PHYSIOLOGY IN MEDICINE: FROM REST TO EXERCISE

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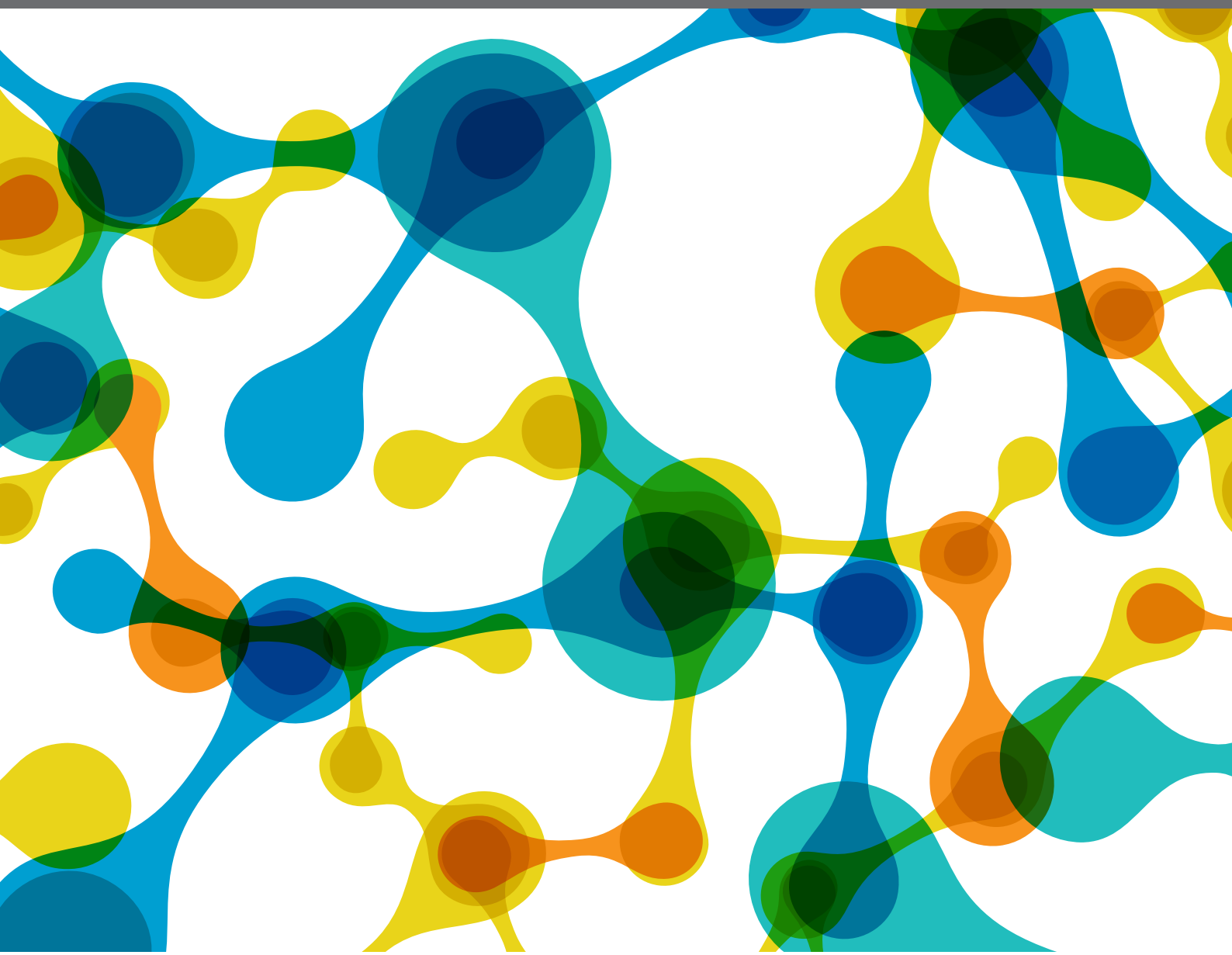

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PHYSIOLOGY IN MEDICINE: FROM REST TO EXERCISE

Topic Editors:
Johannes Van Lieshout, University of Amsterdam, Netherlands
James P. Fisher, The University of Auckland, New Zealand

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EDITORIAL
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Editorial: Physiology in Medicine: From Rest to Exercise

James P. Fisher[1] *and Johannes J. van Lieshout*[2,3,4]*

[1] Department of Physiology, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand, [2] Department of Internal Medicine, University of Amsterdam, Amsterdam, Netherlands, [3] Laboratory for Clinical Cardiovascular Physiology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4] Medical Research Council Versus Arthritis Centre for Musculoskeletal Ageing Research, Division of Physiology, Pharmacology and Neuroscience, School of Life Sciences, The Medical School, University of Nottingham Medical School, Queen's Medical Centre, Nottingham, United Kingdom

Keywords: oxygen consumption, regulation of skeletal muscle mass, Parkinson's disease and autonomic function, artificial intelligence & hemodynamic monitoring, arterial thrombosis & exercise, atrial fibrillation & cognitive decline, breath-hold diving, T2DM & cerebral perfusion/sympathetic control

Editorial on the Research Topic

Physiology in Medicine: From Rest to Exercise

In 1993 the Swedish physiologist Björn Folkow (1921–2012) wrote "*.. in humans, it is particularly difficult to differentiate between manifestations of aging per se and symptoms of morbidity, especially at higher ages when morbidity is common*" (Folkow and Svanborg, 1993). In this Research Topic, the articles address some of the difficulties indicated by Folkow in understanding how the human body functions and the diverse effects of healthy aging and disease.

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Edited and reviewed by:
Yih-Kuen Jan,
University of Illinois at Urbana-Champaign, United States

***Correspondence:**
Johannes J. van Lieshout
j.j.vanlieshout@amsterdamumc.nl
orcid.org/0000-0002-3646-2122

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FEATURED PUBLICATIONS

Hill and Lupton in 1923 were the first to describe the maximal oxygen uptake (VO_{2max}) as "*..the oxygen intake during an exercise intensity at which actual oxygen intake reaches a maximum beyond which no increase in effort can raise it*" (Hill and Lupton, 1923). VO_{2max} is the primary determinant of endurance performance and considered a valid index representing the limits of the cardiorespiratory systems' ability to transport oxygen from the air to the tissues at a given level of physical conditioning and oxygen availability (Hawkins et al., 2007). Martin-Rincon and Calbet demonstrate that the averaging strategy employed to calculate VO_{2max} from breath-by-breath data can change VO_{2max} by 4–10%, and offer practical recommendations for VO_{2max} reporting to permit adequate comparisons in training studies and meta-analyses.

Along with the decline in aerobic capacity, leg extension power, and the number of times that an individual can arise from sit to stand in 30 s starts to decline already at age +50 years (Suetta et al., 2019). Gharahdaghi et al. analyse the importance of hormones like testosterone, estrogen, growth hormone, and insulin-like growth factor in relation to the regulation of skeletal muscle mass and their involvement in the skeletal muscle adaptation to resistance exercise.

The first step to exercise is often the assumption of the upright body position, which itself involves physical activity. The gravitational displacement of blood from the chest to the lower parts of the body elicits a fall in central blood volume and thus cardiac stroke volume. A reduction of the central blood volume in response to postural stress, or immediately after finishing exercise or by blood loss, may be manifest as orthostatic intolerance. A soon as termination of exercise removes the leg muscle pump function the central blood volume is no longer maintained which may provoke post-exercise hypotension. Van der Ster et al. discuss recent developments in artificial

intelligence-based monitoring the central blood volume and predicting arterial hypotension during environmental stress ranging from exercise to hemorrhage on the battlefield and in patients during surgery.

In 1817 James Parkinson summarized the shaking palsy or "paralysis agitans" as follows: "*..Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured*" (Parkinson, 2002). Parkinson's disease (PD) is currently the second most common neurodegenerative disorder. In their review, Sabino-Carvalho et al. evaluate the clinically significant and complex associations between autonomic dysfunction, fatigue and exercise capacity in PD.

Human brain function depends on continuous delivery of oxygen and nutrients (Sick et al., 1982) but exhaustive exercise evokes a competition for the supply of oxygenated blood between the brain and the working muscles. Kim et al. allege evidence that an inability to increase cardiac output sufficiently during exercise may jeopardize cerebral perfusion in diabetic patients. The effects of functional activation on the brain by exercise are considered in relation to the regularly limited exercise tolerance in T2D patients experienced as early fatigue. They address the cerebral vs. cardiovascular responses with a focus on the brain's attenuated vascular response to exercise in these patients as compared to healthy subjects.

Exercise training is a well-recognized tool in the management of T2D due to its many cardiometabolic benefits, however T2D may negatively affect cardiovascular responses to exercise. In T2D patients the ability to adjust the circulation during exercise may become impaired, for instance with an augmented blood pressure response but attenuation of blood flow to contracting skeletal muscle. Grotle et al. summarize the current understanding of these altered exercise responses in T2D and the potential underlying mechanisms, with an emphasis on the sympathetic nervous system and its regulation during exercise.

Acute arterial thrombosis is the cause of myocardial infarction and stroke, which in the past decades have collectively become the most common causes of death in the developed countries. Regular physical activity has protective effects on these manifestations of cardiovascular disease, but acute exercise impacts on the coagulation system with a transient increase in the risk of arterial thrombosis. Olsen et al. examine this risk-benefit paradox with regard to physical activity, summarize the experimental methodology presently available to assess the integrated risk of arterial thrombosis and discuss the influence of acute exercise and exercise training on biomarkers of arterial thrombosis.

Atrial fibrillation (AF) is characterized by rapid and irregular beating of the atrial chambers of the heart that increases the risk of cardioembolic events (Naccarelli, 2000). Junejo et al. present evidence for diminished cerebral blood flow and malfunction of its control mechanisms in AF patients and consider the role of cerebrovascular dysfunction as one reason for the heightened risk of cognitive decline, depression, and dementia in AF patients. The associations between exercise and AF are complex. Both low levels of physical activity and very high levels of endurance exercise training appear to increase the risk of developing AF (Flannery et al., 2017), while there is relatively little evidence from randomized controlled trials regarding the benefits and risks of exercise training in adults with AF (Risom et al., 2017).

When studying the diving behavior of Cuvier's beaked whales (*Ziphius cavirostris*) off the Southern California coast using satellite-linked tags the depth record was established in a whale who dived to 2,992 m (9,816ft) without breathing for more than 2 h (Schorr et al., 2014). In contrast, humans are not physiologically and anatomically well-adapted to the environmental stress of diving which involves both exercise and asphyxia during progressive elevations in hydrostatic pressure. Nevertheless, breath-hold diving as another example of environmental stress is an ubiquitous activity. Patrician et al. review the physiology of deep diving focussing on the acute risks of diving but also on the potential long-term medical consequences to breath-hold diving.

SUMMARY

The issues covered in this Frontier's Clinical and Translational Physiology topic *en passant* illustrate the importance of encouraging crosstalk between physiologists and clinicians who only by joining in research from bench to bedside will get a better understanding how the body functions in health and disease for the benefit of all.

Or in the words of August Steenberg Krogh (1874–1949) awarded the 1920 Nobel Prize in Physiology or Medicine for discovery of the capillary motor-regulating mechanism, when he addressed the International Physiology Congress in 1929 (Krogh, 1929): "*.. I suppose that almost every worker in our science has given some thought to the general progress of physiology and to the problems raised by its growth, and I cannot doubt that some have pondered deeply over these problems and have much more insight into them than I possess, but you must admit that on the whole the thoughts have been kept private, and nobody seems to have considered it worthwhile to bring the matter up for a general discussion among physiologists. When I venture to do so it is because I feel deeply the importance of the subject, and in spite of the fact that I feel even more deeply my own lack of competence in all questions involving organization. My aim is only to draw your attention to some of the problems in the hope that means may be found to solve them.*"

AUTHOR CONTRIBUTIONS

JvL and JF wrote and revised the manuscript. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Progress Update and Challenges on $\dot{V}O_{2max}$ Testing and Interpretation

Marcos Martin-Rincon[1,2] *and Jose A. L. Calbet*[1,2,3]*

[1] Department of Physical Education, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain, [2] Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain, [3] Department of Physical Performance, The Norwegian School of Sport Sciences, Oslo, Norway

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Edited by:
Johannes Van Lieshout, University of Amsterdam, Netherlands

Reviewed by:
Marko S. Laaksonen, Mid Sweden University, Sweden
Ashril Yusof, University of Malaya, Malaysia

***Correspondence:**
Jose A. L. Calbet
lopezcalbet@gmail.com

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The maximal oxygen uptake ($\dot{V}O_{2max}$) is the primary determinant of endurance performance in heterogeneous populations and has predictive value for clinical outcomes and all-cause mortality. Accurate and precise measurement of $\dot{V}O_{2max}$ requires the adherence to quality control procedures, including combustion testing and the use of standardized incremental exercise protocols with a verification phase preceded by an adequate familiarization. The data averaging strategy employed to calculate the $\dot{V}O_{2max}$ from the breath-by-breath data can change the $\dot{V}O_{2max}$ value by 4–10%. The lower the number of breaths or smaller the number of seconds included in the averaging block, the higher the calculated $\dot{V}O_{2max}$ value with this effect being more prominent in untrained subjects. Smaller averaging strategies in number of breaths or seconds (less than 30 breaths or seconds) facilitate the identification of the plateau phenomenon without reducing the reliability of the measurements. When employing metabolic carts, averaging intervals including 15–20 breaths or seconds are preferable as a compromise between capturing the true $\dot{V}O_{2max}$ and identifying the plateau. In training studies, clinical interventions and meta-analysis, reporting of $\dot{V}O_{2max}$ in absolute values and inclusion of protocols and the averaging strategies arise as imperative to permit adequate comparisons. Newly developed correction equations can be used to normalize $\dot{V}O_{2max}$ to similar averaging strategies. A lack of improvement of $\dot{V}O_{2max}$ with training does not mean that the training program has elicited no adaptations, since peak cardiac output and mitochondrial oxidative capacity may be increased without changes in $\dot{V}O_{2max}$.

Keywords: calibration, cardiopulmonary exercise testing, ramp exercise, indirect calorimetry, reproducibility, breath-by-breath, metabolic cart, performance

INTRODUCTION

Relevance of $\dot{V}O_{2max}$ Determination in Performance and Health

The maximal oxygen uptake ($\dot{V}O_{2max}$) is the highest flow of oxygen (O_2) that can be used by the organism, representing the integrated capacity of the pulmonary, cardiovascular and muscle systems to take up, transport and utilize O_2. Classically, the determination of the $\dot{V}O_{2max}$ has been considered the gold standard for the assessment of the functional limits of the cardiorespiratory system (Taylor et al., 1955; Mitchell et al., 1958; Di Prampero, 2003; Levine, 2008). The $\dot{V}O_{2max}$ is one of the main factors associated with endurance performance (Joyner and Coyle, 2008) in various exercise modalities (Magel and Faulkner, 1967; Holmér et al., 1974; Maughan and Leiper, 1983). When a wide range of performances is included, $\dot{V}O_{2max}$ is the single best predictor of performance as shown in trained non-elite athletes, in whom $\dot{V}O_{2max}$ explained 90.2% of the total variance in a 16 km running time trial (McLaughlin et al., 2010). Although $\dot{V}O_{2max}$ does not predict performance in homogeneous groups of athletes (i.e., elite level), an exceptionally high $\dot{V}O_{2max}$ constitutes a prerequisite to compete at world-class level (Joyner and Coyle, 2008; Losnegard et al., 2013).

The terms cardiorespiratory fitness and $\dot{V}O_{2max}$ are used interchangeably, particularly in epidemiological studies. The assessment of $\dot{V}O_{2max}$ is gaining interest in clinical populations since it constitutes the strongest predictor of all-cause mortality when compared with other risk factors such as hypertension, smoking, obesity and diabetes (Myers et al., 2002; Lee et al., 2010). Furthermore, $\dot{V}O_{2max}$ is one of the objective criteria used to select candidates for heart transplantation (Mehra et al., 2016) and predicts the success of thoracic surgery (Brunelli et al., 2014). Thus, both in sport science and clinical medicine fields, there is a necessity for an accurate and precise determination of $\dot{V}O_{2max}$.

ASSESSMENT OF $\dot{V}O_{2max}$: EVOLUTION OF PROCEDURES AND THE PLATEAU PHENOMENON

Hill and Lupton (1923) are credited for performing the first assessments of $\dot{V}O_{2max}$. Years later, Taylor et al. (1955) proposed standardized procedures to determine $\dot{V}O_{2max}$, which were based on discontinuous protocols using three-min constant-intensity exercise periods carried out on subsequent days. At that time, $\dot{V}O_2$ measurements were based on the use of Douglas Bags and Tissot spirometers (Macfarlane, 2001) combined with Haldane's or Scholander's methods to obtain the concentration of O_2, which turned to be the gold-standard method for the assessment of $\dot{V}O_{2max}$. Taylor et al. (1955) defined the "plateau" in the $\dot{V}O_2$/intensity relationship as an increase in $\dot{V}O_2$ lower than 150 $mL.min^{-1}$ or ~2 $mL.kg^{-1}.min^{-1}$ with increasing exercise intensity. Continuous exercise protocols which allow for the assessment of additional variables of cardiorespiratory fitness were developed during the years to follow (Balke and Ware, 1959; Bruce, 1971; Froelicher et al., 1974a,b). However, these continuous protocols often failed to fulfill Taylor's criteria for the plateauing effect (Froelicher et al., 1974a,b; Pollock et al., 1976).

