr. Opin. Anaesthesiol.* 24, 693–697. doi: 10.1097/ACO.0b013e32834c7aa1

Plachky, J., Hofer, S., Volkmann, M., Martin, E., Bardenheuer, H. J., and Weigand, M. A. (2004). Regional cerebral oxygen saturation is a sensitive marker of cerebral hypoperfusion during orthotopic liver transplantation. *Anesth. Analg.* 99, 344–349. doi: 10.1213/01.ANE.0000124032.31843.61

Pohl, A., and Cullen, D. J. (2005). Cerebral ischemia during shoulder surgery in the upright position: a case series. *J. Clin. Anesth.* 17, 463–469. doi: 10.1016/j.jclinane.2004.09.012

Pugliese, F., Ruberto, F., Tosi, A., Martelli, S., Bruno, K., Summonti, D., et al. (2009). Regional cerebral saturation versus transcranial Doppler during carotid endarterectomy under regional anaesthesia. *Eur. J. Anaesthesiol.* 26, 643–647. doi: 10.1097/EJA.0b013e32832b89c2

Rigamonti, A., Scandroglio, M., Minicucci, F., Magrin, S., Carozzo, A., and Casati, A. (2005). A clinical evaluation of near-infrared cerebral oximetry in the awake patient to monitor cerebral perfusion during carotid endarterectomy. *J. Clin. Anesth.* 17, 426–430. doi: 10.1016/j.jclinane.2004.09.007

Ritter, J. C., Green, D., Slim, H., Tiwari, A., Brown, J., and Rashid, H. (2011). The role of cerebral oximetry in combination with awake testing in patients undergoing carotid endarterectomy under local anaesthesia. *Eur. J. Vasc. Endovasc. Surg.* 41, 599–605. doi: 10.1016/j.ejvs.2010.12.009

Rokamp, K. Z., Staalsoe, J. M., Gartmann, M., Sletgaard, A., Nordsborg, N. B., Secher, N. H., et al. (2013). G16R single nucleotide polymorphism but not haplotypes of the β(2)-adrenergic receptor gene alters cardiac output in humans. *Clin. Sci.* 125, 191–198. doi: 10.1042/CS20120555

Roth, S. (2009). Perioperative visual loss: what do we know, what can we do? *Br. J. Anaesth.* 103, i31–i40. doi: 10.1093/bja/aep295

Salazar, D., Sears, B. W., Aghdasi, B., Only, A., Francois, A., Tonino, P., et al. (2013a). Cerebral desaturation events during shoulder arthroscopy in the beach chair position: patient risk factors and neurocognitive effects. *J. Shoulder Elbow Surg.* 22, 1228–1235. doi: 10.1016/j.jse.2012.12.036

Salazar, D., Sears, B. W., Andre, J., Tonino, P., and Marra, G. (2013b). Cerebral desaturation during shoulder arthroscopy: a prospective observational study. *Clin. Orthop. Relat. Res.* 471, 4027–4034. doi: 10.1007/s11999-013-2987-6

Samra, S. K., Dorje, P., Zelenock, G. B., and Stanley, J. C. (1996). Cerebral oximetry in patients undergoing carotid endarterectomy under regional anesthesia. *Stroke* 27, 49–55. doi: 10.1161/01.STR.27.1.49

Samra, S. K., Dy, E. A., Welch, K., Dorje, P., Zelenock, G. B., and Stanley, J. C. (2000). Evaluation of a cerebral oximeter as a monitor of cerebral ischemia during carotid endarterectomy. *Anesthesiology* 93, 964–970. doi: 10.1097/00000542-200010000-00015

Samra, S. K., Stanley, J. C., Zelenock, G. B., and Dorje, P. (1999). An assessment of contributions made by extracranial tissues during cerebral oximetry. *J. Neurosurg. Anesthesiol.* 11, 1–5. doi: 10.1097/00008506-199901000-00001

Sehic, A., and Thomas, M. H. (2000). Cerebral oximetry during carotid endarterectomy: signal failure resulting from large frontal sinus defect. *J. Cardiothorac. Vasc. Anesth.* 14, 444–446. doi: 10.1053/jcan.2000.7946

Shang, Y., Cheng, R., Dong, L., Ryan, S. J., Saha, S. P., and Yu, G. (2011). Cerebral monitoring during carotid endarterectomy using near-infrared diffuse optical spectroscopies and electroencephalogram. *Phys. Med. Biol.* 56, 3015–3032. doi: 10.1088/0031-9155/56/10/008

Slater, J. P., Guarino, T., Stack, J., Vinod, K., Bustami, R. T., Brown, J. M. 3rd., et al. (2009). Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. *Ann. Thorac. Surg.* 87, 36–44. doi: 10.1016/j.athoracsur.2008.08.070

Snyder, E. M., Beck, K. C., Dietz, N. M., Eisenach, J. H., Joyner, M. J., Turner, S. T., et al. (2006). Arg16Gly polymorphism of the beta2-adrenergic receptor is associated with differences in cardiovascular function at rest and during exercise in humans. *J. Physiol.* 15, 121–130. doi: 10.1113/jphysiol.2005.098558

Song, I., Kim, D. Y., and Kim, Y. J. (2012). The effect of tourniquet deflation on hemodynamics and regional cerebral oxygen saturation in aged patients undergoing total knee replacement surgery. *Korean J. Anesthesiol.* 63, 425–430. doi: 10.4097/kjae.2012.63.5.425

Sørensen, H., Secher, N. H., Siebenmann, C., Nielsen, H. B., Kohl-Bareis, M., Lundby, C., et al. (2012). Cutaneous vasoconstriction affects near-infrared spectroscopy determined cerebral oxygen saturation during administration of norepinephrine. *Anesthesiology* 117, 263–270. doi: 10.1097/ALN.0b013e3182605afe

Sørensen, L. T. (2012). Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. *Ann. Surg.* 255, 1069–1079. doi: 10.1097/SLA.0b013e31824f632d

Stilo, F., Spinelli, F., Martelli, E., Pipitó, N., Barillà, D., De Caridi, G., et al. (2012). The sensibility and specificity of cerebral oximetry, measured by INVOS - 4100, in patients undergoing carotid endarterectomy compared with awake testing. *Minerva Anestesiol.* 78, 1126–1135.

Stoneham, M. D., Lodi, O., de Beer, T. C., and Sear, J. W. (2008). Increased oxygen administration improves cerebral oxygenation in patients undergoing awake carotid surgery. *Anesth. Analg.* 107, 1670–1675. doi: 10.1213/ane.0b013e318184d6c3

Takeda, N., Fujita, K., Katayama, S., and Tamaki, N. (2000). Cerebral oximetry for the detection of cerebral ischemia during temporary carotid artery occlusion. *Neurol. Med. Chir. (Tokyo).* 40, 557–562. doi: 10.2176/nmc.40.557

Tambakis, C. L., Papadopoulos, G., Sergentanis, T. N., Lagos, N., Arnaoutoglou, E., Labropoulos, N., et al. (2011). Cerebral oximetry and stump pressure as indicators for shunting during carotid endarterectomy: comparative evaluation. *Vascular* 19, 187–194. doi: 10.1258/vasc.2010.oa0277

Tang, L., Kazan, R., Taddei, R., Zaouter, C., Cyr, S., and Hemmerling, T. M. (2012). Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction. *Br. J. Anaesth.* 108, 623–629. doi: 10.1093/bja/aer501

Tange, K., Kinoshita, H., Minonishi, T., Hatakeyama, N., Matsuda, N., Yamazaki, M., et al. (2010). Cerebral oxygenation in the beach chair position before and during general anesthesia. *Minerva Anestesiol.* 76, 485–490.

Tobias, J. D., Johnson, G. A., Rehman, S., Fisher, R., and Caron, N. (2008). Cerebral oxygenation monitoring using near infrared spectroscopy during one-lung ventilation in adults. *J. Minim. Access Surg.* 4, 104–107. doi: 10.4103/0972-9941.45206

Torella, F., Haynes, S. L., and McCollum, C. N. (2002). Cerebral and peripheral near-infrared spectroscopy: an alternative transfusion trigger? *Vox Sang.* 83, 254–257. doi: 10.1046/j.1423-0410.2002.00223.x

Torella, F., Haynes, S. L., and McCollum, C. N. (2003). Cerebral and peripheral oxygen saturation during red cell transfusion. *J. Surg. Res.* 110, 217–221. doi: 10.1016/S0022-4804(03)00037-4

Torella, F., and McCollum, C. N. (2004). Regional haemoglobin oxygen saturation during surgical haemorrhage. *Minerva Med.* 95, 461–467.

Tzimas, P., Liarmakopoulou, A., Arnaoutoglou, H., and Papadopoulos, G. (2010). Importance of perioperative monitoring of cerebral tissue saturation in elderly patients: an interesting case. *Minerva Anestesiol.* 76, 232–235.

Uchino, H., Nakamura, T., Kuroda, S., Houkin, K., Murata, J., and Saito, H. (2012). Intraoperative dual monitoring during carotid endarterectomy using motor evoked potentials and near-infrared spectroscopy. *World Neurosurg.* 78, 651–657. doi: 10.1016/j.wneu.2011.10.039

van Lieshout, J. J., Toska, K., van Lieshout, E. J., Eriksen, M., Walløe, L., and Wesseling, K. H. (2003). Beat-to-beat noninvasive stroke volume from arterial pressure and Doppler ultrasound. *Eur. J. Appl. Physiol.* 90, 131–137. doi: 10.1007/s00421-003-0901-8

Van Lieshout, J. J., Wieling, W., Karemaker, J. M., and Secher, N. H. (2003). Syncope, cerebral perfusion, and oxygenation. *J. Appl. Physiol.* 94, 833–848. doi: 10.1152/japplphysiol.00260.2002

Vets, P., ten Broecke, P., Adriaensen, H., Van Schil, P., and De Hert, S. (2004). Cerebral oximetry in patients undergoing carotid endarterectomy: preliminary results. *Acta Anaesthesiol. Belg.* 55, 215–220.

Williams, D. J., Laws, P., Imray, C., Lambert, A. W., and Horrocks, M. (1999). Vascular surgical society of Great Britain and Ireland: near-infrared spectroscopic monitoring of patients undergoing carotid endarterectomy under locoregional anaesthesia. *Br. J. Surg.* 86, 692. doi: 10.1046/j.1365-2168.1999.0692b.x

Williams, I. M., Picton, A., Farrell, A., Mead, G. E., Mortimer, A. J., and McCollum, C. N. (1994a). Light-reflective cerebral oximetry and jugular bulb venous oxygen saturation during carotid endarterectomy. *Br. J. Surg.* 81, 1291–1295. doi: 10.1002/bjs.1800810911

Williams, I. M., Picton, A., Hardy, S. C., Mortimer, A. J., and McCollum, C. N. (1994b). Cerebral hypoxia detected by near infrared spectroscopy. *Anaesthesia* 49, 762–766. doi: 10.1111/j.1365-2044.1994.tb04446.x

Williams, I. M., Vohra, R., Farrell, A., Picton, A. J., Mortimer, A. J., and McCollum, C. N. (1994c). Cerebral oxygen saturation, transcranial Doppler ultrasonography and stump pressure in carotid surgery. *Br. J. Surg.* 81, 960–964. doi: 10.1002/bjs.1800810711

Yadeau, J. T., Liu, S. S., Bang, H., Shaw, P. M., Wilfred, S. E., Shetty, T., et al. (2011). Cerebral oximetry desaturation during shoulder surgery performed in a sitting position under regional anesthesia. *Can. J. Anaesth.* 58, 986–992. doi: 10.1007/s12630-011-9574-7

Yamamoto, K., Miyata, T., and Nagawa, H. (2007). Good correlation between cerebral oxygenation measured using near infrared spectroscopy and stump pressure during carotid clamping. *Int. Angiol.* 26, 262–265.

Yoshitani, K., Kawaguchi, M., Iwata, M., Sasaoka, N., Inoue, S., Kurumatani, N., et al. (2005). Comparison of changes in jugular venous bulb oxygen saturation and cerebral oxygen saturation during variations of haemoglobin concentration under propofol and sevoflurane anaesthesia. *Br. J. Anaesth.* 94, 341–346. doi: 10.1093/bja/aei046

Zheng, Y., Villamayor, A. J., Merritt, W., Pustavoitau, A., Latif, A., Bhambhani, R., et al. (2012). Continuous cerebral blood flow autoregulation monitoring in patients undergoing liver transplantation. *Neurocrit. Care* 17, 77–84. doi: 10.1007/s12028-012-9721-1

Zogogiannis, I. D., Iatrou, C. A., Lazarides, M. K., Vogiatzaki, T. D., Wachtel, M. S., Chatzigakis, P. K., et al. (2011). Evaluation of an intraoperative algorithm based on near-infrared refracted spectroscopy monitoring, in the intraoperative decision for shunt placement, in patients undergoing carotid endarterectomy. *Mid. East J. Anesthesiol.* 21, 367–373.

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 30 September 2013; accepted: 21 February 2014; published online: 17 March 2014.

Citation: Nielsen HB (2014) Systematic review of near-infrared spectroscopy determined cerebral oxygenation during non-cardiac surgery. Front. Physiol. ***5****:93. doi: 10.3389/fphys.2014.00093*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 23 April 2014
doi: 10.3389/fphys.2014.00157

Arterial pressure variations as parameters of brain perfusion in response to central blood volume depletion and repletion

Anne-Sophie G. T. Bronzwaer[1,2], Wim J. Stok[2,3], Berend E. Westerhof[2,4] and Johannes J. van Lieshout[1,2,5]*

[1] Department of Internal Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands
[2] Laboratory for Clinical Cardiovascular Physiology, Center for Heart Failure Research, Academic Medical Center, Amsterdam, Netherlands
[3] Anatomy, Embryology and Physiology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands
[4] Edwards Lifesciences BMEYE, Amsterdam, Netherlands
[5] MRC/Arthritis Research UK Centre for Musculoskeletal Ageing Research, Queen's Medical Centre, School of Life Sciences, University of Nottingham Medical School, Nottingham, UK

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Caroline Alice Rickards, The University of North Texas Health Science Center, USA
Phil Neil Ainslie, University of British Columbia, Canada

***Correspondence:**
Johannes J. van Lieshout, Acute Admissions Unit, Department of Internal Medicine, F7-252, Academic Medical Center, University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, Netherlands
e-mail: j.j.vanlieshout@amc.uva.nl

Rationale: A critical reduction in central blood volume (CBV) is often characterized by hemodynamic instability. Restoration of a volume deficit may be established by goal-directed fluid therapy guided by respiration-related variation in systolic- and pulse pressure (SPV and PPV). Stroke volume index (SVI) serves as a surrogate end-point of a fluid challenge but tissue perfusion itself has not been addressed.

Objective: To delineate the relationship between arterial pressure variations, SVI and regional brain perfusion during CBV depletion and repletion in spontaneously breathing volunteers.

Methods: This study quantified in 14 healthy subjects (11 male) the effects of CBV depletion [by 30 and 70 degrees passive head-up tilt (HUT)] and a fluid challenge (by tilt back) on CBV (thoracic admittance), mean middle cerebral artery (MCA) blood flow velocity (V_{mean}), SVI, cardiac index (CI), PPV, and SPV.

Results: PPV ($103 \pm 89\%$, $p < 0.05$) and SPV ($136 \pm 117\%$, $p < 0.05$) increased with progression of central hypovolemia manifested by a reduction in thoracic admittance ($11 \pm 5\%$, $p < 0.001$), SVI ($28 \pm 6\%$, $p < 0.001$), CI ($6 \pm 8\%$, $p < 0.001$), and $MCAV_{mean}$ ($17 \pm 7\%$, $p < 0.05$) but not in arterial pressure. The reduction in $MCAV_{mean}$ correlated to the fall in SVI ($R^2 = 0.52$, $p < 0.0001$) and inversely to PPV and SPV [$R^2 = 0.46$ ($p < 0.0001$) and $R^2 = 0.45$ ($p < 0.0001$), respectively]. PPV and SPV predicted a $\geq$15% reduction in $MCAV_{mean}$ and SVI with comparable sensitivity (67/67% vs. 63/68%, respectively) and specificity (89/94 vs. 89/94%, respectively). A rapid fluid challenge by tilt-back restored all parameters to baseline values within 1 min.

Conclusion: In spontaneously breathing subjects, a reduction in $MCAV_{mean}$ was related to an increase in PPV and SPV during graded CBV depletion and repletion. Specifically, PPV and SPV predicted changes in both SVI and $MCAV_{mean}$ with comparable sensitivity and specificity, however the predictive value is limited in spontaneously breathing subjects.

Keywords: arterial pulse pressure, arterial systolic pressure, cerebrovascular circulation, fluid therapies, body fluids, head-up tilt, spontaneous breathing

INTRODUCTION

Severe hypovolemia is associated with a critical reduction in central blood volume (CBV) quite often related to hemorrhage or dehydration. This results in hemodynamic instability with a reduction in cardiac output (CO) and tissue oxygen delivery.

Volume depletion is usually of acute onset, and neurocardiovascular control mechanisms including reflexes from high and low pressure area receptors initiate the body's defending response (Guyton et al., 1980). In contrast, in chronic hypovolemia, the capillary fluid shift transfers fluid to the intravascular space (Guyton, 1980), whereas the humoro-cardiovascular and long-term renal blood volume control systems with a longer time constant come into operation (Shepherd and Vanhoutte, 1979; DiBona and Wilcox, 1992).

Restoration of adequate tissue perfusion and oxygenation is of major importance in hemodynamically unstable patients. In anesthesia and intensive care medicine, establishing this therapeutic goal typically involves intravascular fluid administration as the cornerstone of treatment for central hypovolemia.

However, diagnosing a volume deficit is not straightforward. In present clinical practice, volume treatment is commonly adjusted by recordings of the heart rate (HR) and arterial blood

pressure (BP). The experience is, however, that fluid infusion by focusing on these hemodynamic variables allows for wide variation in administered volume because neither BP nor HR accurately reflects changes in CBV (Secher and Van Lieshout, 2005; Bundgaard-Nielsen et al., 2007; Maizel et al., 2007; Secher and Van Lieshout, 2010). Observations in hypotensive patients during hemorrhage indicate that reversible hypotensive hypovolemic shock is in fact characterized by a decrease in HR reflecting an increase in vagal tone (Sander-Jensen et al., 1986). Thus the sensitivity of HR as an early indicator is low and highly non-specific. This is further supported by data obtained in a human model of acute hypovolemic shock by either lower body negative pressure (Cooke et al., 2004; Rickards et al., 2014) or passive head-up tilt (Matzen et al., 1991; Ten Harkel et al., 1992; Westerhof et al., 2006).

Also, clinical signs of hypovolemia including diminished skin turgor and high urine osmolarity do not accurately reflect reductions in CBV (McGee et al., 1999).

An increase in stroke volume (SV) or CO in response to fluid therapy is considered favorable. A meta-analysis of 12 clinical studies showed that with current clinical practice, between 40 and 70% of critically ill patients are so-called responders (Michard and Teboul, 2002). The substantial number of patients not responding to fluid therapy calls for physiological monitors capable of predicting fluid responsiveness.

Respiration-related variations in left ventricular preload which are transferred to variations in arterial pressure [e.g., systolic pressure variation (SPV) and pulse pressure variation (PPV)] are being introduced in clinical medicine as potentially useful tools to guide volume administration (Michard et al., 2000; Michard and Teboul, 2002; Bendjelid and Romand, 2003; Preisman et al., 2005).

In the majority of studies aiming for candidate indices predictive for fluid responsiveness, however, the investigated end-point of a fluid challenge has been a change in SV (index; SVI) or CO / cardiac index (CI) (Marik et al., 2009).

Although SV and CO serve as surrogate end-points of a fluid challenge, brain perfusion as the actual therapeutic endpoint is as yet not being addressed by present research. The large metabolic needs of the brain reflected by respectively 20 and 25% of oxygen and glucose consumption by neuronal activity renders it extremely sensitive to sufficient and uninterrupted blood supply. In this study, the hypothesis is tested that arterial pressure variations during progressive central hypovolemia relate to changes in brain perfusion. We therefore set out to gauge the relationship between arterial pressure variations, SVI and cerebral blood flow velocity during CBV depletion and repletion in spontaneously breathing subjects.

METHODS

SUBJECTS

Fourteen healthy volunteers (11 males) with a median (range) age of 25 (23–37) year, height 180 (173–204) cm and weight 72 (62–86) kg, without taking any medication and/or history of regular fainting or cardiac arrhythmia participated in this study. Phase of menstrual cycle in female subjects was not accounted for. This study was approved by the institutional Medical Ethics Committee and took place in the Laboratory for Clinical Cardiovascular Physiology in the Academic Medical Center in Amsterdam. The subjects abstained from heavy physical exercise and caffeinated beverages 4 h prior to the experiment. Diurnal variations in body fluid contents were accounted for by strictly adhering the experiment to the same hour of the day. All procedures and risks associated with the study were explained to the subjects and written informed consents were obtained.

EXPERIMENTAL PROTOCOL

Measurements were performed between 11 am and 3 pm in a quiet room with the subjects on a custom built computer controlled tilt table that minimizes muscle tensing and limits its vestibular stimulation during tilting (Gisolf et al., 2004a). Resting supine measurements represented normovolemic conditions. Next, subjects were head-up tilted (HUT) to respectively 30 and 70 degrees causing progressive central hypovolemia of acute onset and subsequently tilted back to the supine position mimicking a rapid volume repletion. Following each angle change of the tilt table, that body position was maintained for five minutes to obtain a stable hemodynamic situation. The last 60 s of these adjustment periods were used for analysis. Following tilt-back to the supine position, the subjects rested again. Subsequently they were tilted in a sinusoidal fashion (tilting frequency varying from 0.042 to 0.2 Hz or 5 to 12/min) enhancing BP variation for evaluation of cerebrovascular autoregulatory efficacy. The breathing was paced at 13 breaths/min by auditory support. This breathing frequency was continued throughout the sinusoidal tilts, to separate the influence of gravity and the influence of respiration on the measured cardiovascular signals.

MEASUREMENTS

Continuous arterial BP was non-invasively measured (Nexfin, Edwards Lifesciences BMEYE, Amsterdam, the Netherlands) (Eeftinck Schattenkerk et al., 2009; Martina et al., 2012) using the volume clamp method (Truijen et al., 2012). A finger cuff fastened on the middle finger was held at heart level. A pulse contour method (Nexfin CO-trek, Edwards Lifesciences BMEYE, Amsterdam, the Netherlands)—adapted for age, gender, height and weight (Bogert et al., 2010)—provided left ventricular SV and CO by multiplying SV by instantaneous HR. SVI and CI were SV and CO divided by body surface area (Du Bois and Du Bois, 1916). SPV and PPV were calculated per breath from the BP signal according to the following formula:

$$100 \times \frac{A_{max} - A_{min}}{(A_{max} + A_{min})/2} \quad (1)$$

with A equal to, respectively, systolic arterial pressure (SAP) and pulse pressure [PP; equal to SAP minus diastolic arterial pressure (DAP)]. Arterial pressure variations were calculated per breath and then averaged over five consecutive breaths (see **Figure 1**).

Cerebral perfusion pressure (CPP) was determined by subtracting critical closing pressure (CCP) from BP at brain level. BP at brain level was estimated by subtracting hydrostatic difference between the finger cuff and the level of transcranial insonation by Transcranial Doppler (TCD) ultrasonography and CCP was

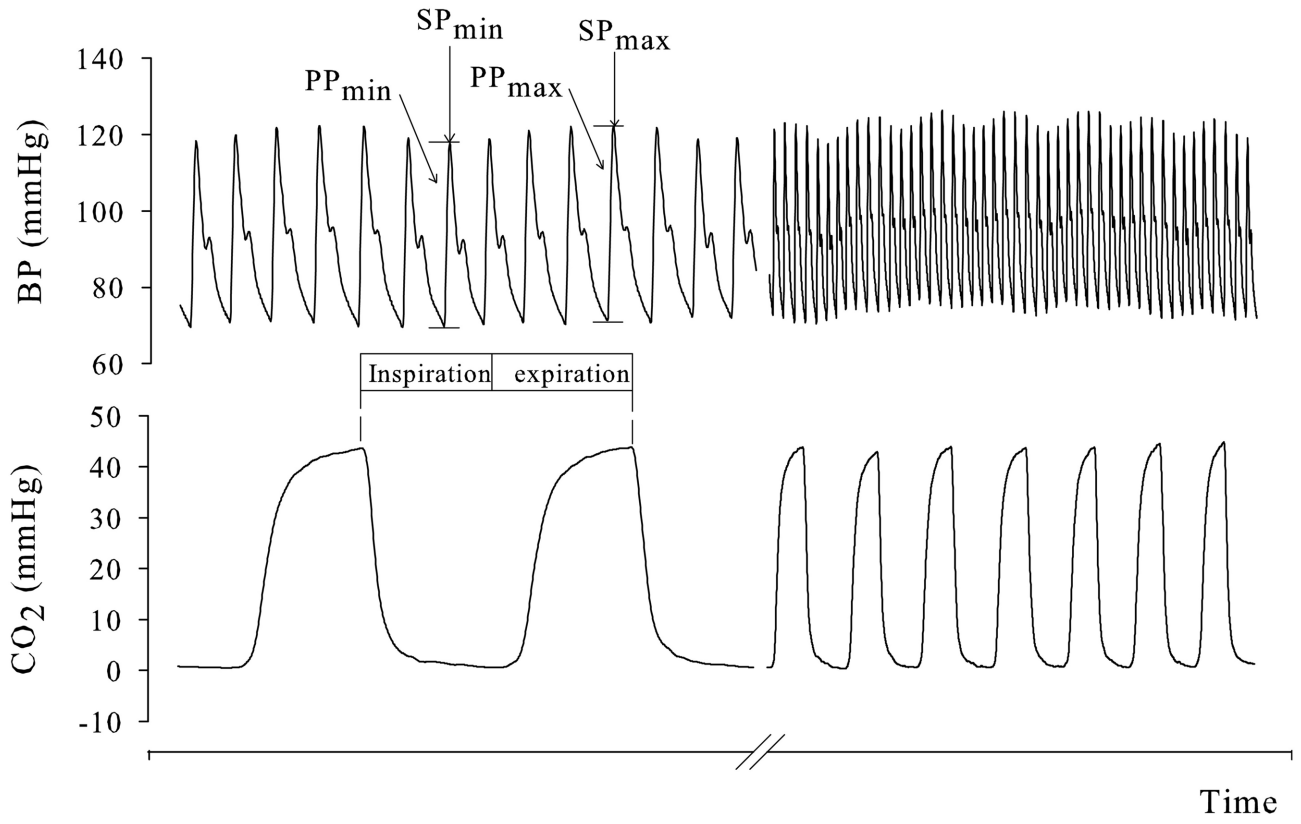


FIGURE 1 | Variation in pulse and systolic pressure (PP and SP, respectively), induced by respiration. PPV and SPV were first calculated (Equation 1) per breath and then averaged over five consecutive breaths.

estimated by first harmonic Fourier filtered normal arterial pressure and velocity wave heart beat data as described by Aaslid et al. (2003).

Regional brain perfusion of the anterior circulation was investigated by the assessment of mean middle cerebral artery (MCA) flow velocity (V_{mean}) followed in the proximal segments by means of TCD (DWL Multidop X4, Sipplingen, Germany). The MCA was insonated through the temporal window just above the zygomatic arch at a depth of 40–60 mm with a pulsed 2 MHz probe. After the Doppler signal was optimized, the probe was attached to the skull in a fixed angle by means of a head-band.

The HUT induced translocation of CBV to the lower extremities was monitored by electrical impedance plethysmography (350 μA at 50 kHz; Nihon Kohden, AI-601G, Japan) measured at the level of the thorax (Krantz et al., 2000) and expressed as changes in thoracic admittance (Van Lieshout et al., 2005). Airway flow and pressure were measured by means of the Alveotest flowmeter (Jaeger, Würzburg, Germany) and end-tidal CO_2 ($PetCO_2$) was measured using a capnograph (Tonocap, Datex-Ohmeda, Madison, USA). Tidal volume (TV) was calculated by integration of the flow signal. All data were sampled at 200 Hz and collected using an Analog Devices RTI815 PC-card with custom made software. Signals were visually inspected for artifacts and analyzed offline (Matlab R2007b, Mathworks Inc. MA, USA).

Dynamic cerebral autoregulation (CA) was quantified as the counter-regulatory capacity to maintain $MCAV_{mean}$ during oscillatory tilt induced changes in BP. Dynamic CA was assessed by means of cross-spectral density analysis of beat-to-beat data of MAP at brain level and $MCAV_{mean}$ after spline interpolation and resampling at 4 Hz. Gain and phase were obtained for the frequencies equal to the oscillatory tilt frequencies (ranging from 0.042 to 0.2 Hz). The gain reflects the effective amplitude dampening of BP fluctuations and phase shift was defined positive where $MCAV_{mean}$ leads MAP at brain level. Coherence examined the strength of the relationship between MAP and $MCAV_{mean}$ (Immink et al., 2004). To account for inter-subject variability, the gain was normalized for MAP and $MCAV_{mean}$ and expressed as the percentage change in cm/sec per percentage change in mmHg (Panerai et al., 1999).

STATISTICAL ANALYSIS

Results are presented as mean ± *SD*. The effect of HUT on measured parameters was assessed using a One Way Repeated Measures Analysis of Variance (ANOVA) test together with the Holm-Sidak method to perform pairwise multiple comparisons. When data were not normally distributed, they are presented as medians and range and non-parametric statistical tests were used.

Linear Mixed Model analysis was performed (IBM SPSS statistics 20, IBM corporation, USA) to examine the relation between

brain perfusion (referred to as dependent variable) and hemodynamic and respiratory variables (fixed covariates). R^2 was calculated according to the following formula:

$$R^2 = 1 - \frac{\sum_i (y_i - f_i)^2}{\sum_i (y_i - \bar{y})^2} \quad (2)$$

where y and f refers to, respectively, the observed and predicted values (Edwards et al., 2008). A multivariate, stepwise regression model was constructed with $MCAV_{mean}$ as the dependent variable and mean arterial pressure at heart level (MAP), CPP, SVI, HR, total peripheral resistance (TPR), $PetCO_2$ and thoracic admittance as the independent variables (Kim et al., 2008). The model was developed by forward entry and removal of the independent variables according to their significant contribution (according to the *F*-test) in explaining the variance in the dependent variable. Baseline measurements for both the dependent as independent variables were normalized to zero and the effect of tilt was expressed as absolute change with respect to the baseline value.

The subjects were divided into two groups according to the percent decrease in SVI or $MCAV_{mean}$ during progressive CBV depletion related to the resting supine value. A 15% increase in SVI in response to fluid infusion is considered clinically relevant according to previously published criteria (Michard et al., 2000; Heenen et al., 2006; Jellema et al., 2006; Soubrier et al., 2007). In this study, subjects with >15% decrease in SVI or $MCAV_{mean}$ were classified as having a CBV deficit. Receiver operating characteristics (ROC) curves evaluated the predictive value of PPV and SPV on volume deficits by determination of sensitivity and specificity values and its corresponding optimal threshold value (Akobeng, 2007). Accuracy was assessed by the area under the curve (AUC) values presented as area ± *SD*. A *p*-value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

All subjects completed the protocol. **Figures 2**, **3** and **Table 1** summarize the hemodynamic and brain perfusion response to graded HUT and tilt back.

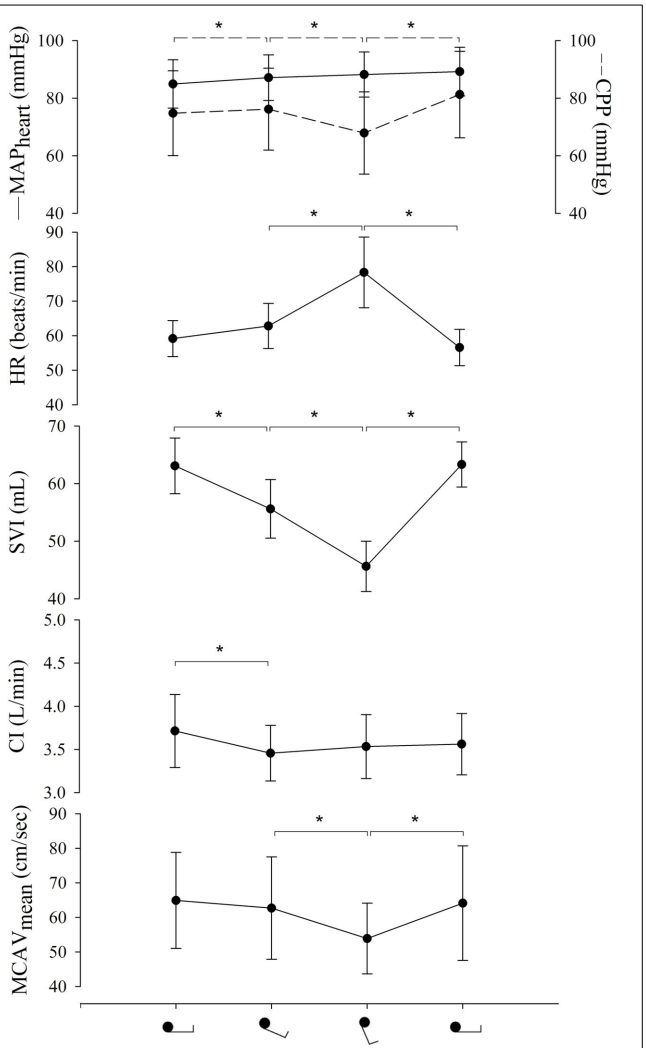


FIGURE 2 | Hemodynamic response to graded HUT and tilt back. MAP, mean arterial pressure; CPP, cerebral perfusion pressure; HR, heart rate; SVI, stroke volume index; CI, cardiac index; $MCAV_{mean}$, mean middle cerebral artery flow velocity. *$p < 0.001$.

CENTRAL BLOOD VOLUME DEPLETION (HUT)

Mean arterial pressure and SAP remained constant while DAP increased (11 ± 12%, $p < 0.001$) with 70 degrees HUT resulting in a 19 ± 11% ($p < 0.001$) reduction in PP. Although a decrease in CPP was demonstrated during HUT, this was not significantly different from the supine position. SVI (28 ± 6%, $p < 0.001$), thoracic admittance (11 ± 5%, $p < 0.001$) and $MCAV_{mean}$ (17 ± 7%, $p < 0.05$) declined while an increase was seen in HR (32 ± 14%, $p < 0.001$). CI declined (6 ± 8%, $p < 0.001$) and TPR increased (10 ± 11%, $p < 0.001$) only from 0 to 30 degrees without further change at 70 degrees HUT. PPV and SPV did not change from supine to 30 degrees HUT but substantially increased (103 ± 89% ($p < 0.05$) and 136 ± 117% ($p < 0.05$), respectively) with 70 degrees HUT. TV and breathing frequency did not change during HUT vs. the supine position while $PetCO_2$ declined (8 ± 11%, $p < 0.001$) with 70 degrees HUT.

CENTRAL BLOOD VOLUME REPLETION (TILT BACK)

Every changing parameter returned to baseline values following tilt back except TPR which remained elevated compared to the baseline measurement ($p < 0.05$, **Table 1**).

CEREBRAL BLOOD FLOW VELOCITY AND STROKE VOLUME

Forward stepwise regression analysis revealed that absolute change in $MCAV_{mean}$ was mainly predicted by absolute change in SVI ($r^2 = 0.53$, $p < 0.001$). Absolute change in $PetCO_2$ was secondly added to this prediction model, resulting in a slightly stronger regression ($r^2 = 0.57$, $p < 0.001$). Single linear plots of the dependent variable ($MCAV_{mean}$) and its strongest prediction variable (SVI) are shown in **Figure 4**. There was only a weak relation between CPP and $MCAV_{mean}$ ($r^2 = 0.16$, $p = 0.007$; **Figure 5**). The median (range) of individual correlation coefficients for the relation between SVI and $MCAV_{mean}$ and for CPP

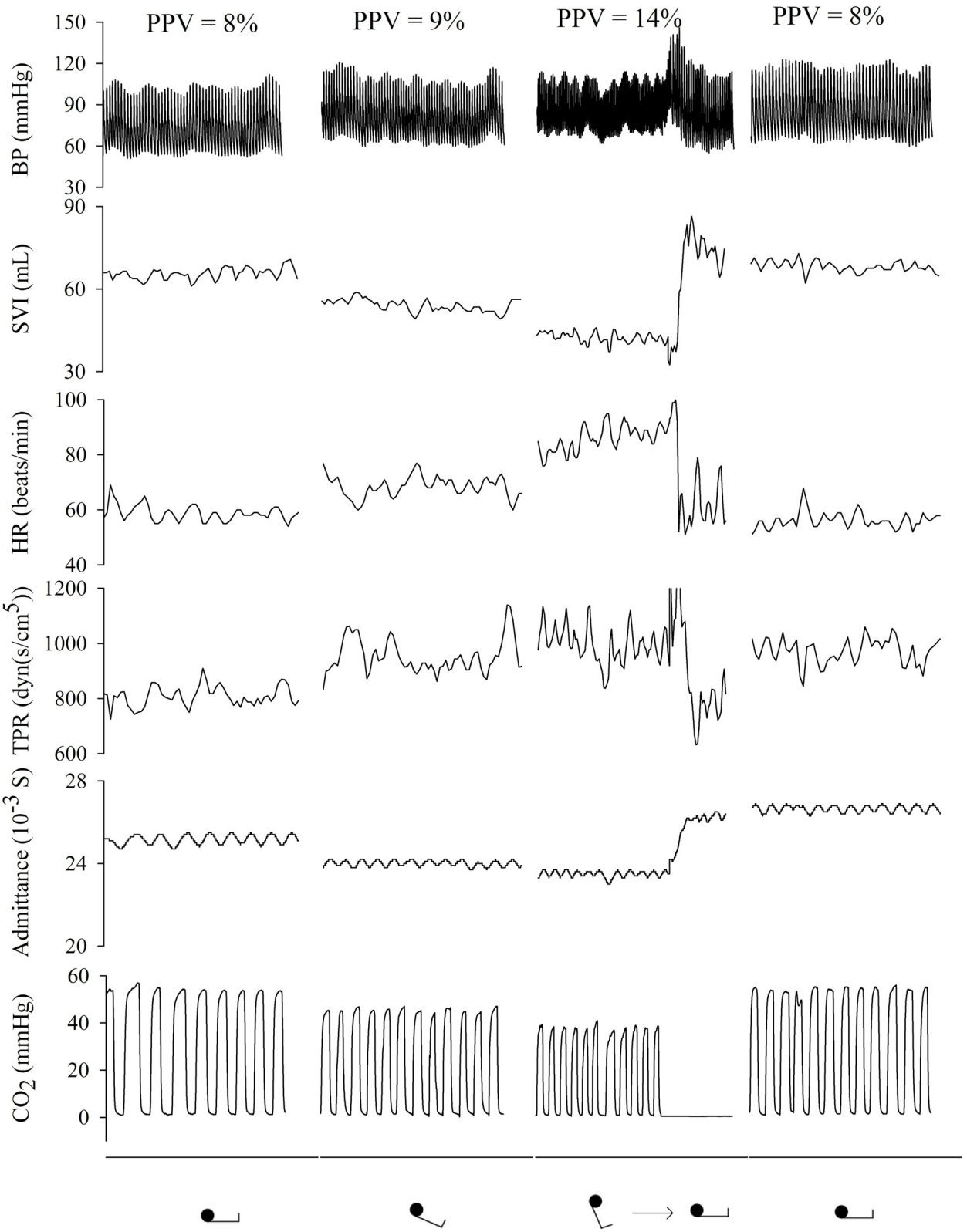


FIGURE 3 | Representative example (subject 11) of hemodynamic response to graded HUT and tilt back. BP, blood pressure; SVI, stroke volume index; HR, heart rate; TPR, total peripheral resistance; PPV, pulse pressure variation.

Table 1 | Effect of tilt on measured parameters.

		Supine	Volume depletion		Volume repletion
					
MAP	(mmHg)	85 ± 8	87 ± 8	88 ± 8	89 ± 8
SAP	(mmHg)	120 ± 12	119 ± 11	116 ± 10	122 ± 9
DAP	(mmHg)	66 ± 6	69 ± 5	73 ± 6*	69 ± 6
PP	(mmHg)	55 ± 7	50 ± 7*	44 ± 5*	53 ± 5*
CPP	(mmHg)	75 ± 15	76 ± 14	68 ± 14	81 ± 15*
HR	(beats/min)	59 ± 5	63 ± 7*	78 ± 10*	57 ± 5*
SVI	(mL/m^2)	64 ± 4	56 ± 5*	46 ± 4*	63 ± 4*
CI	[(L/min)/m^2]	3.7 ± 0.4	3.5 ± 0.3*	3.5 ± 0.4	3.6 ± 0.4
T. adm.	(10^{-3} S)	29 ± 3	27 ± 3*	26 ± 3*	29 ± 3*
TPR	dyn(s/cm^5)	962 ± 165	1052 ± 145*	1053 ± 185	1052 ± 156‡
$MCAV_{mean}$	(cm/s)	65 ± 14	63 ± 15	54 ± 10*	64 ± 17*
PPV	(%)	11 ± 4	12 ± 3	20 ± 5*	10 ± 3*
SPV	(%)	6 ± 3	6 ± 2	11 ± 3*	5 ± 2*
TV	(mL/Kg)	11 ± 3	11 ± 3	11 ± 3	10 ± 3
$PetCO_2$	(mmHg)	39 ± 5	39 ± 3	35 ± 4*	38 ± 4*

Values are presented as mean ± SD.

*MAP, mean arterial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; PP, pulse pressure; CPP, cerebral perfusion pressure; HR, heart rate; SVI, stroke volume index; CI, cardiac index; T.adm., thoracic admittance; TPR, total peripheral resistance; $MCAV_{mean}$, mean middle cerebral artery flow velocity; PPV, pulse pressure variation; SPV, systolic pressure variation; TV, tidal volume; $PetCO_2$, end-tidal CO_2. *$p < 0.05$ with respect to the previous tilt position. ‡$p < 0.05$ volume repletion vs. baseline supine position.*

and $MCAV_{mean}$ was: $r^2 = 0.902$ (0.059–0.999) and $r^2 = 0.345$ (−0.672–0.998) respectively.

ARTERIAL PRESSURE VARIATIONS

Figure 6, panel (A) displays single linear regression plots between ΔSVI and ΔPPV or ΔSPV. Regression analysis between ΔSVI and ΔPPV/ ΔSPV showed linear correlations (PPV: $r^2 = 0.74$, $p < 0.0001$ and SPV: $r^2 = 0.76$, $p < 0.0001$) with a higher slope for ΔPPV compared to ΔSPV. Single linear regression analysis was also applied on $\Delta MCAV_{mean}$ and ΔPPV or ΔSPV [see panel (B) of **Figure 6**]. Correlations were seen between ΔPPV/ ΔSPV and $\Delta MCAV_{mean}$ (PPV: $r^2 = 0.46$, $p < 0.0001$ and SPV: $r^2 = 0.43$, $p < 0.0001$). The slope of the regression plots for both ΔPPV and ΔSPV were comparable with those between ΔPPV/ ΔSPV and ΔSVI. Again, the highest slope was seen for ΔPPV.

In **Figure 7**, ROC curves for the performance of arterial pressure variations in predicting ≥15% decrease in SVI (left panel) and ≥15% decrease in $MCAV_{mean}$ (right panel) are shown. The AUC values were the highest for PPV and SPV when predicting a decrease in $MCAV_{mean}$ compared to predicting a decrease in SVI (PPV: 0.93 vs. 0.73 and SPV: 0.93 vs. 0.80). The cutoff thresholds and its corresponding sensitivity and specificity values are described in **Table 2**. PPV and SPV predicted a ≥15% reduction in $MCAV_{mean}$ and SVI with comparable sensitivity (67/67% vs. 63/68%, respectively) and specificity (94 vs. 89% for both PPV and SPV). In **Figure 8**, dot histograms associated with the ROC curves are shown for the prediction of ≥15% decrease in both SVI and $MCAV_{mean}$.

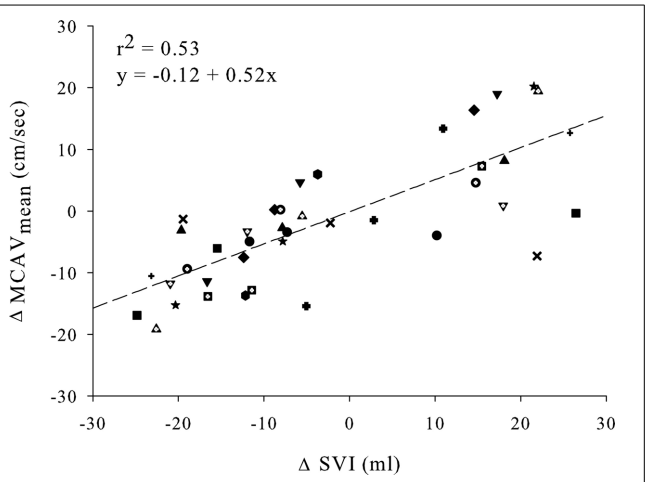


FIGURE 4 | Linear regression plot of absolute change in $MCAV_{mean}$ and SVI. All subjects contributed three points in each regression line (during 30 and 70 degrees + 0 degrees after tilt back). The regression function is equal to $y = -0.12 + 0.52x$ with corresponding correlation coefficient of $r^2 = 0.53$ ($p < 0.0001$). $MCAV_{mean}$, mean middle cerebral artery flow velocity; SVI, stroke volume index.

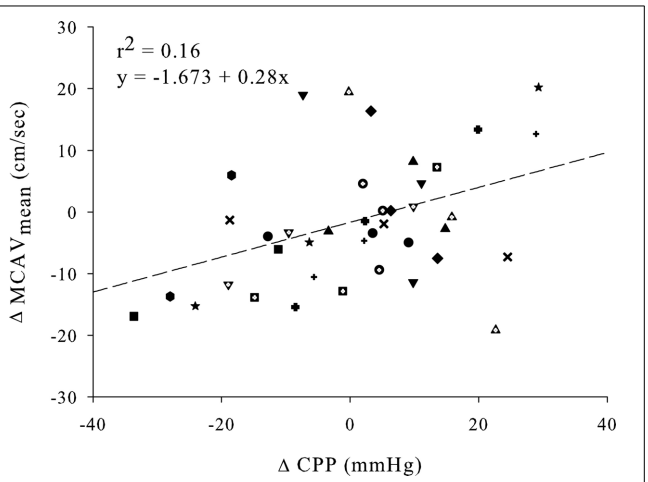


FIGURE 5 | Single linear regression plot of absolute change in $MCAV_{mean}$ and CPP. All subjects contributed three points in each regression line (during 30 and 70 degrees + 0 degrees after tilt back). The regression function is equal to $y = -1.673 - 0.28x$ with corresponding correlation coefficient of $r^2 = 0.16$ ($p = 0.007$). $MCAV_{mean}$, mean middle cerebral artery flow velocity; CPP, cerebral perfusion pressure.

DYNAMIC CA

The $MCAV_{mean}$-to-MAP at brain level transfer functions displayed the expected high-pass filter characteristics of dynamic autoregulation, with a decrease in phase lead and increase in normalized gain with increasing sinusoidal tilt frequency (**Figure 9**). Phase and gain at 0.1 Hz were, respectively, 45 degrees and 0.89%/%.

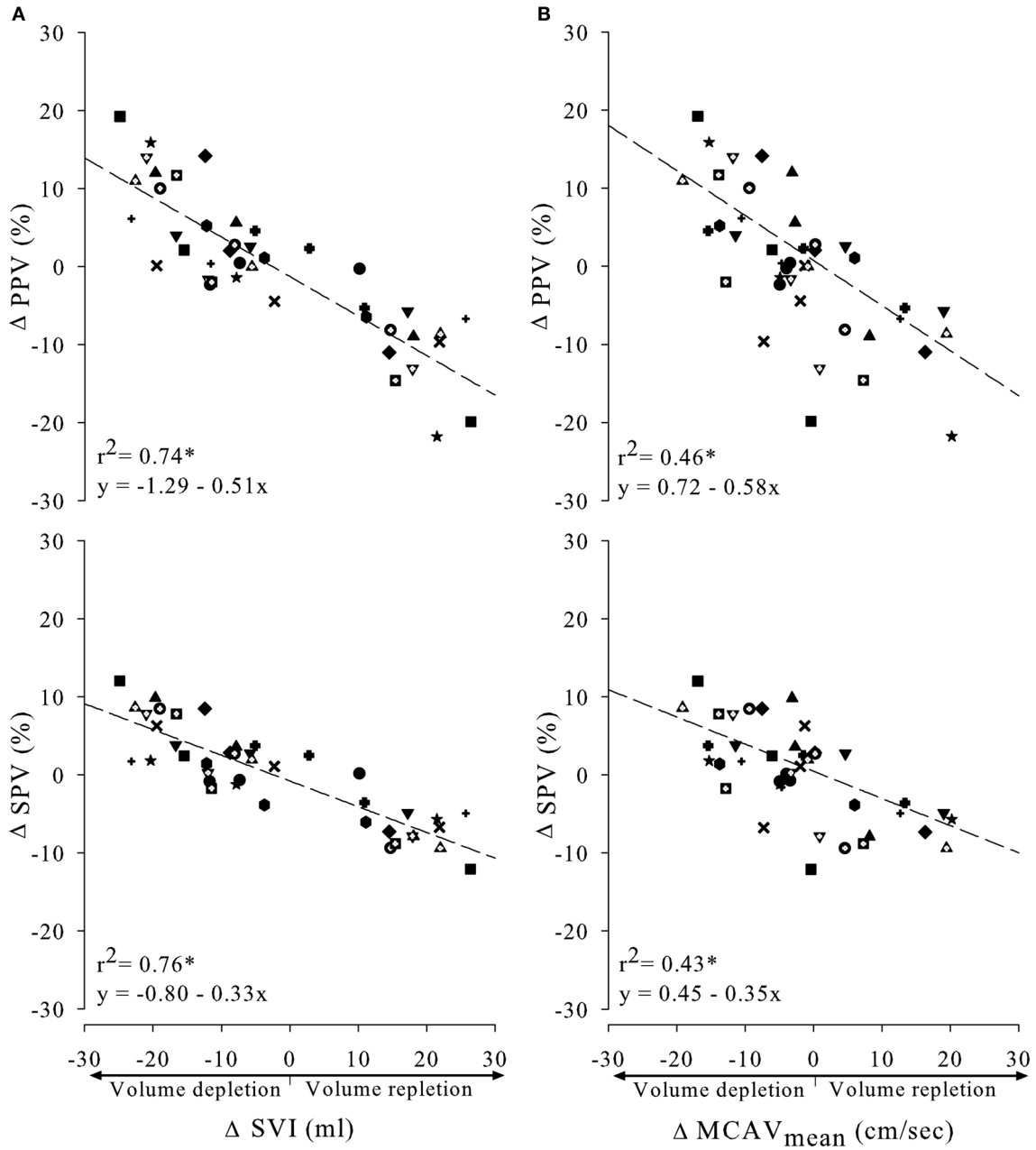


FIGURE 6 | Relationship between absolute change in pulse or systolic pressure variation (PPV and SPV, respectively), and absolute change in SVI (A) or $MCAV_{mean}$ (B). All subjects were indicated by symbols and contributed three points in each regression line (during 30 and 70 degrees HUT + 0 degrees during tilt back). $^{*}p < 0.0001$.

DISCUSSION

The main new finding of this study is that in spontaneously breathing subjects under conditions of depletion and repletion of CBV, $MCAV_{mean}$ was linearly related to arterial pressure variations. Specifically, arterial pressure variations predicted a decline in $MCAV_{mean}$ and SVI with comparable sensitivity and specificity.

POSTURE AND CENTRAL BLOOD VOLUME DEPLETION

Clinically, hypovolemia is manifested by a reduced CBV. With passive HUT, approximately 700 ml of CBV redistributes from the chest into the gravitational dependent regions, largely contained in the venous compartment and therefore not contributing effectively to the circulating blood volume (Sjöstrand, 1953; Rowell, 1986). In this study, a postural reduction in CBV coincided with a decline in SVI (Friedman et al., 1990; Matzen et al., 1991; Pawelczyk et al., 1994; Cai et al., 2000). This is attributed to blood pooling in the lower parts of the body and to a reduction in venous return which is in agreement with data from earlier studies (Harms et al., 2003; Immink et al., 2009). Constant values of MAP by a baroreflex mediated increase in TPR counterbalancing

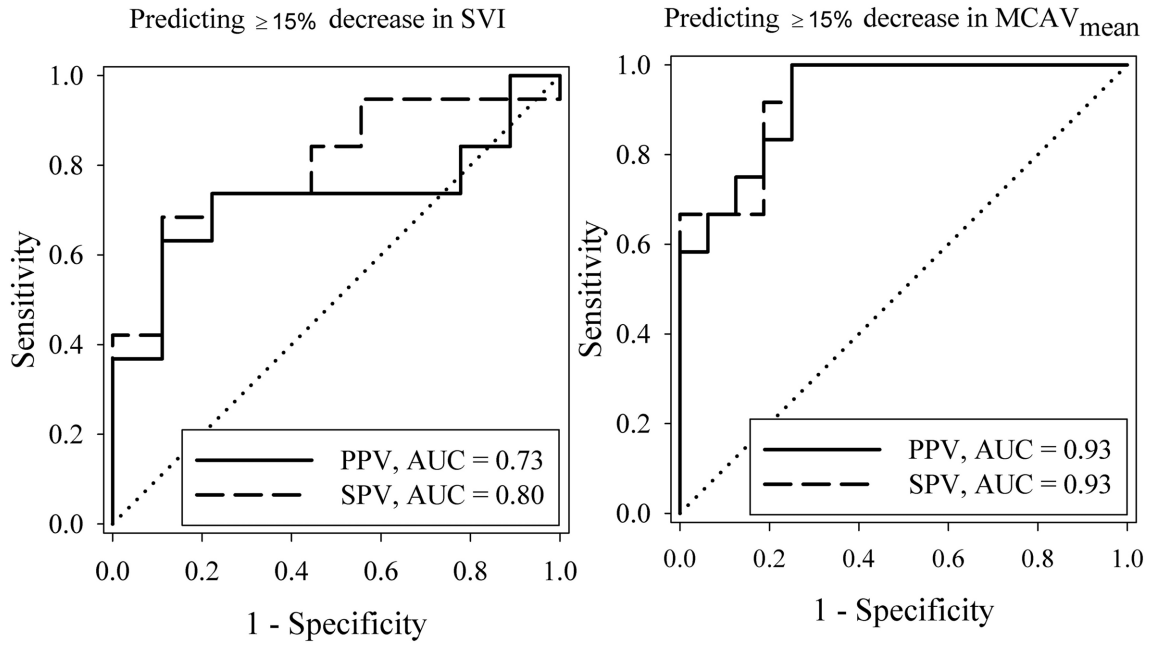


FIGURE 7 | Receiver operating characteristics (ROC) curves for the performance of PPV and SPV in predicting ≥15% decrease in SVI (left) and ≥15% decrease in MCAV$_{mean}$ (right). PPV, pulse pressure variation; SPV, systolic pressure variation; AUC, area under curve; SVI, stroke volume index; MCAV$_{mean}$, mean middle cerebral artery velocity.

Table 2 | Predictive value of PPV and SPV for (changes in) SVI and MCAV$_{mean}$ with cutoff thresholds and corresponding sensitivity of specificity.

		Cutoff threshold	Sensitivity (%)	Specificity (%)
≥15% change in SVI	PPV	>15	63	89
	SPV	>8	68	89
≥15% change in MCAV$_{mean}$	PPV	>18	67	94
	SPV	>11	67	94

PPV, pulse pressure variation; SPV, systolic pressure variation; SVI, stroke volume index; MCAV$_{mean}$, mean middle cerebral artery flow velocity.

the postural reduction in SVI and CI illustrates the contention that MAP does not reflect changes in CBV (Van Lieshout and Wesseling, 2001; Secher and Van Lieshout, 2005).

POSTURE AND PCO$_2$

Increased ventilation and corresponding lowering of $PaCO_2$ associated with postural stress, is considered to be contributory to the reduction in MCAV$_{mean}$ (Kapoor, 2002; Chen-Scarabelli and Scarabelli, 2004; Donnelly et al., 2011). The mechanisms that drive breathing during postural stress are not well understood but likely find their origin in both the brain and the periphery. We earlier considered that in the upright position the larger BP variability and less stable blood flow enhance fluctuation of $PaCO_2$ as an input signal to the carotid body chemoreceptors (Immink et al., 2013). The interaction of enhanced baroreceptor activity and carotid body chemoreceptor stimulation may modify the respiratory drive (Biscoe and Purves, 1967a,b). Arterial hypocapnia has been associated with orthostatic intolerance and lowering of $PaCO_2$ may reduce the prevailing peripheral vasomotor tone (Shoemaker et al., 2001). Thus, the postural reduction in $PetCO_2$ suggests a contribution of mild hypocapnia to the reduction in cerebral perfusion. We consider that $PetCO_2$ tracks changes in arterial carbon dioxide tension ($PaCO_2$) in a fixed body position only, whereas the $PaCO_2$ -to- $PetCO_2$ gradient is enhanced by the postural reduction in CO. This results in an increased VE/Q ratio (Riley et al., 1959; Gisolf et al., 2004b; Immink et al., 2006) with overestimation of the reduction in P_aCO_2 (Immink et al., 2006, 2009). Also, when during passive head-up tilt $PetCO_2$ is clamped to the level in the supine position, MCA V_{mean} declines in the first minute of tilt only. Afterwards the postural reduction in MCA V_{mean} has become independent of the ∼4 mmHg reduction in $PetCO_2$ for at least 5 min in the HUT 70 position (Immink et al., 2009). In the present study, postural stress, duration of tilt and reduction in $PetCO_2$ were comparable to the unclamped limb in that study supporting that the decrease in $PetCO_2$ during HUT does not explain the reduction seen in MCAV$_{mean}$.

POSTURE AND CEREBROVASCULAR AUTOREGULATION

The decline in CPP is explained by the HUT induced hydrostatic pressure gradient when the cerebral circulation is positioned above the level of the heart. According to the traditional concept of CA, cerebral blood flow (CBF) is maintained more or less constant in the face of changing CPP (Roy and Sherrington, 1890; Lassen, 1974). Nevertheless, postural stress elicits reductions in

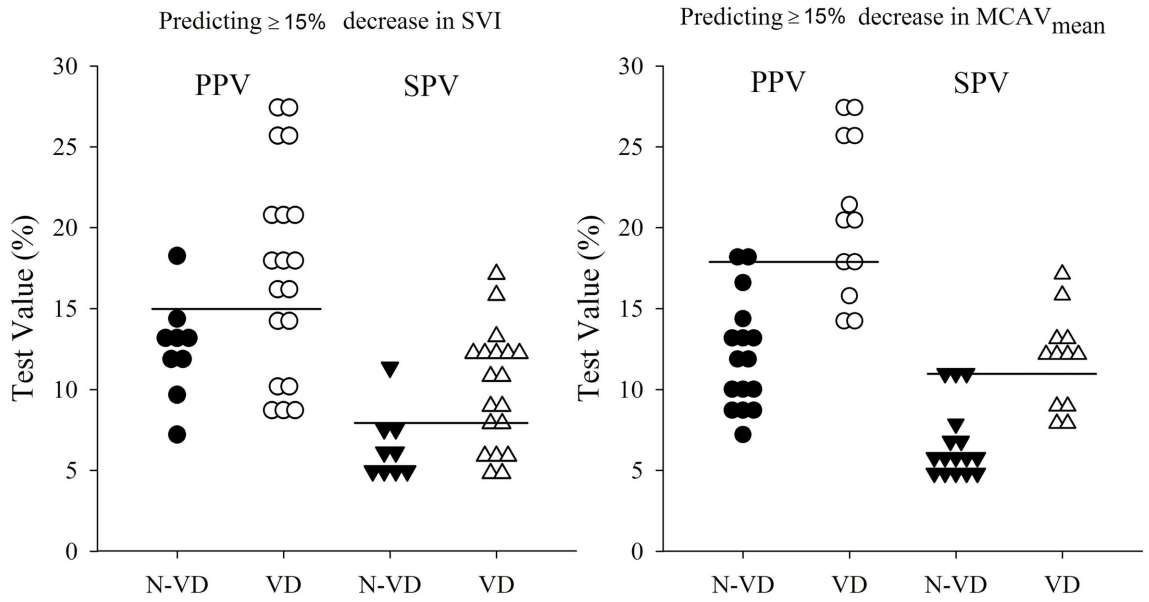


FIGURE 8 | Dot histograms of having a volume deficit (VD) or not having a volume deficit (N-VD) defined by ≥15% HUT induced decrease in SVI (left) or $MCAV_{mean}$ (right). PPV is depicted by the circles and SPV is depicted by the triangles. The cutoff threshold values are represented as a horizontal line and described in **Table 2**. PPV, pulse pressure variation; SPV, systolic pressure variation; SVI, stroke volume index; $MCAV_{mean}$, mean middle cerebral artery flow velocity.

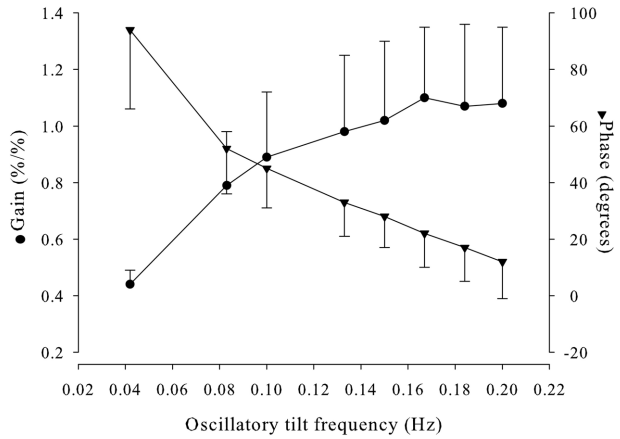


FIGURE 9 | $MCAV_{mean}$-MAP transfer function displayed by gain and phase for each oscillatory tilt frequency. $MCAV_{mean}$, mean middle cerebral artery flow velocity; MAP, mean arterial pressure.

indices of CBF irrespective of the fact that CPP remains within the so called autoregulatory range, challenging the concept of CA as a plateau (Immink et al., 2010; Lucas et al., 2010). In fact, constant CBF would require an infinite gain which is generally not operative in humans (Van Lieshout et al., 2003; Panerai, 2004; Immink et al., 2013; Willie et al., 2014). Assessment of CA is based on introducing CCP fluctuations and quantifying their transfer to the blood velocity in a large cerebral artery in terms of phase angle and gain. This approach addresses specifically the dynamic component of CA. CA is, however, considered to encompass both static (long-term) and dynamic (short-term) components (Van Lieshout et al., 2003). It remains unclear whether short- and long-term regulation of CBF are separate mechanistic entities (Ainslie and Brassard, 2014). Reference values have not been defined and overlap exists between healthy subjects vs. patients with impaired dynamic CA. We demonstrated the expected high-pass filter characteristics and therefore assume that in the young adult subjects in this study dCA was intact. However, CA integrity does in itself not preclude some influence of the postural reduction in CPP on $MCAV_{mean}$. Of interest, the postural reduction in CPP was only minor and the correlation between changes in CPP and $MCAV_{mean}$ weak, supporting that the effect of the reduction in CPP on MCA flow velocity, if anything, must have been limited.

CEREBRAL BLOOD FLOW VELOCITY AND STROKE VOLUME

Cerebral blood flow velocity and its relation with CO has been investigated in several studies. Under conditions of 30 Torr lower body negative pressure (Zhang et al., 1998) and HUT (Jorgensen et al., 1993) both CO and $MCAV_{mean}$ decreased whereas in response to moderate exercise (Brys et al., 2003; Ogoh et al., 2005) CO and $MCAV_{mean}$ increase together with CBV without changes in $PaCO_2$. In this study, the change in CI from 0 to 30 degrees HUT was limited. From 30 to 70 degrees HUT, SVI and CBV decreased further but CO was maintained, probably attributable to the baroreflex mediated increase in HR. During progressive central hypovolemia a reduction in $MCAV_{mean}$ coincided with the fall in SVI, and vice versa $MCAV_{mean}$ and SVI both increased in response to a simulated fluid challenge by repositioning from upright to supine, supporting a dependency of $MCAV_{mean}$ on CBV. Furthermore, SVI appeared to be the strongest hemodynamic predictor for changes in $MCAV_{mean}$.

Collectively, these findings suggest that in spontaneously breathing volunteers subjected to simulated progressive central hypovolemia, changes in SVI reflect those in $MCAV_{mean}$ in a linear manner (see **Figure 4**).

PREDICTIVE VALUE OF ARTERIAL PRESSURE VARIATIONS

During surgery or in an intensive care setting, an increase in SVI in response to fluid administration in the anesthetized patient is considered to indicate fluid responsiveness. This study demonstrated an increase in arterial pressure variations in response to a clinical relevant decrease in SVI during HUT and vice versa during tilt back. This strong correlation between SVI and arterial pressure variations is in agreement with earlier research (Hofer et al., 2005; Jacques et al., 2011). A new finding is that under the conditions of this study $MCAV_{mean}$ and arterial pressure variations are related too.

Although arterial pressure variations have been proven valuable to predict fluid responsiveness in patients receiving mechanical ventilation, their predictive value in spontaneously breathing patients is lower (Bendjelid and Romand, 2003; Heenen et al., 2006; Soubrier et al., 2007). Our findings are in agreement with these data, whereas the present study extends this knowledge by demonstrating that arterial pressure variations predict changes in MCAVmean with comparable sensitivity and specificity values, and a higher accuracy during graded hypovolemia. Extrapolating this to clinical practice, a fluid challenge targeting SVI also targets brain perfusion.

Potential limitations inherent to the study design should be considered. Transcranial Doppler ultrasonography is used to monitor changes in CBF. This technique has been widely used under the assumption that the cross-sectional area of the MCA is maintained during the measurement. Possible changes in the diameter of the insonated vessel by enhanced sympathetic activity could modulate velocity independently of flow. Previous research showed that increases in sympathetic outflow by baroreflex disengagement or chemoreflex activation do not alter MCA diameter (Serrador et al., 2000), and we therefore assume that a constant MCA diameter links changes in cerebral blood velocity to changes in flow.

Detecting a volume deficit is considered as the major goal of determining fluid responsiveness. However, recent studies indicate that under certain conditions fluid bolus administration is associated with an increased mortality (Maitland et al., 2011). It is recognized that fluid administration should be practiced with much greater caution and increased vigilance and a more conservative fluid management seems appropriate (Myburgh, 2011). The values represented in **Table 2** are therefore optimized for high specificity rather than high sensitivity.

In summary, the present study shows for the first time in awake humans subjected to progressive central hypovolemia that arterial pressure variations are related to both CBF velocity and SVI. Specifically, PPV and SPV predicted changes in both SVI and $MCAV_{mean}$ with comparable sensitivity and specificity, however the predictive value is limited in spontaneously breathing subjects.

AUTHOR CONTRIBUTIONS

Anne-Sophie G. T. Bronzwaer contributed to the experimental design, data acquisition, data analysis and writing the manuscript. Wim J. Stok contributed to data acquisition, data analysis and manuscript revision. Berend E. Westerhof contributed to the experimental design, data analysis and manuscript revision. Johannes J. van Lieshout supervised the study, contributing to the experimental design, data analysis and writing the manuscript.

REFERENCES

Aaslid, R., Lash, S. R., Bardy, G. H., Gild, W. H., and Newell, D. W. (2003). Dynamic pressure–flow velocity relationships in the human cerebral circulation. *Stroke* 34, 1645–1649. doi: 10.1161/01.STR.0000077927.63758.B6

Ainslie, P. N., and Brassard, P. (2014). Why is the neural control of cerebral autoregulation so controversial? *F1000Prime Rep.* 6:14. doi: 10.12703/P6-14

Akobeng, A. K. (2007). Understanding diagnostic tests 3: receiver operating characteristic curves. *Acta Paediatr.* 96, 644–647. doi: 10.1111/j.1651-2227.2006.00178.x

Bendjelid, K., and Romand, J. A. (2003). Fluid responsiveness in mechanically ventilated patients: a review of indices used in intensive care. *Intensive Care Med.* 29, 352–360. doi: 10.1007/s00134-003-1777-0

Biscoe, T. J., and Purves, M. J. (1967a). Observations on carotid body chemoreceptor activity and cervical sympathetic discharge in the cat. *J. Physiol.* 190, 413–424.

Biscoe, T. J., and Purves, M. J. (1967b). Observations on the rhythmic variation in the cat carotid body chemoreceptor activity which has the same period as respiration. *J. Physiol.* 190, 389–412.

Bogert, L. W., Wesseling, K. H., Schraa, O., Van Lieshout, E. J., De Mol, B. A., Van, G. J., et al. (2010). Pulse contour cardiac output derived from non-invasive arterial pressure in cardiovascular disease. *Anaesthesia* 65, 1119–1125. doi: 10.1111/j.1365-2044.2010.06511.x

Brys, M., Brown, C. M., Marthol, H., Franta, R., and Hilz, M. J. (2003). Dynamic cerebral autoregulation remains stable during physical challenge in healthy persons. *Am. J. Physiol. Heart Circ. Physiol.* 285, H1048–H1054. doi: 10.1152/ajpheart.00062.2003

Bundgaard-Nielsen, M., Holte, K., Secher, N. H., and Kehlet, H. (2007). Monitoring of perioperative fluid administration by individualized goal-directed therapy. *Acta Anaesthesiol. Scand.* 51, 331–340. doi: 10.1111/j.1399-6576.2006.01221.x

Cai, Y., Boesen, M., Stromstad, M., and Secher, N. H. (2000). An electrical admittance based index of thoracic intracellular water during head-up tilt in humans. *Eur. J. Appl. Physiol.* 83, 356–362. doi: 10.1007/s004210000296

Chen-Scarabelli, C., and Scarabelli, T. M. (2004). Neurocardiogenic syncope. *BMJ* 329, 336–341. doi: 10.1136/bmj.329.7461.336

Cooke, W. H., Ryan, K. L., and Convertino, V. A. (2004). Lower body negative pressure as a model to study progression to acute hemorrhagic shock in humans. *J. Appl. Physiol.* 96, 1249–1261. doi: 10.1152/japplphysiol.01155.2003

DiBona, G. F., and Wilcox, C. S. (1992). "The kidney and the sympathetic nervous system," in *Autonomic Failure*, eds R. Bannister and C. J. Mathias (Oxford: Oxford), 178–196.

Donnelly, J., Lucas, S. J., Thomas, K. N., Galvin, S. D., and Ainslie, P. N. (2011). Profound hyperventilation and development of periodic breathing during exceptional orthostatic stress in a 21-year-old man. *Respir. Physiol. Neurobiol.* 177, 66–70. doi: 10.1016/j.resp.2011.02.012

Du Bois, B., and Du Bois, E. F. (1916). A formula to estimate the approximate surface area if height and weight be known. *Arch. Intern. Med.* 17, 863–871.

Edwards, L. J., Muller, K. E., Wolfinger, R. D., Qaqish, B. F., and Schabenberger, O. (2008). An R2 statistic for fixed effects in the linear mixed model. *Stat. Med.* 27, 6137–6157. doi: 10.1002/sim.3429

Eeftinck Schattenkerk, D. W., Van Lieshout, J. J., Van den Meiracker, A. H., Wesseling, K. R., Blanc, S., Wieling, W., et al. (2009). Nexfin noninvasive continuous blood pressure validated against Riva-Rocci/Korotkoff. *Am. J. Hypertens.* 22, 378–383. doi: 10.1038/ajh.2008.368

Friedman, D. B., Jensen, F. B., Matzen, S., and Secher, N. H. (1990). Non-invasive blood pressure monitoring during head-up tilt using the Penaz principle. *Acta Anaesthesiol. Scand.* 34, 519–522. doi: 10.1111/j.1399-6576.1990.tb03137.x

Gisolf, J., Akkerman, E. M., Schreurs, A. W., Strackee, J., Stok, W. J., and Karemaker, J. M. (2004a). Tilt table design for rapid and sinusoidal posture change with minimal vestibular stimulation. *Aviat. Space Environ. Med* 75, 1086–1091.

Gisolf, J., Wilders, R., Immink, R. V., Van Lieshout, J. J., and Karemaker, J. M. (2004b). Tidal volume, cardiac output and functional residual capacity determine end-tidal CO_2 transient during standing up in humans. *J. Physiol.* 554(Pt 2), 579–590. doi: 10.1113/jphysiol.2003.056895

Guyton, A. C. (1980). "Control theory and its application to arterial pressure regulation: proportional control, integral control, gain, and damping mechanism," in *Circulatory Physiology III. Arterial Pressure and Hypertension*, ed A. C. Guyton (Philadelphia: Saunders W.B.), 30–54.

Guyton, A. C., Cowley, A. W., Norman, A. R., Coleman, T. G., and Samar, R. E. (1980). "The arterial baroreceptor reflex, a pressure buffering system," in *Circulatory Physiology III. Arterial Pressure and Hypertension*, ed A. C. Guyton (Philadelphia, PA: Saunders W.B.), 248–265.

Harms, M. P. M., Van Lieshout, J. J., Jenstrup, M., Pott, F., and Secher, N. H. (2003). Postural effects on cardiac output and mixed venous oxygen saturation in humans. *Exp. Physiol.* 88, 611–616. doi: 10.1113/eph8802580

Heenen, S., De, B. D., and Vincent, J. L. (2006). How can the response to volume expansion in patients with spontaneous respiratory movements be predicted? *Crit. Care* 10, R102. doi: 10.1186/cc4970

Hofer, C. K., Muller, S. M., Furrer, L., Klaghofer, R., Genoni, M., and Zollinger, A. (2005). Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting. *Chest* 128, 848–854. doi: 10.1378/chest.128.2.848

Immink, R. V., Hollmann, M. W., Truijen, J., Kim, Y. S., and Van Lieshout, J. J. (2010). The cerebrovascular pressure-flow relationship: a simple concept but a complex phenomenon. *Hypertension* 56:e2. doi: 10.1161/HYPERTENSIONAHA.110.152728

Immink, R. V., Pott, F. C., Secher, N. H., and Van Lieshout, J. J. (2013). Hyperventilation, cerebral perfusion and syncope. *J. Appl. Physiol.* 116, 844–851. doi: 10.1152/japplphysiol.00637.2013

Immink, R. V., Secher, N. H., Roos, C. M., Pott, F. C., Madsen, P. L., and Van Lieshout, J. J. (2006). The postural reduction in middle cerebral artery blood velocity is not explained by $PaCO_2$. *Eur. J. Appl. Physiol.* 96, 609–614. doi: 10.1007/s00421-006-0136-6

Immink, R. V., Truijen, J., Secher, N. H., and Van Lieshout, J. J. (2009). Transient influence of end-tidal carbon dioxide tension on the postural restraint in cerebral perfusion. *J. Appl. Physiol.* 107, 816–823. doi: 10.1152/japplphysiol.91198.2008

Immink, R. V., van den Born, B. J., Van Montfrans, G. A., Koopmans, R. P., Karemaker, J. M., and Van Lieshout, J. J. (2004). Impaired cerebral autoregulation in patients with malignant hypertension. *Circulation* 110, 2241–2245. doi: 10.1161/01.CIR.0000144472.08647.40

Jacques, D., Bendjelid, K., Duperret, S., Colling, J., Piriou, V., and Viale, J. P. (2011). Pulse pressure variation and stroke volume variation during increased intra-abdominal pressure: an experimental study. *Crit. Care* 15:R33. doi: 10.1186/cc9980

Jellema, W. T., Groeneveld, A. B., Wesseling, K. H., Thijs, L. G., Westerhof, N., and Van Lieshout, J. J. (2006). Heterogeneity and prediction of hemodynamic responses to dobutamine in patients with septic shock. *Crit. Care Med.* 34, 2392–2398. doi: 10.1097/01.CCM.0000233871.52553.CD

Jorgensen, L. G., Perko, M., Perko, G., and Secher, N. H. (1993). Middle cerebral artery velocity during head-up tilt induced hypovolaemic shock in humans. *Clin. Physiol.* 13, 323–336. doi: 10.1111/j.1475-097X.1993.tb00333.x

Kapoor, W. N. (2002). Current evaluation and management of syncope. *Circulation* 106, 1606–1609. doi: 10.1161/01.CIR.0000031168.96232.BA

Kim, Y. S., Immink, R. V., Stok, W. J., Karemaker, J. M., Secher, N. H., and van Lieshout, J. J. (2008). Dynamic cerebral autoregulatory capacity is affected early in Type 2 diabetes. *Clin. Sci. (Lond).* 115, 255–262. doi: 10.1042/CS20070458

Krantz, T., Cai, Y., Lauritsen, T., Warberg, J., and Secher, N. H. (2000). Accurate monitoring of blood loss: thoracic electrical impedance during hemorrhage in the pig. *Acta Anaesthesiol. Scand.* 44, 598–604. doi: 10.1034/j.1399-6576.2000.00519.x

Lassen, N. A. (1974). Autoregulation of cerebral blood flow. *Circ. Res.* 15(Suppl. 1), 201–204.

Lucas, S. J., Tzeng, Y. C., Galvin, S. D., Thomas, K. N., Ogoh, S., and Ainslie, P. N. (2010). Influence of changes in blood pressure on cerebral perfusion and oxygenation. *Hypertension* 55, 698–705. doi: 10.1161/HYPERTENSIONAHA.109.146290

Maitland, K., Kiguli, S., Opoka, R. O., Engoru, C., Olupot-Olupot, P., Akech, S. O., et al. (2011). Mortality after fluid Bolus in African Children with severe infection. *N. Engl. J. Med.* 364, 2483–2495. doi: 10.1056/NEJMoa1101549

Maizel, J., Airapetian, N., Lorne, E., Tribouilloy, C., Massy, Z., and Slama, M. (2007). Diagnosis of central hypovolemia by using passive leg raising. *Intensive Care Med.* 33, 1133–1138. doi: 10.1007/s00134-007-0642-y

Marik, P. E., Cavallazzi, R., Vasu, T., and Hirani, A. (2009). Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit. Care Med.* 37, 2642–2647. doi: 10.1097/CCM.0b013e3181a590da

Martina, J. R., Westerhof, B. E., Van, G. J., de Beaumont, E. M., Truijen, J., Kim, Y. S., et al. (2012). Noninvasive continuous arterial blood pressure monitoring with Nexfin(R). *Anesthesiology* 116, 1092–1103. doi: 10.1097/ALN.0b013e31824f94ed

Matzen, S., Perko, G., Groth, S., Friedman, D. B., and Secher, N. H. (1991). Blood volume distribution during head-up tilt induced central hypovolaemia in man. *Clin. Physiol.* 11, 411–422. doi: 10.1111/j.1475-097X.1991.tb00813.x

McGee, S., Abernethy, W. B. III., and Simel, D. L. (1999). The rational clinical examination. Is this patient hypovolemic? *J. Am. Med. Assoc.* 281, 1022–1029. doi: 10.1001/jama.281.11.1022

Michard, F., Boussat, S., Chemla, D., Anguel, N., Mercat, A., Lecarpentier, Y., et al. (2000). Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am. J. Respir. Crit. Care Med.* 162, 134–138. doi: 10.1164/ajrccm.162.1.9903035

Michard, F., and Teboul, J. L. (2002). Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* 121, 2000–2008. doi: 10.1378/chest.121.6.2000

Myburgh, J. A. (2011). Fluid resuscitation in acute illness–time to reappraise the basics. *N. Engl. J. Med.* 364, 2543–2544. doi: 10.1056/NEJMe1105490

Ogoh, S., Brothers, R. M., Barnes, Q., Eubank, W. L., Hawkins, M. N., Purkayastha, S., et al. (2005). The effect of changes in cardiac output on middle cerebral artery mean blood velocity at rest and during exercise. *J. Physiol.* 569(Pt 2), 697–704. doi: 10.1113/jphysiol.2005.095836

Panerai, R. B. (2004). System identification of human cerebral blood flow regulatory mechanisms. *Cardovasc. Eng. Int. J.* 4, 59–71. doi: 10.1023/B:CARE.0000025123.43747.e1

Panerai, R. B., Dawson, S. L., and Potter, J. F. (1999). Linear and nonlinear analysis of human dynamic cerebral autoregulation. *Am. J. Physiol. Heart Circ. Physiol.* 277(3 Pt 2), H1089–H1099.

Pawelczyk, J., Matzen, S., Friedman, D. B., and Secher, N. H. (1994). "Cardiovascular and hormonal responses to central hypovolaemia in humans," in *Blood Loss and Shock,* eds N. H. Secher, J. A. Pawelczyk, and J. Ludbrook (London: Edward Arnold), 25–36.

Preisman, S., Kogan, S., Berkenstadt, H., and Perel, A. (2005). Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the Respiratory Systolic Variation Test and static preload indicators. *Br. J. Anaesth.* 95, 746–755. doi: 10.1093/bja/aei262

Rickards, C. A., Vyas, N., Ryan, K. L., Ward, K. R., Andre, D., Hurst, G. M., et al. (2014). Are you bleeding? Validation of a machine-learning algorithm for determination of blood volume status: application to remote triage. *J. Appl. Physiol* (1985) 116, 486–494. doi: 10.1152/japplphysiol.00012.2013

Riley, R. L., Permutt, S., Said, S., Godfey, M., Cheng, T. O., Howell, J. B. L., et al. (1959). Effect of posture on pulmonary dead space in man. *J. Appl. Physiol.* 14, 339–344.

Rowell, L. B. (1986). *Human Circulation Regulation During Physical Stress*. Oxford: Oxford University Press.

Roy, C. S., and Sherrington, C. S. (1890). On the regulation of the blood supply to the brain. *J. Physiol. (Lond.)* 11, 85–108.

Sander-Jensen, K., Secher, N. H., Bie, P., Warberg, J., and Schwartz, T. W. (1986). Vagal slowing of the heart during haemorrhage: observations from 20 consecutive hypotensive patients. *Br. Med. J.* 292, 364–366. doi: 10.1136/bmj.292.6517.364

Secher, N. H., and Van Lieshout, J. J. (2005). Normovolaemia defined by central blood volume and venous oxygen saturation. *Clin. Exp. Pharmacol. Physiol* 32, 901–910. doi: 10.1111/j.1440-1681.2005.04283.x

Secher, N. H., and Van Lieshout, J. J. (2010). Heart rate during haemorrhage: time for reappraisal. *J. Physiol.* 588(Pt 1), 19. doi: 10.1113/jphysiol.2009.184499

Serrador, J. M., Picot, P. A., Rutt, B. K., Shoemaker, J. K., and Bondar, R. L. (2000). MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke* 31, 1672–1678. doi: 10.1161/01.STR.31.7.1672

Shepherd, J. T., and Vanhoutte, P. M. (1979). *The Human Cardiovascular System. Facts and Concepts*. New York, NY: Raven Press.

Shoemaker, J. K., O'Leary, D. D., and Hughson, R. L. (2001). PET(CO2) inversely affects MSNA response to orthostatic stress. *Am. J. Physiol. Heart Circ. Physiol.* 281, H1040–H1046.

Sjöstrand T. (1953). Volume and distribution of blood and their significance in regulating the circulation. *Physiol. Rev.* 33, 202–225.

Soubrier, S., Saulnier, F., Hubert, H., Delour, P., Lenci, H., Onimus, T., et al. (2007). Can dynamic indicators help the prediction of fluid responsiveness in spontaneously breathing critically ill patients? *Intensive Care Med.* 33, 1117–1124. doi: 10.1007/s00134-007-0644-9

Ten Harkel, A. D. J., Baisch, F., and Karemaker, J. M. (1992). Increased orthostatic blood pressure variability after prolonged head down tilt. *Acta Physiol. Scand.* 144(S604), 89–99.

Truijen, J., Van Lieshout, J. J., Wesselink, W. A., and Westerhof, B. E. (2012). Noninvasive continuous hemodynamic monitoring. *J Clin. Monit. Comput.* 26, 267–278. doi: 10.1007/s10877-012-9375-8

Van Lieshout, J. J., Harms, M. P., Pott, F., Jenstrup, M., and Secher, N. H. (2005). Stroke volume of the heart and thoracic fluid content during head-up and head-down tilt in humans. *Acta Anaesthesiol. Scand.* 49, 1287–1292. doi: 10.1111/j.1399-6576.2005.00841.x

Van Lieshout, J. J., and Wesseling, K. H. (2001). Continuous cardiac output by pulse contour analysis? *Br. J. Anaesth.* 86, 467–469. doi: 10.1093/bja/86.4.467

Van Lieshout, J. J., Wieling, W., Karemaker, J. M., and Secher, N. H. (2003). Syncope, cerebral perfusion, and oxygenation. *J. Appl. Physiol.* 94, 833–848.

Westerhof, B. E., Gisolf, J., Karemaker, J. M., Wesseling, K. H., Secher, N. H., and Van Lieshout, J. J. (2006). Time course analysis of baroreflex sensitivity during postural stress. *Am. J. Physiol. Heart Circ. Physiol.* 291, H2864–H2874. doi: 10.1152/ajpheart.01024.2005

Willie, C. K., Tzeng, Y. C., Fisher, J. A., and Ainslie, P. N. (2014). Integrative regulation of human brain blood flow. *J. Physiol.* 592, 841–859. doi: 10.1113/jphysiol.2013.268953

Zhang, R., Zuckerman, J. H., and Levine, B. D. (1998). Deterioration of cerebral autoregulation during orthostatic stress: insights from the frequency domain. *J. Appl. Physiol.* 85, 1113–1122.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 29 November 2013; accepted: 03 April 2014; published online: 23 April 2014.
*Citation: Bronzwaer A-SGT, Stok WJ, Westerhof BE and van Lieshout JJ (2014) Arterial pressure variations as parameters of brain perfusion in response to central blood volume depletion and repletion. Front. Physiol. **5**:157. doi: 10.3389/fphys.2014.00157*
This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in
PHYSIOLOGY

REVIEW ARTICLE
published: 07 April 2014
doi: 10.3389/fphys.2014.00120

Arterial pressure and cerebral blood flow variability: friend or foe? A review

Caroline A. Rickards[1]* and Yu-Chieh Tzeng[2]

[1] *Department of Integrative Physiology, Cardiovascular Research Institute, University of North Texas Health Science Center, Fort Worth, TX, USA*
[2] *Cardiovascular Systems Laboratory, Centre for Translational Physiology, University of Otago, Wellington, New Zealand*

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
James Todd Pearson, Monash University, Australia
Johannes J. Van Lieshout, University of Amsterdam, Netherlands

****Correspondence:***
Caroline A. Rickards, Department of Integrative Physiology, University of North Texas Health Science Center, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107, USA
e-mail: caroline.rickards@unthsc.edu

Variability in arterial pressure and cerebral blood flow has traditionally been interpreted as a marker of cardiovascular decompensation, and has been associated with negative clinical outcomes across varying time scales, from impending orthostatic syncope to an increased risk of stroke. Emerging evidence, however, suggests that increased hemodynamic variability may, in fact, be protective in the face of acute challenges to perfusion, including significant central hypovolemia and hypotension (including hemorrhage), and during cardiac bypass surgery. This review presents the dichotomous views on the role of hemodynamic variability on clinical outcome, including the physiological mechanisms underlying these patterns, and the potential impact of increased and decreased variability on cerebral perfusion and oxygenation. We suggest that reconciliation of these two apparently discrepant views may lie in the time scale of hemodynamic variability; short time scale variability appears to be cerebroprotective, while mid to longer term fluctuations are associated with primary and secondary end-organ dysfunction.

Keywords: blood pressure variability, cerebral blood flow variability, cerebral blood flow (CBF), end organ damage, hemodynamic oscillations

INTRODUCTION

Traditionally, clinicians have assessed the cardiovascular status of their patients with static "snapshot" techniques, such as radial pulse for heart rate, brachial sphygmomanometry for arterial pressure, and chest excursions for respiration rate. Subsequently, clinical judgment about health status and identification of potential risk factors was based on average values, without consideration of the inherent dynamic nature of these variables. While the notion that arterial blood pressure is not constant, but fluctuates dynamically over time has been known since the 18th century, the clinical importance of this phenomenon is only now being recognized. There is growing recognition that assessment of hemodynamic variability (e.g., heart rate and arterial pressure) across multiple time scales may provide important insight into acute and long-term clinical outcomes, such as risk of stroke (Shimbo et al., 2012), myocardial infarction (Kjellgren and Gomes, 1993), and end organ damage from hypertension (Mancia et al., 2007; Verdecchia et al., 2007; Leoncini et al., 2013). With advances both in monitoring technologies and data analysis capabilities, we now have the capacity to capture dynamic changes in patient status by recording and analyzing non-invasive, high frequency hemodynamic waveform data, including ECG, arterial pressure, and most recently, cerebral blood flow and oxygenation. These high fidelity recordings have advanced assessment of hemodynamic variability from intermittent day-to-day or visit-to-visit measures, to a beat-to-beat time scale.

In particular, the advent of transcranial Doppler (TCD) ultrasound monitoring in the 1980s by Aaslid et al. (1982) rapidly moved assessment of cerebral blood flow from invasive, technically cumbersome techniques with poor spatial (global cerebral perfusion) and temporal (minutes) resolution [e.g., the Kety-Schmidt diffusible tracer method (Kety and Schmidt, 1948)], to a relatively easy, non-invasive method, overcoming these resolution limitations (i.e., spatial resolution: individual intracranial vessels; temporal resolution: beat-to-beat). TCD ultrasound is now routinely utilized in both the research and clinical settings (Newell and Aaslid, 1992; Willie et al., 2011), and, in combination with non-invasive cerebral oxygen monitoring technologies (e.g., near infra-red spectroscopy, NIRS), continuous assessment of both cerebral blood flow *and* oxygenation are possible.

The evolving appreciation that measurement of hemodynamic variability provides important physiological insight is demonstrated by Newell et al. in the early 1990s who cautioned that the variability of cerebral blood velocity obtained from TCD may "interfere" with measurement of mean values (Newell et al., 1992). Since then, cerebral blood flow variability has been extensively examined in the research setting in an effort to understand underlying regulatory mechanisms, particularly the role of adrenergic (Zhang et al., 2002; Ogoh, 2008; Hamner et al., 2010; Peebles et al., 2012; Purkayastha et al., 2013), cholinergic (Hamner et al., 2012), and myogenic modulation (Langager et al., 2007; Tzeng et al., 2011; Tan et al., 2013) of the cerebral vasculature with changes in arterial pressure. Assessment of cerebral blood flow variability in the clinical setting, however, has lagged the abundance of studies investigating the role of blood pressure variability (BPV), despite clear implications for the subsequent integrity of cerebral tissues (Tzeng et al., 2012b).

Furthermore, the potential role of increased variability in arterial pressure and cerebral blood flow on clinical outcome is somewhat disparate, with studies suggesting both protective (e.g. Sanderson et al., 1972; Allen et al., 2012; Koning et al., 2012), and

detrimental (e.g., Lipsitz et al., 1997; Zhang et al., 1998b; Parati, 2005; Kilpatrick et al., 2010; Ko et al., 2010; Rothwell, 2010) effects. This review will provide a brief background on some of the underlying physiological mechanisms responsible for variability in pressure and flow, and then examine the evidence on both sides of the debate, including potential reasons for this apparent dichotomy.

TIME SCALE OF PRESSURE AND FLOW VARIABILITY

Fluctuations in arterial pressure and cerebral blood flow occur across multiple time scales, from beat-to-beat (**Figure 1**) to day-to-day variability, all associated with a multitude of over-lapping and interacting physiological processes. The most commonly reported metrics of pressure and flow variability include time domain means and standard deviations, which can represent both "static," long-term variations (hours to days) and short-term (minute to minute) variability, while methods such as power spectral analysis, often assessed using various discrete frequency bands, are generally only suitable for assessment of short-term variations (e.g., 5–20 min).

The underlying physiological mechanisms associated with these different methodological approaches align with the time scale of measurement. For example, changes in mean and standard deviations of pressure and flow over hours to days are most likely associated with long time scale cycles, such as circadian rhythms, hormonal fluctuations, hydration status, fatigue, and associated variations in vascular properties such as compliance (Kotsis et al., 2011; Schillaci et al., 2012; Garcia-Garcia et al., 2013). In comparison, beat-to-beat or minute to minute variability quantifies physiological mechanisms operating within this time scale, such as the cardiac cycle (e.g., approx. $\geq$1 Hz), respiratory frequency (e.g., high frequency (HF); 0.15–0.4 Hz) (Brown et al., 1993; Cooke et al., 1998), sympathetic/baroreflex modulation (e.g., low frequency (LF); 0.04–0.15 Hz) (Julien, 2006; Stauss, 2007), and myogenic activity (e.g., very low frequency (VLF); 0.004-0.04 Hz) (Stauss, 2007; Tzeng et al., 2011; Tan et al., 2013).

It is important to note that the terminology used to describe hemodynamic variability differs between disciplines; while in the clinical setting, "short-term" variability may describe changes in arterial pressure every 15 min over a 24-h period (Schillaci et al., 2012), this same designation can also be used to describe beat-to-beat variations quantified in the frequency domain. In the case of this review, we will use the latter definition for short-term variability (i.e., 5–10 min recordings with quantification of VLF, LF and HF power), and longer time scales will be described as mid- (within 24-h) and long-term variability (day-to-day, or visit-to-visit).

"FOE"

The idea that exaggeration of hemodynamic variability may be detrimental for vital organs such as the brain is both physiologically plausible and intuitive. Because the brain has a high metabolic demand for oxygen, any process that enhances perfusion variability has the potential to destabilize tissue oxygenation leading to ischemic injury. Conversely, excessive perfusion can result in the breakdown of the blood-brain barrier, permit the transudation of fluid into the interstitium, and incite hyperperfusion syndromes that are characterized by debilitating neurological sequelae including seizures, headaches, encephalopathy and stroke (van Mook et al., 2005). Therefore, stringent control of cerebral blood flow is pivotal for normal brain function.

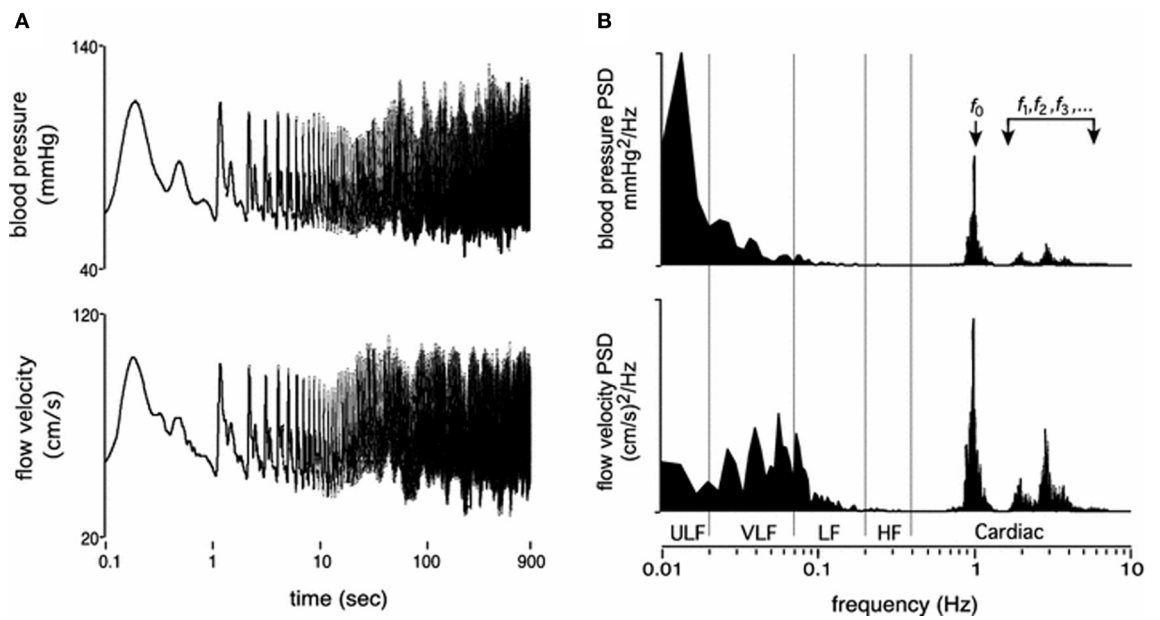


FIGURE 1 | Resting time domain arterial pressure and cerebral blood velocity tracings (A) and corresponding power spectrums across the frequency range of 0.01–10 Hz (B). Panels are presented on log axes. ULF, ultra low frequency; VLF, very low frequency; LF, low frequency; HF, high frequency. f_0, $f_{1...}f_n$, refers to the fundamental cardiac frequency and its higher frequency harmonics (From Tzeng and Ainslie, 2014).

However, while it is generally recognized that blood pressure is an important determinant of cerebral blood flow, the exact relationship between pressure and flow is more complex when viewed in light of a contemporary model of cerebral autoregulation (CA) (Tzeng and Ainslie, 2014). The classic model of CA is that cerebral blood flow is maintained constant across a wide range of cerebral perfusion pressures (60–150 mm Hg) (Lassen, 1959). This concept implies that mechanisms normally involved in systemic blood pressure control are relatively unimportant for cerebral blood flow in the presence of intact CA, which is assumed to effect near-perfect compensation of blood pressure variations within the autoregulatory range. Blood pressure, however, is not a static entity that can be described purely in steady-state terms. Blood pressure is highly dynamic and the capacity of the cerebrovasculature to counter-regulate against blood pressure changes is relative and depends on the timescale of the presenting stimuli. Available data supports the idea that the slower, low frequency, components of blood pressure are more effectively buffered than faster, higher frequency, components (such as those associated with respiration), and elevations in blood pressure may be better buffered than reductions in blood pressure (Zhang et al., 1998a). Although the precise mechanisms underpinning these features of CA are still under investigation (Tzeng et al., 2011, 2012a), it is clear that cerebral blood flow exhibits variability, and that BPV is an important determinant of this variability (Tzeng and Macrae, 2013).

Unlike the case for cerebral perfusion variability being a "friend" with protective properties, little data exists that directly implicate perfusion variability being a "foe" for organ function. Rather, the case for exaggerated haemodynamic variability being a negative predictor for organ dysfunction is mainly built on studies of blood pressure dynamics that came initially with the advent of ambulatory blood pressure monitoring in the 1960s (Parati et al., 2001), and since then, other non-invasive blood pressure monitoring devices that allow detailed blood pressure assessment down to timescales of seconds. The successful application of non-invasive blood pressure monitoring technology has firmly established the idea that identifying elevated BPV across a wide range of timescales (as distinct from average blood pressure) may be useful in predicting poorer health outcome (Rothwell, 2010). Notwithstanding the limitations of drawing inferences on cerebral perfusion from blood pressure, we herein present a summary of research that suggest exaggerated systemic hemodynamic variability is associated with poor clinical outcomes.

BPV AND PRIMARY ORGAN INJURY

As previously described, short-term variations in blood pressure are commonly characterized in the frequency domain using power spectral analysis typically of short recordings (e.g. range 5–10 min) (Tzeng and Macrae, 2013). Such variations encompass beat-to-beat changes due to mechanically induced changes in cardiac output caused by respiratory activity (Sin et al., 2010), and longer term fluctuations related to a myriad of cardiovascular control mechanisms including the arterial baroreflex (Tzeng et al., 2009), the renin-angiotensin system (Gouedard et al., 1996), the vascular myogenic response (Bayliss, 1902), and endothelial nitric oxide release (Nafz et al., 1996). As a result, enhanced short term variability may occur due to altered central autonomic drive, impaired arterial baroreflex function, changes in humoral factors, and well as changes in ventilatory parameters (Stauss, 2007). Compared to longer-term variations, which are clearly associated with end-organ disease (Sega et al., 2002), there is little direct evidence implicating short-term BPV in these pathophysiological processes. However, some investigations have suggested a role of increased LF variability in arterial pressure (Lipsitz et al., 1997) and cerebral blood flow (Zhang et al., 1998b) in acute orthostatic intolerance, associated with enhanced vasomotor activity mediated by variations in sympathetic activity (Lipsitz et al., 1997) and impaired CA (reducing the ability to buffer fluctuations in arterial pressure) (Zhang et al., 1998b). Augmentation of spontaneously occurring oscillations in blood pressure and cerebral blood velocity and cerebral oxygenation in the 0.06–0.40 Hz range have also been documented in hypertensive patients (Li et al., 2013). The clinical significance of these hemodynamic changes are presently unclear but may reflect alterations in metabolic and or vascular myogenic function in hypertensive individuals.

Mid-term blood pressure variations are usually defined as blood pressure fluctuations that occur within a 24-h period. There is considerable overlap in the mechanisms that are responsible for both mid-term and short-term blood pressure variations. Therefore, impairment of baroreflex function, or central sympathetic drive can both augment mid-term BPV. In an early investigation into the link between elevated mid-term BPV to end organ damage, Parati et al., showed that 24-h mean blood pressure and 24-h BPV were independently associated with the magnitude of mid-term BPV (Parati et al., 1987). Subsequently, elevated mid-term BPV has been found to be independently linked to a number of outcome measures that indicated widespread vascular and end-organ damage to the heart, blood vessels, and the kidneys. In particular, there is substantive data pointing to an enhanced propensity for carotid intimal media thickening and atherosclerosis progression (Mancia et al., 2001), increased arterial stiffness (Schillaci et al., 2012), and the development of left ventricular hypertrophy (Schutte et al., 2011). Interestingly, the relationships between BPV and left ventricular hypertrophy is apparent in patients with and without elevations in absolute blood pressure (Palatini et al., 1992), suggesting that surveillance for elevated mid-term BPV may help identify apparently normotensive individuals who are otherwise at increased risk of cardiovascular complications. In other studies that have primarily focused on clinical outcome measures, elevated mid-term BPV is associated with a higher risk of coronary artery restenosis after percutaneous coronary intervention (Cay et al., 2011), cognitive dysfunction in the elderly (Sakakura et al., 2007), and increased radiological presence of cerebral micro-bleeds and white matter hyper-intensities on MRI (Liu et al., 2012).

There is also an emerging body of literature relating BPV and disease outcomes based on clinical measurements of day-to-day or visit-to-visit brachial blood pressures that provide information on long-term blood pressure variability (Mancia et al., 2012). In studies involving the general population, day-to-day systolic and diastolic BPV have been linked to increased all-cause mortality, cardiac mortality, and stroke-related mortality (Kikuya et al., 2008; Johansson et al., 2012). Likewise in patients with

co-morbidities such as diabetes and chronic kidney disease, visit-to-visit systolic BPV has been linked to elevated risk of death, and accelerated deterioration of renal function (McMullan et al., 2013).

It needs to be acknowledged that while the majority of research has linked elevated mid- and long-term BPV with increased risk of end-organ disease, there is some data suggesting that the impact of BPV are no greater than can be explained by mean pressure alone. For example, Schutte et al., have argued that in a large unbiased population sample ($n = 2944$), BPV does not contribute to risk stratification over and beyond mean systolic pressure (Schutte et al., 2012). However, blood pressure recordings in this particular trial involved five consecutive blood pressure recordings taken on only two occasions separated 2–4 weeks apart. Given the complexities of BPV, it seems that such a protocol is unlikely to yield a comprehensive summary of true BPV.

BPV AND SECONDARY ORGAN INJURY

Not only are increases in mid- and long-term BPV associated with accelerated end-organ damage and acute primary cardiovascular events (e.g., acute stroke) (Pringle et al., 2003), there is growing recognition that BPV (beat-to-beat and reading-to-reading) is also a crucial determinant of acute secondary organ damage, once an initial vascular insult has occurred (Stead et al., 2006; Sykora et al., 2009; Tsivgoulis and Ntaios, 2012). Secondary damage is particularly important for organs such as the heart and brain that have no regenerative capacity and have a high metabolic demand for oxygen and therefore low tolerance for hypoxia. Accumulating clinical data shows that patients who are admitted to hospital with acute stroke are more likely to suffer poor function outcomes if BPV is acutely elevated (Dawson et al., 2000). Enhanced beat-to-beat, or reading-to-reading BPV during the acute stroke period predicts the risk of secondary stroke complications such as hemorrhagic transformation of an ischemic stroke (Ko et al., 2010). Because major cardiovascular events such as stroke are often accompanied by increased absolute blood pressure, a major challenge for data interpretation is separating the effects of elevated BPV from that of average increases in mean blood pressure (Schutte et al., 2012). Although Ko et al., has convincingly demonstrated that individuals with high reading-to-reading BPV are more likely to develop secondary complications following stroke event regardless of whether absolute blood pressure is high or low (Ko et al., 2010) (**Figure 2**), not all studies have fully accounted for likely interactions between these two facets of blood pressure. Further, it must be recognized that Ko et al., did not specifically quantify cerebral perfusion variability. The relationships between elevated BPV and perfusion stability in neurocritical care populations remains poorly understood.

MECHANISMS AND IMPLICATIONS FOR ENHANCED BPV AND END-ORGAN DAMAGE

The precise mechanisms underpinning the regulation of BPV are multi-factorial and involve factors that drive and attenuate blood pressure changes. Behavioral factors (Pickering et al., 1982) such as physical activity, changes in body posture, and sleep, can induce blood pressure changes at varying time scales. Likewise, centrally driven influences (e.g., sympathetic neural outflow) can also enhance BPV (Poletto et al., 2011; Yoshimoto et al., 2011). Recent genome-wide association studies have identified potential genetic markers for enhanced BPV (Xu et al., 2013), which suggests that BPV elevation may be a heritable trait like hypertension. On the other hand, neural blood pressure control mechanisms, in particular the arterial baroreflex, functions to attenuate blood pressure changes (Bristow et al., 1969). Therefore, the balance between factors that favor and oppose blood pressure variations ultimately determines mid- and long-term BPV.

The precise mechanisms underpinning the links between elevated BPV and end-organ damage are not yet fully understood, but available evidence suggest that both functional impairment and structural vascular changes are involved (**Figure 3**). Several studies have shown in sino-aortic denervated (SAD) rats that a chronic increase in BPV induces aortic hypertrophy and left ventricular hypertrophy (Su and Miao, 2001; Miao and Su, 2002). The mechanical cardiac changes are typified by enhanced cardiac wall thickness and increased total myocardial wall area, and relative reduction in elastin (Su and Miao, 2001). There is also evidence that increased BPV induced by SAD increases cardiac expression of type I and III collagen, and atrial natriuretic peptide (Flues et al., 2012). These findings suggest that the hypertrophic cardiac changes in SAD are the consequence of collagen accumulation in addition to smooth muscle proliferation. The time course of these changes are poorly understood but preliminary evidence suggests that cardiac changes usually arise only after elevations in BPV. In contrast, evidence suggests that vascular changes occur early and can be the first signs of BPV related organ damage. In SAD rats for example, vascular changes emerge as early as 2 weeks whereas cardiac changes occur around 10–16 weeks (Miao and Su, 2002). The trigger for these abnormal structural changes are unclear but enhanced stress on the arterial wall associated with increased rate of blood pressure variations may play a role (Miao et al., 2006). In contrast, the downstream effects of stiff arteries on the cardiovascular system are well recognized. The loss of arterial compliance leads to the loss of the Windkessel function which can lead to enhanced linear transmission pulse waves along the arterial path (Bateman, 2004), as well as increase left ventricular load (Yano et al., 1997). This may explain why vascular changes appear to precede cardiac changes in animal experimental models such as the SAD rat (Miao and Su, 2002). It is important to recognize that associations between BPV and end-organ dysfunction do not imply causality and it is possible that BPV elevation may be the product, rather than the cause of organ damage.

Furthermore, in addition to vascular structural changes, elevated BPV can also lead to end-organ dysfunction by disturbing organ perfusion and oxygenation. Because the vital organs such as the brain and heart have high metabolic demand, any process that enhances perfusion variability has the potential to destabilize tissue oxygenation and therefore result in organ dysfunction. This means that, in addition to BPV, the integrity of flow-stabilizing mechanisms such as CA may partly underlie the relationship between elevated BPV and end-organ disease, particularly in the context of secondary brain injury (Reinhard et al., 2005, 2012; Aries et al., 2010). The complexities that CA introduces may also be of importance when

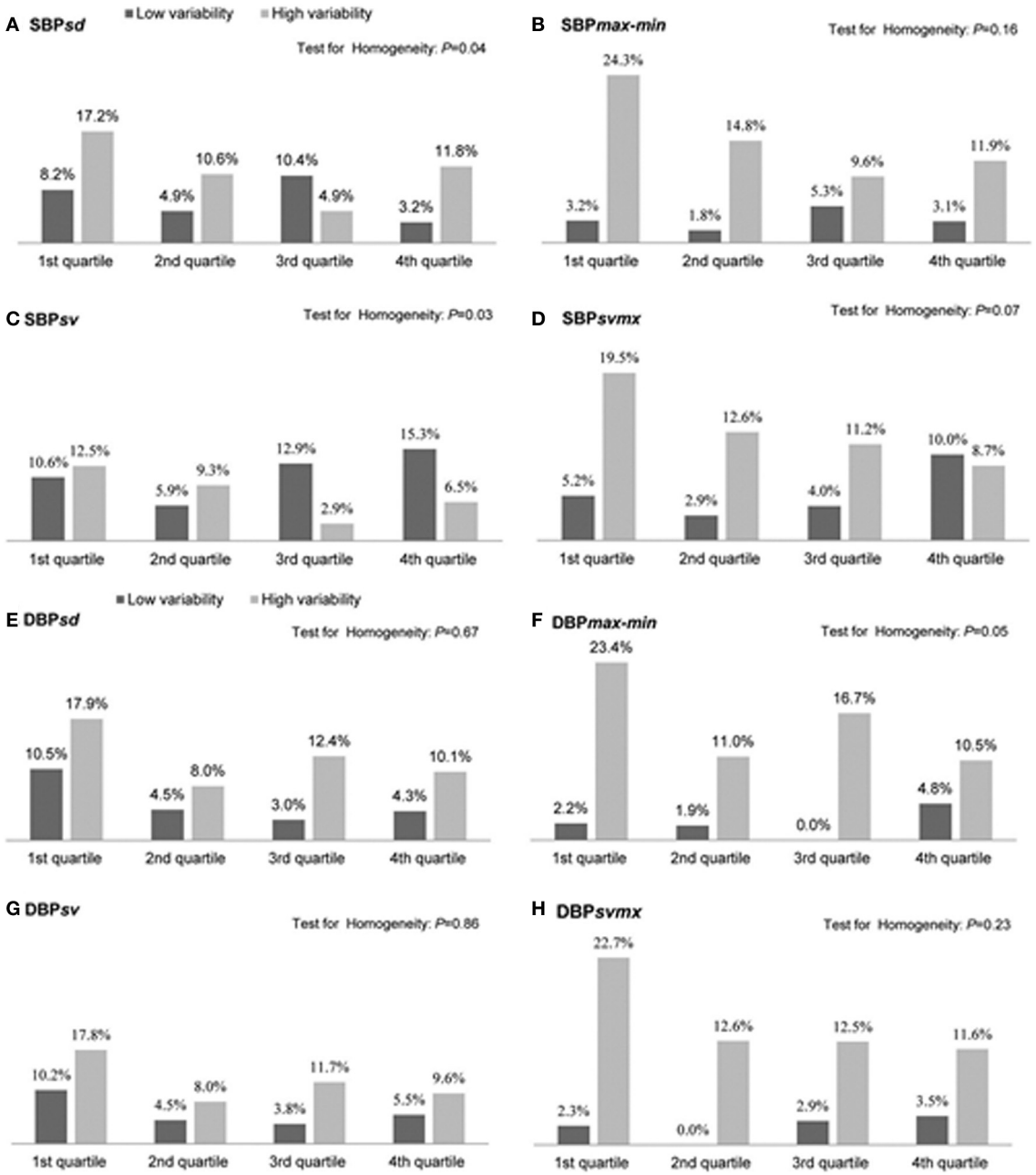


FIGURE 2 | Proportion (%) of patients with hemorrhagic transformation following an initial ischemic stroke in the low and high blood pressure variability groups of each quartile of mean systolic blood pressure (SBP) or mean diastolic blood pressure (DBP) during the first 72 h. Measures of blood pressure variability include the standard deviation (SD), difference between maximum and minimum (max-min), the successive variation index (sv), and the maximum successive variation index (svmax). The successive variation was defined as the square root of average difference in blood pressure between successive measurements (From Ko et al., 2010, with permission).

considering the pathogenesis of BPV related disease as well as therapeutic treatment effects. Recently, Matsui et al. (2012) reported that day-by-day BPV is lower in patients treated with an angiotensin II receptor blocker/calcium channel blocker combination compared to those treated with an angiotensin II receptor blocker/diuretic combination. This raised the possibility that elevated BPV and or cerebral blood flow variability can be treated using conventional antihypertensive agents (Parati and Bilo, 2012) (**Figure 4**).

"FRIEND"

While a wealth of studies have assessed the *negative* clinical consequences of high BPV (and most likely variability in cerebral blood flow) as highlighted in the "foe" section of this review, the

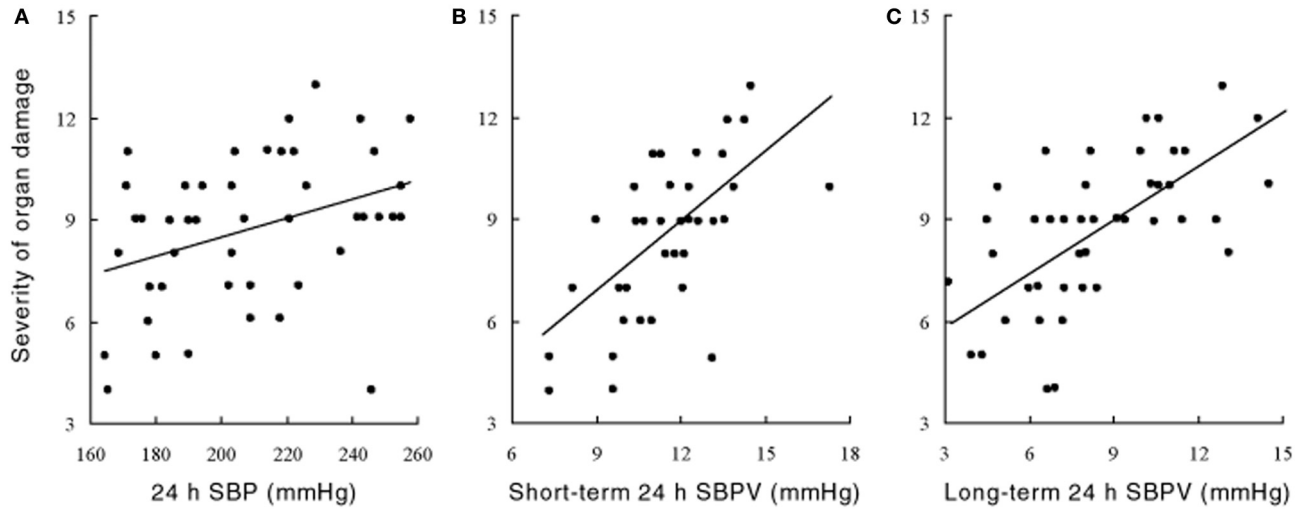


FIGURE 3 | Relationship between the severity of organ damage and (A) 24 h systolic blood pressure (SBP) and (B,C) its variability (SBPV) in the short (B) and long term (C) spontaneously hypertensive rat at 60 weeks of age. For **(A)**: $n = 50$, $r = 0.31$, $P < 0.05$; for **(B)**: $n = 50$, $r = 0.65$, $P < 0.001$; for **(C)**: $n = 50$, $r = 0.63$, $P < 0.001$. Severity of organ damage are composite scores calculated from the scoring criteria outlined in Shan et al. (1999). Rats are assigned scores ranging from 0 (no evidence of damage) to 2 (severe damage) for a broad range of clinically relevant gross-anatomic and light micro-scopic end-points. Specific items include left/right ventricular thickness, renal cortical thickness, myocardial infarction/ischaemia, coronary atherosclerosis, thickness of myocardial fibers, atrophy or compensative enlargement of glomeruli, and tubules, Arterial sclerosis and degeneration of kidney, Basilar artery arteriosclerosis of cerebrum, Cerebral hemorrhage or infarction, mesenteric artery hypertrophy, and stroke and hemiplegia (Data and results from Su and Miao, 2001, with permission).

potentially *protective* effect of pulsatile arterial pressure and/or cerebral blood flow has also been demonstrated in a variety of experimental and clinical settings, focused primarily on what we define as "short-term" variability.

"HIGH" FREQUENCY PULSATILE FLOW

In 1972, Sanderson et al. (1972) demonstrated that pulsatile cerebral blood flow was associated with decreased neuronal damage following prolonged cardiac arrest in dogs (up to 3 h). The frequency of the pulsatile perfusion was 1.7 Hz (i.e., 100 cycles/minute), consistent with the estimated heart rate, and was able to generate pulse pressures of 25–90 mm Hg, compared with only 2–15 mm Hg with non-pulsatile perfusion (Sanderson et al., 1972). Mean arterial pressure and blood flow, however, were approximately 50 and 12% lower with pulsatile perfusion, but peripheral vascular resistance was also 57% lower; increased shear stress with pulsatile perfusion increases endothelial nitric oxide production (Nakano et al., 2000; Lanzarone et al., 2009), subsequently decreasing resistance (Nakano et al., 2000). The observed decrease in neuronal damage indicates that pulsatile flow improves perfusion and oxygenation of vital tissue, even with lower perfusion pressures. In reviewing the literature, Sanderson et al. (1972) suggest that pulsatile flow may also promote baroreflex-mediated vasodilation, increase the rate of tissue respiration, reduce cerebral critical closing pressure, and prevent the depression of kidney function. In a study of prolonged cardiopulmonary bypass (up to 80 min) combined with hypothermia in dogs, Onoe et al. also demonstrated an increase in cerebral blood flow with pulsatile perfusion, although once rewarming was complete this only persisted in the group arrested for 60 min (Onoe et al., 1994). While some of these findings have been substantiated in subsequent studies of extracorporeal perfusion with cardiac bypass surgery in patient populations, with increased microcirculatory perfusion of the sublingual mucosa (Koning et al., 2012; O'Neil et al., 2012) (**Figure 5**), increased oxygen consumption (Koning et al., 2012), reduced leukocyte activation (O'Neil et al., 2012), and decreased morbidity and mortality (Taylor et al., 1982; Murkin et al., 1995), pulsatile perfusion therapy is still not a standard procedure in this setting (Hornick and Taylor, 1997; Murkin, 2006; O'Neil et al., 2012).

Pulsatile flow has also been shown to improve cerebral hemodynamic status in other clinically relevant states, including prolonged cerebral ischemia as a model of stroke (Allen et al., 2012), and severe hemorrhage (Bassuk et al., 2010). In a pig model of prolonged (30-min) isolated global normothermic brain ischemia, Allen et al. (Allen et al., 2012) demonstrated that 20-min of pulsatile perfusion at a frequency of 1.3 Hz (80 cycles/min) and a flow rate of 750 ml/min resulted in reduced neurological deficit and cerebral tissue edema, no post-ischemic seizures (compared to 100% of animals in the non-pulsatile perfusion group), and an attenuated increases in oxygen radical damage. While these studies show benefit with pulsatile perfusion at or around the cardiac frequency, Adams et al. (Adams et al., 2000, 2001) have introduced a novel approach to induce pulsatile flow by applying whole body periodic acceleration in the head-to-foot axis (Gz) at a frequency of approximately 3–4 Hz (180–240 cycles/min) and an acceleration of $\pm 0.4\ m/s^2$. These investigators have demonstrated that periodic acceleration can increase vital organ blood flow in pigs, including the brain, heart, kidneys, and liver at rest (Adams et al., 2001), and following significant

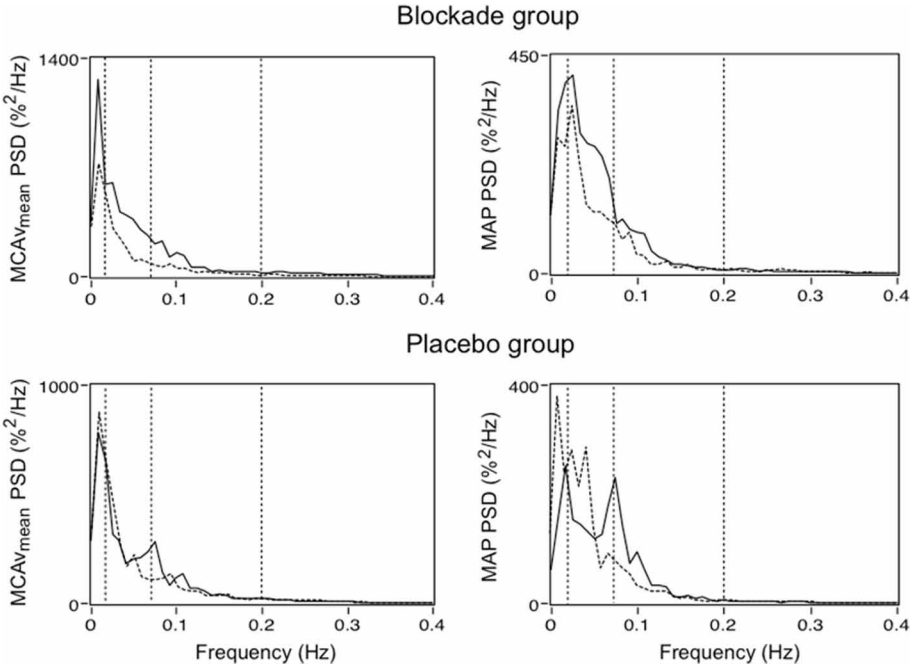


FIGURE 4 | Power spectral density (PSD) for mean middle cerebral artery flow velocity ($MCAv_{mean}$) and mean arterial blood pressure (MAP) in patients treated with a low dose calcium channel blocker (oral Nimodipine 60 mg) and placebo pill. Solid and dashed lines represent group median PSD before and following treatment, respectively. Dashed vertical lines illustrate boundaries of the very low frequency (VLF; 0.02–0.07 Hz), low frequency (LF; 0.07–0.20 Hz), and high frequency (HF; 0.20–0.30 Hz) bands (Adapted from Tzeng and Macrae, 2013).

clinical events such as severe hemorrhage (Bassuk et al., 2010), and cardiac arrest (Adams et al., 2011); subsequent survival from hemorrhage also increased from 0 to 50% (Bassuk et al., 2010). In studies using rats and piglets, these protective effects have been shown to be mediated by shear-stress induced release of vasoactive mediators including endothelial nitric oxide, prostacyclin, and prostaglandin E2, with subsequent vasodilation leading to improved tissue perfusion (Adams et al., 2005; Uryash et al., 2009). The potential role of periodic acceleration in recovery from stroke has also been established, with reduced brain damage up to 7 days following ischemia, indicated by reduced infarct size, and decreased markers of autophagy (beclin 1) and apoptosis (fractin) (Martinez-Murillo et al., 2009). Combined, these studies provide intriguing evidence in support of pulsatile perfusion induced by periodic acceleration as a therapy for the protection of cerebral tissues in a variety of clinical scenarios that challenge cerebral blood flow and oxygenation, such as ischemic stroke; human studies investigating these effects appear warranted.

Pulsatile flow patterns around the cardiac frequency can also be assessed via calculation of pulsatility, generally derived as systolic-diastolic/mean flow. Studies have reported a role of increased cerebral blood flow pulsatility and tolerance to central hypovolemia in healthy human subjects following head-up tilt and lower body negative pressure (LBNP) (Thomas et al., 2009), in hemorrhaging sheep (Lewis et al., 1999), and in patients with head injury (Czosnyka et al., 1994). In these studies, increased pulsatility resulted from a reduction in diastolic cerebral blood velocity, and was interpreted as a mechanism of protecting blood supply to the cerebral tissues with decreasing perfusion pressures (Czosnyka et al., 1994; Lewis et al., 1999; Thomas et al., 2009). Less energy may be required to maintain forward flow if the flow is pulsatile vs. non-pulsatile, as higher mean flow rates can be generated for equal mean arterial blood pressures (Shepard et al., 1966; Sanderson et al., 1972; Czosnyka et al., 1994).

"LOW" FREQUENCY PULSATILE FLOW

The studies described thus far have utilized pulsatile perfusion therapy at frequencies at or above the cardiac frequency (i.e., $\geq$1 Hz). Other investigations, however, have also assessed pulsatile flow at much lower frequencies, generally associated with patterns of respiration, sympathetic nerve activity, and myogenic activity, among other factors.

Under conditions of experimentally induced central hypovolemia in healthy human subjects, such as LBNP and head-up tilt, increased oscillatory power in arterial pressure and/or cerebral blood flow has been associated with increased tolerance to these stressors. In a number of studies using head-up tilt alone, or combined with LBNP, individuals with poor tolerance (i.e., display symptoms of presyncope or syncope) exhibited reduced LF oscillations in arterial pressure (Gulli et al., 2001; Kamiya et al., 2005) and muscle sympathetic nerve activity (MSNA) (Kamiya et al., 2005), compared with non-syncopal subjects who showed a persistent elevation in LF power (**Figure 6**). The reduction in blood pressure and MSNA LF variability was associated with reduced absolute MSNA (Kamiya et al., 2005). Additional studies have demonstrated a clear relationship between changes

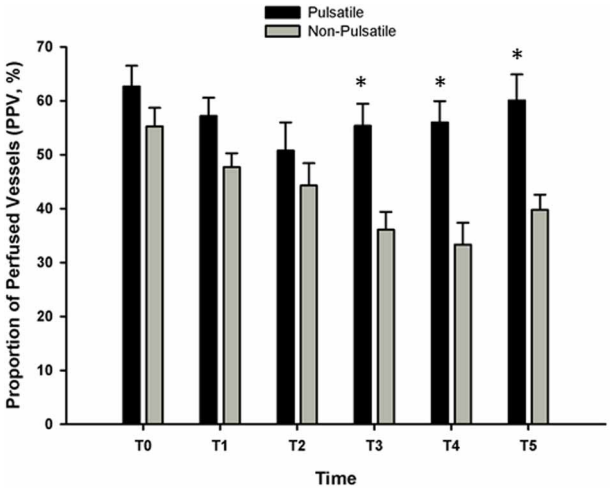


FIGURE 5 | The proportion of perfused sublingual microvessels (PPV, %) with and without pulsatile perfusion before, during, and after cardiac bypass surgery (CPB). Sublingual microcirculation was assessed using orthogonal polarization spectral imaging. Three to five 30 s steady state video images were obtained from the lateral side of the tongue, 2 cm from the tip at each time point. An investigator blind to the study performed the analysis of each video clip. T_0 = baseline; T_1 = 30-min on CPB; T_2 = 90-min on CPB; T_3 = 1 h post CPB; T_4 = 24 h post CPB; T_5 = 48 h post CPB. For the data presented, blood flow was classified as "normal" at approximately 250–350 μm/s. At each time point, the number of vessels that were classified as "normal" was divided by the total number of vessels and reported as PPV%. (Data modified from O'Neil et al., 2012). $^*P < 0.05$ compared with non-pulsatile group.

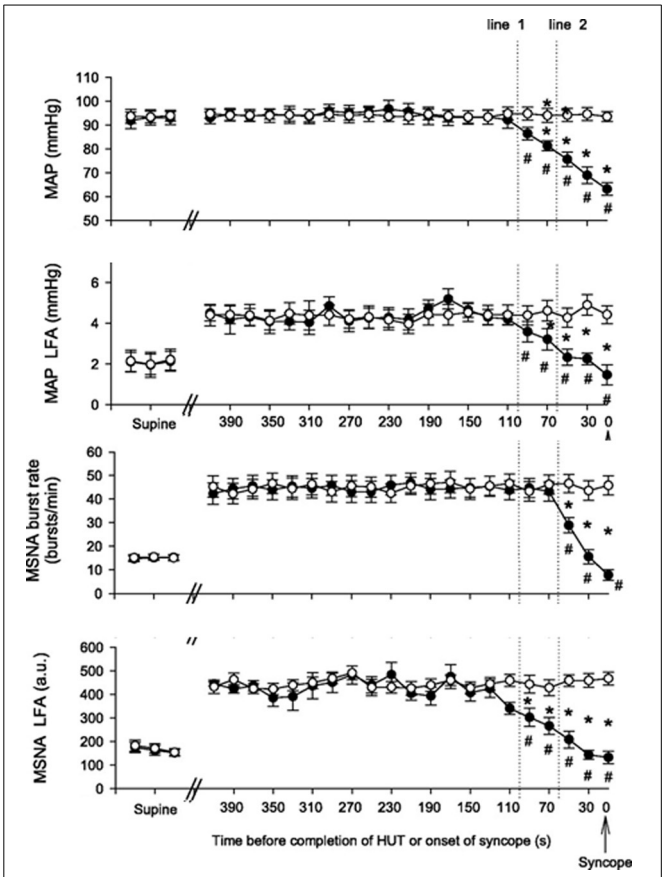


FIGURE 6 | Mean arterial pressure (MAP), MAP low frequency amplitude (LFA), muscle sympathetic nerve activity (MSNA), and MSNA LFA responses to head-up tilt (HUT) in syncopal (closed circles) and non-syncopal subjects (open circles). Line 1 and line 2 represent 100 and 60 s time points prior to presyncope or completion of the HUT protocol (From Kamiya et al., 2005, with permission).

in the LF oscillatory characteristics of MSNA and the magnitude and direction of MSNA responses, such as during severe hypovolemic stress (Cooke et al., 2009) (**Figure 7**), underscoring the role of sympathetic variability on arterial pressure variability within the LF range. In studies assessing physiological responses to pre-syncopal limited LBNP, we observed increases in reflex-mediated endogenous LF variability in arterial pressure *and* cerebral blood velocity in subjects with high tolerance (HT) to this stress compared with low tolerant (LT) subjects (Rickards et al., 2011); this was despite similar reductions in absolute arterial pressure and cerebral blood flow between groups (∼20–30%) (**Figure 8**). Breathing through an inspiratory threshold device also increased LF variability in arterial pressure and cerebral blood flow in subjects undergoing LBNP, which was associated with the delayed onset of presyncopal symptoms, and increased tolerance (Rickards et al., 2007). These exogenously-induced oscillations were also coincident with profound reductions in absolute cerebral blood velocity, which was not protected compared with the control condition (i.e., no resistance breathing) (Rickards et al., 2007) (**Figure 9**). Interestingly, posture dependent increases in LF power of cerebral oxygen (derived from NIRS) have also been shown in healthy subjects transitioning from the supine to seated, or supine to standing position, coincident with higher LF power in arterial pressure. Absolute cerebral oxygen levels were not protected, however, and the role of these oscillations on orthostatic tolerance was not assessed (Tachtsidis et al., 2004).

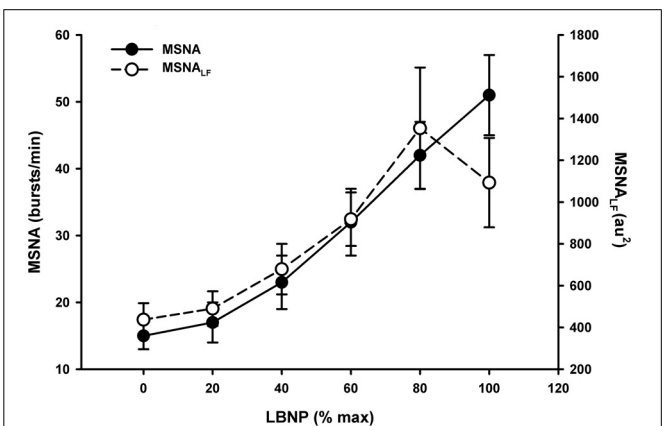


FIGURE 7 | Muscle sympathetic nerve activity (MSNA) and MSNA low frequency (LF) power in response to progressive central hypovolemia induced via lower body negative pressure (LBNP). Data presented as a percentage of maximum LBNP tolerance (Data modified from Cooke et al., 2009).

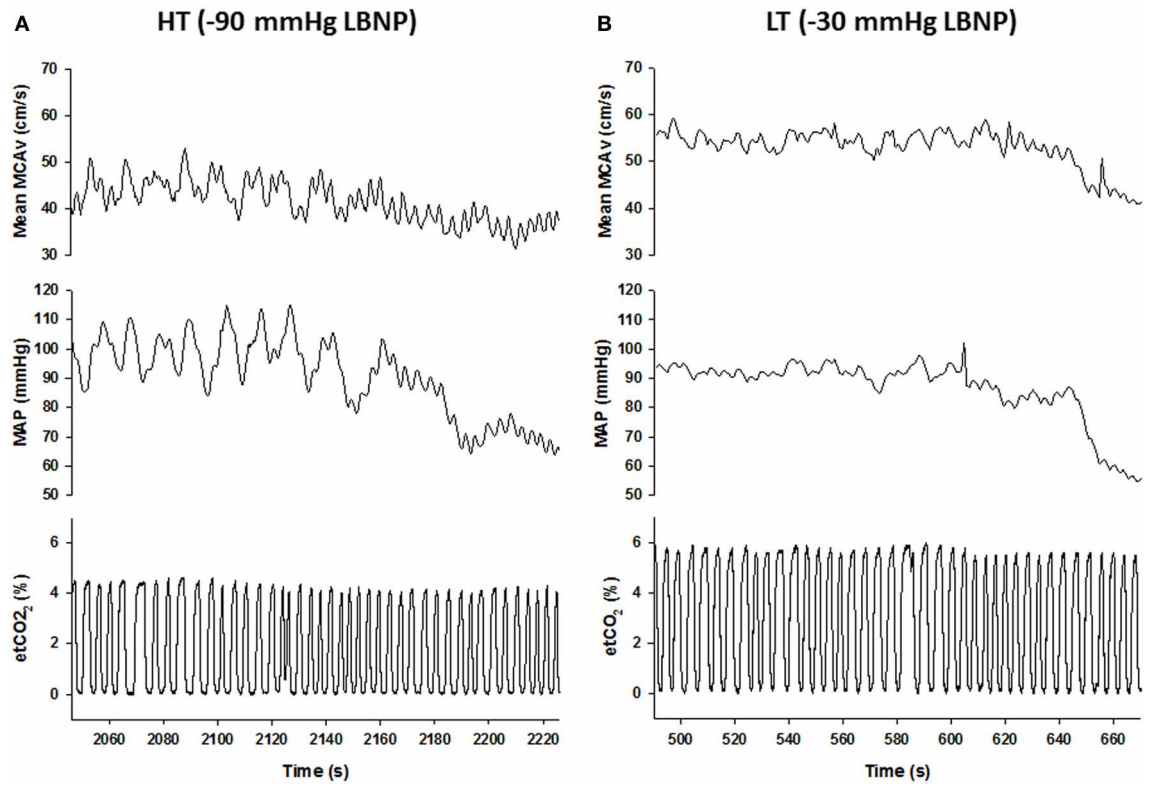


FIGURE 8 | Mean middle cerebral artery velocity (MCAv), mean arterial pressure (MAP), and end-tidal (et) CO_2 responses during progressive central hypovolemia in a representative high tolerant (HT; A) and low tolerant (LT; B) subject. Data are from the final 3-min prior to presyncope. Note the enhanced oscillatory characteristics of the MCAv and MAP tracings in the HT subject compared with the LT subject, and the transition from low frequency (LF) to high frequency (HF) oscillations at presyncope in the HT subject (From Rickards et al., 2011).

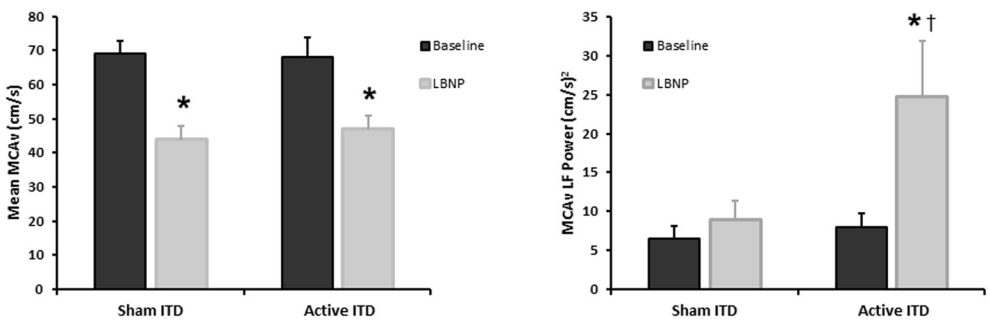


FIGURE 9 | Mean middle cerebral artery velocity (MCAv), and MCAv low frequency (LF) power during progressive central hypovolemia induced by lower body negative pressure (LBNP) while breathing through a sham or active inspiratory threshold device (ITD). Breathing through an ITD further decreases intra-thoracic pressure upon inspiration, subsequently increasing venous return and stroke volume (Data modified from Rickards et al., 2007). $^{*}P < 0.05$ compared with baseline, $^{\dagger}P < 0.05$ compared with sham condition.

In these aforementioned studies where respiration was reported, the elevation in LF power was not associated with breathing rate, as subjects, on average, were breathing outside of the LF range (i.e., >0.15 Hz or >9 breaths/min) (Gulli et al., 2001; Kamiya et al., 2005; Rickards et al., 2007, 2011). There is, however, a potentially important role of breathing rate in the generation of LF variability in arterial pressure and cerebral blood flow, which can lead to improved orthostatic tolerance. Recently, Lucas et al. (2013) observed a 15% increase in tolerance to combined head-up tilt and LBNP in subjects breathing at a fixed rate of 6 breaths/min (i.e., 0.1 Hz) vs. spontaneous breathing at 16–20 breaths/min (i.e., 0.27–0.33 Hz), thereby forcing a marked increase in LF power of mean arterial pressure and mean cerebral blood velocity; again, the reduction in cerebral blood velocity was similar between the two breathing conditions, so did not account for the improvement in tolerance.

While these improvements in tolerance to central hypovolemia were not associated with the preservation of absolute cerebral blood flow, the effect of LF pulsatile cerebral blood flow on cerebral tissue oxygenation is a plausible underlying mechanism based on the animal and human clinical studies outlined above using pulsatile perfusion at higher frequencies. Some of these studies have demonstrated the role of nitric oxide-induced vasodilation and improved oxygen delivery at high oscillatory frequencies (Nakano et al., 2000; Lanzarone et al., 2009; Uryash et al., 2009; Adams et al., 2011). Additionally, forcing oscillations in arterial pressure at 0.1 Hz has also been shown to elicit an acute antihypertensive effect (over the first 8 h of a 24 h recording) in a dog model via liberation of nitric oxide (Nafz et al., 2000), which could improve tissue perfusion and oxygenation. The role of LF cerebral blood flow variability on the release of nitric oxide and subsequent regulation of cerebral blood flow in humans, however, is unclear. Zhang et al. showed that inhibition of nitric oxide synthase (NOS; via infusion of L-NMMA) did not alter the generation of LF oscillations in cerebral blood velocity or arterial pressure in healthy humans at rest or during head-up tilt, and did not affect transfer function estimates of cerebral autoregulation (Zhang et al., 2004). Cerebral blood flow at rest and in response to head-up tilt were also not affected by NOS inhibition, suggesting that nitric oxide may not be liberated from the endothelium under conditions of increased LF variability. It is possible, however, that other shear-stress induced vasoactive mediators may be improving perfusion and oxygenation of the cerebral tissues under these conditions, such as histamine (DeForrest and Hollis, 1978), or prostaglandins, but these effects have not been elucidated. In comparison, while cerebral blood flow responses were not assessed, Castellano et al. (1995) demonstrated that NOS inhibition reduced systolic arterial pressure LF power for up to 40-min following infusion of L-LMMA, likely due to baroreflex-mediated reductions in sympathetic activity as a result of increased arterial pressure. These investigators only assessed these effects at rest, however, and did not perturb the system (e.g., forcing 0.1 Hz oscillations, or performing a head-up tilt maneuver to induce sympathetically-mediated LF oscillations) to determine if LF power was also reduced under these conditions.

It has been speculated that the spontaneous generation of oscillations in cerebral blood flow and cerebral oxygenation in the lower frequency ranges (i.e., <1 Hz) is associated with changes in vascular properties, such as arterial compliance (Schroeter et al., 2004, 2005). Theoretically, a decrease in arterial compliance could result in increased oscillatory characteristics of arterial pressure and cerebral blood flow due to the reduced buffering capacity of the vasculature. However, in a study of elderly subjects (62–71 years), LF variability in cerebral oxygenation (via NIRS as a measurement of the microvasculature) was lower at rest and during a visual stimulation task compared with young subjects (19–29 years) (Schroeter et al., 2004). These investigators suggested that this response was due to decreased compliance of the arteries with aging, and a reduction in the reactivity of the microvascular smooth muscle cells (Schroeter et al., 2004), although they did not quantify arterial compliance to confirm this hypothesis. Similarly, in studies of patients with cerebral microangiopathy (Schroeter et al., 2005) or a history of cerebral infarction (Li et al., 2010), conditions associated with an increase in arterial stiffness (and decreased arterial compliance), spontaneous LF (Schroeter et al., 2005; Li et al., 2010) and VLF (Li et al., 2010) power of oxy-hemoglobin was also reduced compared with age matched controls, but again, cerebral vascular compliance was not directly assessed. Finally, VLF BPV was lower in stroke-prone hypertensive rats compared with stroke-resistant hypertensive rats, reflective of reduced cerebrovascular myogenic function, which usually protects the brain from hemorrhagic stroke (Stauss et al., 2008). The direct role of arterial compliance on the generation of these short-term oscillations in arterial pressure, cerebral blood flow, and/or cerebral oxygenation has not been clearly quantified, and should be investigated further.

CONCLUSION

In this review we have attempted to highlight the complexities inherent in the characterization of hemodynamic variables such as blood pressure and cerebral blood flow. We have contrasted evidence that supports hemodynamic variability as a protective feature of physiology against evidence suggesting that hemodynamic variability heralds expansive damage to organ function. Our review suggests that reconciliation of these two apparently discrepant views may lie in the time scale of hemodynamic variability; short time scale variability appears to be cerebroprotective, while mid-to-longer term fluctuations are associated with primary and secondary end-organ dysfunction. The extent to which knowledge of the positive and deleterious influences of hemodynamic variability will lead to improve health outcomes are presently unknown, but the case is mounting against classical approaches to hemodynamic assessment that focuses narrowly on absolute blood pressure and/or cerebral blood flow.

AUTHOR CONTRIBUTIONS

Caroline A. Rickards and Yu-Chieh Tzeng contributed equally to this manuscript in terms of conception of the work, drafting the work and revising it critically for important intellectual content, and final approval of the version to be published. Caroline A. Rickards and Yu-Chieh Tzeng agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

Yu-Chieh Tzeng is supported by grants from the New Zealand Health Research Council (Ref 11/125). Caroline A. Rickards is supported, in part, by a grant from the US Army Medical Research and Material Command (W81XWH-11-2-0137). The content is solely the responsibility of the authors and does not necessarily represent the official views the US Department of Defense.

REFERENCES

Aaslid, R., Markwalder, T. M., and Nornes, H. (1982). Noninvasive transcranial doppler ultrasound recording of flow velocity in basal cerebral arteries. *J. Neurosurg.* 57, 769–774. doi: 10.3171/jns.1982.57.6.0769

Adams, J. A., Bassuk, J., Wu, D., Grana, M., Kurlansky, P., and Sackner, M. A. (2005). Periodic acceleration: effects on vasoactive, fibrinolytic, and coagulation factors. *J. Appl. Physiol.* 98, 1083–1090. doi: 10.1152/japplphysiol.00662.2004

Adams, J. A., Mangino, M. J., Bassuk, J., Inman, D. M., and Sackner, M. A. (2000). Noninvasive motion ventilation (NIMV): a novel approach to ventilatory support. *J. Appl. Physiol.* 89, 2438–2446.