The development of fast gas analyzers and flow sensors during the 1960s and 1970s together with the progressive miniaturization of computers resulted in the proposal of shorter continuous protocols which used the "limit of tolerance" of the subject (volitional exhaustion) as the criterion for test finalization (Whipp et al., 1981; Buchfuhrer et al., 1983). The duration of continuous protocols was judged as a critical variable for the achievement of "true" maximal $\dot{V}O_{2max}$ values (Buchfuhrer et al., 1983). These authors reported that durations between 8 and 17 min yielded the highest $\dot{V}O_{2max}$ values in five low to moderately trained subjects during treadmill and cycling ergometry, intuitively proposing 10 ± 2 min as the ideal duration. A critical factor that determines the length of the test is the rate at which intensity is increased over time or ramp slope, usually expressed in Watts/min (or speed/min). Research carried out in the last 40 years has confirmed that a similar $\dot{V}O_{2max}$ can be attained despite wide differences in the magnitude of the increments and duration of the tests (Zhang et al., 1991; Takaishi et al., 1992). Midgley et al. (2008) concluded that durations of 5 to 26 min could be optimal to achieve $\dot{V}O_{2max}$ in healthy individuals, provided that those with shorter durations are preceded by proper warm-up. Moreover, even repeated all-out sprint exercise has been shown to allow for the achievement of true $\dot{V}O_{2max}$ values, particularly when an active recovery is applied during the resting periods (Dorado et al., 2004; Gelabert-Rebato et al., 2018).

The utilization of gas exchange indirect calorimetry evolved rapidly from the Douglas Bag into technologies capable of examining the time course of gas exchange during exercise more comprehensively, namely mixing chambers and breath-by-breath systems. However, the Douglas Bag method is still considered as the gold-standard method (Shephard, 2017). Mixing-chamber automated systems measure expired gas fractions from several breaths collected into a small chamber (Wilmore and Costill, 1974; Wilmore et al., 1976), while breath-by-breath technology analyses the gas content of each breath by measuring instantaneous expiratory flow in conjunction with simultaneous tidal concentrations of exhaled gases (Beaver et al., 1973, 1981). Modern breath-by-breath metabolic carts are equipped with fast responding O_2 and CO_2 sensors and permit a precise and accurate assessment of the end-tidal O_2 and CO_2 pressures (Losa-Reyna et al., 2015). The latter can be used in conjunction with pulse oximetry for an indirect evaluation of pulmonary gas exchange, thus enhancing the utility of ergometry in clinical populations (Macfarlane, 2001; Sun et al., 2002).

Nevertheless, several technical limitations may undermine the precision and accuracy of breath-by-breath analyses if not adequately addressed (Di Prampero and Lafortuna, 1989). Yet, with state-of-the-art, well-calibrated and fast-responding metabolic carts, it is possible to closely match the levels of accuracy and precision of the Douglas bag method (Medbo et al., 2012; Nieman et al., 2013; Perez-Suarez et al., 2018; Martin-Rincon et al., 2019).

CONFIRMING THE ATTAINMENT OF $\dot{V}O_{2max}$: FROM THE PLATEAU PHENOMENON TO THE NECESSITY OF A VERIFICATION PHASE

Despite considerable technical improvements in metabolic carts, ergometers and exercise protocols, there is yet no universal agreement on the criteria for the attainment of a "true" $\dot{V}O_{2max}$. Until recent years, the most referenced criteria to confirm $\dot{V}O_{2max}$ attainment has been the presence of a plateau or leveling off in $\dot{V}O_2$, even though several investigations have shown that the incidence of the plateau is population-dependent (Achten et al., 2002; Huggett et al., 2005) and may not be manifested despite the attainment of a valid $\dot{V}O_{2max}$ (Day et al., 2003; Rossiter et al., 2006). In addition to the 150 mL or 2 $mL.kg^{-1}.min^{-1}$ criterion previously proposed by Taylor et al. (1955) for the attainment of the plateau, other cut-off values have been postulated, as the $\Delta\dot{V}O_2 < 80$ $mL.min^{-1}$ proposed by Astrand (1960) or the presence of a slope not different from zero with an increase in exercise intensity (Myers et al., 1990). However, the efficacy of these criteria to detect the plateau depends on the specific exercise protocol (Duncan et al., 1997), the population studied (Doherty et al., 2003; Beltrami et al., 2014), the subjects' experience (Gordon et al., 2015) and the breath-by-breath averaging strategy (Astorino, 2009; Nolan et al., 2014; Martin-Rincon et al., 2019). For example, attainment of a plateau may require to exercise with a marked recruitment of anaerobic metabolism during 1–3 min, entailing a high perception of effort and a strong central command to avoid task failure (Torres-Peralta et al., 2016a,b). Not surprisingly, subjects achieving a plateau present 4–5% higher levels of pulmonary ventilation (an indication of higher central command activation), respiratory exchange ratio (RER), and blood lactate concentration than those not reaching a plateau (Edvardsen et al., 2014). Given the limited duration of the plateau phase, its identification is facilitated by using shorter (15, 30 s) than longer (i.e., 60 s) time-averaging strategies (Astorino, 2009; Nolan et al., 2014).

This is further complicated by the influence that different exercise protocols and modes (Millet et al., 2009) may have on the highest $\dot{V}O_2$ value attainable (Midgley et al., 2008). Consequently, when uncertainty exists regarding whether a $\dot{V}O_{2max}$ value is real or not, the highest $\dot{V}O_2$ recorded is named $\dot{V}O_{2peak}$. Since many individuals reach a higher $\dot{V}O_{2max}$ value during a supramaximal rather than during an incremental exercise test, it is necessary to include a verification test few minutes after the end of the incremental test (Poole and Jones, 2017), even in clinical populations (Moreno-Cabanas et al., 2020).

RECOMMENDED PROCEDURES FOR QUALITY CONTROL OF METABOLIC CARTS

Quality control procedures are mandatory to avoid technical errors. Most advanced metabolic carts are equipped with automated calibration routines that should be followed according to the recommendations of the manufacturers and using high-grade calibration O_2 and CO_2 gases. Besides the standard automated calibration, the flow sensors should be checked regularly with calibration syringes or commercially available metabolic simulators. Proper maintenance and replacement of flowmeters, O_2 cells, Nafion tubing and any other tubing and valves should follow the recommendations of the manufacturers. In addition, combustion tests of pure fuels such as methanol, butane or propane can be used to perform an integral check on the precision and accuracy of the metabolic carts. The combustion tests have the advantage of generating heat and some moisture, similar to the combustion present in living organisms (see, for example, Perez-Suarez et al., 2018). It is also advisable to perform regular checks at low and high exercise intensities, for example, on laboratory members holding a steady physical fitness level, as an additional biological check.

Verification of the performance of ergometers and treadmills is also necessary. In addition to the recommendations made by manufacturers, cross-validation biological checks with other ergometers are recommended. For example, repeated cardiorespiratory measurements at target intensities in the same person can be used to verify the stability of physiological variables. Treadmill speed and inclination can be easily verified manually or with odometer wheels.

IMPACT OF DATA PROCESSING STRATEGIES ON THE $\dot{V}O_2$ IMPUTED AS THE $\dot{V}O_{2max}$

Until recently, not much attention had been paid to the influence of the averaging interval or strategy on the $\dot{V}O_2$ value imputed as $\dot{V}O_{2max}$ and its reproducibility (Myers et al., 1990; Hill et al., 2003; Midgley et al., 2007; Astorino, 2009; Nolan et al., 2014; Smart et al., 2015; Dideriksen and Mikkelsen, 2017). Despite the inherent high variability between breaths, there is no universal consensus on how to average indirect calorimetry data (Robergs et al., 2010). We have recently demonstrated that the $\dot{V}O_2$ value imputed as $\dot{V}O_{2max}$ can fluctuate between 4 and 10% depending on the averaging strategy and the fitness levels (Martin-Rincon et al., 2019; **Figure 1**). We have shown that in subjects with a $\dot{V}O_{2max}$ lower than ∼40 mL/kg/min (13–40 mL/kg/min), the $\dot{V}O_{2max}$ value is ∼10% higher when using shorter (i.e., 10 breaths or seconds) averaging strategies rather than longer (i.e., 60 breaths or seconds in averaging block). This effect was slightly smaller (∼6.5%) in higher fitness ($\dot{V}O_{2max}$ between 40 and 60 mL/kg/min) subjects. Similarly, from a short (i.e., 10 breaths or seconds) to an intermediate length in the averaging block (i.e., 30 breaths or seconds), the decrease is ∼7.5% in low-fit and ∼5% in those with higher fitness. Therefore, with shorter averaging strategies the $\dot{V}O_2$ value considered as $\dot{V}O_{2max}$ is larger, with this effect being more marked in untrained subjects, regardless of the use of breath- or time-based averaging strategies (Martin-Rincon et al., 2019). The time- and breath-averaged $\dot{V}O_2$ values produce similar results for a given length of the averaging block

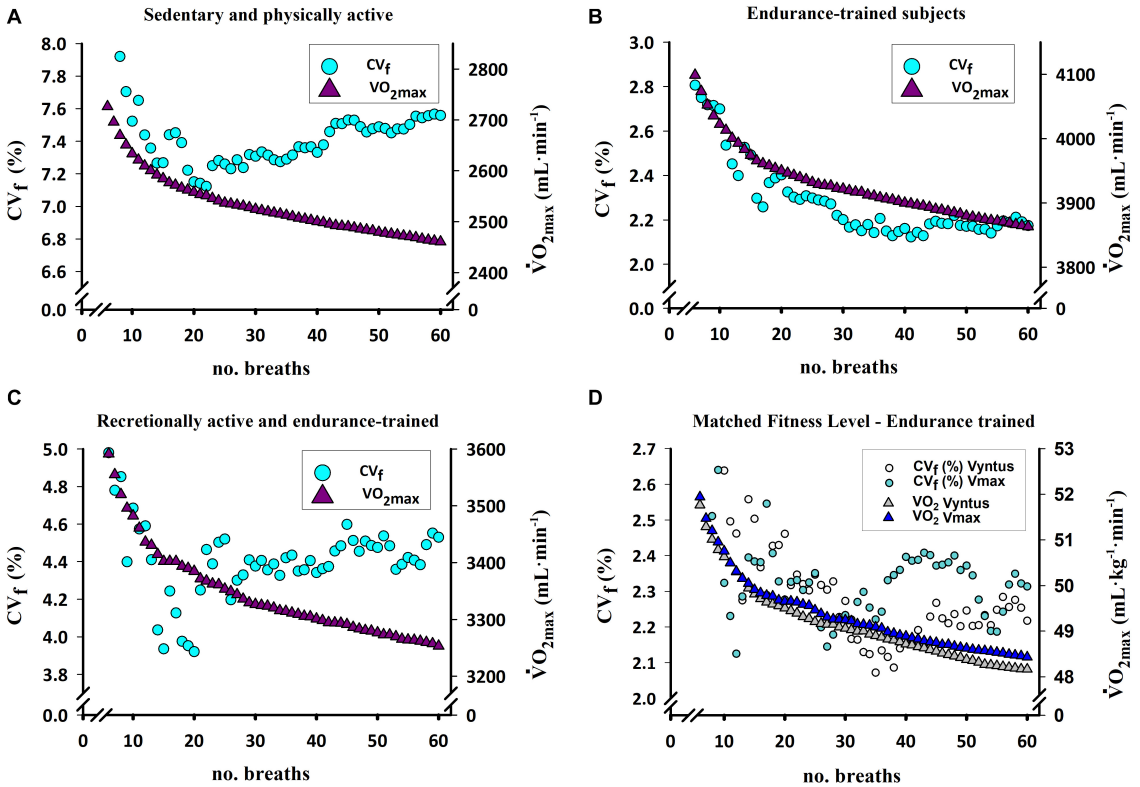

FIGURE 1 | Change in the $\dot{V}O_{2max}$ value and its reproducibility in subjects divergent for fitness status using two different automated metabolic carts operated in breath-by-breath mode with different rolling breath-averages. **(A)** $\dot{V}O_{2max}$ response in a heterogeneous group of sedentary and physically active overweight and obese subjects ($\dot{V}O_{2max}$ range: 13–40 mL/kg/min) assessed with Vmax N29 Sensormedics (n = 51). **(B)** $\dot{V}O_{2max}$ response in a group of endurance-trained subjects ($\dot{V}O_{2max}$ range: 40–60 mL/kg/min) assessed with Vyntus CPX (n = 11). **(C)** $\dot{V}O_{2max}$ response in a group of recreationally active and endurance-trained subjects ($\dot{V}O_{2max}$ range: 35–60 mL/kg/min) performing one test with Vmax N29 and a duplicate test with Vyntus CPX in random order (n = 11). **(D)** $\dot{V}O_{2max}$ response assessed with the Vmax N29 and Vyntus metabolic carts in two groups of nine subjects each of similar $\dot{V}O_{2max}$ ($\dot{V}O_{2max}$ range: 40–60 mL/kg/min) **(B)**. CV_f (%), coefficient of variation calculated as proposed by Forkman (2009). Note the clear trend for lower reproducibility and a larger decay of the $\dot{V}O_{2max}$ the lower the fitness of the subjects. Modified from Martin-Rincon et al. (2019) with kind permission.

in breaths or seconds (Martin-Rincon et al., 2019; **Figure 2**). The values of $\dot{V}O_{2max}$ obtained with different averaging strategies can be interconverted with specific equations (Martin-Rincon et al., 2019). Given the fact that the $\dot{V}O_{2max}$ can be maintained only for a short time, the identification of the plateau is facilitated by short averaging intervals, as previously mentioned, without a negative impact of shorter averaging strategies on the reliability of the measurements (Martin-Rincon et al., 2019).

PHYSIOLOGICAL INTERPRETATION OF THE $\dot{V}O_{2max}$

The $\dot{V}O_{2max}$ value obtained in an exercise test should be checked against normative data (Edvardsen et al., 2013; Loe et al., 2013; Kaminsky et al., 2017), taking into consideration the exercise intensity achieved at the end of the test, exercise mode, age, sex, health status, fitness level, familiarization and the averaging strategy used to obtain the reference values. Since there is a close linear association between exercise intensity and $\dot{V}O_2$, there are several linear equations that can be used to predict the $\dot{V}O_2$ associated with a submaximal load as well as the $\dot{V}O_{2max}$ (Storer et al., 1990; Hall et al., 2004). The predicted or normative value can be confronted with the measured one, having in mind that departures up to 20% are possible (Malek et al., 2004). In the case of large differences between measured and estimated or reference values, assessment errors should be ruled out.

Since the $\dot{V}O_{2max}$ is a lumped parameter reflecting the flow of O_2 from the atmosphere to the mitochondria, the flow in downwards steps of the transport chain can never be higher than in the precedent step. $\dot{V}O_{2max}$ cannot be higher than O_2 delivery, and O_2 delivery cannot be higher than the O_2 flow in the lungs. For the correct physiological interpretation of the $\dot{V}O_{2max}$, it is critical to identify which the limiting step/factor is, holding in mind that the limiting factor may change with training (Zinner et al., 2016). In other words, it is essential to find out whether the limitation is mostly due to pulmonary ventilation, pulmonary gas exchange, cardiac output, muscle blood flow, arterial O_2 content, muscle O_2 diffusion capacity or the mitochondrial capacity to utilize O_2. In general, in healthy people, including elite athletes, the main limiting factor for $\dot{V}O_{2max}$ is O_2 delivery (Saltin and Calbet, 2006). Nevertheless, couch potatoes may

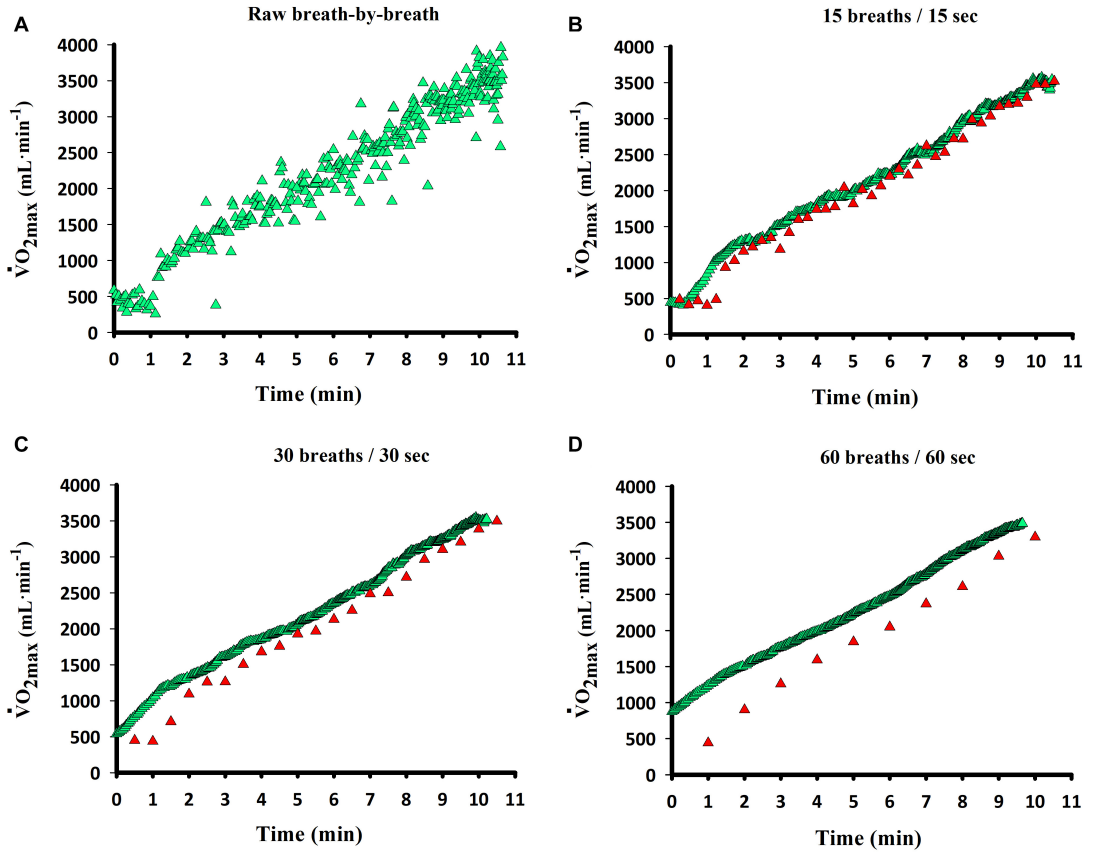

FIGURE 2 | Representative $\dot{V}O_2$ data during an incremental exercise to exhaustion in one demonstrative subject using different averaging blocks (breaths and seconds). Calculation of averaging blocks for the breath-based strategy refers to a "rolling" breath average, while time-based data were stationary time-averaged, both with the corresponding length of the block (e.g., 10 breaths or 10 s). Data are presented as **(A)** raw breath-by-breath, **(B)** 15 breaths and 15 s, **(C)** 30 breaths and 30 s, **(D)** 60 breaths and 60 s. Note the slightly higher values of breath-based averages compared to time-based averages of the same number, although a high concordance (concordance correlation coefficient = CCC > 0.97) is present. Modified from Martin-Rincon et al. (2019) with kind permission.

be limited by their capacity to use O_2, which can be readily tested by performing an incremental exercise test in hyperoxia (Cardus et al., 1998). Optimally, during the exercise test, the arterial hemoglobin saturation should be assessed indirectly by pulse oximetry. It is important to account for the impact that blood hemoglobin concentration may have on $\dot{V}O_{2max}$, and thus it is convenient to measure this variable before the tests (Calbet et al., 2002).