Adams, J. A., Mangino, M. J., Bassuk, J., Kurlansky, P., and Sackner, M. A. (2001). Regional blood flow during periodic acceleration. *Crit. Care Med.* 29, 1983–1988. doi: 10.1097/00003246-200110000-00022

Adams, J. A., Uryash, A., Wu, H., Bassuk, J. A., Nadkarni, V., Berg, R., et al. (2011). Microcirculatory and therapeutic effects of whole body periodic acceleration (pGz) applied after cardiac arrest in pigs. *Resuscitation* 82, 767–775. doi: 10.1016/j.resuscitation.2011.02.012

Allen, B. S., Ko, Y., Buckberg, G. D., and Tan, Z. (2012). Studies of isolated global brain ischaemia: III. Influence of pulsatile flow during cerebral perfusion and its link to consistent full neurological recovery with controlled reperfusion following 30 min of global brain ischaemia. *Eur. J. Cardiothorac. Surg.* 41, 1155–1163. doi: 10.1093/ejcts/ezr318

Aries, M. J., Elting, J. W., De Keyser, J., Kremer, B. P., and Vroomen, P. C. (2010). Cerebral autoregulation in stroke: a review of transcranial doppler studies. *Stroke* 41, 2697–2704. doi: 10.1161/STROKEAHA.110.594168

Bassuk, J. I., Wu, H., Arias, J., Kurlansky, P., and Adams, J. A. (2010). Whole body periodic acceleration (pGz) improves survival and allows for resuscitation in a model of severe hemorrhagic shock in pigs. *J. Surg. Res.* 164, e281–e289. doi: 10.1016/j.jss.2010.07.047

Bateman, G. A. (2004). Pulse wave encephalopathy: a spectrum hypothesis incorporating Alzheimer's disease, vascular dementia and normal pressure hydrocephalus. *Med. Hypotheses* 62, 182–187. doi: 10.1016/S0306-9877(03)00330-X

Bayliss, W. M. (1902). On the local reactions of the arterial wall to changes of internal pressure. *J. Physiol.* 28, 220–231.

Bristow, J. D., Gribbin, B., Honour, A. J., Pickering, T. G., and Sleight, P. (1969). Diminished baroreflex sensitivity in high blood pressure and ageing man. *J. Physiol.* 202, 45P–46P.

Brown, T. E., Beightol, L. A., Koh, J., and Eckberg, D. L. (1993). Important influence of respiration on human R-R interval power spectra is largely ignored. *J. Appl. Physiol.* 75, 2310–2317.

Castellano, M., Rizzoni, D., Beschi, M., Muiesan, M. L., Porteri, E., Bettoni, G., et al. (1995). Relationship between sympathetic nervous system activity, baroreflex and cardiovascular effects after acute nitric oxide synthesis inhibition in humans. *J. Hypertens.* 13, 1153–1161. doi: 10.1097/00004872-199510000-00010

Cay, S., Cagirci, G., Demir, A. D., Balbay, Y., Erbay, A. R., Aydogdu, S., et al. (2011). Ambulatory blood pressure variability is associated with restenosis after percutaneous coronary intervention in normotensive patients. *Atherosclerosis* 219, 951–957. doi: 10.1016/j.atherosclerosis.2011.09.039

Cooke, W. H., Cox, J. F., Diedrich, A. M., Taylor, J. A., Beightol, L. A., Ames, J. E. IV., et al. (1998). Controlled breathing protocols probe human autonomic cardiovascular rhythms. *Am. J. Physiol.* 274, H709–H718.

Cooke, W. H., Rickards, C. A., Ryan, K. L., Kuusela, T. A., and Convertino, V. A. (2009). Muscle sympathetic nerve activity during intense lower body negative pressure to presyncope in humans. *J. Physiol.* 587, 4987–4999. doi: 10.1113/jphysiol.2009.177352

Czosnyka, M., Guazzo, E., Iyer, V., Kirkpatrick, P., Smielewski, P., Whitehouse, H., et al. (1994). Testing of cerebral autoregulation in head injury by waveform analysis of blood flow velocity and cerebral perfusion pressure. *Acta Neurochir. Suppl. (Wien)* 60, 468–471.

Dawson, S. L., Manktelow, B. N., Robinson, T. G., Panerai, R. B., and Potter, J. F. (2000). Which parameters of beat-to-beat blood pressure and variability best predict early outcome after acute ischemic stroke? *Stroke* 31, 463–468. doi: 10.1161/01.STR.31.2.463

DeForrest, J. M., and Hollis, T. M. (1978). Shear stress and aortic histamine synthesis. *Am. J. Physiol.* 234, H701–705.

Flues, K., Moraes-Silva, I. C., Mostarda, C., Souza, P. R., Diniz, G. P., Moreira, E. D., et al. (2012). Cardiac and pulmonary arterial remodeling after sinoaortic denervation in normotensive rats. *Auton. Neurosci.* 166, 47–53. doi: 10.1016/j.autneu.2011.10.005

Garcia-Garcia, A., Garcia-Ortiz, L., Recio-Rodriguez, J. I., Patino-Alonso, M. C., Agudo-Conde, C., Rodriguez-Sanchez, E., et al. (2013). Relationship of 24-h blood pressure variability with vascular structure and function in hypertensive patients. *Blood Press. Monit.* 18, 101–106. doi: 10.1097/MBP.0b013e32835ebc58

Gouedard, O., Blanc, J., Gaudet, E., Ponchon, P., and Elghozi, J. L. (1996). Contribution of the renin-angiotensin system to short-term blood pressure variability during blockade of nitric oxide synthesis in the rat. *Br. J. Pharmacol.* 119, 1085–1092. doi: 10.1111/j.1476-5381.1996.tb16008.x

Gulli, G., Wight, V. L., Hainsworth, R., and Cevese, A. (2001). Spectral and cross-spectral autoregressive analysis of cardiovascular variables in subjects with different degrees of orthostatic tolerance. *Clin. Auton. Res.* 11, 19–27. doi: 10.1007/BF02317798

Hamner, J. W., Tan, C. O., Lee, K., Cohen, M. A., and Taylor, J. A. (2010). Sympathetic control of the cerebral vasculature in humans. *Stroke* 41, 102–109. doi: 10.1161/STROKEAHA.109.557132

Hamner, J. W., Tan, C. O., Tzeng, Y. C., and Taylor, J. A. (2012). Cholinergic control of the cerebral vasculature in humans. *J. Physiol.* 590, 6343–6352. doi: 10.1113/jphysiol.2012.245100

Hornick, P., and Taylor, K. (1997). Pulsatile and nonpulsatile perfusion: the continuing controversy. *J. Cardiothorac. Vasc. Anesth.* 11, 310–315. doi: 10.1016/S1053-0770(97)90100-2

Johansson, J. K., Niiranen, T. J., Puukka, P. J., and Jula, A. M. (2012). Prognostic value of the variability in home-measured blood pressure and heart rate: the Finn-Home Study. *Hypertension* 59, 212–218. doi: 10.1161/HYPERTENSIONAHA.111.178657

Julien, C. (2006). The enigma of Mayer waves: facts and models. *Cardiovasc. Res.* 70, 12–21. doi: 10.1016/j.cardiores.2005.11.008

Kamiya, A., Hayano, J., Kawada, T., Michikami, D., Yamamoto, K., Ariumi, H., et al. (2005). Low-frequency oscillation of sympathetic nerve activity decreases during development of tilt-induced syncope preceding sympathetic withdrawal and bradycardia. *Am. J. Physiol.* 289, H1758–H1769. doi: 10.1152/ajpheart.01027.2004

Kety, S. S., and Schmidt, C. F. (1948). The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. *J. Clin. Invest.* 27, 476–483. doi: 10.1172/JCI101994

Kikuya, M., Ohkubo, T., Metoki, H., Asayama, K., Hara, A., Obara, T., et al. (2008). Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: the Ohasama study. *Hypertension* 52, 1045–1050. doi: 10.1161/HYPERTENSIONAHA.107.104620

Kilpatrick, E. S., Rigby, A. S., and Atkin, S. L. (2010). The role of blood pressure variability in the development of nephropathy in type 1 diabetes. *Diabetes Care* 33, 2442–2447. doi: 10.2337/dc10-1000

Kjellgren, O., and Gomes, J. A. (1993). Heart rate variability and baroreflex sensitivity in myocardial infarction. *Am. Heart J.* 125, 204–215. doi: 10.1016/0002-8703(93)90076-L

Ko, Y., Park, J. H., Yang, M. H., Ko, S. B., Han, M. K., Oh, C. W., et al. (2010). The significance of blood pressure variability for the development of hemorrhagic transformation in acute ischemic stroke. *Stroke* 41, 2512–2518. doi: 10.1161/STROKEAHA.110.595561

Koning, N. J., Vonk, A. B., van Barneveld, L. J., Beishuizen, A., Atasever, B., van den Brom, C. E., et al. (2012). Pulsatile flow during cardiopulmonary bypass preserves postoperative microcirculatory perfusion irrespective of systemic hemodynamics. *J. Appl. Physiol.* 112, 1727–1734. doi: 10.1152/japplphysiol.01191.2011

Kotsis, V., Stabouli, S., Karafillis, I., Papakatsika, S., Rizos, Z., Miyakis, S., et al. (2011). Arterial stiffness and 24 h ambulatory blood pressure monitoring in young healthy volunteers: the early vascular ageing Aristotle University Thessaloniki Study (EVA-ARIS Study). *Atherosclerosis* 219, 194–199. doi: 10.1016/j.atherosclerosis.2011.07.111

Langager, A. M., Hammerberg, B. E., Rotella, D. L., and Stauss, H. M. (2007). Very low-frequency blood pressure variability depends on voltage-gated L-type Ca2+ channels in conscious rats. *Am. J. Physiol. Heart Circ. Physiol.* 292, H1321–H1327. doi: 10.1152/ajpheart.00874.2006

Lanzarone, E., Gelmini, F., Tessari, M., Menon, T., Suzuki, H., Carini, M., et al. (2009). Preservation of endothelium nitric oxide release by pulsatile flow cardiopulmonary bypass when compared with continuous flow. *Artif. Organs* 33, 926–934. doi: 10.1111/j.1525-1594.2009.00888.x

Lassen, N. A. (1959). Cerebral blood flow and oxygen consumption in man. *Physiol. Rev.* 39, 183–238.

Leoncini, G., Viazzi, F., Storace, G., Deferrari, G., and Pontremoli, R. (2013). Blood pressure variability and multiple organ damage in primary hypertension. *J. Hum. Hypertens.* 27, 663–670. doi: 10.1038/jhh.2013.45

Lewis, S. B., Wong, M. L., Bannan, P. E., Piper, I. R., and Reilly, P. L. (1999). Transcranial Doppler assessment of the lower cerebral autoregulatory threshold. *J. Clin. Neurosci.* 6, 42–45. doi: 10.1016/S0967-5868(99)90602-1

Li, Z., Wang, Y., Li, Y., Wang, Y., Li, J., and Zhang, L. (2010). Wavelet analysis of cerebral oxygenation signal measured by near infrared spectroscopy in subjects with cerebral infarction. *Microvasc. Res.* 80, 142–147. doi: 10.1016/j.mvr.2010.02.004

Li, Z., Zhang, M., Xin, Q., Luo, S., Zhou, W., Cui, R., et al. (2013). Assessment of cerebral oxygenation oscillations in subjects with hypertension. *Microvasc. Res.* 88, 32–41. doi: 10.1016/j.mvr.2013.04.003

Lipsitz, L. A., Morin, R., Gagnon, M., Kiely, D., and Medina, A. (1997). Vasomotor instability preceding tilt-induced syncope: does respiration play a role? *J. Appl. Physiol.* 83, 383–390.

Liu, W., Liu, R., Sun, W., Peng, Q., Zhang, W., Xu, E., et al. (2012). Different impacts of blood pressure variability on the progression of cerebral microbleeds and white matter lesions. *Stroke* 43, 2916–2922. doi: 10.1161/STROKEAHA.112.658369

Lucas, S. J., Lewis, N. C., Sikken, E. L., Thomas, K. N., and Ainslie, P. N. (2013). Slow breathing as a means to improve orthostatic tolerance: a randomized sham-controlled trial. *J. Appl. Physiol.* 15, 202–211. doi: 10.1152/japplphysiol.00128.2013

Mancia, G., Bombelli, M., Facchetti, R., Madotto, F., Corrao, G., Trevano, F. Q., et al. (2007). Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension* 49, 1265–1270. doi: 10.1161/HYPERTENSIONAHA.107.088708

Mancia, G., Facchetti, R., Parati, G., and Zanchetti, A. (2012). Visit-to-visit blood pressure variability, carotid atherosclerosis, and cardiovascular events in the European Lacidipine Study on Atherosclerosis. *Circulation* 126, 569–578. doi: 10.1161/CIRCULATIONAHA.112.107565

Mancia, G., Parati, G., Hennig, M., Flatau, B., Omboni, S., Glavina, F., et al. (2001). Relation between blood pressure variability and carotid artery damage in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis (ELSA). *J. Hypertens.* 19, 1981–1989. doi: 10.1097/00004872-200111000-00008

Martinez-Murillo, R., Serrano, J., Fernandez, A. P., and Martinez, A. (2009). Whole-body periodic acceleration reduces brain damage in a focal ischemia model. *Neuroscience* 158, 1390–1396. doi: 10.1016/j.neuroscience.2008.12.005

Matsui, Y., O'Rourke, M. F., Hoshide, S., Ishikawa, J., Shimada, K., and Kario, K. (2012). Combined effect of angiotensin II receptor blocker and either a calcium channel blocker or diuretic on day-by-day variability of home blood pressure: the Japan combined treatment with olmesartan and a calcium-channel blocker versus olmesartan and diuretics randomized efficacy study. *Hypertension* 59, 1132–1138. doi: 10.1161/HYPERTENSIONAHA.111.189217

McMullan, C. J., Bakris, G. L., Phillips, R. A., and Forman, J. P. (2013). Association of BP variability with mortality among African Americans with CKD. *Clin. J. Am. Soc. Nephrol.* 8, 731–738. doi: 10.2215/CJN.10131012

Miao, C. Y., and Su, D. F. (2002). The importance of blood pressure variability in rat aortic and left ventricular hypertrophy produced by sinoaortic denervation. *J. Hypertens.* 20, 1865–1872. doi: 10.1097/00004872-200209000-00033

Miao, C. Y., Xie, H. H., Zhan, L. S., and Su, D. F. (2006). Blood pressure variability is more important than blood pressure level in determination of end-organ damage in rats. *J. Hypertens.* 24, 1125–1135. doi: 10.1097/01.hjh.0000226203.57818.88

Murkin, J. M. (2006). Pulsatile versus nonpulsatile perfusion revisited. *J. Card. Surg.* 21, 355–356. doi: 10.1111/j.1540-8191.2006.00270.x

Murkin, J. M., Martzke, J. S., Buchan, A. M., Bentley, C., and Wong, C. J. (1995). A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. I. Mortality and cardiovascular morbidity. *J. Thorac. Cardiovasc. Surg.* 110, 340–348. doi: 10.1016/S0022-5223(95)70229-6

Nafz, B., Just, A., Stauss, H. M., Wagner, C. D., Ehmke, H., Kirchheim, H. R., et al. (1996). Blood-pressure variability is buffered by nitric oxide. *J. Auton. Nerv. Syst.* 57, 181–183. doi: 10.1016/0165-1838(95)00080-1

Nafz, B., Stegemann, J., Bestle, M. H., Richter, N., Seeliger, E., Schimke, I., et al. (2000). Antihypertensive effect of 0.1-Hz blood pressure oscillations to the kidney. *Circulation* 101, 553–557. doi: 10.1161/01.CIR.101.5.553

Nakano, T., Tominaga, R., Nagano, I., Okabe, H., and Yasui, H. (2000). Pulsatile flow enhances endothelium-derived nitric oxide release in the peripheral vasculature. *Am. J. Physiol. Heart Circ. Physiol.* 278, H1098–H1104.

Newell, D. W., and Aaslid, R. (1992). Transcranial Doppler: clinical and experimental uses. *Cerebrovasc. Brain Metab. Rev.* 4, 122–143.

Newell, D. W., Aaslid, R., Stooss, R., and Reulen, H. J. (1992). The relationship of blood flow velocity fluctuations to intracranial pressure B waves. *J. Neurosurg.* 76, 415–421. doi: 10.3171/jns.1992.76.3.0415

O'Neil, M. P., Fleming, J. C., Badhwar, A., and Guo, L. R. (2012). Pulsatile versus nonpulsatile flow during cardiopulmonary bypass: microcirculatory and systemic effects. *Ann. Thorac. Surg.* 94, 2046–2053. doi: 10.1016/j.athoracsur.2012.05.065

Ogoh, S. (2008). Autonomic control of cerebral circulation: exercise. *Med. Sci. Sports Exerc.* 40, 2046–2054. doi: 10.1249/MSS.0b013e318180bc6f

Onoe, M., Mori, A., Watarida, S., Sugita, T., Shiraishi, S., Nojima, T., et al. (1994). The effect of pulsatile perfusion on cerebral blood flow during profound hypothermia with total circulatory arrest. *J. Thorac. Cardiovasc. Surg.* 108, 119–125.

Palatini, P., Penzo, M., Racioppa, A., Zugno, E., Guzzardi, G., Anaclerio, M., et al. (1992). Clinical relevance of nighttime blood pressure and of daytime blood pressure variability. *Arch. Intern. Med.* 152, 1855–1860. doi: 10.1001/archinte.1992.00400210081013

Parati, G. (2005). Blood pressure variability: its measurement and significance in hypertension. *J. Hypertens. Suppl.* 23, S19–S25. doi: 10.1097/01.hjh.0000165624.79933.d3

Parati, G., and Bilo, G. (2012). Calcium antagonist added to angiotensin receptor blocker: a recipe for reducing blood pressure variability?: evidence from day-by-day home blood pressure monitoring. *Hypertension* 59, 1091–1093. doi: 10.1161/HYPERTENSIONAHA.112.193037

Parati, G., Pomidossi, G., Albini, F., Malaspina, D., and Mancia, G. (1987). Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. *J. Hypertens.* 5, 93–98. doi: 10.1097/00004872-198702000-00013

Parati, G., Tortorici, E., Glavina, F., Zaniboni, D., Gritti, S., Groppelli, A., et al. (2001). [Blood pressure variability]. *Ital. Heart J. Suppl.* 2, 455–471.

Peebles, K. C., Ball, O. G., MacRae, B. A., Horsman, H. M., and Tzeng, Y. C. (2012). Sympathetic regulation of the human cerebrovascular response to carbon dioxide. *J. Appl. Physiol.* 113, 700–706. doi: 10.1152/japplphysiol.00614.2012

Pickering, T. G., Harshfield, G. A., Kleinert, H. D., Blank, S., and Laragh, J. H. (1982). Blood pressure during normal daily activities, sleep, and exercise. Comparison of values in normal and hypertensive subjects. *JAMA* 247, 992–996. doi: 10.1001/jama.1982.03320320028025

Poletto, R., Janczak, A. M., Marchant-Forde, R. M., Marchant-Forde, J. N., Matthews, D. L., Dowell, C. A., et al. (2011). Identification of low and high frequency ranges for heart rate variability and blood pressure variability analyses using pharmacological autonomic blockade with atropine and propranolol in swine. *Physiol. Behav.* 103, 188–196. doi: 10.1016/j.physbeh.2011.01.019

Pringle, E., Phillips, C., Thijs, L., Davidson, C., Staessen, J. A., de Leeuw, P. W., et al. and Syst-Eur i. (2003). Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. *J. Hypertens.* 21, 2251–2257. doi: 10.1097/00004872-200312000-00012

Purkayastha, S., Saxena, A., Eubank, W. L., Hoxha, B., and Raven, P. B. (2013). alpha1-Adrenergic receptor control of the cerebral vasculature in humans at rest and during exercise. *Exp. Physiol.* 98, 451–461. doi: 10.1113/expphysiol.2012.066118

Reinhard, M., Roth, M., Guschlbauer, B., Harloff, A., Timmer, J., Czosnyka, M., et al. (2005). Dynamic cerebral autoregulation in acute ischemic stroke assessed from spontaneous blood pressure fluctuations. *Stroke* 36, 1684–1689. doi: 10.1161/01.STR.0000173183.36331.ee

Reinhard, M., Rutsch, S., Lambeck, J., Wihler, C., Czosnyka, M., Weiller, C., et al. (2012). Dynamic cerebral autoregulation associates with infarct size and outcome after ischemic stroke. *Acta Neurol. Scand.* 125, 156–162. doi: 10.1111/j.1600-0404.2011.01515.x

Rickards, C. A., Ryan, K. L., Cooke, W. H., and Convertino, V. A. (2011). Tolerance to central hypovolemia: the influence of oscillations in arterial pressure and cerebral blood velocity. *J. Appl. Physiol.* 111, 1048–1058. doi: 10.1152/japplphysiol.00231.2011

Rickards, C. A., Ryan, K. L., Cooke, W. H., Lurie, K. G., and Convertino, V. A. (2007). Inspiratory resistance delays the reporting of symptoms with central hypovolemia: association with cerebral blood flow. *Am. J. Physiol.* 293, R243–R250. doi: 10.1152/ajpregu.00087.2007

Rothwell, P. M. (2010). Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet* 375, 938–948. doi: 10.1016/S0140-6736(10)60309-1

Sakakura, K., Ishikawa, J., Okuno, M., Shimada, K., and Kario, K. (2007). Exaggerated ambulatory blood pressure variability is associated with cognitive dysfunction in the very elderly and quality of life in the younger elderly. *Am. J. Hypertens.* 20, 720–727. doi: 10.1016/j.amjhyper.2007.02.001

Sanderson, J. M., Wright, G., and Sims, F. W. (1972). Brain damage in dogs immediately following pulsatile and non-pulsatile blood flows in extracorporeal circulation. *Thorax* 27, 275–286. doi: 10.1136/thx.27.3.275

Schillaci, G., Bilo, G., Pucci, G., Laurent, S., Macquin-Mavier, I., Boutouyrie, P., et al. (2012). Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. *Hypertension* 60, 369–377. doi: 10.1161/HYPERTENSIONAHA.112.197491

Schroeter, M. L., Bucheler, M. M., Preul, C., Scheid, R., Schmiedel, O., Guthke, T., et al. (2005). Spontaneous slow hemodynamic oscillations are impaired in cerebral microangiopathy. *J. Cereb. Blood Flow Metab.* 25, 1675–1684. doi: 10.1038/sj.jcbfm.9600159

Schroeter, M. L., Schmiedel, O., and von Cramon, D. Y. (2004). Spontaneous low-frequency oscillations decline in the aging brain. *J. Cereb. Blood Flow Metab.* 24, 1183–1191. doi: 10.1097/01.WCB.0000135231.90164.40

Schutte, A. E., Schutte, R., Huisman, H. W., van Rooyen, J. M., Fourie, C. M., Malan, N. T., et al. (2011). Blood pressure variability is significantly associated with ECG left ventricular mass in normotensive Africans: the SABPA Study. *Hypertens. Res.* 34, 1127–1134. doi: 10.1038/hr.2011.104

Schutte, R., Thijs, L., Liu, Y. P., Asayama, K., Jin, Y., Odili, A., et al. (2012). Within-subject blood pressure level–not variability–predicts fatal and non-fatal outcomes in a general population. *Hypertension* 60, 1138–1147. doi: 10.1161/HYPERTENSIONAHA.112.202143

Sega, R., Corrao, G., Bombelli, M., Beltrame, L., Facchetti, R., Grassi, G., et al. (2002). Blood pressure variability and organ damage in a general population: results from the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni). *Hypertension* 39, 710–714. doi: 10.1161/hy0202.104376

Shan, Z. Z., Dai, S. M., and Su, D. F. (1999). Relationship between baroreceptor reflex function and end-organ damage in spontaneously hypertensive rats. *Am. J. Physiol.* 277, H1200–H1206.

Shepard, R. B., Simpson, D. C., and Sharp, J. F. (1966). Energy equivalent pressure. *Arch. Surg.* 93, 730–740. doi: 10.1001/archsurg.1966.01330050034005

Shimbo, D., Newman, J. D., Aragaki, A. K., LaMonte, M. J., Bavry, A. A., Allison, M., et al. (2012). Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: data from the Women's Health Initiative. *Hypertension* 60, 625–630. doi: 10.1161/HYPERTENSIONAHA.112.193094

Sin, P. Y., Galletly, D. C., and Tzeng, Y. C. (2010). Influence of breathing frequency on the pattern of respiratory sinus arrhythmia and blood pressure: old questions revisited. *Am. J. Physiol. Heart Circ. Physiol.* 298, H1588–H1599. doi: 10.1152/ajpheart.00036.2010

Stauss, H. M. (2007). Identification of blood pressure control mechanisms by power spectral analysis. *Clin. Exp. Pharmacol. Physiol.* 34, 362–368. doi: 10.1111/j.1440-1681.2007.04588.x

Stauss, H. M., Petitto, C. E., Rotella, D. L., Wong, B. J., and Sheriff, D. D. (2008). Very low frequency blood pressure variability is modulated by myogenic vascular function and is reduced in stroke-prone rats. *J. Hypertens.* 26, 1127–1137. doi: 10.1097/HJH.0b013e3282fb81c8

Stead, L. G., Gilmore, R. M., Vedula, K. C., Weaver, A. L., Decker, W. W., and Brown, R. D. Jr. (2006). Impact of acute blood pressure variability on ischemic stroke outcome. *Neurology* 66, 1878–1881. doi: 10.1212/01.wnl.0000219628.78513.b5

Su, D. F., and Miao, C. Y. (2001). Blood pressure variability and organ damage. *Clin. Exp. Pharmacol. Physiol.* 28, 709–715. doi: 10.1046/j.1440-1681.2001.03508.x

Sykora, M., Diedler, J., and Steiner, T. (2009). Prognostic significance of blood pressure variability after thrombolysis in acute stroke. *Neurology* 72, 1792–1793. author reply: 1792–1793. doi: 10.1212/01.wnl.0000349651.21293.7f

Tachtsidis, I., Elwell, C. E., Leung, T. S., Lee C-W., Smith, M., and Delpy, D. T. (2004). Investigation of cerebral haemodynamics by near-infrared spectroscopy in young healthy volunteers reveals posture-depedent spontaneous oscillations. *Physiol. Meas.* 25, 437–445. doi: 10.1088/0967-3334/25/2/003

Tan, C. O., Hamner, J. W., and Taylor, J. A. (2013). The role of myogenic mechanisms in human cerebrovascular regulation. *J. Physiol.* 591(Pt 20), 5095–5105. doi: 10.1113/jphysiol.2013.259747

Taylor, K. M., Bain, W. H., Davidson, K. G., and Turner, M. A. (1982). Comparative clinical study of pulsatile and non-pulsatile perfusion in 350 consecutive patients. *Thorax* 37, 324–330. doi: 10.1136/thx.37.5.324

Thomas, K. N., Cotter, J. D., Galvin, S. D., Williams, M. J., Willie, C. K., and Ainslie, P. N. (2009). Initial orthostatic hypotension is unrelated to orthostatic tolerance in healthy young subjects. *J. Appl. Physiol.* 107, 506–517. doi: 10.1152/japplphysiol.91650.2008

Tsivgoulis, G., and Ntaios, G. (2012). Blood pressure variability in subacute ischemic stroke: a neglected potential therapeutic target. *Neurology* 79, 2014–2015. doi: 10.1212/WNL.0b013e3182749f7e

Tzeng, Y. C., and Ainslie, P. N. (2014). Blood pressure regulation IX: cerebral autoregulation under blood pressure challenges. *Eur. J. Appl. Physiol.* 114, 545–559. doi: 10.1007/s00421-013-2667-y

Tzeng, Y. C., Ainslie, P. N., Cooke, W. H., Peebles, K. C., Willie, C. K., Macrae, B. A., et al. (2012a). Assessment of cerebral autoregulation: the quandary of quantification. *Am. J. Physiol. Heart Circ. Physiol.* 303, H658–H671. doi: 10.1152/ajpheart.00328.2012

Tzeng, Y. C., Chan, G. S., Willie, C. K., and Ainslie, P. N. (2011). Determinants of human cerebral pressure-flow velocity relationships: new insights from vascular modelling and Ca2+ channel blockade. *J. Physiol.* 589, 3263–3274. doi: 10.1113/jphysiol.2011.206953

Tzeng, Y. C., Macrae, B., and Rickards, C. A. (2012b). A recipe for reducing blood pressure variability: adding blood flow to the mix. *Hypertension* 60, e12. doi: 10.1161/HYPERTENSIONAHA.112.198531

Tzeng, Y. C., and Macrae, B. A. (2013). Interindividual relationships between blood pressure and cerebral blood flow variability with intact and blunted cerebrovascular control. *J. Appl. Physiol.* 114, 888–895. doi: 10.1152/japplphysiol.01388.2012

Tzeng, Y. C., Sin, P. Y., Lucas, S. J., and Ainslie, P. N. (2009). Respiratory modulation of cardiovagal baroreflex sensitivity. *J. Appl. Physiol.* 107, 718–724. doi: 10.1152/japplphysiol.00548.2009

Uryash, A., Wu, H., Bassuk, J., Kurlansky, P., Sackner, M. A., and Adams, J. A. (2009). Low-amplitude pulses to the circulation through periodic acceleration induces endothelial-dependent vasodilatation. *J. Appl. Physiol.* 106, 1840–1847. doi: 10.1152/japplphysiol.91612.2008

van Mook, W. N., Rennenberg, R. J., Schurink, G. W., van Oostenbrugge, R. J., Mess, W. H., Hofman, P. A., et al. (2005). Cerebral hyperperfusion syndrome. *Lancet Neurol.* 4, 877–888. doi: 10.1016/S1474-4422(05)70251-9

Verdecchia, P., Angeli, F., Gattobigio, R., Rapicetta, C., and Reboldi, G. (2007). Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. *Am. J. Hypertens.* 20, 154–161. doi: 10.1016/j.amjhyper.2006.07.017

Willie, C. K., Colino, F. L., Bailey, D. M., Tzeng, Y. C., Binsted, G., Jones, L. W., et al. (2011). Utility of transcranial doppler ultrasound for the integrative assessment of cerebrovascular function. *J. Neurosci. Methods* 196, 221–237. doi: 10.1016/j.jneumeth.2011.01.011

Xu, X., Ding, X., Zhang, X., Su, S., Treiber, F. A., Vlietinck, R., et al. (2013). Genetic and environmental influences on blood pressure variability: a study in twins. *J. Hypertens.* 31, 690–697. doi: 10.1097/HJH.0b013e32835e2a4a

Yano, M., Kohno, M., Konishi, M., Obayashi, M., Kobayashi, S., Seki, K., et al. (1997). Effect of aortic impedance on preload-afterload mismatch in canine hearts in situ. *Basic Res. Cardiol.* 92, 115–122. doi: 10.1007/BF00805572

Yoshimoto, T., Eguchi, K., Sakurai, H., Ohmichi, Y., Hashimoto, T., Ohmichi, M., et al. (2011). Frequency components of systolic blood pressure variability reflect vasomotor and cardiac sympathetic functions in conscious rats. *J. Physiol. Sci.* 61, 373–383. doi: 10.1007/s12576-011-0158-7

Zhang, R., Wilson, T. E., Witkowski, S., Cui, J., Crandall, G. G., and Levine, B. D. (2004). Inhibition of nitric oxide synthase does not alter dynamic cerebral autoregulation in humans. *Am. J. Physiol. Heart Circ. Physiol.* 286, H863–H869. doi: 10.1152/ajpheart.00373.2003

Zhang, R., Zuckerman, J. H., Giller, C. A., and Levine, B. D. (1998a). Transfer function analysis of dynamic cerebral autoregulation in humans. *Am. J. Physiol.* 274, H233–H241.

Zhang, R., Zuckerman, J. H., and Levine, B. D. (1998b). Deterioration of cerebral autoregulation during orthostatic stress: insights from the frequency domain. *J. Appl. Physiol.* 85, 1113–1122.

Zhang, R. P., Zuckerman, J. H. R. N., Iwasaki, K. M. D., Wilson, T. E. P., Crandall, C. G. P., and Levine, B. D. M. D. (2002). Autonomic neural control of dynamic cerebral autoregulation in humans. *Circulation* 106, 1814–1820. doi: 10.1161/01.CIR.0000031798.07790.FE

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 December 2013; accepted: 13 March 2014; published online: 07 April 2014.

*Citation: Rickards CA and Tzeng Y-C (2014) Arterial pressure and cerebral blood flow variability: friend or foe? A review. Front. Physiol. **5**:120. doi: 10.3389/fphys.2014.00120*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in
PHYSIOLOGY

REVIEW ARTICLE
published: 04 March 2014
doi: 10.3389/fphys.2014.00092

Cerebral oxygenation and hyperthermia

Anthony R. Bain[1]*, Shawnda A. Morrison[2] and Philip N. Ainslie[1]

[1] *Centre for Heart, Lung and Vascular Health, University of British Columbia, Okanagan, BC, Canada*
[2] *Faculty of Professional Studies, Kinesiology, Acadia University, Wolfville, NS, Canada*

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Lars Nybo, University of Copenhagen, Denmark
R. Matthew Brothers, University of Texas at Austin, USA

****Correspondence:***
Anthony R. Bain, Faculty of Health and Social Development, University of British Columbia Okanagan, 3333 University Way, Kelowna, BC, V1V 1V7, ART360, Canada
e-mail: anthony.bain@ubc.ca

Hyperthermia is associated with marked reductions in cerebral blood flow (CBF). Increased distribution of cardiac output to the periphery, increases in alveolar ventilation and resultant hypocapnia each contribute to the fall in CBF during passive hyperthermia; however, their relative contribution remains a point of contention, and probably depends on the experimental condition (e.g., posture and degree of hyperthermia). The hyperthermia-induced hyperventilatory response reduces arterial CO_2 pressure ($PaCO_2$) causing cerebral vasoconstriction and subsequent reductions in flow. During supine passive hyperthermia, the majority of recent data indicate that reductions in $PaCO_2$ may be the primary, if not sole, culprit for reduced CBF. On the other hand, during more dynamic conditions (e.g., hemorrhage or orthostatic challenges), an inability to appropriately decrease peripheral vascular conductance presents a condition whereby adequate cerebral perfusion pressure may be compromised secondary to reductions in systemic blood pressure. Although studies have reported maintenance of pre-frontal cortex oxygenation (assessed by near-infrared spectroscopy) during exercise and severe heat stress, the influence of cutaneous blood flow is known to contaminate this measure. This review discusses the governing mechanisms associated with changes in CBF and oxygenation during moderate to severe (i.e., 1.0°C to 2.0°C increase in body core temperature) levels of hyperthermia. Future research directions are provided.

Keywords: hyperthermia, heat stress, cerebral blood flow, cerebral oxygenation, hemorrhage, syncope

INTRODUCTION

The dependence to maintain body core temperature within critically functioning limits (i.e., 37 ± 3°C) has led to seminal thermoregulatory research spanning the past 100 years (e.g., Haldane, 1905; Lindhard, 1910). From this, the capacity to effectively dissipate heat through convective and evaporative means and the concomitant cardiovascular adjustments to maintain thermoregulatory homeostasis has been topic of several extensive literature reviews (e.g., Rowell, 1974; Crandall and González-Alonso, 2010; Johnson and Proppe, 2011). Only in the last decade, however, have we begun to appropriately understand the cerebrovascular adjustments to hyperthermia. The integrative components of cerebrovascular control and ultimately oxygenation, with focus on commonly occurring levels of hyperthermia (i.e., up to +2°C core temperature) form the basis of this review. Adjustments to the three variables germane to cerebral oxygenation, fundamentally the components of the Fick equation; (1) cerebral metabolism, (2) cerebral O_2 extraction, and (3) oxygen delivery (cerebral blood flow—CBF), are discussed. We further highlight the implications of cerebral heat balance and oxygenation during hyperthermic exercise, and provide methodological considerations for future work.

CEREBRAL METABOLISM

The metabolic demand of human cerebral tissue is such that ∼20% of total body oxygen consumption is taken up by the brain, despite only occupying 2–3% of total body mass. During passive hyperthermia of 1.5°C to 2°C above resting core temperature, whole body metabolic rate increases by ∼25% (Saxton, 1981). It remains unclear whether cerebral tissue significantly contributes to the rise in whole-body metabolism during passive hyperthermia. For example, the Arrhenius activation law (or Q10, temperature coefficient), which describes the relation of biological activity to changes in temperature, implies that a rise in 2°C from 37°C should yield an increase in metabolic rate of ∼10%, (South, 1958). However, the change in metabolic rate associated with the Q10 effect *in vitro* may be more sensitive during hypothermia, compared to hyperthermia (Sébert et al., 2003). Nonetheless, several animal preparations have demonstrated that local cerebral or whole-body passive heating yields an increase in cerebral glucose utilization (McCulloch et al., 1982; Mickley et al., 1997) and cerebral metabolic rate ($CMRO_2$) by 5 to 10% per degree Celsius rise in core temperature (Nemoto and Frankel, 1970a,b; Carlsson et al., 1976; Busija et al., 1988). In the dog, $CMRO_2$ was elevated by 21% at a rectal temperature (T_{re}) of 42.1°C compared to baseline (T_{re} of 37.7); however, it began to fall at 43°C (Nemoto and Frankel, 1970b). These latter data likely reflect the temperature dependence on critical cellular activity, whereby nucleotide degradation and blood brain barrier disruption (and imminent death if not treated) begins to occur at extreme core temperatures (i.e., ≧42°C in the human) (Bynum et al., 1978). The molecular mechanisms that might impact on cerebral metabolism and oxygenation beyond a rise of 3°C have not been explored in humans, and are therefore beyond the scope of this review.

In humans, positron emission tomography measurements during passive heating to roughly +2°C rectal temperature show an increased metabolic rate of glucose in the hypothalamus, thalamus, corpus callosum, cingulate gyrus, and cerebellum (Nunneley et al., 2002). However, in the same study, significant declines in metabolic rate were observed in the caudate, putamen, insula, and posterior cingulum. To date, although regional differences are apparent, no study exists (to our knowledge) in the healthy awake human providing a measure of global cerebral metabolic rate during passive hyperthermia. In healthy humans during exercise, however, Nybo et al., (Nybo et al., 2002a) demonstrated with arterial and jugular venous sampling that cerebral metabolic rate is higher by ∼7–8% when subjects are hyperthermic (see Discussion on Exercise). Whether the confounding factor of exercise precludes the conclusion that hyperthermia alone causes an increase in cerebral metabolism, remains unknown. Still, given the theoretical Q10 (temperature coefficient) considerations, in conjunction with animal studies, human positron emission tomography data and exercise studies, it is likely that hyperthermia (of up to +3°C) proffers a dose-dependent response to increase cerebral metabolic rate.

OXYGEN EXTRACTION

Oxygen is transported into cerebral tissue by diffusion, the speed of which is determined by the oxygen conductivity of cerebral tissue. Oxygen conductivity of cerebral tissue is fundamentally determined by the geometry of the capillaries and surrounding tissue (diffusion area and distance), and the tissue metabolism for a given oxygen gradient from the capillary to tissue (Gjedde, 2005). The speed of oxygen transport, or O_2 extraction, can therefore be described as being inversely proportional to blood flow (when metabolism is held constant), and directly proportional to metabolism (when flow is held constant), and the surface area between the tissue and capillaries. As CBF, and subsequently O_2 delivery is reduced, tissue extraction increases. However, because of the inverse relationship between blood flow and O_2 extraction, when CBF is reduced by ∼50–60%, the corresponding increase in O_2 extraction (i.e., of 50–60%) is no longer sufficient to maintain a constant $CMRO_2$ or adequate cerebral oxygenation (Lennox et al., 1935; Gjedde, 2005); i.e., a critical blood flow limit is reached. It follows that this theoretical critical flow limit is altered if metabolism changes; that is, the brain has a reduced critical CBF reserve for the maintenance of adequate cerebral oxygenation when metabolism (O_2 demand) is increased. Given the above theoretical considerations, if brain metabolism increases by a liberal 10% following a 2°C increase in tissue temperature, the critical reduction in blood flow to maintain oxygenation would be ∼40–50%.

CEREBRAL BLOOD FLOW

During passive hyperthermia, respiratory and cardiovascular adjustments disrupt the natural coupling between $CMRO_2$ and CBF. A neurogenic mechanism, i.e., cerebral vasoconstriction from increases in sympathetic nerve activity (SNA), has also been suggested to contribute to reductions in CBF during hyperthermia (e.g., Brothers et al., 2009b). Recent work in partitioning the roles of respiratory and cardiovascular mechanisms and considerations for neurogenic control of CBF during passive hyperthermia is discussed next.

RESPIRATORY—ARTERIAL PCO_2 ($PaCO_2$)

Hyperthermia in humans (among other species) is accompanied by a hyperventilatory response, and subsequently marked respiratory alkalosis. In 1905, Haldane was the first to describe, "breathing being more deeper and more frequent than usual" when hyperthermic (Haldane, 1905). The magnitude of the hyperventilatory response is highly variable between individuals, and is likely dependent upon the rate and magnitude of rise in skin and core temperature; however, the reflex hyperventilation is not usually pronounced until a threshold increase in core temperature of at least 1°C (Barltrop, 1954 and for review see White, 2006). On average, a 1.5–2.0°C increase in core temperature during passive heating yields a reduction in end tidal CO_2 ($PETCO_2$), a validated surrogate for $PaCO_2$ (Brothers et al., 2011a) of ∼ 5–15 mmHg (see **Table 1**). However, the reported decline in $PaCO_2$ varies considerably for a give increase in core temperature, which is likely governed by whether the external heating (i.e., skin temperature) was continued or attenuated to provide a steady-state core temperature. In some studies, $PaCO_2$ can drop below 20 mmHg, and with severe passive heating (≥2°C) pronounced hyperventilation can lead to hypocapnia-induced carpopedal spasms and tetany (Iampietro et al., 1966 and unpublished observations). The exact mechanisms responsible for the hyperventilatory response during hyperthermia in humans have not been fully delineated. It is likely that a medullar integration of skin, and deep tissue temperature, principally hypothalamic temperature (Ingram and Whittow, 1962; Boden et al., 2000), primarily determine the magnitude of hyperventilatory response to hyperthermia. Temperature reception at the carotid bodies may also play an independent role (Zapata et al., 1994). For example, perfusion of warmed blood to the isolated carotid bifurcation elicits a transient hyperventilation in dogs (Bernthal and Weeks, 1939), while bilateral dissection of the carotid nerves mitigates the ventilatory increase to whole body heating in cats (Fadic et al., 1991).

It is well established that $PaCO_2$ is a potent modulator of CBF (Ainslie and Duffin, 2009). At rest, each mmHg change in $PaCO_2$ above and below eupnia yields an approximate 4% increase and 2% decrease in CBF, respectively (Willie et al., 2012; and Willie et al., 2014 for review). During passive supine hyperthermia of +1–1.5°C core temperature above resting, a 10–20% reduction in cerebral blood flow is typically observed (see **Figure 1** and **Table 1**). The role of $PaCO_2$ in the reduction of CBF during hyperthermia remains debatable. Bain et al. (2013) recently demonstrated, using both volumetric and intra-cranial velocity measurements, that global (anterior and posterior) CBF during supine severe (+2°C esophageal temperature) hyperthermia is completely restored to normothermic values upon returning $P_{ET}CO_2$ back to normothermic levels (**Figure 2**). This finding is notionally corroborated by other studies (Fan et al., 2008; Nelson et al., 2011). It should be noted, however, that although middle cerebral artery (MCAv) and posterior cerebral artery (PCAv) velocities were statistically restored to normothermic values following $P_{ET}CO_2$ restoration during +2°C hyperthermia in Nelson et al. (2011), they were still 9 and 3% lower respectively,

Table 1 | Summary of human cerebral blood flow blood velocities and flow [CBF(v)] measurements during supine passive hyperthermia.

Authors	Year	*n*	Hyperthermia		ΔMAP	ΔPETCO2	ΔCBF(v)			
			Δcore	Δskin			ICA (%)	VA (%)	PCAv (%)	MCAv (%)
Bain et al.	2013	19	+2.0°C T_{es}	+5.0°C	−1 mmHg	−7 mmHg	−20	−31	−18	−23
Brothers et al.	2009a	9	+1.1°C T_{gi}	+3.8°C	−1 mmHg	−4 mmHg	–	–	–	−18
Brothers et al.	2009b	7	*+1.4°C* T_{gi}	+4.3°C	−1 mmHg	−6 mmHg	–	–	–	−31
Fan et al.	2008	10	+0.5°C T_{es}	+3.7°C	−14 mmHg	−3 mmHg	–	–	–	−6
			+1.0°C T_{es}	+3.8°C	−19 mmHg	−5 mmHg	–	–	–	−13
			+1.5°C T_{es}	+4.6°C	−17 mmHg	−11 mmHg	–	–	–	−23
			+2.0°C T_{es}	+4.8°C	−16 mmHg	−17 mmHg	–	–	–	−32
Low et al.	2008	9	+1.1°C T_{gi}	+3.7°C	−2 mmHg	−3 mmHg	–	–	–	−13
Nelson et al.	2011	10	+0.9°C T_{gi}	+3.5°C	0 mmHg	−2 mmHg	–	–	−10	−7
		8	+1.8°C T_{gi}	+5.8°C	−2 mmHg	−15 mmHg	–	–	−23	−26
Ogoh et al.	2013	12	+0.3°C T_{es}	+3.8°C	−1 mmHg	−2 mmHg	−5	−8	–	−15
			+0.7°C T_{es}	+4.7°C	−4 mmHg	−2 mmHg	−5	−9	–	−15
			+1.2°C T_{es}	+5.1°C	−3 mmHg	−5 mmHg	−12	−12	–	−26
			+1.4°C T_{es}	+5.1°C	−6 mmHg	−6 mmHg	−18	−17	–	−23
Wilson et al.	2006	15	+0.9°C T_{gi}	+4.2°C	0 mmHg	−2 mmHg	–	–	–	−15*

Asterisks (*) indicate values estimated from figure representation. T_{re}, T_{es}, and T_{gi} represent rectal, esophageal, and gastrointestinal temperature respectively. n = sample size. MAP = mean arterial pressure. $P_{ET}CO_2$ = end-tidal CO_2 partial pressure. ICA = Internal carotid artery blood flow. VA = vertebral artery blood flow. MCAv = middle cerebral artery blood velocity. PCAv = posterior artery blood velocity.

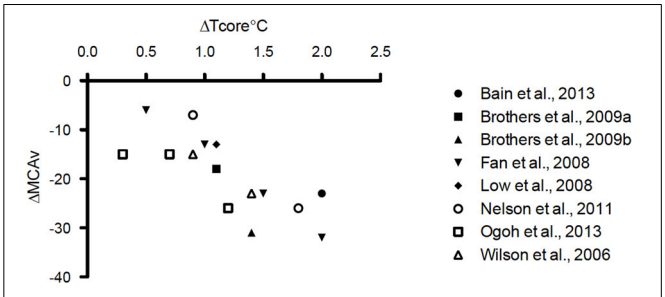


FIGURE 1 | Representation of the reported percent reductions in middle cerebral artery blood velocity (MCAv) (x axis) as a function of delta core temperature (esophageal, gastrointestinal, or rectal) (y axis) during supine passive hyperthermia up to +2°C.

than baseline values. To that end, in opposition of complete CBF restoration following a return to eucapnia, Brothers et al. (2009b) reported that MCAv was only 50% restored back to normothermic values upon the restoration of $P_{ET}CO_2$during supine hyperthermia. Although difficult to reconcile, these divergent findings may be explained by the variability in "steady-state" CBF following baseline $P_{ET}CO_2$ restoration. For example, although absolute CO_2 reactivity appears to be maintained during hyperthermia (Low et al., 2008), the dynamics of the CBF response to eucapnic restoration will in part be determined by the magnitude of the hyperventilation response (and resultant respiratory alkalosis) (Ide et al., 2003). That is, those with a larger hyperventilatory response will likely require a longer time to reach steady-state CBF values upon restoration of baseline $PaCO_2$ due to a larger extra-cellular pH gradient. Moreover, sustained hypoventilation may eventually lead to an adaptive response whereby restoration of baseline eucapnia will yield a temporary overshoot in CBF (compared to pre-stimulus values) (Ide et al., 2003). The mechanisms of this CBF overshoot remains unclear, but may involve changes in lactate and bicarbonate (Albrecht et al., 1987; Marder et al., 1990). The transient magnitude of the CBF overshoot therefore probably depends upon the length of time and magnitude of the hypocapnia. It is clear that this can influence "steady-state eucapnic" CBF measures, and may explain the variable conclusions for the role of $PaCO_2$ in reducing CBF during hyperthermia. Nonetheless, taken the most recent data (Nelson et al., 2011; Bain et al., 2013), it is more than likely that $PaCO_2$ explains the majority of the CBF reduction during passive hyperthermia, at least when subjects are kept in the supine position. Still, future research is warranted to better clarify this role.

In contrast to supine hyperthermia, during upright seated hyperthermia, Fujii et al. (2008) and Ross et al. (2012), found that MCAv is only partially restored back to normothermic levels upon restoration of $P_{ET}CO_2$ with the addition of 5% CO_2 to the inspired air. Furthermore, Nelson et al. (2011) found that head up tilt exacerbated the decline in MCAv and PCAv while hyperthermic, in the absence of significant further reductions in $P_{ET}CO_2$. It is therefore evident that, during hyperthermia, CBF is declined by increased hydrostatic pressure associated with posture (see Cardiovascular Section), independently of $PaCO_2$.

Do Changes in $PaCO_2$ Alter Tolerance Time to a Simulated Hemorrhage?

Tolerance time to a simulated hemorrhage is clearly reduced while hyperthermic compared to normothermic (Allan and Crossley, 1972; Wilson et al., 2006; Keller et al., 2009; Brothers et al., 2011b). Reductions in $PaCO_2$ associated with hyperthermia-induced hyperventilation appear to have little influence on the reduced

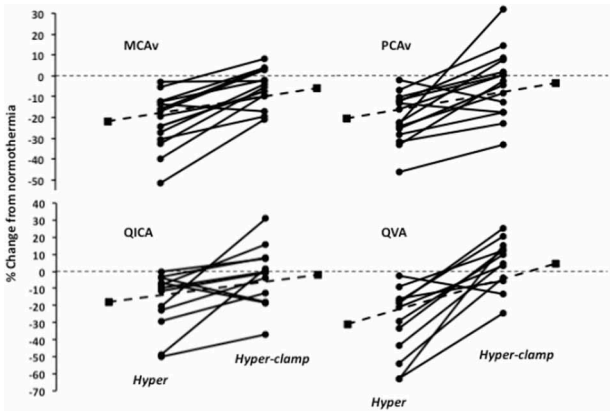


FIGURE 2 | Change in middle cerebral artery blood velocity (MCAv), posterior cerebral artery blood velocity (PCAv), internal carotid artery blood flow (QICA) and vertebral artery blood flow (QVA) following a 2.0°C rise in esophageal temperature with and without restoration of end-tidal CO_2. Adapted from (Bain et al., 2013).

ability to withstand simulated hemorrhage (Lucas et al., 2013; Pearson et al., 2013). This suggests that cardiovascular adjustments contribute more to tolerance time (i.e., minimum cerebral oxygenation levels before syncope) than baseline CBF during a graded hemorrhage simulation. This notion is supported by findings from our laboratory where tolerance to graded lower body negative pressure was unaltered even when baseline CBF was reduced by ∼30% via administration of indomethacin, independently of changes in $PaCO_2$ (Lewis et al., under review). Such findings may be attributed to the fact that simulated hemorrhage time is typically determined by the time elapsed before ethically low blood pressure levels (usually a SBP of <80 mmHg) are attained, rather than syncope itself. A perhaps more ecological stance is the view that a reduction in CBF at baseline, although not effecting tolerance time to simulated hemorrhage, effectively reduces the buffer zone for CBF to change before syncope occurs. As such, when $PaCO_2$ and subsequently CBF, is reduced from hyperthermia, any condition eliciting a faster or larger perturbation in BP (i.e., a period when cerebral autoregulation is less effective) (Tzeng and Ainslie, 2013) compared to graded lower body negative pressure, may pose an increased risk of syncope. It should be noted, however, that dynamic cerebral autoregulation, as indexed by steady-state linear transfer function analysis, appears to be maintained (Low et al., 2009) or perhaps even improved, with hyperthermia (Brothers et al., 2009a).

CARDIOVASCULAR CONTROL

In order to promote heat loss via evaporative and convective means during severe passive hyperthermia, cutaneous blood flow can increase upwards of 25-fold (e.g., from ∼300 to 7500 $mL \cdot min^{-1}$) (Rowell et al., 1969; Rowell, 1986). The large increase in cutaneous vascular conductance is met by concomitant increases in cardiac output (at times up to 13 $mL \cdot min^{-1}$) (Rowell et al., 1969; Rowell, 1986), accomplished almost exclusively via increases in heart rate. In turn, it is now well accepted that resting BP, and therefore perfusion pressure to the brain during passive, supine hyperthermia, is generally preserved, or only moderately decreased (see Crandall and González-Alonso, 2010 for a comprehensive review on the cardiovascular functioning during hyperthermia). It is interesting to note, however, that BP estimations during passive hyperthermia vary considerably (see **Table 1**). These variations likely reflect the difficulty in acquiring accurate BP measurements without measuring it intra-arterially during hyperthermia (Ganio et al., 2011). Nonetheless, in contrast to passive supine hyperthermia, it is generally accepted that adequate BP is not maintained under dynamic hyperthermic conditions, e.g., with an orthostatic challenge or hemorrhage.

Any condition that compromises CBF maintenance inherently increases the risk of syncope/reduction of cerebral oxygenation. As mentioned, tolerance to an orthostatic challenge or simulated hemorrhage is reduced when hyperthermic (Allan and Crossley, 1972; Wilson et al., 2006; Keller et al., 2009; Brothers et al., 2011b). Given that changes $PaCO_2$ seem to play a negligible role in determining tolerance time to a simulated hemorrhage (see section *Do changes in $PaCO_2$ alter tolerance time to a simulated hemorrhage?*), two key cardiovascular adjustments are likely responsible; (1) the inability to decrease systemic vascular compliance (SVC) (Wilson et al., 2002a; Ganio et al., 2012), and (2) a greater reduction in stroke volume for a given reduction in left ventricular filling pressure (i.e., a leftward shift of the operating point to a steeper portion on the Frank Starling curve) (Wilson et al., 2009). Clearly, the former dictates the latter. When normothermic, it is well established that SVC decreases during a simulated hemorrhage (Murray et al., 1968). Why SVC does not also decrease when hyperthermic, is not entirely understood. However, it is generally accepted that an inhibition of cutaneous vasoconstriction is likely at play (Crandall et al., 2010). An improvement to orthostatic tolerance following acute skin cooling while hyperthermic lends evidence to this hypothesis (Wilson et al., 2002b). The mechanisms of cutaneous vasculature control remains a complex field of study, riddled with redundant mechanistic pathways (for a review see Charkoudian, 2010). Nonetheless, it appears that human physiology places a hierarchy for heat loss during hyperthermia, potentially to the detriment of adequate central blood volume and subsequently CBF/consciousness.

Dehydration (i.e., ≥2% loss of body mass) often follows prolonged sweating, and is therefore closely tied to hyperthermia. A major cardiovascular consequence of dehydration is a dose-dependent decrease in blood volume (Kempton et al., 2009). In turn, dehydration impairs the ability to maintain adequate central blood volumes, and thus CBF during an orthostatic challenge (Harrison et al., 1986; Romero et al., 2011). Carter et al. (2006) demonstrated that the transient reductions in MCAv were larger upon standing from sitting when dehydrated (3.0% reduction in body mass), compared to euhydrated. Consistent with this finding, Moralez et al. (2012) demonstrated that dehydration (2.7% reduction in body mass) exacerbated the reductions in BP and MCAv upon standing following a 10-rep maximum leg press. It is therefore reasonable to assume that when hyperthermia is coupled with dehydration, the ability to maintain adequate CBF is further reduced during orthostatic challenges or hemorrhage.

In contrast to the apparent reduction in CBF with an orthostatic challenge when dehydrated, Fan et al., (Fan et al., 2008)

demonstrated that when subjects were supine, dehydration (1.5% reduction in body mass) increased resting MCAv by ∼11%. When subjects were made hyperthermic, however, dehydration appeared to have little or no effect on the reduction in MCAv. It is difficult to reconcile why MCAv was increased with normothermic dehydration compared to euhydration. Increases in CBF during passive supine dehydration may be related to the increased osmolality of extracellular fluid via cerebral cellular shrinkage [i.e., increased concentrations of solutes in the extracellular fluid cause an intra-to extra cellular fluid shift (Kempton et al., 2009)]. In turn, CBF during supine dehydration may be increased to maintain an appropriate ionic milieu for neuronal function. Nonetheless, during passive supine hyperthermia, the marked reductions in MCAv associated with the reduced $PaCO_2$ seem to shadow any effect of dehydration (Fan et al., 2008).

NEUROGENIC CONTROL

Sympathetic nerve activity in the muscle and skin vasculature is significantly elevated during hyperthermia (Bini et al., 1980; Niimi et al., 1997; Cui et al., 2004; Keller et al., 2006). Hyperthermia decreases vascular conductance of the splanchnic and renal tissue, presumably also via increased SNA (Rowell, 1983). Indeed, it is commonly accepted that the primary mechanism of blood flow redistribution to the cutaneous tissue during hyperthermia is driven by SNA (Rowell, 1990). Whether increased SNA during hyperthermia affects the cerebral vasculature, however, remains speculative. It is well recognized that perivascular adrenergic nerves richly innervate the cerebral arteries, (Edvinsson and Hamel, 2002), while the smooth muscle cells of the arterioles possess both alpha- and beta-adrenergic receptors (Edvinsson, 1982). This suggests that the cerebral vascular has the potential to be mediated by neurogenic factors. In animal models, CBF is reduced with stimulation of the superior cervical ganglion (Heistad et al., 1978; Cassaglia et al., 2008). In humans, unilateral trigeminal ganglion stimulation decreases CBF (Visocchi et al., 1996), while stellate ganglionic blockade increases CBF (Umeyama et al., 1995; Ide et al., 2000). The above animal and human studies support a tonic neurogenic control of CBF. Therefore, several authors have speculated that reductions in CBF during hyperthermia may, in part, be due to increases in cerebral SNA (see Crandall and González-Alonso, 2010 and related references). However, this notion is based primarily by deduction when $PaCO_2$ and MAP cannot explain the full reduction in CBF (see Discussion on the Role of Arterial PCO_2). Although an attractive hypothesis, several caveats persist to accept that SNA decreases CBF during hyperthermia. First, redundant mechanisms (e.g., dilator agents such as nitric oxide, prostanoids, and histamine) may act to counteract a noradrenaline-induced vasoconstriction of the cerebral vasculature. Specifically, when brain metabolism is elevated (see Discussion on Metabolism and Hyperthermia), a "functional sympatholysis" or "metabolic restraint" might mitigate the influence of SNA (Gross et al., 1983; Busija and Leffler, 1987). This is in agreement with animal studies that report a global increase in CBF to passive hyperthermia (Carlsson et al., 1976; Busija et al., 1988) that cannot be entirely explained by changes in $PaCO_2$. Second, the density of alpha- and beta-adrenergic receptors on the cerebral arterioles varies depending on vessel size (Edvinsson, 1982), suggesting that a heterogeneous response, potentially modified by hyperthermia, may exists for a given increase in SNA. Third, the relative influence of SNA on the cerebral vascular seems to be dependent upon levels of blood pressure. That is, sympathetic activation has a larger influence during hypertension, compared to normotension (Bill and Linder, 1976; Edvinsson et al., 1976; and reviewed in Willie et al., 2014). Lastly, the cerebral vasculature has been shown to exhibit a "vasomotor escape" following prolonged maximal SNA stimulation of over 5 ± 7 min (Sercobe et al., 1979), suggesting that the influence of SNA on the cerebral vasculature may be dependent on the duration of the stimulation. That CBF has recently been shown to fully recover to normothermic values when $PaCO_2$ is returned to eucapnia (Bain et al., 2013) supports the notion that increases in SNA during hyperthermia proffer a negligible effect on global CBF. Nonetheless, future studies are required to better understand this potential mechanism. Administration of a centrally acting α2-adrenoreceptor agonist (provided no changes in MAP), cervical ganglion block, or measurements of cerebral noradrenaline spillover (Mitchell et al., 2009) during hyperthermia with concomitant measures of global CBF and maintenance of eupnia, is likely warranted.

CEREBRAL HEAT BALANCE, OXYGENATION, AND EXERCISE

Human cerebral tissue uses oxygen at a metabolic rate of between 3 to 3.5 $mLO_2 \cdot 100\ g\ cerebral\ tissue^{-1} \cdot min^{-1}$ (Lassen, 1985), producing approximately 0.6 $j\ g^{-1} \cdot\ min^{-1}$ heat, which must then be removed via cerebral circulation (reviewed in: Nybo and Secher, 2004). During hyperthermia, cerebral heat balance is compromised from reductions in CBF (Nybo et al., 2002b) and therefore reductions in convective heat loss (arguably the only avenue for cerebral heat loss). An increased cerebral temperature can impair blood-brain barrier integrity (Watson et al., 2005), particularly when combined with dehydration (Watson et al., 2006). The exact interaction between temperature, blood brain barrier opening and cerebral oxygenation remains obscure.

During hyperthermia exercise capacity is reduced (e.g., Rowell et al., 1966, and for reviews of the potential mechanisms involved see Nybo, 2007 and Cheuvront et al., 2010). Reductions in exercise capacity and a faster onset of fatigue likely stem from interactions of both central and peripheral factors (Nybo and Secher, 2004), including observed alterations in EEG α/β arousal levels with greater perceived exertion and decreased motor unit activation (Nybo and Nielsen, 2001; Morrison et al., 2004; Todd et al., 2005; Périard et al., 2011). Decreases in voluntary activation tend to correlate to reductions in MCAv (measured via Doppler ultrasound), but these reductions can be partially restored when breathing a hypercapnic gas mixture to offset changes in ventilation and $P_{ET}CO_2$ levels from heat-induced hyperventilation (Ross et al., 2012). However, although preventing hypocapnia during normothermic exhaustive cycling exercise can exhibit increases in MCAv, performance is unchanged (Subudhi et al., 2011). As such, it is likely that a direct effect of increased temperature on CNS and neuromuscular functioning, rather than detriments to cerebral oxygenation, is the primary factor governing decreased exercise capacity while hyperthermic.

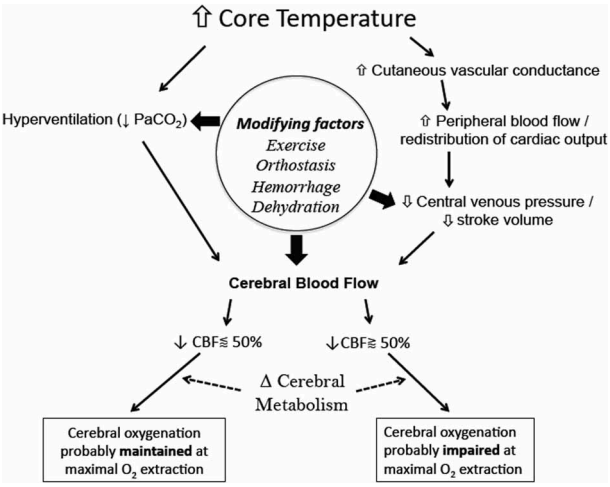


FIGURE 3 | Simplified schematic of the mechanisms and modifying factors involved with reductions in cerebral blood flow and ultimately cerebral oxygenation during whole-body hyperthermia. Global cerebral oxygenation is likely impaired when CBF is reduced beyond 50%, i.e., a critical blood flow is reached at maximal levels of oxygen extraction. Changes in cerebral metabolism will alter the theoretical critical blood flow limit, while regional changes in metabolism and blood flow can yield regional differences in cerebral oxygenation.

Examinations of cerebral oxygenation during exercise using near-infrared spectroscopy (NIRS) suggest that cerebral oxygenation is not impaired, including when subjects are passively heated to core temperatures up to 39.5°C (Morrison et al., 2009). However, it is now clear that changes in skin blood flow can alter the NIRS-derived oxygenation values (e.g., Davis et al., 2006); thus, data using only this measure must be interpreted with caution. Using the Kety-Schmidt protocol to measure global CBF, Nybo et al. (2002a) and Rasmussen et al. (2010) reported that uncompensable hyperthermic exercise elicited reductions in CBF by ∼18 and 15% greater than "normothermic" exercise respectively. Of note, Rasmussen et al. (2010) further estimated cerebral mitochondrial oxygen tension, and found it to be declined by ∼5 mmHg during hyperthermic compared to normothermic exercise. This reduction was attributed to the fact that cerebral metabolic rate of oxygen increased by 8 ± 7% from the beginning to the end of hyperthermic exercise, while CBF decreased by 15%, and O_2 extraction only increased by 7% (Rasmussen et al., 2010). Given these data, it can be rationalized that cerebral oxygenation is in fact compromised during exhaustive hyperthermic exercise. However, the finding that O_2 extraction did not increase sufficiently to maintain mitochondrial oxygenation in the face of moderate increase in metabolic demand (8%) and reduction in CBF (15%), is in contradiction to theoretical considerations (see Oxygen Extraction section). Furthermore, the estimations of mitochondrial oxygen tension are inherently based on several assumptions. For example, the diffusibility of O_2 must remain constant (Rasmussen et al., 2007) [supported by the lack of capillary recruitment in rats during hypoxia (Göbel et al., 1989)]; and the potential for cerebral oxygen stores via *neuroglobin* (Burmester et al., 2000) to preserve mitochondrial oxygenation when O_2 availability declines, are also ignored. Nonetheless, these calculations provide the best estimations of cerebral mitochondrial oxygen tension to date in humans. However, it remains that a consensus on global cerebral oxygenation during hyperthermic exercise is difficult to ascertain, and requires further experimentation.

CONCLUSIONS AND FUTURE DIRECTIONS

The fate of cerebral oxygenation during hyperthermia of up to +2°C core temperature is dependent upon the integrative balance between increases in metabolism and oxygen extraction, with declines in cerebral perfusion pressure from reductions in $PaCO_2$ and increased systemic vascular conductance (**Figure 3**). When left in the supine position, a ∼10 mmHg drop in $PaCO_2$ following a 2°C increase in core temperature yields an average CBF reduction by ∼25%. At which point, it stands to reason that the global theoretical capacity to increase cerebral O_2 extraction is, on average, effective in maintaining cerebral oxygenation, even with an increase in cerebral metabolism of ∼10%. On the other hand, the inability of the cardiovascular system to maintain perfusion pressure to the brain during more dynamic conditions (e.g., hemorrhage or orthostatic challenge), coupled with a reduced CBF baseline from reductions in $PaCO_2$, potentiates a condition whereby cerebral oxygenation could be compromised following maximal O_2 extraction potential. This fact is clearly evidenced by the reduced tolerance time to simulated hemorrhage, and the increased occurrence of syncope during hyperthermia.

Recent data have collectively provided a salient understanding of cerebral oxygenation during varying degrees of whole-body hyperthermia, however several avenues of experimentation remain. First, it is evident that direct measurements of arterial and cerebral venous blood in humans are required to experimentally verify changes in cerebral metabolism and oxygenation with separate levels of CBF during hyperthermia. Second, albeit inherently difficult to execute, a conclusive study on the role of SNA on CBF during hyperthermia is required. Third, the importance of extra-cranial contamination on NIRS-derived oxygenation values has been highlighted during changes in skin blood flow (Davis et al., 2006) and also where scalp ischemia induced by inflation of a circumferential cranial tourniquet impacted NIRS readings (Davie and Grocott, 2012). Although newer clinically available NIRS monitors use algorithms to subtract light absorption from superficial tissue (e.g., scalp, skin, bone, pia matter) from deeper tissue (Zheng et al., 2013), the utility during hyperthermia and/or exercise remains to be established. Lastly, the interactive role of dehydration, heat acclimatization and certain pathologies (e.g., heart failure, diabetes, autonomic disorders, etc.) on cerebral oxygenation during heat stress should be focus for future work.

REFERENCES

Ainslie, P. N., and Duffin, J. (2009). Integration of cerebrovascular CO2 reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 296, R1473–R1495. doi: 10.1152/ajpregu.91008.2008

Albrecht, R. F., Miletich, D. J., and Ruttle, M. (1987). Cerebral effects of extended hyperventilation in unanesthetized goats. *Stroke* 18, 649–655. doi: 10.1161/01.STR.18.3.649

Allan, J. R., and Crossley, R. J. (1972). Effect of controlled elevation of body temperature on human tolerance to +G z acceleration. *J. Appl. Physiol.* 33, 418–420.

Bain, A. R., Smith, K. J., Lewis, N. C., Foster, G. E., Wildfong, K. W., Willie, C. K., et al. (2013). Regional changes in brain blood flow during severe passive hyperthermia: effects of PaCO2 and extracranial blood flow. *J. Appl. Physiol.* 115, 653–659. doi: 10.1152/japplphysiol.00394.2013

Barltrop, D. (1954). The relation between body temperature and respiration. *J. Physiol.* 125, 19–20.

Bernthal, T., and Weeks, W. F. (1939). Respiratory and vasomotor effects of variations in carotid body temperature: a study of the mechanism of chemoceptor stimulation. *Am. J. Physiol.* 127, 94–105.

Bill, A., and Linder, J. (1976). Sympathetic control of cerebral blood flow in acute arterial hypertension. *Acta Physiol. Scand.* 96, 114–121. doi: 10.1111/j.1748-1716.1976.tb10176.x

Bini, G., Hagbarth, K. E., Hynninen, P., and Wallin, B. G. (1980). Thermoregulatory and rhythm-generating mechanisms governing the sudomotor and vasoconstrictor outflow in human cutaneous nerves. *J. Physiol.* 306, 537–552.

Boden, A. G., Harris, M. C., and Parkes, M. J. (2000). The preoptic area in the hypothalamus is the source of the additional respiratory drive at raised body temperature in anaesthetised rats. *Exp. Physiol.* 85, 527–537. doi: 10.1017/S0958067000020534

Brothers, R. M., Ganio, M. S., Hubing, K. A., Hastings, J. L., and Crandall, C. G. (2011a). End-tidal carbon dioxide tension reflects arterial carbon dioxide tension in the heat-stressed human with and without simulated hemorrhage. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 300, R978–R983. doi: 10.1152/ajpregu.00784.2010

Brothers, R. M., Keller, D. M., Wingo, J. E., Ganio, M. S., and Crandall, C. G. (2011b). Heat-stress-induced changes in central venous pressure do not explain interindividual differences in orthostatic tolerance during heat stress. *J. Appl. Physiol.* 110, 1283–1289. doi: 10.1152/japplphysiol.00035.2011

Brothers, R. M., Wingo, J. E., Hubing, K. A., and Crandall, C. G. (2009b). The effects of reduced end-tidal carbon dioxide tension on cerebral blood flow during heat stress. *J. Physiol.* 587, 3921–3927. doi: 10.1113/jphysiol.2009.172023

Brothers, R. M., Zhang, R., Wingo, J. E., Hubing, K. A., and Crandall, C. G. (2009a). Effects of heat stress on dynamic cerebral autoregulation during large fluctuations in arterial blood pressure. *J. Appl. Physiol.* 107, 1722–1729. doi: 10.1152/japplphysiol.00475.2009

Burmester, T., Weich, B., Reinhardt, S., and Hankeln, T. (2000). A vertebrate globin expressed in the brain. *Nature* 407, 520–523. doi: 10.1038/35035093

Busija, D. W., and Leffler, C. W. (1987). Eicosanoid synthesis elicited by norepinephrine in piglet parietal cortex. *Brain Res.* 403, 243–248. doi: 10.1016/0006-8993(87)90061-8

Busija, D. W., Leffler, C. W., and Pourcyrous, M. (1988). Hyperthermia increases cerebral metabolic rate and blood flow in neonatal pigs. *Am. J. Physiol.* 255, H343–H346.

Bynum, G. D., Pandolf, K. B., Schuette, W. H., Goldman, R. F., Lees, D. E., Whang-Peng, J., et al. (1978). Induced hyperthermia in sedated humans and the concept of critical thermal maximum. *Am. J. Physiol. Reg. Integr. Comp. Physiol.* 235, R228–R236.

Carlsson, C., Hägerdal, M., and Siesjö, B. K. (1976). The effect of hyperthermia upon oxygen consumption and upon organic phosphates, glycolytic metabolites, citric and cycle intermediates and associated amino acids in rat cerebral cortes. *J. Neurochem.* 26, 1001–1006. doi: 10.1111/j.1471-4159.1976.tb06484.x

Carter, R., Cheuvront, S. N., Vernieuw, C. R., and Sawka, M. N. (2006). Hypohydration and prior heat stress exacerbates decreases in cerebral blood flow velocity during standing. *J. Appl. Physiol.* 101, 1744–1750. doi: 10.1152/japplphysiol.00200.2006

Cassaglia, P. A., Griffiths, R. I., and Walker, A. M. (2008). Sympathetic nerve activity in the superior cervical ganglia increases in response to imposed increases in arterial pressure. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 294, R1255–R1261. doi: 10.1152/ajpregu.00332.2007

Charkoudian, N. (2010). Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. *J. Appl. Physiol.* 109, 1221–1228. doi: 10.1152/japplphysiol.00298.2010

Cheuvront, S. N., Kenefick, R. W., Montain, S. J., and Sawka, M. N. (2010). Mechanisms of aerobic performance impairment with heat stress and dehydration. *J. Appl. Physiol.* 109, 1989–1995. doi: 10.1152/japplphysiol.00367.2010

Crandall, C. G., and González-Alonso, J. (2010). Cardiovascular function in the heat-stressed human. *Acta Physiol. (Oxf.).* 199, 407–423. doi: 10.1111/j.1748-1716.2010.02119.x

Crandall, C. G., Shibasaki, M., and Wilson, T. E. (2010). Insufficient cutaneous vasoconstriction leading up to and during syncopal symptoms in the heat stressed human. *Am. J. Physiol. Heart Circ. Physiol.* 299, H1168–H1173. doi: 10.1152/ajpheart.00290.2010

Cui, J., Zhang, R., Wilson, T. E., and Crandall, C. G. (2004). Spectral analysis of muscle sympathetic nerve activity in heat-stressed humans. *Am. J. Physiol. Heart Circ. Physiol.* 286, H1101–H1106. doi: 10.1152/ajpheart.00790.2003

Davie, S. N., and Grocott, H. P. (2012). Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology* 116, 834–840. doi: 10.1097/ALN.0b013e31824c00d7

Davis, S. L., Fadel, P. J., Cui, J., Thomas, G. D., and Crandall, C. G. (2006). Skin blood flow influences near-infrared spectroscopy-derived measurements of tissue oxygenation during heat stress. *J. Appl. Physiol.* 100, 221–224. doi: 10.1152/japplphysiol.00867.2005

Edvinsson, L. (1982). Sympathetic control of cerebral circulation. *Trends Neurosci.* 5, 425–429. doi: 10.1016/0166-2236(82)90232-6

Edvinsson, L., and Hamel, E. (2002). "Perivascular nerves in brain vessels," in *Cerebral Blood Flow and Metabolism*, eds L. Edvinsson and D. Krause (Philadelphia: Lippincott Williams and Wilkins), 30–42.

Edvinsson, L., Owman, C., and Siesjö, B. (1976). Physiological role of cerebrovascular sympathetic nerves in the autoregulation of cerebral blood flow. *Brain Res.* 117, 519–523. doi: 10.1016/0006-8993(76)90760-5

Fadic, R., Larrain, C., and Zapata, P. (1991). Thermal effects on ventilation in cats: participation of carotid body chemoreceptors. *Resp. Physiol.* 86, 51–63. doi: 10.1016/0034-5687(91)90039-L

Fan, J.-L., Cotter, J. D., Lucas, R. A. I., Thomas, K., Wilson, L., and Ainslie, P. N. (2008). Human cardiorespiratory and cerebrovascular function during severe passive hyperthermia: effects of mild hypohydration. *J. Appl. Physiol.* 105, 433–445. doi: 10.1152/japplphysiol.00010.2008

Fujii, N., Honda, Y., Hayashi, K., Kondo, N., Koga, S., and Nishiyasu, T. (2008). Effects of chemoreflexes on hyperthermic hyperventilation and cerebral blood velocity in resting heated humans. *Exp. Physiol.* 93, 994–1001. doi: 10.1113/expphysiol.2008.042143

Ganio, M. S., Brothers, R. M., Lucas, R. A. I., Hastings, J. L., and Crandall, C. G., (2011). Validity of auscultatory and Penaz blood pressure measurements during profound heat stress alone and with an orthostatic challenge. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 301, R1510–R1516. doi: 10.1152/ajpregu.00247.2011

Ganio, M. S., Overgaard, M., Seifert, T., Secher, N. H., Johansson, P. I., Meyer, M. A., et al.(2012). Effect of heat stress on cardiac output and systemic vascular conductance during simulated hemorrhage to presyncope in young men. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 302, H1756–H1761. doi: 10.1152/ajpheart.00941.2011

Gjedde, A. (2005). The pathways of oxygen in brain. I. Delivery and metabolism of oxygen. *Adv. Exp. Med. Biol.* 566, 269–275. doi: 10.1007/0-387-26206-7_36

Göbel, U., Klein, B., Schröck, H., and Kuschinsky, W. (1989). Lack of capillary recruitment in the brains of awake rats during hypercapnia. *J. Cereb. Blood Flow Metab.* 9, 491–499. doi: 10.1038/jcbfm.1989.72

Gross, P. M., Harper, A. M., and Teasdale, G. M. (1983). Interaction of histamine with noradrenergic constrictory mechanisms in cat cerebral arteries and veins. *Can. J. Physiol. Pharmacol.* 61, 756–763. doi: 10.1139/y83-117

Haldane, J. S. (1905). The influence of high air temperatures. No. I. *J. Hyg.* 5, 494–513. doi: 10.1017/S0022172400006811

Harrison, M. H., Hill, L. C., Spaul, W. A., and Greenleaf, J. E. (1986). Effect of hydration on some orthostatic and haematological responses to head-up tilt. *Eur. J. Appl. Physiol. Occup. Physiol.* 55, 187–194. doi: 10.1007/BF00715003

Heistad, D. D., Marcus, M. L., and Gross, P. M. (1978). Effects of sympathetic nerves on cerebral vessels in dog, cat, and monkey. *Am. J. Physiol.* 235, H544–H552.

Iampietro, P. F., Fiorica, V., Higgins, E. A., Mager, M., and Goldman, R. F. (1966). Exposure to heat: comparison of responses of dog and man. *Int. J. Biometeorol.* 10, 175–185. doi: 10.1007/BF01426864

Ide, K., Boushel, R., Sørensen, H. M., Fernandes, A., Cai, Y., Pott, F., et al.(2000). Middle cerebral artery blood velocity during exercise with beta-1 adrenergic and unilateral stellate ganglion blockade in humans. *Acta Physiol. Scand.* 170, 33–38. doi: 10.1046/j.1365-201x.2000.00757.x

Ide, K., Eliasziw, M., and Poulin, M. J. (2003). Relationship between middle cerebral artery blood velocity and end-tidal PCO2 in the hypocapnic-hypercapnic range in humans. *J. Appl. Physiol.* 95, 129–137. doi: 10.1152/japplphysiol.01186

Ingram, D. L., and Whittow, G. C. (1962). The effect of heating the hypothalamus on respiration in the ox (Bos taurus). *J. Physiol.* 163, 200–210.

Johnson, J. M., and Proppe, D. W. (2011). Cardiovascular adjustments to heat stress. *Comp. Physiol.* doi: 10.1002/cphy.cp040111

Keller, D. M., Cui, J., Davis, S. L., Low, D. A., and Crandall, C. G. (2006). Heat stress enhances arterial baroreflex control of muscle sympathetic nerve activity via increased sensitivity of burst gating, not burst area, in humans. *J. Physiol.* 573, 445–451. doi: 10.1113/jphysiol.2006.108662

Keller, D. M., Low, D. A., Wingo, J. E., Brothers, R. M., Hastings, J., Davis, S. L., et al. (2009). Acute volume expansion preserves orthostatic tolerance during whole-body heat stress in humans. *J. Physiol.* 587, 1131–1139. doi: 10.1113/jphysiol.2008.165118

Kempton, M. J., Ettinger, U., Schmechtig, A., Winter, E. M., Smith, L., McMorris, T., et al. (2009). Effects of acute dehydration on brain morphology in healthy humans. *Hum. Brain Mapp.* 30, 291–298. doi: 10.1002/hbm.20500

Lassen, N. A. (1985). Normal average value of cerebral blood flow in younger adults is 50 ml/100 g/min. *J. Cereb. Blood Flow Metab.* 5, 347–349. doi: 10.1038/jcbfm.1985.48

Lennox, W. G., Gibbs, F. A., and Gibbs, E. L. (1935). Relationship of unconsciousness to cerebral blood flow and to anoxemia. *Arch. Neurol. Psychiatry* 34, 1001. doi: 10.1001/archneurpsyc.1935.02250230073006

Lindhard, J. (1910) "Investigations into the conditions governing the temperature of the body," in *Danmark-ekspeditionen til Gronlands Nordostkyst 1906–1908*, ed L. Mylius-Erichsen (Kobenhavn: Bianco Lunos Bogtrykkeri), 3–53.

Low, D. A., Wingo, J. E., Keller, D. M., Davis, S. L., Cui, J., Zhang, R., et al. (2009). Dynamic cerebral autoregulation during passive heat stress in humans. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 296, R1598–R1605. doi: 10.1152/ajpregu.90900.2008

Low, D. A., Wingo, J. E., Keller, D. M., Davis, S. L., Zhang, R., and Crandall, C. G. (2008). Cerebrovascular responsiveness to steady-state changes in end-tidal CO2 during passive heat stress. *J. Appl. Physiol.* 104, 976–981. doi: 10.1152/japplphysiol.01040.2007

Lucas, R. A. I., Pearson, J., Schlader, Z. J., and Crandall, C. G. (2013). Hypercapnia-induced increases in cerebral blood flow do not improve lower body negative pressure tolerance during hyperthermia. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 305, R604–R609. doi: 10.1152/ajpregu.00052.2013

Marder, J., Eylath, U., Moskovitz, E., and Sharir, R. (1990). The effect of heat exposure on blood chemistry of the hyperthermic rabbit. *Comp. Biochem. Physiol. A Comp. Physiol.* 97, 245–247. doi: 10.1016/0300-9629(90)90179-V

McCulloch, J., Savaki, H. E., Jehle, J., and Sokoloff, L. (1982). Local cerebral glucose utilization in hypothermic and hyperthermic rats. *J. Neurochem.* 39, 255–258. doi: 10.1111/j.1471-4159.1982.tb04729.x

Mickley, G. A., Cobb, B. L., and Farrell, S. T. (1997). Brain hyperthermia alters local cerebral glucose utilization: a comparison of hyperthermic agents. *Int. J. Hyperthermia* 13, 99–114. doi: 10.3109/02656739709056434

Mitchell, D., Lambert, G., Secher, N., Raven, P., Van Lieshout, J., and Esler, M. (2009). Jugular venous overflow of noradrenaline from the brain: a neurochemical indicator of cerebrovascular sympathetic nerve activity in humans. *J. Physiol.* 587, 2589–2597. doi: 10.1113/jphysiol.2008.167999

Moralez, G., Romero, S. A., Rickards, C. A., Ryan, K. L., Convertino, V. A., and Cooke, W. H. (2012). Effects of dehydration on cerebrovascular control during standing after heavy resistance exercise. *J. Appl. Physiol.* 112, 1875–1883. doi: 10.1152/japplphysiol.01217.2011

Morrison, S., Sleivert, G. G., and Cheung, S. S. (2004). Passive hyperthermia reduces voluntary activation and isometric force production. *Eur. J. Appl. Physiol.* 91, 729–736. doi: 10.1007/s00421-004-1063-z

Morrison, S. A., Sleivert, G. G., Neary, J. P., and Cheung, S. S. (2009). Prefrontal cortex oxygenation is preserved and does not contribute to impaired neuromuscular activation during passive hyperthermia. *Appl. Physiol. Nutr. Metab.* 34, 66–74. doi: 10.1139/H08-139

Murray, R. H., Thompson, L. J., Bowers, J. A., and Albright, C. D. (1968). Hemodynamic effects of graded hypovolemia and vasodepressor syncope induced by lower body negative pressure. *Am. Heart J.* 76, 799–811. doi: 10.1016/0002-8703(68)90266-4

Nelson, M. D., Haykowsky, M. J., Stickland, M. K., Altamirano Diaz, L. A., Willie, C. K., Smith, K. J., et al. (2011). Reductions in cerebral blood flow during passive heat stress in humans: partitioning the mechanisms. *J. Physiol.* 589, 4053–4064. doi: 10.1113/jphysiol.2011.212118

Nemoto, E. M., and Frankel, H. M. (1970a). Cerebral oxygenation and metabolism during progressive hyperthermia. *Am. J. Physiol.* 219, 1784–1788.

Nemoto, E. M., and Frankel, H. M. (1970b). Cerebrovascular response during progressive hyperthermia in dogs. *Am. J. Physiol.* 218, 1060–1064.

Niimi, Y., Matsukawa, T., Sugiyama, Y., Shamsuzzaman, A. S., Ito, H., Sobue, G., et al. (1997). Effect of heat stress on muscle sympathetic nerve activity in humans. *J. Auton. Nerv. Syst.* 63, 61–67. doi: 10.1016/S0165-1838(96)00134-8

Nunneley, S. A., Martin, C. C., Slauson, J. W., Hearon, C. M., Nickerson, L. D., and Mason, P. A. (2002). Changes in regional cerebral metabolism during systemic hyperthermia in humans. *J. Appl. Physiol.* 92, 846–851. doi: 10.1152/japplphysiol.00072.2001

Nybo, L. (2007). Exercise and heat stress: cerebral challenges and consequences. *Prog. Brain Res.* 162, 29–43. doi: 10.1016/S0079-6123(06)62003-7

Nybo, L., Møller, K., Volianitis, S., Nielsen, B., and Secher, N. H. (2002a). Effects of hyperthermia on cerebral blood flow and metabolism during prolonged exercise in humans. *J. Appl. Physiol.* 93, 58–64. doi: 10.1152/japplphysiol.00049.2002

Nybo, L., and Nielsen, B. (2001). Hyperthermia and central fatigue during prolonged exercise in humans. *J. Appl. Physiol.* 91, 1055–1060.

Nybo, L., and Secher, N. H. (2004). Cerebral perturbations provoked by prolonged exercise. *Prog. Neurobiol.* 72, 223–261. doi: 10.1016/j.pneurobio.2004.03.005

Nybo, L., Secher, N. H., and Nielsen, B. (2002b). Inadequate heat release from the human brain during prolonged exercise with hyperthermia. *J. Physiol.* 545, 697–704. doi: 10.1113/jphysiol.2002.030023

Ogoh, S., Sato, K., Okazaki, K., Miyamoto, T., Hirasawa, A., Morimoto, K., et al. (2013). Blood flow distribution during heat stress: cerebral and systemic blood flow. *J. Cereb. Blood Flow Metab.* 33, 1915–1920. doi: 10.1038/jcbfm.2013.149

Pearson, J., Ganio, M. S., Lucas, R. A. I., Babb, T. G., and Crandall, C. G. (2013). Heat stress does not augment ventilatory responses to presyncopal limited lower body negative pressure. *Exp. Physiol.* 98, 1156–1163. doi: 10.1113/expphysiol.2013.072082

Périard, J. D., Caillaud, C., and Thompson, M. W. (2011). Central and peripheral fatigue during passive and exercise-induced hyperthermia. *Med. Sci. Sports Exerc.* 43, 1657–1665. doi: 10.1249/MSS.0b013e3182148a9a

Rasmussen, P., Dawson, E.A., Nybo, L., van Lieshout, J.J., Secher, N.H., and Gjedde, A. (2007). Capillary-oxygenation- level-dependent near-infrared spectrometry in frontal lobe of humans. *J. Cereb. Blood Flow Metab.* 27, 1082–1093. doi: 10.1038/sj.jcbfm.9600416

Rasmussen, P., Nybo, L., Volianitis, S., Møller, K., Secher, N. H., and Gjedde, A. (2010). Cerebral oxygenation is reduced during hyperthermic exercise in humans. *Acta Physiol. (Oxf.).* 199, 63–70. doi: 10.1111/j.1748-1716.2010.02084.x

Romero, S. A., Moralez, G., Rickards, C. A., Ryan, K. L., Convertino, V. A., Fogt, D. L., et al. (2011). Control of cerebral blood velocity with furosemide-induced hypovolemia and upright tilt. *J. Appl. Physiol.* 110, 492–498. doi: 10.1152/japplphysiol.01060.2010

Ross, E. Z., Cotter, J. D., Wilson, L., Fan, J.-L., Lucas, S. J. E., and Ainslie, P. N. (2012). Cerebrovascular and corticomotor function during progressive passive hyperthermia in humans. *J. Appl. Physiol.* 112, 748–758. doi: 10.1152/japplphysiol.00988.2011

Rowell, L. B. (1974). Human cardiovascular adjustments to exercise and thermal stress. *Physiol. Rev.* 54, 75–159.

Rowell, L. B. (1983). "Chap 27, Cardiovascular adjustments to thermal stress," in *Handbook of Physiology, Section 2*, eds F. M. Abbound and J. T. Shepherd (Bethesda, Md: American Physiological Society), 967–1023.

Rowell, L. B. (1986). *Human Circulation: Regulation During Physical Stress*. New York, NY: Oxford University Press.

Rowell, L. B. (1990). Hyperthermia: a hyperadrenergic state. *Hypertension* 15, 505–507. doi: 10.1161/01.HYP.15.5.505

Rowell, L. B., Brengelmann, G. L., and Murray, J. A. (1969). Cardiovascular responses to sustained high skin temperature in resting man. *J. Appl. Physiol.* 27, 673–680.

Rowell, L. B., Marx, H. J., Bruce, R. A., Conn, R. D., and Kusumi, F. (1966). Reductions in cardiac output, central blood volume, and stroke volume with thermal stress in normal men during exercise. *J. Clin. Invest.* 45, 1801–1816. doi: 10.1172/JCI105484

Saxton, C. (1981). Effects of severe heat stress on respiration and metabolic rate in resting man. *Aviat. Space Environ. Med.* 52, 281–286.

Sébert, P., Kervran, C., and L'Her, E. (2003). Temperature sensitivity of glycolysis during sepsis. *Crit. Care Med.* 31, 246–249. doi: 10.1097/00003246-200301000-00038

Sercobe, R., Lacombe, P., Aubineau, P., Mamo, H., Pinard, E., Reynier-Rebuffel, A. M., et al. (1979). Is there an active mechanism limiting the influence of the sympathetic system on the cerebral vascular bed? Evidence for vasomotor escape from sympathetic stimulation in the rabbit. *Brain Res.* 164, 81–102. doi: 10.1016/0006-8993(79)90008-8

South, F. E. (1958). Rates of oxygen consumption and glycolysis of ventricle and brain slices, obtained from hibernating and non-hibernating mammals, as function of temperature. *Physiol. Zool.* 31, 6–15.

Subudhi, A. W., Olin, J. T., Dimmen, A. C., Polaner, D. M., Kayser, B., and Roach, R. C. (2011). Does cerebral oxygen delivery limit incremental exercise performance? *J. Appl. Physiol.* 111, 1727–1734. doi: 10.1152/japplphysiol.00569.2011

Todd, G., Butler, J. E., Taylor, J. L., and Gandevia, S. C. (2005). Hyperthermia: a failure of the motor cortex and the muscle. *J. Physiol.* 563, 621–631. doi: 10.1113/jphysiol.2004.077115

Tzeng, Y. C., and Ainslie, P. N. (2013). Quantification of cerebral hemodynamics. *Eur. J. Appl. Physiol.* 113, 2869–2870. doi: 10.1007/s00421-013-2719-3

Umeyama, T., Kugimiya, T., Ogawa, T., Kandori, Y., Ishizuka, A., and Hanaoka, K. (1995). Changes in cerebral blood flow estimated after stellate ganglion block by single photon emission computed tomography. *J. Auton. Nerv. Syst.* 50, 339–346. doi: 10.1016/0165-1838(94)00105-S

Visocchi, M., Chiappini, F., Cioni, B., and Meglio, M. (1996). Cerebral blood flow velocities and trigeminal ganglion stimulation. A transcranial Doppler study. *Stereotact. Funct. Neurosurg.* 66, 184–192. doi: 10.1159/000099687

Watson, P., Black, K. E., Clark, S. C., and Maughan, R. J. (2006). Exercise in the heat: effect of fluid ingestion on blood-brain barrier permeability. *Med. Sci. Sports Exerc.* 38, 2118–2124. doi: 10.1249/01.mss.0000235356.31932.0a

Watson, P., Shirreffs, S. M., and Maughan, R. J. (2005). Blood-brain barrier integrity may be threatened by exercise in a warm environment. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 288, R1689–R1694. doi: 10.1152/ajpregu.00676.2004

White, M. D. (2006). Components and mechanisms of thermal hyperpnea. *J. Appl. Physiol.* 101, 655–663. doi: 10.1152/japplphysiol.00210.2006

Willie, C. K., Macleod, D. B., Shaw, A. D., Smith, K. J., Tzeng, Y. C., Eves, N. D., et al. (2012). Regional brain blood flow in man during acute changes in arterial blood gases. *J. Physiol.* 590, 3261–3275. doi: 10.1113/jphysiol.2012.228551

Willie, C. K., Tzeng, Y. C., Fisher, J. A., and Ainslie, P. N. (2014). Integrative regulation of human brain blood flow. *J. Physiol.* doi:10.1113/jphysiol.2013.268953

Wilson, T. E., Brothers, R. M., Tollund, C., Dawson, E. A., Nissen, P., Yoshiga, C. C., et al. (2009). Effect of thermal stress on Frank-Starling relations in humans. *J. Physiol.* 587, 3383–3392. doi: 10.1113/jphysiol.2009.170381

Wilson, T. E., Cui, J., and Crandall, C. G. (2002a). Effect of whole-body and local heating on cutaneous vasoconstrictor responses in humans. *Auton. Neurosci.* 97, 122–128. doi: 10.1016/S1566-0702(02)00046-2

Wilson, T. E., Cui, J., Zhang, R., and Crandall, C. G. (2006). Heat stress reduces cerebral blood velocity and markedly impairs orthostatic tolerance in humans. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 291, R1443–R1448. doi: 10.1152/ajpregu.00712.2005

Wilson, T. E., Cui, J., Zhang, R., Witkowski, S., and Crandall, C. G. (2002b). Skin cooling maintains cerebral blood flow velocity and orthostatic tolerance during tilting in heated humans. *J. Appl. Physiol.* 93, 85–91. doi: 10.1152/japplphysiol.01043.2001

Zapata, P., Larrain, C., Iturriaga, R., and Alcayaga, J. (1994). The carotid bodies as thermosensors: experiments *in vitro* and *in situ*, and importance for ventilatory regulation. *Adv. Exp. Med. Biol.* 360, 253–255. doi: 10.1007/978-1-4615-2572-1_40

Zheng, F., Sheinberg, R., Yee, M. S., Ono, M., Zheng, Y., and Hogue, C. W. (2013). Cerebral Near-Infrared Spectroscopy (NIRS) monitoring and neurologic outcomes in adult cardiac surgery patients and neurologic outcomes: a systematic review. *Anesth. Analg.* 116, 663–676. doi: 10.1213/ANE.0b013e318277a255

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 09 January 2014; accepted: 18 February 2014; published online: 04 March 2014.

*Citation: Bain AR, Morrison SA and Ainslie PN (2014) Cerebral oxygenation and hyperthermia. Front. Physiol. **5**:92. doi: 10.3389/fphys.2014.00092*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 27 February 2014
doi: 10.3389/fphys.2014.00079

Influence of intranasal and carotid cooling on cerebral temperature balance and oxygenation

Lars Nybo[1]*, Michael Wanscher[2] and Niels H. Secher[3]

[1] *Department of Nutrition, Exercise and Sport Sciences, University of Copenhagen, Copenhagen, Denmark*
[2] *Department of Cardiothoracic Anaesthesia, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark*
[3] *Copenhagen Muscle Research Center, Department of Anaesthesia, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Edited by:
Phil N. Ainslie, University of British Columbia, Canada

Reviewed by:
Phil N. Ainslie, University of British Columbia, Canada
Anthony R. Bain, University of British Columbia, Canada

****Correspondence:***
Lars Nybo, Section of Human Physiology, Department of Nutrition, Exercise and Sport Sciences, University of Copenhagen, Universitetsparken 13, DK-2100 Copenhagen Ø, Denmark
e-mail: lnnielsen@ifi.ku.dk

The present study evaluated the influence of intranasal cooling with balloon catheters, increased nasal ventilation, or percutaneous cooling of the carotid arteries on cerebral temperature balance and oxygenation in six healthy male subjects. Aortic arch and internal jugular venous blood temperatures were measured to assess the cerebral heat balance and corresponding paired blood samples were obtained to evaluate cerebral metabolism and oxygenation at rest, following 60 min of intranasal cooling, 5 min of nasal ventilation, and 15 min with carotid cooling. Intranasal cooling induced a parallel drop in jugular venous and arterial blood temperatures by 0.30 ± 0.08°C (mean ± SD), whereas nasal ventilation and carotid cooling failed to lower the jugular venous blood temperature. The magnitude of the arterio-venous temperature difference across the brain remained unchanged at -0.33 ± 0.05°C following intranasal and carotid cooling, but increased to -0.44 ± 0.11°C ($P < 0.05$) following nasal ventilation. Calculated cerebral capillary oxygen tension was 43 ± 3 mmHg at rest and remained unchanged during intranasal and carotid cooling, but decreased to 38 ± 2 mmHg ($P < 0.05$) following increased nasal ventilation. In conclusion, percutaneous cooling of the carotid arteries and intranasal cooling with balloon catheters are insufficient to influence cerebral oxygenation in normothermic subjects as the cooling rate is only 0.3°C per hour and neither intranasal nor carotid cooling is capable of inducing selective brain cooling.

Keywords: balloon catheter, brain temperature, cerebral oxygenation, cooling, hypothermia

INTRODUCTION

Cooling of the brain is of relevance for preventing cerebral ischemia during anesthesia and after cardiac arrest hypothermia may improve neurological outcome and even survival (Hoesch and Geocadin, 2007; Holzer, 2008, 2013; Lay and Badjatia, 2010; Harris et al., 2012). Cerebral cooling can be induced by global lowering of the body temperature as arterial blood will gradually lower brain temperature (Nybo et al., 2002; Holzer, 2008). However, methods have been developed in attempt to selectively cool the brain, i.e., without affecting other parts of the body (for review see Harris et al., 2012) in order to attenuate the risk of, e.g., pneumonia and sepsis (Geurts et al., 2014). Selective-brain cooling is defined as a lowering of the average brain temperature to below that of arterial blood as observed in several animal species including mammals with a carotid rete (Jessen, 2001). Whether humans, despite the lack of a carotid rete, have the ability to selectively cool their brain remains controversial (Brengelmann, 1993; Cabanac, 1993; White et al., 2010), but is probably unlikely under normal circumstances (Nybo et al., 2002; Maloney et al., 2007; Nybo and Secher, 2011). Yet, various intranasal cooling techniques have been developed (Harris et al., 2012) and Covaciu et al. (2011) report from a magnetic resonance (MR) spectroscopic-based evaluation of cerebral temperature that intranasal cooling with balloon catheter induced a rapid and substantial lowering of the brain temperature. Springborg et al. (2013) also find that intranasal cooling lowers cerebral temperature in hyperthermic brain-injured patients. However, in contrast to the observations presented by Covaciu et al. (2011), Springborg et al. (2013) report brain cooling to take place in parallel with normalization of the core temperature in their hyperthermic patients. Hence, it remains unclear whether intranasal cooling can induce selective brain cooling and to what extend it lowers brain temperature in normothermic subjects and thereby influences the cerebral metabolic rate and its oxygenation.

Cooling of the carotid arteries, either by percutaneous cooling of the neck or through augmented heat release from upper respiratory airway induced by increased ventilation could influence the temperature of arterial blood entering the brain (Rasch et al., 1991). As demonstrated during exercise, hyperpnea lowers tissue temperature adjacent to the carotid arteries and could thereby narrow the arterio-venous temperature difference across the brain (Nybo et al., 2002). However, in resting subjects the effect of increased nasal ventilation on brain temperature is not clear. Therefore, the present study was conducted to evaluate the effects of intranasal cooling, percutaneous cooling of the carotid arteries, and nasal ventilation on cerebral temperature balance and oxygenation.

MATERIALS AND METHODS

Six healthy male subjects at a mean age of 30 ± 4 years (± SD), height of 185 ± 5 cm and weight 79 ± 8 kg participated in the study as approved by the local ethics committee (protocol

H-4-2010-081) and conducted in accordance to the Declaration of Helsinki.

The subjects arrived at the laboratory in the morning ∼1 h before the start of the experiment and were instrumented with thermocouples to record forehead, cheek, and neck (over the left carotid artery) skin temperature (Ellab, Copenhagen, Denmark) an ultra sound transcranial Doppler probe, and a heart rate (HR) monitor. Then, the subjects were provided with a 18 G catheter (32 mm; BD A/S, Denmark) in the brachial artery of the non-dominant arm and, under local anesthesia, a 5 F Swan-Ganz catheter (Edwards; USA) was placed in the right internal jugular vein and advanced to the bulb of the vein. A thermocouple (model MAC-07170-A, Ellab) was inserted via the arterial catheter and advanced to the aortic arch to record arterial temperature (Nybo et al., 2002), while the internal jugular venous blood temperature was obtained from the temperature sensor positioned at the bulb of the internal jugular vein. Furthermore, intra-nasal temperature was measured 1 cm into the nostrils with a thin thermocouple (MHA model, Ellab, Copenhagen, Denmark) inserted for 2 min (and until the measure was stable) with the tip/electrode directed outward; i.e., during the nasal cooling period into the tissue and away from the balloon catheter.

Simultaneous blood samples were obtained from the two catheters at baseline (after 45 min of supine rest), following 1 h of intra-nasal cooling, following 15 min of carotid cooling, and at the end of a 5 min period with increased nasal ventilation during which the subjects were instructed to double their ventilation and inhale exclusively through the nose and exhale through the mouth. All blood samples were immediately analyzed for PO_2, PCO_2, oxygen saturation, hemoglobin, glucose, and lactate (ABL 800, Radiometer, Copenhagen, Denmark). Cerebral arterio-venous differences for oxygen (a-vDO_2), glucose (a-v$D_{glucose}$), and lactate (a-v$D_{lactate}$) were determined on basis of paired blood samples. Furthermore, changes in mean cerebral capillary oxygen saturation and capillary oxygen tension were calculated according to Rasmussen et al. (2006) with the assumption that oxygen extraction rises linearly with distance as blood traverses the capillary network from the arterial to venous end, and the average capillary bed satisfy coequal amounts of brain tissue.

Middle cerebral artery mean blood velocity (MCA V_{mean}) was monitored by transcranial Doppler (Transcan, EME, Überlingen, Germany) to estimate changes in cerebral blood flow (CBF). The best signal–noise ratio at the proximal part of the MCA was selected and the vessel was insonated at a depth of ∼50 mm with the probe secured with a headband. MCA V_{mean} was computed from the integral of the maximum frequency Doppler shifts over each heartbeat and the average from 2 min was determined for rest, nasal cooling, carotid cooling, and nasal ventilation. It was assumed that the diameter of the insonated vessel remains unchanged across the evaluated conditions. Serrador et al. (2000) found no variation in vessel diameter with changes in P_aCO_2 and it appears that the CBF is regulated distal to the proximal part of MCA, although some effect of P_aCO_2 on vessel diameter cannot be excluded (Valdueza et al., 1999). However, changes in MCA velocity correlate with those in ^{133}Xenon determined CBF (Jørgensen, 1995) and we estimated changes in CBF from the percentage change in MCA V_{mean}.

COOLING INTERVENTIONS

The intra-nasal cooling was applied via two single-use intranasal balloon catheters (QuickCool Disposable Balloon Catheter, QuickCool AB, Lund, Sweden) perfused with cold isotonic saline from a heat exchanger in a closed circuit system (ComVic, QuickCool AB, Lund, Sweden). The pressure in the balloons was maintained between 20 and 30 mmHg and flow exchange was set to 200 ml per min with the temperature in the heat exchanger at 1°C. The cooling period was 1 h and all six subjects tolerated and completed the entire period without any adverse effects.

Nasal ventilation was initiated 2 min after removal of the balloon catheters in attempt to increase cooling of the upper respiratory airways while the tissue in the nasal sinuses was low.

The subject was instructed to inhale forcefully through the nose and exhale via the mouth for 5 min to maximize the potential cooling effects and that was accomplished by all subjects. Blood samples were drawn and temperatures registered during the last 30 s of the 5 min intervention. Following the nasal ventilation test, the subject rested for at least 45 min or until arterial blood temperature and P_aCO_2 had returned to baseline values. Thereafter 15 min of carotid cooling was applied by placing ice packets on both sides of the neck (∼10 cm long and 5 cm thick plastic bag filled with crushes ice and wrapped in a thin piece of fabric to avoid freezing the skin). One subject however tolerated this intervention for only 10 min, but developed a similar drop in skin temperature as the other five subjects.

STATISTICAL ANALYSIS

Values are presented as mean ± SD unless otherwise indicated. Changes over time, i.e., during the period with nasal cooling or across conditions (baseline, intra-nasal cooling, nasal ventilation and carotid cooling) were evaluated with repeated One-Way ANOVA and the significance level was set at $P < 0.05$. In case of a significant difference across conditions, a Tukey *post-hoc* test with Bonferroni correction was used to identify differences.

RESULTS

There was a small but significant decline in internal jugular venous blood temperature during the 1 h period with nasal cooling (**Figure 1**) occurring in parallel with the drop in body temperature as the arterio-venous temperature difference across the brain remained unchanged at −0.33 ± 0.05°C. Furthermore, the arterio-venous temperature difference across the brain was not changed during carotid cooling, whereas it was widened to −0.44 ± 0.11°C following the period with nasal ventilation. Thus, the jugular venous blood temperature remained in the range 0.3–0.44°C above that of the arterial blood despite marked reductions in intranasal, neck, and face skin temperatures as illustrated in **Figure 2**.

MCA V_{mean} remained unchanged (within 2% of baseline values) during intranasal and carotid cooling, whereas it declined to 45 ± 7% of the baseline value at the end of the 5 min period with nasal ventilation. Accordingly, $PaCO_2$ was similar at baseline (39.2 ± 0.7 mmHg) during intra-nasal (39.1 ± 0.9 mmHg) and carotid cooling (39.5 ± 0.9 mmHg), but declined to 20.9 ± 3.2 mmHg following 5 min of nasal ventilation. Furthermore, PaO_2 and saturation were similar at baseline, following intranasal

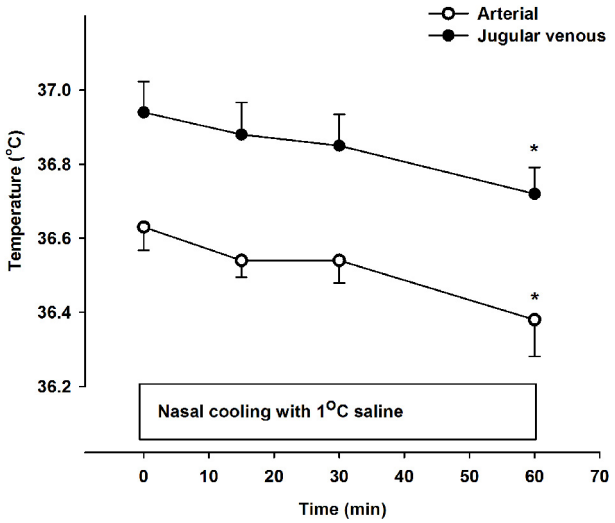


FIGURE 1 | Arterial (open symbols) and jugular venous blood temperature (filled symbols) at rest (0 min) and during 60 min of nasal cooling with 1°C saline circulated through the nasal catheters at a flow rate of 200 ml/min. *Signifies that the value is lower compared to corresponding value at 0 min ($P < 0.05$). The jugular venous blood temperature was significantly higher than that of the arterial blood at all time points ($P < 0.001$).

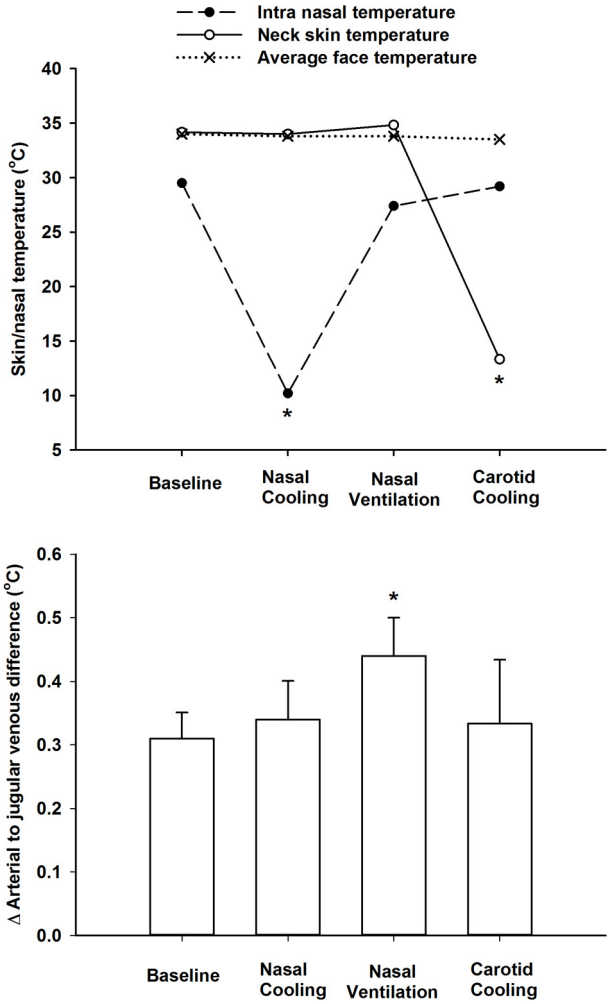


FIGURE 2 | Top panel. Average face skin (mean of cheek and forehead), neck skin over the carotid arteries, and intra-nasal temperatures at rest (baseline), during intranasal cooling, increased nasal ventilation and carotid cooling. **Lower panel** shows the delta difference between arterial (aortic arch) and internal jugular venous blood temperatures at rest during intranasal cooling, increased nasal ventilation and carotid cooling. *Indicates that the value is significantly different from corresponding value at rest ($P < 0.05$).

and carotid cooling (average PaO_2 ~100 mmHg and saturation ~97.5%), but increased to 125.1 ± 3.7 mmHg and 99.6 ± 0.2% following the 5 min period with increased nasal ventilation (**Figure 3**). However, a-v DO_2 increased from 83.5 ± 5.5 ml·l^{-1} at rest to 119.1 ± 7.0 ml·l^{-1} following the nasal ventilation period and the jugular venous and mean cerebral capillary oxygen tension were lowered by ~10 and 5 mmHg, respectively. In contrast, a-v DO_2, jugular venous PO_2 and mean cerebral capillary oxygen tension remained unchanged following intranasal and carotid cooling (**Figure 3**, lower panel). Also, a-v$D_{glucose}$ was similar at rest, following intranasal, and carotid cooling with an average of 0.55 ± 0.08 mmol·l^{-1} and the cerebral release of lactate remained low with an a-v$D_{lactate}$ of −0.05 ± 0.03 mmol·l^{-1}. In contrast, a-v$D_{glucose}$ increased to 1.04 ± 0.16 mmol·l^{-1} and a-v$D_{lactate}$ was widened to −0.20 ± 0.07 mmol·l^{-1} following the period with nasal ventilation.

DISCUSSION

The present study shows that intranasal cooling may lower the cerebral venous blood temperature indicating that the technique is capable of affecting the average brain tissue temperature. However, the cooling was modest and related to body core cooling and intranasal cooling did not selectively cool the brain. In the studied healthy normothermic subjects, the cooling rate was 0.3°C per hour and insufficient to influence cerebral oxygenation following 60 min. In addition, neither nasal ventilation nor carotid cooling was capable of providing a significant lowering of the cerebral venous blood temperature and also failed to increase cerebral capillary oxygenation. On the basis of these observations we conclude that intranasal cooling with balloon catheters is not recommendable for rapid cooling of the brain or to improve cerebral oxygenation and it does not selectively cool the brain.

The cerebral cooling rate achieved with intranasal cooling was comparable to that reported by other head cooling device applications in normothermic subjects (Koehn et al., 2012; Poli et al., 2013), but the rate was somewhat lower than that obtained in hyperthermic (Abou-Chebl et al., 2011; Springborg et al., 2013) and normothermic stroke patients (Poli et al., 2014) with intranasal cooling. Also the cerebral cooling was substantially slower than the rates obtained in normothermic patients with cooling induced via veno-venous extracorporeal circulation which may lower the arterial blood and brain temperatures in parallel with cooling rates of ~ 3.5°C per hour (Piepgras et al., 1998) or even faster (Testori et al., 2013). That the cerebral cooling

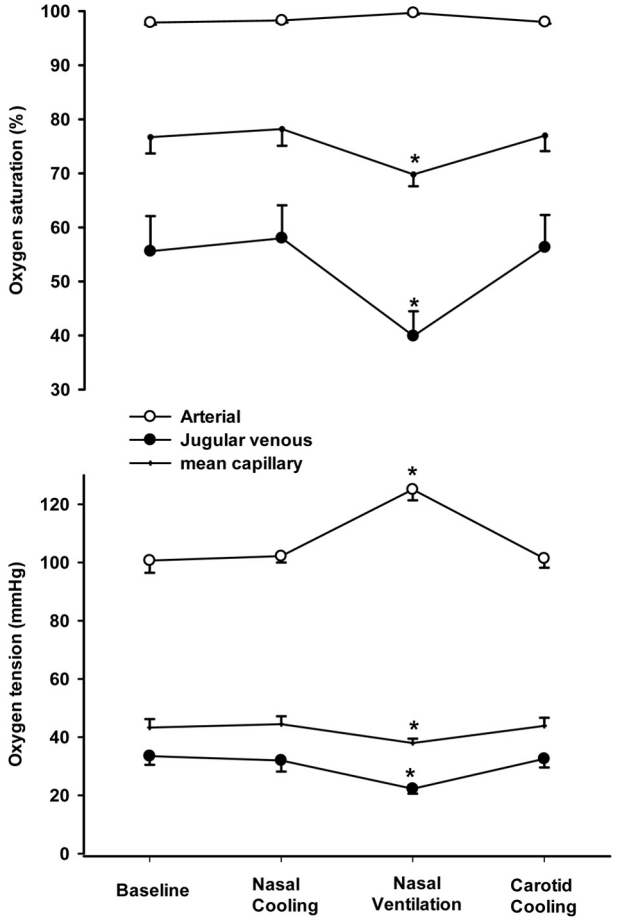


FIGURE 3 | Arterial, jugular venous and mean capillary oxygen tension (lower panel) and saturation (top panel) at rest (baseline), following 1 h of intranasal cooling, after 5 min of increased nasal ventilation and 15 min of carotid cooling. *Indicates that the value is different from corresponding value at rest ($P < 0.05$).

induced via intranasal cooling relates to general body core cooling and not to selective brain cooling is in accordance with the observations by Springborg et al. (2013) in hyperthermic brain-injured comatic patients. In contrast, Covaciu et al. (2011) report that the balloon catheter method we used with intra-nasal cooling induced a drop in brain temperature which exceeded the decline in rectal temperature indicating that the method could introduce semi-selective cooling of the brain. However, while we tracked changes in cerebral temperature by a continuous measure of the cerebral venous blood temperature and Springborg et al. (2013) measured brain temperature directly, Covaciu et al. (2011) evaluated brain temperature changes using MR spectroscopic imaging and they tracked changes in body core temperature by measures of rectal temperature that responds only slowly to changes in core temperature (Nielsen and Nielsen, 1962). Thus, methodological differences may explain the discrepancy between observations.

The Q_{10} effect on the cerebral metabolic rate for oxygen is ~2 (Klementavicius et al., 1996; Nybo et al., 2002). Considering, the modest cooling of ~0.3 degrees achieved in the present study and the unchanged CBF and P_aO_2 it seems reasonable that the cerebral oxygenation remained unchanged following the 60 min period with intranasal cooling or following the carotid cooling. The increased nasal ventilation immediately following the nasal cooling was introduced in attempt to increase the heat release from the upper respiratory track that has been hypothesized to influence brain temperature (Rasch et al., 1991; Mariak et al., 1999). However, increased heat release from the brain was presumably not established following nasal ventilation as MCA V_{mean} declined by more than 50% indicating a marked lowering of CBF in the hypocapnic condition. Heat release from the brain is determined by the product of the arterio-venous temperature difference across the brain, CBF and the specific heat capacity of blood (Nybo et al., 2002) and although the present data do not allow for calculation of the cerebral heat balance, a marked lowering of CBF would outweigh the increased blood temperature difference across the brain following the period with nasal hyperventilation. Furthermore, the hyperventilation-induced hypocapnia was associated with increased lactate release from the brain indicating that reduced CBF and consequently lower cerebral oxygen delivery may have compromised aerobic metabolism and we observed that the mean capillary and venous oxygen tension were reduced following the period with nasal ventilation. All subjects tolerated the 5 min period with nasal ventilation without reporting signs of dizziness, but the hypocapnic level and marked reduction in MCA V_{mean} indicate that they were close to levels that may lead to syncope (Immink et al., in press). If normal alveolar ventilation and consequently also P_aCO_2 had been maintained during the nasal ventilation, it is almost certain that cerebral oxygenation had also remained stable, however, we asked the subjects to inhale forcefully through the nose to maximize the potential cooling effects this could have on the upper respiratory tract. Therefore, hyperventilation-induced hypocapnia was introduced and the associated lowering of cerebral oxygen delivery was expected (Kety and Schmidt, 1948) during this part of the experiment targeted at optimizing cooling and not at enhancing the cerebral oxygenation.

CONCLUDING REMARKS

Intranasal cooling with balloon catheters was insufficient to influence the cerebral oxygenation in awake, healthy subjects. The cooling procedure lowered the temperature within the nasal cavity by ~ 20°C but the effect on the cerebral temperature was modest with an estimated cooling rate of 0.3°C per hour and the cooling was not selective for the brain as the arterio-venous temperature difference across the brain remained unchanged. In addition, neither nasal ventilation nor bilateral percutaneous cooling of the carotid arteries was capable of providing significant lowering of the cerebral venous blood temperature and these methods also failed to increase cerebral capillary oxygenation.

AUTHOR CONTRIBUTIONS

Lars Nybo designing, planning and conducting the experiments, analysis of data and writing the manuscript; Michael Wanscher designing, planning and conducting the experiments and contributing to the manuscript; Niels H. Secher designing, planning and conducting the experiments and contributing to the manuscript

ACKNOWLEDGMENTS

The authors would like to thank the subjects for their time and effort and the Danish Ministry of Culture for supporting the studies.

REFERENCES

Abou-Chebl, A., Sung, G., Barbut, D., and Torbey, M. (2011). Local brain temperature reduction through intranasal cooling with the RhinoChill device: preliminary safety data in brain-injured patients. *Stroke* 42, 2164–2169. doi: 10.1161/STROKEAHA.110.613000

Brengelmann, G. L. (1993). Specialized brain cooling in humans? *FASEB J.* 7, 1148–1153.

Cabanac, M. (1993). Selective brain cooling in humans: "fancy" or fact? *FASEB J.* 7, 1143–1146.

Covaciu, L., Weis, J., Bengtsson, C., Allers, M., Lunderquist, A., Ahlstrom, H., et al. (2011). Brain temperature in volunteers subjected to intranasal cooling. *Int. Care Med.* 37, 1277–1284. doi: 10.1007/s00134-011-2264-7

Geurts, M., MacLeod, M. R., Kollmar, R., Kremer, P. H., and van der Worp, H. B. (2014). Therapeutic hypothermia and the risk of infection: a systematic review and meta-analysis. *Crit. Care Med.* 42, 231–242. doi: 10.1097/CCM.0b013e3182a276e8

Harris, B., Andrews, P. J., Murray, G. D., Forbes, J., and Moseley, O. (2012). Systematic review of head cooling in adults after traumatic brain injury and stroke. *Health Technol. Assess.* 16, 1–175. doi: 10.3310/hta16450

Hoesch, R. E., and Geocadin, R. G. (2007). Therapeutic hypothermia for global and focal ischemic brain injury - a cool way to improve neurologic outcomes. *Neurologist* 13, 331–342. doi: 10.1097/NRL.0b013e318154bb79

Holzer, M. (2008). Devices for rapid induction of hypothermia. *Eur. J. Anaesthesiol. Suppl.* 42, 31–38. doi: 10.1017/S0265021507003274

Holzer, M. (2013). Therapeutic hypothermia following cardiac arrest. *Best Pract. Res. Clin. Anaesthesiol.* 27, 335–346. doi: 10.1016/j.bpa.2013.07.003

Immink, R. V., Pott, F., Secher, N. H., and van Lieshout, J. J. (in press). Hyperventilation, cerebral perfusion and syncope. *J. Appl. Physiol.* doi: 10.1152/japplphysiol.00637.2013

Jessen, C. (2001). Selective brain cooling in mammals and birds. *Jpn. J. Physiol.* 51, 291–301. doi: 10.2170/jjphysiol.51.291

Jørgensen, L. (1995). Transcranial Doppler ultrasound for cerebral perfusion. *Acta Physiol. Scand.* 154(Suppl. 625), 1–44.

Kety, S., and Schmidt, C. (1948). The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. *J. Clin. Invest.* 27, 484–492. doi: 10.1172/JCI101995

Klementavicius, R., Nemoto, E. M., and Yonas, H. (1996). The Q_{10} ratio for basal cerebral metabolic rate of oxygen in rats. *J. Neurosurg.* 85, 482–487. doi: 10.3171/jns.1996.85.3.0482

Koehn, J., Kollmar, R., Cimpianu, C. L., Kallmunzer, B., Moeller, S., Schwab, S., et al. (2012). Head and neck cooling decreases tympanic and skin temperature, but significantly increases blood pressure. *Stroke* 43, 2142–2148. doi: 10.1161/STROKEAHA.112.652248

Lay, C., and Badjatia, N. (2010). Therapeutic hypothermia after cardiac arrest. *Curr. Atheroscler. Rep.* 12, 336–342. doi: 10.1007/s11883-010-0119-2

Maloney, S. K., Mitchell, D., Mitchell, G., and Fuller, A. (2007). Absence of selective brain cooling in unrestrained baboons exposed to heat. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 292, R2059–R2067. doi: 10.1152/ajpregu.00809.2006

Mariak, Z., White, M. D., Lewko, J., Lyson, T., and Piekarski, P. (1999). Direct cooling of the human brain by heat loss from the upper respiratory tract. *J. Appl. Physiol.* 87, 1609–1613.

Nielsen, B., and Nielsen, M. (1962). Body temperature during work at different environmental temperatures. *Acta Physiol. Scand.* 56, 120–129. doi: 10.1111/j.1748-1716.1962.tb02489.x

Nybo, L., and Secher, N. H. (2011). Counterpoint: humans do not demonstrate selective brain cooling during hyperthermia. *J. Appl. Physiol.* 110, 571–573. doi: 10.1152/japplphysiol.00992.2010a

Nybo, L., Secher, N. H., and Nielsen, B. (2002). Inadequate heat release from the human brain during prolonged exercise with hyperthermia. *J. Physiol.* 545, 697–704. doi: 10.1113/jphysiol.2002.030023

Piepgras, A., Roth, H., Schurer, L., Tillmans, R., Quintel, M., Herrmann, P., et al. (1998). Rapid active internal core cooling for induction of moderate hypothermia in head injury by use of an extracorporeal heat exchanger. *Neurosurgery* 42, 311–317. doi: 10.1097/00006123-199802000-00058

Poli, S., Purrucker, J., Priglinger, M., Diedler, J., Sykora, M., Popp, E., et al. (2013). Induction of cooling with a passive head and neck cooling device: effects on brain temperature after stroke. *Stroke* 44, 708–713. doi: 10.1161/STROKEAHA.112.672923

Poli, S., Purrucker, J., Priglinger, M., Sykora, M., Diedler, J., Rupp, A., et al. (2014). Safety evaluation of nasopharyngeal cooling (RhinoChill) in stroke patients: an observational study. *Neurocrit. Care* 20, 98–105. doi: 10.1007/s12028-013-9904-4

Rasch, W., Samson, P., Cote, J., and Cabanac, M. (1991). Heat loss from the human head during exercise. *J. Appl. Physiol.* 71, 590–595.

Rasmussen, P., Dawson, E. A., Nybo, L., van Lieshout, J. J., Secher, N. H., and Gjedde, A. (2006). Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. *J. Cereb. Blood Flow Metab.* 27, 1082–1093. doi: 10.1038/sj.jcbfm.9600416

Serrador, J. M., Picot, P. A., Rutt, B. K., Shoemaker, J. K., and Bondar, R. L. (2000). MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke* 31, 1672–1678. doi: 10.1161/01.STR.31.7.1672

Springborg, J. B., Springborg, K. K., and Romner, B. (2013). First clinical experience with intranasal cooling for hyperthermia in brain-injured patients. *Neurocrit. Care* 18, 400–405. doi: 10.1007/s12028-012-9806-x

Testori, C., Holzer, M., Sterz, F., Stratil, P., Hartner, Z., Moscato, F., et al. (2013). Rapid induction of mild therapeutic hypothermia by extracorporeal veno-venous blood cooling in humans. *Resuscitation* 84, 1051–1055. doi: 10.1016/j.resuscitation.2013.03.013

Valdueza, J. M., Draganski, B., Hoffmann, O., Dirnagl, U., and Einhaupl, K. M. (1999). Analysis of CO2 vasomotor reactivity and vessel diameter changes by simultaneous venous and arterial Doppler recordings. *Stroke* 30, 81–86. doi: 10.1161/01.STR.30.1.81

White, M. D., Greiner, J. G., and McDonald, P. L. (2010). Point: counterpoint "Humans do/do not demonstrate selective brain cooling during hyperthermia." *J. Appl. Physiol.* 110, 569–571. doi: 10.1152/japplphysiol.00992.2010

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 12 November 2013; paper pending published: 27 January 2014; accepted: 07 February 2014; published online: 27 February 2014.

*Citation: Nybo L, Wanscher M and Secher NH (2014) Influence of intranasal and carotid cooling on cerebral temperature balance and oxygenation. Front. Physiol. **5**:79. doi: 10.3389/fphys.2014.00079*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 11 February 2014
doi: 10.3389/fphys.2014.00045

Glycopyrrolate does not influence the visual or motor-induced increase in regional cerebral perfusion

Kim Z. Rokamp[1]*, Niels D. Olesen[1], Henrik B. W. Larsson[2], Adam E. Hansen[2], Thomas Seifert[1], Henning B. Nielsen[1], Niels H. Secher[1] and Egill Rostrup[2]

[1] Department of Anaesthesia, Rigshospitalet, Copenhagen, Denmark
[2] Functional Imaging Unit, Department of Diagnostics, Glostrup Hospital, Glostrup, Denmark

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Can O. Tan, Harvard Medical School, USA
Jasper Truijen, Academic Medical Centre, Netherlands

***Correspondence:**
Kim Z. Rokamp, Department of Anaesthesia, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark
e-mail: kimzillo@hotmail.com

Acetylcholine may contribute to the increase in regional cerebral blood flow (rCBF) during cerebral activation since glycopyrrolate, a potent inhibitor of acetylcholine, abolishes the exercise-induced increase in middle cerebral artery mean flow velocity. We tested the hypothesis that cholinergic vasodilatation is important for the increase in rCBF during cerebral activation. The subjects were 11 young healthy males at an age of 24 ± 3 years (mean ± *SD*). We used arterial spin labeling and blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) to evaluate rCBF with and without intravenous glycopyrrolate during a handgrip motor task and visual stimulation. Glycopyrrolate increased heart rate from 56 ± 9 to 114 ± 14 beats/min (mean ± *SD*; $p < 0.001$), mean arterial pressure from 86 ± 8 to 92 ± 12 mmHg, and cardiac output from 5.6 ± 1.4 to 8.0 ± 1.7 l/min. Glycopyrrolate had, however, no effect on the arterial spin labeling or BOLD responses to the handgrip motor task or to visual stimulation. This study indicates that during a handgrip motor task and visual stimulation, the increase in rCBF is unaffected by blockade of acetylcholine receptors by glycopyrrolate. Further studies on the effect of glycopyrrolate on middle cerebral artery diameter are needed to evaluate the influence of glycopyrrolate on mean flow velocity during intense exercise.

Keywords: Cholinergic receptor antagonist, regional cerebral blood flow

INTRODUCTION

Cerebral blood flow (CBF) is 50–60 ml 100 g^{-1} min^{-1} (Lassen, 1974) and its regional distribution is affected by cerebral neuronal activity and metabolism (Lassen, 1959). Thus, a motor task is followed by an increase in regional CBF (rCBF) (Olesen, 1971). Although regulation of activity-related CBF is not fully understood, it is considered to depend mainly on synaptic release of glutamate that releases a series of vaso-active substances from neurons and astrocytes (Attwell et al., 2010). However, other substances such as acetylcholine may be involved in maintaining CBF during, e.g., a change in perfusion pressure (Hamner et al., 2012). The endothelium is important for cerebral vasoregulation and acetylcholine interacts with endothelial muscarinic receptors (Tsukahara et al., 1986) to facilitate vasodilation (Faraci and Heistad, 1991). Intrinsic and extrinsic regulation of cerebral vessels and in turn CBF is described by Hamel (2006), and cerebral blood vessels receive cholinergic innervation originating mainly from the sphenopalatine ganglion and the nucleus basalis of Meynert (NBM) (Seylaz et al., 1988; Suzuki et al., 1990). The increase in rCBF during walking appears to include excitation of this NBM-originating cholinergic vasodilation system (Sato and Sato, 1995), suggesting a link between acetylcholine mediated control of vessels, and activity-dependent changes in perfusion. Similarly, the transcranial Doppler (TCD) ultrasound determined mean blood velocity for the contralateral middle cerebral artery (MCA V_{mean}) increases during handgrip exercise (Jørgensen et al., 1993) and V_{mean} increases for the contralateral anterior cerebral artery (ACA) during movement of one foot while cycling exercise is associated with a bilateral increase in both MCA and ACA V_{mean} (Linkis et al., 1995). Activity of the cholinergic fibers induces increase in rCBF in dogs (D'Alecy and Rose, 1977; Toda et al., 2000) although there are conflicting findings as to the effect of atropine in blocking this dilation (D'Alecy and Rose, 1977; Busija and Heistad, 1981; Toda et al., 2000). However, there may be important differences among species. In swine the absence of change in perfusion to cortical areas of cerebrum during running (Delp et al., 2001) suggests that in quadrupeds running does not require higher brain activation. Accordingly, Hamner et al. (2012) suggest that cholinergic involvement in human CBF regulation needs to be directly addressed.

Acetylcholinesterase inhibitors that pass the blood brain barrier are used to reduce symptoms of Alzheimer's disease and vascular cognitive impairment (Birks and Harvey, 2006; Levine and Langa, 2011) possibly indicating a cholinergic contribution to regulation of CBF and cerebral metabolism. For other drugs crossing the blood brain barrier, such as atropine, the effect on CBF may be secondary to changes in cerebral metabolism. Glycopyrrolate is a similar muscarinic blocker that does not cross the blood brain barrier (Proakis and Harris, 1978) and during handgrip and cycling exercise, glycopyrrolate abolishes the exercise-induced increase in MCA V_{mean} (Seifert et al., 2010). This leads to the hypothesis that cholinergic vasodilatation is important for the motor task-induced increase in cerebral perfusion, not only during strenuous exercise, but also at a moderate

activity level. We hypothesized that cholinergic vasodilation would induce an increase in rCBF upon cerebral activation. In order to test that hypothesis, we used arterial spin labeling (ASL) and blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) to assess CBF with and without glycopyrrolate at rest and during a handgrip motor task and also during visual light stimulation.

METHODS

The subjects were 11 young healthy males at an age of 24 ± 3 years (height and weight 183 ± 6 cm, and 78 ± 9 kg; mean ± *SD*). The study was approved by the local ethical committee (J.nr. H-4-2010-066) and by the Danish Data Protection Agency (J.nr. 2011-41-6602) and written informed consent was obtained prior to participation in accordance with the Declaration of Helsinki. Inclusion criteria were male gender, being healthy non-smoker without taking any medication. The subjects abstained from strenuous physical activity on the day prior to the study and from caffeine on study days.

A catheter was inserted in an arm vein for administration of glycopyrrolate and also a catheter was placed in the radial artery of the non-dominant arm for blood sampling and cardiovascular measurements. Heart rate (HR) was monitored using a lead II ECG and arterial pressure was measured with a transducer (Edwards Life Sciences, Irvine, CA) at heart level and connected to a monitor (Dialogue-2000 IBC-Danica Electronic, Copenhagen, Denmark). Heart rate variability was quantified from data acquired at rest as the standard deviation of RR-interval duration divided by the mean duration. Mean arterial pressure (MAP), cardiac stroke volume (SV) and output (CO) were determined from the radial arterial pressure using pulse contour methodology (Nexfin, BMEYE B.V, Amsterdam, The Netherlands) (Bogert and Van Lieshout, 2005).

Magnetic resonance imaging was performed on a 3.0T Intera Achieva scanner (Philips Medical Systems, Best, The Netherlands) using an eight-element phased array receiver head coil. Structural imaging was performed using a 3D T1 weighted gradient echo sequence [repetition time (TR) = 10 ms, echo time (TE) = 5 ms, flip angle 8°, matrix 240 × 200, voxel size 1 × 1 × 1 mm, sensitivity encoding (SENSE) factor = 2]. The structural scan was used for tissue segmentation and calculation of brain volume.

Global brain perfusion was determined with velocity mapping using phase subtraction of a flow compensated and flow sensitive gradient echo sequence. Measurements were obtained with a matrix of 320 × 320 (TR = 12 ms, TE = 7 ms, flip angle 10°, voxel size 0.75 × 0.75 × 8 mm). The sequence was ECG gated (retrospective gating, 20 frames/cycle), using a velocity encoding of 150 cm/s. Any aliasing of the phase-difference was corrected using an in-house written routine for Matlab v 7.9 (The MathWorks Inc., Natick, MA). A fast angiography was performed and reconstructed in order for the imaging section to be positioned perpendicular to the cavernous segment of the internal carotid and basilar arteries.

Regional perfusion maps were obtained with ASL using the QUASAR sequence (Petersen et al., 2006). The sequence is based on multi-slice pulsed arterial labeling technique (EPISTAR) in which both the labeling and the control experiment are preceded by a saturation pulse and followed by a QUIPSS-II type saturation pulse. The readout was performed using a dual flip angle Look-Locker strategy and both crushed and non-crushed control-label pairs were acquired. General scan parameters were: TR = 4000 ms; TE = 22 ms, multiple time-point interval (ΔTI) = 300 ms, time of first readout ($TI1$) = 40 ms, flip angle 35/11.7°, matrix 80 × 80, voxel size 3 × 3 × 6 mm, gap 1.5 mm, SENSE factor = 2.5, 84 averages [48 at velocity encoding (V_{enc}) = 4 cm/s, 24 without velocity encoding, 12 at low flip angle]. Seven transaxial perfusion slices parallel to the lower edges of the corpus callosum were acquired with a total scan duration of 6 min.

Functional imaging was carried out at rest and during task conditions using a standard gradient-echo EPI sequence with 32 slices positioned parallel to and overlapping the ASL acquisition. Variables were: TR = 3000 ms, TE = 35 ms, flip angle 90°, FOV 230 × 230 mm^2, in plane resolution 2.9 × 2.9 mm^2, slice thickness 4.0 mm, and inter slice gap 0.1 mm. For each run during task paradigms, 70 frames were obtained and for the resting state experiments, 300 frames were obtained.

The subjects were placed supine and run through a sequence of 2 times 30 min of scanning, the first being without influence of glycopyrrolate (**Table 1**). Measurements of global (velocity mapping) and regional (ASL) brain perfusion were performed with the subject at rest and while squeezing a rubber ball which required 36 N for 50% compression (Thera-Band® Hand Exerciser, prod. no. 26050, The Hygenic Corporation, 1245 Home Ave., Akron, OH 44310, USA). We instructed the subjects to compress the rubber ball by rhythmic squeezing ∼30–60 times per minute with as much effort as possible, while lying still with the rest of the body.

Two runs of BOLD imaging were performed with different tasks, one in which the subject was stimulated visually with a checkerboard pattern reversing at 8 Hz. Furthermore, the subject was instructed to carry out sequential finger-thumb opposition on both hands while the checkerboard was on. In the other run, the subject squeezed the rubber ball intermittently with no visual stimulation. Both runs included 5 resting periods interleaved with 4 active, each lasting 30 s. Additionally, for assessment of intrinsic connectivity, BOLD data were acquired with the same variables, but for 900 s without any tasks imposed.

Arterial samples were obtained at rest in 8 subjects. The samples were emptied of any atmospheric content and immediately analyzed for carbon dioxide tension ($PaCO_2$) (ABL 725, Radiometer, Copenhagen, Denmark), before and after the scanning sequence with and without glycopyrrolate. To induce cholinergic receptor blockade the subjects received 1.9 ± 0.34 mg of glycopyrrolate by stepwise infusions of 0.2 mg until no further increase in HR could be established.

REGION BASED fMRI ANALYSIS

Motor cortex (BA1) on the contralateral side of the activated dominant hand was drawn in the center of the anatomically defined region, around the area of maximal activation. Similarly, in the activated area in visual cortex (BA17) a central and extended area was delineated. The extended BA17 area corresponds to the entire region (left side) as defined the MNI/Juelich atlas. Data are derived from 22 measurements in 11 subjects.

Table 1 | The study protocol.

Time (min)	Baseline vs. glycopyrrolate	Scanning sequence	Arterial blood gas measurement
00 min	Baseline	Survey/reference scan	
		Fast angio sequence	
		3D anatomy	
			1. $PaCO_2$
		Global flow—rest	
		ASL—rest	
		Global flow—motor task	
		ASL—motor task	
		BOLD-fMRI—visual and motor task	
		BOLD-fMRI—motor task	
			2. $PaCO_2$
50 min	Glycopyrrolate injection		
65 min	Glycopyrrolate	Survey/reference scan	
		Fast angio sequence	
			3. $PaCO_2$
		Global flow—rest	
		ASL—rest	
		Global flow—motor task	
		ASL—motor task	
		BOLD-fMRI—visual and motor task	
		BOLD-fMRI—motor task	
110 min			4. $PaCO_2$

With the subjects placed in the scanner, two sets of measurements were obtained, the first (baseline) being without influence of glycopyrrolate. Global flow was obtained by velocity mapping in the carotid and basilar arteries, using phase subtraction. In addition, measurements included arterial spin labeling (ASL) and blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI).

STATISTICAL ANALYSIS

Variables were analyzed in STATA/SE v 11.2 (www.stata.com) using a random effect linear model and a p-value < 0.05 was considered statistically significant. Results are presented as mean ± *SD*. Functional BOLD data were analyzed using FSL v. 4.1.2 (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl). Data were spatially aligned to correct for subject motion and slice timing differences and filtered with a temporal highpass filter matched to the paradigm period (60 s). Spatial filtering was with a 5 mm gaussian filter. Thresholding for positive and negative effects was done using a cluster based approach with a primary threshold of $z > 2.3$ and a cluster-level p-value of 0.05. The response magnitude was calculated and reported as average over all activation periods. Other data analyses were performed in Matlab.

Table 2 | Cardiovascular variables.

Cardiovascular	Resting	Resting + glycopyrrolate	Motor task	Motor task + glycopyrrolate
SYS (mmHg)	119 ± 15	119 ± 12^{ns}	124 ± 19^{ns}	123 ± 15^{ns}
DIA (mmHg)	69 ± 7	82 ± 10*	72 ± 8^{ns}	84 ± 8**
MAP (mmHg)	86 ± 8	92 ± 12^{ns}	89 ± 10^{ns}	93 ± 10^{ns}
HR (B min^{-1})	56 ± 9	114 ± 14**	61 ± 7^{ns}	115 ± 13**
SV (ml)	101 ± 20	71 ± 16*	101 ± 22^{ns}	72 ± 14*
CO (l min^{-1})	5.6 ± 1.4	8.0 ± 1.7*	6.2 ± 1.6^{ns}	8.1 ± 1.3*
CBF (ml/min)	797 ± 162	817 ± 203^{ns}	856 ± 162^{ns}	837 ± 204^{ns}

*SYS, DIA, MAP systolic, diastolic, and mean arterial pressure, respectively; HR, heart rate; SV, cardiac stroke volume; CO, cardiac output; CBF, cerebral blood flow. Values are mean ± SD. Testing performed with paired t-test vs. Resting (without glycopyrrolate). ns, non-significant; *$p < 0.05$ and **$p < 0.001$.*

RESULTS

CARDIOVASCULAR VARIABLES

The cardiovascular effects of glycopyrrolate and the handgrip motor task are presented in **Table 2**. Glycopyrrolate increased HR from 56 ± 9 to 114 ± 14 beats/min ($p < 0.001$), diastolic (DIA) and MAP from 69 ± 7 to 82 ± 10 mmHg and from 86 ± 8 to 92 ± 12 mmHg, respectively, and CO from 5.6 ± 1.4 to 8.0 ± 1.7 l/min, while HR variability decreased from 5.0 ± 1.6 to 1.5 ± 0.4% ($P < 0.001$). In contrast, no effect was observed for systolic pressure (SYS). The handgrip motor task increased DIA and MAP by 4 and 5 mmHg, respectively ($P < 0.001$), but no significant changes were observed for SYS, HR, or CO. There was no interaction between glycopyrrolate and the handgrip motor task or visual stimulation on any of the cardiovascular variables. Also there was no significant difference between data obtained during the different MR measurements or the arterial blood gas samples (**Table 3**).

Table 3 | Arterial pH and carbon dioxide tension ($PaCO_2$).

	Rest	Resting + glycopyrrolate	Motor task	Motor task + glycopyrrolate
pH	7.40 ± 0.01	7.40 ± 0.02	7.40 ± 0.02	7.41 ± 0.02
$PaCO_2$ (kPa)	5.4 ± 0.2	5.5 ± 0.5	5.5 ± 0.3	5.2 ± 0.4

Values are mean ± SD.

WHOLE BRAIN FLOW VELOCITY MAPPING BY PHASE ENCODING

The total arterial flow to the brain was 801 ml/min, with an inter-subject SD of 156 ml/min (19.5%) and an intra-subject SD of 64 ml/min (8%) (**Table 2**). There was no significant effect of activation of handgrip or glycopyrrolate for the total or any of the three vessels [right and left internal carotid artery (ICA) or basilar artery]. The average maximal velocity for, e.g., the left ICA was 76 cm/s, with almost equal inter and intra-subject SD of 33 and 32 cm/s. For the right and the left ICA there was no significant effect of glycopyrrolate.