To facilitate the interpretation of results, the $\dot{V}O_{2max}$ should always be reported in absolute terms (i.e., $mL.min^{-1}$), together with the protocol used for its assessment and the averaging strategy. The $\dot{V}O_{2max}$ value adjusted for body weight has different meanings depending on the body composition, although the relative value (i.e., $\dot{V}O_{2max}$ in $mL.kg^{-1}.min^{-1}$) predicts better performance than the absolute value in competitions lasting from 60 to 90 s to several hours (Joyner and Coyle, 2008). In training studies and clinical interventions, the absolute value should imperatively be reported such that a mechanistic explanation for the changes in $\dot{V}O_{2max}$, connected to the limiting factors, can be elaborated. Lack of improvement in $\dot{V}O_{2max}$ with training does not mean that the training program has failed or that it has elicited no adaptations. Actually, in elite athletes, peak cardiac output may be increased, as well as mitochondrial oxidative capacity, without changes in $\dot{V}O_{2max}$, due to an impairment of pulmonary gas exchange caused by the reduction of capillary blood mean transit time in the lung (Skattebo et al., 2020a). Moreover, peripheral adaptations may enhance the $\dot{V}O_{2peak}$ and O_2 extraction during small mass exercise without increasing the $\dot{V}O_{2max}$ measured during whole-body exercise (Skattebo et al., 2020b). Meta-analyses on the effects of an intervention on $\dot{V}O_{2max}$ should be based on absolute values, after taking into consideration the averaging strategies used in each study and the exercise modality, as previously discussed (Martin-Rincon et al., 2019).

FUTURE PERSPECTIVES

Although the $\dot{V}O_{2max}$ value varies depending on the averaging strategy, the fact that the values obtained with different averaging strategies are closely related allows the assumption that they hold a similar physiological meaning. However, the fact that $\dot{V}O_{2max}$ increases log-linearly with the shortening of the averaging interval (breath or time) (Martin-Rincon et al., 2019) implies that the real $\dot{V}O_{2max}$ value should be measured with a small number of breaths or a short time interval. Since the reproducibility is not significantly lowered by reducing the averaging interval between 6 and 60 breaths (or 6 and 60 s) (Martin-Rincon et al., 2019), the most appropriate approach would be using the shortest interval, since only one true $\dot{V}O_{2max}$ value must exist. From a physiological perspective it is not the same to compute the $\dot{V}O_{2max}$ value with a 6-s than a 60-s averaging strategy, since the latest may be 4–10% lower, depending on the fitness status. Given the relatively low trainability of $\dot{V}O_{2max}$ (Montero and Lundby, 2017), scientists and clinicians may easily misjudge the real condition of patients or the effects elicited by an intervention without accounting for the impact of the averaging strategy. Imputing an underestimated $\dot{V}O_{2max}$ has important implications for integrative physiology and pathophysiology. This is the case when comparing the $\dot{V}O_{2max}$ with maximal mitochondrial respiration values obtained *in vitro*, where the values of $\dot{V}O_{2max}$ used to represent the whole-body $\dot{V}O_{2max}$ will be smaller, and the excess mitochondrial respiratory capacity will be overestimated. Since the $\dot{V}O_{2max}$ is used to calculate cardiac output by the direct Fick method, for a given systemic arteriovenous O_2 (a-vO_2) difference, a $\dot{V}O_{2max}$ value obtained with a longer averaging interval will result in a lower calculated cardiac output by the Fick method. Likewise, the calculated pulmonary O_2 diffusing capacity would also be greater the higher the $\dot{V}O_{2max}$ imputed. Moreover, defining the $\dot{V}O_{2max}$ with a shorter averaging interval results in a value that can be maintained for a shorter time, affecting the procedures to determine the velocity or intensity at $\dot{V}O_{2max}$ (Billat and Koralsztein, 1996; Billat et al., 1999).

In the case that the $\dot{V}O_{2max}$ is used to calculate the systemic a-vO_2 difference using the indirect Fick method, attributing a higher $\dot{V}O_{2max}$ value would result in lower mixed venous O_2 contents and higher systemic O_2 extractions. Thus, when comparing the effect of different studies on variables determined by calculation from the $\dot{V}O_{2max}$, it is crucial to have into consideration the averaging strategy applied in each investigation. Therefore, these facts may contribute to explain some of the variability in the literature when secondary-outcome variables have been based on $\dot{V}O_{2max}$ values computed with large or small averaging strategies.

Based on the reproducibility of measurements, no particular sampling strategy seem superior for assessment of $\dot{V}O_{2max}$. Notwithstanding, given that the $\dot{V}O_{2max}$ can be sustained for a limited time, a shorter averaging strategy offers a higher probability for capturing the true $\dot{V}O_{2max}$, while facilitating the identification of the plateauing criteria (Martin-Rincon et al., 2019). Thus, when using modern metabolic carts, averaging intervals including those between 15 and 20 breaths (or seconds) are preferable as a compromise between capturing a $\dot{V}O_2$ value close to the true $\dot{V}O_{2max}$ and identifying the plateau. So far, the time resolution of the assessment of cardiac output and blood gases has not been sufficient as to clarify what factors determine the plateau phenomenon.

AUTHOR CONTRIBUTIONS

Both authors contributed similarly and approved the final version of the manuscript.

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Cerebrovascular Dysfunction in Atrial Fibrillation

Rehan T. Junejo[1†], Gregory Y. H. Lip[1] and James P. Fisher[2]*

[1]*Liverpool Centre for Cardiovascular Science, Liverpool Heart and Chest Hospital, University of Liverpool, Liverpool, United Kingdom,* [2]*Department of Physiology, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand*

It is now well established that besides being the most common sustained arrhythmia, atrial fibrillation (AF) is a major healthcare burden. Risk of debilitating stroke is increased in AF patients, but even in the absence of stroke, this population is at heightened risk of cognitive decline, depression, and dementia. The reasons for this are complex, multifactorial, and incompletely understood. One potential contributing mechanism is cerebrovascular dysfunction. Cerebral blood flow is regulated by chemical, metabolic, autoregulatory, neurogenic, and systemic factors. The dysfunction in one or more of these mechanisms may contribute to the elevated risk of cognitive decline and cerebrovascular events in AF. This short review presents the evidence for diminished cerebral blood flow, cerebrovascular carbon dioxide reactivity (i.e., cerebrovascular vasodilatory reserve), cerebral autoregulation, and neurovascular coupling in AF patients when compared to control participants in sinus rhythm. Further work is needed to understand the physiological mechanisms underpinning these observations and their clinical significance in atrial fibrillation patients.

Keywords: atrial fibrillation, cerebral blood flow, carbon dioxide, hypertension, cerebral autoregulation, neurovascular coupling

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***Correspondence:**
James P. Fisher
jp.fisher@auckland.ac.nz

[†]***Present address:***
Rehan T. Junejo, Department of Life Sciences, Manchester Metropolitan University, Manchester, United Kingdom

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia characterized by an irregularly irregular cardiac output that leads to disrupted peripheral blood flow kinetics. Recognized as a major healthcare burden (Ball et al., 2013; Chugh et al., 2014), incidence and prevalence of AF is increasing in part due to the aging global population, better management of acute myocardial infarcts, and increasing occurrence of obesity and obstructive sleep apnoea (Wolf et al., 1996; Lane et al., 2017). The lifetime risk of developing AF in individuals aged ≥55 is currently reported as being 22 to 48% depending on the presence of risk factors (Heeringa et al., 2006; Weng et al., 2018).

AF is often accompanied by structural heart disease, vascular endothelial damage/dysfunction (Conway et al., 2003; Freestone et al., 2008), and abnormal blood constituents (Pourtau et al., 2017), which confer a prothrombotic hypercoagulable state. The risk of stroke is increased 5-fold in AF (Wolf et al., 1991) with cardioembolic events often being more severe, substantially increasing the risk of morbidity and mortality (Lin et al., 1996). However, AF patients, even if anticoagulated and with no clinical history of overt embolic ischemic stroke, present a heightened risk of cognitive decline, dementia, and depression (Bellomo et al., 2012; Marzona et al., 2012; Diener et al., 2019). This perhaps reflects silent infarcts (Conen et al., 2019), hypertension (Kim et al., 2020), systolic heart failure (Lee et al., 2019), hypercholesterolemia (Chao et al., 2015), and sleep apnoea (Leng et al., 2017), conditions that are individually associated with AF and cognitive impairment,

necessitating holistic management of AF patients (Dagres et al., 2018). Nonetheless, one largely unexplored mechanism potentially contributing to the severe cerebrovascular events and cognitive dysfunction in AF patients is cerebrovascular dysfunction.

Cerebral blood flow is guided by the careful interplay of chemical, metabolic, autoregulatory, neurogenic, and systemic factors. The dysfunction in one or more of these mechanisms may contribute to the adverse cerebral events associated with AF. This mini-review will present evidence that AF modifies these aspects of cerebral blood flow regulation and the potential underlying mechanisms will be briefly discussed.

CEREBRAL BLOOD FLOW

Compromised cerebral perfusion may increase the risk of white matter damage and lower cognition (Thome et al., 1996; Jefferson et al., 2015). Lavy et al. (1980) and Gardarsdottir et al. (2017) documented a ~13% reduction in cerebral blood flow and cerebral perfusion in AF patients. Similarly, Junejo et al. (2019b) observed that cerebral perfusion, assessed using transcranial Doppler ultrasound measures of middle cerebral artery blood velocity (MVC Vm), was ~16% lower in AF patients [n = 31, 69 (64,72) years, median (interquartile range); 51.0 (12.9) cm s^{-1}, mean (standard deviation)] when compared to healthy controls in sinus rhythm [n = 30, 69 (66,73) years; 60.9 (12.9) cm s^{-1}; $p < 0.01$]. To assess AF irrespective of cardiac rhythm, comparisons were also made of AF patients diagnosed with paroxysmal (transient episodes that resolve spontaneously within 48 h) vs. persistent (untreated episodes last longer than 7 days) AF. Notably, fibrillating patients (55% of the total AF patients) exhibit a lower cerebral perfusion [44.4 (10.9) cm s^{-1}] than non-fibrillating AF patients [59.2 (10.5) cm s^{-1}; $p < 0.01$; Junejo et al., 2019b]. This supports the contention that the decreased cerebral blood flow in AF is driven by cardiac rhythm *per se*. A potential limitation of Junejo et al. (2019b) is that cerebral perfusion was assessed with transcranial Doppler ultrasound, which is limited to quantifying blood velocity but not blood flow, although a good correlation has been reported between transcranial Doppler ultrasound measures of velocity and cerebral blood flow (Clark et al., 1996; Poeppel et al., 2007). Similar findings regarding cerebral perfusion in fibrillating and non-fibrillating AF patients have been documented with phase-contrast MRI in a cross-sectional study (Gardarsdottir et al., 2017). Moreover, longitudinal studies with Xenon inhalation, single photon emission CT, arterial spin labeling, and phase-contrast MRI, where AF patients have undergone restoration of sinus rhythm, also demonstrate increases in global and regional cerebral perfusion (Petersen et al., 1989; Efimova et al., 2012; Gardarsdottir et al., 2019).

CEREBRAL CARBON DIOXIDE REACTIVITY

The cerebral vasculature is very sensitive to changes in partial pressure of arterial carbon dioxide (CO_2), with hypercapnia profoundly increasing cerebral blood flow and hypocapnia evoking cerebral vasoconstriction (Kety and Schmidt, 1946, 1948). Impaired cerebrovascular reactivity to CO_2 (CVR_{CO2}), indicative of an attenuated cerebrovascular reserve, is recognized as an independent predictor of ischemic stroke (Silvestrini et al., 2000; Markus and Cullinane, 2001) and cardiovascular mortality (Portegies et al., 2014). A poor CVR_{CO2} may increase the risk of severe ischemic stroke and delay functional recovery in AF patients.

Junejo et al. (2019b) investigated whether CVR_{CO2} is impaired in AF patients [n = 31, 69 (64,72) years]. CVR_{CO2} was assessed using the slope of MCA Vm (transcranial Doppler ultrasonography) vs. partial pressure of end-tidal CO_2 ($P_{ET}CO_2$; capnograph) by two 4-min step-increases in inspired CO_2 fraction (4 and 7% CO_2, respectively, ~21% oxygen and nitrogen balanced, open-circuit two-way valve method). Strikingly, CVR_{CO2} was ~31% lower in AF patients [1.90 (1.13) cm s^{-1} $mmHg^{-1}$] compared to healthy [n = 30, 69 (66,73) years; 2.73 (0.69) cm s^{-1} $mmHg^{-1}$; $p < 0.001$; **Figure 1**]. Given the potentially confounding effects of medications and comorbidities, comparisons were also made between AF patients and primary hypertension patients in sinus rhythm [n = 31, 68 (65,72) years] as a "disease" control group (Junejo et al., 2019b). CVR_{CO2} was documented to be ~34% lower in AF patients compared to hypertension patients [2.90 (0.92) cm s^{-1} $mmHg^{-1}$; **Figure 1**; Junejo et al., 2019b]. The rationale for studying patients with hypertension was that hypertension heralds a 40–50% excess risk of developing AF (Benjamin et al., 1994), and is the most common coexisting cardiovascular disease in AF with prevalence ranging from 20–80% in patients diagnosed with AF (Heeringa et al., 2006; Miyasaka et al., 2006; Nabauer et al., 2009; Le Heuzey et al., 2010; Weng et al., 2018). To further control for comorbidities, all participants were free from left ventricular systolic dysfunction, valvular heart disease, history of myocardial infarction, stroke, secondary hypertension, insulin-dependent diabetes, malignancy, or uncontrolled thyroid disorders (Junejo et al., 2019b).

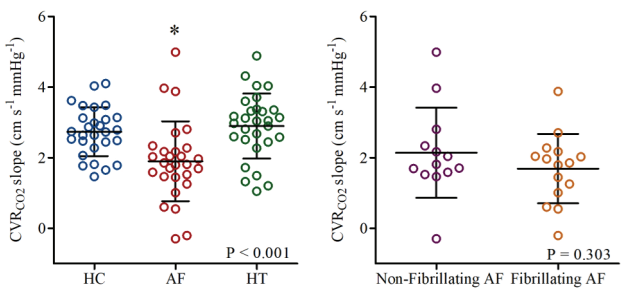

FIGURE 1 | Cerebrovascular carbon dioxide reactivity (CVR_{CO2} slope) in healthy controls (HC: blue), patients with atrial fibrillation (AF: red), and hypertension (HT: green). Responses in AF-sub-groups (non-fibrillating and fibrillating AF patients) are shown on the right. Horizontal bars show mean and standard deviation (SD) for each group. *$p < 0.05$ vs. HC and HT. Reproduced from Junejo et al. (2019b; open access article – Elsevier figure reuse license: 4825301232885; license date: May 10, 2020).

Whether the poor CVR_{CO2} identified in AF patients is primarily the result of cardiac rhythm *per se*, or is the result of damage caused by AF, is a key issue. One potential explanation for these findings is that a poor cerebral perfusion, secondary to the arrhythmia, may lead to a cerebral vasodilation that reduces the cerebral vasodilatory reserve (Aaslid et al., 1989). Indeed, as described above, AF patients exhibited a reduced MCA Vm particularly when fibrillating. However, Junejo et al. (2019b) observed that the attenuation in vasodilatory reserve of AF patients was unaffected by cardiac rhythm with no differences being observed between fibrillating [1.69 (0.98) cm s^{-1} $mmHg^{-1}$] and non-fibrillating AF [2.14 (1.28) cm s^{-1} $mmHg^{-1}$; $p = 0.707$] patients (**Figure 1**). Thus, suggesting that cerebrovascular dysfunction and specifically attenuated CVR_{CO2} in AF patients are independent of the cardiac rhythm and baseline cerebral perfusion *per se*.

Evidence of age- and hypertension-associated decline in CVR_{CO2} exists (Lipsitz et al., 2000; Walsh et al., 2009; Miller et al., 2019). However, findings of attenuated CVR_{CO2} in AF patients are novel and warrant further investigations. A potential explanation for the blunted CVR_{CO2} in AF patients is endothelial damage/dysfunction. AF evokes a turbulent blood flow pattern, loss of shear stress (Frangos et al., 1985; Noris et al., 1995) and oxidative stress (Sovari and Dudley, 2012), which collectively decrease the bioavailability of nitric oxide (NO), and arachidonic-acid derived vasodilators. Further, in AF, an attenuated brachial artery flow mediated dilatation response (FMD) (Freestone et al., 2008) and raised plasma von Willlebrand concentrations (Conway et al., 2003; Freestone et al., 2008), a factor related to adverse cardiovascular outcomes (Conway et al., 2003; Lip et al., 2006), have been identified and indicate endothelial damage/dysfunction. Both NO and arachidonic-acid derivatives are important in controlling cerebral blood flow during hypercapnia (Schmetterer et al., 1997; Kastrup et al., 1999). Indeed, administration of a NO-donor improves CVR_{CO2} in patients at risk of cardiovascular disease (Zimmermann and Haberl, 2003). Therefore, reduced production and bioavailability of endothelium-dependent vasoactive agents may underpin observations of reduced CVR_{CO2} in AF.

Debate surrounds the optimal method of assessing CVR_{CO2}, and despite the wide use of fixed gas fractions and their relative ease to administer, they have received some criticism (Fierstra et al., 2013; Fisher, 2016). Junejo et al. (2019b) reported that MCA Vm and CVR_{CO2} showed good between-day test-retest reliability, nonetheless issues regarding between-subject and inter-operator variability remain. $P_{ET}CO_2$ is commonly used as a surrogate of arterial CO_2 for measuring CVR_{CO2}. Despite strong linear correlation between $P_{ET}CO_2$ and partial pressure of arterial CO_2 (Peebles et al., 2007; McSwain et al., 2010), arterial CO_2 concentrations can vary between participants and are dependent on multiple variables (e.g., metabolic state of individuals at the time of testing and alveolar ventilation variability), and $P_{ET}CO_2$ may underestimate arterial CO_2 (Robbins et al., 1990; Delerme et al., 2010). Computerized sequential gas delivery offers fairly accurate estimates of arterial CO_2 (Ito et al., 2008) and subsequently better estimates of CVR_{CO2}. However, despite their advantages, financial setup costs and operator expertise (Fisher, 2016) have limited their widespread use. To date, only unidirectional (hypercapnic) cross-sectional comparisons of CVR_{CO2} using fixed gas fractions in AF patients either fibrillating or non-fibrillating have been made (Junejo et al., 2019b). Further, the impact of AF burden on progression of cerebrovascular dysfunction is currently not known. Longitudinal investigations of cerebral blood flow and tissue oxygenation/metabolism, both before and after restoration of sinus rhythm, warrant undertaking in combination with advanced imaging modalities.

CEREBRAL AUTOREGULATION

The cerebral vasculature possesses intrinsic mechanisms that maintain adequate perfusion despite fluctuations in blood pressure (i.e., cerebral autoregulation), thereby mitigating the risk of ischemia or hemorrhage by preventing under- or over-perfusion, respectively. Cerebral autoregulation functions as a high-pass filter whereby slower changes in perfusion pressure (>0.02 Hz) appear to pass unhindered, but more rapid pressure oscillation (<0.02 Hz) are dampened more effectively (Diehl et al., 1998).

Junejo et al. (2019a) assessed cerebral autoregulation in AF patients [n = 30, 69 (63,72) years], primary hypertensives [n = 29, 68 (65,72) years], and healthy controls [n = 24, 68 (66,70) years]. Cerebral autoregulation was determined using transfer-function analysis of the MCA Vm and blood pressure (finger photoplethysmography) responses to repeated squat-to-stand maneuver. AF patients exhibited greater changes in MCA Vm for a given change in blood pressure [gain normalized to baseline; 1.46 (1.16–2.16)% $mmHg^{-1}$] compared to hypertensives [1.13 (1.00–1.45)% $mmHg^{-1}$] and healthy controls [1.12 (0.99–1.37)% $mmHg^{-1}$; $p < 0.01$], revealing impaired autoregulation. However, unexpectedly, sub-group comparison between AF patients showed that fibrillating AF patients (53% of total) were better able to delay blood pressure oscillations from transmitting into brain blood flow [phase; 0.63 (0.25) radians] compared to non-fibrillating AF patients [0.35 (0.17) radians; $p < 0.01$], and more effective at damping blood pressure driven changes to absolute measures of cerebral perfusion [absolute gain; 0.64 (0.22) vs. 0.92 (0.37) cm s^{-1} $mmHg^{-1}$, respectively; $p = 0.02$]. However importantly, normalized gain failed to show any group differences between fibrillating [1.39 (1.11–1.80)% $mmHg^{-1}$] and non-fibrillating [1.56 (1.30–2.23)% $mmHg^{-1}$; $p = 0.29$] patients.

Impaired autoregulation may result from a number of interactive mechanisms, including mechanosensitive myogenic ion channels (Davis et al., 1992; Tan et al., 2013), neurogenic/autonomic influences (Hamner et al., 2012; Hamner and Tan, 2014), metabolic influences (Panerai et al., 1999), and NO (White et al., 2000). More specifically, autonomic disturbances (Chen et al., 2014), endothelial damage/dysfunction (Conway et al., 2003; Freestone et al., 2008), and diminished bioavailability of endothelial vasodilators (Minamino et al., 1997) in AF could contribute to autoregulatory dysfunction of AF. Further, the reduced cerebral blood flow and vasodilatory reserve observed in AF patients (Junejo et al., 2019b) may also impair cerebral autoregulation. Further investigations into the mechanisms of impaired autoregulation of AF are warranted.

Collectively, these observations suggest that cerebral vasculature in AF patients is less able to buffer blood pressure driven fluctuations in brain blood flow (i.e., cerebral autoregulation is impaired) in comparison with primary hypertensives and healthy individuals in sinus rhythm. The apparently conflicting finding of improved absolute gain in fibrillating AF patients may just reflect fibrillation itself, rather than an improvement in cerebrovascular health during fibrillation.

NEUROVASCULAR COUPLING

The regional metabolic needs of neuronal activation share a close spatial and temporal fidelity with local blood flow, as such ensuring commensurate functional perfusion within the brain (Phillips et al., 2016). This phenomenon is commonly referred to as neurovascular coupling. An impaired neurovascular coupling, indicative of cerebrovascular dysfunction, has been reported post-stroke, associated with cognitive decline, and linked to endothelial dysfunction (Girouard and Iadecola, 2006; Graves and Baker, 2020).

Junejo et al. (2019a,c) investigated whether neurovascular coupling is blunted in AF patients [n = 12, 71 (66,72) years] compared to primary hypertensives [n = 13, 66 (65,69) years] and healthy controls [n = 12, 69 (57,70) years]. Beat-to-beat posterior cerebral artery (PCA), MCA Vm (temporal transcranial Doppler ultrasonography), and vascular conductance (calculated as Vm/mean blood pressure) responses to repeated visual-stimuli (30 s eyes-open, 30 s eyes-closed for 5 min) were spline interpolated and then averages and percentage changes calculated (Phillips et al., 2016). This allowed account of changes to blood velocity and vascular diameter along with any inadvertent blood pressure fluctuations during testing. Neurovascular coupling was defined as the visually evoked increase in PCA conductance, since the PCA supplies the visual cortex.

A blunted peak PCA conductance was observed in AF [18 (8)%] and hypertensive patients [17 (8)%] compared to healthy controls [26 (9)%; $p < 0.05$], indicative of blunted neurovascular coupling in people with either AF or hypertension, relative to control participants (**Figure 2**). However, the change in MCA conductance in AF patients [17 (6)%] was greater than hypertensives [10 (4)%; $p < 0.05$], suggesting non-specific neurovascular engagement of cerebral areas in AF patients. To explore this issue further, visual stimulation related task-specificity was calculated as the difference between the PCA and MCA conductance responses. This analysis revealed that the neurovascular coupling response was near-completely abolished in AF patients [1.0 (7.5)%] compared to hypertensives [6.6 (9.4)%] and healthy controls [12.9 (9.2)%; $p < 0.01$].

These results indicate reduced neurovascular coupling responses in AF patients; however, the underlying mechanisms remain unclear. Neurovascular coupling is mediated by a complex array of feed-forward and feedback mechanisms, (e.g., hydrogen, potassium, adenosine, prostaglandins, NO, acetylcholine, glutamate, and dopamine; Girouard and Iadecola, 2006; Phillips et al., 2016). Further, recent evidence from animal models also suggests an active role of nicotinamide mononucleotide in neurovascular coupling response (Tarantini et al., 2019a,b).

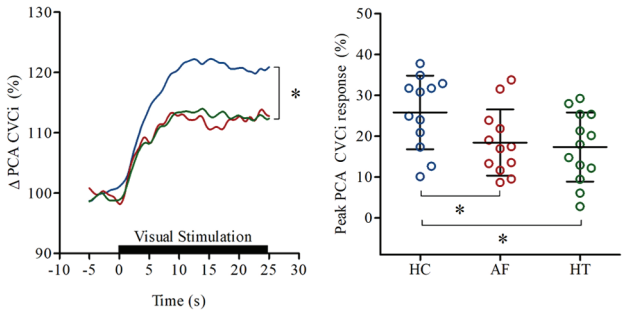

FIGURE 2 | Increase in PCA perfusion in response to neurovascular coupling observed in healthy controls (HC: blue), patients with atrial fibrillation (AF: red), and hypertension (HT: green). Lines on the **left panel** represent the mean responses; black bar indicates where eyes of the participants were open. **Right panel** shows the (%) peak posterior cerebral artery (PCA) conductance (CVC_i) responses of individuals. Horizontal bars show mean and SD values for each group. $^*p < 0.05$ vs. HC. Modified from Junejo et al. (2019a; open access article published under CC-BY 4.0 license).

Evidence exists for age- and hypertension-associated decline in neurovascular coupling response (Girouard and Iadecola, 2006; Lipecz et al., 2019), alongside some conflicting reports (Stefanidis et al., 2019). However, mechanistic studies in humans are limited and it remains to be investigated whether the attenuated neurovascular coupling responses reported in AF patients (Junejo et al., 2019a,c) reflect neurodegenerative blunting or disrupted coupling between neurons and vasculature. Moreover, to our knowledge, to date, neurovascular coupling has only been assessed in AF patients using visual stimulation (i.e., reading) and whether this diminished response persists during other stimuli (e.g., finger tapping) is unknown.

MITIGATION STRATEGIES

Improvements in cerebral perfusion and cognitive function have been observed with cardiac rhythm control following pharmacological (Damanti et al., 2018), cardioversion (Petersen et al., 1989), ablation, and pacemaker treatments (Efimova et al., 2012). Besides the improvements in ventricular filling and systolic function, rhythm control strategies offer improvements in endothelial function (Noris et al., 1995; Topper et al., 1996; Skalidis et al., 2007). Nonetheless, it is important that any rhythm control strategies employed in AF patients to improve cerebral and systemic perfusion, and vascular/endothelial health are carried out alongside parallel and continued antithrombotic therapy. Indeed, the heightened risk of ischemic strokes continues even after cardiac arrhythmia correction in AF patients (Lip, 1995; Thibault et al., 2004).

Increased concentrations of circulating inflammatory markers observed in AF suggest their contribution to endothelial damage and prothrombotic platelet activation (Patel et al., 2010; Guo et al., 2012). However, in a feedback loop, coagulation can also influence inflammation and encourage vascular dysfunction (Levi et al., 2004; Esmon, 2005). Thus, it is possible that besides the reduction in procoagulants and subsequent reduction in

stroke risk (Members et al., 2012), factor Xa, thrombin, and/or vitamin K antagonists also help attenuate cerebrovascular and peripheral vascular dysfunction in AF.

Exercise training, whether endurance (Lautenschlager et al., 2008; Green and Smith, 2017) or resistance (Cassilhas et al., 2007), oral antioxidant (Wray et al., 2012) and nitrite (Lara et al., 2016) supplementation, ischemic preconditioning (Jones et al., 2014), and heat therapy (Brunt et al., 2016) have all been associated with improved cardiovascular and/or cerebrovascular health. Their employment to improve cerebrovascular function and mitigate the risk of cognitive decline in AF patients remains a valid proposition; however, objective evidence for their effectiveness in AF remains lacking.

CONCLUSION

AF is associated with an increased stroke risk, and even anticoagulated AF patients are at an increased risk of cognitive decline, depression, and dementia. Emerging evidence suggests impaired cerebral vasodilatory reserve, autoregulation, and neurovascular coupling in AF patients compared to "disease" (primary hypertension) controls and healthy controls in sinus rhythm. These findings may be important in explaining the severity of ischemic strokes, morbidity, and mortality risk from such events, cognitive decline, and cerebral dysfunction in AF. Further cross-sectional and longitudinal studies are needed to better understand the pathophysiological underpinnings and clinical significance of these findings.

AUTHOR CONTRIBUTIONS

RJ drafted the manuscript which was critically revised by GL and JF. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: GL is a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and DaiichiSankyo. No fees are directly received personally. JF has received funding from BMS/Pfizer for an investigator-led and competitively reviewed research project. RJ was previously employed by University of Birmingham as a research fellow on BMS/Pfizer funded, investigator-led and competitively reviewed research project which he managed. This required regular contact with funders for continued project grant support. No fees/funds were directly received personally.

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Cerebral vs. Cardiovascular Responses to Exercise in Type 2 Diabetic Patients

*Yu-Sok Kim[1,2,3], Björn J. P. van der Ster[1,4], Patrice Brassard[5], Niels H. Secher[6] and Johannes J. van Lieshout[1,2,7,8]**

[1]Laboratory for Clinical Cardiovascular Physiology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, [2]Department of Medical Biology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, [3]Department of Internal Medicine, Medisch Centrum Leeuwarden, Leeuwarden, Netherlands, [4]Department of Anesthesiology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, [5]Department of Kinesiology, Faculty of Medicine, Research Center of the Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Québec, QC, Canada, [6]Department of Anesthesia, The Copenhagen Muscle Research Center, University of Copenhagen, Copenhagen, Denmark, [7]MRC/Arthritis Research UK Centre for Musculoskeletal Ageing Research, School of Life Sciences, University of Nottingham Medical School, Queen's Medical Centre, Nottingham, United Kingdom, [8]Department of Internal Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

The human brain is constantly active and even small limitations to cerebral blood flow (CBF) may be critical for preserving oxygen and substrate supply, e.g., during exercise and hypoxia. Exhaustive exercise evokes a competition for the supply of oxygenated blood between the brain and the working muscles, and inability to increase cardiac output sufficiently during exercise may jeopardize cerebral perfusion of relevance for diabetic patients. The challenge in diabetes care is to optimize metabolic control to slow progression of vascular disease, but likely because of a limited ability to increase cardiac output, these patients perceive aerobic exercise to be more strenuous than healthy subjects and that limits the possibility to apply physical activity as a preventive lifestyle intervention. In this review, we consider the effects of functional activation by exercise on the brain and how it contributes to understanding the control of CBF with the limited exercise tolerance experienced by type 2 diabetic patients. Whether a decline in cerebral oxygenation and thereby reduced neural drive to working muscles plays a role for "central" fatigue during exhaustive exercise is addressed in relation to brain's attenuated vascular response to exercise in type 2 diabetic subjects.

Keywords: cardiac output, cerebral blood flow, cerebral oxygenation, cerebral metabolism, diabetes, vascular conductance

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***Correspondence:**
Johannes J. van Lieshout
j.j.vanlieshout@amsterdamumc.nl
orcid.org/0000-0002-3646-2122

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INTRODUCTION

Animals like the Crucian carp and the aquatic turtle can survive anoxia for extended periods of time (Sick et al., 1982; Lutz et al., 1985; Hochachka and Lutz, 2001; Nilsson and Lutz, 2004), but human brain function depends on continuous delivery of oxygen and nutrients. Thus, interruption of blood supply to the brain for only a few seconds results in loss of consciousness (Rossen et al., 1943; Finnerty et al., 1954; Smith et al., 2011). Accordingly, even minor limitations to cerebral blood flow (CBF) may be critical in preserving oxygen and substrate supply to the brain and in that regard the human brain is challenged by exercise

and hypoxia (Kim, 2014). When the brain is activated to perform exercise, the increment in CBF enhances brain oxygenation whereas skeletal muscle oxygenation decreases progressively with work rate. Thus, functional activation of the brain initially leads to hyperperfusion, while the large increase in skeletal muscle blood flow during exercise may be taken to be insufficient (Quistorff et al., 2008).