CEREBRAL PERFUSION (ARTERIAL SPIN LABELING)

Six subjects were evaluated with handgrip activation. Handgrip increased total gray matter CBF from 46 to 51 ml 100 mg^{-1} min^{-1} ($P = 0.01$), but the increase was not significantly altered by glycopyrrolate. Similarly, arterial spin labeling maps showed an area of significant flow increase corresponding to the left primary motor cortex during handgrip ($p < 0.001$, uncorrected), with no significant modulation during glycopyrrolate. However, a decrease in perfusion was seen in areas corresponding to the posterior cingulate and parietal cortices during glycopyrrolate ($p < 0.001$, uncorrected).

BLOOD OXYGEN LEVEL DEPENDENT ACTIVATION DURING HANDGRIP

There was an increase of the BOLD signal during activation of the motor cortex (BA1) on the contra-lateral side of the activated dominant hand by 2.16% compared with the resting value ($P < 0.001$), but there was no effect of glycopyrrolate at voxel level.

BLOOD OXYGEN LEVEL DEPENDENT ACTIVATION DURING COMBINED VISUAL STIMULATION AND MOTOR TASK

The main effect of visuo-motor stimulation was a massive activation in extended areas centered around motor cortex (bilateral BA1), and visual cortex (BA17) and also including basal ganglia and cerebellum (**Figure 1**). In area BA1 on the contralateral side of the activated dominant hand, the BOLD response increased 1.9% during finger tapping and visual stimulation when compared to rest. In area (BA17) of the visual cortex the BOLD response increased by 2.76% in the central area and 1.16% in the extended area in response to visual stimulation and finger tapping when compared to rest ($P < 0.001$). No effect of glycopyrrolate was observed.

DISCUSSION

As expected, motor activation increased rCBF in motor cortex as indicated by BOLD and arterial spin labeling. The increase in rCBF did not affect total CBF as measured by phase mapping and apparently only whole body exercise increases total CBF. The dynamic behavior of CBF is supported by the increase in CBF during whole body exercise as detected by ^{133}Xe clearance (Thomas et al., 1989) and by TCD (Jørgensen et al., 1992a,b), but in the present study we did not find any increase in CBF in spite of an increase in CO from 5.7 to 7.9 l/min during infusion of glycopyrrolate, nor an effect on rCBF during motor- and visual activation. Furthermore, we were not able to demonstrate that glycopyrrolate affected CBF increase during visual stimulation or a handgrip motor task.

Seifert et al. (2010) report that glycopyrrolate attenuated the increase in CBF during sustained handgrip and cycle exercise. There are several differences between the two studies, the most apparent being different modes of motor- and neural activation of the subjects and different methods of measuring brain blood velocity and flow. In our study handgrip increased MAP by about 5 mmHg, while no significant differences were induced in HR or CO, whereas, in comparison sustained handgrip in the study of Seifert et al. increased MAP, HR, and CO, 30 mmHg, 45 beats min^{-1} and 3.5 L min^{-1}, respectively. Cerebral blood vessels are surrounded by nerve fibers that originate, respectively, from extrinsic peripheral nerve ganglia (sphenopalatine, otic, or trigeminal ganglion) and intrinsic brain neurons and contributes to the functional "neurovascular unit" where the vascular tone is regulated by both intrinsic and extrinsic innervation (Hamel, 2006). In our study the test persons may not be considered to perform "exercise," but rather a light motor task and therefore, one can speculate that the intrinsic regulation is dominating an intravascular cholinergic stimulus. The study of Seifert et al. (2010) measured differences after strenuous exercise, including muscular pain, increased HR, CO, and respiratory frequency, where an extrinsic component might be of more importance. Since glycopyrrolate does not cross the blood brain barrier and therefore cannot affect the intrinsic regulation, a possible effect of blocking the cholinergic response might have been unobserved, or the cholinergic vasodilatation is only important under conditions where acetylcholine release from neuromuscular junctions influences total cerebrovascular reactivity, but not for the exercise-induced increase in regional cerebral perfusion during a handgrip motor task or visual stimulation.

The methods for measuring blood velocity and flow were different in the two studies. Seifert et al. (2010) used TCD of the middle cerebral artery. When measuring cerebral blood velocity using Q-flow, we considered that the small diameter of MCA would lead to an underestimate of flow because of a partial volume effect. We therefore, used the ICA although this measurement is directed toward total CBF compared to MCA where the motor cortex would represent a larger percentage of the distribution area. For measuring local cerebral blood perfusion we used ASL and BOLD. Being an indirect method of measuring cerebral perfusion, the BOLD technique measures changes in deoxyhemoglobin concentration that correlates to changes in local perfusion in the absence of metabolic changes, the cerebral tissue being uninfluenced by glycopyrrolate that does not cross the blood brain barrier. Importantly the CBF/perfusion baseline was not altered after administration of glycopyrrolate in neither study.

This study could be underpowered considering the increase in CBF during motor activity is about 60 ml/min during placebo and 20 ml/min during glycopyrrolate, but with the standard

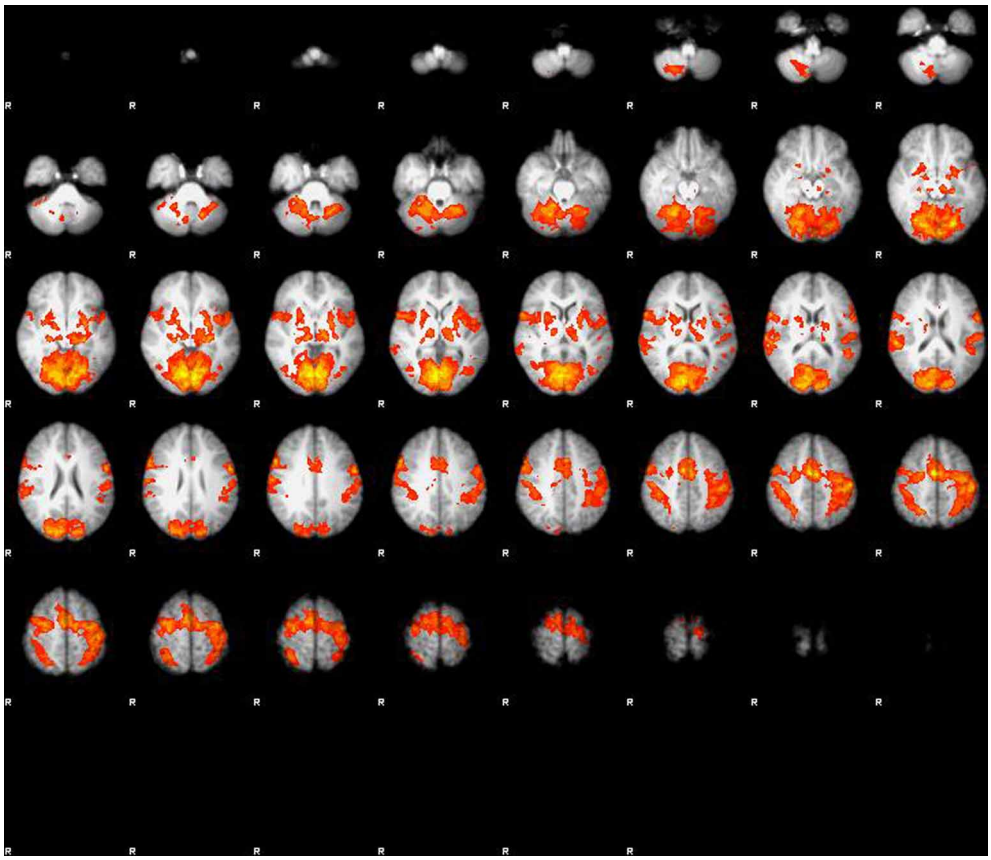


FIGURE 1 | Main effect of visuo-motor stimulation, large activation in extended areas centered around motor cortex (bilateral BA1), and visual cortex (BA17), but also including basal ganglia and cerebellum. When properly corrected for multiple comparison or corrected voxel level ($p < 0.05$) there is no effect of glycopyrrolate.

deviations above 150 ml/min, a very large sample would be needed in order to detect a potential effect of hand activity on global perfusion.

Although not a primary endpoint, we observed scattered areas of decreased perfusion during glycopyrrolate, especially in the posterior cingulate area. This finding is of potential interest, since posterior and parietal areas are affected early in the course of Alzheimer's disease in which cholinergic innervation may be deficient. A regionally specific effect of glycopyrrolate on brain perfusion has not been described and would need investigation in future studies.

LIMITATIONS

The study is limited by the use of glycopyrrolate that does not cross the blood brain barrier and therefore, does not have any metabolic effect on cerebral tissue. Glycopyrrolate is therefore limited to influence the extrinsic innervation of the functional "neurovascular unit" leaving the intrinsic innervation unaffected. When performing a handgrip motor task or visual stimulation, the intrinsic innervation might be dominating and therefore mask the effect of cholinergic blockade.

Compressing an ergo ball rhythmically with the same force is not easily standardized and therefore, different levels of cerebral activation could bias the results, but there is no difference between handgrip task and light stimulation in interindividual cerebral blood perfusion response which supports the validity of the handgrip data.

The measurement of BOLD is an indirect measurement of cerebral perfusion as it determines changes in deoxyhemoglobin concentration that correlates to those in local perfusion in the absence of metabolic changes. The cerebral tissue being uninfluenced by glycopyrrolate, that do not cross the blood brain barrier, should therefore be without metabolic influence leaving the effect of cholinergic blockade to the extrinsic part of the neurovascular unit.

CONCLUSION

Cerebral blood flow is not altered by glycopyrrolate during a motor task or visual stimulation as measured by fMRI. Further studies on the effect of glycopyrrolate on CBF comparing strenuous and light exercise using fMRI is needed to contribute to understanding the role of extrinsic vs. intrinsic cholinergic innervation on the regulation of CBF.

AUTHOR CONTRIBUTIONS

Kim Z. Rokamp participated in study design, collected the data, performed data analysis, and wrote the first draft of the paper. Niels D. Olesen collected the data and contributed to

the preparation of the paper. Henrik B. W. Larsson, Adam E. Hansen, Thomas Seifert, Henning B. Nielsen, Niels H. Secher, Egill Rostrup participated in the study design, performed data analysis and contributed to the preparation of the paper.

REFERENCES

Attwell, D., Buchan, A. M., Charpak, S., Lauritzen, M., Macvicar, B. A., and Newman, E. A. (2010). Glial and neuronal control of brain blood flow. *Nature* 468, 232–243. doi: 10.1038/nature09613

Birks, J., and Harvey, R. J. (2006). Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst. Rev.* 25:CD001190. doi: 10.1002/14651858.CD001190.pub2

Bogert, L. W. J., and Van Lieshout, J. J. (2005). Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Exp. Physiol.* 90, 437–446. doi: 10.1113/expphysiol.2005.030262

Busija, D. W., and Heistad, D. D. (1981). Effects of cholinergic nerves on cerebral blood flow in cats. *Circ. Res.* 48, 62–69. doi: 10.1161/01.RES.48.1.62

D'Alecy, L. G., and Rose, C. J. (1977). Parasympathetic cholinergic control of cerebral blood flow in dogs. *Circ. Res.* 41, 324–331. doi: 10.1161/01.RES.41.3.324

Delp, M. D., Armstrong, R. B., Godfrey, D. A., Laughlin, M. H., Ross, C. D., and Wilkerson, M. K. (2001). Exercise increases blood flow to locomotor, vestibular, cardiorespiratory and visual regions of the brain in miniature swine. *J. Physiol.* 533, 849–859. doi: 10.1111/j.1469-7793.2001.t01-1-00849.x

Faraci, F. M., and Heistad, D. D. (1991). Regulation of cerebral blood vessels by humoral and endothelium-dependent mechanisms. Update on humoral regulation of vascular tone. *Hypertension* 17, 917–922. doi: 10.1161/01.HYP.17.6.917

Hamel, E. (2006). Perivascular nerves and the regulation of cerebrovascular tone. *J. Appl. Physiol.* 100, 1059–1064. doi: 10.1152/japplphysiol.00954.2005

Hamner, J. W., Tan, C. O., Tzeng, Y.-C., and Taylor, J. A. (2012). Cholinergic control of the cerebral vasculature in humans. *J. Physiol.* 590, 6343–6352. doi: 10.1113/jphysiol.2012.245100

Jørgensen, L. G., Perko, G., Payne, G., and Secher, N. H. (1993). Effect of limb anesthesia on middle cerebral response to handgrip. *Am. J. Physiol.* 264, H553–H559.

Jørgensen, L. G., Perko, G., and Secher, N. H. (1992a). Regional cerebral artery mean flow velocity and blood flow during dynamic exercise in humans. *J. Appl. Physiol.* 73, 1825–1830.

Jørgensen, L. G., Perko, M., Hanel, B., Schroeder, T. V., and Secher, N. H. (1992b). Middle cerebral artery flow velocity and blood flow during exercise and muscle ischemia in humans. *J. Appl. Physiol.* 72, 1123–1132.

Lassen, N. A. (1959). Cerebral blood flow and oxygen consumption in man. *Physiol. Rev.* 39, 183–238.

Lassen, N. A. (1974). Control of cerebral circulation in health and disease. *Circ. Res.* 34, 749–760. doi: 10.1161/01.RES.34.6.749

Levine, D. A., and Langa, K. M. (2011). Vascular cognitive impairment: disease mechanisms and therapeutic implications. *Neurotherapeutics* 8, 361–373. doi: 10.1007/s13311-011-0047-z

Linkis, P., Jørgensen, L. G., Olesen, H. L., Madsen, P. L., Lassen, N. A., and Secher, N. H. (1995). Dynamic exercise enhances regional cerebral artery mean flow velocity. *J. Appl. Physiol.* 78, 12–16.

Olesen, J. (1971). Contralateral focal increase of cerebral blood flow in man during arm work. *Brain* 94, 635–646. doi: 10.1093/brain/94.4.635

Petersen, E. T., Lim, T., and Golay, X. (2006). Model-free arterial spin labeling quantification approach for perfusion MRI. *Magn. Reson. Med.* 55, 219–232. doi: 10.1002/mrm.20784

Proakis, A. G., and Harris, G. B. (1978). Comparative penetration of glycopyrrolate and atropine across the blood–brain and placental barriers in anesthetized dogs. *Anesthesiology* 48, 339–344. doi: 10.1097/00000542-197805000-00007

Sato, A., and Sato, Y. (1995). Cholinergic neural regulation of regional cerebral blood flow. *Alzheimer Dis. Assoc. Disord.* 9, 28–38. doi: 10.1097/00002093-199505000-00007

Seifert, T., Fisher, J. P., Young, C. N., Hartwich, D., Ogoh, S., Raven, P. B., et al. (2010). Glycopyrrolate abolishes the exercise-induced increase in cerebral perfusion in humans. *Exp. Physiol.* 95, 1016–1025. doi: 10.1113/expphysiol.2010.054346

Seylaz, J., Hara, H., Pinard, E., Mraovitch, S., MacKenzie, E. T., and Edvinsson, L. (1988). Effect of stimulation of the sphenopalatine ganglion on cortical blood flow in the rat. *J. Cereb. Blood Flow Metab.* 8, 875–878. doi: 10.1038/jcbfm.1988.145

Suzuki, N., Hardebo, J. E., Kåhrström, J., and Owman, C. (1990). Selective electrical stimulation of postganglionic cerebrovascular parasympathetic nerve fibers originating from the sphenopalatine ganglion enhances cortical blood flow in the rat. *J. Cereb. Bood Flow Metab.* 10, 383–391. doi: 10.1038/jcbfm.1990.68

Thomas, S. N., Schroeder, T., Secher, N. H., and Mitchell, J. H. (1989). Cerebral blood flow during submaximal and maximal dynamic exercise in humans. *J. Appl. Physiol.* 67, 744–748.

Toda, N., Ayajiki, K., Tanaka, T., and Okamura, T. (2000). Preganglionic and postganglionic neurons responsible for cerebral vasodilation mediated by nitric oxide in anesthetized dogs. *J. Cereb. Blood Flow Metab.* 20, 700–708. doi: 10.1097/00004647-200004000-00007

Tsukahara, T., Usui, H., Taniguchi, T., Shimohama, S., Fujiwara, M., and Handa, H. (1986). Characterization of muscarinic cholinergic receptors in human and dog cerebral arteries. *Stroke* 17, 300–305. doi: 10.1161/01.STR.17.2.300

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 December 2013; accepted: 24 January 2014; published online: 11 February 2014.

Citation: Rokamp KZ, Olesen ND, Larsson HBW, Hansen AE, Seifert T, Nielsen HB, Secher NH and Rostrup E (2014) Glycopyrrolate does not influence the visual or motor-induced increase in regional cerebral perfusion. Front. Physiol. ***5****:45. doi: 10.3389/fphys.2014.00045*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 19 March 2014
doi: 10.3389/fphys.2014.00101

Effect of acute resistance exercise on carotid artery stiffness and cerebral blood flow pulsatility

Wesley K. Lefferts, Jacqueline A. Augustine and Kevin S. Heffernan*

Department of Exercise Science, Syracuse University, Syracuse, NY, USA

Edited by:
Phil Neil Ainslie, University of British Columbia, Canada

Reviewed by:
Samuel J.E. Lucas, University of Birmingham, UK
Aaron Alexander Phillips, University of British Columbia, Canada

***Correspondence:**
Kevin S. Heffernan, The Human Performance Laboratory, Department of Exercise Science, Syracuse University, 820 Comstock Ave., Syracuse, NY 13244, USA
e-mail: ksheffer@syr.edu

Arterial stiffness is associated with cerebral flow pulsatility. Arterial stiffness increases following acute resistance exercise (RE). Whether this acute RE-induced vascular stiffening affects cerebral pulsatility remains unknown. Purpose: To investigate the effects of acute RE on common carotid artery (CCA) stiffness and cerebral blood flow velocity (CBFv) pulsatility. Methods: Eighteen healthy men (22 ± 1 yr; 23.7 ± 0.5 $kg \cdot m^{-2}$) underwent acute RE (5 sets, 5-RM bench press, 5 sets 10-RM bicep curls with 90 s rest intervals) or a time control condition (seated rest) in a randomized order. CCA stiffness (β-stiffness, Elastic Modulus (Ep)) and hemodynamics (pulsatility index, forward wave intensity, and reflected wave intensity) were assessed using a combination of Doppler ultrasound, wave intensity analysis and applanation tonometry at baseline and 3 times post-RE. CBFv pulsatility index was measured with transcranial Doppler at the middle cerebral artery (MCA). Results: CCA β-stiffness, Ep and CCA pulse pressure significantly increased post-RE and remained elevated throughout post-testing ($p < 0.05$). No changes in MCA or CCA pulsatility index were observed ($p > 0.05$). There were significant increases in forward wave intensity post-RE ($p < 0.05$) but not reflected wave intensity ($p > 0.05$). Conclusion: Although acute RE increases CCA stiffness and pressure pulsatility, it does not affect CCA or MCA flow pulsatility. Increases in pressure pulsatility may be due to increased forward wave intensity and not pressure from wave reflections.

Keywords: arterial stiffness, blood pressure, exercise, wave reflection

INTRODUCTION

Increases in arterial stiffness with age and/or disease increases risk for cardiovascular events such as myocardial infarction and stroke (Sutton-Tyrrell et al., 2005; Mitchell et al., 2010). Increased arterial stiffness also contributes to target organ damage such as renal dysfunction and retinal damage (Katsi et al., 2012; Safar et al., 2012). The elastic properties of the large central arteries (i.e., aorta and carotid) function to dampen the amplitude of fluctuations in pressure and flow, thereby preventing transmission of excess energy into target organs (Mitchell et al., 2011). Similar to the kidney and eye, the brain is a high flow organ particularly susciptible to hemodynamic pulsatility (Mitchell, 2008). Repeated exposure of the cerebral vasculature to pulsatile pressure/flow may precipitate microvascular hypoperfusion and subsequent ischemia contributing to rarefaction, white matter hyperintensities and ultimately cerebrovascular impairment (Mitchell et al., 2005). Recent studies note a strong assocation between arterial stiffness, pressure/flow pulsatility and cerebral perfusion (Kwater et al., 2009; Tarumi et al., 2011; Webb et al., 2012). Studies to date examining associations between arterial stiffness and cerebrovascular pulsatility have been cross-sectional. It is largely unknown if acute elevations in arterial stiffness affect cerebrovascular pulsatility.

Resistance exercise (RE) is an accepted lifestyle strategy to increase muscular strength and attenuate sarcopenia-related functional impairment (Miyachi et al., 2004; Miyachi, 2013) and is currently recommended by major health organizations for health promotion/disease prevention (Pollock et al., 2000). Paradoxically, despite functional and musculoskeletal benefits, RE may impair vascular function (Miyachi et al., 2004; Heffernan et al., 2007b; Collier et al., 2010). Higher intensity RE training typically increases arterial stiffness (Miyachi, 2013) and recent evidence suggests that RE training may contribute to reductions in cerebral blood flow velocity (CBFv) (Jung et al., 2012). Acute RE has consistently been shown to increase large central artery stiffness (Heffernan et al., 2007a; Collier et al., 2010) immediately after and for upwards of 30 min after perturbation (DeVan et al., 2005). Given the strong cross-sectional association between arterial stiffness, pressure/flow pulsatility, and cerebral perfusion, it is possible that acute RE-induced increases in arterial stiffness may transiently increase CBFv pulsatility. The purpose of this study was to test the hypothesis that acute RE-induced increases in arterial stiffness would lead to increases in carotid pressure/flow pulsatility and CBFv pulsatility.

Abbreviations: RE, Resistance exercise; CBFv, Cerebral blood flow velocity; RM, Repetition maximum; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; CCA, Common carotid artery; IMT, Intima-media thickness; MAP, Mean arterial pressure; PI, Pulsatility index; WIA, Wave intensity analysis; NA, Negative area; Ep, Elastic modulus; β, β Stiffness index, PP, Pulse pressure; Aix, Augmentation index; WSA, Wave separation analysis; Pf, Forward wave pressure; Pb, Backwards wave pressure; MCA, Middle cerebral artery; TCD, Transcranial Doppler; CVRi, Cerebrovascular resistance index.

METHODS

PARTICIPANTS

Eighteen recreationally active men, ranging in age from 19–28 yrs, were recruited from the local University community for this randomized, crossover-design study. None were highly trained in an exclusive exercise modality (i.e., distance runners, bodybuilders, or power lifters). Exclusion criteria included self-reported smoking, hypertension, diabetes mellitus, hyperlipidemia, pulmonary disease, renal disease, neurological disease or peripheral artery disease and/or use of medications of any kind. This study was approved by the Institutional Review Board of Syracuse University and all participants provided written informed consent prior to study initiation. Vascular testing was conducted at the same time of day in a quiet, dimly lit, temperature-controlled laboratory. Participants were instructed to fast for $\geq$3 h and avoid vigorous exercise and consuming caffeine/alcohol $\geq$12 h before testing. Height and weight were assessed via wall-mounted ruler and electronic scale, respectively, and body composition was estimated via air displacement plethysmography (BodPod; COSMED, Concord, CA).

DESIGN

Upon arrival, participants rested for 10 min in the supine position. This was followed by all vascular and hemodynamic measures. Participants then performed (a) upper body RE, or (b) seated rest with minimal movement (time control) in a randomized order on two separate days. The RE protocol consisted of 5 sets of 5-repetitions for bench press and 5 sets of 10-repetitions for biceps curl, with each set being separated by 90 s of rest. Exercises were performed at 100% of participants 5 repetition maximum (RM) and 10 RM for bench press and biceps curl respectively. If participants could not complete the designated number of repetitions, a "drop set" was instituted whereby the total load was reduced in small increments until participants successfully completed target repetitions. Participants RMs for each exercise were determined previously on a separate day. This acute RE protocol has previously been shown to acutely increase arterial stiffness (Fahs et al., 2009). Post-testing vascular and hemodynamic measures were made 10, 20, and 30 min following acute RE based on previous findings noting prominent changes in arterial stiffness to occur at these times (DeVan et al., 2005; Heffernan et al., 2007a; Fahs et al., 2009). Carotid pressure, flow, stiffness, and cerebral velocity measures were obtained simultaneously.

MEASURES

Brachial blood pressure

Systolic blood pressure (SBP) and diastolic brachial blood pressure (DBP) was measured prior to each set of vascular measures (baseline, post-1, post-2, post-3) using a validated, automated oscillometric cuff (EW3109, Panasonic Electric Works, Secaucus NJ). Pressures were taken in duplicate and averaged. If values were different by more than 5 mmHg a third measure was obtained and the average of the 2 closest measures used for subsequent analyses.

Carotid doppler ultrasonography

Images of the common carotid artery (CCA) were obtained using Doppler ultrasound (ProSound α7, Aloka, Tokyo, Japan) and 7.5–10.0 mHz linear-array probe. CCA intima-media thickness (IMT) was assessed using a longitudinal view with both near wall and far wall lumen-IMT boundaries visible. Wall thickness was measured across a 5 mm region of interest via semi-automated digital calipers during systole and diastole (determined from ECG gating). The distance from the lumen-intima interface to the media-adventitia interface was measured as the IMT. CCA systolic and diastolic diameters were measured from inside the near-wall IMT to far-wall IMT. CCA mean blood velocities (Vm) were measured using Doppler-ultrasound and calculated as: $Vm = \int V(t)dt/FT$, where $\int V(t)dt$ is the velocity-time integral of the velocity waveform and FT is flow time. CCA flow and shear rate were calculated as $\pi \times (1/3 \text{ systolic radius} + 2/3 \text{ diastolic radius})^2 \times Vm \times 60$ and $4 \times (Vm/\text{systolic diameter})$, respectively. CCA mean circumferential wall tension was calculated as [mean arterial pressure x mean radius], where mean arterial pressure (MAP) is expressed in dyne·cm^2. CCA tensile wall stress was calculated by dividing circumferential wall tension by IMT where both mean radius and IMT are expressed in cm (Carallo et al., 1999) CCA pulsatility index (PI) was calculated with a semi-automated flow tracing software using the following equation: $(V_s–V_d)$/mean V, where V_s is the peak systolic velocity, V_d diastolic velocity and mean V the mean velocity. CCA flow resistance index (RI) was calculated as $(V_s–V_d)/V_s$.

Wave intensity analysis (WIA) combined with eTracking was used to derive forward and reflected wave intensity as measures related to pulsatile cerebrovascular burden and arterial stiffness in the carotid artery. WIA was performed simultaneously with carotid applanation tonometry on the contralateral artery. The distance from the near wall to far wall lumen-intima interface is continuously traced using eTracking software, creating a distension waveform almost identical to pressure waveforms (Van Bortel et al., 2001; Niki et al., 2002). WIA distension waveforms were calibrated against carotid systolic and diastolic pressures obtained via applanation tonometry described below. Flow waveforms were measured using range gated color Doppler signals averaged along the Doppler beam. An insonation angle $\leq$60° was maintained for all measures and sample volume was manually adjusted to encompass the entire vessel. At least 8 carotid waveforms were averaged to gain a representative average waveform. Wave intensity was calculated using time derivatives of blood pressure (P) and velocity (U), where wave intensity = $(dP/dt \times dU/dt)$; the area under the $dP/dt \times dU/dt$ curve represents the energy transfer of the wave (Sugawara et al., 2009b). W_1 represents a forward compression wave produced during early systole, accelerating flow and increasing pressure; 2 the negative area (NA) occurring immediately after W_1 is a backward travelling compression wave due to reflected waves from the periphery that decelerate flow but increase pressure. NA measured in the CCA has been suggesting as a measure of cerebrovascular tone (Bleasdale et al., 2003).

Arterial stiffness measures included beta stiffness index (β), and Peterson's pressure-strain elastic modulus (Ep) and were calculated as:

$$\beta = \ln(P_{Max}/P_{Min})/[(D_{Max} - D_{Min})/D_{Min}]$$

$$Ep = (P_{Max} - P_{Min})/[(D_{Max} - D_{Min})/D_{Min}]$$

where P and D correspond to pressure and diameter respectively, and Max and Min refer to maximum (systolic) and minimum (diastolic) values during the cardiac cycle. CCA characteristic impedance (Zc) was calculated by re-arranging the Water-Hammer equation as $Zc = (PWVx\rho)/A$, where ρ is blood density (assumed constant 1.055 kg/cm^3) and A is carotid area. A one-point pulse wave velocity (PWV) was derived from local wave speed (c) as $(\beta P/2\rho)^{1/2}$ (Harada et al., 2002; Hanya, 2013).

Carotid and aortic blood pressure waveform analysis

Pressure waveforms were obtained simultaneously in the contralateral CCA from a 10 s epoch and measured in duplicate using applanation tonometry (SphygmoCor, AtCor Medical, Syndey, Australia). CCA pressure waveforms were calibrated to brachial MAP and DBP. Additionally, aortic pressure waveforms were derived from radial pressure waveforms measured in duplicate (10 s epochs) and a generalized transfer function. Pulse pressure (PP) was calculated as SBP minus DBP. Augmentation index was calculated as the difference between the early- and late systolic peaks of the pressure waveforms to the total PP expressed as a percentage (P2-P1/PP × 100) and standardized to a heart rate of 75 beats per min (AIx75).

Wave separation analyses (WSA) were performed in order to obtain complimentary data to WIA and to gain further insight into origins of pressure pulsatility following acute RE. Pressure waveforms were separated into forward (Pf) and backwards/reflected (Pb) components. This technique uses a modified average-flow waveform based on the original flow triangulation method of Westerhof et al. and has been described previously in detail (Westerhof et al., 2006). Additionally, aortic pulse wave velocity (PWV) was estimated using the time lag between aortic Pf and Pb (Qasem and Avolio, 2008). Carotid-femoral distance was estimated by multiplying body height by 0.29 which may reduce measurement bias due to body disproportion that can occur with the standard tape measure method (Filipovsky et al., 2010).

Cerebral blood flow velocity

Middle cerebral artery (MCA) blood velocity was assessed using a 2-mHz transcranial Doppler (TCD) ultrasound probe (DWL Doppler Box-X, Compumedics, Germany) applied to the temporal window. Mean CBFv and pulsatility index were measured at a depth of 50–65 mm (Jung et al., 2012; Xu et al., 2012). The envelope of the velocity spectrum and mean velocity were calculated by a standard algorithm implemented on the instrument with use of a fast Fourier transform. MCA PI was calculated via an automated waveform tracking function using the same equation described for CCA PI. Cerebrovascular resistance index (CVRi) was calculated as MAP/V_{mean}.

STATISTICAL ANALYSES

All data is reported as mean ± standard error of the mean and statistical significance was established *a priori* as $p < 0.05$. Normality of distribution for variables was assessed qualitatively using histograms and Q-Q plots as well as quantitatively using the Shapiro-Wilk test. Data that were not normally distributed were log transformed to meet assumptions for parametric analyses. An analysis of variance with repeated measures (2 conditions × 4 time points) was used to analyze main outcome variables. *Post-hoc t*-tests were used to investigate significant interactions.

RESULTS

Participants' age, body mass index, and body fat were, 22 ± 1 years, 23.7 ± 0.5 kg·m^{-2} and 11.4 ± 0.9%, respectively. The average load for the 5-RM bench press and 10-RM biceps curl were 76 ± 4 and 32 ± 2 kg, respectively. Carotid and cerebral measures are displayed independently in **Tables 1–5**. There were significant group-by-time interactions for brachial and carotid SBP, DBP, and PP. *Post-hoc* analyses revealed brachial SBP significantly increased immediately following RE and remained elevated for all post-RE time points compared to baseline ($p < 0.05$; **Table 1**). Similarly, carotid SBP at post-1 was significantly different from baseline following RE ($p < 0.05$; **Table 1**). Carotid SBP at post-2 and post-3 did not differ from baseline for the RE condition ($p > 0.05$). DBP decreased post-exercise compared to baseline for all time points resulting in overall increases in PP ($p < 0.05$; **Table 1**). There was a significant interaction detected for heart rate, as it was significantly elevated following RE for the duration of post-testing compared to baseline ($p < 0.05$; **Table 1**). Changes in carotid PP are displayed in **Figure 1**.

There were no significant changes in CCA systolic or diastolic IMT (data not shown), CCA mean blood flow, or CCA PI following acute RE (**Table 2** and **Figure 2**). Both CCA Ep and β-stiffness significantly increased following RE, and remained significantly elevated throughout post-testing ($p < 0.05$; **Table 3**). Changes in β-stiffness are displayed in **Figure 3**. A condition-by-time interaction was detected for carotid W_1, which significantly increased post-RE and remained elevated throughout post-testing ($p < 0.05$; **Table 3**). Carotid AIx75 was not significantly altered by acute RE ($p > 0.05$). NA was not normally distributed and was log transformed to meet assumptions for parametric statistical analyses. There were no statistically significant changes in carotid lnNA ($p > 0.05$). WSA could not be performed for 6 participants as reflection time was outside of the measurement device's acceptable range (<50 ms) for calculations. Data for the remaining 12 are reported herein. Carotid Pf had a significant condition-by-time interaction; *post-hoc* testing revealed Pf significantly increased following RE, remaining elevated through post-3 ($p < 0.05$; **Table 3**). There were no statistically significant changes in carotid Pb ($p > 0.05$).

There was a significant interaction for aortic AIx75 ($p < 0.05$) and a trend for an interaction for aortic stiffness as values were elevated following acute RE but not following the time control ($p = 0.08$; **Table 4**). There was no significant change in aortic Pf or Pb following acute RE ($p > 0.05$). A significant condition-by-time interaction was detected for aortic time to Pb, indicative of faster wave reflection speed. Values significantly decreased post-RE compared to baseline and remained different through post-3 ($p < 0.05$). Mean MCA CBFv, MCA PI (**Figure 4**), and MCA CVRi did not differ across time or between conditions ($p > 0.05$, **Table 5**).

Table 1 | Common carotid artery (CCA) and brachial pressures across testing time points between control and resistance exercise ($n = 18$).

Variable	Condition	Baseline	Post-1	Post-2	Post-3	Interaction
Brachial SBP (mmHg)	Control	122 ± 1	121 ± 2	117 ± 2	119 ± 2	0.009
	RE	122 ± 1	131 ± 3[a,b]	126 ± 2	125 ± 2	
Brachial DBP (mmHg)	Control	74 ± 1	73 ± 1	71 ± 1[a]	73 ± 1	0.002
	RE	73 ± 1	65 ± 1[a,b]	65 ± 2[a,b]	66 ± 1[a,b]	
Brachial MAP (mmHg)	Control	90 ± 1	89 ± 1	86 ± 1	88 ± 1	0.220
	RE	89 ± 1	87 ± 1	85 ± 1	85 ± 1	
Brachial PP (mmHg)	Control	48 ± 1	48 ± 2	46 ± 2	46 ± 2	<0.001
	RE	49 ± 2	66 ± 3[a,b]	61 ± 2[a,b]	59 ± 2[a,b]	
CCA SBP (mmHg)	Control	115 ± 2	114 ± 2	110 ± 2	111 ± 2	0.043
	RE	116 ± 2	123 ± 3[a,b]	119 ± 3	120 ± 3	
CCA DBP (mmHg)	Control	73 ± 1	73 ± 1	70 ± 1[a]	72 ± 1	<0.001
	RE	73 ± 1	65 ± 1[a,b]	66 ± 2[a,b]	66 ± 1[a,b]	
CCA PP (mmHg)	Control	42 ± 2	40 ± 2	40 ± 2	40 ± 2	<0.001
	RE	43 ± 2	58 ± 4[a,b]	53 ± 3[a,b]	54 ± 3[a,b]	
Heart rate ($b \cdot min^{-1}$)	Control	60 ± 2	58 ± 2[a]	60 ± 3	58 ± 2[a]	<0.001
	RE	64 ± 3	86 ± 4[a,b]	82 ± 4[a,b]	79 ± 3[a,b]	

[a] *Significantly different from within-condition baseline, $p < 0.05$.*

[b] *Significantly different from other condition, same time point, $p < 0.05$.*

Table 2 | Common carotid dimensions/hemodynamics across testing time points between control and resistance exercise ($n = 18$).

Variable	Condition	Baseline	Post-1	Post-2	Post-3	Interaction
Mean diameter (mm)	Control	5.54 ± 0.09	5.55 ± 0.11	5.57 ± 0.10	5.69 ± 0.10	0.539
	RE	5.48 ± 0.11	5.35 ± 0.11	5.51 ± 0.11	5.54 ± 0.09	
Blood flow ($mL \cdot s^{-1}$)	Control	612.5 ± 21.3	656.6 ± 36.4	616.7 ± 20.8	626.3 ± 29.7	0.255
	RE	635.0 ± 27.6	664.8 ± 35.4	700.3 ± 28.8	672.5 ± 26.7	
Shear rate (sec^{-1})	Control	279.1 ± 13.1	293.7 ± 17.5	275.9 ± 14.2	259.3 ± 9.6	0.105
	RE	296.9 ± 12.7	339.9 ± 16.7	336.2 ± 15.9	305.76 ± 10.9	
Mean circumferential wall tension ($dynes \cdot cm^{-1}$)	Control	3.4 ± 0.1	3.4 ± 0.1	3.3 ± 0.1	3.4 ± 0.1	0.287
	RE	3.3 ± 0.1	3.2 ± 0.1	3.2 ± 0.1	3.2 ± 0.1	
Mean tensile stress (10^4 $dynes \cdot cm^{-1}$)	Control	89.5 ± 2.9	92.2 ± 2.7	84.0 ± 2.9	91.4 ± 3.8	0.157
	RE	87.5 ± 3.2	81.2 ± 3.8	78.9 ± 3.1	81.5 ± 3.2	
Resistance Index	Control	0.77 ± 0.01	0.77 ± 0.01	0.76 ± 0.01	0.76 ± 0.01	0.013
	RE	0.76 ± 0.01	0.80 ± 0.01[a,b]	0.78 ± 0.01	0.78 ± 0.01	
Pulsatility Index	Control	2.07 ± 0.08	2.10 ± 0.08	2.06 ± 0.10	2.11 ± 0.09	0.094
	RE	2.01 ± 0.09	2.16 ± 0.08	1.95 ± 0.05	2.02 ± 0.06	

[a] *Significantly different from within-condition Baseline, $p < 0.05$.*

[b] *Significantly different from other condition, same time point, $p < 0.05$.*

DISCUSSION

The novel finding of the present study was that while acute RE does increase carotid artery stiffness and pressure pulsatility, acute RE may not affect carotid or cerebral flow pulsatility. Moreover, using novel methods of hemodynamic appraisal (WIA and WSA) we provide unique insight into the origin of increased pressure pulsatility after acute RE; increased pressure pulsatility in the carotid artery is likely due to increased forward wave

Table 3 | Measures of common carotid wave reflection/stiffness across testing time points between control and resistance exercise ($n = 18$).

Variable	Condition	Baseline	Post-1	Post-2	Post-3	Interaction
β stiffness (AU)	Control	3.94 ± 0.37	3.63 ± 0.27	3.80 ± 0.24	3.53 ± 0.21	0.025
	RE	3.86 ± 0.35	5.30 ± 0.35[a,b]	4.82 ± 0.38[a,b]	5.00 ± 0.33[a,b]	
Ep (kPa)	Control	48.72 ± 4.76	44.28 ± 3.24	44.89 ± 3.03	42.06 ± 2.28	0.032
	RE	47.22 ± 4.11	64.78 ± 4.61[a,b]	56.33 ± 4.26[a,b]	59.78 ± 4.15[a,b]	
Zc (DSC)	Control	1846 ± 103	1796 ± 90	1777 ± 70	1649 ± 45	0.094
	RE	1868 ± 89	2215 ± 100	1959 ± 87	1977 ± 68	
W_1 (mmHg·m·sec^{-3})	Control	9.39 ± 0.84	10.65 ± 1.25	9.66 ± 1.24	9.13 ± 0.80	0.015
	RE	9.31 ± 0.97	16.61 ± 2.04[a,b]	13.51 ± 1.45[a,b]	11.71 ± 1.31[a]	
lnNA (mmHg·m·s^{-2})	Control	3.25 ± 0.45	3.58 ± 0.30	3.47 ± 0.23	3.27 ± 0.28	0.160
	RE	3.85 ± 0.35	4.89 ± 0.47	4.22± 0.42	3.22 ± 0.47	
AIx75 (%)	Control	−25 ± 2	−26 ± 3	−27 ± 3	−27 ± 3	0.945
	RE	−29 ± 3	−30 ± 3	−31 ± 2	−31 ± 3	
WAVE SEPARATION ($n = 12$)						
Pf (mmHg)	Control	40 ± 2	38 ± 3	44 ± 5	39 ± 2	<0.001
	RE	41 ± 3	58 ± 4[a,b]	47 ± 3[a,b]	49 ± 4[a,b]	
Pb (mmHg)	Control	16 ± 1	15 ± 1	15 ± 1	16 ± 1	0.649
	RE	15 ± 1	16 ± 1	14 ± 1	16 ± 1	

[a] *Significantly different from within-condition BL, $p < 0.05$.*

[b] *Significantly different from other condition, same time point, $p < 0.05$.*

AIx75, augmentation index at a heart rate of 75 bpm; NA, negative area; Pf, forward pressure; Pb, backwards pressure, DSC, dynes x s/cm^5.

Table 4 | Measures of aortic wave reflection/stiffness across testing time points between control and resistance exercise ($n = 12$).

Variable	Condition	Baseline	Post-1	Post-2	Post-3	Interaction
PWV (m·s^{-1})	Control	7.4 ± 0.2	7.4 ± 0.2	7.3 ± 0.2	7.1 ± 0.2	0.080
	RE	7.1 ± 0.1	8.1 ± 0.2	7.6 ± 0.1	7.3 ± 0.1	
Pf (mmHg)	Control	32 ± 1	34 ± 2	34 ± 2	36 ± 3	0.867
	RE	35 ± 2	35 ± 3	38 ± 3	40 ± 2	
Pb (mmHg)	Control	13 ± 1	14 ± 1	14 ± 1	13 ± 1	0.249
	RE	12 ± 1	15 ± 1	13 ± 1	13 ± 1	
Time to Pb (ms)	Control	284 ± 14	276 ± 11	278 ± 15	286 ± 15	0.040
	RE	272 ± 8	249 ± 5[a,b]	246 ± 4[a,b]	246 ± 5[a,b]	
AIx75	Control	−11 ± 3	−8 ± 4	−13 ± 4	−11 ± 3	0.013
	RE	−9 ± 2	7 ± 4	1 ± 3[a,b]	−3 ± 3[a,b]	

[a] *significantly different from within-condition BL, $p < 0.05$.*

[b] *significantly different from other condition, same time point, $p < 0.05$.*

AIx75, augmentation index at a heart rate of 75 bpm; PWV, pulse wave velocity; Pf, forward pressure; Pb, backwards pressure.

pressure (Pf and W_1) and not pressure from wave reflections (Pb or NA).

Studies examining cerebrovascular responses to RE have traditionally focused on the steady component of pressure-flow relationships during and immediately after (<60 s) RE and whether changes in mean arterial pressure alter cerebral autoregulation (Edwards et al., 2002; Pott et al., 2003; Koch et al., 2005). The current study was designed to investigate changes in *pulsatile* hemodynamics (not the steady component or mean flow) during previously established times of elevated arterial stiffness following RE. The steady and pulsatile components of pressure/flow each differentially associate with cerebral structure and function

Table 5 | Cerebral variables across testing time points between control and resistance exercise ($n = 18$).

Variable	Condition	Baseline	Post-1	Post-2	Post-3	Interaction
Mean velocity ($cm \cdot s^{-1}$)	Control	56 ± 5	56 ± 4	56 ± 4	56 ± 5	0.491
	RE	57 ± 4	54 ± 4	55 ± 4	55 ± 4	
Pulsatility index	Control	0.85 ± 0.03	0.85 ± 0.04	0.86 ± 0.03	0.84 ± 0.04	0.325
	RE	0.87 ± 0.03	0.89 ± 0.03	0.84 ± 0.03	0.83 ± 0.03	
Resistance index ($mmHg^{-1} \cdot cm \cdot s^{-1}$)	Control	1.79 ± 0.13	1.71 ± 0.12	1.68 ± 0.12	1.74 ± 0.12	0.162
	RE	1.67 ± 0.11	1.76 ± 0.13	1.65 ± 0.10	1.72 ± 0.13	

(Mitchell et al., 2011). Many studies note no associations between mean cerebrovascular inflow and cerebral structure/function (Bateman, 2002; Patankar et al., 2006; Henry-Feugeas et al., 2009; Jolly et al., 2013). Conversely, pulsatile flow has been shown to more consistently associate with cerebrovascular damage (Mitchell et al., 2011; Webb et al., 2012; Jolly et al., 2013).

In the present study, despite substantial increases in carotid stiffness for upwards of 30-min after acute RE, there were minimal change in CBFv pulsatility. Carotid artery stiffness increased following RE, reinforcing previous observations regarding the acute effects of RE on central artery stiffness (DeVan et al., 2005; Heffernan et al., 2007b; Fahs et al., 2009; Collier et al., 2010; Yoon et al., 2010). Increased arterial stiffness has previously been linked to pulsatile *flow* in the cerebrovascular bed (Xu et al., 2012), higher white matter hyperintensities, lower executive function, and increased risk for subcortical infarcts (Mitchell, 2008) separate from the effects of pressure pulsatility. In the current study, RE-induced increases in arterial stiffness did not alter measures of CCA or MCA flow pulsatility. Thus physiological changes in arterial stiffness measured 10–30 min after acute RE may not alter cerebral flow profiles as occurs inherently/chronically with aging or in pathological settings.

Arterial stiffness has also been associated with pulsatile *pressure* (Tarumi et al., 2011) and in turn impaired cerebrovascular function (Kwater et al., 2009; Webb et al., 2012). In the present study there were increases in carotid pressure pulsatility evidenced by a significant increase in carotid PP post-RE. The blood pressure waveform is an amalgam of forward and backward travelling waves. Left ventricular ejection instigates the genesis of forward travelling pressure waves. These pressure waves may be partially reflected from peripheral vessels with the timing and magnitude of this reflection affected by several hemodynamic factors including arterial stiffness, peripheral vascular tone, and physical distance to the peripheral reflection sites. Using two different novel yet complementary methods of assessing carotid hemodynamics (WIA and WSA), the present study noted that increased pressure pulsatility in the CCA was largely driven by an increase in forward wave pressure (increases in Pf and W_1) as there were no statistically significant changes in pressure from wave reflections (Pb or NA). This is consistent with recent findings from Schultz et al. noting that increases in central pressure during exercise are largely mediated by increases in forward wave pressure and not pressure from wave reflections (Schultz et al., 2013). It should be underscored that changes in central hemodynamics following acute RE may not be completely devoid of risk. Clinical consequences of increased forward wave pressure and subsequent pulsatile pressure transmission to the cerebrovascular bed following acute RE require further scrutiny.

Wave reflections detected in the CCA have been shown to be related to altered cerebrovascular tone (Bleasdale et al., 2003; Curtis et al., 2007). Increases in cerebral resistance affect the timing and magnitude of pressure waves being reflected from the head (cerebral circulation) (Bleasdale et al., 2003; Curtis et al., 2007). In general, resistance in the cereobrovascular bed is low allowing for possible transmission of damaging pulsatile energy to penetrate deeply into the intracranial cavity. An increase in cerebrovascular tone would increase pressure from wave reflections (from the brain to the carotid) and might serve to protect against entry of pulsatile energy into the delicate cerebral capillary bed. An increase in wave reflections from the cerebral vasculature would be expected to increase carotid pressure but attenuate flow (Kohara et al., 1999; Curtis et al., 2007). In the current study, there were no statistically significant changes in carotid NA or Pb (measures of wave reflections) and this mirrored the lack of change seen in carotid and cerebral flow measures. Thus despite large increases in forward wave *pressure* and overall *pressure* pulsatility, RE and/or RE-induced stiffness may not alter cerebrovascular *flow* pulsatility at the time points investigated. In young healthy adults, cerebrovascular flow pulsatility may be dampened via other mechanisms.

Our data offer insight into flow pulsatility buffering following acute RE and suggest that some may occur at the level of the CCA. It has been suggested that as much as a quarter to half of cerebrovascular resistance may be determined at the level of the carotid arteries (Willie et al., 2014). In the present study, the modest increases in CCA Zc after acute RE were associated with reduced CCA PI ($r = -0.61$, $p < 0.05$). Eighty percent of CCA blood flow at rest feeds the internal carotid artery with subsequent branching giving way to the MCA that in turn supplies approximately 80% of the blood supply to the brain (Farkas and Luiten, 2001). Compared to the external carotid artery (ECA), the internal carotid artery (ICA) is a lower resistance/impedance vessel with a lower reflection coefficient (Taylor and Tukmachi, 1985) favoring a flow differential at rest. The input impedance of the CCA is thus largely determined by the ECA; parenthetically, the CCA flow pattern approximates that of the lower impedance ICA rather than the ECA (Taylor and Tukmachi, 1985). Owing to the intracranial anastomoses through the orbit, ICA occlusion

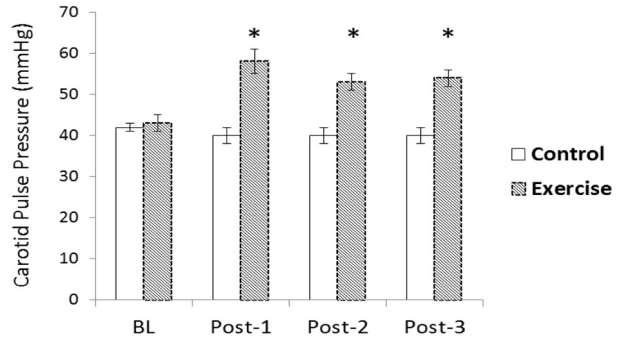


FIGURE 1 | Change in carotid pulse pressure (PP) following acute resistance exercise (RE) vs. a time control condition. A significant condition-by-time interaction was detected for carotid PP ($p < 0.05$). Carotid PP was elevated 10, 20, and 30-min after exercise compared to baseline ($p < 0.05$)*.

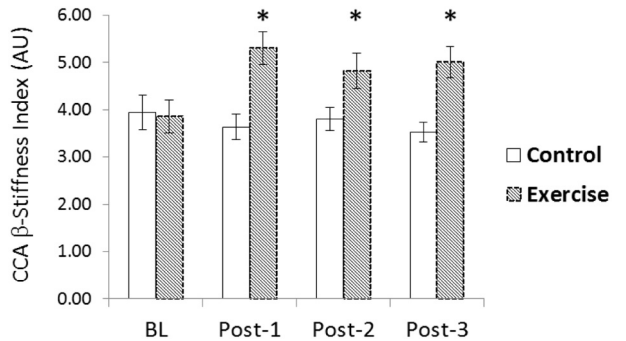


FIGURE 3 | Change in common carotid artery (CCA) β-stiffness index following acute resistance exercise (RE) vs. a time control condition. A significant condition-by-time interaction was detected for (CCA) β-stiffness index ($p < 0.05$). β-stiffness index was elevated 10, 20, and 30-min after exercise compared to baseline ($p < 0.05$)*.

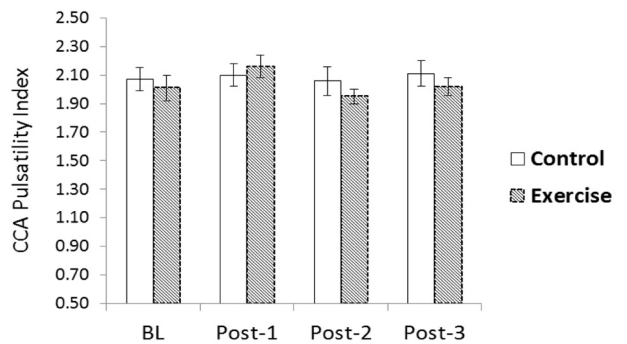


FIGURE 2 | Common carotid artery (CCA) blood flow velocity pulsatility index (PI) following acute resistance exercise (RE) vs. a time control condition. No significant changes were noted ($p > 0.05$).

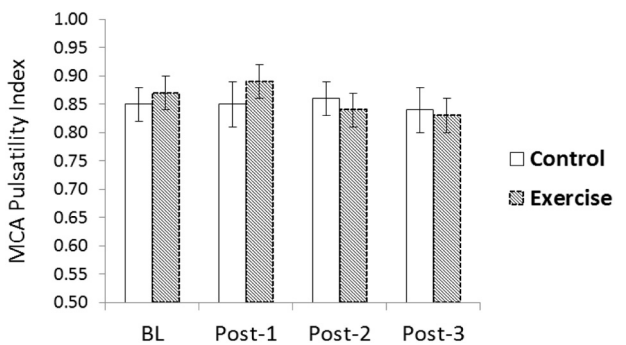


FIGURE 4 | Middle cerebral artery (MCA) blood flow velocity pulsatility index (PI) following acute resistance exercise (RE) vs. a time control condition. No significant changes were noted ($p > 0.05$).

results in flow redistribution to the ipsilateral ECA and a change in the ECA flow profile to match that of a typical ICA/CCA contour (Taylor and Tukmachi, 1985). During exercise, it has been shown that there is an increase in ECA flow relative to the ICA for thermoregulatory purposes (Sato et al., 2011). Taken together and these observations suggest that changes in CCA/ICA/ECA impedance matching during/following exercise may affect pulsatile flow transmission at these crucial interfaces.

Some buffering of hemodynamic pulsatility may also occur at the carotid-aortic interface (Mitchell et al., 2011). We noted disparate changes in carotid and aortic hemodynamics following acute RE. While there was no change in carotid AIx, there was a significant increase in aortic AIx following acute RE (Yoon et al., 2010). Increases in aortic AIx were due to changes in timing of wave reflection travel likely from an increase in aortic PWV and not changes in magnitude as there were minimal changes in aortic Pb. Arterial stiffness and pressure from wave reflections have been shown to affect retrograde flow in the femoral/aorta (Hashimoto and Ito, 2010; Heffernan et al., 2013) which has been linked to flow in the CCA (Hashimoto and Ito, 2013). There were also disparate changes in forward wave pressure (Pf) between CCA and aorta. Thus, alterations in impedance matching at the carotid-aorta interface may also affect CCA pressure and flow pulsaility following acute RE. An additional alternative mechanism for buffering of flow pulsatility to the MCA may reside in the geometry of the ICA. The carotid siphon describes the tortuous distal part of the internal carotid artery that may bend beyond 180° with minimal inter-individual variability (Schubert et al., 2011). This shape has been shown to enhance pulsatile energy dispersion and markedly attenuate flow pulsatility *in vivo* (Schubert et al., 2011). Finally, it is also possible that some hemodynamic buffering occurs within the intracranial vessels via their capacitance properties. The cerebral Windkessel may extinguish pulsatilite hemodynamic energy via matching cerebrospinal fluid ejection to venous flow volume out of the intracranial cavity (Chan et al., 2011).

Elevations in HR after acute RE support previous studies noting increases in sympathetic nervous system (SNS) activity during recovery from this exercise modality (Heffernan et al., 2006). The role of the SNS in modulating cerebral hemodynamics in humans remains conflicting (Willie et al., 2014). While select studies suggest an important role for the SNS in affecting mean flow

patterns and autoregulation in cerebral vessels, studies directly examining associations between the SNS and cerebrovascular flow pulsatility are lacking. The effect of SNS activity on carotid artery mechanical properties in humans are also conflicting with some studies suggesting a link (Sugawara et al., 2009a; Liu et al., 2011) and others noting no association (Kosch et al., 2002). It is possible that increases in sympathetic activation following acute RE contribute to increases in CCA stiffness/impedance while concomitantly preventing forced dilation of the cerebral arterioles; both of which may prevent regional over-perfusion and protect against blood-brain barrier breakdown from transmission of excessive pressure/flow fluctuations (Ogoh and Ainslie, 2009).

MCA PI is elevated immediately (within 2-min) after acute RE (Koch et al., 2005) thus it is possible an important window for data acquisition was missed. We intentionally chose not to assess vascular properties during this time point as marked changes in MAP, HR and ventilation with subsequent changes in CO_2 could confound interpretation of findings (Wilkinson et al., 2002; Romero and Cooke, 2007). Of central importance for the present study and in accordance with previously published studies (DeVan et al., 2005) CCA stiffness was elevated at all time-points assessed. Despite these changes in CCA stiffness, there was no change in CCA or MCA flow pulsatility at these time points reinforcing our conclusion that acute RE-mediated increases in arterial stiffness may not detrimentally impact cerebrovascular flow pulsatility. Future research is needed to explore central hemodynamic and cerebrovascular changes during earlier time points following acute RE.

LIMITATIONS

Additional limitations to this study should be noted. This study utilized healthy young men. Results may not be directly applicable to women, older adults or other clinical populations. TCD cannot measure blood flow *per se* since diameter is not measured. Although previous research has suggested that the diameter of large cerebral vessels do not change across different physiological stimuli (Stroobant and Vingerhoets, 2000), this has never been demonstrated empirically following acute exercise. The WSA method used in this study was not completed on 6 participants due to wave reflection times occurring outside of the analysis software's acceptable range (reflection times <50 ms). This occurred most notably after acute RE. It is possible that RE-induced tachycardia and the concomitant decrease in ejection duration changed wave reflection timing such that reflected waves arrived during early systole. Despite incomplete results using this technique, values obtained from the subset of participants with complete CCA WSA data confirmed findings from CCA WIA. Finally, it must be noted that cerebral autoregulation was not measured as it was not the purpose of this investigation. Cerebrovascular regulation is preserved following acute aerobic exercise (Willie et al., 2013). Future research is needed to explore associations between CCA stiffness and cerebral autoregulation during/following various physiologic stressors including resistance exercise.

CONCLUSION

Acute RE increases carotid artery stiffness and pressure pulsatility without affecting cerebral flow pulsatility. RE-induced increases in carotid pressure pulsatility may be due to increases in forward wave pressure and not pressure from wave reflections.

ACKNOWLEDGMENTS

No external funding was provided for this study. We thank all participants for the generous giving of their time and arteries.

REFERENCES

Bateman, G. A. (2002). Pulse-wave encephalopathy: a comparative study of the hydrodynamics of leukoaraiosis and normal-pressure hydrocephalus. *Neuroradiology* 44, 740–748. doi: 10.1007/s00234-002-0812-0

Bleasdale, R. A., Mumford, C. E., Campbell, R. I., Fraser, A. G., Jones, C. J., and Frenneaux, M. P. (2003). Wave intensity analysis from the common carotid artery: a new noninvasive index of cerebral vasomotor tone. *Heart Vessels* 18, 202–206. doi: 10.1007/s00380-003-0711-2

Carallo, C., Irace, C., Pujia, A., De Franceschi, M. S., Crescenzo, A., Motti, C., et al. (1999). Evaluation of common carotid hemodynamic forces. Relations with wall thickening. *Hypertension* 34, 217–221. doi: 10.1161/01.HYP.34.2.217

Chan, G. S., Ainslie, P. N., Willie, C. K., Taylor, C. E., Atkinson, G., Jones, H., et al. (2011). Contribution of arterial Windkessel in low-frequency cerebral hemodynamics during transient changes in blood pressure. *J. Appl. Physiol. (1985)* 110, 917–925. doi: 10.1152/japplphysiol.01407.2010

Collier, S. R., Diggle, M. D., Heffernan, K. S., Kelly, E. E., Tobin, M. M., and Fernhall, B. (2010). Changes in arterial distensibility and flow-mediated dilation after acute resistance vs. *aerobic exercise. J. Strength Cond. Res.* 24, 2846–2852. doi: 10.1519/JSC.0b013e3181e840e0

Curtis, S. L., Zambanini, A., Mayet, J., McG Thom, S. A., Foale, R., Parker, K. H., et al. (2007). Reduced systolic wave generation and increased peripheral wave reflection in chronic heart failure. *Am. J. Physiol. Heart Circ. Physiol.* 293, H557–H562. doi: 10.1152/ajpheart.01095.2006

DeVan, A. E., Anton, M. M., Cook, J. N., Neidre, D. B., Cortez-Cooper, M. Y., and Tanaka, H. (2005). Acute effects of resistance exercise on arterial compliance. *J. Appl. Physiol.* 98, 2287–2291. doi: 10.1152/japplphysiol.00002.2005

Edwards, M. R., Martin, D. H., and Hughson, R. L. (2002). Cerebral hemodynamics and resistance exercise. *Med. Sci. Sports Exerc.* 34, 1207–1211. doi: 10.1097/00005768-200207000-00024

Fahs, C. A., Heffernan, K. S., and Fernhall, B. (2009). Hemodynamic and vascular response to resistance exercise with L-arginine. *Med. Sci. Sports Exerc.* 41, 773–779. doi: 10.1249/MSS.0b013e3181909d9d

Farkas, E., and Luiten, P. G. (2001). Cerebral microvascular pathology in aging and Alzheimer's disease. *Prog. Neurobiol.* 64, 575–611. doi: 10.1016/S0301-0082(00)00068-X

Filipovsky, J., Mayer, O., Dolejsova, M., and Seidlerova, J. (2010). The assessment of carotid–femoral distance for aortic pulse wave velocity: should it be estimated from body height? *Artery Res.* 4, 19–23. doi: 10.1016/j.artres.2010.01.002

Hanya, S. (2013). Validity of the water hammer formula for determining regional aortic pulse wave velocity: comparison of one-point and two-point (Foot-to-Foot) measurements using a multisensor catheter in human. *Ann. Vasc. Dis.* 6, 150–158. doi: 10.3400/avd.oa.13-00046

Harada, A., Okada, T., Niki, K., Chang, D., and Sugawara, M. (2002). On-line noninvasive one-point measurements of pulse wave velocity. *Heart Vessels* 17, 61–68. doi: 10.1007/s003800200045

Hashimoto, J., and Ito, S. (2010). Pulse pressure amplification, arterial stiffness, and peripheral wave reflection determine pulsatile flow waveform of the femoral artery. *Hypertension* 56, 926–933. doi: 10.1161/HYPERTENSIONAHA.110.159368

Hashimoto, J., and Ito, S. (2013). Aortic stiffness determines diastolic blood flow reversal in the descending thoracic aorta: potential implication for retrograde embolic stroke in hypertension. *Hypertension* 62, 542–549. doi: 10.1161/HYPERTENSIONAHA.113.01318

Heffernan, K. S., Collier, S. R., Kelly, E. E., Jae, S. Y., and Fernhall, B. (2007a). Arterial stiffness and baroreflex sensitivity following bouts of aerobic and resistance exercise. *Int. J. Sports Med.* 28, 197–203. doi: 10.1055/s-2006-924290

Heffernan, K. S., Jae, S. Y., Echols, G. H., Lepine, N. R., and Fernhall, B. (2007b). Arterial stiffness and wave reflection following exercise in resistance-trained men. *Med. Sci. Sports Exerc.* 39, 842–848. doi: 10.1249/mss.0b013e318031b03c

Heffernan, K. S., Kelly, E. E., Collier, S. R., and Fernhall, B. (2006). Cardiac autonomic modulation during recovery from acute endurance vs. resistance exercise. *Eur. J. Cardiovasc. Prev. Rehabil.* 13, 80–86. doi: 10.1097/01.hjr.0000197470.74070.46

Heffernan, K. S., Lefferts, W. K., Kasprowicz, A. G., Tarzia, B. J., Thijssen, D. H., and Brutsaert, T. D. (2013). Manipulation of arterial stiffness, wave reflections, and retrograde shear rate in the femoral artery using lower limb external compression. *Physiol. Rep.* 1, e00022. doi: 10.1002/phy2.22

Henry-Feugeas, M. C., Roy, C., Baron, G., and Schouman-Claeys, E. (2009). Leukoaraiosis and pulse-wave encephalopathy: observations with phase-contrast MRI in mild cognitive impairment. *J. Neuroradiol.* 36, 212–218. doi: 10.1016/j.neurad.2009.01.003

Jolly, T. A., Bateman, G. A., Levi, C. R., Parsons, M. W., Michie, P. T., and Karayanidis, F. (2013). Early detection of microstructural white matter changes associated with arterial pulsatility. *Front. Hum. Neurosci.* 7:782. doi: 10.3389/fnhum.2013.00782

Jung, J., Kang, H., Shim, S., Cho, K., and Yu, J. (2012). Effects of resistive exercise on cerebral blood flow velocity and pulsatility index of healthy people. *J. Phys. Ther. Sci.* 24, 915–917. doi: 10.1589/jpts.24.915

Katsi, V., Vlachopoulos, C., Souretis, G., Baou, K., Dagalaki, I., Alexopoulos, N., et al. (2012). Association between retinal microcirculation and aortic stiffness in hypertensive patients. *Int. J. Cardiol.* 157, 370–373. doi: 10.1016/j.ijcard.2010.12.074

Koch, A., Ivers, M., Gehrt, A., Schnoor, P., Rump, A., and Rieckert, H. (2005). Cerebral autoregulation is temporarily disturbed in the early recovery phase after dynamic resistance exercise. *Clin. Auton. Res.* 15, 83–91. doi: 10.1007/s10286-005-0249-8

Kohara, K., Jiang, Y., Igase, M., and Hiwada, K. (1999). Effect of reflection of arterial pressure on carotid circulation in essential hypertension. *Am. J. Hypertens.* 12, 1015–1020. doi: 10.1016/S0895-7061(99)00091-6

Kosch, M., Barenbrock, M., Kisters, K., Rahn, K. H., and Hausberg, M. (2002). Relationship between muscle sympathetic nerve activity and large artery mechanical vessel wall properties in renal transplant patients. *J. Hypertens.* 20, 501–508. doi: 10.1097/00004872-200203000-00026

Kwater, A., Gasowski, J., Gryglewska, B., Wizner, B., and Grodzicki, T. (2009). Is blood flow in the middle cerebral artery determined by systemic arterial stiffness? *Blood Press.* 18, 130–134. doi: 10.1080/08037050902975114

Liu, J., Cao, T. S., Duan, Y. Y., Yang, Y. L., and Yuan, L. J. (2011). Effects of cold pressor-induced sympathetic stimulation on the mechanical properties of common carotid and femoral arteries in healthy males. *Heart Vessels* 26, 214–221. doi: 10.1007/s00380-010-0069-1

Mitchell, G. F. (2008). Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J. Appl. Physiol.* 105, 1652–1660. doi: 10.1152/japplphysiol.90549.2008

Mitchell, G. F., Hwang, S. J., Vasan, R. S., Larson, M. G., Pencina, M. J., Hamburg, N. M., et al. (2010). Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 121, 505–511. doi: 10.1161/CIRCULATIONAHA.109.886655

Mitchell, G. F., van Buchem, M. A., Sigurdsson, S., Gotal, J. D., Jonsdottir, M. K., Kjartansson, O., et al. (2011). Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility–Reykjavik study. *Brain* 134, 3398–3407. doi: 10.1093/brain/awr253

Mitchell, G. F., Vita, J. A., Larson, M. G., Parise, H., Keyes, M. J., Warner, E., et al. (2005). Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness: the Framingham Heart Study. *Circulation* 112, 3722–3728. doi: 10.1161/CIRCULATIONAHA.105.551168

Miyachi, M. (2013). Effects of resistance training on arterial stiffness: a meta-analysis. *Br. J. Sports Med.* 47, 393–396. doi: 10.1136/bjsports-2012-090488

Miyachi, M., Kawano, H., Sugawara, J., Takahashi, K., Hayashi, K., Yamazaki, K., et al. (2004). Unfavorable effects of resistance training on central arterial compliance: a randomized intervention study. *Circulation* 110, 2858–2863. doi: 10.1161/01.CIR.0000146380.08401.99

Niki, K., Sugawara, M., Chang, D., Harada, A., Okada, T., Sakai, R., et al. (2002). A new noninvasive measurement system for wave intensity: evaluation of carotid arterial wave intensity and reproducibility. *Heart Vessels* 17, 12–21. doi: 10.1007/s003800200037

Ogoh, S., and Ainslie, P. N. (2009). Cerebral blood flow during exercise: mechanisms of regulation. *J. Appl. Physiol. (1985)* 107, 1370–1380. doi: 10.1152/japplphysiol.00573.2009

Patankar, T., Widjaja, E., Chant, H., McCollum, C., Baldwin, R., Jeffries, S., et al. (2006). Relationship of deep white matter hyperintensities and cerebral blood flow in severe carotid artery stenosis. *Eur. J. Neurol.* 130, 10–16. doi: 10.1111/j.1468-1331.2006.01115.x

Pollock, M. L., Franklin, B. A., Balady, G. J., Chaitman, B. L., Fleg, J. L., Fletcher, B., et al. (2000). AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: an advisory from the committee on exercise, rehabilitation, and prevention, council on clinical cardiology, american heart association; position paper endorsed by the american college of sports medicine. *Circulation* 101, 828–833. doi: 10.1161/01.CIR.101.7.828

Pott, F., Van Lieshout, J. J., Ide, K., Madsen, P., and Secher, N. H. (2003). Middle cerebral artery blood velocity during intense static exercise is dominated by a Valsalva maneuver. *J. Appl. Physiol.* 94, 1335–1344. doi: 10.1152/japplphysiol.00457.2002

Qasem, A., and Avolio, A. (2008). Determination of aortic pulse wave velocity from waveform decomposition of the central aortic pressure pulse. *Hypertension* 51, 188–195. doi: 10.1161/HYPERTENSIONAHA.107.092676

Romero, S. A., and Cooke, W. H. (2007). Hyperventilation before resistance exercise: cerebral hemodynamics and orthostasis. *Med. Sci. Sports Exerc.* 39, 1302–1307. doi: 10.1249/mss.0b013e3180653636

Safar, M. E., Nilsson, P. M., Blacher, J., and Mimran, A. (2012). Pulse pressure, arterial stiffness, and end-organ damage. *Curr. Hypertens. Rep.* 14, 339–344. doi: 10.1007/s11906-012-0272-9

Sato, K., Ogoh, S., Hirasawa, A., Oue, A., and Sadamoto, T. (2011). The distribution of blood flow in the carotid and vertebral arteries during dynamic exercise in humans. *J. Physiol.* 589, 2847–2856. doi: 10.1113/jphysiol.2010.204461

Schubert, T., Santini, F., Stalder, A. F., Bock, J., Meckel, S., Bonati, L., et al. (2011). Dampening of blood-flow pulsatility along the carotid siphon: does form follow function? *AJNR Am. J. Neuroradiol.* 32, 1107–1112. doi: 10.3174/ajnr.A2426

Schultz, M. G., Davies, J. E., Roberts-Thomson, P., Black, J. A., Hughes, A. D., and Sharman, J. E. (2013). Exercise central (aortic) blood pressure is predominantly driven by forward traveling waves, not wave reflection. *Hypertension* 62, 175–182. doi: 10.1161/HYPERTENSIONAHA.111.00584

Stroobant, N., and Vingerhoets, G. (2000). Transcranial Doppler ultrasonography monitoring of cerebral hemodynamics during performance of cognitive tasks: a review. *Neuropsychol. Rev.* 10, 213–231. doi: 10.1023/A:1026412811036

Sugawara, J., Komine, H., Hayashi, K., Yoshizawa, M., Otsuki, T., Shimojo, N., et al. (2009a). Reduction in alpha-adrenergic receptor-mediated vascular tone contributes to improved arterial compliance with endurance training. *Int. J. Cardiol.* 135, 346–352. doi: 10.1016/j.ijcard.2008.04.007

Sugawara, M., Niki, K., Ohte, N., Okada, T., and Harada, A. (2009b). Clinical usefulness of wave intensity analysis. *Med. Biol. Eng. Comput.* 47, 197–206. doi: 10.1007/s11517-008-0388-x

Sutton-Tyrrell, K., Najjar, S. S., Boudreau, R. M., Venkitachalam, L., Kupelian, V., Simonsick, E. M., et al. (2005). Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation* 111, 3384–3390. doi: 10.1161/CIRCULATIONAHA.104.483628

Tarumi, T., Shah, F., Tanaka, H., and Haley, A. P. (2011). Association between central elastic artery stiffness and cerebral perfusion in deep subcortical gray and white matter. *Am. J. Hypertens.* 24, 1108–1113. doi: 10.1038/ajh.2011.101

Taylor, D. E., and Tukmachi, E. S. (1985). Contribution of internal and external carotid beds to common carotid artery input impedance in the dog. *Q. J. Exp. Physiol.* 70, 177–187.

Van Bortel, L. M., Balkestein, E. J., van der Heijden-Spek, J. J., Vanmolkot, F. H., Staessen, J. A., Kragten, J. A., et al. (2001). Non-invasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking. *J. Hypertens.* 19, 1037–1044. doi: 10.1097/00004872-200106000-00007

Webb, A. J., Simoni, M., Mazzucco, S., Kuker, W., Schulz, U., and Rothwell, P. M. (2012). Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. *Stroke* 43, 2631–2636. doi: 10.1161/STROKEAHA.112.655837

Westerhof, B. E., Guelen, I., Westerhof, N., Karemaker, J. M., and Avolio, A. (2006). Quantification of wave reflection in the human aorta from

pressure alone: a proof of principle. *Hypertension* 48, 595–601. doi: 10.1161/01.HYP.0000238330.08894.17

Wilkinson, I. B., Mohammad, N. H., Tyrrell, S., Hall, I. R., Webb, D. J., Paul, V. E., et al. (2002). Heart rate dependency of pulse pressure amplification and arterial stiffness. *Am. J. Hypertens.* 15, 24–30. doi: 10.1016/S0895-7061(01)02252-X

Willie, C. K., Ainslie, P. N., Taylor, C. E., Eves, N. D., and Tzeng, Y. C. (2013). Maintained cerebrovascular function during post-exercise hypotension. *Eur. J. Appl. Physiol.* 113, 1597–1604. doi: 10.1007/s00421-012-2578-3

Willie, C. K., Tzeng, Y. C., Fisher, J. A., and Ainslie, P. N. (2014). Integrative regulation of human brain blood flow. *J. Physiol.* 592, 841–859. doi: 10.1113/jphysiol.2013.268953

Xu, T. Y., Staessen, J. A., Wei, F. F., Xu, J., Li, F. H., Fan, W. X., et al. (2012). Blood flow pattern in the middle cerebral artery in relation to indices of arterial stiffness in the systemic circulation. *Am. J. Hypertens.* 25, 319–324. doi: 10.1038/ajh.2011.223

Yoon, E. S., Jung, S. J., Cheun, S. K., Oh, Y. S., Kim, S. H., and Jae, S. Y. (2010). Effects of acute resistance exercise on arterial stiffness in young men. *Korean Circ. J.* 40, 16–22. doi: 10.4070/kcj.2010.40.1.16

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 02 January 2014; paper pending published: 23 January 2014; accepted: 28 February 2014; published online: 19 March 2014.

*Citation: Lefferts WK, Augustine JA and Heffernan KS (2014) Effect of acute resistance exercise on carotid artery stiffness and cerebral blood flow pulsatility. Front. Physiol. **5**:101. doi: 10.3389/fphys.2014.00101*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 15 September 2014
doi: 10.3389/fphys.2014.00349

Cerebral hemodynamics during graded Valsalva maneuvers

Blake G. Perry[1]*, James D. Cotter[2], Gaizka Mejuto[3], Toby Mündel[1] and Samuel J. E. Lucas[4,5]

[1] School of Sport and Exercise, Massey University, Palmerston North, New Zealand
[2] School of Physical Education, Sport and Exercise Sciences, University of Otago, Dunedin, New Zealand
[3] Laboratory of Sport Performance Analysis, Sport and Physical Education Department, Faculty of Sport Sciences, University of the Basque Country, Vitoria-Gasteiz, Spain
[4] Department of Physiology, University of Otago, Dunedin, New Zealand
[5] School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, Birmingham, UK

Edited by:
Phil Neil Ainslie, University of British Columbia, Canada

Reviewed by:
Dragomir N. Serban, "Gr. T. Popa" University of Medicine and Pharmacy, Romania
Aaron Alexander Phillips, University of British Columbia, Canada

***Correspondence:**
Blake G. Perry, School of Sport and Exercise, Massey University, Private bag 11 222, Palmerston North 4442, New Zealand
e-mail: b.g.perry@massey.ac.nz

The Valsalva maneuver (VM) produces large and abrupt changes in mean arterial pressure (MAP) that challenge cerebral blood flow and oxygenation. We examined the effect of VM intensity on middle cerebral artery blood velocity (MCAv) and cortical oxygenation responses during (phases I–III) and following (phase IV) a VM. Healthy participants ($n = 20$ mean ± SD: 27 ± 7 years) completed 30 and 90% of their maximal VM mouth pressure for 10 s (order randomized) whilst standing. Beat-to-beat MCAv, cerebral oxygenation (NIRS) and MAP across the different phases of the VM are reported as the difference from standing baseline. There were significant interaction (phase * intensity) effects for MCAv, total oxygenation index (TOI) and MAP (all $P < 0.01$). MCAv decreased during phases II and III ($P < 0.01$), with the greatest decrease during phase III (−5 ± 8 and −19 ± 15 cm·s^{-1} for 30 and 90% VM, respectively). This pattern was also evident in TOI (phase III: −1 ± 1 and −5 ± 4%, both $P < 0.05$). Phase IV increased MCAv (22 ± 15 and 34 ± 23 cm·s^{-1}), MAP (15 ± 14 and 24 ± 17 mm Hg) and TOI (5 ± 6 and 7 ± 5%) relative to baseline (all $P < 0.05$). Cerebral autoregulation, indexed, as the %MCAv/%MAP ratio, showed a phase effect only ($P < 0.001$), with the least regulation during phase IV (2.4 ± 3.0 and 3.2 ± 2.9). These data illustrate that an intense VM profoundly affects cerebral hemodynamics, with a reactive hyperemia occurring during phase IV following modest ischemia during phases II and III.

Keywords: cerebral blood flow, hyperaemia, syncope, Valsalva maneuver, oxygenation

INTRODUCTION

The Valsalva maneuver (VM) is commonly recruited during everyday activities such as lifting (Mac Dougall et al., 1992), defecation and coughing (Hamilton et al., 1944), and is characterized by changes in intrathoracic pressure that have a pronounced effect on venous return, cardiac output and blood pressures (Tiecks et al., 1995). Phase I of the VM is characterized by an increase in mean arterial blood pressure (MAP) at the onset of strain as the elevated intrathoracic pressure is translated to the arterial circulation; during phase IIa a reduction in atrial filling pressure decreases stroke volume with a baroreflex-mediated recovery in blood pressure, via an increased heart rate (phase IIb); phase III features a rapid decline in MAP as the strain is released, and; phase IV has a rapid recovery and overshoot of MAP as the now restored cardiac output is ejected into a constricted systemic vasculature (Goldberg et al., 1952; Tiecks et al., 1995; Pott et al., 2000).

The abrupt reduction in MAP during phase III challenges the regulation of cerebral perfusion and can result in syncope (Duvoisin, 1961) even after brief (10 s) VMs when standing (Perry et al., 2014). Syncope occurs due to an acute reduction in cerebral oxygenation leading to unconsciousness (Van Lieshout et al., 2003). The intrathoracic pressure perturbations during the VM are translated to the cerebrospinal fluid (Hamilton et al., 1944) such that increases in intracranial pressure (ICP) ensue (Greenfield et al., 1984), reducing transmural pressure in the cerebral arteries and thus flow (Haykowsky et al., 2003). Large changes in ICP potentially impair cerebral perfusion and have been used to induce occlusion (Gourley and Heistad, 1984). Whilst more intense VMs produce greater reductions in cerebral blood flow (CBF) velocity during Phase III (Perry et al., 2014), it is not known whether these fluctuations in flow coincide with changes in oxygenation.

Various tissues display reactive hyperemic responses, such as skeletal muscle and skin in response to exercise. The brain also displays reactive hyperemic flow following injury (Martin et al., 1997), stroke (Olsen et al., 1981) and surgical intervention (van Mook et al., 2005). Work in animals has shown that brief cerebral ischemia (5 s) can lead to a near-maximal hyperemic response (Gourley and Heistad, 1984). However, studies in healthy conscious humans exhibiting cerebral reactive hyperemia are scarce. Whilst a hyperemic response has been suggested during the phase IV response (Zhang et al., 2004), no concurrent beat-to-beat

measures of CBF and oxygenation have been reported during a VM.

Therefore, the purpose of this investigation was to examine the cerebral hemodynamic response to graded VMs whilst standing. We hypothesized that the more intense VMs would result in greater reductions in both middle cerebral artery blood flow velocity (MCAv) and cortical oxygenation, and that the reduction in oxygenation would be matched by an increased flow velocity in phase IV of the VM in a dose-dependent manner.

MATERIALS AND METHODS

Twenty healthy non-smoking male participants were recruited for the study (mean ± SD: age, 27 ± 7 years; body mass, 82 ± 17 kg; height, 176 ± 10 cm). Participants were informed of the potential risks and experimental procedures, and informed written consent was obtained. All procedures and protocols were approved by the University of Otago Human Ethics Committee and performed in accordance with the *Declaration of Helsinki*. All participants were free from disease and were not taking any medication. Participants abstained from strenuous exercise, alcohol and caffeine for at least 24 h before the experimental trial.

STUDY DESIGN

Participants visited the laboratory on two occasions; one familiarization and one experimental trial. During the familiarization session the participants were familiarized with all experimental procedures and equipment, including practicing VMs at end-inspiration following a quiet period of spontaneous breathing. This enabled pre-VM hyperventilation to be minimized during experimental trials. Mouth pressure served as a surrogate for intrathoracic pressure (Mac Dougall et al., 1985; Morgan et al., 1993; Convertino et al., 2003; Heffernan et al., 2007) and reportedly reflects changes in esophageal pressure (Goldberg et al., 1952; Flemale et al., 1988). All VMs were performed in the standing position.

EXPERIMENTAL PROTOCOL

During the experimental trial each participant first stood for 5 min, during which baseline measures were obtained, then completed a maximal VM for 10 s. Following recovery (i.e., when all values returned to baseline), relative VMs of 30 and 90% of the maximal Valsalva pressure were performed for 10 s, the order of which was randomized between participants. We have used these relative pressures previously to demonstrate graded cerebral blood flow velocity restriction (Perry et al., 2014). Visual feedback of the absolute mouth pressure was given in real time to aid the participant. Each VM was separated by 5 min or until values had returned to baseline. Participants were verbally instructed what pressure and duration to obtain, immediately before the performance.

MEASUREMENTS

Blood flow velocity in the right middle cerebral artery (MCAv) was measured using a 2-MHz pulsed Doppler ultrasound (DWL, Compumedics Ltd, Germany) using search techniques described elsewhere (Aaslid et al., 1982; Willie et al., 2011). The probe was secured with a plastic headband (DWL) to maintain insonation angle. Prefrontal cortical hemodynamics were obtained non-invasively ($n = 10$) using near infrared spectroscopy (NIRS, NIRO-200; Hamamatsu Photonics KK; Japan). Using NIRS, the concentration of oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb) as well as total hemoglobin (tHB) are obtained using the Modified Beer-Lambet law (Al-Rawi et al., 2001). Using these indices, total cortical oxygenation index (TOI% = O2Hb/tHb × 100) was calculated by the NIRS system (Spatially Resolved Spectroscopy method) from the light attenuation slope along the distance from the emitting point as detected by two photodiodes in the detection probe (emitter to detector distance was 4.5 cm). The probes were placed in an optically dense plastic holder to minimize extraneous light, and taped to the forehead (right side) with opaque tape.

Participants breathed through an adjustable mouthpiece, which allowed for the measurement of mouth pressure and the partial pressure of end-tidal CO_2 ($P_{ET}CO_2$; gas analyser model ML206, ADInstruments, Australia). Mouth pressure was measured via a transducer attached to the mouthpiece and was used to measure the pressure during all VMs. Blood pressure was measured non-invasively and continuously using finger photoplethysmography (Finapres Medical Systems, Biomedical Instruments, The Netherlands), and heart rate was measured via three-lead electrocardiogram (ADInstruments). All data were acquired continuously via an analog-to-digital converter (PowerLab ML870; ADInstruments) at 1 kHz. Data were displayed in real time and recorded for off-line analysis using commercially-available software (v7.3.3 Lab Chart, ADInstruments).

Mean blood flow velocity ($MCAv_{mean}$) and mean arterial blood pressure (MAP) were calculated as the integral for each cardiac cycle divided by the corresponding pulse interval. An index of cerebral vascular conductance (CVCi) was calculated via the equation $MCAv_{mean}$/MAP.

DATA ANALYSES

Baseline data were acquired in the last minute of each baseline period between VMs, and presented as the mean across that minute. All variables were attained at each of the four phases of the VM. This included the peak Phase I response, the average over the phase II, the nadir of phase III and the peak of phase IV. The short duration of the VM performed here did not lead to a clearly defined phase IIb response and as such all variables were averaged following the peak of the phase I response until the release of the VM, to represent phase II. Additionally, the area under the curve (AUC) for data during phase IV (from time when the variable exceeded, and subsequently declined back to, the pre VM value) was calculated to determine the total impulse of perturbation in accordance with the method described by Pruessner et al. (2003). To index the cerebral autoregulation response during Phases I and IV, the percentage change in $MCAv_{mean}$ was divided by the percentage change in MAP from baseline or phase III, respectively, to assess differences in the MAP contribution to the $MCAv_{mean}$ change. The Gosling pulsatility index for MCAv was calculated as ($MCAv_{systolic}$ − $MCAv_{diastolic}$)/$MCAv_{mean}$(Gosling and King, 1974).

Inferential statistical analyses of dependent variables were performed using a Two-Way ANOVA (phase × pressure). Data were

assessed for approximation to a normal distribution and sphericity, with no corrections required. Main effects, AUC and time above baseline for MCAv were isolated using *post-hoc* pairwise comparisons (Bonferroni corrected, where necessary). Linear regression was used to determine the correlation between the phase dependent changes in MCAv, MAP, and TOI. All data were analyzed using SPSS statistical software (v20, Chicago, USA), with *a priori* statistical significance set at $P \leq 0.05$. All data are presented as the mean ± SD absolute change from the baseline preceding the VM, unless stated otherwise.

RESULTS

A typical trace during a 90% VM is shown in **Figure 1**. Absolute changes from baseline during all phases of the VM are displayed in **Table 1** and **Figure 2**. Mouth pressures were 24 ± 7 and 72 ± 21 for 30 and 90% VM respectively. Baseline data including $P_{ET}CO_2$ (grouped mean 33 ± 4 mm Hg) were unchanged between baseline periods. MAP, $MCAv_{mean}$, TOI, O_2Hb, HHb and tHb all demonstrated significant interaction effects ($P < 0.01$, **Figure 2**). Despite the greater increase in MAP during Phase I at 90% VM ($P < 0.001$, **Figure 2**), this did not correspond with greater increases in $MCAv_{mean}$ ($P = 0.85$). Phase III at 90% VM produced the lowest $MCAv_{mean}$, MAP, and TOI values (**Figure 2**).

Peak $MCAv_{mean}$ during phase IV was greater at 90% VM compared to 30% and phase I (both $P < 0.05$) despite a similar absolute MAP to that observed in phase I ($P = 0.91$) (**Figure 2**). Similarly, peak $MCAv_{mean}$ during phase IV at 30% VM showed this higher flow velocity between phase I and IV ($P < 0.05$) despite similar MAP between the phases. TOI also showed these response profiles between VM intensities and between phases I and IV (**Figure 2**). The phase IV AUC for MCAv was not reliably affected by VM pressure (123 ± 73 and 257 ± 414 aU for 30 and 90% respectively; $P = 0.17$). Nor was time above baseline for MCAv (11 ± 6 and 12 ± 8 s for 30 and 90% respectively; $P = 0.70$).

The %MCAv/%MAP ratio demonstrated a significant effect of Phase only ($P < 0.001$), with a trend for an effect of VM intensity ($P = 0.085$). Specifically, the phase IV response showed the greatest ratio, of 2.4 ± 3.0 and 3.2 ± 2.9 for 30 and 90% VMs, respectively, which was significantly larger than the phase I response (0.8 ± 3.6 and 1.1 ± 1.3, $P = 0.05$). Time to peak for $MCAv_{mean}$ during phase IV was 3.8 ± 1.8 and 4.4 ± 1.6 s for 30 and 90%, respectively ($P = 0.34$), and occurred before MAP (4.9 ± 2.0 and 6.4 ± 2.8 s, $P = 0.007$) and TOI (5.3 ± 1.4 and 8.0 ± 2.9 s, $P = 0.008$). Further, $MCAv_{mean}$ had decreased from the Phase IV peak when TOI peaked ($P = 0.02$).

Finally, the decrease in $MCAv_{mean}$ during phase III was not correlated with the increase during phase IV ($R^2 = 0.15$; $P = 0.2$), nor did the decrease in TOI during phase III predict the increase in MCAv during phase IV ($R^2 = 0.07$; $P = 0.09$).

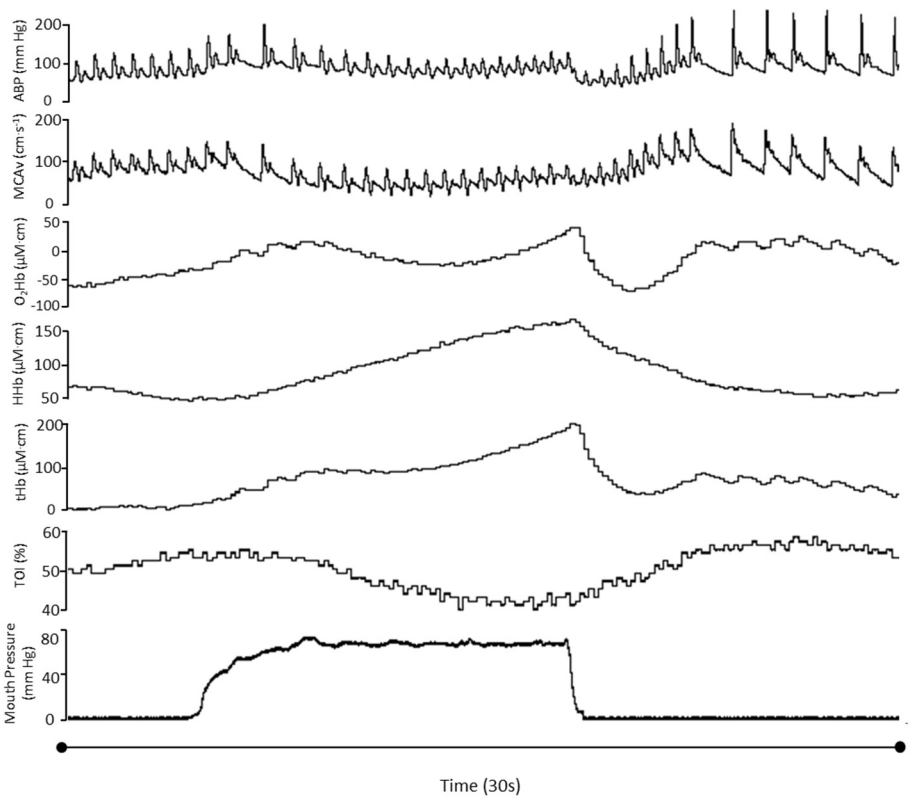


FIGURE 1 | Hemodynamic variables in one participant during a 90%VM. ABP, Arterial blood pressure; $MCAv_{mean}$, mean middle cerebral artery blood flow velocity; TOI, total oxygenation index; O_2Hb, oxyhemoglobin; HHb, deoxyhemoglobin; tHb, total hemoglobin.

Table 1 | Change from baseline during all phases for 30 and 90% VM.

Variable	Baseline	Pressure	Δ From baseline				*P*-values		
			Phase I	Phase II	Phase III	Phase IV	Pressure	Phase	Interaction
Systolic MCAv, cm·s^{-1}	98 ± 19	90	11 ± 12$^{\underline{A}ABCD\dagger}$	−22 ± 15$^{\underline{B}AD*\dagger}$	−23 ± 18$^{\underline{C}AD*\dagger}$	40 ± 20$^{\underline{D}ABC*\dagger}$	<0.001	0.06	<0.001
		30	9 ± 7	−8 ± 8	−11 ± 10	23 ± 18			
Diastolic MCAv, cm·s^{-1}	41 ± 9	90	13 ± 10$^{\underline{A}ABCD\dagger}$	−18 ± 14$^{\underline{B}AD*\dagger}$	−19 ± 15$^{\underline{C}AD*\dagger}$	27 ± 19$^{\underline{D}BC*\dagger}$	<0.001	0.01	<0.001
		30	11 ± 7	−3 ± 6	−2 ± 8	19 ± 13			
CVCi, cm·s^{-1} mm Hg^{-1}	0.74 ± 0.23	90	−0.04 ± 0.1$^{\underline{A}ABD*}$	−0.3 ± 0.3$^{\underline{B}ACD*\dagger}$	−0.1 ± 0.2$^{\underline{C}BD*}$	0.2 ± 0.1$^{\underline{D}ABC\dagger}$	<0.001	<0.001	<0.001
		30	0.02 ± 0.09	−0.02 ± 0.1	0.06 ± 0.09	0.2 ± 0.1			
PI	1.0 ± 0.1	90	0.8 ± 0.2$^{\underline{A}ABC\dagger}$	1.3 ± 0.7$^{\underline{B}AD*}$	1.4 ± 0.7$^{\underline{C}AE*}$	0.8 ± 0.2$^{\underline{D}BC\dagger}$	<0.001	0.009	<0.001
		30	0.8 ± 0.01	1.0 ± 0.2	0.9 ± 0.2	0.8 ± 0.1			
Systolic BP, mm Hg	115 ± 17	90	32 ± 20$^{\underline{A}BC*\dagger}$	−4 ± 21$^{\underline{B}ACD}$	−29 ± 18$^{\underline{C}ABD*\dagger}$	31 ± 26$^{\underline{D}BC*\dagger}$	<0.001	<0.001	<0.001
		30	20 ± 17	−6 ± 9	−14 ± 12	23 ± 21			
Diastolic BP, mm Hg	68 ± 16	90	28 ± 16$^{\underline{A}BC*\dagger}$	5 ± 16$^{\underline{B}ACD*}$	−20 ± 8$^{\underline{C}ABD*\dagger}$	17 ± 14$^{\underline{D}BC*\dagger}$	<0.001	<0.001	<0.001
		30	13 ± 8	−3 ± 7	−9 ± 6	12 ± 12			
HR, beats·min^{-1}	74 ± 13	90	7 ± 15$^{\underline{A}BC}$	19 ± 14$^{\underline{B}ACD*\dagger}$	30 ± 16$^{\underline{C}ABD*\dagger}$	6 ± 14$^{\underline{D}BC*}$	<0.001	<0.001	<0.001
		30	4 ± 10	8 ± 10	15 ± 10	−3 ± 14			

*Values are absolute mean ± SD change from baseline. VM, Valsalva maneuver; MCAv, middle cerebral artery velocity; CVCi, cerebrovascular conductance index; PI, Pulsatility index; BP, blood pressure; HR, heart rate; †, statistically different from baseline, P = 0.05. *Statistically different from 30% within respective phase, P = 0.05. The bolded and underlined letters A–D represent the respective stages of the VM. The italicized letters represent differences between the phases (P < 0.05).*

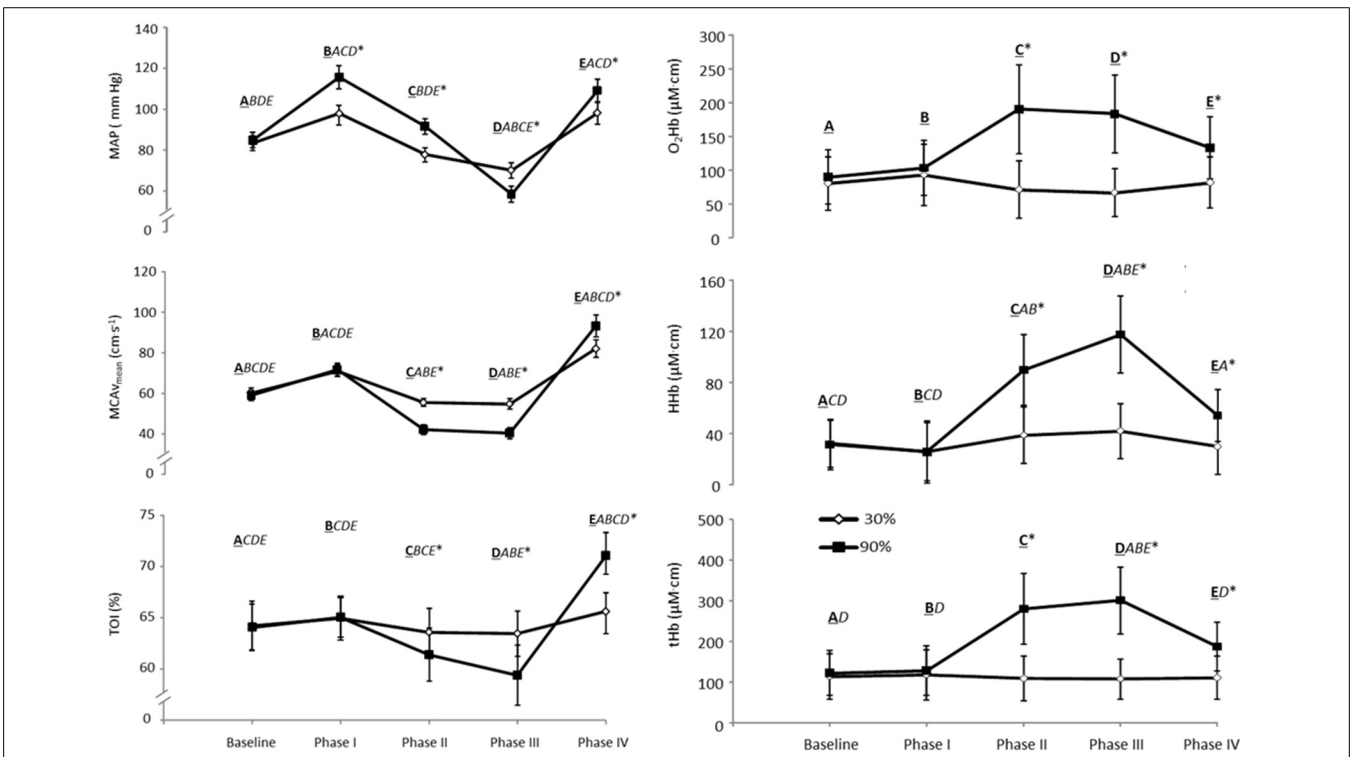


FIGURE 2 | MAP, Maximal mean arterial blood pressure; $MCAv_{mean}$, Maximal mean middle cerebral artery blood flow velocity; TOI, Maximal total oxygenation index; O_2Hb, Maximal oxyhemoglobin; HHb, Maximal deoxyhemoglobin; tHb, Maximal total hemoglobin (tHb, *n* = 10 for NIRS data) for each phase of the VM during a 30 and 90% relative intensity VM held for 10 s. The bolded and underlined letters A–E represent the respective stages of the VM (baseline and phase I–IV on the x axis). The italicized letters represent differences between the phases ($P < 0.05$). *Significant difference between 30 and 90%, $P \leq 0.05$. Values are means ± SE.

DISCUSSION

The main novel findings of this study were that: (1) a more intense VM produced greater reductions in cortical prefrontal oxygenation during phases II and III; (2) the more intense VM resulted in higher peak $MCAv_{mean}$ and TOI during phase IV; (3) during the phase IV response the %MCAv/%MAP ratio was above 2 for both mild and severe VMs—it was much greater than the phase I response and was indicative of a hyperemic response.

Consistent with our hypothesis, the more intense VM produced greater reductions in flow velocity and oxygenation (TOI) during phases II and III and greater increases in both oxygenation and peak $MCAv_{mean}$ during phase IV. However, the phase IV elevations in MCAv and TOI were unrelated to the preceding reductions in oxygenation and flow velocity at phase III.

Cerebral blood flow becomes restricted during and immediately following VMs, as evidenced by the reductions in $MCAv_{mean}$ during phases II and III (**Figure 2**). The elevated venous pressure during a VM will increase cerebral blood volume (Pott et al., 2000; Gisolf et al., 2004), reduce venous outflow and contribute to the reduction in MCAv. Our NIRS measures of prefrontal oxygenation indicated that this reduction in flow (velocity) was sufficient to threaten cortical oxygenation, consistent with others measuring jugular oxygen tension during a VM (Meyer et al., 1966). This reduced flow, however, will be partially mitigated via an increase in arterial oxygen extraction (Trangmar et al., 2014). The continued increase in deoxygenated hemoglobin during phase II and III is consistent with this (HHb, see **Figures 1**, **2**), resulting in an overall decrease in total oxygenation (TOI). We also observed an increase in total hemoglobin at phase III, which is indicative of increased cerebral blood volume; however, the pooling of blood in the venous system occurring at the site we measured seems unlikely, as it is more likely to occur in the larger veins and/or sinuses. One possibility is that this may reflect skin vascular pooling, since extracranial contamination may be present in these NIRS signals (Canova et al., 2011). However, the demand of extracranial tissue would not explain the large increase in HHb we observed, thus indicative of cerebral metabolism. More research is needed to clarify these contributions to the NIRS-derived parameters. Nevertheless, the concomitant reduction in blood flow and oxygenation (as indexed via Spatially Resolved Spectroscopy) can be sufficient to induce syncope during a VM, which has been reported as early as 3 s following the onset of the strain (Diehl et al., 2000). Indeed, some of our participants reported presyncope symptoms whilst performing the maximal and 90% VMs.

In response to cerebral occlusion, venous oxygen saturation has also been reported to increase substantially following occlusion (Symon et al., 1972; Gourley and Heistad, 1984). This mismatch between flow and demand has been termed "luxury perfusion" and has been reported following cerebral injury (Lassen, 1966) and neurosurgical procedures (van Mook et al., 2005). Although on a much shorter timescale than the aforementioned reports, our data are consistent with this luxury perfusion notion as evidenced by an observed temporal mismatch between peak reactive flow and oxygenation (∼2–4 s). Gourley and Heistad (1984) have previously shown, in animals, that peak reactive cerebral hyperaemia is apparent after short periods of occlusion (5 s), with the duration of the hyperaemic flow dependent on the duration of ischemia. As both VMs were of the same duration in the current study, this may explain the similar AUC and duration for the phase IV $MCAv_{mean}$ responses between relative pressures.

The brain demonstrates high-pass filter characteristics, with high frequency oscillations in MAP being translated to the cerebral circulation (Zhang et al., 1998). Whilst the increase in CBF during phase I may be restrained by the mechanical increase in ICP and subsequent reduction in transmural pressure (Haykowsky et al., 2003), the proportional increase in MCAv during phase IV was ∼2- and ∼3-fold greater than was explainable by MAP; (for 30 and 90%, respectively). In one participant who became syncopal, the peak phase IV response was associated with a near tripling of MCAv from baseline (no TOI measures available for this individual). A similar tripling of CBF has been reported in an animal-based study following an elevation of ICP above mean arterial pressure for 15 s (Gourley and Heistad, 1984). Thus, the increase in MCAv appears to be mediated by additional factors over-and-above that induced via the rapid rise in MAP, i.e., a reactive hyperaemia.

Although the more intense VM produced a greater reduction and subsequent overshoot in both TOI and MCAv during phase III and IV respectively, the two variables did not display a strong correlation. This may be due in part to the variable cerebral autoregulatory responses between individuals (Zhang et al., 2000), but is consistent with previous reports where a CBF:oxygenation mismatch was demonstrated during hyperaemic responses (Lassen, 1966). From our data it is difficult to ascertain the cause of the observed increase in CVCi during phase IV. A number of factors may have contributed to this response: (1) a residual vasodilation in response to the reduction in cerebral perfusion pressure during phases II and III as a result of the inherent latency of dynamic cerebral autoregulation (∼5 s) (Zhang et al., 1998) (although for the given change in MAP when MCAv peak occurred, the proportionate contribution of MAP to this increase appears relatively small); (2) Following the release of the strain the sharp reduction in ICP and central venous pressure normalizes the transmural and arterial-venous pressures gradients respectively, aiding in flow restoration, and (3) The response is hyperemic in nature. When the MAP phase IV response is ablated the increase an MCAv is still apparent, which supports the notion of cerebral hyperemic flow (Zhang et al., 2004) even following VMs at moderate mouth pressures of 30 mm Hg, as we observed. Further, the VMs were performed in the standing position, which induces larger changes in MAP and MCAv (Pott et al., 2000; Perry et al., 2014). Therefore, it seems reasonable to assume that this response is, at least in part, hyperemic in nature, with peak reactive hyperemic flow velocity but not duration affected. Longer VMs may be required to induce longer hyperemic responses.

TECHNOLOGICAL CONSIDERATIONS

We used NIRS to provide a non-invasive measure of cerebral tissue oxygenation. The potential exists for extracranial contamination. Although NIRS strongly reflects cerebral oxygenation (Al-Rawi et al., 2001), the large perturbations in arterial blood pressure would produce some concomitant flow changes in extracranial vessels. During thigh cuff release, internal carotid artery flow recovers at the expense of external carotid artery flow and is a pertinent regulatory phenomenon to preserve CBF during acute hypotension (Ogoh et al., 2014a). The decrease in external carotid artery flow may reflect an arterial baroreflex mediated vasoconstriction (Ogoh et al., 2014a), which may

falsely present as a decrease in cortical oxygenation (as measured using NIRS), despite an unchanged MCAv (Ogoh et al., 2014b). In contrast, in the current experiment both flow and oxygenation are in agreement, with changes in MCAv and TOI occurring concomitantly, indicative of a flow-mediated reduction in oxygenation in the brain parenchyma. Furthermore, the extracranial vessels are not subjected to changes in ICP. An abrupt decrease in intracranial CVCi, as demonstrated here during phase I, may shunt blood extracranially, maintaining flow in this vascular bed. As mentioned above, the steady rise in HHb from phase I to phase III seems likely to reflect the constant metabolic demand of the cerebral tissue (**Figures 1**, **2**), which seems independent of the changes in O_2Hb (and hence tHb) (**Figure 2**). While the initial rise in O_2Hb during phase I may reflect the spike in BP and some extracranial shunting and associated increase in flow to the skin and face, the plateau and then late rise up until the strain release at phase III seems unlikely to be attributable to extracranial flow changes.

This study utilized blood flow velocity in the middle cerebral artery as a surrogate for global CBF. Changes in flow are adequately reflected by changes in flow velocity only when conduit artery diameter is unchanged (Valdueza et al., 1997), which appears to be true during moderate changes in MAP (Giller et al., 1993). Further, the retest reliability has been shown to be strong during repeated VMs using transcranial Doppler (Wallasch and Kropp, 2012). We have previously attempted to measure carotid artery diameter in order to clarify the effect of the VM on conduit artery diameter (Perry et al., 2014). However, the large changes in pressure within the jugular vein displace the internal and external carotid arteries making data acquisition within the time frame of the VM difficult. Therefore, the exact response of the conduit arteries is unknown with further examination required to establish blood distribution in both extracranial (face and skin) and intracranial circulations during the VM.

Alterations in arterial CO_2 alter the efficacy of cerebral autoregulation (Aaslid et al., 1989). The $P_{ET}CO_2$, as a substitute for arterial PCO_2, was unchanged between baselines, so cerebral tone would have been similar at the onset of the VM. The time course of the vascular response to changes in arterial CO_2 is asymmetric with the "on" constant much slower than the "off" (Poulin et al., 1996). The time constant of the increase in MCAv during a step change in $P_{ET}CO_2$ is ∼6 s (Poulin et al., 1996, 1998). Pott et al. (2000) reported that the reduction in arterial PCO_2 contributed 10–15% to the reduction in MCAv during a 15-s VM. As VM duration in the current experiment was 10 s the influence of changes in arterial PCO_2 would be expected to be less, although the exact effect of possible changes in arterial CO_2 tension during the VM performed here is unknown. However, due to the delay in the vascular response and moderate changes in arterial PCO_2 reported during longer VMs (Pott et al., 2000),the main driving factor during and initially following the VM appears to be the rapid changes in perfusion pressure rather than CO_2.

CONCLUSIONS

Performing a VM has dose-dependent effects on cerebral hemodynamics. Cerebral blood flow velocity and oxygenation decreases more during phase II and III of a 90% of maximum VM compared to a 30% effort, and is associated with a larger overshoot in flow velocity and oxygenation following the release of the strain (phase IV). Regardless of the magnitude of the reduction in flow and oxygenation, the subsequent overshoot was 2–3-fold greater than the increase in driving pressure (MAP), and was indicative of a reactive hyperaemia response.

FUNDING

This study was funded by the Massey University School of Sport and Exercise.

AUTHOR CONTRIBUTIONS

Blake G. Perry, James D. Cotter, Gaizka Mejuto, and Samuel J. E. Lucas were involved in conception and design of research. Blake G. Perry, James D. Cotter, Gaizka Mejuto and Samuel J. E. Lucas conducted experiment. All authors were involved in data analysis and interpretation. All authors edited and revised manuscript with all authors approving the final version of this article.

ACKNOWLEDGMENTS

We thank the participants for their willingness, time and effort.

REFERENCES

Aaslid, R., Lindegaard, K. F., Sorteberg, W., and Nornes, H. (1989). Cerebral autoregulation dynamics in humans. *Stroke* 20, 45–52. doi: 10.1161/01.STR.20.1.45

Aaslid, R., Markwalder, T. M., and Nornes, H. (1982). Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J. Neurosurg.* 57, 769–774. doi: 10.3171/jns.1982.57.6.0769

Al-Rawi, P. G., Smielewski, P., and Kirkpatrick, P. J. (2001). Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. *Stroke* 32, 2492–2500. doi: 10.1161/hs1101.098356

Canova, D., Roatta, S., Bosone, D., and Micieli, G. (2011). Inconsistent detection of changes in cerebral blood volume by near infrared spectroscopy in standard clinical tests. *J. Appl. Physiol.* 110, 1646–1655. doi: 10.1152/japplphysiol.00003.2011

Convertino, V. A., Ratliff, D. A., Doerr, D. F., Ludwig, D. A., Muniz, G. W., Benedetti, E., et al. (2003). Effects of repeated Valsalva maneuver straining on cardiac and vasoconstrictive baroreflex responses. *Aviat. Space Environ. Med.* 74, 212–219.

Diehl, R. R., Linden, D., Bünger, B., Schäfer, M., and Berlit, P. (2000). Valsalva-induced syncope during apnea diving. *Clin. Auton. Res.* 10, 343–345. doi: 10.1007/BF02322258

Duvoisin, R. C. (1961). The Valsalva maneuver in the study of syncope. *Electroencephalogr. Clin. Neurophysiol.* 13, 622–626. doi: 10.1016/0013-4694(61)90178-X

Flemale, A., Gillard, C., and Dierckx, J. (1988). Comparison of central venous, oesophageal and mouth occlusion pressure with water-filled catheters for estimating pleural pressure changes in healthy adults. *Eur. Respir. J.* 1, 51–57.

Giller, C. A., Bowman, G., Dyer, H., Mootz, L., and Krippner, W. (1993). Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery* 32, 737–742. doi: 10.1227/00006123-199305000-00006

Gisolf, J., Van Lieshout, J., Van Heusden, K., Pott, F., Stok, W., and Karemaker, J. (2004). Human cerebral venous outflow pathway depends on posture and central venous pressure. *J. Physiol.* 560, 317–327. doi: 10.1113/jphysiol.2004.070409

Goldberg, H., Elisberg, E., and Katz, L. (1952). The effects of the Valsalva-like maneuver upon the circulation in normal individuals and patients with mitral stenosis. *Circulation* 5, 38–47. doi: 10.1161/01.CIR.5.1.38

Gosling, R., and King, D. (1974). Arterial assessment by Doppler-shift ultrasound. *Proc. R. Soc. Med.* 67(6 Pt 1), 447–449.

Gourley, J. K., and Heistad, D. D. (1984). Characteristics of reactive hyperemia in the cerebral circulation. *Am. J. Physiol. Heart Circ. Physiol.* 246, H52–H58.

Greenfield, J. C., Rembert, J. C., and Tindall, G. T. (1984). Transient changes in cerebral vascular resistance during the Valsalva maneuver in man. *Stroke* 15, 76–79. doi: 10.1161/01.STR.15.1.76

Hamilton, W., Woodbury, R., and Harper, H. (1944). Arterial, cerebrospinal and venous pressures in man during cough and strain. *Am. J. Physiol.* 141, 42–50.

Haykowsky, M. J., Eves, N. D., Warburton, D. E., and Findlay, M. J. (2003). Resistance exercise, the Valsalva maneuver, and cerebrovascular transmural pressure. *Med. Sci. Sports Exerc.* 35, 65–68. doi: 10.1097/00005768-200301000-00011

Heffernan, K. S., Jae, S. Y., Edwards, D. G., Kelly, E. E., and Fernhall, B. (2007). Arterial stiffness following repeated Valsalva maneuvers and resistance exercise in young men. *Appl. Physiol. Nutr. Metab.* 32, 257–264. doi: 10.1139/h06-107

Lassen, N. (1966). The luxury-perfusion syndrome and its possible relation to acute metabolic acidosis localised within the brain. *Lancet* 288, 1113–1115. doi: 10.1016/S0140-6736(66)92199-4

Mac Dougall, J., McKelvie, R., Moroz, D., Sale, D., McCartney, N., and Buick, F. (1992). Factors affecting blood pressure during heavy weight lifting and static contractions. *J. Appl. Physiol.* 73, 1590–1597.

Mac Dougall, J., Tuxen, D., Sale, D., Moroz, J., and Sutton, J. (1985). Arterial blood pressure response to heavy resistance exercise. *J. Appl. Physiol.* 58, 785–790.

Martin, N. A., Patwardhan, R. V., Alexander, M. J., Africk, C. Z., Lee, J. H., Shalmon, E., et al. (1997). Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia, and vasospasm. *J. Neurosurg.* 87, 9–19. doi: 10.3171/jns.1997.87.1.0009

Meyer, J. S., Gotoh, F., Takagi, Y., and Kakimi, R. (1966). Cerebral hemodynamics, blood gases, and electrolytes during breath-holding and the Valsalva maneuver. *Circulation* 33, II35–II48. doi: 10.1161/01.CIR.33.5S2.II-35

Morgan, B. J., Denahan, T., and Ebert, T. J. (1993). Neurocirculatory consequences of negative intrathoracic pressure vs. asphyxia during voluntary apnea. *J. Appl. Physiol.* 74, 2969–2975.

Ogoh, S., Lericollais, R., Hirasawa, A., Sakai, S., Normand, H., and Bailey, D. M. (2014a). Regional redistribution of blood flow in the external and internal carotid arteries during acute hypotension. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 306, R747–R751. doi: 10.1152/ajpregu.00535.2013

Ogoh, S., Sato, K., Okazaki, K., Miyamoto, T., Secher, F., Sørensen, H., et al. (2014b). A decrease in spatially resolved near-infrared spectroscopy-determined frontal lobe tissue oxygenation by phenylephrine reflects reduced skin blood flow. *Anesth. Analg.* 118, 823–829. doi: 10.1213/ANE.0000000000000145

Olsen, T. S., Larsen, B., Skriver, E. B., Herning, M., Enevoldsen, E., and Lassen, N. (1981). Focal cerebral hyperemia in acute stroke. Incidence, pathophysiology and clinical significance. *Stroke* 12, 598–607. doi: 10.1161/01.STR.12.5.598

Perry, B. G., Mündel, T., Cochrane, D. J., Cotter, J. D., and Lucas, S. J. (2014). The cerebrovascular response to graded Valsalva maneuvers while standing. *Physiol. Rep.* 2: e00233. doi: 10.1002/phy2.233

Pott, F., van Lieshout, J. J., Ide, K., Madsen, P., and Secher, N. H. (2000). Middle cerebral artery blood velocity during a Valsalva maneuver in the standing position. *J. Appl. Physiol.* 88, 1545–1550.

Poulin, M., Liang, P., and Robbins, P. (1996). Dynamics of the cerebral blood flow response to step changes in end-tidal PCO_2 and PO_2 in humans. *J. Appl. Physiol.* 81, 1084–1095.

Poulin, M. J., Liang, P. J., and Robbins, P. A. (1998). Fast and slow components of cerebral blood flow response to step decreases in end-tidal in humans. *J. Appl. Physiol.* 85, 388–397.

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., and Hellhammer, D. H. (2003). Two formulas for computation of the area under the curverepresent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology* 28, 916–931. doi: 10.1016/S0306-4530(02)00108-7

Symon, L., Ganz, J., and Dorsch, N. (1972). Experimental studies of hyperaemic phenomena in the cerebral circulation of primates. *Brain* 95, 265–278. doi: 10.1093/brain/95.2.265

Tiecks, F. P., Lam, A. M., Matta, B. F., Strebel, S., Douville, C., and Newell, D. W. (1995). Effects of the Valsalva maneuver on cerebral circulation in healthy adults: a transcranial Doppler study. *Stroke* 26, 1386–1392. doi: 10.1161/01.STR.26.8.1386

Trangmar, S. J., Chiesa, S. T., Stock, C. G., Kalsi, K. K., Secher, N. H., and González–Alonso, J. (2014). Dehydration affects cerebral blood flow but not its metabolic rate for oxygen during maximal exercise in trained humans. *J. Physiol.* doi: 10.1113/jphysiol.2014.272104. [Epub ahead of print].

Valdueza, J. M., Balzer, J. O., Villringer, A., Vogl, T. J., Kutter, R., and Einh, K. (1997). Changes in blood flow velocity and diameter of the middle cerebral artery during hyperventilation: assessment with MR and transcranial Doppler sonography. *Am. J. Neuroradiol.* 18, 1929–1934.

Van Lieshout, J. J., Wieling, W., Karemaker, J. M., and Secher, N. H. (2003). Syncope, cerebral perfusion, and oxygenation. *J. Appl. Physiol.* 94, 833–848. doi: 10.1152/japplphysiol.00260.2002

van Mook, W. N., Rennenberg, R. J., Schurink, G. W., van Oostenbrugge, R. J., Mess, W. H., Hofman, P. A., et al. (2005). Cerebral hyperperfusion syndrome. *Lancet Neurol.* 4, 877–888. doi: 10.1016/S1474-4422(05)70251-9

Wallasch, T. M., and Kropp, P. (2012). Cerebrovascular response to valsalva maneuver: methodology, normal values, and retest reliability. *J. Clin. Ultrasound* 40, 540–546. doi: 10.1002/jcu.21936

Willie, C., Colino, F., Bailey, D., Tzeng, Y., Binsted, G., Jones, L., et al. (2011). Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function. *J. Neurosci. Methods* 196, 221–237. doi: 10.1016/j.jneumeth.2011.01.011

Zhang, R., Crandall, C. G., and Levine, B. D. (2004). Cerebral hemodynamics during the Valsalva maneuver insights from ganglionic blockade. *Stroke* 35, 843–847. doi: 10.1161/01.STR.0000120309.84666.AE

Zhang, R., Zuckerman, J. H., Giller, C. A., and Levine, B. D. (1998). Transfer function analysis of dynamic cerebral autoregulation in humans. *Am. J. Physiol. Heart Circ. Physiol.* 274, 233–241.

Zhang, R., Zuckerman, J. H., and Levine, B. D. (2000). Spontaneous fluctuations in cerebral blood flow: insights from extended-duration recordings in humans. *Am. J. Physiol. Heart Circ. Physiol.* 278, H1848–H1855.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 30 June 2014; accepted: 25 August 2014; published online: 15 September 2014.

*Citation: Perry BG, Cotter JD, Mejuto G, Mündel T and Lucas SJE (2014) Cerebral hemodynamics during graded Valsalva maneuvers. Front. Physiol. **5**:349. doi: 10.3389/fphys.2014.00349*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 19 February 2014
doi: 10.3389/fphys.2014.00049

Effects of aging on the association between cerebrovascular responses to visual stimulation, hypercapnia and arterial stiffness

Daniela Flück[1,2†‡], Andrew E. Beaudin[2‡], Craig D. Steinback[2], Gopukumar Kumarpillai[3], Nandavar Shobha[3], Cheryl R. McCreary[3,4,5,6], Stefano Peca[6], Eric E. Smith[3,4,6] and Marc J. Poulin[2,3,4,7,8]*

[1] Department of Biology, Institute of Human Movement Sciences and Sport, ETH Zurich, Zurich, Switzerland
[2] Department of Physiology and Pharmacology, Faculty of Medicine, University of Calgary, Calgary, AB, Canada
[3] Department of Clinical Neurosciences, Faculty of Medicine, University of Calgary, Calgary, AB, Canada
[4] Hotchkiss Brain Institute, Faculty of Medicine, University of Calgary, Calgary, AB, Canada
[5] Department of Radiology, Faculty of Medicine, University of Calgary, Calgary, AB, Canada
[6] Seaman Family MR Research Centre, Foothills Medical Centre, Alberta Health Services, Calgary, AB, Canada
[7] Faculty of Kinesiology, University of Calgary, Calgary, AB, Canada
[8] The Libin Cardiovascular Institute of Alberta, Faculty of Medicine, University of Calgary, Calgary, AB, Canada

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Olaf Grisk, University of Greifswald, Germany
Christopher K Willie, University of British Columbia Okanagan, Canada

***Correspondence:**
Marc J. Poulin, Department of Physiology and Pharmacology, Faculty of Medicine, University of Calgary, HMRB-210, 3330 Hospital Drive NW, Calgary, Alberta, T2N 4N1, Canada
e-mail: poulin@ucalgary.ca

†Present address:
Daniela Flück, Zurich Center for Integrative Human Physiology (ZIHP), Institute of Physiology, University of Zurich, Switzerland

‡These authors have contributed equally to this work.

Aging is associated with decreased vascular compliance and diminished neurovascular- and hypercapnia-evoked cerebral blood flow (CBF) responses. However, the interplay between arterial stiffness and reduced CBF responses is poorly understood. It was hypothesized that increased cerebral arterial stiffness is associated with reduced evoked responses to both, a flashing checkerboard visual stimulation (i.e., neurovascular coupling), and hypercapnia. To test this hypothesis, 20 older (64 ± 8 year; mean ± *SD*) and 10 young (30 ± 5 year) subjects underwent a visual stimulation (VS) and a hypercapnic test. Blood velocity through the posterior (PCA) and middle cerebral (MCA) arteries was measured concurrently using transcranial Doppler ultrasound (TCD). Cerebral and systemic vascular stiffness were calculated from the cerebral blood velocity and systemic blood pressure waveforms, respectively. Cerebrovascular (MCA: young = 76 ± 15%, older = 98 ± 19%, $p = 0.004$; PCA: young = 80 ± 16%, older = 106 ± 17%, $p < 0.001$) and systemic (young = 59 ± 9% and older = 80 ± 9%, $p < 0.001$) augmentation indices (AI) were higher in the older group. CBF responses to VS (PCA: $p < 0.026$) and hypercapnia (PCA: $p = 0.018$; MCA: $p = 0.042$) were lower in the older group. A curvilinear model fitted to cerebral AI and age showed AI increases until ~60 years of age, after which the increase levels off (PCA: $R^2 = 0.45$, $p < 0.001$; MCA: $R^2 = 0.31$, $p < 0.001$). Finally, MCA, but not PCA, hypercapnic reactivity was inversely related to cerebral AI (MCA: $R^2 = 0.28$, $p = 0.002$; PCA: $R^2 = 0.10$, $p = 0.104$). A similar inverse relationship was not observed with the PCA blood flow response to VS ($R^2 = 0.06$, $p = 0.174$). In conclusion, older subjects had reduced neurovascular- and hypercapnia-mediated CBF responses. Furthermore, lower hypercapnia-mediated blood flow responses through the MCA were associated with increased vascular stiffness. These findings suggest the reduced hypercapnia-evoked CBF responses through the MCA, in older individuals may be secondary to vascular stiffening.

Keywords: aging, cerebral blood flow, physiology, transcranial doppler, arterial stiffness

INTRODUCTION

Age manifests in systemic decreases in vascular compliance leading to an increased risk of stroke, cerebral white matter lesions, and cognitive decline (Mitchell et al., 2011; Laurent et al., 2012; Poels et al., 2012; Xu et al., 2012). In the brain, decreased resting cerebral blood flow (CBF) and cerebrovascular reactivity to neuronal activation and alterations in arterial blood gases are also associated with an elevated risk of cerebrovascular disease (Jennings et al., 2013) and occur with healthy aging (Nishiyama et al., 1997; Fisher et al., 2013). Thus, the concurrent increase in cerebrovascular stiffness with aging may impact cerebrovascular responses (Fonck et al., 2009; Zhu et al., 2011) and thus contribute to the decreased CBF responses to neuronal stimulation and hypercapnia that occur with aging.

CBF is elevated in response to increased neural activity (i.e., neurovascular coupling) and hypercapnia. Neural activation leads to local increases in CBF via functional hyperemia, whereas hypercapnia produces a global increase in CBF, although there is heterogeneity between brain regions (Noth et al., 2008). With aging, resting CBF, neuronal-mediated increases in CBF, and CBF responses to hypercapnia have all been reported to decrease (Panczel et al., 1999; Niehaus et al., 2001; Fisher et al.,

2013; Jennings et al., 2013), but this is not a consistent finding with other studies reporting no change in neurovascular coupling (Rosengarten et al., 2003) or reactivity to hypercapnia (Schwertfeger et al., 2006; Galvin et al., 2010), and one study even reporting greater hypercapnia reactivity with healthy aging (Zhu et al., 2013). As such, the mechanisms regulating changes in resting CBF and CBF reactivity in response to neuronal activation and hypercapnia with aging are incompletely understood. Contributing mechanisms likely include brain atrophy, altered neuronal activity, and decreased cerebral metabolism (Leenders et al., 1990; Fisher et al., 2013), although endothelial and hemodynamic alterations may also contribute (Secher et al., 2008; Zhu et al., 2011; Fisher et al., 2013).

To assess neural-evoked increases in CBF, the approach of monitoring blood flow through the posterior cerebral artery (PCA) in response to a visual stimulus has been used extensively (Aaslid, 1987; Sturzenegger et al., 1996; Spelsberg et al., 1998; Panczel et al., 1999; Niehaus et al., 2001; Zaletel et al., 2004; Lisak et al., 2005; Smith et al., 2008; Rey et al., 2010), as the PCA supplies the majority of blood to the visual cortex (Edvinsson and Krause, 2002). Moreover, concurrent monitoring of middle cerebral artery (MCA) blood flow can be used as a negative control to confirm the locality of the visually-induced increase in blood flow through the PCA during such challenges since the MCA blood flow response to the same challenges is minimal (Aaslid, 1987; Smith et al., 2008).

The cerebral circulation is exquisitely sensitive to changes in the arterial partial pressure of carbon dioxide (Pa_{CO_2}) (Berne et al., 1981; Poulin and Robbins, 1996), increasing with hypercapnia and decreasing with hypocapnia. In humans, blood velocity through both the PCA and MCA increase ∼3–5% per mmHg increase in Pa_{CO_2} above resting values (Tominaga et al., 1976; Ide et al., 2003), and thus reflect the global influence of hypercapnia on CBF.

Transcranial Doppler ultrasound (TCD) is a useful non-invasive technique to assess both neural- and hypercapnia-mediated changes in CBF as well as cerebral hemodynamics on a beat-to-beat basis because of its high temporal resolution. Changes in CBF are typically monitored via changes in the peak velocity envelope averaged across a heartbeat while cerebral hemodynamics may be assessed by examining specific parameters of the peak blood velocity waveform (Robertson et al., 2008). In turn, these variables can provide measures of CBF reactivity to specific stimuli and cerebrovascular health, respectively.

Analogs to examining the pulse pressure waveform (Wilkinson et al., 1998), analysis of the TCD peak blood velocity waveform can be exploited to obtain a measure of arterial stiffening via calculation of a cerebral augmentation index (AI) (Kurji et al., 2006; Robertson et al., 2008). The AI is based on wave reflections throughout the vascular bed caused by vessel branching, changes in vessel wall diameter and/or material properties (Mitchell et al., 2011). The arrival of the reflected wave depends on the site of reflection as well as on the stiffness of the respective vessel being monitored. The stiffer the vessel, the higher the velocity of the forward and backward travelling waves, which leads to an earlier arrival of the reflected waves. The earlier arrival of the reflected wave is superimposed on the forward travelling wave and consequently higher velocity at the so-called reflective point of the peak blood velocity waveform (Laurent et al., 2006). Thus, an increase in AI is observed as vessels downstream of the monitored artery become less distensible with increasing age (Benetos et al., 1993).

Although mechanisms underlying neural- and hypercapnia-mediated vasodilation are unique to each stimulus, as both may be reduced with age, there is likely a common mechanism contributing to the decrease observed in each with increasing age. We speculate this common mechanism is age-related vascular mechanical dysfunction (i.e., reduced distensibility). As such, it was hypothesized that resting CBF and neural- and hypercapnia-evoked increases in CBF would be attenuated with age, and attenuated neural- and hypercapnia-evoked CBF increases would be associated with elevated arterial stiffness (i.e., AI) within the PCA and MCA, respectively. To test this hypothesis, the relationship between CBF responses to a visual stimulus and a hypercapnic challenge with AI were examined and compared between young and older humans.

METHODS

SUBJECTS

Thirty subjects, 20 older (12 men; 8 women) and 10 younger (4 men, 6 females) participated in this study (**Table 1**). Exclusion criteria included age <55 y for the older group and age <18 or >55 y for the younger group, recent (<60 days) change in blood pressure medication, uncontrolled hypertension, history of stroke, neurological disease, or dementia [defined according to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000)]. A neurologist (Eric E. Smith) obtained clinical and medication histories, performed a neurological examination, and administered the Mini-Mental Status Examination (MMSE) cognitive test to all older volunteers (Folstein et al., 1975). Volunteers scoring <23 on the MMSE were excluded. Prior to experimental testing, subjects provided written and oral informed consent. The study was approved by the University of Calgary Conjoint Health Research Ethics Board.

INSTRUMENTATION

Bilateral TCD was used to measure PCA and MCA blood velocity simultaneously with subjects in a semi-supine position. The P2 segment of the PCA was monitored on the ipsilateral side of the dominant hand while the M2 segment of the MCA was monitored on the contralateral side. TCD probes were held in position by snug-fitting headgear (marc600, Spencer Technologies, Seattle, WA). Heart rate was measured using a 3-lead ECG (Micromon 7142B, Kontron Medical, Milton Keynes, UK); continuous arterial blood pressure was recorded non-invasively via finger photoplethysmography (Portapres, TPD Biomedical Instrumentation, Amsterdam, Netherlands) and intermittently from the brachial artery via an automated cuff (DINAMAP compact5, Critikon, New Jersey, USA); and arterial oxyhemoglobin saturation was collected via finger pulse oximetry (Datex-Ohmeda 3900, Helsinki, Finland). End-tidal partial pressures of oxygen ($P_{ET_{O_2}}$) and carbon dioxide ($P_{ET_{CO_2}}$) were monitored via a nasal cannula while

Table 1 | Demographics of the study cohort and resting end-tidal partial pressures of O_2 and CO_2, and cerebral hemodynamic indices in the posterior and middle cerebral arteries.

	Young	Older	*p*-values
Age, years	30 ± 5	64 ± 8	***p* < 0.001**
Height, cm	171 ± 9	169 ± 0	$p = 0.552$
Weight, kg	67 ± 13	77 ± 15	$p = 0.084$
SBP, mmHg	112 ± 9	120 ± 18	$p = 0.188$
DBP, mmHg	66 ± 6	68 ± 8	$p = 0.571$
MAP, mmHg	82 ± 6	85 ± 10	$p = 0.383$
Systemic AI, %	59.0 ± 9.4	80.3 ± 9.0	***p* < 0.001**
$P_{ET_{O_2}}$, Torr	85.3 ± 3.7	88.6 ± 6.4	$p = 0.149$
$P_{ET_{CO_2}}$, Torr	35.2 ± 3.3	33.2 ± 3.3	$p = 0.133$
POSTERIOR CEREBRAL ARTERY			
Sample size (n)	10	18	
V_{dia}, cm/s	22.6 ± 5.0	21.3 ± 5.0	$p = 0.514$
V_{sys}, cm/s	53.3 ± 12.0	49.7 ± 8.4	$p = 0.354$
V_{mean}, cm/s	34.4 ± 7.5	33.7 ± 7.2	$p = 0.829$
V_{refl}, cm/s	46.3 ± 9.4	51.6 ± 11.6	$p = 0.224$
Cerebral AI, %	80.5 ± 15.8	106.8 ± 16.8	***p* < 0.001**
CVC, cm/s/mmHg	0.43 ± 0.11	0.41 ± 0.12	$p = 0.694$
MIDDLE CEREBRAL ARTERY			
Sample size (n)	10	19	
V_{dia}, cm/s	40.0 ± 5.2	28.4 ± 7.4	***p* < 0.001**
V_{sys}, cm/s	94.2 ± 18.2	68.1 ± 11.8	***p* < 0.001**
V_{mean}, cm/s	60.0 ± 8.8	44.5 ± 9.3	***p* < 0.001**
V_{refl}, cm/s	79.8 ± 13.7	66.8 ± 14.0	***p* = 0.024**
Cerebral AI, %	76.1 ± 15.5	98.0 ± 19.0	***p* = 0.004**
CVC, cm/s/mmHg	0.74 ± 0.15	0.54 ± 0.13	***p* < 0.001**

Values are means ± SD.

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; systemic AI, systemic augmentation index; $P_{ET_{CO_2}}$, end-tidal partial pressure of CO_2; $P_{ET_{O_2}}$, end-tidal partial pressure of O_2; V_{dia}, velocity at diastole; V_{sys}, velocity at systole; V_{mean}, average velocity over cardiac cycle; V_{refl}, velocity at the reflected shoulder of peak systole; cerebral AI, cerebral augmentation index; CVC, cerebrovascular conductance; p-values: older compared to young. The bold p-values are to highlight the significant differences that were observed.

subjects performed a visual stimulation test. Next, a euoxic hypercapnic test was administered using the technique of dynamic end-tidal forcing (DEF) with the subject breathing through a mouthpiece with their nose occluded (Ide et al., 2003). The DEF system uses a negative feedback loop to control $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ at desired levels by adjusting the inspired fraction of CO_2 (F_ICO_2) and O_2 (F_IO_2) on a breath-by-breath basis using custom designed, dedicated software (BreatheM, v2.38, University Laboratory of Physiology, Oxford, UK) (Vantanajal et al., 2007; Beaudin et al., 2011). The DEF system controls $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ at desired levels independent of ventilatory frequency and depth. Respired gases were sampled at 20 mL/min via a fine capillary inserted into the nasal cannula during the visual stimulation test or the mouthpiece during the euoxic hypercapnic test for continuous analysis of F_ICO_2 and F_IO_2 by mass spectrometry (AMIS 2000, Innovision, Odense, Denmark).

VISUAL STIMULATION

To assess the CBF response to visual stimulation, the subject sat ∼50 cm from a 38.1 cm (i.e., 15 in) computer screen with their eyes in line with its center when looking straight ahead (Smith et al., 2008). Following instrumentation, the test started with a 2-min baseline consisting of looking at a black cross (height and width ∼1.5 cm) centered on a dark gray background. Baseline was followed by either 10 cycles of 40 s blocks ($n = 9$ older subjects) or 5 cycles of 80 s blocks ($n = 11$ older subjects and all young subjects) involving the flashing of an alternating black and white checkerboard stimulus for 20 or 40 s (ON), respectively. The ON stage was followed by 20 or 40 s of rest (OFF) where the screens display was the same as baseline conditions. The subject was instructed to always focus their eyes on the computer screen and their thoughts on the present task, and was monitored continuously to verify they were attending to the stimulus. All tests were performed in a darkened room.

This visual stimulation paradigm was chosen to minimize participant burden as it was also used with elderly stroke patients (data not reported), some of whom had mild dementia (Peca et al., 2013) and difficulty following relatively simple tasks. Therefore, using the current visual stimulation paradigm simplified the task by removing the necessity of continuously instructing subjects when to open and close their eyes.

EUOXIC HYPERCAPNIC TEST

The euoxic hypercapnic test began with 10 min of air breathing to determine mean resting $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ values. These mean resting end-tidal values were used to create an individualized hypercapnic protocol (Ide et al., 2003). The euoxic hypercapnic test consisted of three 120 s steps: Baseline ($P_{ET_{CO_2}} = +1.5$ Torr above resting values), Hypercapnia ($P_{ET_{CO_2}} = +6.5$ Torr above resting values), and Recovery ($P_{ET_{CO_2}} = +1.5$ Torr above resting values). Throughout the entire hypercapnic test, $P_{ET_{O_2}}$ was maintained at 88 Torr (mean euoxic $P_{ET_{O_2}}$ for the altitude (1103 m above sea level) at which the laboratory is located). Maintaining $P_{ET_{CO_2}}$ at +1.5 Torr above air breathing resting values during the Baseline and Recovery facilitates $P_{ET_{CO_2}}$ control (Ide et al., 2003) and reduces breath-to-breath variability in CBF velocity (Harris et al., 2006).

ANALYSIS

The peak velocity associated with the maximal Doppler frequency shift was averaged over each heart beat (V_{mean}; cm/s) and utilized as an index of CBF through the PCA and MCA.

Velocity waveform analysis was performed using a custom written Matlab program (Robertson et al., 2008). Output parameters included the diastolic minimum velocity (V_{dia}), velocity at systole (V_{sys}), velocity at the reflective shoulder (V_{refl}), and mean peak velocity (V_{mean}) (**Figure 1**). Next, the cerebral augmentation index (AI) was calculated (Kurji et al., 2006; Robertson et al., 2008):

$$\text{Cerebral AI} = \frac{V_{refl} - V_{dia}}{V_{sys} - V_{dia}} \times 100 \quad (1)$$

Finally, utilizing mean arterial pressure (MAP), beat-to-beat PCA and MCA cerebrovascular conductance (CVC) was calculated as:

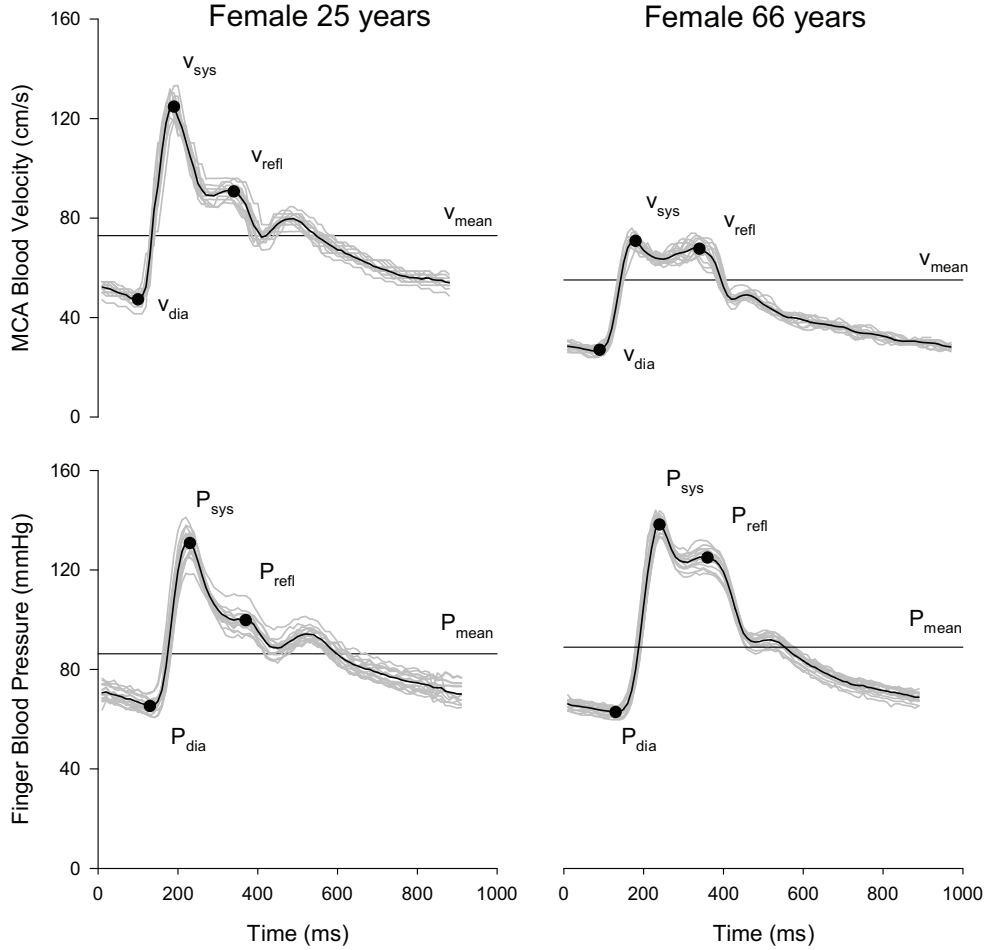


FIGURE 1 | Representative MCA blood velocity and finger blood pressure waveforms of a young (age = 25 years) and older (age = 66 years) volunteer at rest. Each plot shows the overlay of individual cardiac cycles (gray lines) over 15 s, the composite (i.e., mean waveform; black line), and the location of the waveform parameters.

$$\text{CVC} = \frac{V_{\text{mean}}}{\text{MAP}} \tag{2}$$

Visual waveform analysis was performed using the final 60 s of baseline and the final 30 s of a minimum of three ON phases (15 s for 40 s blocks). For the hypercapnic test, the final 60 s of the baseline and hypercapnic stage were analyzed to determine hypercapnic responses. Absolute blood flow changes in response to visual stimulation and hypercapnia were calculated by subtracting the baseline values from the ON phase and hypercapnia values, respectively. In addition, the relative (i.e., percent) change in blood flow from the preceding baseline in response to the visual stimulation and hypercapnia were calculated. Subsequently, PCA and MCA reactivity to hypercapnia was quantified in absolute (cm/s/Torr) and relative (%/Torr) units by dividing the respective increases in PCA and MCA blood velocity by the change in PET_{CO_2} from baseline into hypercapnia.

Systemic pressure waveform parameters were analyzed using the same automated algorithms implemented in Matlab used to analyze the velocity waveforms. Systemic AI was calculated analogically to the cerebral AI using systolic blood pressure (P_{sys}), diastolic blood pressure (P_{dia}) and blood pressure at the reflective shoulder (P_{refl}).

$$\text{Systemic AI} = \frac{P_{\text{refl}} - P_{\text{dia}}}{P_{\text{sys}} - P_{\text{dia}}} \times 100 \tag{3}$$

STATISTICAL ANALYSIS

All measured parameters had a normal distribution as assessed by the Kolmogorov-Smirnov Test. Differences in subject demographics and resting cerebrovascular hemodynamic parameters were compared using independent Student *T*-Tests. Next, within- and between-subject differences in responses to the visual stimulation and euoxic hypercapnia tests were assessed using 2-by-2 mixed factor repeated measures analyses of variance (RM ANOVA). The within-subject factor for the visual stimulation test was Visual Stimulation Stages (OFF and ON) and the within-subject factor for the hypercapnic test was Hypercapnic Test

Stages (Baseline and Hypercapnia). The between-subject factor was Age Groups (Young and Older). If there was a significant main effect of Visual Stimulation Stages or Hypercapnic Stages, *post-hoc* within-subject differences in cerebral blood velocity and waveform parameters between the OFF and ON or the Baseline and Hypercapnic stages (irrespective of Age Groups) were compared using paired Student *T*-Tests. If the interaction between the Visual Stimulation Stages or Hypercapnic Test Stages and Age Groups was significant [or showed a trend to be significant (i.e., $0.05 \leq p \leq 0.100$)], the magnitude of the response (i.e., absolute and relative delta values) for each age group were compared using independent 1-tailed Student *T*-Tests. All *post-hoc* analyses incorporated a Bonferroni correction for multiple comparisons.