Reduced exercise tolerance in type 2 diabetes mellitus (T2DM) is incompletely understood (Estacio et al., 1998; Fang et al., 2005), and has been attributed to cardiac insufficiency and impaired muscle metabolism (Poirier et al., 2000; Taegtmeyer et al., 2002; Scheuermann-Freestone et al., 2003; Stephens et al., 2007). We consider the effects of functional activation by exercise on the brain and how it contributes to understanding the control of CBF in relation to the limited exercise tolerance experienced by type 2 diabetic patients. Analogies and differences between the cerebral vs. skeletal muscle blood flow responses to exercise are highlighted with emphasis on the dependency of the human brain on the distribution of the available blood flow. A decline in cerebral oxygenation in the later stages of exhaustive exercise may reduce the motor drive to working muscles similar to what is observed during exercise in hypoxia (Rasmussen et al., 2010). Whether a decline in cerebral oxygenation with following reduced neural drive to working muscles plays a role in the development of "central" fatigue during exhaustive exercise is addressed in relation to the altered brain vascular response to exercise in type 2 diabetic patients and their accentuated perceived exertion.

AUTONOMIC NEURAL CONTROL OF CBF DURING EXERCISE

The large increase in systolic blood pressure during exhaustive exercise challenges CBF control mechanisms including cerebrovascular or cerebral autoregulation, the cerebrovascular responsiveness (CVR_{CO2}) to carbon dioxide (CO_2) and oxygen (O_2) partial pressures, matching of local cerebral blood supply to the metabolic demand (i.e., neurovascular coupling), neurogenic control (Immink et al., 2014; Ritz et al., 2014; Willie et al., 2014; Phillips et al., 2016), and maintenance of cardiac output (Ide et al., 1998, 1999a; Van Lieshout et al., 2001, 2003; Ogoh et al., 2005a; Bronzwaer et al., 2014, 2017). During exercise, CBF increases as quantified by several methods (for review, see Secher et al., 2008; Smith and Ainslie, 2017). Dynamic exercise enhances the transcranial Doppler ultrasound determined middle cerebral artery blood velocity (MCA *V*) and the ^{133}Xe clearance determined CBF (Jorgensen et al., 1992) and also the blood flow in the internal carotid and vertebral arteries (Sato et al., 2011). Notably, the increase in CBF during cerebral activation is such that cerebral oxygenation is enhanced as expressed by blood-oxygen-level (BOLD) dependent imaging (Laughlin et al., 2012) and for whole-body exercise, a similar increase in cerebral oxygenation is demonstrated by near-infrared spectroscopy (Ide et al., 1999b). Changes in CBF in response to exercise are restricted to specific areas of the brain and, therefore, blood flow in a single brain artery or vein cannot be considered to fully represent flow to or from the brain as a whole, reflecting that the effects of exercise on brain metabolism are heterogeneous. For example, regulation of internal carotid and vertebral artery flow seems different not only during exercise (Sato et al., 2011) but also during simulated orthostatic stress (Ogoh et al., 2015b). Constancy of diameter of an insonated large cerebral artery is required to link changes in cerebral blood velocity to those in CBF (Coverdale et al., 2014; Verbree et al., 2014, 2017).

Sympathetic activity is proposed to enhance cerebral vascular tone to counteract the increase in cerebral perfusion pressure beyond what is designated as the cerebral autoregulatory range (Purkayastha et al., 2013; Ogoh et al., 2015a), with cerebral perfusion pressure defined as the difference between blood pressure at the level of the circle of Willis and the critical closing pressure, the pressure inside a blood vessel below which it collapses and blood flow ceases. Both sympathetic and cholinergic mechanisms are considered important for restricting the exercise-induced increase in CBF without affecting the cerebral metabolic rate for oxygen (Seifert et al., 2010; Purkayastha et al., 2013; Willie et al., 2014; Ogoh et al., 2015a). Of note, erythropoietin has been applied to improve athletic performance and endurance but it actually reduces cerebrovascular conductance during exercise both under normoxic and hypoxic conditions (Rasmussen et al., 2012). The contribution of autonomic neural control of CBF during exercise remains difficult to detangle (Van Lieshout and Secher, 2008; Mitchell et al., 2009; Willie et al., 2014). The presently available evidence for neurogenic CBF control from rest to exercise is mainly from direct sympathetic ganglion blockade studies. At rest, unilateral trigeminal ganglion stimulation reduces CBF as evaluated by transcranial Doppler ultrasound and by single-photon emission computed tomography (Seifert and Secher, 2011). During exercise, β-adrenergic receptor blockade restricts the increase in cardiac output and in MCA *V* whereas this attenuation is eliminated by stellate ganglion blockade (Ide et al., 1998). Intrinsic cerebrovascular sympathetic activity is indicated by jugular venous "spillover" of norepinephrine from the brain in healthy humans but not in patients with autonomic failure who lack sympathetic vasomotor control (Harms et al., 2000; Mitchell et al., 2009). Apart from these selective investigations numerous studies have manipulated CBF pharmacologically by e.g., angiotensin, α-adrenergic receptor agonists and antagonists, nitric oxide donors, and anesthetic agents (Purkayastha et al., 2013; Willie et al., 2014) but the effects of these interventions on cerebrovascular tone remain controversial (Van Lieshout and Secher, 2008; Willie et al., 2014). For instance, the similarity of reductions in arterial pressure and pulsatile change in MCA *V* before vs. during ganglion blockade while maintaining arterial pressure with phenylephrine was taken to suggest that sympathetic vasoconstriction, mediated through α_2-adrenergic receptor activation, is not the underlying mechanism for the reduction in CBF during central hypovolemia (Zhang and Levine, 2007). Yet, it should be considered that phenylephrine may lower CBF while increasing mean arterial pressure (Stewart et al., 2013). In diabetic patients, both cerebral autoregulatory capacity (Kim et al., 2008a; Kim, 2014; Vianna et al., 2015) and CVR_{CO2} as the major operative mechanisms maintaining CBF may have become impaired (Dandona et al., 1978; Fulesdi et al., 1997),

rendering diabetic patients more susceptible to ischemic episodes (Dandona et al., 1978; Kim et al., 2011).

BRAIN VS. SKELETAL MUSCLE BLOOD FLOW RESPONSE TO EXERCISE

A major difference between brain and skeletal muscle is that the brain is active under all living conditions and uses ~15% of cardiac output at rest (Ide et al., 1999a, 2000; Immink et al., 2009; Willie et al., 2014). The effects of exercising in the upright vs. seated position on cardiac preload are exemplified by a higher heart rate in the upright position (Yoshiga and Higuchi, 2002). Equally, the change to the upright posture accompanying the majority of exercise modalities affects both the arterial supply to and the venous drainage from the brain (Van Lieshout et al., 2003; Dawson et al., 2004; Gisolf et al., 2004). When assuming the upright position, global CBF and frontal cortical oxygenation decrease, seemingly at odds with the concept of cerebral autoregulation implicating constancy of CBF for a range of cerebral perfusion pressures. The "constant flow" autoregulation plateau has been constructed from data across different studies rather than quantifying the pressure-flow relationship within individual subjects that, however, is difficult given that the range of blood pressures required for relating flow to pressure remains effectively limited by autonomic cardiovascular reflex activity. Yet, maintaining CBF constant would require an autoregulatory efficacy with an infinite gain, which generally does not apply to biological systems (Van Lieshout et al., 2003; Willie et al., 2014). Obviously, the arterioles rather than large arteries represent the main side of vascular resistance, but also larger arteries contribute to vascular control (Iversen et al., 1995). For the brain, the large extracranial vessels and surface vessels contribute importantly to cerebrovascular resistance, thus being at least passively involved in regulation of CBF (Faraci and Heistad, 1990; Ritz et al., 2014; Willie et al., 2014).

The brain with its small vascular bed being tightly controlled takes up to ~25% of whole-body oxygen consumption at rest (Braz and Fisher, 2016). The vulnerability of the brain is exemplified by the fact that its function deteriorates when cerebral oxygenation is reduced by more than about 10% from the resting level, in contrast to skeletal muscles, that continue their activity despite an O_2 desaturation below 10% (Quistorff et al., 2008; Secher et al., 2008). Continued exhaustive exercise evokes a competition for the supply of oxygenated blood between the brain and the working muscles. The brain activates the muscles, but from then on, the large increase in muscle blood flow and thus skeletal muscle vascular conductance represents a major competitor for continuous provision of oxygen and substrate upon which the brain relies (Secher et al., 2008). Heavy exercise with large muscle groups requests more blood than the heart can provide and thus requires tight sympathetic vasomotor control to maintain arterial pressure (Calbet et al., 2004). When humans exercise at maximal intensity, up to ~80–90% of total cardiac output is being distributed to skeletal and cardiac muscle (Laughlin et al., 2012). At the same time, an increase in regional CBF has to match the enhanced neuronal metabolism exemplified by an elevated cerebral metabolic rate for oxygen at that stage of exercise (Laughlin et al., 2012). Within the brain, in contrast to skeletal muscles, there is no capillary recruitment and creating and maintaining an elevated O_2 gradient is a prerequisite given that the efficacy for O_2 extraction by the brain compared to skeletal muscle is small.

CARDIAC OUTPUT SUPPORTS CBF DURING EXERCISE

The size of cardiac output is important for regulation of CBF beyond arterial pressure both at rest and during exercise (Hellstrøm et al., 1994, 1996; Magnusson et al., 1997; Ide et al., 1998, 1999a,b, 2000; Gruhn et al., 2001; Van Lieshout et al., 2001; Ogoh et al., 2005a; Secher et al., 2008; Braz and Fisher, 2016). In consequence, an incompetence to increase cardiac output sufficiently during exercise may jeopardize cerebral perfusion and thereby the ability of the central nervous system to recruit and adequately drive the motoneurons. The role of cardiac output for distribution of flow is illustrated in patients with moderate heart failure for whom peak skeletal muscle perfusion is maintained, provided that the activated muscle mass is small. Involvement of a larger muscle mass, however, reduces peak leg blood flow, perfusion, and oxygen uptake (Magnusson et al., 1997). Similarly in these patients during one-legged exercise, MCA *V* is maintained but declines with two-legged exercise and exposes a competition between brain and skeletal muscle (Hellstrøm et al., 1996). Thus, the traditional concept that the brain is at the top of the hierarchy of competing physiological needs is challenged when cardiac output no longer matches tissue O_2 requirements. Under these circumstances, exercise evokes cerebral deoxygenation, metabolic changes, and indices of fatigue similar to those observed during exercise in hypoxia (Secher et al., 2008; Rasmussen et al., 2010). Thus, reduced cerebral oxygenation may play a role for the development of central fatigue as an exercise capacity limiting factor (Rasmussen et al., 2010; Kim et al., 2015).

EXERCISE AND BRAIN VASCULAR CONTROL IN TYPE 2 DIABETES

Physiological aging is associated with a decline in resting cerebral metabolism, global CBF, and gray matter flow but does not in itself implicate affected CBF control (for review, see Braz and Fisher, 2016). Specifically, the normal development of an initial increase in CBF in response to exercise is well maintained in the elderly (Laughlin et al., 2012; Fisher et al., 2013; Braz and Fisher, 2016). During maximal exercise in healthy humans, fatigue is preceded by reductions in systemic and skeletal muscle blood flow, and O_2 delivery and uptake (Gonzalez-Alonso et al., 2004).

In middle-aged type 2 diabetic patients, the cardiac output reserve and work capacity are low and the increase in CBF that is present in healthy young and elderly does not develop (**Figures 1, 2**; Kim et al., 2015). Accordingly, these patients demonstrate an early reduction in cerebral oxygenation despite

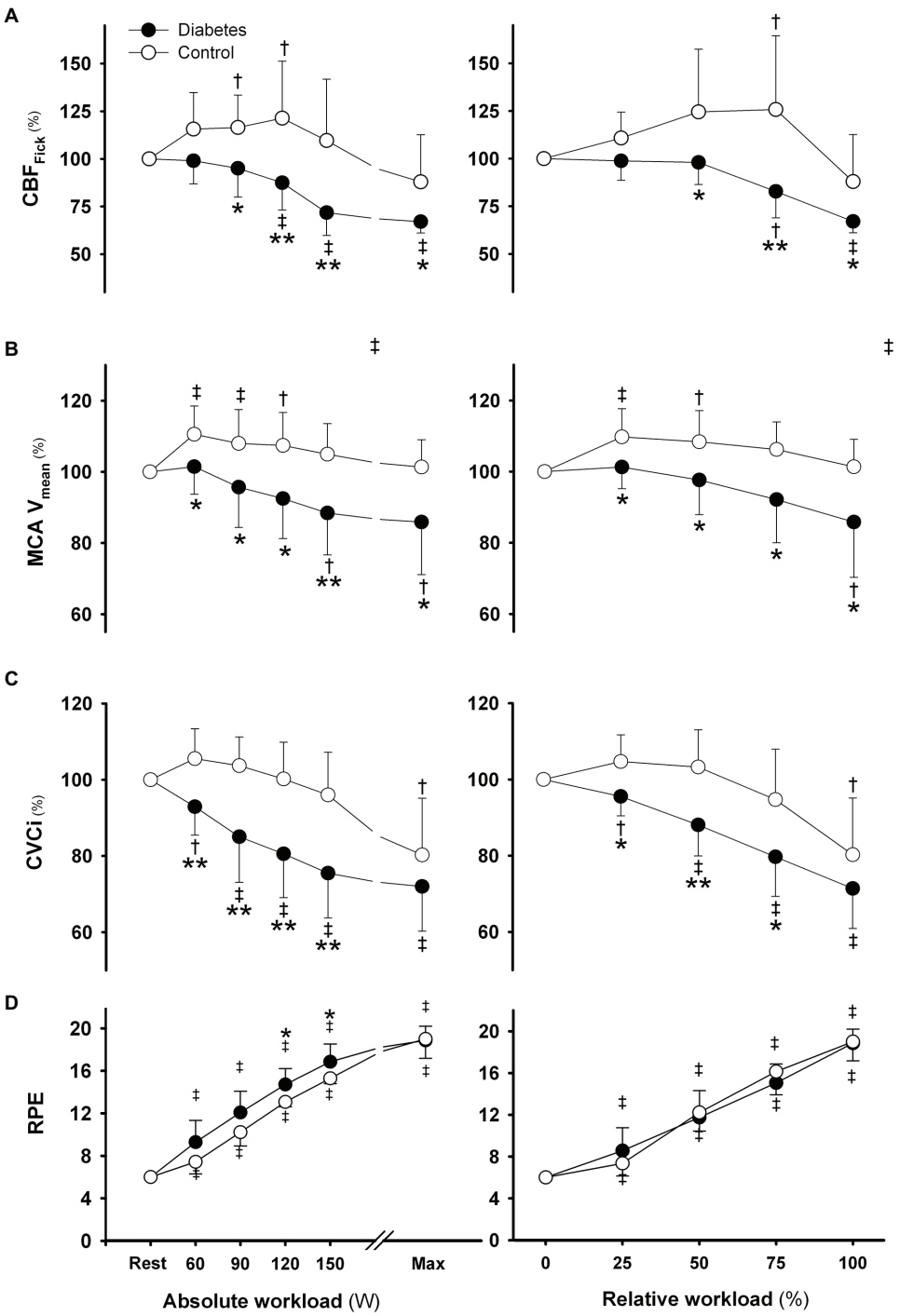

FIGURE 1 | Cerebrovascular response to exercise in eight male type 2 diabetic patients without symptomatic cardio-vascular disease (closed circles) vs. seven age and gender matched healthy subjects (open circles) at the same absolute (left panels) and relative workload (right panels). **(A)** Cerebral blood flow derived from the Fick principle (CBF_{Fick}) from inverse arterial-jugular venous oxygen difference, **(B)** middle cerebral artery mean blood flow velocity (MCA V_{mean}), **(C)** cerebrovascular conductance index (CVCi), and **(D)** rating of perceived exertion (RPE; Borg scale). The patients demonstrated a decline in cerebral perfusion and oxygenation during incremental exercise associated with attenuated increases in cerebral and systemic vascular conductance compared with healthy controls. Cerebral oxygenation reached its lowest level at exhaustion at a 20% lower workload in type 2 diabetes mellitus (T2DM) patients than healthy controls and patients expressed a higher RPE than healthy controls. $^{\dagger}p < 0.05$ and $^{\ddagger}p < 0.01$ vs. rest; $^{*}p < 0.05$ and $^{**}p < 0.01$ vs. control subjects. Values are mean ± SD (modified from Kim et al., 2015).

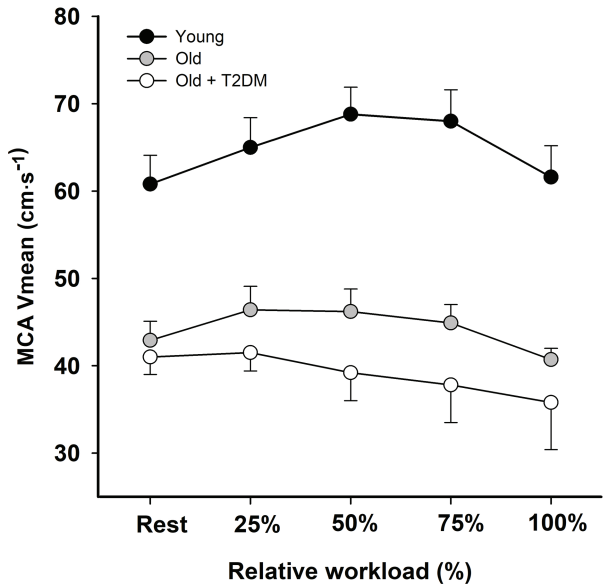

FIGURE 2 | Middle cerebral artery mean blood flow velocity (MCA V_{mean}) at rest and during exercise at the same relative workload in young individuals (black circles), and in middle-aged subjects without (gray circles), and with type 2 diabetes (T2DM; open circles). During submaximal and during maximal exercise, cerebral perfusion was reduced in older individuals compared with young individuals, and the more so in the older diabetic patients. Values are mean ± SEM (adapted from Fisher et al., 2013; Kim et al., 2015).

a larger brain O_2 extraction, and they express enhanced perceived exertion, signifying a fundamental problem in brain vascular control during exercise (Kim et al., 2008a; Vianna et al., 2015). Yet, for these patients, the brain uptake of lactate and glucose is similar to what is found in healthy reference subjects (Kim, 2014; Kim et al., 2015), which points to cerebrovascular rather than brain metabolic derangement. In contrast to the vast amount of studies on the muscle blood flow response to exercise in type 2 diabetic patients, data on the CBF response to exercise in these patients are very sparse. In diabetic patients, progression of microvascular disease interferes with the physiological nocturnal decline in blood pressure, coinciding with a persistently increased arterial pulse pressure and reduced baroreflex sensitivity, contributing to their increased cardiovascular risk (Kim et al., 2019). Treatment of hypertension as a common comorbidity in type 2 diabetes is required to reduce the risk of hypertensive surges during strenuous exercise that challenge the brain vasculature, but intensive blood pressure control may, in contrast to nondiabetic hypertensive patients, reduce their CBF (Kim et al., 2011).