Based upon previously published reports showing a curvilinear relationship between systemic AI and age (Kelly et al., 1989; Mitchell et al., 2004; McEniery et al., 2005), a similar relationship was plotted between cerebral AI and age. Alpha was set *a priori* at $p \leq 0.05$. Finally, the Pearson product-moment correlation was used to examine relationships between cerebral and systemic AI, changes in PCA blood velocity in response to the visual stimulation and cerebral AI, and hypercapnic reactivity for the PCA and MCA and cerebral AI. Statistical analyses were performed using SAS Enterprise Guide (4.3, SAS Institute Inc., Cary, NC, USA).

RESULTS

All study subjects ($n = 30$) completed the study. The TCD signal was of insufficient quality for analysis of PCA blood velocity in two older volunteers and of MCA blood velocity in one older volunteer. Subject demographics, resting blood pressure, resting $P_{ET}O_2$ and $P_{ET}CO_2$, and cerebral blood velocity parameters are presented in **Table 1**. Briefly, the young and older subjects were of similar height ($p = 0.552$) and weight ($p = 0.084$) and had similar systolic (SBP), diastolic (DBP) and mean arterial (MAP) blood pressures ($p \geq 0.188$). Additionally, resting, air breathing $P_{ET}O_2$ and $P_{ET}CO_2$ were similar between the two age groups ($p \geq 0.133$). In contrast, the older group had a significantly higher systemic AI ($p < 0.001$).

RESTING CEREBROVASCULAR HEMODYNAMIC PARAMETERS

At rest, while the subjects were breathing room air, PCA diastolic (V_{dia}), systolic (V_{sys}), mean (V_{mean}), and reflected (V_{refl}) blood velocities, as well as CVC, were similar between the young and older subjects ($p \geq 0.224$). Oppositely, PCA cerebral AI was lower in the young group ($p < 0.001$). For the MCA, all blood velocity waveform parameters (i.e., V_{dia}, V_{sys}, V_{mean}, and V_{refl}) and CVC were higher ($p \leq 0.024$), and cerebral AI was lower in the young group ($p = 0.004$).

RESPONSES TO VISUAL STIMULATION

There was no effect of the Visual Stimulation Stages and the interaction between the Visual Stimulation Stages and Age Groups main effects were not significant for $P_{ET}O_2$ ($p \geq 0.347$), $P_{ET}CO_2$ ($p \geq 0.518$), or MAP ($p \geq 0.107$). Thus, there was no change in $P_{ET}O_2$, $P_{ET}CO_2$, and MAP in response to the visual stimulation, irrespective of age, and any changes in $P_{ET}O_2$, $P_{ET}CO_2$, and MAP that occurred within each age group were similar (**Table 2**).

In the older group, visually evoked increases in PCA blood velocity were similar between those who performed 10 cycles of 40 s blocks and those who performed 5 cycles of 80 s blocks ($p = 0.172$). Thus, responses were grouped to provide a single group mean. The mean change in absolute, and relative, visually evoked changes in PCA and MCA mean blood velocities (V_{mean}) and CVC for both the young and older groups are shown in **Figure 2**. The Visual Stimulation Stages main effect was significant for both PCA ($p < 0.001$), and MCA, V_{mean} ($p = 0.041$) with V_{mean}, being higher during the ON stage for both arteries ($p \leq 0.041$) regardless of age. The increase in PCA V_{mean} was 3.4 ± 2.5 cm/s ($10.3 \pm 7.6\%$), which was greater ($p \leq 0.001$) than the increase in MCA V_{mean} of 1.1 ± 2.4 cm/s ($2.6 \pm 5.7\%$). Moreover, the interaction between the Visual Stimulation Stages and Age Groups main effects was significant for PCA V_{mean} ($p = 0.037$) as a result of a greater increase in absolute (and relative) PCA V_{mean} in the young group ($p \leq 0.026$; **Figure 2A**). The non-significant interaction between Visual Stimulation Stages and Age Groups for the MCA V_{mean} signifies the increase in MCA V_{mean} was similar between the two age groups (**Figure 2A**).

There was a significant effect of the Visual Stimulation Stages on PCA CVC ($p \leq 0.001$), but not MCA CVC ($p = 0.381$). Regardless of age, PCA CVC was higher during the ON stage of the visual stimulation test ($p \leq 0.001$). In addition, there was a trend for the interaction between the Visual Stimulation Stages and Age Groups main effects to be significant for PCA CVC ($p = 0.067$) while the interaction was not significant for MCA CVC ($p = 0.187$; **Figure 2B**). Although the interaction term showed only a trend, *post-hoc* 1-tailed comparisons of the change in PCA CVC (absolute and relative) showed the increase in CVC was greater in the young group ($p \leq 0.034$; **Figure 2B**).

Finally, the Visual Stimulation Stages main effect was significant for PCA V_{dia}, V_{sys}, and V_{refl} ($p \leq 0.001$) as all velocities were elevated in response to the visual stimuli within the young and older groups. In contrast, the Visual Stimulation Stages main effect was significant for only MCA V_{dia} ($p = 0.015$) with it being elevated in response to the visual stimuli (**Table 2**). Additionally, there was a significant interaction between the Visual Stimulation Stages and Age Groups main effects for PCA V_{dia} ($p = 0.032$) and V_{sys} ($p = 0.028$) with the young subjects having a greater increase in the two velocities in response to the visual stimuli (**Table 2**). The interaction was not significant for MCA V_{dia}, V_{sys}, and V_{refl} ($p \geq 0.187$).

RESPONSES TO EUOXIC HYPERCAPNIA

Baseline $P_{ET}O_2$ and $P_{ET}CO_2$were 87.8 ± 2.4 Torr and 37.3 ± 3.0 Torr for the young group and 87.8 ± 1.8 Torr and 35.6 ± 3.3 Torr in the older group ($p \geq 0.172$). Subsequently, $P_{ET}O_2$ and $P_{ET}CO_2$ during the hypercapnic stage were 87.5 ± 2.0 Torr and 41.8 ± 3.2 Torr in the young group and 87.3 ± 1.8 Torr and 40.5 ± 3.0 Torr in the older group ($p \geq 0.277$). There was no interaction between the Hypercapnic Stages and Age Groups for either $P_{ET}O_2$ or $P_{ET}CO_2$ ($p \geq 0.326$). Thus, $P_{ET}O_2$ and the increase in $P_{ET}CO_2$, with hypercapnia were similar between young and older subjects ($p \geq 0.728$; **Table 2**). For MAP, there was a significant effect the Hypercapnic Stages ($p < 0.001$) as MAP was increased with hypercapnia irrespective of age. The interaction between the

Table 2 | Changes in $P_{ET_{CO_2}}$, $P_{ET_{O_2}}$, MAP, and absolute and relative (i.e., percent) changes in cerebral waveform parameters for the posterior and middle cerebral arteries in response to the visual stimulation and CO_2 test in the young and older groups.

	Visual stimulation			CO_2 Test		
	Young	**Older**	***p*-values**	**Young**	**Older**	***p*-values**
$\Delta P_{ET_{CO_2}}$ (Torr)	0.2 ± 1.0	0.1 ± 1.1	$p = 0.681$	4.5 ± 1.0	4.7 ± 1.6	$p = 0.728$
$\Delta P_{ET_{O_2}}$ (Torr)	−1.0 ± 2.7	−0.3 ± 3.5	$p = 0.585$	−0.4 ± 2.4	−0.4 ± 2.4	$p = 0.970$
ΔMAP	−2.2 ± 2.8	1.42 ± 6.5	$p = 0.107$	4.3 ± 4.2	3.6 ± 4.9	$p = 0.712$
POSTERIOR CEREBRAL ARTERY						
Sample size (n)	10	18		10	18	
ΔV_{dia}, cm/s	3.6 ± 1.6	2.2 ± 1.6	**$p = 0.016$**	6.2 ± 1.3	3.4 ± 2.0	**$p < 0.001$**
ΔV_{dia}, %	16.6 ± 7.7	11.3 ± 8.8	$p = 0.059$	24.0 ± 7.5	15.7 ± 8.6	**$p = 0.009$**
ΔV_{sys}, cm/s	5.3 ± 3.6	2.7 ± 2.5	**$p = 0.014$**	7.5 ± 4.6	4.7 ± 3.2	**$p = 0.035$**
ΔV_{sys}, %	10.5 ± 7.1	5.6 ± 4.9	**$p = 0.019$**	13.7 ± 7.5	10.1 ± 6.2	$p = 0.088$
ΔV_{refl}, cm/s	5.7 ± 3.1	3.6 ± 3.2	**$p = 0.047$**	9.0 ± 3.3	5.9 ± 3.3	**$p = 0.012$**
ΔV_{refl}, %	12.8 ± 7.0	7.2 ± 6.6	**$p = 0.022$**	17.1 ± 7.1	11.9 ± 7.3	**$p = 0.041$**
MIDDLE CEREBRAL ARTERY						
Sample size (n)	10	19		10	19	
ΔV_{dia}, cm/s	0.6 ± 1.9	1.3 ± 1.9	$p = 0.174$	10.9 ± 3.2	5.6 ± 2.4	**$p < 0.001$**
ΔV_{dia}, %	1.7 ± 5.2	5.8 ± 9.6	$p = 0.110$	23.6 ± 6.4	18.2 ± 6.8	**$p = 0.024$**
ΔV_{sys}, cm/s	−0.3 ± 4.4	1.4 ± 2.3	$p = 0.093$	11.6 ± 5.2	7.9 ± 5.0	**$p = 0.034$**
ΔV_{sys}, %	−0.2 ± 4.7	2.2 ± 3.4	$p = 0.061$	12.0 ± 4.5	11.7 ± 7.4	$p = 0.465$
ΔV_{refl}, cm/s	0.9 ± 3.7	1.6 ± 3.5	$p = 0.299$	15.7 ± 3.8	10.3 ± 4.8	**$p = 0.002$**
ΔV_{refl}, %	1.2 ± 4.9	2.7 ± 6.3	$p = 0.263$	17.7 ± 3.9	14.9 ± 7.5	$p = 0.150$

Values are means ± SD.

$P_{ET_{CO_2}}$, end-tidal partial pressure of carbon dioxide; $P_{ET_{O_2}}$, end-tidal partial pressure of oxygen; MAP, mean arterial pressure; V_{dia}, velocity at diastole; V_{sys}, velocity at systole; V_{refl}, velocity at the reflected shoulder of peak systole; cerebral AI, cerebral augmentation index; CVC, cerebrovascular conductance.

P-values within table are for older vs. young comparisons. The bold p-values are to highlight the significant differences that were observed.

Hypercapnic Stages and Age Groups main effects was not significant ($p = 0.712$) as the increase in MAP was similar between young and older subjects (**Table 2**).

Absolute and relative increases in PCA and MCA V_{mean}, and CVC with hypercapnia are shown in **Figure 3**. There was a significant interaction between the Hypercapnic Stages and Age Groups main effects for both PCA ($p = 0.004$) and MCA ($p < 0.001$) V_{mean}. In addition, the interaction between the Hypercapnic Stages and Age Groups was significant for CVC in both arteries (PCA: $p = 0.039$; MCA: $p = 0.007$). *Post-hoc* comparisons showed the absolute, and relative, increases in PCA V_{mean} were significantly lower in older subjects ($p \leq 0.031$) while the absolute increase in MCA V_{mean} was lower in the older subjects ($p \leq 0.001$) and the relative increase in MCA V_{mean} showed a trend to be lower in the older group ($p = 0.097$). Also, the absolute increase in CVC with hypercapnia was lower in the older group for both the PCA ($p = 0.025$), and MCA ($p = 0.005$), but the relative increase in CVC showed only a trend to be lower in the older group for the PCA ($p = 0.057$) while MCA CVC was similar between the two groups ($p = 0.237$). The interaction between the Hypercapnic Stages and Age Groups main effects was significant for PCA and MCA V_{dia} ($p \leq 0.001$) and V_{refl} ($p \leq 0.024$), but not V_{sys} ($p \geq 0.068$). **Table 2** shows the results of *post-hoc* age group comparisons of the change in PCA and MCA V_{dia}, V_{sys}, and V_{refl} with hypercapnia.

The smaller absolute, and relative, increases in PCA V_{mean} within the older group translated into lower absolute (i.e., cm/s/Torr) and relative (i.e., %/Torr) reactivities to hypercapnia ($p \leq 0.018$) compared to the young group (**Figure 4**). Similarly, absolute, and relative, MCA hypercapnia reactivity was lower in the older group ($p \leq 0.042$). Relative PCA and MCA hypercapnic reactivity values for the older group have been previously reported in comparison to a patient population (Peca et al., 2013).

VISUALLY-EVOKED AND HYPERCAPNIC CBF RESPONSES: RELATION TO ARTERIAL STIFFNESS

Cerebral AI for both the PCA and the MCA was highly correlated ($p < 0.001$) with systemic AI (**Figure 5A**). Furthermore, the curvilinear model fitted to the cerebral AI and age relationship was significant for both arteries ($p < 0.001$; **Figure 5B**). **Figure 6** shows the relationships between responses in PCA V_{mean} to the visual stimulation and cerebral AI as well as the relationships between PCA and MCA hypercapnia reactivities and cerebral AI. The change in PCA V_{mean} (relative and absolute) in response to the visual stimulation was not related cerebral AI ($p \geq 0.128$). Similarly, the correlations between absolute, and relative, PCA hypercapnia reactivity and cerebral AI were not significant ($p \geq 103$). In contrast, there was a significant negative correlation between relative, and absolute, measures of MCA hypercapnia reactivities and cerebral AI ($p \leq 0.013$) with lower reactivity at higher cerebral AIs.

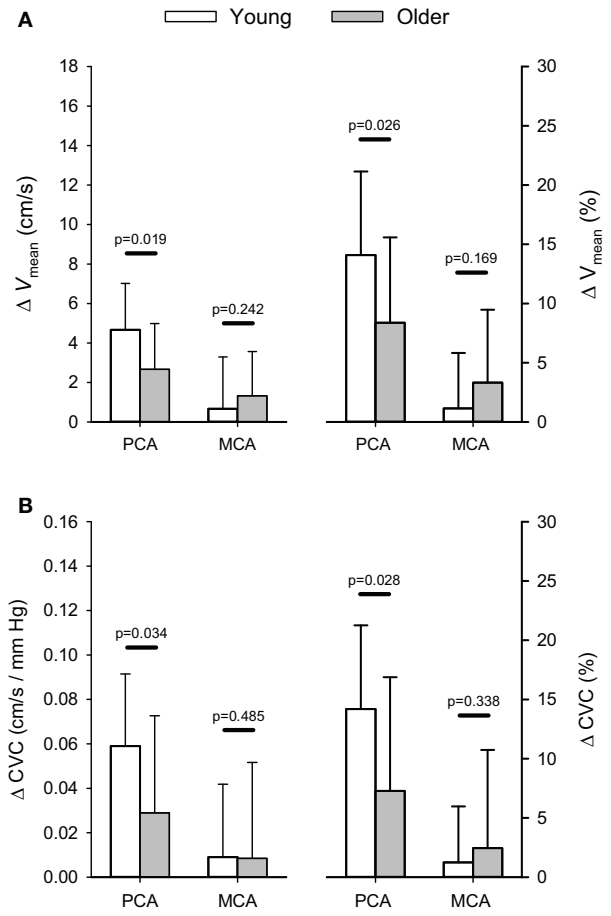


FIGURE 2 | Absolute (cm/s) and relative (%) changes (Δ) in posterior (PCA) and middle cerebral artery (MCA) blood velocity (A) and cerebrovascular conductance (B) in response to visual stimulation. *P*-values provided for comparison between young and older volunteers.

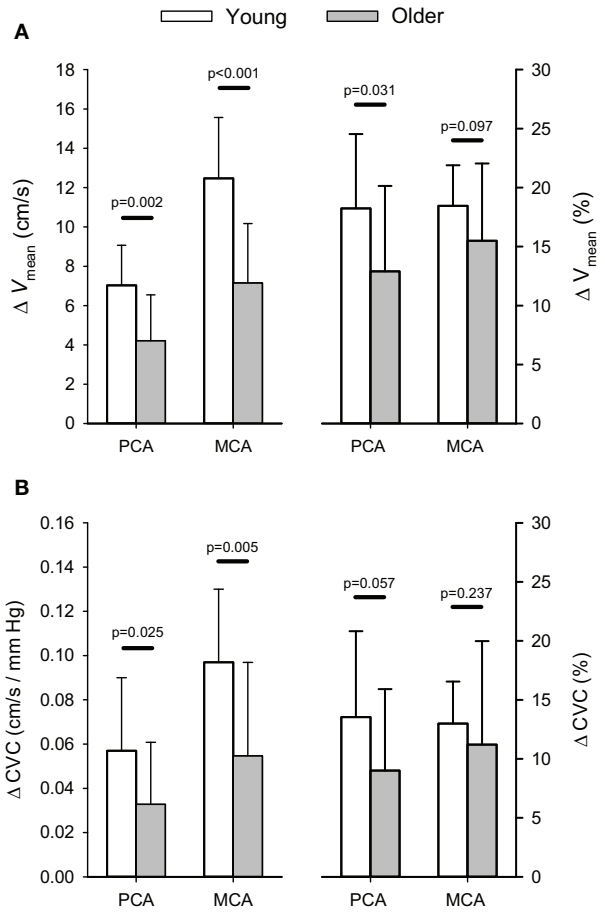


FIGURE 3 | Absolute (cm/s) and relative (%) changes (Δ) in posterior (PCA) and middle cerebral artery (MCA) blood velocity (A) and cerebrovascular conductance (B) in response to euoxic hypercapnic test. *P*-values provided for comparison between young and older volunteers.

DISCUSSION

In this study we assessed age-related changes in resting CBF through two cerebral arteries (PCA and MCA), as well as changes in CBF through the PCA and MCA in response to neuronal activation (via a visual stimulus) and hypercapnia in young and older healthy humans. The main findings were (1) resting PCA blood flow was not reduced with age, but resting MCA blood flow was lower in older subjects, (2) CBF responses to visual stimulation and hypercapnia were lower in older subjects; (3) cerebral and systemic AI increased with age and were highly correlated; and (4) cerebrovascular reactivity to hypercapnia through the MCA was inversely related to cerebral AI.

Resting CBF has been reported to decrease with advancing age (Kety, 1956; Leenders et al., 1990), but this is not a consistent finding (Yamaguchi et al., 1986). Reduced cerebral metabolism and brain atrophy are likely primary contributors to the age-related reduction in CBF (Leenders et al., 1990), but hemodynamic alterations such as increased arterial stiffness may also be involved (Zhu et al., 2011). In the current study, resting PCA blood flow was similar between the young and older groups, while the MCA blood flow was significantly lower in the older group. The lower resting MCA blood flow is consistent with prior studies utilizing TCD (Nishiyama et al., 1997; Ainslie et al., 2008; Secher et al., 2008; Galvin et al., 2010; Zhu et al., 2013), but the maintained resting PCA blood flow in the older group is in contrast to two previous studies that reported concurrent decreases in both PCA, and MCA, blood flow with aging (Muller and Schimrigk, 1994; Demirkaya et al., 2008). However, in the study by Muller and Schimrigk (1994) the age-related decline was more pronounced for the MCA than the PCA—29 vs. 17%. Oppositely, Demirkaya et al. (2008) reported a ∼20% decrease in both MCA and PCA blood flow with increasing age. In conjunction with the findings by Muller and Schimrigk (1994), the observation of a maintained resting PCA blood flow, but a lower resting MCA blood flow, reflect potential regional differences in cerebrovascular changes with aging. These contrasting changes in PCA and MCA blood flow may be the result of the PCA being a smaller artery with, generally, lower blood flow compared to the MCA. As a result,

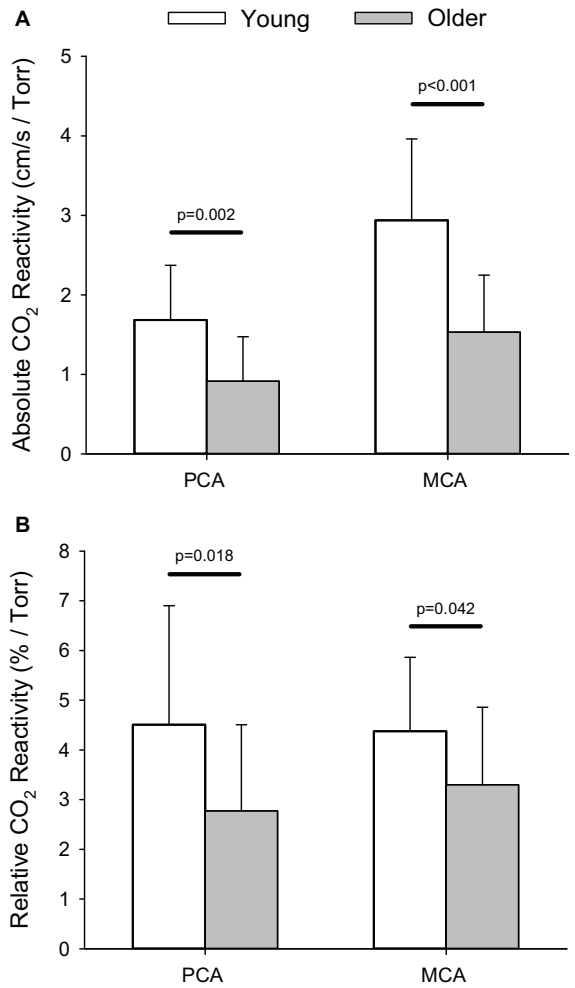


FIGURE 4 | Absolute (i.e., cm/s/Torr; A) and relative (i.e., %/Torr, B) reactivity for posterior (PCA) and middle cerebral artery (MCA) blood velocity in response to the hypercapnic test. *P*-values provided for comparison between young and older volunteers.

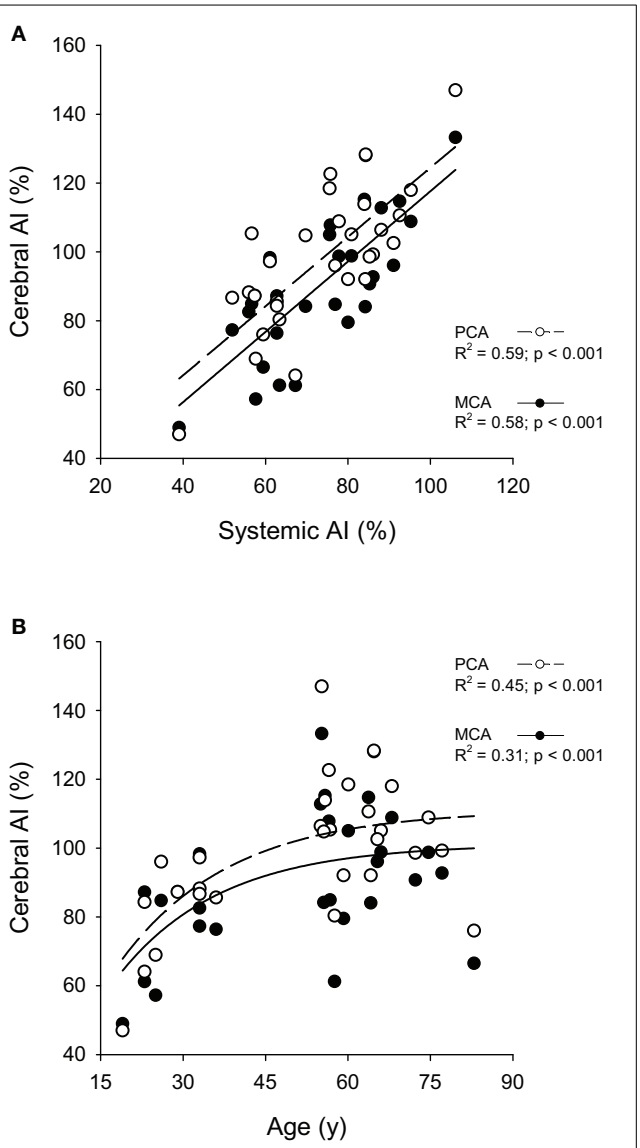


FIGURE 5 | Relationships between the cerebral augmentation index (Cerebral AI) and Systemic AI in the middle (MCA) and posterior cerebral arteries (PCA) (A) and Cerebral AI and Age in MCA and PCA (B).

the PCA likely has a reduced capacity to decrease flow (i.e., floor effect) in comparison to the MCA. An additional explanation of why aging may affect the PCA and MCA differently, is that the PCA and MCA bifurcate from different arteries (basilar artery vs. internal carotid artery, respectively) and perfuse differing volumes of brain tissue. The degree of atrophy with healthy aging varies across brain regions with the visual cortex being the most stable across the lifespan (Raz et al., 2005). However, the reduction in CBF with aging has been reported not to be related to brain atrophy (Chen et al., 2011). Interestingly, cerebral AI values were increased for both the MCA, and PCA, in the older group, but resting CBF was not related to AI for either artery (PCA: $R^2 = 0.08$, $p = 0.138$; MCA: $R^2 = 0.04$, $p = 0.290$; data not shown). Therefore, arterial stiffness does not appear to be involved in age-related changes in resting blood flow through these two arteries.

Although visual-evoked increases in blood flow were observed in both the PCA and MCA, the response observed in the PCA was much greater in both age groups. In young subjects, PCA blood flow increased ∼14% while blood flow through the MCA increased only ∼1%. Similarly, in older subjects, PCA blood flow increased ∼8 vs. a ∼3% increase in MCA blood flow. In contrast, hypercapnia caused similar relative increases in CBF through both the PCA and MCA (18% in the young group and ∼14% in the older group). These contrary responses between the PCA and MCA to these two stimuli reflect the respective local and global responses evoked by the visual stimulation and hypercapnic tests (Tominaga et al., 1976; Aaslid, 1987).

The lower PCA blood flow response to the visual stimulation in the older group is similar to previous studies reporting aging-related declines in PCA blood flow responses to a visual stimulus

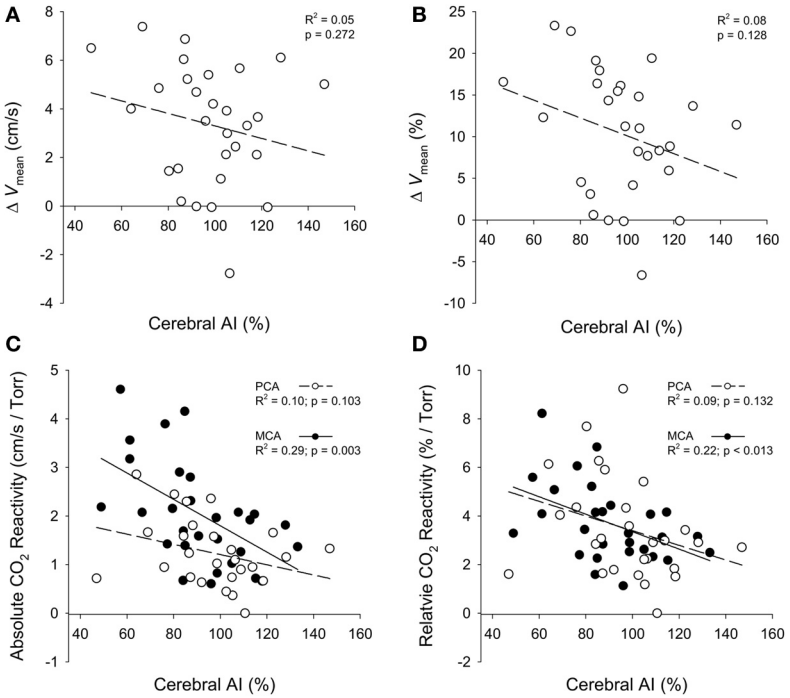


FIGURE 6 | Relationships between the absolute (cm/s) and relative (%) changes in PCA mean blood velocity (ΔV_{mean}) in response to the visual stimulation and cerebral AI (A,B); and the relationships between the absolute (cm/s/Torr) and relative (%/Torr) reactivities to CO_2 for the PCA and MCA with cerebral AI (C,D).

(Niehaus et al., 2001; Zheng et al., 2003), but in contrast to other studies reporting no change with increasing age (Panczel et al., 1999; Rosengarten et al., 2003). The mechanism(s) underlying visually evoked blood flow responses is incompletely defined, but include a critical role of the neurovascular unit (i.e., astrocytes in combination with the neurons and blood vessels), as summarized in recent reviews (Iadecola, 2004; Drake and Iadecola, 2007; Iadecola and Nedergaard, 2007; Lok et al., 2007; Koehler et al., 2009). Thus, the observed decrease in PCA blood flow responses with aging may reflect a disruption of the neurovascular unit with aging resulting from neuronal loss and/or vascular remodeling (Panczel et al., 1999).

For cerebrovascular reactivity to hypercapnia, reports are also inconsistent regarding age-related alterations with studies reporting decreased (Nishiyama et al., 1997; Bakker et al., 2004), maintained (Kastrup et al., 1998; Ito et al., 2002; Galvin et al., 2010) and even enhanced hypercapnia reactivity with advancing age (Zhu et al., 2013). The lower PCA and MCA hypercapnic reactivity in the older group observed in the current study are in agreement with the prior studies reporting cerebrovascular reactivity to hypercapnia is decreased with advancing age.

A novel aspect of the current study is the observed decrease in both PCA and MCA reactivity to hypercapnia. Prior studies investigating changes in cerebrovascular reactivity to hypercapnia with aging via TCD have monitored only changes in MCA reactivity (Nishiyama et al., 1997; Kastrup et al., 1998; Ito et al., 2002; Bakker et al., 2004; Galvin et al., 2010; Zhu et al., 2013), thus ignoring potential regional differences that may occur. Therefore, the lower PCA and MCA hypercapnic reactivity in the older group signifies that, in contrast to the regional differences observed in age-related changes in resting CBF, the decreased cerebrovascular reactivity to hypercapnia is a global cerebral phenomenon. The mechanism responsible for the vascular responses to hypercapnia is thought to be the increase in H^+ concentration in the cerebrospinal fluid which leads to relaxation of the smooth muscle around the cerebral vessels (Gotoh et al., 1961; Kontos et al., 1977a,b; Berne et al., 1981). As a result, the decline in hypercapnic reactivity in both the PCA and MCA reflect a homogenous decline in the capacity of the cerebrovasculature to dilate in response to hypercapnia.

As the mechanisms underlying the regulation of vascular responses to visual stimulation and hypercapnia are different, but both responses are decreased with age, there is a likely common factor that is altered with age contributing to the reduced evoked responses. The mechanical function of the vasculature is involved in both mechanisms and thus, is a likely candidate contributing to the two decreased evoked responses. Furthermore, Zhu et al. (2011) who applied a transfer function method to estimate cerebrovascular impedance, suggested arterial stiffness may contribute to attenuations in CBF with age. With aging, systemic arterial stiffening has been reported to increase in a curvilinear fashion with the greatest increase occurring between 30 and 60 years of age (Kelly et al., 1989; Mitchell et al., 2004; McEniery et al., 2005). Mitchell et al. (2004) reported a leveling off and even a slight decrease of the reflected pressure wave in individuals 50 years of age or older that was explained by an impedance

matching due to marked increases in aortic stiffness compared to only slight increases in the periphery and, thus a reduction of wave reflection. PCA and MCA cerebral AIs were strongly correlated with systemic AI, and increased reflected waves were observed in both the velocity (i.e., cerebral), and pressure (i.e., systemic) waveforms within both arteries. This high degree of correlation between cerebral and system AI is similar to the studies by Kwater et al. (2009) and Xu et al. (2012) reporting significant correlations between MCA and systemic arterial stiffness indices. Based upon the observed high correlation between cerebral and systemic AI, a curvilinear function was fitted to the cerebral AI and age relationship. Although additional data is needed to fully support a curvilinear relationship between cerebral AI and age due to the gap of ∼2 decades between our young and older groups, the curvilinear relationships plotted had moderate coefficients of determination (i.e., R^2) for the PCA (0.45) and MCA (0.31). Moreover, consistent with the systemic arterial stiffness and age relationship (Kelly et al., 1989; Mitchell et al., 2004; McEniery et al., 2005) the greatest increase in cerebral AI occurred between 20 and 60 years of age. Hence, cerebral and system arterial stiffness may increase in parallel with healthy aging.

Although the negative relationship between the increase in PCA blood flow with visual stimulation and cerebral AI is in agreement with our hypothesis (i.e., increased arterial stiffness contributes to decreased blood flow responses), the relationship was not significant. Similarly, the negative relationship between the PCA hypercapnic reactivity and cerebral AI was not significant. In contrast, a lower MCA hypercapnic reactivity was related to an increased cerebral AI. These divergent findings for the hypercapnic reactivity between the PCA and MCA suggest MCA reactivity is more susceptible to arterial stiffening. The non-significant relationship between PCA blood flow responses to the visual and hypercapnic stimuli and cerebral AI may have resulted from the greater variability in the PCA response to hypercapnia and/or the PCA AI having a smaller distribution compared to the MCA AI. Another potential explanation is that AI magnitude is dependent upon wave reflections throughout the vascular bed resulting from vessel branching, changes in vessel wall diameter and/or material properties (Mitchell et al., 2011). Thus, changes in vascular morphology with aging will impact on the relationship between vascular reactivity and cerebral AI. With aging, there is a decrease in the number of downstream blood vessels from the PCA and MCA with a greater decline occurring within the MCA circulation (Bullitt et al., 2010). In contrast, there is a greater increase in vessel tortuosity within the MCA circulation compared to the PCA circulation with advancing age (Bullitt et al., 2010). As a result, the stronger relationship between vascular reactivity through the MCA and cerebral AI may be driven by an increase in vessel tortuosity that occurs with healthy aging.

Lastly, this study has some limitations, which need to be acknowledged. First, TCD measures blood velocity through the insonated artery and not absolute blood flow. However, the two are highly correlated (Brauer et al., 1998). Moreover, the diameter of the PCA during visual stimulation does not change (Aaslid, 1987), and the diameter of both, the PCA, and MCA, has been shown not to change significantly in response to moderate hypercapnia as employed in this study (Giller et al., 1993; Poulin and Robbins, 1996; Serrador et al., 2000; Willie et al., 2012). Thus, in this situation, changes in blood velocity will lead to a corresponding increase in absolute blood flow. As such, assessment of blood velocity through the PCA and MCA with TCD has been accepted as a reliable index of CBF. Secondly, the gold standard to assess vessel stiffness is pulse wave velocity measurement (Tomlinson, 2012). AI is straightforward to measure, by monitoring blood pressure or blood velocity waveforms; however wave reflections are not only dependent on arterial stiffness but also on the site of reflection. In addition, blood pressure is said to influence the vessel wall properties due to the distending pressure (Chirinos, 2012). However, subjects in the present study were assessed at rest and the chosen time periods used for AI calculations was assured to be as stable as possible.

In conclusion, CBF responses to both visual stimulation and hypercapnia decreased with advancing age with a concomitant increase in cerebrovascular stiffness. The decreases in PCA reactivity to a visual stimulus and hypercapnia were not related to increased cerebrovascular stiffness, whereas MCA hypercapnia reactivity decreased as cerebrovascular stiffness increased. Finally, analysis of the cerebral blood velocity waveform offers a non-invasive approach to assess vascular health and provide an index of arterial stiffness.

AUTHOR CONTRIBUTIONS

Daniela Flück participated in study design, collected and analyzed TCD data from the older participants, drafted the manuscript, critically reviewed and revised the manuscript; Andrew E. Beaudin and Craig D. Steinback participated in study design, co-collected and co-analyzed TCD data from young participants, critically reviewed and revised the manuscript. Gopukumar Kumarpillai and Nandavar Shobha performed assessments on older participants, critically reviewed and revised the manuscript; Cheryl R. McCreary and Stefano Peca participated in study design, critically reviewed and revised the manuscript; Eric E. Smith conceived of the study, secured study funding, participated in study design, critically reviewed and revised the manuscript; and Marc J. Poulin conceived the study, secured study funding, supervised trainees (Daniela Flück, Andrew E. Beaudin, Craig D. Steinback) and acquisition and analysis of TCD data, critically reviewed and revised the manuscript for intellectual content. All authors approved the final version of the manuscript.

ACKNOWLEDGMENTS

We thank our dedicated subjects for their participation in this study. This study was supported by operational funds provided by the Canadian Stroke Network (CSN; PI = Eric E. Smith, Co-Applicant = Marc J. Poulin), the Canadian Institutes of Health Research (CIHR; Marc J. Poulin), the Heart and Stroke Foundation of Canada (HSFC; Marc J. Poulin), the Natural Sciences and Engineering Research Council of Canada (NSERC; Marc J. Poulin), the Alzheimer Society of Canada (Eric E. Smith), and the Canadian Foundation for Innovation (CFI; Marc J. Poulin). Andrew E. Beaudin was supported by an Alberta-Innovates-Health Solutions (AI-HS) doctoral fellowship and the CIHR-HSFC Focus on Stroke doctoral fellowship. Craig D. Steinback was supported by NSERC and AI-HS post-doctoral

fellowships. Eric E. Smith receives salary support from AI-HS and is the Kathy Taylor Chair in Vascular Dementia; and Marc J. Poulin is the Brenda Strafford Foundation Chair in Alzheimer Research.

REFERENCES

Aaslid, R. (1987). Visually evoked dynamic blood flow response of the human cerebral circulation. *Stroke* 18, 771–775. doi: 10.1161/01.STR.18.4.771

Ainslie, P. N., Cotter, J. D., George, K. P., Lucas, S., Murrell, C., Shave, R., et al. (2008). Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. *J. Physiol.* 586, 4005–4010. doi: 10.1113/jphysiol.2008.158279

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders (4th Edn., Text Revision)*. Washington, DC: American Psychiatric Publishing.

Bakker, S. L., De Leeuw, F. E., Den Heijer, T., Koudstaal, P. J., Hofman, A., and Breteler, M. M. (2004). Cerebral haemodynamics in the elderly: the rotterdam study. *Neuroepidemiology* 23, 178–184. doi: 10.1159/000078503

Beaudin, A. E., Brugniaux, J. V., Vohringer, M., Flewitt, J., Green, J. D., Friedrich, M. G., et al. (2011). Cerebral and myocardial blood flow responses to euoxic hypercapnia and isocapnic hypoxia in humans. *Am. J. Physiol. Heart Circ. Physiol.* 301, H1678–H1686. doi: 10.1152/ajpheart.00281.2011

Benetos, A., Laurent, S., Hoeks, A. P., Boutouyrie, P. H., and Safar, M. E. (1993). Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries. *Arterioscler. Thromb.* 13, 90–97. doi: 10.1161/01.ATV.13.1.90

Berne, R. M., Winn, H. R., and Rubio, R. (1981). The local regulation of cerebral blood flow. *Prog. Cardiovasc. Dis.* 24, 243–260. doi: 10.1016/0033-0620(81)90030-X

Brauer, P., Kochs, E., Werner, C., Bloom, M., Policare, R., Pentheny, S., et al. (1998). Correlation of transcranial Doppler sonography mean flow velocity with cerebral blood flow in patients with intracranial pathology. *J. Neurosurg. Anesthesiol.* 10, 80–85. doi: 10.1097/00008506-199804000-00003

Bullitt, E., Zeng, D., Mortamet, B., Ghosh, A., Aylward, S. R., Lin, W., et al. (2010). The effects of healthy aging on intracerebral blood vessels visualized by magnetic resonance angiography. *Neurobiol. Aging* 31, 290–300. doi: 10.1016/j.neurobiolaging.2008.03.022

Chen, J. J., Rosas, H. D., and Salat, D. H. (2011). Age-associated reductions in cerebral blood flow are independent from regional atrophy. *Neuroimage* 55, 468–478. doi: 10.1016/j.neuroimage.2010.12.032

Chirinos, J. A. (2012). Arterial stiffness: basic concepts and measurement techniques. *J. Cardiovasc. Transl. Res.* 5, 243–255. doi: 10.1007/s12265-012-9359-6

Demirkaya, S., Uluc, K., Bek, S., and Vural, O. (2008). Normal blood flow velocities of basal cerebral arteries decrease with advancing age: a transcranial Doppler sonography study. *Tohoku J. Exp. Med.* 214, 145–149. doi: 10.1620/tjem.214.145

Drake, C. T., and Iadecola, C. (2007). The role of neuronal signaling in controlling cerebral blood flow. *Brain Lang.* 102, 141–152. doi: 10.1016/j.bandl.2006.08.002

Edvinsson, L., and Krause, D. N. (2002). *Cerebral Blood Flow and Metabolism*. Philadelphia, PA: Lippincott Williams and Wilkins.

Fisher, J. P., Hartwich, D., Seifert, T., Olesen, N. D., McNulty, C. L., Nielsen, H. B., et al. (2013). Cerebral perfusion, oxygenation and metabolism during exercise in young and elderly individuals. *J. Physiol.* 591, 1859–1870. doi: 10.1113/jphysiol.2012.244905

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Fonck, E., Feigl, G. G., Fasel, J., Sage, D., Unser, M., Rufenacht, D. A., et al. (2009). Effect of aging on elastin functionality in human cerebral arteries. *Stroke* 40, 2552–2556. doi: 10.1161/STROKEAHA.108.528091

Galvin, S. D., Celi, L. A., Thomas, K. N., Clendon, T. R., Galvin, I. F., Bunton, R. W., et al. (2010). Effects of age and coronary artery disease on cerebrovascular reactivity to carbon dioxide in humans. *Anaesth. Intensive Care* 38, 710–717.

Giller, C. A., Bowman, G., Dyer, H., Mootz, L., and Krippner, W. (1993). Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery* 32, 737–741. discussion: 741–732.

Gotoh, F., Tazaki, Y., and Meyer, J. S. (1961). Transport of gases through brain and their extravascular vasomotor action. *Exp. Neurol.* 4, 48–58. doi: 10.1016/0014-4886(61)90077-2

Harris, A. D., Ide, K., Poulin, M. J., and Frayne, R. (2006). Control of end-tidal PCO2 reduces middle cerebral artery blood velocity variability: implications for physiological neuroimaging. *Neuroimage* 29, 1272–1277. doi: 10.1016/j.neuroimage.2005.08.023

Iadecola, C. (2004). Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat. Rev. Neurosci.* 5, 347–360. doi: 10.1038/nrn1387

Iadecola, C., and Nedergaard, M. (2007). Glial regulation of the cerebral microvasculature. *Nat. Neurosci.* 10, 1369–1376. doi: 10.1038/nn2003

Ide, K., Eliasziw, M., and Poulin, M. J. (2003). Relationship between middle cerebral artery blood velocity and end-tidal PCO2 in the hypocapnic-hypercapnic range in humans. *J. Appl. Physiol.* 95, 129–137. doi: 10.1152/japplphysiol.01186.2002

Ito, H., Kanno, I., Ibaraki, M., and Hatazawa, J. (2002). Effect of aging on cerebral vascular response to Paco2 changes in humans as measured by positron emission tomography. *J. Cereb. Blood Flow Metab.* 22, 997–1003. doi: 10.1097/00004647-200208000-00011

Jennings, J. R., Heim, A. F., Kuan, D. C., Gianaros, P. J., Muldoon, M. F., and Manuck, S. B. (2013). Use of total cerebral blood flow as an imaging biomarker of known cardiovascular risks. *Stroke* 44, 2480–2485. doi: 10.1161/STROKEAHA.113.001716

Kastrup, A., Dichgans, J., Niemeier, M., and Schabet, M. (1998). Changes of cerebrovascular CO2 reactivity during normal aging. *Stroke* 29, 1311–1314. doi: 10.1161/01.STR.29.7.1311

Kelly, R., Hayward, C., Avolio, A., and O'Rourke, M. (1989). Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 80, 1652–1659. doi: 10.1161/01.CIR.80.6.1652

Kety, S. S. (1956). Human cerebral blood flow and oxygen consumption as related to aging. *J. Chronic. Dis.* 3, 478–486. doi: 10.1016/0021-9681(56)90146-1

Koehler, R. C., Roman, R. J., and Harder, D. R. (2009). Astrocytes and the regulation of cerebral blood flow. *Trends Neurosci.* 32, 160–169. doi: 10.1016/j.tins.2008.11.005

Kontos, H. A., Raper, A. J., and Patterson, J. L. (1977a). Analysis of vasoactivity of local pH, PCO2 and bicarbonate on pial vessels. *Stroke* 8, 358–360. doi: 10.1161/01.STR.8.3.358

Kontos, H. A., Wei, E. P., Raper, A. J., and Patterson, J. L. Jr. (1977b). Local mechanism of CO2 action of cat pial arterioles. *Stroke* 8, 226–229. doi: 10.1161/01.STR.8.2.226

Kurji, A., Debert, C. T., Whitelaw, W. A., Rawling, J. M., Frayne, R., and Poulin, M. J. (2006). Differences between middle cerebral artery blood velocity waveforms of young and postmenopausal women. *Menopause* 13, 303–313. doi: 10.1097/01.gme.0000177905.94515.24

Kwater, A., Gasowski, J., Gryglewska, B., Wizner, B., and Grodzicki, T. (2009). Is blood flow in the middle cerebral artery determined by systemic arterial stiffness? *Blood Press* 18, 130–134. doi: 10.1080/08037050902975114

Laurent, S., Alivon, M., Beaussier, H., and Boutouyrie, P. (2012). Aortic stiffness as a tissue biomarker for predicting future cardiovascular events in asymptomatic hypertensive subjects. *Ann. Med.* 44(Suppl. 1), S93–S97. doi: 10.3109/07853890.2011.653398

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., et al. (2006). Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur. Heart J.* 27, 2588–2605. doi: 10.1093/eurheartj/ehl254

Leenders, K. L., Perani, D., Lammertsma, A. A., Heather, J. D., Buckingham, P., Healy, M. J., et al. (1990). Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. *Brain* 113(Pt 1), 27–47. doi: 10.1093/brain/113.1.27

Lisak, M., Trkanjec, Z., Mikula, I., and Demarin, V. (2005). Mean blood flow velocities in posterior cerebral arteries during visual stimulation. *Mt. Sinai J. Med.* 72, 346–350.

Lok, J., Gupta, P., Guo, S., Kim, W. J., Whalen, M. J., van Leyen, K., et al. (2007). Cell-cell signaling in the neurovascular unit. *Neurochem. Res.* 32, 2032–2045. doi: 10.1007/s11064-007-9342-9

McEniery, C. M., Yasmin., Hall, I. R., Qasem, A., Wilkinson, I. B., and Cockcroft, J. R. (2005). Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J. Am. Coll. Cardiol.* 46, 1753–1760. doi: 10.1016/j.jacc.2005.07.037

Mitchell, G. F., Parise, H., Benjamin, E. J., Larson, M. G., Keyes, M. J., Vita, J. A., et al. (2004). Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension* 43, 1239–1245. doi: 10.1161/01.HYP.0000128420.01881.aa

Mitchell, G. F., van Buchem, M. A., Sigurdsson, S., Gotal, J. D., Jonsdottir, M. K., Kjartansson, Ó., et al. (2011). Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility—Reykjavik Study. *Brain* 134, 3398–3407. doi: 10.1093/brain/awr253

Muller, M., and Schimrigk, K. (1994). A comparative assessment of cerebral haemodynamics in the basilar artery and carotid territory by transcranial Doppler sonography in normal subjects. *Ultrasound Med. Biol.* 20, 677–687. doi: 10.1016/0301-5629(94)90025-6

Niehaus, L., Lehmann, R., Roricht, S., and Meyer, B. U. (2001). Age-related reduction in visually evoked cerebral blood flow responses. *Neurobiol. Aging* 22, 35–38. doi: 10.1016/S0197-4580(00)00212-8

Nishiyama, T., Sugai, N., and Hanaoka, K. (1997). Cerebrovascular CO2 reactivity in elderly and younger adult patients during sevoflurane anaesthesia. *Can. J. Anaesth.* 44, 160–164. doi: 10.1007/BF03013004

Noth, U., Kotajima, F., Deichmann, R., Turner, R., and Corfield, D. R. (2008). Mapping of the cerebral vascular response to hypoxia and hypercapnia using quantitative perfusion MRI at 3 T. *NMR Biomed.* 21, 464–472. doi: 10.1002/nbm.1210

Panczel, G., Daffertshofer, M., Ries, S., Spiegel, D., and Hennerici, M. (1999). Age and stimulus dependency of visually evoked cerebral blood flow responses. *Stroke* 30, 619–623. doi: 10.1161/01.STR.30.3.619

Peca, S., McCreary, C. R., Donaldson, E., Kumarpillai, G., Shobha, N., Sanchez, K., et al. (2013). Neurovascular decoupling is associated with severity of cerebral amyloid angiopathy. *Neurology* 81, 1659–1665. doi: 10.1212/01.wnl.0000435291.49598.54

Poels, M. M., Zaccai, K., Verwoert, G. C., Vernooij, M. W., Hofman, A., van der Lugt, A., et al. (2012). Arterial stiffness and cerebral small vessel disease: the Rotterdam Scan Study. *Stroke* 43, 2637–2642. doi: 10.1161/STROKEAHA.111.642264

Poulin, M. J., and Robbins, P. A. (1996). Indexes of flow and cross-sectional area of the middle cerebral artery using doppler ultrasound during hypoxia and hypercapnia in humans. *Stroke* 27, 2244–2250. doi: 10.1161/01.STR.27.12.2244

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., et al. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb. Cortex* 15, 1676–1689. doi: 10.1093/cercor/bhi044

Rey, B., Naranjo, V., Parkhutik, V., Tembl, J., and Alcaniz, M. (2010). A new visually evoked cerebral blood flow response analysis using a low-frequency estimation. *Ultrasound Med. Biol.* 36, 383–391. doi: 10.1016/j.ultrasmedbio.2009.11.001

Robertson, J. W., Debert, C. T., Frayne, R., and Poulin, M. J. (2008). Variability of middle cerebral artery blood flow with hypercapnia in women. *Ultrasound Med. Biol.* 34, 730–740. doi: 10.1016/j.ultrasmedbio.2007.07.024

Rosengarten, B., Aldinger, C., Spiller, A., and Kaps, M. (2003). Neurovascular coupling remains unaffected during normal aging. *J. Neuroimaging* 13, 43–47. doi: 10.1177/1051228402239716

Schwertfeger, N., Neu, P., Schlattmann, P., Lemke, H., Heuser, I., and Bajbouj, M. (2006). Cerebrovascular reactivity over time course in healthy subjects. *J. Neurol. Sci.* 249, 135–139. doi: 10.1016/j.jns.2006.06.009

Secher, N. H., Seifert, T., and Van Lieshout, J. J. (2008). Cerebral blood flow and metabolism during exercise: implications for fatigue. *J. Appl. Physiol. (1985)* 104, 306–314. doi: 10.1152/japplphysiol.00853.2007

Serrador, J. M., Picot, P. A., Rutt, B. K., Shoemaker, J. K., and Bondar, R. L. (2000). MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke* 31, 1672–1678. doi: 10.1161/01.STR.31.7.1672

Smith, E. E., Vijayappa, M., Lima, F., Delgado, P., Wendell, L., Rosand, J., et al. (2008). Impaired visual evoked flow velocity response in cerebral amyloid angiopathy. *Neurology* 71, 1424–1430. doi: 10.1212/01.wnl.0000327887.64299.a4

Spelsberg, B., Bohning, A., Kompf, D., and Kessler, C. (1998). Visually induced reactivity in posterior cerebral artery blood flow. *J. Neuroophthalmol.* 18, 263–267. doi: 10.1097/00041327-199812000-00008

Sturzenegger, M., Newell, D. W., and Aaslid, R. (1996). Visually evoked blood flow response assessed by simultaneous two-channel transcranial Doppler using flow velocity averaging. *Stroke* 27, 2256–2261. doi: 10.1161/01.STR.27.12.2256

Tominaga, S., Strandgaard, S., Uemura, K., Ito, K., and Kutsuzawa, T. (1976). Cerebrovascular CO2 reactivity in normotensive and hypertensive man. *Stroke* 7, 507–510. doi: 10.1161/01.STR.7.5.507

Tomlinson, L. A. (2012). Methods for assessing arterial stiffness: technical considerations. *Curr. Opin. Nephrol. Hypertens*. 21, 655–660. doi: 10.1097/MNH.0b013e32835856e3

Vantanajal, J. S., Ashmead, J. C., Anderson, T. J., Hepple, R. T., and Poulin, M. J. (2007). Differential sensitivities of cerebral and brachial blood flow to hypercapnia in humans. *J. Appl. Physiol.* 102, 87–93. doi: 10.1152/japplphysiol.00772.2006

Wilkinson, I. B., Fuchs, S. A., Jansen, I. M., Spratt, J. C., Murray, G. D., Cockcroft, J. R., et al. (1998). Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J. Hypertens* 16, 2079–2084. doi: 10.1097/00004872-199816121-00033

Willie, C. K., Macleod, D. B., Shaw, A. D., Smith, K. J., Tzeng, Y. C., Eves, N. D., et al. (2012). Regional brain blood flow in man during acute changes in arterial blood gases. *J. Physiol.* 590, 3261–3275. doi: 10.1113/jphysiol.2012.228551

Xu, T.-Y., Staessen, J. A., Wei, F.-F., Xu, J., Li, F.-H., Fan, W.-X., et al. (2012). Blood flow pattern in the middle cerebral artery in relation to indices of arterial stiffness in the systemic circulation. *Am. J. Hypertens* 25, 319–324. doi: 10.1038/ajh.2011.223

Yamaguchi, T., Kanno, I., Uemura, K., Shishido, F., Inugami, A., Ogawa, T., et al. (1986). Reduction in regional cerebral metabolic rate of oxygen during human aging. *Stroke* 17, 1220–1228. doi: 10.1161/01.STR.17.6.1220

Zaletel, M., Strucl, M., Rodi, Z., and Zvan, B. (2004). The relationship between visually evoked cerebral blood flow velocity responses and visual-evoked potentials. *Neuroimage* 22, 1784–1789. doi: 10.1016/j.neuroimage.2004.04.019

Zheng, X.-N., Zhu, X.-C., Xu, Q.-F., Huang, Y.-N., and Liu, Y. (2003). TCD study of hemodynamic changes in PCA response to photic stimulation. *J. Zhejiang Univ. Sci.* 4, 228–231. doi: 10.1631/jzus.2003.0228

Zhu, Y. S., Tarumi, T., Tseng, B. Y., Palmer, D. M., Levine, B. D., and Zhang, R. (2013). Cerebral vasomotor reactivity during hypo- and hypercapnia in sedentary elderly and Masters athletes. *J. Cereb. Blood Flow Metab.* 33, 1190–1196. doi: 10.1038/jcbfm.2013.66

Zhu, Y. S., Tseng, B. Y., Shibata, S., Levine, B. D., and Zhang, R. (2011). Increases in cerebrovascular impedance in older adults. *J. Appl. Physiol. (1985)* 111, 376–381. doi: 10.1152/japplphysiol.01418.2010

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 28 November 2013; accepted: 26 January 2014; published online: 19 February 2014.

*Citation: Flück D, Beaudin AE, Steinback CD, Kumarpillai G, Shobha N, McCreary CR, Peca S, Smith EE and Poulin MJ (2014) Effects of aging on the association between cerebrovascular responses to visual stimulation, hypercapnia and arterial stiffness. Front. Physiol. **5**:49. doi: 10.3389/fphys.2014.00049*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in
PHYSIOLOGY

MINI REVIEW ARTICLE
published: 21 January 2014
doi: 10.3389/fphys.2014.00006

Cerebral hemodynamics of the aging brain: risk of Alzheimer disease and benefit of aerobic exercise

Takashi Tarumi*[1,2] *and Rong Zhang*[1,2,3]

[1] *Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, Dallas, TX, USA*
[2] *Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA*
[3] *Department of Neurology and Neurotherapeutics, Alzheimer's Disease Center, University of Texas Southwestern Medical Center, Dallas, TX, USA*

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Andrea Weinstein, University of Pittsburgh, USA
Jean Chen, University of Toronto, Canada

****Correspondence:***
Rong Zhang, Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, University of Texas Southwestern Medical Center at Dallas, 7232 Greenville Ave, Dallas, TX 75231, USA
e-mail: rongzhang@texashealth.org

Alzheimer disease (AD) and cerebrovascular disease often coexist with advanced age. Mounting evidence indicates that the presence of vascular disease and its risk factors increase the risk of AD, suggesting a potential overlap of the underlying pathophysiological mechanisms. In particular, atherosclerosis, endothelial dysfunction, and stiffening of central elastic arteries have been shown to associate with AD. Currently, there are no effective treatments for the cure and prevention of AD. Vascular risk factors are modifiable via either pharmacological or lifestyle intervention. In this regard, habitual aerobic exercise is increasingly recognized for its benefits on brain structure and cognitive function. Considering the well-established benefits of regular aerobic exercise on vascular health, exercise-related improvements in brain structure and cognitive function may be mediated by vascular adaptations. In this review, we will present the current evidence for the physiological mechanisms by which vascular health alters the structural and functional integrity of the aging brain and how improvements in vascular health, via regular aerobic exercise, potentially benefits cognitive function.

Keywords: cerebral hemodynamics, aging, Alzheimer's disease, vascular dementia, regular aerobic exercise

INTRODUCTION

Alzheimer's disease (AD) is a devastating neurological disorder characterized by progressive deterioration of brain structure and function (Querfurth and LaFerla, 2010). Advanced age is the strongest risk factor for AD such that the risk doubles every 5 years after age of 65. Due to the rapid aging of the population, the prevalence of AD is facing an exponential growth. However, there remains a dearth of effective treatments, cures, and most importantly preventions (Thies and Bleiler, 2013).

Mounting evidence indicates that vascular disease and risk factors not only elevate the risk of vascular dementia (VaD) but also AD (de la Torre, 2004). Traditional views on the etiology of AD and VaD have been divergent. AD develops as a result of brain amyloid depositions, leading to a pathological cascade of neurodegeneration and cognitive impairment (Selkoe, 1991; Hardy and Selkoe, 2002). On contrary, VaD is attributed to cerebral hypoperfusion and ischemia that are associated with impairment of synaptic activity and protein synthesis, glutamate excitotoxicity, and neuronal apoptosis (Hossmann, 1994; Gorelick et al., 2011). Despite these traditional perspectives, large population-based prospective studies have demonstrated that vascular risk factors in midlife, such as systolic hypertension and hyperlipidemia, led to a significant elevation of AD risk in later life (Kivipelto et al., 2001).

Vascular risk and dysfunction are modifiable through lifestyle modifications (Ornish et al., 1990). In particular, physical activity has been shown to improve cognitive outcomes in patients with mild cognition impairment (Lautenschlager et al., 2008). In contrast to the pharmacological interventions, habitual physical activity such as "regular aerobic exercise" is low cost, has virtually no adverse effects, and can be important for primary prevention of AD (Selkoe, 2012). Nonetheless, the physiological benefits of regular aerobic exercise on AD prevention are not completely understood and are only supported by a limited amount of data. Accordingly, the primary objective of this review is to overview the current evidence of the association between vascular aging and AD pathology. Secondarily, we will extend our discussion to the potential mechanism by which regular aerobic exercise may attenuate AD pathology via improvements in vascular health.

CEREBROVASCULAR ANATOMY AND BLOOD FLOW REGULATION

The brain relies critically on a constant supply of blood due to its high rate of oxidative metabolism and lack of energy substrate. ∼15% of cardiac output is directed to the brain which only weighs ∼2% of body mass yet accounts for ∼20% of total blood glucose and oxygen utilizations (Attwell et al., 2010). To sustain the high volume blood supply, cerebrovascular resistance is low. However, this makes the brain sensitive to changes in cerebral blood flow (CBF) during hypo- or hypertension (Faraci and Heistad, 1990). Importantly, the majority of cerebrovascular resistance is controlled outside of the parenchyma by extracerebral arteries (i.e., large cerebral arteries and pial arterioles) while intracerebral arterioles and capillaries account for the remaining resistance (Faraci and Heistad, 1990).Therefore, the coordinated adjustment of extra- and intracerebral arteries in response to changes in perfusion pressure is crucial in maintaining adequate perfusion and normal brain function.

Cerebral autoregulation (CA) maintains CBF relatively constant in the face of changes in arterial pressure (Lassen, 1959; Paulson et al., 1990). In particular, extracerebral adjustment of arteriolar resistance ensures adequate perfusion to the parenchyma (Rowbotham and Little, 1965; Faraci and Heistad, 1990). Watershed areas of deep and periventricular white matter are particularly vulnerable to hypoperfusion and hypoxia, especially with age-related vascular disease and dysfunction (Rowbotham and Little, 1965; Faraci and Heistad, 1990; Matsushita et al., 1994). Dysregulation of CBF and perfusion pressure may cause ischemic brain injuries such as white matter hyperintensities (WMH) and silent infarcts which are often associated AD pathology (Snowdon et al., 1997). Below we will discuss steady-state and dynamic regulations of CBF and its implications on the aging brain and AD pathology.

REGULATION OF STEADY-STATE CBF

CBF decreases with advancing age and is lower in patients with AD compared with age-matched healthy individuals (Leenders et al., 1990; Matsuda, 2001). Age- and/or AD-related reductions in CBF are, at least in part, explained by the concurrent atrophy or lower metabolic rate of brain tissue (Matsuda, 2001). However, the recent evidence demonstrating the association between vascular disease and a higher incidence of AD also raises a potential hypothesis that dysregulation of CBF may cause an insufficient supply of energy and nutrients and accelerate the AD pathology (de la Torre, 2004). In healthy individuals, CBF and metabolism are tightly coupled via the neurovascular unit which regulates microvascular resistance upon neuronal activities (Attwell et al., 2010). In contrast, in patients with amnestic mild cognitive impairment, a prodromal stage of AD, global CBF and metabolic rate of oxygen were reduced and cerebrovascular resistance was elevated when compared with the normal controls (Liu et al., 2013). Furthermore, a linear relation that was observed in healthy subjects between global CBF and metabolic rate of oxygen was absent in patients with amnestic mild cognitive impairment. These findings suggest the presence of neurovascular decoupling of CBF and metabolism in the individual who is at greater risk of AD. Pathologically, cerebral hypoperfusion or hypoxic ischemia have been shown to increase amyloid plaque depositions, the pathological hallmark of AD, which precedes neurodegeneration and cognitive impairment (Zhang et al., 2007; Okamoto et al., 2012).

Physiological mechanisms by which vascular disease and risk factors promote the AD pathology are likely to be multi-factorial and related to a number of changes in vascular structure and function (Breteler, 2000). Although the relative degree to which each component of vascular abnormalities plays a role remains unclear, endothelial dysfunction, a hallmark of vascular aging, has been observed in patients with AD (Dede et al., 2007). Vascular endothelium, the most internal layer of the arterial wall, is susceptible to blood-derived chemical and mechanical stimuli. In response to these stimuli, the endothelium releases vasoactive substances to maintain vascular homeostasis. In particular, constitutive nitric oxide (NO) plays a crucial role in maintaining vasomotor tone and its dynamic regulation facilitates functional hyperemia in response to changes in metabolic demand (Fujii et al., 1991; Dietrich et al., 1996). Importantly, NO also inhibits atherogenesis by reducing oxidative modification of low-density lipoprotein (LDL) cholesterol and preventing the proliferation of vascular smooth muscle cells (Davignon and Ganz, 2004). Oxidation of LDL has been proposed as a major mechanism of the atherosclerotic process (Davignon and Ganz, 2004). In patients with AD, age-related impairment of endothelial function is exacerbated such that endothelium-dependent NO-mediated vasodilatory function, as assessed by brachial flow-mediated dilation, is lower when compared with healthy subjects (Dede et al., 2007). Consistently, exposure of cerebrovascular endothelium to amyloid-β (Aβ) peptide acutely impairs endothelium-dependent vasodilation by augmenting oxidative stress (Thomas et al., 1996). Moreover, autopsy studies have demonstrated a greater atherosclerotic burden in patients with AD than healthy controls (Roher et al., 2003). Collectively, these findings suggest that cerebral endothelial dysfunction, Aβ induced vasoconstriction, and atherosclerotic encroachment of cerebral arteries may elevate cerebrovascular resistance leading to brain hypoperfusion which in turn may accelerate the AD pathology.

AD and atherosclerosis also share the common genetic risk factors, such as the ε4 allele of apolipoprotein E (APOE4) (Casserly and Topol, 2004). Apolipoprotein E is a polymorphic protein arising from three alleles (i.e., ε2, ε3, and ε4), which differs by only a single amino acid substitute. Yet these changes have the profound influences on the brain and peripheral lipid metabolism (Mahley and Rall, 2000). Although the underlying cellular and molecular mechanism remains to be established, APOE4 is associated with greater Aβ depositions in the brain (Bu, 2009; Kim et al., 2009) and higher plasma concentrations of LDL. Increased LDL elevates the risk of atherogenesis, especially when associated with endothelial dysfunction (Wilson et al., 1994, 1996).

REGULATION OF DYNAMIC CBF: BEAT-TO-BEAT LOW FREQUENCY OSCILLATIONS

The brain is susceptible to dynamic changes in arterial pressure which spontaneously oscillates at the low frequencies below heart rate at rest (Zhang et al., 2000). CA during dynamic beat-to-beat changes in arterial pressure more or less is a frequency dependent phenomenon which may dampen oscillations of CBF in response to changes in arterial pressure at the low frequencies (Lassen, 1959; Paulson et al., 1990; Zhang et al., 1998). CA is an inherent property of cerebral arteries and arterioles that are controlled by myogenic, neurogenic, and metabolic mechanisms. In effect, CA ensures a constant supply of oxygen and nutrients during hypotension while attenuating hyperperfusion during hypertension.

Contrary to the general pattern of age-related impairment of vascular function, CA appears to remain intact in older adults (van Beek et al., 2008). Furthermore, recent studies suggest that CA is also preserved in patients with AD (Claassen et al., 2009; Zazulia et al., 2010), although the presence of cerebral amyloid angiopathy, which often accompanies advanced AD pathology, may alter CA. Cerebral amyloid angiopathy is characterized by the accumulation of $A\beta_{1-40}$ proteins in the cerebral vessel wall (Christie et al., 2001). $A\beta_{1-40}$ is highly toxic to cerebral vasculature such that that exogenous application of $A\beta_{1-40}$ impairs

endothelial-dependent vasodilation and exaggerates vasoconstriction (Thomas et al., 1996). Using a transgenic mouse model of AD, profound impairment of CA has been observed (Niwa et al., 2002). Of note, the inconsistent findings between the preclinical and clinical studies of CA in AD clearly warrants future studies to determine whether CA is indeed impaired in AD and whether changes in CA are related to the AD onset or progression.

AD may also impair cerebral tissue oxygenation during dynamic changes in CBF. Cerebral tissue oxygenation, measured non-invasively be near-infrared spectroscopy, predominantly reflects the oxygen saturation of venous blood (Madsen and Secher, 1999; Claassen et al., 2006; Rowley et al., 2007; Murkin and Arango, 2009). In patients with AD, transfer function gain of cerebral tissue oxygenation in response to changes in CBF has been reported lower while the phase was reduced when compared with controls subjects (van Beek et al., 2010). These findings suggest that more arterial oxygen is transmitted to the venous circulation and a possibility of microvascular dysfunction in which the brain tissue is less able to extract oxygen from the arterial blood. If this is the case, it can be speculated that neurovascular coupling of CBF and metabolism may be disrupted during hemodynamic challenges in patients with AD.

REGULATION OF DYNAMIC CBF: CARDIAC FREQUENCY

The human heart is an intermittent pump which generates a stroke volume every cardiac cycle. During healthy youth, left ventricular afterload, as well as systolic blood pressure generated to overcome the afterload, is low (Avolio et al., 1983). In addition, the compliance of central arteries effectively dampens the hemodynamic pulsations via the Windkessel effect and creates a continuous blood flow in the microcirculation of peripheral vascular beds (Nichols et al., 2005). With advancing age, central elastic arteries stiffen and total peripheral resistance increases. As a result, left ventricular afterload increases and so does systolic blood pressure (Avolio et al., 1983).

Advancing age is also associated with a premature timing of arterial wave reflection. In the circulatory system with arterial branching and tapering, a forward-traveling pressure wave generated from the left ventricle encounters the discontinuity of vascular impedance/resistance and reflects back a portion of the incident waves (Nichols et al., 2005). With the age-related increase in aortic pulse wave velocity, a reflected pressure wave collides prematurely with the incident pressure waves, thus leading to the augmentation of systolic and attenuation of diastolic pressures (Nichols et al., 2005). As discussed above, dynamic CA is effective in dampening changes in arterial pressure only at low frequency (<0.1 Hz) (Zhang et al., 1998). Therefore, age-related increase in hemodynamic pulsatility at cardiac frequency may be transmitted passively (i.e., without the counteraction of CA) into the brain and lead to brain structural damage.

Cerebrovascular impedance is elevated in the elderly while the brain is exposed to a greater magnitude of hemodynamic pulsatility (Zhu et al., 2010). Vascular impedance represents an opposition to pulsatile blood flow and is determined by the intrinsic property (i.e., elasticity) and diameter (i.e., resistance) of blood vessels (O'Rourke and Taylor, 1967). Age-related increases in cerebrovascular impedance with the concurrent elevations in CBF pulsatility observed in the basal cerebral arteries may reflect a compensatory mechanism of cerebral vasculature which attenuates the transmission of CBF pulsatility into the delicate microcirculation. In support of this, vascular adaptations to hemodynamic pulsatility have been shown from the peripheral vasculature (Laurent et al., 2009). For example, central arterial stiffness and higher systolic blood pressure were positively associated with thicker wall of resistance vessels relative to the lumen diameter (Muiesan et al., 2013). Moreover, greater central pulse pressure was positively associated with wall-to-lumen ratio of retinal arterioles which is an independent risk factor for stroke (Wong et al., 2001; Ott et al., 2013). Such adaptations of the microvasculature increase vascular impedance which would attenuate the transmission of hemodynamic pulsatility, reduce vascular damage, and facilitate oxygen extraction. However, these adaptations may occur at the expense of increases in vascular resistance and thus reduction in steady-state brain perfusion. Indeed, central arterial stiffness is negatively correlated with CBF in the deep white matter where a high prevalence of WMH are observed (Tarumi et al., 2011). Moreover, central arterial stiffness and pressure pulsatility are associated with higher prevalence of subcortical infarct, atrophy of brain parenchyma, and greater levels of brain amyloid plaques (Mitchell et al., 2011; Hughes et al., 2013; Nation et al., 2013). These findings collectively indicate the potential importance of age-related changes in central hemodynamics to cerebrovascular remodeling and structural brain changes. In addition, prevention of central arterial aging may alleviate pulsatile-induced cerebral microvascular disease and age-related cognitive decline.

AEROBIC EXERCISE AND THE BRAIN STRUCTURE AND FUNCTION

There is an increasing recognition that habitual aerobic exercise enhances cognitive function and attenuates age-related deterioration of brain structure. Earlier studies in animals showed the greater benefits of voluntary aerobic exercise in improving cognitive function when compared with other stimuli such as expanded learning opportunities (van Praag et al., 1999). Furthermore, exercise-related improvements in cognitive function were associated with the neurogenesis of hippocampal dentate gyrus in the adult mouse (van Praag et al., 1999). Human studies also demonstrated that regular walking increased the hippocampal size and improved the memory performance in the previously sedentary elderly individuals (Erickson et al., 2011).

Regular aerobic exercise preserves the structural integrity of white matter (Gons et al., 2013; Tseng et al., 2013). As assessed by diffusion tensor MR imaging, Master's athletes, who have participated in a lifelong high intensity, high volume aerobic exercise training, attenuated age-related reductions in axonal fiber integrity, as shown by higher fractional anisotropy and lower mean diffusivity in the network of front-to-back connections (Tseng et al., 2013). Moreover, there was a strong positive correlation between maximal oxygen uptake and fractional anisotropy in the left superior longitudinal fasciculus (Tseng et al., 2013). These findings suggest that regular aerobic exercise preserves the microstructural integrity of white matter that is responsible for

visuospatial function, motor control, and coordination (Tseng et al., 2013).