FROM DECONDITIONING TO PHYSICAL EXERCISE – A CHALLENGE OF BRAIN VASCULAR CONTROL

Loss of skeletal muscle mass is a main factor for the increased incidence of type 2 diabetes with aging. Deconditioning as a result of physical inactivity vs. resistance exercise is associated with opposing adaptive responses. Resistance exercise provides better metabolic control (Baldi and Snowling, 2003), mitigates disuse-associated tendon stiffness, maintains or increases skeletal muscle mass, and improves whole body glucose disposal (Fenicchia et al., 2004). Thus, a focus on resistance exercise has been recommended for type 2 diabetic patients, specifically for the subgroup of sarcopenic or severely deconditioned older patients (Sigal et al., 2006). Resistance vs. endurance exercise has different cardiovascular effects. Resistance-type activities produce a considerably larger increase in arterial pressure, because of the mechanical compression of blood vessels together with repeated Valsalva-like maneuvers (MacDougall et al., 1985). Unlike aerobic exercise, resistance training affects central arterial compliance in healthy men (Miyachi et al., 2004).

In healthy young adults, isometric resistance exercise with vs. without concomitant straining produces a greater cerebrovascular challenge (Perry et al., 2020), whereas straining dominates the central and cerebral hemodynamic response to intense static exercise (Pott et al., 2003). Although acute changes in arterial blood pressure during physiological challenges are transmitted to the cerebral circulation, under normal conditions, CBF returns to its baseline value within a few seconds (Panerai et al., 2001; Pott et al., 2003; Immink et al., 2005; Labrecque et al., 2020). Cerebral vasoconstriction constantly plays a protective role during exercise of moderate to heavy intensity, in particular when pulse pressure exceeds the autoregulatory range (Ogoh et al., 2005b). When autoregulatory mechanisms are failing (Immink et al., 2005; Kim et al., 2008a; Frosch et al., 2017; Vranish et al., 2020) or overwhelmed by acute blood pressure surges beyond the autoregulatory range, e.g., grave hypertension, CBF becomes more directly related to its perfusion pressure, resulting in cerebral hyperperfusion manifested by retinal edema and encephalopathy (Immink et al., 2004).

PERSPECTIVE

In the European Union, 55 million individuals suffer from type 2 diabetes and 66 million have impaired glucose tolerance, with an estimated ~4% annual increase. Optimizing metabolic control by behavioral modification including regular physical activity, thus slowing down progression of vascular disease is a task for diabetes care. From that point of view, physical activity represents a "medicine" for metabolic disease (Pedersen and Saltin, 2015; Pedersen, 2019). The challenge to optimize metabolic control in individuals with type 2 diabetes may be achieved at least in part by behavioral modification including regular physical activity (Kim et al., 2008b; Pedersen, 2017). Indeed, physical activity by patients with type 2 diabetes markedly improves the impaired insulin action and is considered a cornerstone in the treatment along with diet and medication. Unfortunately, however, type 2 diabetic patients perceive sustained aerobic exercise to be more strenuous than healthy, non-diabetic subjects. This sets a limit to the effectiveness

of physical activity as a preventive lifestyle intervention for this patient population (Praet and van Loon, 2008, 2009; Huebschmann et al., 2009, 2015; Nadeau et al., 2009; Regensteiner et al., 2014; Senefeld et al., 2020). Left ventricular diastolic dysfunction may be an early manifestation of diabetic cardiomyopathy. When cardiac function deteriorates, the blood supply to the brain seems no longer safeguarded, pointing to the hitherto underexposed functional connection between heart and brain. Aerobic exercise itself may reveal arterial dysfunction associated with latent and overt cerebrovascular disease (Robertson et al., 2019).

In mice, exercise training increased brain mitochondrial biogenesis (Steiner et al., 2011) and a liver-to-brain axis was identified by which plasma glycosylphosphatidylinositol-specific phospholipase could transfer the benefits of exercise on neurogenesis in the brain from young to old mice (Ansere and Freeman, 2020; Horowitz et al., 2020). Nevertheless, regular physical exercise arguably continues to remain the most consistently effective health-enhancing strategy to attenuate the deterioration in brain structure and function related to aging and type 2 diabetes (Hillman et al., 2008; Mayhan et al., 2011; Espeland et al., 2018; Pedersen, 2019). When applying the concept that failure in regulation at multiple levels is common in diseases like diabetes (Pedersen and Saltin, 2015), a limited ability to increase cardiac output together with reduced systemic and cerebral vasodilatory capacity become primary targets for prevention and treatment, challenging integrative physiologists and clinicians alike.

AUTHOR CONTRIBUTIONS

Y-SK contributed to the experimental design, data acquisition, data analysis, and writing the manuscript. BS contributed to data analysis and manuscript revision. PB contributed to manuscript writing. NS contributed to experimental design of studies and writing. JL supervised the study and contributed to the experimental design, data analysis, and writing the manuscript. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Links Between Testosterone, Oestrogen, and the Growth Hormone/Insulin-Like Growth Factor Axis and Resistance Exercise Muscle Adaptations

Nima Gharahdaghi, Bethan E. Phillips, Nathaniel J. Szewczyk, Ken Smith, Daniel J. Wilkinson and Philip J. Atherton**

Medical Research Council-Versus Arthritis Centre for Musculoskeletal Ageing Research and Nottingham National Institute for Health Research Nottingham Biomedical Research Centre, School of Medicine, University of Nottingham, Derby, United Kingdom

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***Correspondence:**
Philip J. Atherton
philip.atherton@nottingham.ac.uk
Daniel J. Wilkinson
Daniel.wilkinson@nottingham.ac.uk

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Maintenance of skeletal muscle mass throughout the life course is key for the regulation of health, with physical activity a critical component of this, in part, due to its influence upon key hormones such as testosterone, estrogen, growth hormone (GH), and insulin-like growth factor (IGF). Despite the importance of these hormones for the regulation of skeletal muscle mass in response to different types of exercise, their interaction with the processes controlling muscle mass remain unclear. This review presents evidence on the importance of these hormones in the regulation of skeletal muscle mass and their responses, and involvement in muscle adaptation to resistance exercise. Highlighting the key role testosterone plays as a primary anabolic hormone in muscle adaptation following exercise training, through its interaction with anabolic signaling pathways and other hormones via the androgen receptor (AR), this review also describes the potential importance of fluctuations in other hormones such as GH and IGF-1 in concert with dietary amino acid availability; and the role of estrogen, under the influence of the menstrual cycle and menopause, being especially important in adaptive exercise responses in women. Finally, the downstream mechanisms by which these hormones impact regulation of muscle protein turnover (synthesis and breakdown), and thus muscle mass are discussed. Advances in our understanding of hormones that impact protein turnover throughout life offers great relevance, not just for athletes, but also for the general and clinical populations alike.

Keywords: hormone, resistance exercise, muscle growth, protein synthesis, hypertrophy

INTRODUCTION

Skeletal muscle accounts for ∼40–45% of total body mass (Romagnoli et al., 2020). Following a rapid post-natal growth phase, skeletal muscle mass is typically maintained at a steady state in adulthood through a controlled balance between muscle protein synthesis (MPS) and breakdown (MPB)—unless in the presence of physiological (exercise) or pathological (age or disease) stimuli. The mitigation of age and disease-related muscle wasting and dysfunction remains a major research effort. Even today after significant efforts to develop pharmaceutical strategies to mitigate muscle

wasting (Sepulveda et al., 2015), contractile activity in the form of resistance exercise (RE) remains the most efficacious intervention. RE training (RET) leads to muscle hypertrophy through a sustained elevation of MPS (Hooper et al., 2017)—responses which are driven by a combination of mechanical overload, and an associated release of hormones; e.g., androgens and insulin-like growth factor-1 (IGF-1) (Romagnoli et al., 2020) and by muscle mechano-sensitive signals.

While the fundamental roles of hormones in muscle development and their decline in aging are well-established, the impact of physiological fluctuations (e.g., due to circadian rhythms or transient increases following bouts of RE) in hormones remains unclear (Schroeder et al., 2013). RE induces marked anabolic hormone responses, in particular those involving testosterone, growth hormone (GH) and IGF-1 (Spiering et al., 2008). These hormonal elevations in response to RE take place in a unique physiological environment, whereby acute elevations in circulating blood hormone concentrations, resulting from a combination of either e.g., increased secretion, reduced hepatic clearance, reduced plasma volume or reduced degradation rates—interact with receptors on the target tissue cell membranes or with nuclear/cytoplasmic receptors located within the target tissue (e.g., steroid receptors); which, alongside mechano-signaling, initiates a sequence of molecular events, leading to muscle adaptive responses such as an increase in MPS and/or a decrease in MPB (Kraemer and Ratamess, 2005). Given the apparent complexity of RE-induced hormonal responses and their impact on muscle adaptation, we aim to provide an update on advances in this area.

TESTOSTERONE

The principal androgen, testosterone, is an anabolic-androgenic steroid hormone which is synthesized from cholesterol—produced mainly in Leydig cells in men, and the ovary (25%) and adrenalzona fasciculata (25%) in women, via conversion from progesterone, with the remaining ∼50% being produced from circulating androstenedione (Burger, 2002). Homeostatic processes maintain systemic testosterone levels within the range of 7.7–29.4 nmol.L^{-1} in healthy young men and 0.1–1.7 nmol.L^{-1} in healthy menstruating women under 40 y (Handelsman et al., 2018). In contrast, there are no differences observed between men and women in relation to intramuscular testosterone concentrations and steroidogenic enzymes (Vingren et al., 2008). Systemic testosterone is taken up by the muscle through its binding to membrane-bound or cytoplasmic androgen receptors (AR), in turn stimulating subsequent myocellular signaling (Vingren et al., 2010; Kraemer et al., 2020) and altering the expression of thousands of genes, many of which are involved in the regulation of skeletal muscle structure, fiber type (Dubois et al., 2014), intramyocellular metabolism (White et al., 2013), and mRNA transcription (MacLean et al., 2008) (**Figure 1**). Once bound to the AR, testosterone is irreversibly converted to dihydrotestosterone (DHT) through the enzymatic action of 5-α reductase (Wilborn et al., 2010). It is generally accepted that DHT is the more potent hormone due to its receptor binding kinetics (Ly et al., 2001); however, testosterone has also been shown to regulate a multitude of ergogenic, anabolic, and anti-catabolic functions in skeletal muscle, without prior conversion to DHT (Bhasin et al., 2003). Testosterone also effects the development of bone, connective and neural tissues (Hoffman et al., 2009), leading to increased muscle strength, power, endurance, and hypertrophy in a dose-dependent manner (Sinha-Hikim et al., 2006; Kraemer et al., 2017). The importance of androgens for mediating muscle growth are substantiated through numerous lines of evidence, including: (1) that exogenous administration, potentiates gains in muscle strength and muscle mass (Gharahdaghi et al., 2019); (2) that gonadotropin-releasing hormone analogs, which inhibit endogenous testosterone release, prevent gains in muscle strength and attenuate gains in muscle mass (Kvorning et al., 2007); and (3) that AR antagonists, which inhibit endogenous testosterone from binding to the AR, impair radical muscle growth during synergist overload (Inoue et al., 1994). Together, these findings suggest a significant role for testosterone in regulating adult muscle growth in response to mechanical loading (i.e., RE).

Exercise-Induced Testosterone Release, and Links With Muscle Adaptation by Sex and Age

The relationship between RE and testosterone responses have been extensively reviewed in young men (Ahtiainen et al., 2003, 2005; West et al., 2009; West and Phillips, 2012), with the majority of studies suggesting that it is the *acute* transient elevations in testosterone that likely drive the proposed hormonal adaptations associated with muscle growth. For example, immediately following RE, serum testosterone levels peak [∼from 13 (resting levels) to 38 (at ∼30 mins) nmol.L^{-1}] with a concomitant upregulation of AR mRNA and protein content within the muscle (Willoughby and Taylor, 2004; Hooper et al., 2017). It seems high intensity RE stimulates basophilic cells of the anterior pituitary to release luteinizing hormone (LH) from gonadotrophs in the anterior pituitary which then acts as the primary regulator of testosterone secretion from the Leydig cells of the testes (Fry and Kraemer, 1997). High affinity binding of LH at the Leydig cells of the testes activates a cyclic adenosine mono phosphate (cAMP) mechanism, resulting in increased testosterone synthesis (Dufau and Catt, 1979; Fry and Kraemer, 1997). This activation is dependent on the frequency and amplitude of LH secretion, with pulses occurring in the human at the rate of ∼8–14 pulses.day^{-1} in men. Secretion of LH is principally regulated by LH releasing hormone (LHRH) via portal circulation from the hypothalamus. High affinity binding of LHRH in the anterior pituitary activates LH secretion by a calcium-dependent mechanism, resulting in LH secretion (Dufau and Catt, 1979; Fry and Kraemer, 1997). Further, early increased circulating testosterone levels during RE are also LH-independent and it seems they may be directly stimulated via increases in lactate levels induced by an increase in the production of cAMP in testicular tissues (Lin et al., 2001). However, the mechanisms of lactate action on testosterone

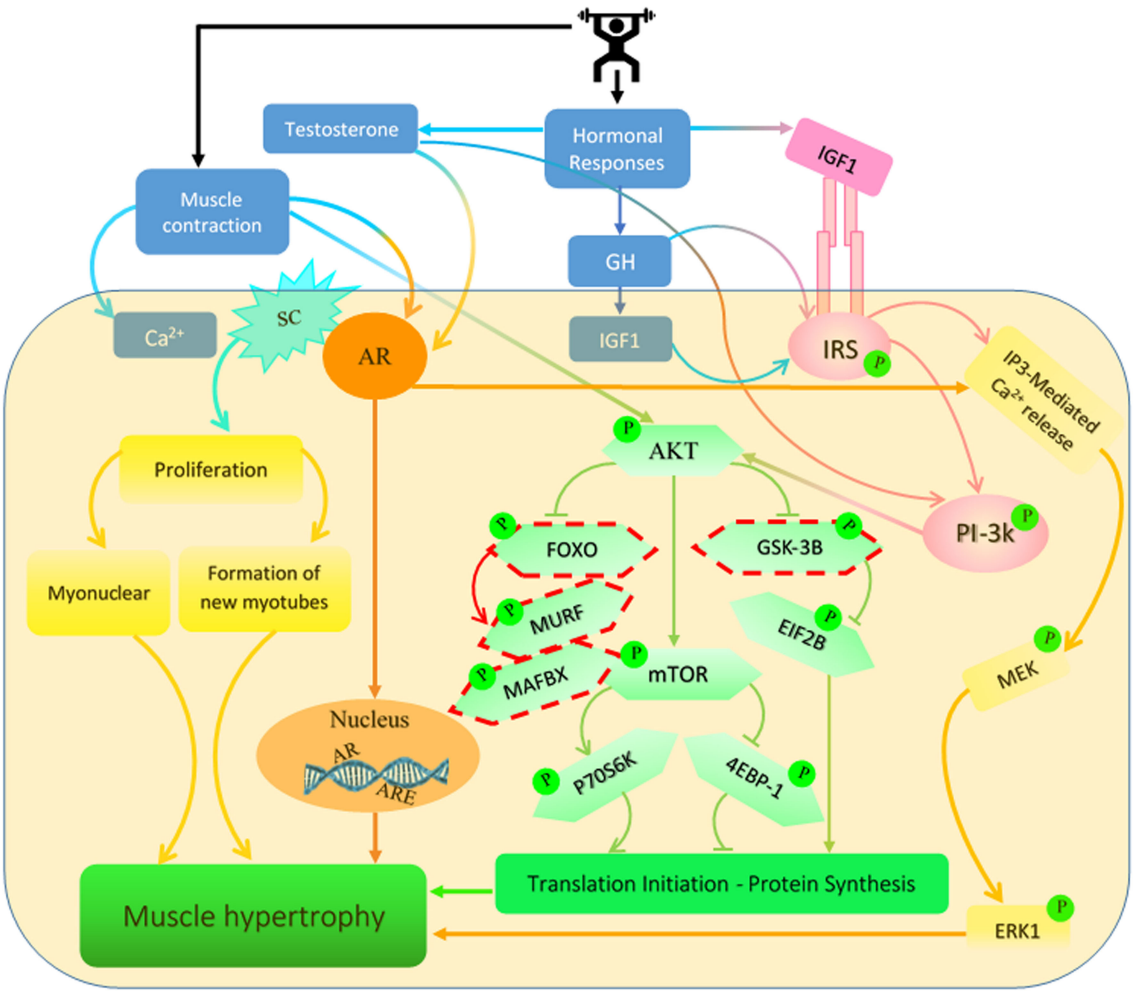

FIGURE 1 | Signaling pathways regulated by testosterone, growth hormone (GH) and insulin-like growth factor 1 (IGF-1) are induced by resistance exercise (RE). RE has been shown to increase the concentration of these hormones which activate several different signaling pathways in the muscle. These pathways lead to increases in muscle protein synthesis (MPS) and net protein accretion which result in an increase in muscle mass. SC, satellite cell; AR, androgen receptor; IRS, insulin receptor substrate; ARE, androgen response element. *Dashed outline represents inhibitory protein cascades.

production by Leydig cells are not clear yet. While the acute response of testosterone returns to baseline rapidly post exercise and has been shown to not be elevated chronically following repeated bouts of RE (Hooper et al., 2017); the acute upregulation of AR mRNA and protein content can last up to 1–2 days post RE (Ratamess et al., 2005), thereby augmenting testosterone uptake into the muscle, and potentiating the anabolic effects of testosterone over longer periods (Murphy and Koehler, 2020; Tinline-Goodfellow et al., 2020). It therefore may be that the combined effects of acute testosterone elevation post exercise and sustained AR upregulation in the muscle may represent an additional mechanism through which RE might regulate muscle growth. Notably, while some studies have indicated correlative relationships between RE-induced elevations in testosterone and muscle strength and hypertrophy (Hansen et al., 2001; Ahtiainen et al., 2003, 2005), this remains equivocal (West et al., 2009; West and Phillips, 2012) perhaps since the magnitude of acute responses in young males can be influenced by many factors e.g., timing of sampling etc. Additionally, there is evidence that RE loads of <70% 1-RM (Tremblay et al., 2004; Yarrow et al., 2007; Fry and Lohnes, 2010; Hough et al., 2011); programs incorporating only upper body exercises, even at a relatively high intensity and volume (Migiano et al., 2010); and those with the long rest periods between repetitions do not stimulate a significant post exercise testosterone response (McCaulley et al., 2009), despite post exercise increases in MPS, anabolic signaling and associated muscle growth adaptive responses being observed (West et al., 2009; West and Phillips, 2012). In an attempt to better understand the discrepancies between testosterone and muscle adaptive responses, Phillips and colleagues devised a unique experimental approach, whereby they compared a "high" vs. "low" hormone environment (induced by working distinct muscle bulk) (West et al., 2010). Despite the contrasting hormonal profiles and significantly different acute testosterone

responses in these environments, muscle mass and strength gains were comparable, suggesting that the role of testosterone (and other hormones) in exercise induced muscle adaptation is minimal. Conversely, other studies using similar procedures reported that the "high" hormone environment potentiated muscle strength gains after 9 weeks RET (Hansen et al., 2001) and acute AR content 180 min after RE (Spiering et al., 2009), which was associated with increased MPS, muscle growth and recovery (Sheffield-Moore, 2000). The differences in outcomes between these studies may be driven by the experimental design (different biopsy location; i.e., biceps brachii vs. vastus lateralis and different testosterone inducing exercise regimes, which resulted in different peak testosterone; i.e., 27 (West et al., 2010) vs. 38 nmol.L^{-1} (Spiering et al., 2009) and also the time course of muscle sampling (between 3 and 4 h post-RE). These differences may be important since the duration and magnitude of testosterone and AR elevation and AR exposure to testosterone appear to play a crucial role in skeletal muscle adaptations both *in vitro* (Bloomer et al., 2000) and *in vivo* (Antonio et al., 1999; Ferrando et al., 2002). In turn, as the pituitary-gonadal axis works in a negative feedback loop, increasing AR content will likely result in enhanced tissue uptake of testosterone, thus lowering circulating testosterone. Reductions in circulating testosterone concentrations (due to enhanced cellular uptake) are monitored by the hypothalamus, which releases gonadotropin-releasing hormone (GnRH) to stimulate LH secretion, then testosterone synthesis/secretion (Kraemer et al., 2006). Herein, it is suggested that AR protein content itself may be critical in RE-induced skeletal muscle protein accretion, with AR content, and not circulating testosterone being more closely associated with adaptations in muscle mass (Morton et al., 2018) and fiber CSA (Mitchell et al., 2013) in young men.

Whilst the majority of investigations into the role of testosterone in muscle adaptive response have been performed in males (reflecting male biology), the importance of circulating concentrations of testosterone in adult women should not be underestimated based on its biological role in the conversion of progesterone to the principal oestrogens—oestradiol and oestrone (Cui et al., 2013). That being said, the importance of testosterone in women remains unclear since while there is an indispensable role e.g., on bone health, in older males (Mohamad et al., 2016), a reduction in testosterone generally does not occur independently of other hormones (such as the oestrogens) in females (e.g., following the menopause) (Chakravarti et al., 1976). Moreover, females do not have Leydig cells; the cells which are likely the source of the acute RE-induced increase in testosterone in men (Kvorning et al., 2007). That said, increases in testosterone in females have been reported in response to RE in some (Nindl et al., 2001; Copeland et al., 2002), but not all (Marx et al., 2001; Linnamo et al., 2005) studies, albeit with claims of no, or limited, effects of acute testosterone elevations in relation to muscle growth in women (Kraemer et al., 2017). Therefore, the links between the testosterone response and exercise adaptation in women remain contentious and require further investigation.

Finally, it is important when overviewing the role of testosterone in controlling muscle mass, to consider older adults. With aging, there is a linear decline in bioavailable circulating testosterone in both men and women (Kraemer et al., 1998; Hakkinen et al., 2000), with these reductions leading to osteoporosis in both sexes (Mohamad et al., 2016). Testosterone is ∼98% bound to serum proteins (sex hormone-binding globulin (SHBG) and albumin) and only 1–2% of testosterone is unbound or free. Because testosterone is bound to SHBG with high affinity, it is not available to most tissues for action. Given the concentration of SHBG increases across the lifespan in men (Liu et al., 2007) and only increase after ∼60 y in women (Maggio et al., 2008), bioavailable testosterone (free plus albumin-bound testosterone) concentrations decline even more markedly than total testosterone levels with aging (Matsumoto, 2002). This reduction can eventually lead to very low resting concentrations of circulating testosterone particularly in men, creating the so-called andropause (Vingren et al., 2010). Intriguingly, this reduction in testosterone tracks with the gradual decline in muscle mass observed with age, i.e., ∼1–3% decline in circulating testosterone and 1–2% loss of muscle mass in men (Vingren et al., 2010; Gharahdaghi et al., 2019), perhaps suggesting declines in endogenous testosterone may be linked to loss of muscle mass. Moreover, while RE in older men (> 59 yr old) still elicits an acute elevation in circulating testosterone, the magnitude of elevation is smaller than that of younger men performing the same RE (Kraemer et al., 1998; Hakkinen et al., 2000), i.e., ∼1 nmol.L^{-1} in young vs. ∼0.1 nmol.L^{-1} in older men (Brook et al., 2016), ostensibly leading to reduced muscle AR content, MPS and ultimately blunted muscle adaptive responses to chronic RET (Brook et al., 2016; Gharahdaghi et al., 2019). With provision of exogenous testosterone helping to restore this blunting somewhat (Gharahdaghi et al., 2019), the influence of testosterone on muscle may be small and permissive in the young, but the need for hormonal input for the control of muscle mass may be more important as we age to overcome age-related deficits in the responsiveness of older muscle to exercise training.

Metabolic and Molecular Effects of Testosterone in Skeletal Muscle

Anabolic effects of AR and testosterone upregulation after RE occur through a combination of both genomic i.e., transcriptional capacity, and non-genomic i.e., translational efficiency, pathways (Kraemer et al., 2020). RE and androgens up-regulate muscle AR content via distinct mechanisms; RE increases AR mRNA transcription via RhoA (a member of the Rho family of small GTPases which is involved in muscle transcription factor) and serum response factor (MADS-box transcription factor which is essential for muscle-specific gene expression) signaling (Lee et al., 2003); in contrast, testosterone increases muscle AR via enhanced AR mRNA association with polyribosomes, increasing AR mRNA translation (Mora and Mahesh, 1999) and doubling AR half-life from ∼3.1 to 6.6 h (Syms et al., 1985). Due to these contrasting mechanisms of action, a combination of RE and RE-induced testosterone secretion will likely potentiate post exercise AR responses for longer, thereby augmenting adaptive muscle growth. Conversely, impaired testosterone responsiveness to RE in older adults, likely attenuates the AR response, due to lack of testosterone mediated

AR increases, and subsequently, limits muscle mass gains with RET. When testosterone binds to the AR, the AR transforms, dimerizes and translocates to the nucleus, binding to androgen-response elements (ARE) therein, as a homodimer. Activation of these AREs stimulates the transcription of protein targets and other anabolic systems, such as the local production of IGF-1 which is related to muscle protein accretion through a decrease in IGFBP-4 mRNA concentration coupled with an increase in IGF-1 mRNA (Bamman et al., 2001; West et al., 2010) (see IGF-1 section). In addition to these genomic signaling pathways, testosterone is thought to independently activate the Akt/mTOR/S6K1 pathway, which represents an integrated step in the hypertrophic response (Basualto-Alarcón et al., 2013); and also through activation of G protein-linked membrane receptors, which result in calcium dependent phosphorylation of ERK1/2 (a mitogen-activated protein kinases), potentially leading to the phosphorylation of transcription factors associated with cellular growth (Kadi, 2008). However, transient activation of ERK1/2 induced by testosterone was not found to be directly related to the hypertrophic signaling cascade; though activated ERK can phosphorylate co-activators of the intracellular receptor at the nuclear level (Bratton et al., 2012), through potentiation of estrogen receptor activation function 1 (AF-1) by Src/JNK (serine 118-Independent pathway) which promotes cellular growth (Feng et al., 2001; Estrada et al., 2003). In sum, the combined effects of RE and RE-induced testosterone release induced upregulation of AR anabolism is driven via genomic and non-genomic signaling pathways which likely augment protein turnover in muscle resulting in increases in net protein accretion and hypertrophy (Wolfe et al., 2000; Roberts et al., 2018).

METABOLIC AND MOLECULAR EFFECTS OF EXERCISE ON OESTROGEN IN SKELETAL MUSCLE

Oestrogens are steroid hormones, primarily produced in the ovaries from testosterone via an aromatase enzyme, of which women have four times the amount compared with men, until the menopause (Hansen and Kjaer, 2014). While less studied in this sphere, endogenous oestrogens seem to have a metabolic role in regulating skeletal muscle; for instance, being critical for the regrowth of atrophied skeletal muscle (Sitnick et al., 2006)- an action mediated by the estrogen receptors, located within skeletal muscle tissue that function as transcription factors (Hansen and Kjaer, 2014). Indeed, as with testosterone (and perhaps as a function of its metabolic regulation through testosterone), estrogen is believed to be important in the regulation of both muscle function (Chidi-Ogbolu and Baar, 2019) and hypertrophy in response to exercise—with rapid changes in systemic concentration occurring immediately post RE, that are dependent upon RE intensity (Copeland et al., 2002), however, baseline circulating concentrations are unaltered following chronic RET for up to 6 months (Gil et al., 2012; Yoon et al., 2018). It is reported that RE acutely augments the activity of the aromatase enzyme which results in an increase in the biosynthesis of estrogen from androgens (Nelson and Bulun, 2001; Luk et al., 2015); in turn explaining the effects of RE-induced testosterone increase on an increase in estrogen levels in women (Luk et al., 2015). The effects of acute estrogen release may relate to a reduction in exercise-induced muscle damage and improved recovery (Hansen, 2018), possibly via its indirect antioxidant properties and stabilization of cell membranes (Paroo et al., 2002) and decreased post-exercise production of protein chaperones- i.e., heat shock protein (HSP) 72 (Paroo et al., 1999) and HSP70 (Enns and Tiidus, 2010). HSPs act as an index of cellular damage and activate inflammatory cell populations (e.g., neutrophils and macrophages) thereby regulating the extent of inflammatory responses after muscle injury (Senf et al., 2013). In addition, estrogen is also known to activate insulin/IGF-1 (Lee et al., 2004) and PI3K/Akt (Mangan et al., 2014) pathways, potentially enhancing the mechanisms regulating MPS (Hansen et al., 2012) and consequently muscle growth (Smith et al., 2014). The latter is suggested to occur through increased expression of Pax7 and MyoD transcription factors (Thomas et al., 2010; Sambasivan et al., 2011) which induce satellite cell expansion, differentiation, and self-renewal of muscle function and mass (Kitajima and Ono, 2016; Chidi-Ogbolu and Baar, 2019). Given that estrogen stimulates post-RE myogenesis, decreased estrogen levels in post-menopausal women may be a contributing factor to the development of sarcopenia, diminishing the rate of muscle repair and adaptive capacity in older women (Thomas et al., 2010). Indeed estrogen replacement has been shown to attenuate the age-related decline in muscle mass observed in postmenopausal women (Enns and Tiidus, 2010). However, the proposed effects of estrogen may be defined by the stage of the menstrual cycle. For example, low estrogen in the early follicular stage, may negatively affect RE-induced increases in estrogen levels (Hansen et al., 2012), while, in the luteal phase where circulating progesterone is relatively high, may also counteract the sensitizing effects of estrogen on muscle impairing any benefit of acute RE-induced during these phases (Hansen, 2018). In contrast, RET in the late part of the follicular phase, when circulating estrogen is enhanced, appears to result in increased fiber type II CSA, nuclei to fiber ratio and muscle mass, compared to RET during luteal phase (Sung et al., 2014; Wikström-Frisén et al., 2017). However, this has not been confirmed (Miller et al., 2006; Sakamaki-Sunaga et al., 2016) as no differences between follicular phase and luteal phase RET responses have also been observed, at least with regard to strength gains and hypertrophy; and as such, the role of estrogen in mediating responses to RE, remains unclear. Future trials are needed to clarify the effects of the oestrogens on muscle biology under different conditions e.g., phase of menstrual cycle, pre or post-menopause, and the response to nutrition (fasting/feeding) and exercise training (Hansen, 2018).

GROWTH HORMONE (GH), EXERCISE, AND EFFECTS ON MUSCLE METABOLISM

Human growth hormone (GH) is secreted from somatotroph cells of the anterior pituitary. It is released in 6–8 bursts.day^{-1}, with negligible secretion outside of these bursts, and is under the

control of the hypothalamic hormones: GH-releasing hormone (GHRH), which promotes secretion, and somatostatin which inhibits release of GH (Giustina et al., 2008). Following GH release, which induces the hepatic generation of IGF-1, circulating levels of IGF-1 and GH, feedback to the hypothalamus to inhibit further GH secretion (Daughaday, 2000). RE is the most potent physiological stimulus for GH release in both men (Nicholls and Holt, 2016; Fink et al., 2017) and women (Hymer et al., 2001), but little is known about how RE alters somatotroph content and function. GH begins to rise 10–20 min after commencing RE and peaks at the end of the RE (Gibney et al., 2007; Fink et al., 2018a), returning to baseline values around 60 min post RE (Häkkinen and Pakarinen, 1995; Fink et al., 2018a). RE increases the amplitude of each GH pulse rather than the frequency. Accordingly, whole-body RE induces GH increases from basal levels of 5 ug.L^{-1} (Fink et al., 2018b) to 24 ug.L^{-1} (Kraemer et al., 1990) while localized RE of individual muscle groups (biceps and triceps) leads to increases of only half of this; up to 12 ug.L^{-1} (Fink et al., 2018a). These increases in post RE GH levels are blunted in older adults, and a progressive decline in GH secretion and clearance is observed after the age of 40 y (Zaccaria et al., 1999). In younger adults, exercise-induced GH release is relatively non-specific occurring in response to both RE and aerobic exercise (e.g., 60% VO_2 max) (Godfrey et al., 2003). It has also been reported that when lactate is elevated beyond anaerobic threshold, which is associated with greater demands on anaerobic glycolysis, the hypothalamus is highly stimulated (Kraemer et al., 1990, 1993; Hartman et al., 1993). This is further supported during RE protocols of moderate intensity (10-RM vs. 5-RM) with short rest periods (1 vs. 3 min) between sets (Hoffman et al., 2003), which result in higher circulating concentrations of GH in both men and women (Kraemer et al., 1993). The exact mechanism of exercise-induced GH release remain ill-defined, however are likely driven via higher intensities of RE directly stimulating the anterior pituitary, facilitated via increasing circulating of catecholamines, lactate, nitric oxide and changes in acid-base balance (Godfrey et al., 2003). Increases in post RE GH levels have also been associated with increased estrogen levels in women; i.e., area under curve (AUC) of increase in GH after RE was higher in midluteal phase than increases in early follicular phases of menstrual cycle (Nakamura et al., 2011). It seems there is a close interplay between estrogen levels and GH secretion and prevailing estrogen concentrations may modulate both GH secretion and action (Leung et al., 2004). This effect of estrogen may be due to a combination of a reduction of somatostatin's inhibitory tone, amplification of endogenous GHRH levels or its pituitary actions, and activation of additional mechanisms; e.g., estrogen stimulates GH secretion by decreasing liver secretion of IGF-1, resulting in stimulation of the pituitary to synthesize and secrete GH (Cook, 2004; Nakamura and Aizawa, 2017).