Exercise-related improvements in brain function and structure may be conferred by the concurrent adaptations in vascular function and structure. Aerobic exercise increases the peripheral levels of growth factors (e.g., BDNF, IFG-1, and VEGF) which cross the blood-brain barrier (BBB) and stimulate neurogenesis and angiogenesis (Trejo et al., 2001; Lee et al., 2002; Fabel et al., 2003; Lopez-Lopez et al., 2004). Consistent with this, exercise-related enlargement of hippocampus was accompanied by increases in cerebral blood volume and capillary densities (Pereira et al., 2007). Enhanced cerebral perfusion may not only facilitate the delivery of energy substrates, but also lower the risk of vascular-related brain damages, including WMH and silent infarct (Tseng et al., 2013). Furthermore, regular aerobic exercise is associated with lower levels of Aβ deposition in individuals with APOE4 positive (Head et al., 2012), which may also reduce the risk of cerebral amyloid angiopathy and microbleeds (Poels et al., 2010).

Regular aerobic exercise ameliorates endothelial dysfunction and central arterial stiffness (Seals et al., 2008). As discussed above, central arteries serve as an important interface between the cerebral and peripheral circulations (Nichols et al., 2005). A recent study which compared middle-aged endurance-trained and sedentary adults demonstrated that higher aerobic fitness in endurance-trained adults was correlated positively with better cognitive performance and negatively with central arterial stiffness, independent of other lifestyle factors (e.g., sleep and diet) (Tarumi et al., 2013). Furthermore, lower central arterial stiffness, as assessed by carotid artery distensibility, showed positive associations with cognitive performance and resting CBF in the occipito-parietal area (Tarumi et al., 2013). In addition, exercise-related enhancement of endothelial function may facilitate neurovascular coupling and protect cerebral arteries from atherogenesis. In humans, endothelium-dependent vasodilatation measured from the peripheral (e.g., brachial and radial) arteries is considered a systemic index of vascular endothelial function (Celermajer et al., 1994; DeSouza et al., 2000). If this is also the case for cerebral circulation, exercise-related improvement in endothelial function is likely to benefit CBF regulation, structural integrity of BBB, and cognitive outcome. Currently, there is a relative lack of data as to the impact of exercise-related improvement in endothelial function on brain structure and function. Future studies are needed to confirm whether a reversal of endothelial dysfunction translates into better brain structural and cognitive outcomes.

SUMMARY

AD and cerebrovascular disease often coexist in the aging brain. Traditional view that AD and VaD are two divergent clinical entities with few or no overlap between their pathologies is challenged by an accumulating body of evidence indicating a close association between vascular disease and the risk of AD development. More recently, physiological studies also have demonstrated that vascular dysregulation of CBF elevate the risk of both cerebrovascular disease and AD. Specifically, presence of central arterial stiffness and endothelial dysfunction elevates the risk of pressure pulsatility or flow-related damage to brain structure and function. Further study of these modifiable risk factors through pharmacological or non-pharmacological approaches is likely to be important for developing an effective prevention or treatment for AD. In particular, further mechanistic study of the effect of regular aerobic exercise on arterial aging, brain perfusion and structure may provide new insights into how to prevent or slow the age-related cognitive decline, AD, and other age-related cerebrovascular diseases.

AUTHOR CONTRIBUTIONS

Takashi Tarumi drafted the manuscript. Rong Zhang revised the manuscript critically for important intellectual content. Rong Zhang and Takashi Tarumi approved the final version of the manuscript.

ACKNOWLEDGMENTS

This study was supported in part by the NIH grant R01AG033106-01and R01HL102457.

REFERENCES

Attwell, D., Buchan, A. M., Charpak, S., Lauritzen, M., Macvicar, B. A., and Newman, E. A. (2010). Glial and neuronal control of brain blood flow. *Nature* 468, 232–243. doi: 10.1038/nature09613

Avolio, A. P., Chen, S. G., Wang, R. P., Zhang, C. L., Li, M. F., and O'Rourke, M. F. (1983). Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. *Circulation* 68, 50–58. doi: 10.1161/01.CIR.68.1.50

Breteler, M. M. (2000). Vascular risk factors for Alzheimer's disease: an epidemiologic perspective. *Neurobiol. Aging* 21, 153–160. doi: 10.1016/S0197-4580(99)00110-4

Bu, G. (2009). Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nat. Rev. Neurosci.* 10, 333–344. doi: 10.1038/nrn2620

Casserly, I., and Topol, E. (2004). Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. *Lancet* 363, 1139–1146. doi: 10.1016/S0140-6736(04)15900-X

Celermajer, D. S., Sorensen, K. E., Bull, C., Robinson, J., and Deanfield, J. E. (1994). Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. *J. Am. Coll. Cardiol.* 24, 1468–1474. doi: 10.1016/0735-1097(94)90141-4

Christie, R., Yamada, M., Moskowitz, M., and Hyman, B. (2001). Structural and functional disruption of vascular smooth muscle cells in a transgenic mouse model of amyloid angiopathy. *Am. J. Pathol.* 158, 1065–1071. doi: 10.1016/S0002-9440(10)64053-9

Claassen, J. A., Colier, W. N., and Jansen, R. W. (2006). Reproducibility of cerebral blood volume measurements by near infrared spectroscopy in 16 healthy elderly subjects. *Physiol. Meas.* 27, 255–264. doi: 10.1088/0967-3334/27/3/004

Claassen, J. A., Diaz-Arrastia, R., Martin-Cook, K., Levine, B. D., and Zhang, R. (2009). Altered cerebral hemodynamics in early Alzheimer disease: a pilot study using transcranial Doppler. *J. Alzheimers Dis.* 17, 621–629. doi: 10.3233/JAD-2009-1079

Davignon, J., and Ganz, P. (2004). Role of endothelial dysfunction in atherosclerosis. *Circulation* 109, III27–III32. doi: 10.1161/01.CIR.0000131515.03336.f8

Dede, D. S., Yavuz, B., Yavuz, B. B., Cankurtaran, M., Halil, M., Ulger, Z., et al. (2007). Assessment of endothelial function in Alzheimer's disease: is Alzheimer's disease a vascular disease? *J. Am. Geriatr. Soc.* 55, 1613–1617. doi: 10.1111/j.1532-5415.2007.01378.x

de la Torre, J. C. (2004). Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurol.* 3, 184–190. doi: 10.1016/S1474-4422(04)00683-0

DeSouza, C. A., Shapiro, L. F., Clevenger, C. M., Dinenno, F. A., Monahan, K. D., Seals, D.R., et al. (2000). Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation* 102, 1351–1357. doi: 10.1161/01.CIR.102.12.1351

Dietrich, H. H., Kajita, Y., and Dacey, R. G. Jr. (1996). Local and conducted vasomotor responses in isolated rat cerebral arterioles. *Am J Physiol.* 271, H1109–H1116.

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., et al. (2011). Exercise training increases size of hippocampus and improves memory. *Proc. Natl. Acad. Sci. U.S.A.* 108, 3017–3022. doi: 10.1073/pnas.1015950108

Fabel, K., Tam, B., Kaufer, D., Baiker, A., Simmons, N., Kuo, C. J., et al. (2003). VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur. J. Neurosci.* 18, 2803–2812. doi: 10.1111/j.1460-9568.2003.03041.x

Faraci, F. M., and Heistad, D. D. (1990). Regulation of large cerebral arteries and cerebral microvascular pressure. *Circ. Res.* 66, 8–17. doi: 10.1161/01.RES.66.1.8

Fujii, K., Heistad, D. D., and Faraci, F. M. (1991). Flow-mediated dilatation of the basilar artery *in vivo*. *Circ. Res.* 69, 697–705. doi: 10.1161/01.RES.69.3.697

Gons, R. A., Tuladhar, A. M., de Laat, K. F., van Norden, A. G., van Dijk, E. J., Norris, D. G., et al. (2013). Physical activity is related to the structural integrity of cerebral white matter. *Neurology* 81, 971–976. doi: 10.1212/WNL.0b013e3182a43e33

Gorelick, P. B., Scuteri, A., Black, S. E., Decarli, C., Greenberg, S. M., Iadecola, C., et al. (2011). Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke* 42, 2672–2713. doi: 10.1161/STR.0b013e3182299496

Hardy, J., and Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 297, 353–356. doi: 10.1126/science.1072994

Head, D., Bugg, J. M., Goate, A. M., Fagan, A. M., Mintun, M. A., Benzinger, T., et al. (2012). Exercise engagement as a moderator of the effects of APOE genotype on amyloid deposition. *Arch. Neurol.* 69, 636–643. doi: 10.1001/archneurol.2011.845

Hossmann, K. A. (1994). Viability thresholds and the penumbra of focal ischemia. *Ann. Neurol.* 36, 557–565. doi: 10.1002/ana.410360404

Hughes, T. M., Kuller, L. H., Barinas-Mitchell, E. J., Mackey, R. H., McDade, E. M., Klunk, W. E., et al. (2013). Pulse wave velocity is associated with beta-amyloid deposition in the brains of very elderly adults. *Neurology* 81, 1711–1718. doi: 10.1212/01.wnl.0000435301.64776.37

Kim, J., Basak, J. M., and Holtzman, D. M. (2009). The role of apolipoprotein E in Alzheimer's disease. *Neuron* 63, 287–303. doi: 10.1016/j.neuron.2009.06.026

Kivipelto, M., Helkala, E. L., Laakso, M. P., Hanninen, T., Hallikainen, M., Alhainen, K., et al. (2001). Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 322, 1447–1451. doi: 10.1136/bmj.322.7300.1447

Lassen, N. A. (1959). Cerebral blood flow and oxygen consumption in man. *Physiol. Rev.* 39, 183–238.

Laurent, S., Briet, M., and Boutouyrie, P. (2009). Large and small artery cross-talk and recent morbidity-mortality trials in hypertension. *Hypertension* 54, 388–392. doi: 10.1161/HYPERTENSIONAHA.109.133116

Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J., et al. (2008). Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA* 300, 1027–1037. doi: 10.1001/jama.300.9.1027

Lee, J., Duan, W., and Mattson, M. P. (2002). Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. *J. Neurochem.* 82, 1367–1375. doi: 10.1046/j.1471-4159.2002.01085.x

Leenders, K. L., Perani, D., Lammertsma, A. A., Heather, J. D., Buckingham, P., Healy, M. J., et al. (1990). Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. *Brain* 113(Pt 1), 27–47. doi: 10.1093/brain/113.1.27

Liu, J., Zhu, Y. S., Khan, M. A., Brunk, E., Martin-Cook, K., Weiner, M. F., et al. (2013). Global brain hypoperfusion and oxygenation in amnestic mild cognitive impairment. *Alzheimers Dement.* doi: 10.1016/j.jalz.2013.04.507. [Epub ahead of print].

Lopez-Lopez, C., LeRoith, D., and Torres-Aleman, I. (2004). Insulin-like growth factor I is required for vessel remodeling in the adult brain. *Proc. Natl. Acad. Sci. U.S.A.* 101, 9833–9838. doi: 10.1073/pnas.0400337101

Madsen, P. L., and Secher, N. H. (1999). Near-infrared oximetry of the brain. *Prog. Neurobiol.* 58, 541–560. doi: 10.1016/S0301-0082(98)00093-8

Mahley, R. W., and Rall, S. C. Jr. (2000). Apolipoprotein E: far more than a lipid transport protein. *Annu. Rev. Genomics Hum. Genet.* 1, 507–537. doi: 10.1146/annurev.genom.1.1.507

Matsuda, H. (2001). Cerebral blood flow and metabolic abnormalities in Alzheimer's disease. *Ann. Nucl. Med.* 15, 85–92. doi: 10.1007/BF02988596

Matsushita, K., Kuriyama, Y., Nagatsuka, K., Nakamura, M., Sawada, T., and Omae, T. (1994). Periventricular white matter lucency and cerebral blood flow autoregulation in hypertensive patients. *Hypertension* 23, 565–568. doi: 10.1161/01.HYP.23.5.565

Mitchell, G. F., van Buchem, M. A., Sigurdsson, S., Gotal, J. D., Jonsdottir, M. K., Kjartansson, O., et al. (2011). Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility-Reykjavik study. *Brain* 134, 3398–3407. doi: 10.1093/brain/awr253

Muiesan, M. L., Salvetti, M., Rizzoni, D., Paini, A., Agabiti-Rosei, C., Aggiusti, C., et al. (2013). Pulsatile hemodynamics and microcirculation: evidence for a close relationship in hypertensive patients. *Hypertension* 61, 130–136. doi: 10.1161/HYPERTENSIONAHA.111.00006

Murkin, J. M., and Arango, M. (2009). Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br. J. Anaesth.* 103(Suppl. 1), i3–i13. doi: 10.1093/bja/aep299

Nation, D. A., Edland, S. D., Bondi, M. W., Salmon, D. P., Delano-Wood, L., Peskind, E. R., et al. (2013). Pulse pressure is associated with Alzheimer biomarkers in cognitively normal older adults. *Neurology* 81, 2024–2027. doi: 10.1212/01.wnl.0000436935.47657.78

Nichols, W. W., O'Rourke, M., and Vlachopoulos, C. (2005). *"McDonald's Blood Flow in Arteries"*. London: Hodder Arnold.

Niwa, K., Kazama, K., Younkin, L., Younkin, S. G., Carlson, G. A., and Iadecola, C. (2002). Cerebrovascular autoregulation is profoundly impaired in mice overexpressing amyloid precursor protein. *Am. J. Physiol. Heart Circ. Physiol.* 283, H315–H323. doi: 10.1152/ajpheart.00022.2002

O'Rourke, M. F., and Taylor, M. G. (1967). Input impedance of the systemic circulation. *Circ Res.* 20, 365–380. doi: 10.1161/01.RES.20.4.365

Okamoto, Y., Yamamoto, T., Kalaria, R. N., Senzaki, H., Maki, T., Hase, Y., et al. (2012). Cerebral hypoperfusion accelerates cerebral amyloid angiopathy and promotes cortical microinfarcts. *Acta Neuropathol.* 123, 381–394. doi: 10.1007/s00401-011-0925-9

Ornish, D., Brown, S. E., Scherwitz, L. W., Billings, J. H., Armstrong, W. T., Ports, T. A., et al. (1990). Can lifestyle changes reverse coronary heart disease? The lifestyle heart trial. *Lancet* 336, 129–133. doi: 10.1016/0140-6736(90)91656-U

Ott, C., Raff, U., Harazny, J. M., Michelson, G., and Schmieder, R. E. (2013). Central pulse pressure is an independent determinant of vascular remodeling in the retinal circulation. *Hypertension* 61, 1340–1345. doi: 10.1161/HYPERTENSIONAHA.111.00617

Paulson, O. B., Strandgaard, S., and Edvinsson, L. (1990). Cerebral autoregulation. *Cerebrovasc. Brain Metab. Rev.* 2, 161–192.

Pereira, A. C., Huddleston, D. E., Brickman, A. M., Sosunov, A. A., Hen, R., McKhann, G. M., et al. (2007). An *in vivo* correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc. Natl. Acad. Sci. U.S.A.* 104, 5638–5643. doi: 10.1073/pnas.0611721104

Poels, M. M., Vernooij, M. W., Ikram, M. A., Hofman, A., Krestin, G. P., van der Lugt, A., et al. (2010). Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. *Stroke* 41, S103–S106. doi: 10.1161/STROKEAHA.110.595181

Querfurth, H. W., and LaFerla, F. M. (2010). Alzheimer's disease. *N. Engl. J. Med.* 362, 329–344. doi: 10.1056/NEJMra0909142

Roher, A. E., Esh, C., Kokjohn, T. A., Kalback, W., Luehrs, D. C., Seward, J. D., et al. (2003). Circle of willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. *Arterioscler. Thromb. Vasc. Biol.* 23, 2055–2062. doi: 10.1161/01.ATV.0000095973.42032.44

Rowbotham, G. F., and Little, E. (1965). Circulations of the cerebral hemispheres. *Br. J. Surg.* 52, 8–21. doi: 10.1002/bjs.1800520104

Rowley, A. B., Payne, S. J., Tachtsidis, I., Ebden, M. J., Whiteley, J. P., Gavaghan, D. J., et al. (2007). Synchronization between arterial blood pressure and cerebral oxyhaemoglobin concentration investigated by wavelet cross-correlation. *Physiol. Meas.* 28, 161–173. doi: 10.1088/0967-3334/28/2/005

Seals, D. R., Desouza, C. A., Donato, A. J., and Tanaka, H. (2008). Habitual exercise and arterial aging. *J. Appl. Physiol. (1985)* 105, 1323–1332. doi: 10.1152/japplphysiol.90553.2008

Selkoe, D. J. (1991). The molecular pathology of Alzheimer's disease. *Neuron* 6, 487–498. doi: 10.1016/0896-6273(91)90052-2

Selkoe, D. J. (2012). Preventing Alzheimer's disease. *Science* 337, 1488–1492. doi: 10.1126/science.1228541

Snowdon, D. A., Greiner, L. H., Mortimer, J. A., Riley, K. P., Greiner, P. A., and Markesbery, W. R. (1997). Brain infarction and the clinical expression of Alzheimer disease. The nun study. *JAMA* 277, 813–817. doi: 10.1001/jama.1997.03540340047031

Tarumi, T., Gonzales, M. M., Fallow, B., Nualnim, N., Pyron, M., Tanaka, H., et al. (2013). Central artery stiffness, neuropsychological function, and cerebral perfusion in sedentary and endurance-trained middle-aged adults. *J. Hypertens*. 31, 2400–2409. doi: 10.1097/HJH.0b013e328364decc

Tarumi, T., Shah, F., Tanaka, H., and Haley, A. P. (2011). Association between central elastic artery stiffness and cerebral perfusion in deep subcortical gray and white matter. *Am. J. Hypertens*. 24, 1108–1113. doi: 10.1038/ajh.2011.101

Thies, W., and Bleiler, L. (2013). 2013 Alzheimer's disease facts and figures. *Alzheimers Dement*. 9, 208–245. doi: 10.1016/j.jalz.2013.02.003

Thomas, T., Thomas, G., McLendon, C., Sutton, T., and Mullan, M. (1996). beta-Amyloid-mediated vasoactivity and vascular endothelial damage. *Nature* 380, 168–171. doi: 10.1038/380168a0

Trejo, J. L., Carro, E., and Torres-Aleman, I. (2001). Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J. Neurosci*. 21, 1628–1634.

Tseng, B. Y., Gundapuneedi, T., Khan, M. A., Diaz-Arrastia, R., Levine, B. D., Lu, H., et al. (2013). White matter integrity in physically fit older adults. *Neuroimage* 82, 510–516. doi: 10.1016/j.neuroimage.2013.06.011

van Beek, A. H., Claassen, J. A., Rikkert, M. G., and Jansen, R. W. (2008). Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. *J. Cereb. Blood Flow Metab.* 28, 1071–1085. doi: 10.1038/jcbfm.2008.13

van Beek, A. H., Sijbesma, J. C., R. W. Jansen, Rikkert, M. G., and Claassen, J. A. (2010). Cortical oxygen supply during postural hypotension is further decreased in Alzheimer's disease, but unrelated to cholinesterase-inhibitor use. *J. Alzheimers Dis*. 21, 519–526. doi: 10.3233/JAD-2010-100288

van Praag, H., Kempermann, G., and Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat. Neurosci*. 2, 266–270. doi: 10.1038/6368

Wilson, P. W., Myers, R. H., Larson, M. G., Ordovas, J. M., Wolf, P. A., and Schaefer, E. J. (1994). Apolipoprotein E alleles, dyslipidemia, and coronary heart disease. The Framingham Offspring Study. *JAMA* 272, 1666–1671. doi: 10.1001/jama.1994.03520210050031

Wilson, P. W., Schaefer, E. J., Larson, M. G., and Ordovas, J. M. (1996). Apolipoprotein E alleles and risk of coronary disease. A meta-analysis. *Arterioscler. Thromb. Vasc. Biol*. 16, 1250–1255. doi: 10.1161/01.ATV.16.10.1250

Wong, T. Y., Klein, R., Couper, D. J., Cooper, L. S., Shahar, E., Hubbard, L. D., et al. (2001). retinal microvascular abnormalities and incident stroke: the atherosclerosis risk in communities study. *Lancet* 358, 1134–1140. doi: 10.1016/S0140-6736(01)06253-5

Zazulia, A. R., Videen, T. O., Morris, J. C., and Powers, W. J. (2010). Autoregulation of cerebral blood flow to changes in arterial pressure in mild Alzheimer's disease. *J. Cereb. Blood Flow Metab*. 30, 1883–1889. doi: 10.1038/jcbfm.2010.135

Zhang, R., Zuckerman, J. H., Giller, C. A., and Levine, B. D. (1998). Transfer function analysis of dynamic cerebral autoregulation in humans. *Am. J. Physiol*. 274, H233–H241.

Zhang, R., Zuckerman, J. H., and Levine, B. D. (2000). Spontaneous fluctuations in cerebral blood flow: insights from extended-duration recordings in humans. *Am. J. Physiol. Heart Circ. Physiol*. 278, H1848–H1855.

Zhang, X., Zhou, K., Wang, R., Cui, J., Lipton, S. A., Liao, F. F., et al. (2007). Hypoxia-inducible factor 1alpha (HIF-1alpha)-mediated hypoxia increases BACE1 expression and beta-amyloid generation. *J. Biol. Chem*. 282, 10873–10880. doi: 10.1074/jbc.M608856200

Zhu, Y. S., Tseng, B. Y., Shibata, S., Levine, B. D., and Zhang, R. (2010). Increases in cerebrovascular impedance in older adults. *J. Appl. Physiol. (1985)* 111, 376–381. doi: 10.1152/japplphysiol.01418.2010

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 30 November 2013; accepted: 05 January 2014; published online: 21 January 2014.

*Citation: Tarumi T and Zhang R (2014) Cerebral hemodynamics of the aging brain: risk of Alzheimer disease and benefit of aerobic exercise. Front. Physiol. **5**:6. doi: 10.3389/fphys.2014.00006*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in
PHYSIOLOGY

OPINION ARTICLE
published: 28 May 2014
doi: 10.3389/fphys.2014.00204

Possibilities for examining the neural control of gait in humans with fNIRS

Stéphane Perrey*

Movement to Health (M2H), Montpellier-1 University, EuroMov, Montpellier, France
**Correspondence: stephane.perrey@univ-montp1.fr*

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
Noel Keijsers, Sint Maartenskliniek, Netherlands

Keywords: locomotion control, NIRS, humans, cortical activation, analysis

Although the existence of a central pattern generator system modulated by sensory information has become broadly accepted in the control of gait, many findings indicate that the cortex also plays a role of primary importance in human walking (Miyai et al., 2001; Gwin et al., 2011; Petersen et al., 2012). Examining the neural control of gait in humans requires recording cortical activity during gait. Direct evidence for cortical involvement in human locomotion comes from neuroimaging studies using position emission tomography (la Fougère et al., 2010), electroencephalography (EEG, Gwin et al., 2011) and functional near-infrared spectroscopy (fNIRS, Miyai et al., 2001) methods. Among possible neuroimaging methods, fNIRS is ideally suited to perform brain imaging during walking as it represents several advantages over other methods (Perrey, 2008).

In this opinion article, we concentrate on the possibilities of examining the neural control of gait in humans with fNIRS method. Until now this versatile neuroimaging technique has been used rarely while the subject is moving in neuroscientific research and clinical setting (e.g., Holtzer et al., 2011). While clinical gait evaluation belongs to the neurological examination, very little research on gait with fNIRS measurement from a neurological perspective has been done. Because fNIRS is still at its infancy, it suffers from the lack of standards for a well understanding of signals obtained and signal-processing method. Based on a quick review of recent studies using fNIRS modality for studying gait in humans, this paper aims to address the sensitivity and pitfalls of fNIRS to activation over multiple cortical areas involved in gait control in humans.

Traditional neuroimaging has focused on detecting brain activity in response to a task. However, due to the lack of flexibility of most imaging techniques (e.g., functional magnetic resonance imaging or fMRI), little is known about brain activity during everyday motor tasks and when a patient undergoes gait training. Like fMRI, fNIRS is a non-invasive imaging technique for measuring local variations of hemoglobin concentration changes related to neuronal activity by the phenomenon of neurovascular coupling. By measuring absorption properties of hemoglobin at two or more wavelengths, fNIRS exploits the changes of the wavelength-dependent extinction spectra of the oxygenated (O_2Hb) and deoxygenated (HHb) form. Although some pitfalls are to consider using fNIRS during gait (i.e., low spatial resolution, inter-subject variability of the hemodynamic response, positioning of the optodes and systemic interference), the advantages of fNIRS, such as non-invasiveness, highly portable make it a promising method for studying the cortical activation patterns associated with whole-body tasks by wearable multichannel fNIRS system (Piper et al., 2014).

In healthy people, the first study using multichannel fNIRS demonstrated significantly increased levels of O_2Hb in bilateral supplementary motor area (SMA) and primary motor (M1) and somatosensory (S1) cortical regions during treadmill walking (with arm swing) at 1 km/h (Miyai et al., 2001). Walking at 3 and 4 km/h induced evoked hemodynamic responses from the bilateral primary sensorimotor areas (SM1, Suzuki et al., 2004). Running at 9 km/h led to additional oxygenation changes in premotor cortex (PMC) and especially in prefrontal cortex (PFC). While clear SMA and PFC activation changes are also well documented (Holtzer et al., 2011; Koenraadt et al., 2014), changes in speed had little effect on M1 or S1 activity (Suzuki et al., 2004). fNIRS studies have shown that SMA is playing a role in the period prior to the start of gait (Mihara et al., 2007) and for the more difficult task (such as backward walking at 1.6 km/h in Kurz et al., 2012). Although coordinated movement during walking appear relatively effortless, motor commands are important because of the added need for control of stability (Yang and Gorassini, 2006), especially during backward walking (Kurz et al., 2012). Preliminary data from Mazerie et al. (2012) showed that varied terrains (downhill and uphill) activated differently the cortical motor networks (including SM1, SMA, and PFC) than steady-speed treadmill walking due to larger contribution from sensory afferents in walking control and a higher degree of movement difficulty. Besides investigating cortical patterns related to different walking speed and terrain, a verbal cue while walking leads profoundly to different PFC and PMC activation patterns than walking without a verbal cue (Suzuki et al., 2008). This indicates that anticipated adaptations of gait to changes of treadmill speed readily affect regional activations in PFC, SMA, PMC, and SMC. Altogether, an involvement of M1 remains controversial during normal gait in humans (Miyai

et al., 2001; Kurz et al., 2012), while the PMC, SMA, and PFC are predominantly involved in adapting to increasing speed and generally during complex gait. These findings indicated that areas involved in planning and allocating attentional resources play a crucial role in controlling locomotion. Hence, fNIRS studies on gait under challenging conditions of walking are likely better suitable to discriminate the involvement of multiple cortical regions. Recently, Koenraadt et al. (2014) did not find a difference in SMA, M1, and S1 activity between precision stepping (challenging condition) and normal walking at 3 km/h but precision stepping placed larger demand on the PFC. Possible discrepancies between the aforementioned studies could originate from different analysis methods, location of the optodes and experimental design. Overall these results highlight that the cortical processing in gait control is influenced by gait parameter (speed, stride-time variability) and cognitive load during the walking task.

Predicting recovery of walking within the context of rehabilitation following stroke is still difficult. We can consider desirable to allow for an adaptation of the optimal rehabilitation strategies not only by behavioral performance but also depending on the patterns of brain activation. The rationale to measure brain activation is that plasticity of the neuronal network entertaining sensorimotor function can be considered the basis of effective rehabilitation. With regard to stroke patients, SMC and PMC activation has been observed during walking (Miyai et al., 2002). Consequently, a rehabilitation training program may be targeted to facilitate motor recovery with early exposure to somatosensory stimulations of these brain regions after stroke. Further the PMC was suggested to be involved in mediating the proximal leg movements and the control of speed of walking in stroke patients (Miyai et al., 2002). A long-term follow-up is still needed to determine how different forms of gait training with improved clinical outcomes influence cortical activation patterns with fNIRS.

Despite feasibility of NIRS for recording brain activation during gait, a number of limitations of fNIRS should be considered. fNIRS is unsuitable for activation of deeper structure than the cerebral gray matter. Further, NIRS suffers from limited spatial resolution (beyond 3–5 mm based on modeling and simulation procedure, Strangman et al., 2002; close to 2–3 cm in practice because NIRS detects near-infrared light scattered and reflected in the brain) and does not enable exact localization of the measured activity within the cortex even if fNIRS time series are closely related to fMRI signals (Muthalib et al., 2013). Correction for measurement error in both optode position and skull reference points (based on standard brain templates) have been recently proposed to overcome this issue (Fekete et al., 2011). Then, the hemodynamic change measured from the scalp may contamine the signal. NIRS provides data both on O_2Hb and HHb. Surprisingly, there seems to be limited additional information in the two hemoglobin signals. Primary focus is usually on the O_2Hb measurement due to the better signal-to-noise ratio (relative to HHb) following functional activation (Miyai et al., 2001; Leff et al., 2011); hence a restricted area of statistical significant changes in [HHb] occurs (Sato et al., 2007). Note that brain activation among various brain areas may underlie different patterns of O_2Hb and HHb changes (Koenraadt et al., 2012) and explain inter-individual variability of fNIRS signals during sensorimotor cortex activation (Sato et al., 2005). Recently Kurz et al. (2012) suggested that HHb should be disregarded for evaluating cortical activation during gait. However, one important problem for the monitoring of brain activation is that extracortical changes (due to systemic changes e.g., in blood pressure or heart rate) are more likely to influence O_2Hb than HHb (Kirilina et al., 2012). Hence, physiological artifacts induced during gait condition need to be carefully controlled for, especially due to blood flow and hemoglobin changes in the extracortical (i.e., superficial) tissue. Heart rate fluctuations cause changes in the arterial compartment. Because O_2Hb is representative of the arterial compartment, it is more affected by these systemic fluctuations than HHb which comes mostly from the venous compartment. Kirilina et al. (2012) suggested that looking at the changes [HHb] may allow identification of false positive in NIRS activation maps (i.e., erroneously attributing NIRS responses to cortical changes). Using methods to separate cortical and extracortical signals in NIRS signals include the use of additional short source-detector separation optodes as regressors (Gagnon et al., 2012) and the analysis of the photon time-of-flight distribution in time-domain NIRS (Aletti et al., 2012).

Of note that large body movements during gait may lead to optical fibers displacements on the head, which would translate into a large hemoglobin artifact in the fNIRS signal. Tight fixation of the fibers and the fNIRS probes is crucial while walking. A combination of a customized head cap that holds the fiber holders together with a proper fiber bundle suspension to provide further stability without interfering with the subject's movement is warranted. Different motion artifact techniques (e.g., adaptive filtering Zhang et al., 2009, Kalman filter and independent component analysis) and the use of co-located channels have been proposed for their ability to minimize the effects of physiological motion artifacts in near-infrared imaging (see Robertson and Douglas, 2010).

No standardized methods for fNIRS data analysis have been established yet. Up to date, the only invariant is that different experimental designs require different analysis techniques driven by the underlying neurophysiological mechanism and with a good comprehension of neurovascular coupling. For gait, increased cortical processing is related to large gait parameter changes (Gwin et al., 2011; Kurz et al., 2012) during the stimulation period (e.g., varied terrain and speed) as compared to steady-speed walking conditions. The relevant temporal window for fNIRS signals analysis in detecting brain activity should be determined accordingly. Averaging and baseline correction are conventional signal-processing methods used for the NIRS signal (Derosière et al., 2014) and appears suitable for a block-design for detecting differences in stimuli. During the early phase of locomotor performance, effect size should be calculated to overcome the influence of differential pathlength factors among subjects and brain regions on O_2Hb and HHb (Suzuki et al., 2004). In the context

of gait, the intensity (e.g., speed) and/or complexity of the gait modulates likely the hemodynamic response (Leff et al., 2011). Therefore, temporal window selection where cortical activation is expected to occur should incorporate variable duration for estimating the "true" time to peak of O_2Hb and the time of nadir of HHb by considering the onset of the stimulus (Leff et al., 2011). Completing this analysis by an evaluation of the activation dynamics (e.g., by an analysis of the slope of the O_2Hb from onset of the stimulus to peak) might be relevant (Mandrick et al., 2013). Alternatively, individual channel time series of fNIRS data can be reconstructed by using a reference waveform (i.e., trapezoidal function) corresponding to the expected hemodynamic response function (Kurz et al., 2012). Finally, occurrence probability of typical activation pattern has to be evaluated individually, due various sources of noise (see above).

The potential of fNIRS application in the study of human brain activation during gait is promising, motivating further application-specific development toward neuroscience and clinical questions. The investigation of cortical activity by fNIRS presents real advantages especially when measurement in ecologically valid conditions is required. However, neuroimaging of gait is not straightforward and remains difficult. A signal-processing method to extract walking-related components has still to be proposed for fNIRS signals during gait. Also while fNIRS use during gait training in clinical settings might be viewed as an interesting diagnostic tool, many potential confounding variables resulting from disease itself and from extracortical changes need to be carefully controlled.

REFERENCES

Aletti, F., Re, R., Pace, V., Contini, D., Molteni, E., Cerutti, S., et al. (2012). Deep and surface hemodynamic signal from functional time resolved transcranial near infrared spectroscopy compared to skin flow motion. *Comput. Biol. Med.* 42, 282–289. doi: 10.1016/j.compbiomed.2011.06.001

Derosière, G., Alexandre, F., Bourdillon, N., Mandrick, K., Ward, T. E., and Perrey, S. (2014). Similar scaling of contralateral and ipsilateral cortical responses during graded unimanual force generation. *Neuroimage* 85(Pt 1), 471–477. doi: 10.1016/j.neuroimage.2013.02.006

Fekete, T., Rubin, D., Carlson, J. M., and Mujica-Parodi, L. R. (2011). A stand-alone method for anatomical localization of NIRS measurements. *Neuroimage* 56, 2080–2088. doi: 10.1016/j.neuroimage.2011.03.068

Gagnon, L., Cooper, R. J., Yücel, M. A., Perdue, K. L., Greve, D. N., and Boas, D. A. (2012). Short separation channel location impacts the performance of short channel regression in NIRS. *Neuroimage* 59, 2518–2528. doi: 10.1016/j.neuroimage.2011.08.095

Gwin, J. T., Gramann, K., Makeig, S., and Ferris, D. P. (2011). Electrocortical activity is coupled to gait cycle phase during treadmill walking. *Neuroimage* 54, 1289–1296. doi: 10.1016/j.neuroimage.2010.08.066

Holtzer, R., Mahoney, J. R., Izzetoglu, M., Izzetoglu, K., Onaral, B., and Verghese, J. (2011). fNIRS study of walking and walking while talking in young and old individuals. *J. Gerontol. A Biol. Sci. Med. Sci.* 66, 879–887. doi: 10.1093/gerona/glr068

Kirilina, E., Jelzow, A., Heine, A., Niessing, M., Wabnitz, H., Brühl, R., et al. (2012). The physiological origin of task-evoked systemic artefacts in functional near infrared spectroscopy. *Neuroimage* 61, 70–81. doi: 10.1016/j.neuroimage.2012.02.074

Koenraadt, K. L., Duysens, J., Smeenk, M., and Keijsers, N. L. (2012). Multi-channel NIRS of the primary motor cortex to discriminate hand from foot activity. *J. Neural Eng.* 9:046010. doi: 10.1088/1741-2560/9/4/046010

Koenraadt, K. L., Roelofsen, E. G., Duysens, J., and Keijsers, N. L. (2014). Cortical control of normal gait and precision stepping: an fNIRS study. *Neuroimage* 85(Pt 1), 415–422. doi: 10.1016/j.neuroimage.2013.04.070

Kurz, M. J., Wilson, T. W., and Arpin, D. J. (2012). Stride-time variability and sensorimotor cortical activation during walking. *Neuroimage* 59, 1602–1607. doi: 10.1016/j.neuroimage.2011.08.084

la Fougère, C., Zwergal, A., Rominger, A., Förster, S., Fesl, G., Dieterich, M., et al. (2010). Real versus imagined locomotion: a [18F]-FDG PET-fMRI comparison. *Neuroimage* 50, 1589–1598. doi: 10.1016/j.neuroimage.2009.12.060

Leff, D. R., Orihuela-Espina, F., Elwell, C. E., Athanasiou, T., Delpy, D. T., Darzi, A. W., et al. (2011). Assessment of the cerebral cortex during motor task behaviours in adults: a systematic review of functional near infrared spectroscopy (fNIRS) studies. *Neuroimage* 54, 2922–2936. doi: 10.1016/j.neuroimage.2010.10.058

Mandrick, K., Derosiere, G., Dray, G., Coulon, D., Micallef, J. P., and Perrey, S. (2013). Utilizing slope method as an alternative data analysis for functional near-infrared spectroscopy-derived cerebral hemodynamic responses. *Int. J. Ind. Ergon.* 43, 335–341. doi: 10.1016/j.ergon.2013.05.003

Mazerie, J., Bourdillon, N., Derosiere, G., Alexandre, F. and Perrey, S. (2012). Larger brain oxygenation changes during downhill than uphill walking. *Fund. Clin. Pharmacol.* 26(suppl. 1), 61. doi: 10.1111/j.1472-8206.2012.01032.x

Mihara, M., Miyai, I., Hatakenaka, M., Kubota, K., and Sakoda, S. (2007). Sustained prefrontal activation during ataxic gait: a compensatory mechanism for ataxic stroke? *Neuroimage* 37, 1338–1345. doi: 10.1016/j.neuroimage.2007.06.014

Miyai, I., Tanabe, H. C., Sase, I., Eda, H., Oda, I., Konishi, I., et al. (2001). Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. *Neuroimage* 14, 1186–1192. doi: 10.1006/nimg.2001.0905

Miyai, I., Yagura, H., Oda, I., Konishi, I., Eda, H., Suzuki, T., et al. (2002). Premotor cortex is involved in restoration of gait in stroke. *Ann. Neurol.* 52, 188–194. doi: 10.1002/ana.10274

Muthalib, M., Anwar, A. R., Perrey, S., Dat, M., Galka, A., Wolff, S., et al. (2013). Multimodal integration of fNIRS, fMRI and EEG neuroimaging. *Clin. Neurophysiol.* 124, 2060–2062. doi: 10.1016/j.clinph.2013.03.018

Perrey, S. (2008). Non-invasive NIR spectroscopy of human brain function during exercise. *Methods* 45, 289–299. doi: 10.1016/j.ymeth.2008.04.005

Petersen, T. H., Willerslev-Olsen, M., Conway, B. A., and Nielsen, J. B. (2012). The motor cortex drives the muscles during walking in human subjects. *J. Physiol.* 590, 2443–2452. doi: 10.1113/jphysiol.2012.227397

Piper, S. K., Krueger, A., Koch, S. P., Mehnert, J., Habermehl, C., Steinbrink, J., et al. (2014). A wearable multi-channel fNIRS system for brain imaging in freely moving subjects. *Neuroimage* 85(Pt 1), 64–71. doi: 10.1016/j.neuroimage.2013.06.062

Robertson, F. C., and Douglas, T. S. (2010). Motion artifact removal for functional near infrared spectroscopy: a comparison of methods. *IEEE Trans. Biomed. Eng.* 57, 1377–1387. doi: 10.1109/TBME.2009.2038667

Sato, H., Fuchino, Y., Kiguchi, M., Katura, T., Maki, A., Yoro, T., et al. (2005). Intersubject variability of near-infrared spectroscopy signals during sensorimotor cortex activation. *J. Biomed. Opt.* 10:44001. doi: 10.1117/1.1960907

Sato, T., Ito, M., Suto, T., Kameyama, M., Suda, M., Yamagishi, Y., et al. (2007). Time courses of brain activation and their implications for function: a multichannel near-infrared spectroscopy study during finger tapping. *Neurosci. Res.* 58, 297–304. doi: 10.1016/j.neures.2007.03.014

Strangman, G., Boas, D. A., and Sutton, J. P. (2002). Non-invasive neuroimaging using near-infrared light. *Biol. Psychiatry* 52, 679–693. doi: 10.1016/S0006-3223(02)01550-0

Suzuki, M., Miyai, I., Ono, T., and Kubota, K. (2008). Activities in the frontal cortex and gait performance are modulated by preparation. An fNIRS study. *Neuroimage* 39, 600–607. doi: 10.1016/j.neuroimage.2007.08.044

Suzuki, M., Miyai, I., Ono, T., Oda, I., Konishi, I., Kochiyama, T., et al. (2004). Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study. *Neuroimage* 23, 1020–1026. doi: 10.1016/j.neuroimage.2004.07.002

Yang, J. F., and Gorassini, M. (2006). Spinal and brain control of human walking: implications for retraining of walking. *Neuroscientist* 12, 379–389. doi: 10.1177/1073858406292151

Zhang, Q., Strangman, G. E., and Ganis, G. (2009). Adaptive filtering to reduce global interference in non-invasive NIRS measures of brain activation: how well and when does it work? *Neuroimage* 45, 788–794. doi: 10.1016/j.neuroimage.2008.12.048

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 31 January 2014; accepted: 12 May 2014; published online: 28 May 2014.
*Citation: Perrey S (2014) Possibilities for examining the neural control of gait in humans with fNIRS. Front. Physiol. **5**:204. doi: 10.3389/fphys.2014.00204*
This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in
PHYSIOLOGY

OPINION ARTICLE
published: 18 December 2013
doi: 10.3389/fphys.2013.00360

Future uncertainties in the development of clinical cerebral oximetry

***Hilary P. Grocott*[1,2]* and Sophie N. Davie*[1]**

[1] Department of Anesthesia & Perioperative Medicine, University of Manitoba, Winnipeg, MB, Canada
[2] Department of Surgery, University of Manitoba, Winnipeg, MB, Canada
*Correspondence: hgrocott@sbgh.mb.ca

Edited by:
Patrice Brassard, Laval University, Canada

Keywords: cerebral oximetry, cardiac surgery, near infrared spectroscopy, postoperative outcome, brain protection

Since the first report in 1954 outlining the *in vivo* use of a double-beam spectrophotometer to measure the absorption of near-infrared light by various light absorbing pigments (or chromophores) involved in the mitochondrial respiratory chain (Chance, 1954), substantive advancements have been made in the use of near-infrared spectroscopy (NIRS) to monitor the oxidative state of various human tissues. Indeed, when Chance first reported the measurement of cytochrome c oxidase in yeast cells (Chance, 1954), he likely had little inclination that this would one day lead to the development of the modern day cerebral oximeter, an increasingly utilized monitor aimed at optimizing patient outcomes in a range of surgical settings. However, it was almost 25 years later that Jöbsis published a series of investigations in animals (and in human volunteers) demonstrating that blood flow related changes in brain oxygenation could be monitored non-invasively. These studies established that NIRS could be used to monitor regional brain oxygen saturation (rSO_2) in a potentially clinically useful manner (Jobsis, 1977). However, as is the case with many clinical developments, it took decades of further advancements before the first cerebral oximeter was approved by the United States Food and Drug Administration (Widman, 1997). Indeed, now more than 20 years since its first approval (and 60 years after the seminal work by Chance), we are arguably at a cross roads in the further development and understanding of how to use cerebral oximetry in clinical practice. Although substantial potential exists for NIRS-associated advancements in patient monitoring (and related improvements in outcome) in a wide variety of clinical situations, there are a number of uncertainties that could prevent these devices from reaching their full potential.

Although there are hundreds of reports outlining numerous plausible uses for cerebral oximetry, notably in the operating room and intensive care unit (Grocott et al., 2010; Ghosh et al., 2012; Zheng et al., 2013), we are still years from having large scale, randomized controlled clinical trials definitively examining the full potential clinical benefit of this device. The results of smaller trials, if they are to be confidently believed, need to be replicated and corroborated on a much larger scale. Indeed, there are a number of reasons for the considerable uncertainty regarding the capability of cerebral oximeters, despite substantive promise. Inter-device variability, variability in oxygen saturation targets and thresholds, issues related to absolute vs. relative saturation changes, along with studies limited by their observational nature, have all contributed to this current lack of confidence. Understanding the true clinical value of this device is further obscured by wide inter-study variability.

With respect to the variability in technology amongst the individual devices, it is not entirely certain whether information gained from one manufacturer's device can be appropriately compared to that of another. The differences in technology, including the choice of light source (i.e., laser vs. light emitting diodes) and specific wavelengths, the various proprietary absorption and processing algorithms, as well as the validation sequences used, all contribute to questions of their broader comparability (Ghosh et al., 2012). Variability might also exist with respect to how the devices account for differences in skin pigmentation (Bickler et al., 2013). Furthermore, the manner in which these devices handle issues related to spatial resolution could have the largest impact on whether rSO_2 measurements are affected by extracranial contamination (Davie and Grocott, 2012). That is, how much non-cerebral saturation signal from the superficial tissues, contaminating the deeper cerebral saturation signal, does each of these devices contain? Indeed, we recently determined, using an experimental design that allowed the separation of scalp oxygen saturation from that of cerebral oxygen saturation, that the scalp contamination can lead to as much as a 17% change in the NIRS signal. Importantly, newer generation devices were much less prone to the contamination. Comparative studies using more than one technology will be needed to determine if the differences in technology are clinically relevant.

Optimizing outcome is predicated on understanding what brain oxygen saturation thresholds are worrisome enough to clinically warrant intervention. Reports thus far have substantive inconsistencies as to what the optimal cerebral saturation target should be—which leads us to the question: what is the desaturation threshold, that when crossed, increases the risk of adverse outcomes? (Murkin et al., 2007; Hemmerling et al., 2008; Kazan et al., 2009; Fischer et al., 2011; Heringlake et al., 2011; Tang et al., 2012). Specifically, is there an *absolute* saturation threshold at which there is an increased risk of adverse clinical outcomes, such has been demonstrated with jugular bulb desaturation in carotid endarterectomy surgery (Moritz et al., 2008), or is there a *relative* change (from a pre-determined baseline saturation) that is more important to signal impending danger? Furthermore, if it is

a relative change, how much of a relative change? Defining desaturation is further complicated by the influence of oxygen supplementation on relative changes in cerebral oxygenation. For example, breathing 100% oxygen can elevate baseline rSO_2 and artificially widen the difference between baseline rSO_2 and the lowest rSO_2 value during a surgical procedure (Bussieres et al., 2012). Finally, it is uncertain as to whether there is a "dose response" with respect to cerebral desaturation. That is, does a brief but substantial desaturation portend a worse outcome compared to a lesser degree of desaturation occurring for a more prolonged period of time? Early data examining the relationship between the area under the curve for various rSO_2 thresholds suggests the latter may be the case (Fischer et al., 2011). Whether it is an absolute or relative change in rSO_2 that is important will only be determined by analyzing both variables in adequately sized observational trials (see below).

The interventional algorithms used to optimize saturation are also incompletely described with respect to which of the commonly used interventions (FiO_2, $PaCO_2$, blood pressure, cardiac output, hemoglobin) are considered best to optimize rSO_2 (Denault et al., 2007). Each one of these interventions could conceivably improve outcome, or make it worse. Increasing the $PaCO_2$, blood pressure and cardiac output could increase cerebral blood flow while augmenting the FiO_2 and hemoglobin (with transfusion) could also increase the oxygen content. Combined, this would increase overall cerebral oxygen delivery. Conversely, there is the potential for substantive morbidity related to inappropriate transfusion, targeted hypercapnia and/or hypertension. For example, erroneously increasing the $PaCO_2$ above the normal physiologic level in the setting of cardiopulmonary bypass (CPB) could lead to increases of cerebral blood flow in excess of what is needed for cerebral metabolism, with a subsequent increased delivery of CPB-related air bubbles and particulate debris. This is similar to the use of pH-stat blood gas management, where the addition of CO_2 to the CPB fresh gas flow (thus correcting the CO_2 for hypothermic temperature) has been associated with worse postoperative cognitive outcomes (Patel et al., 1996). Ultimately, the safety of various interventional algorithms will be borne out from prospective randomized controlled trials of large size and multi-center nature.

Arguably, one of the greatest limitations thus far in our understanding of cerebral oximetry has been the failure to confidently delineate which clinical outcomes have relevance to rSO_2measurements. That is, one would intuitively expect that because it is a direct cerebral oximeter, neurologic outcomes themselves would have the best relationship to brain oxygen saturation. However, a cogent argument can easily be made regarding the biologic plausibility that non-cerebral outcomes could be better related to measurements of cerebral saturation. Murkin has logically argued that the brain serves as an "index organ" for other tissue saturation (Murkin, 2011). However, the brain's inherent protective mechanisms (such as metabolic and pressure related autoregulation) suggest that if brain desaturation does occur, it is likely that other tissues have long since desaturated (Boston et al., 2001; Grocott, 2011). That is, the brain in effect is the last organ to be compromised, and in some respects is not an early warning system such as a canary in the coalmine (Grocott, 2012), but just the opposite (i.e., a late indicator of trouble).

Determining which endpoints to target in outcome studies employing cerebral oximetry-guided intervention could be the largest roadblock to the clinical progress of cerebral oximetry. Our understanding of how oximetry could impact patient outcomes has been limited by the variable endpoints outlined in multiple, but mostly small, observational studies. These outcomes have been so diverse that there is considerable uncertainty as to which ones could confidently be the focus in larger trials. We would argue that there is still a desperate need for a large prospective observational trial involving at least 1000 patients, if not more (an arbitrary number, but seemingly large enough study), to determine which outcomes may be related to desaturation. Only then would it be possible to design a randomized controlled trial to investigate the ability of an interventional algorithm, aimed at restoring cerebral saturation, to modify the previously determined target outcomes. This could also serve to delineate a potential saturation threshold to maintain (such as a relative or absolute change). A good example of this is the recent work that we performed in a small observational study ($n = 109$) in cardiac surgery (Arenson et al., 2013). Firstly, we demonstrated that a somewhat conservative threshold (of an absolute saturation of less than 50%) showed a far stronger relationship to adverse outcomes [such as acute kidney injury (AKI)] than any of the relative changes from baseline. Furthermore, and as previously hypothesized, it was the non-neurologic outcomes that had substantive relationship to desaturation, with renal dysfunction demonstrating the strongest relationship. This is consistent with other recent work demonstrating that when patients were managed at low blood pressures (i.e., those below cerebral autoregulatory thresholds as defined by cerebral oximetry), they had an increased incidence of AKI (Ono et al., 2013).

Thus, the field of cerebral oximetry research is still relatively young and contains as many questions as it does certainty. In order to move forward in an expedited and confident fashion, taking advantage of the last 60 years of research in cerebral NIRS, we will need to reconsider our approach regarding further clinical development. Otherwise, we risk wasting this potentially valuable technology, and most importantly, depriving our patients the benefit of improved clinical outcomes with its universal use.

REFERENCES

Arenson, B. G., Raban, R., Arora, R. C., Hiebert, B. M., McVagh, J., and Grocott, H. (2013). Cerebral desaturation in cardiac surgery: the importance of monitoring in the ICU. *Can. J. Cardiol.* 29, S374–S375. doi: 10.1016/j.cjca.2013.07.642

Bickler, P. E., Feiner, J. R., and Rollins, M. D. (2013). Factors affecting the performance of 5 cerebral oximeters during hypoxia in healthy volunteers. *Anesth. Analg.* 117, 813–823. doi: 10.1213/ANE.0b013e318297d763

Boston, U. S., Slater, J. M., Orszulak, T. A., and Cook, D. J. (2001). Hierarchy of regional oxygen delivery during cardiopulmonary bypass. *Ann. Thorac. Surg.* 71, 260–264. doi: 10.1016/S0003-4975(00)01883-X

Bussieres, J. S., Desjardins, P., and Brassard, P. (2012). Cerebral oxygen desaturation during single lung ventilation: a potential role for vasopressors and baseline oxygen levels? *Br. J. Anaesth.* Available online at: http://bja.oxfordjournals.org/content/108/4/623/reply#brjana_el_9385

Chance, B. (1954). Spectrophotometry of intracellular respiratory pigments. *Science* 120, 767–775. doi: 10.1126/science.120.3124.767

Davie, S. N., and Grocott, H. P. (2012). Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology* 116, 834–840. doi: 10.1097/ALN.0b013e31824c00d7

Denault, A., Deschamps, A., and Murkin, J. M. (2007). A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy. *Semin. Cardiothorac. Vasc. Anesth.* 11, 274–281. doi: 10.1177/1089253207311685

Fischer, G. W., Lin, H. M., Krol, M., Galati, M. F., Di Luozzo, G., Griepp, R. B., et al. (2011). Noninvasive cerebral oxygenation may predict outcome in patients undergoing aortic arch surgery. *J. Thorac. Cardiovasc. Surg.* 141, 815–821. doi: 10.1016/j.jtcvs.2010.05.017

Ghosh, A., Elwell, C., and Smith, M. (2012). Review article: cerebral near-infrared spectroscopy in adults: a work in progress. *Anesth. Analg.* 115, 1373–1383. doi: 10.1213/ANE.0b013e31826dd6a6

Grocott, H. P. (2011). Avoid hypotension and hypoxia: an old anesthetic adage with renewed relevance from cerebral oximetry monitoring. *Can. J. Anaesth.* 58, 697–702. doi: 10.1007/s12630-011-9529-z

Grocott, H. P. (2012). Monitoring the brain in cardiac surgery–an evolving area for research. *Anaesthesia* 67, 216–219. doi: 10.1111/j.1365-2044.2012.07076.x

Grocott, H. P., Davie, S., and Fedorow, C. (2010). Monitoring of brain function in anesthesia and intensive care. *Curr. Opin. Anaesthesiol.* 23, 759–764. doi: 10.1097/ACO.0b013e3283404641

Hemmerling, T. M., Bluteau, M. C., Kazan, R., and Bracco, D. (2008). Significant decrease of cerebral oxygen saturation during single-lung ventilation measured using absolute oximetry. *Br. J. Anaesth.* 101, 870–875. doi: 10.1093/bja/aen275

Heringlake, M., Garbers, C., Kabler, J. H., Anderson, I., Heinze, H., Schon, J., et al. (2011). Preoperative cerebral oxygen saturation and clinical outcomes in cardiac surgery. *Anesthesiology* 114, 58–69. doi: 10.1097/ALN.0b013e3181fef34e

Jobsis, F. F. (1977). Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 198, 1264–1267. doi: 10.1126/science.929199

Kazan, R., Bracco, D., and Hemmerling, T. M. (2009). Reduced cerebral oxygen saturation measured by absolute cerebral oximetry during thoracic surgery correlates with postoperative complications. *Br. J. Anaesth.* 103, 811–816. doi: 10.1093/bja/aep309

Moritz, S., Kasprzak, P., Woertgen, C., Taeger, K., and Metz, C. (2008). The accuracy of jugular bulb venous monitoring in detecting cerebral ischemia in awake patients undergoing carotid endarterectomy. *J. Neurosurg. Anesthesiol.* 20, 8–14. doi: 10.1097/ANA.0b013e31814b1459

Murkin, J. M. (2011). Cerebral oximetry: monitoring the brain as the index organ. *Anesthesiology* 114, 12–13. doi: 10.1097/ALN.0b013e3181fef5d2

Murkin, J. M., Adams, S. J., Novick, R. J., Quantz, M., Bainbridge, D., Iglesias, I., et al. (2007). Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesth. Analg.* 104, 51–58. doi: 10.1213/01.ane.0000246814.29362.f4

Ono, M., Arnaoutakis, G. J., Fine, D. M., Brady, K., Easley, R. B., Zheng, Y., et al. (2013). Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. *Crit. Care Med.* 41, 464–471. doi: 10.1097/CCM.0b013e31826ab3a1

Patel, R. L., Turtle, M. R., Chambers, D. J., James, D. N., Newman, S., and Venn, G. E. (1996). Alpha-stat acid-base regulation during cardiopulmonary bypass improves neuropsychologic outcome in patients undergoing coronary artery bypass grafting. *J. Thorac. Cardiovasc. Surg.* 111, 1267–1279. doi: 10.1016/S0022-5223(96)70230-1

Tang, L., Kazan, R., Taddei, R., Zaouter, C., Cyr, S., and Hemmerling, T. M. (2012). Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction. *Br. J. Anaesth.* 108, 623–629. doi: 10.1093/bja/aer501

Widman, R. A. (1997). Available online at: http://www.accessdata.fda.gov/cdrh_docs/pdf/K971628.pdf (Accessed August 20, 2013)

Zheng, F., Sheinberg, R., Yee, M. S., Ono, M., Zheng, Y., and Hogue, C. W. (2013). Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. *Anesth. Analg.* 116, 663–676. doi: 10.1213/ANE.0b013e318277a255

Received: 19 November 2013; accepted: 22 November 2013; published online: 18 December 2013.

*Citation: Grocott HP and Davie SN (2013) Future uncertainties in the development of clinical cerebral oximetry. Front. Physiol. **4**:360. doi: 10.3389/fphys.2013.00360*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

frontiers in PHYSIOLOGY

OPINION ARTICLE
published: 22 January 2014
doi: 10.3389/fphys.2013.00403

A note on arterial to venous oxygen saturation as reference for NIRS-determined frontal lobe oxygen saturation in healthy humans

Henrik Sørensen*, Niels H. Secher and Peter Rasmussen

Department of Anesthesia, The Copenhagen Muscle Research Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
**Correspondence: hs770@hotmail.com*

Edited by:
Patrice Brassard, Laval University, Canada

Reviewed by:
J. Patrick Neary, University of Regina, Canada

Keywords: cerebral oxygenation, humans, hypocapnia, hypercapnia, hypoxia, jugular vein, NIRS

Near infrared spectroscopy (NIRS) offers non-invasive assessment of oxygenation within the human brain (S_cO_2) by appreciating the different absorption of near infrared light by hemoglobin and oxyhemoglobin (Jobsis, 1977). Since the length the light has passed when traveling from the skin to the cortex and then returning to the skin remains unknown, there is a need to adjust the signal according to an assumed ratio between the arterial vs. venous blood that is appreciated. Apparently, most NIRS devices use a fixed reference ratio between the arterial (25%) and venous contribution (75%) to the signal despite not eligible mismatch (Bickler et al., 2013). This assumption is based on anatomical evidence (Pollard et al., 1996), but might be confounded by changes in cerebral blood volume during, e.g., hypoxia and changes in the arterial carbon dioxide tension (P_aCO_2) (Ito et al., 2005). A standard reference arterial to venous ratio may therefore not exist for application of NIRS to determine S_cO_2 in humans. Thus, an estimate of cerebral capillary hemoglobin oxygen saturation ($S_{cap}O_2$) to express cerebral oxygenation is based on 50% jugular and arterial saturations (Gjedde et al., 2005) and has been reported to follow changes in S_cO_2 (Rasmussen et al., 2007). In this report we made a meta-analysis on published data (Rasmussen et al., 2007; Sørensen et al., 2012, in press) in order to evaluate which ratio between arterial and internal jugular venous hemoglobin saturation that fits best to the concomitant determined S_cO_2 in healthy humans exposed to a wide range of interventions.

Thirty seven subjects [age 27(9) years, height 181(10) cm, mass 79(13) kg, mean (*SD*)] were catheterized in the right internal jugular vein with the tip of the catheter advanced to the bulb of the vein and with a catheter in the brachial artery of the non-dominant arm, while S_cO_2 was monitored by the Invos Cerebral Oximetry (Covidien, Mansfield, MI). Arterial partial pressure for oxygen and carbon dioxide, and oxygen saturations were measured in the jugular and arterial blood (P_aO_2; P_aCO_2; S_aO_2; S_jO_2) (ABL-800, Radiometer, Brønshøj, Denmark). The subjects were exposed to hypoxia ($F_iO_2 = 10\%$; $n = 23$), inspiration of 100% oxygen ($n = 8$), atmospheric air ($n = 37$), hypercapnia ($F_iCO_2 = 5\%$; $n = 8$) and asked to hyperventilate (~2–3 kPa reduction in P_aCO_2; $n = 32$) with separate controls. By linear regression the contribution from arterial and jugular blood to S_cO_2 was estimated and R-squared (R^2) and root mean square error (RMSE) between S_cO_2 and the arterial fraction in the reference saturation were calculated (SAS Institute Inc., Cary, NC). Only data points where $S_jO_2 \leq S_cO_2 \leq S_aO_2$ were included. All reference saturations were calculated, e.g., $S_{cap}O_2 = 0.50 \cdot S_aO_2 + 0.50 \cdot S_jO_2$. The following equation, $0 = S_cO_2 - [a \cdot S_aO_2 + (a - 1) \cdot S_jO_2]$, was used to calculate the arterial fraction (a) for which the difference between S_cO_2 and the reference saturation was zero.

S_aO_2 and S_jO_2 ranged from 70 to 100% and 33 to 87%, respectively, while S_cO_2 ranged from 48 to 95%. P_aCO_2 was manipulated from 1.6 to 6.3 kPa. According to the linear regression analysis, S_cO_2 demonstrated a correlation to a wide range of ratios between the arterial and venous hemoglobin saturations. The highest RMSE was obtained when it was considered that there was no arterial contribution to S_cO_2 and the RMSE became gradually lower when the arterial contribution was considered to increase (**Figure 1A**). The lowest RMSE was observed for a 75% arterial and 25% jugular venous blood contribution to S_cO_2(RMSE = 2.70; $R^2 = 0.644$; $P < 0.0001$; **Figure 1A**). For the often-used calibration ratio (25% arterial) R^2 was 0.505 ($P < 0.0001$) with a RMSE of 4.233. In contrast, $S_{cap}O_2$ (50% arterial) had a R^2 of 0.606 ($P < 0.0001$; RMSE = 3.276; **Figure 1A**). Zero was within the 95% confidence interval only with a calculated 40–50% arterial contribution to the reference ratio. When S_cO_2 was compared with the calibration ratio, the mean difference was zero in 2.9% of the blood samples, whereas it was 10.5% when $S_{cap}O_2$ was used as reference (**Figure 1B**).

This meta-analysis of published data suggests that the optimal reference ratio has a larger arterial contribution than the ratio defined by anatomical models and likely incorporated in most NIRS devices (Pollard et al., 1996; Bickler et al., 2013). The subjects were not only exposed to conditions that changes the venous oxygen saturation, i.e., hyperventilation, but also to conditions known to affect arterial and venous cerebral blood volume and oxygen content without influencing extracerebral blood (Ito et al., 2005). From these interventions, linear regression analysis demonstrated that the correlation between

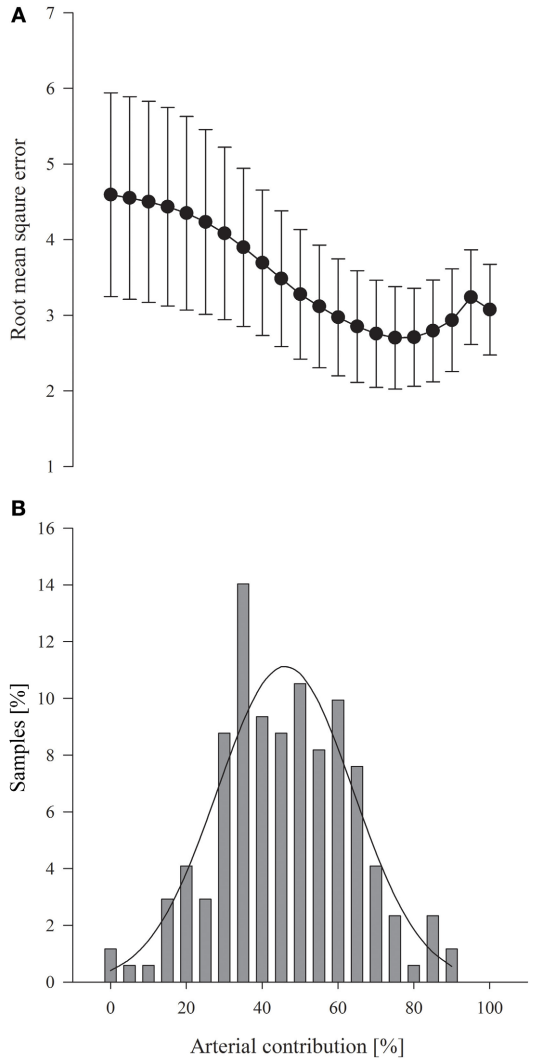


FIGURE 1 | (A) Root mean square error for the arterial fraction determined by the linear regression analysis. Values are mean (95% confidence interval). **(B)** Zero difference between the Invos-determined cerebral oxygenation (S_cO_2) and the calculated reference saturation related to the considered arterial contribution for 171 blood samples; average arterial contribution 46 ± 17% (*SD*). Solid line represents the distribution.

S_cO_2 and the arterial contribution to the reference saturation was highest when a 75% arterial contribution was considered ($R^2 = 0.644$) and also for that ratio the RMSE was the lowest (2.70) (**Figure 1A**). The calibration ratio (25% arterial) typically incorporated in the algorithms had a R^2 of 0.505 and a RMSE of 4.233 while $S_{cap}O_2$ demonstrated a stronger correlation with a R^2 of 0.606 ($P < 0.0001$; RMSE = 3.276). In addition, the mismatch between S_cO_2 and the reference ratio was more likely to be zero when a more arterial weighted reference was applied (**Figure 1B**). Thus, our findings demonstrate that $S_{cap}O_2$ is an accurate reference for S_cO_2 at least when determined with the Invos apparatus.

Similar to these findings, no eligible mismatch between S_cO_2 values and the calibration ratio (25% arterial) is observed in five different NIRS devices used to determine cerebral oxygenation in healthy subjects exposed to isocapnic hypoxemia (Bickler et al., 2013). Hypercapnia and isocapnic hypoxemia induce cerebral vasodilation and affect cerebral blood volume mainly by an increase in the arterial fraction (Ito et al., 2005). Thus, it is likely that the illuminated area of the brain encompasses more arterial blood and that could explain the aggravated mismatch between S_cO_2 and the calibration ratio during hypoxia (Bickler et al., 2013). Cerebral blood flow and jugular venous oxygen saturation are decreased with hyperventilation that reduce the calibration ratio more compared to $S_{cap}O_2$. Interestingly, when healthy humans hyperventilate the S_cO_2 overestimated the calibration ratio by 11.2% while the mean bias was only 0.2% for $S_{cap}O_2$ (Sørensen et al. unpublished). Thus, the mismatch between the calibration ratio and S_cO_2 is aggravated when only jugular venous oxygen saturation is altered, which indicates that S_cO_2 accounts for more than 25% arterial blood and that evaluations of reference saturations for NIRS must also involve conditions known to affect arterial oxygen content.

The arterial to venous balance within the brain may differ between individuals and explains the inter-individual variation in absolute S_cO_2 readings (Rasmussen et al., 2007; Bickler et al., 2013), especially the heterogeneity of blood vessels in the illuminated area of the brain seems to affect light absorption because the photons are "lost" in major blood vessel, e.g., the sagittal sinuses (Kishi et al., 2003). Other factors affecting light absorption and thereby the S_cO_2 readings may be variation in skull thickness and amount of cerebrospinal fluid (Yoshitani et al., 2007; Strangman et al., 2014). Also, skin pigmentation (Bickler et al., 2013) and degradation products of heme can affect S_cO_2 because of competitive absorption of light (Madsen et al., 2000).

Despite absolute S_cO_2 values are not comparable and exhibit large variations when compared to the calibration ratio, NIRS offers a unique non-invasive method for assessment of cerebral oxygen delivery vs. consumption and its clinical utility relies on changes from baseline rather than on absolute values (Murkin et al., 2007). Yet, at present the NIRS technology for evaluation of S_cO_2 is limited when skin blood flow is affected either by scalp ischemia or administration of sympathomimetic agents that affect skin blood flow (Davie and Grocott, 2012; Sørensen et al., 2012).

In summary, this report suggests that the reference saturations applied when using Invos cerebral oximetry should be weighted more to arterial hemoglobin

saturation than accepted by anatomical models.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the design, data analysis, and interpretation, drafting the manuscript and critical revision. All authors approved the final version before submission.

REFERENCES

Bickler, P. E., Feiner, J. R., and Rollins, M. D. (2013). Factors affecting the performance of 5 cerebral oximeters during hypoxia in healthy volunteers. *Anesth. Analg.* 117, 813–823. doi: 10.1213/ANE.0b013e318297d763

Davie, S. N., and Grocott, H. P. (2012). Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology* 116, 834–840. doi: 10.1097/ALN.0b013e31824c00d7

Gjedde, A., Johannsen, P., Cold, G. E., and Østergaard, L. (2005). Cerebral metabolic response to low blood flow: possible role of cytochrome oxidase inhibition. *J. Cereb. Blood Flow Metab.* 25, 1183–1196. doi: 10.1038/sj.jcbfm.9600113

Ito, H., Ibaraki, M., Kanno, I., Fukuda, H., and Miura, S. (2005). Changes in the arterial fraction of human cerebral blood volume during hypercapnia and hypocapnia measured by positron emission tomography. *J. Cereb. Blood Flow Metab.* 25, 852–857. doi: 10.1038/sj.jcbfm.9600076

Jobsis, F. F. (1977). Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 198, 1264–1267. doi: 10.1126/science.929199

Kishi, K., Kawaguchi, M., Yoshitani, K., Nagahata, T., and Furuya, H. (2003). Influence of patient variables and sensor location on regional cerebral oxygen saturation measured by INVOS 4100 near-infrared spectrophotometers. *J. Neurosurg. Anesthesiol.* 15, 302–306. doi: 10.1097/00008506-200310000-00002

Madsen, P. L., Skak, C., Rasmussen, A., and Secher, N. H. (2000). Interference of cerebral near-infrared oximetry in patients with icterus. *Anesth. Analg.* 90, 489–493. doi: 10.1213/00000539-200002000-00046

Murkin, J. M., Adams, S. J., Novick, R. J., Quantz, M., Bainbridge, D., Iglesias, I., et al. (2007). Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesth. Analg.* 104, 51–58. doi: 10.1213/01.ane.0000246814.29362.f4

Pollard, V., Prough, D. S., Demelo, A. E., Deyo, D. J., Uchida, T., and Stoddart, H. F. (1996). Validation in volunteers of a near-infrared spectroscope for monitoring brain oxygenation *in vivo*. *Anesth. Analg.* 82, 269–277. doi: 10.1213/00000539-199602000-00010

Rasmussen, P., Dawson, E. A., Nybo, L., Van Lieshout, J. J., Secher, N. H., and Gjedde, A. (2007). Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. *J Cereb. Blood Flow Metab.* 27, 1082–1093. doi: 10.1038/sj.jcbfm.9600416

Sørensen, H., Rasmussen, P., Sato, K., Persson, S., Olesen, N. D., Nielsen, H. B., et al. (in press). External carotid artery flow maintains NIRS-determined frontal lobe oxygenation during ephedrine administration. *Br J. Anaesth*. doi: 10.1093/bja/aet481

Sørensen, H., Secher, N. H., Siebenmann, C., Nielsen, H. B., Kohl-Bareis, M., Lundby, C., et al. (2012). Cutaneous vasoconstriction affects near-infrared spectroscopy determined cerebral oxygen saturation during administration of norepinephrine. *Anesthesiology* 117, 263–270. doi: 10.1097/ALN.0b013e3182605afe

Strangman, G. E., Zhang, Q., and Li, Z. (2014). Scalp and skull influence on near infrared photon propagation in the Colin27 brain template. *Neuroimage* 85, 136–149. doi: 10.1016/j.neuroimage.2013.04.090

Yoshitani, K., Kawaguchi, M., Miura, N., Okuno, T., Kanoda, T., Ohnishi, Y., et al. (2007). Effects of hemoglobin concentration, skull thickness, and the area of the cerebrospinal fluid layer on near-infrared spectroscopy measurements. *Anesthesiology* 106, 458–462. doi: 10.1097/00000542-200703000-00009

Received: 01 December 2013; accepted: 22 December 2013; published online: 22 January 2014.

*Citation: Sørensen H, Secher NH and Rasmussen P (2014) A note on arterial to venous oxygen saturation as reference for NIRS-determined frontal lobe oxygen saturation in healthy humans. Front. Physiol. **4**:403. doi: 10.3389/fphys.2013.00403*

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.