The physiological relevance of increases in GH levels after RE may be increases in protein synthesis and its ability to aid in muscle repair (Gibney et al., 2007; Liu et al., 2008) and impact on muscle mass (Hermansen et al., 2017), without any impact on muscle function (Hermansen et al., 2017). It was reported that there is a correlation between acute RE-induced GH increases and long term muscle and fiber type I and II hypertrophy (McCall et al., 1999). GH *per se* has also been associated with whole body protein synthesis (e.g., reflecting in part, connective tissues); but directly, may *not* augment MPS (Doessing et al., 2010; West et al., 2010). Conversely, acute GH infusion studies (eliciting a similar to post RE increase in GH levels) have shown this hormone may have a role in stimulating MPS (Fryburg et al., 1991; Fryburg and Barrett, 1993) while associated increases in insulin inhibit MPB (Fryburg et al., 1992). Thus, while GH is a positive regulator of extracellular matrix (ECM) synthesis (Kragstrup et al., 2011) which is important in morphogenesis (Rozario and DeSimone, 2010), there is still debate surrounding its role in the regulation of muscle mass in adults; however what may be key is the lack of effect on muscle function regardless of its impact on growth pathways and MPS.

In terms of mechanisms, following release, GH binds to its receptor leading to the recruitment and phosphorylation of Janus kinase 2 (JAK2) and its most recognized downstream target, signal transducer and activator of transcription 5 (STAT5) (Jørgensen et al., 2006). In addition, GH stimulates the IRS1/Akt (Costoya et al., 1999; Consitt et al., 2017) and mitogen-activated protein kinase (MAPK) pathways which are thought to be the main pathways contributing to GH/IGF-1-induced muscle hypertrophy via p42/p44 and p38 pathways (Consitt et al., 2017) (**Figure 1**). The activation of Akt results in skeletal muscle growth/maintenance since it controls the phosphorylation of a number of substrates involved in MPS including mTOR (and its downstream targets 4E-binding protein 1 (4E-BP1) and p70S6 kinase) and glycogen synthase kinase 3β (GSK3β), as well as, the inhibition of protein degradation via the forkhead transcription factor (FOXO) pathway (Consitt et al., 2017). To support these molecular effects that GH has on muscle mass, GH receptor knock-out results in a decrease in myofiber CSA and muscle mass loss in mice (Sotiropoulos et al., 2006). Nevertheless, as these mice had a reduction in circulating IGF-1 and tissue IGF-1 expression; at least in part GH dependent, it is difficult to separate the effects of the two hormones (Velloso, 2008) and further investigations are needed to clarify the main effects of GH on muscle growth in adults, in particular after RE. However, the main muscle anabolic effects of GH are believed to be indirect—via inducing the hepatic generation of IGF-1 triggering the IGF-1-Akt-mTOR pathway; in turn resulting in MPS augmentation and as a consequence muscle maintenance and growth (Sandri et al., 2013; Schiaffino et al., 2013).

IGF-1, EXERCISE, AND EFFECTS ON MUSCLE METABOLISM

As previously discussed, GH acts through its receptor; however, many effects linked to RE and muscle growth are believed to act indirectly through an increase in hepatic release of IGF-1. IGF-1 can also promote muscle growth in the absence of GH; and unlike GH, IGF-1 is critical for intrauterine growth (Velloso, 2008). A liver-specific knockout mouse exhibited some postnatal growth reduction, but not as severe as with global IGF knockout (Baker et al., 1993; Tahimic et al., 2013). Bikle et al. also showed muscle

atrophy was more pronounced after ablation of muscle IGF-1 production than when hepatic IGF-1 production was suppressed (Bikle et al., 2015); exhibiting circulating levels of IGF-1 (i.e., endocrine factor) do not effect overall growth responses (Ohlsson et al., 2000; Velloso, 2008). This implies that locally produced, autocrine/paracrine IGF-1 plays an important role in both pre- and postnatal growth. The local production of IGF-1 is controlled primarily by GH and other hormones (e.g., parathyroid and thyroid hormones) (Bikle et al., 2015); suggesting GH's effect on growth may be mediated in part via increased local IGF-1 production and/or action. These results indicated GH has local effects that may be independent of increased levels of the circulating IGF-I (Ohlsson et al., 2009). However, a role for circulating liver-derived IGF-I could not be excluded. Reflecting this, it has been reported that IGF-1 levels are associated with improvements in handgrip strength and physical performance as well as life-span (Birnie et al., 2012; Yusuf et al., 2020); in addition, higher circulating IGF-1 has been linked with increases in MPS, muscle free fatty acid utilization, and improvements insulin sensitivity (Kraemer et al., 2017), which may explain its often linked importance in exercise training adaptations. Systemic IGF-1 levels are rapidly increased in humans in response to RE from ∼45 (resting levels) to 65 nM (immediately after RE) (Schwarz et al., 1996; West et al., 2009; Ogasawara et al., 2013) and return to baseline levels ∼30 min after RE (Kraemer et al., 2017), which may play an important role for exercise-induced hypertrophy (Kido et al., 2016), neurogenesis (Trejo et al., 2001), and improved muscle strength with RET (Bjersing et al., 2017) by improving translational efficiency (Schiaffino and Mammucari, 2011) and satellite cell proliferation (Velloso, 2008) in muscle and in the central nervous system (CNS) (Mainardi et al., 2015). GH-induced IGF-1 released from the liver in response to RE is involved in two negative feedback loops. One directly affects the somatotropic cells of the anterior pituitary, itself inhibiting further release of GH, whilst the other affects GH releasing hormone and somatostatin release from the hypothalamus to reduce the secretion of GH. Repeated bouts of RE resulted in an exercise-induced GH response to each acute exercise episode, thereby increasing the 24-h secretion of GH and then IGF-1. Thus, exercise counters negative feedback and so IGF-1 secretion is maintained or increased (Godfrey et al., 2003). Further, to what we already showed [i.e., testosterone increased IGF-1 gene expression during RET (Gharahdaghi et al., 2019)], both testosterone and estrogen blunted IGF-I feedback-dependent inhibition of GH secretion (Veldhuis et al., 2004, 2005); and as it was reported in prepubertal boys, lead to increase in GH and then IGF-1 levels; which in turn exhibit the further and indirect anabolic links between androgens and muscle growth (Mauras et al., 2003). Like testosterone levels, older adults experience a lower basal level of IGF-1 (the so-called somatopause which refers to the diminishment of the GH-IGF-1 system) which attenuates post-RE levels of IGF-1 (Kraemer et al., 1999). However, RE increases IGF-1 mRNA and IGF-1 peptide production in younger adults which result in increases in muscle DNA and protein content (Adams and Haddad, 1996). Increased expression of IGF-1 in muscle leads to muscle hypertrophy in mice; which is independent of effects of circulating levels of IGF-1 (Coleman et al., 1995). Therefore, serum levels of IGF-1 (resting levels or acutely after RE) may not be a good reflection of local effects of IGF-1 (Bartke and Darcy, 2017; Van Nieuwpoort et al., 2018), especially in those tissues that have capabilities of producing the hormone themselves, such as skeletal muscle (Barclay et al., 2019). Indeed, circulating IGF-1 levels have even been shown to decrease during periods of active muscle building, likely due to a redistribution of IGF-1 from the circulation into the muscle (Arnarson et al., 2015). If such a sequestration of IGF-1 into muscle increases during RE (with a decrease in cellular GH receptors), it might occur as a result of reduced GH-induced hepatic production (Eliakim et al., 1998) and it may be speculated that the effect would be more pronounced in individuals experiencing greater activation of intracellular muscle signaling and subsequent muscle hypertrophy and performance (Velloso, 2008; Arnarson et al., 2015; Morton et al., 2016). This suggests that intrinsic secretion (i.e. autocrine) of muscle IGF-1, beside circulating IGF-1, may be a determinant for switching on anabolic pathways (Morton et al., 2018) and fusion of satellite cells (Velloso, 2008).

Given the fairly short half-life of unbound IGF-1 in serum (i.e., 5–10 min), binding to an IGF binding protein (IGFBP-3 is the most prevalent) in serum or in ECM increases IGF-1 half-life to around 25 min (Allard and Duan, 2018). In addition, IGFBPs are important in potentiating IGF-1 anabolic signaling. The potentiating action occurs when the IGF-1-IGFBP binds to the target cell's ECM components, which results in activation of IGF-1 receptor (IGFR) and then IGF-1 enters the cell and triggers phosphoinositide 3-kinase (P13-K) to generate phosphatidylinositol-bisphosphate (PIP2) (Pinedo-Villanueva et al., 2019), leading to the production of phosphatidylinositol 3,4,5-trisphosphate (PIP3) (O'Neill et al., 2015). PIP3 is then free to bind to phosphoinositide-dependent kinase-1 (PDK1) which activates the Akt-mTORC1 pathway (Schiaffino and Mammucari, 2011) promoting ribosomal biogenesis and translation to permit increases in MPS and the formation myofibrillar proteins, which allows muscle mass growth (Menon et al., 2014; Wen et al., 2016) (**Figure 1**). Similar to GH, IGF-1 alone stimulates the IRS1/Akt (Costoya et al., 1999; Consitt et al., 2017) and mitogen-activated protein kinase (MAPK) pathways which are thought to be main pathways contributing to GH/IGF-1-induced muscle hypertrophy (Consitt et al., 2017). Also, RE-induced IGF1-Akt activation phosphorylates AS160 (Akt substrate of 160 kDa) resulting in enhanced GLUT4 translocation and glucose uptake, reflecting the mediator role of IGF-1 in glycaemic control via insulin-IGF-1-Akt pathway activation in muscle (Kido et al., 2016). Taken together, IGF-1 signaling, including prolonged Akt and AS160 phosphorylation, may be a specific signal response to acute RE; which transduces mechanical signals leading to anabolic responses and allow IGF-1 signaling to stimulate the competing processes of muscle cellular growth.

CONCLUSION

RE-induced increases in key endogenous steroid and peptide hormone responses are likely to be an integral part of the

integrated response to acute exercise and exercise-induced muscle growth. The combined effects of RE and RE-induced androgen release lead to upregulation of anabolic signaling pathways which likely augment net protein accretion and hypertrophy. However, the anabolic effects of RE-induced GH release act indirectly via stimulation of hepatic-IGF-1 production; in turn resulting in the activation of anabolic signaling pathways, and muscle growth and maintenance.

Lower levels of these anabolic hormones in older adults induces anabolic resistance during RE which may partially explain their low sensitivity to a given anabolic stimulus. Hormonal patterns are obviously physiologically distinct in females and males, complicating true clarity of the isolated effects e.g., of the sex hormones (higher testosterone levels may play an important role for the adaption to RET in men; whereas in premenopausal women, estrogen may enhance the sensitivity to anabolic stimuli). Further studies are required to isolate clear hierarchical roles of the key anabolic hormones/peptides in regulating muscle growth in adults, in particular after RE, and to elucidate sex differences and their mechanisms.

AUTHOR CONTRIBUTIONS

NG, DW, and PA drafted the manuscript and BP, NS, KS, DW, and PA helped in literature search and edited the manuscript. All authors approved the submitted version.

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MINI REVIEW
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Does Exercise Influence the Susceptibility to Arterial Thrombosis? An Integrative Perspective

Line Nørregaard Olsen[1†], Mads Fischer[1†], Phillip Adrian Evans[2,3], Lasse Gliemann[1] and Ylva Hellsten[1]*

[1] Department of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark, [2] Haemostasis Biomedical Research Unit, Welsh Centre for Emergency Medicine Research, Morriston Hospital, SBU Health Board, Swansea, United Kingdom, [3] College of Medicine, Swansea University, Swansea, United Kingdom

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Barcelona, Spain

***Correspondence:**
Ylva Hellsten
yhellsten@nexs.ku.dk

[†] These authors have contributed equally to this work

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Arterial thrombosis is the primary cause of death worldwide, with the most important risk factors being smoking, unhealthy diet, and physical inactivity. However, although there are clear indications in the literature of beneficial effects of physical activity in lowering the risk of cardiovascular events, exercise can be considered a double-edged sword in that physical exertion can induce an immediate pro-thrombotic environment. Epidemiological studies show an increased risk of cardiovascular events after acute exercise, a risk, which appear to be particularly apparent in individuals with lifestyle-related disease. Factors that cause the increased susceptibility to arterial thrombosis with exercise are both chemical and mechanical in nature and include circulating catecholamines and vascular shear stress. Exercise intensity plays a marked role on such parameters, and evidence in the literature accordingly points at a greater susceptibility to thrombus formation at high compared to light and moderate intensity exercise. Of importance is, however, that the susceptibility to arterial thrombosis appears to be lower in exercise-conditioned individuals compared to sedentary individuals. There is currently limited data on the role of acute and chronic exercise on the susceptibility to arterial thrombosis, and many studies include incomplete assessments of thrombogenic clotting profile. Thus, further studies on the role of exercise, involving valid biomarkers, are clearly warranted.

Keywords: physical activity, exercise, thrombogenicity, blood clots, platelet reactivity, clot microstructure, plasma biomarkers

INTRODUCTION

Thrombosis is the formation of a blood clot inside a blood vessel, leading to obstruction of blood flow in the arterial or venous circulatory system (Mackman, 2008). Acute arterial thrombosis is the cause of myocardial infarction and stroke, which collectively are the most common causes of death in developed countries (Mozaffarian et al., 2016). The risk of thrombosis and the consequent cardiovascular events are closely coupled to aging and lifestyle factors such as a diet, smoking, and physical inactivity.

A primary trigger of arterial thrombosis is rupture of an atherosclerotic plaque, which leads to a rapid recruitment of platelets to the injured site, through interaction of platelet surface receptors with collagen and other proteins exposed at the site of injury in the vessel wall. Subsequent activation of the coagulation cascade, leading to generation of thrombin and fibrin, results in clot formation and occlusion of the artery (Mackman, 2008). The ultimate microstructure of the formed blood clot is of significance; less dense clots can be dissolved naturally through the process of fibrinolysis, whereas more dense blood clots cannot easily be dissolved, and consequently, dense blood clots are associated with higher risk of thromboembolic events (Collet et al., 2000; Mills et al., 2002). Thus, the severity of a blood clot is closely associated with the structure of the fibrin network, which is supported by the finding that the rate of fibrinolysis is dependent on the structure formed by the fibrin fibers (Collet et al., 2006). Therefore, the potential for thrombosis formation, the density of the thrombus, and the efficacy of fibrinolysis are of clinical importance in evaluating the risk of arterial thrombosis.

Lifestyle changes, such as regular physical activity, have protective effects on cardiovascular disease, such as acute myocardial infarction and stroke (Buckley et al., 2019) and habitual physical activity is accordingly recommended for populations at risk (Arnett et al., 2019; Pelliccia et al., 2020). Nevertheless, there is a risk-benefit paradox with regard to physical activity; acute exercise influences the coagulation system with a consequent transient increase in the risk of arterial thrombosis, with the magnitude of risk being influenced by physical fitness and relative exercise intensity (Thompson et al., 2007, 2020). This brief review covers some of the known effects of acute and habitual exercise on risk markers of arterial thrombosis. We first provide a short overview over experimental methods used to assess the integrated risk of arterial thrombosis, followed by a discussion on the influence of acute exercise and exercise training on biomarkers of arterial thrombosis.

BIOMARKERS INDICATING THE SUSCEPTIBILITY TO ARTERIAL THROMBOSIS

Platelet Reactivity

Platelets play an important role for many physiological and pathophysiological processes including healing of injured blood vessels and the development of arterial thrombosis (Nachman and Rafii, 2008; de Groot et al., 2012). Platelets circulate with the blood in an inactivated state until they come into contact with activating molecules, such as circulating epinephrine and collagen exposed upon injury to the vessel wall. The activated platelets adhere and initiate a tightly regulated process leading to the formation of a hemostatic plug (de Groot et al., 2012).

Evaluation of platelet aggregation can include platelet number, morphology, and function (Vinholt et al., 2014) and there are several available methods for these assessments as described in detail elsewhere (Vinholt et al., 2014). The present review only focuses on the assessment of platelet reactivity. For this assessment, light transmission aggregometry is often used (Born, 1962; O'brien, 1962; Vinholt et al., 2017), and reactivity is determined by assessing the propensity of platelets to aggregate in response to different concentrations of platelet receptor agonists (Algahtani and Heptinstall, 2017). Physiologically relevant agonists for the assay are collagen, adenosine diphosphate (ADP), and thrombin receptor-activating peptide (TRAP) (Born, 1962; Davidson et al., 1988; Lundberg Slingsby et al., 2017; Vinholt et al., 2017).

Although light transmission aggregometry is a useful method for the assessment of platelet function, a few aspects are useful to keep in mind when interpreting the data. One limitation of assessing platelet function *per se* as a marker of blood clot susceptibility is that it only provides indication of one, albeit important, step in hemostasis. Methodological limitations include preparation time of platelet rich plasma to be used in the assay, which may influence aggregation, and that the measurement is made *in vitro*, without immediate influence of hemodynamic factors. Nevertheless, with careful methodological considerations and in combination with other markers of thrombogenicity, the platelet aggregometry method provides a useful indication of the susceptibility to thrombosis, and the method also has the advantage that a large number of samples, and many different agonists, can be tested simultaneously (Salehi et al., 2014; Paniccia et al., 2015; Vinholt et al., 2017).

Plasma Markers of Thrombogenicity

Various markers of hemostasis and fibrinolysis have been identified as independent cardiovascular risk factors (Koenig and Ernst, 2000) and have been widely used in clinical practice. Standard coagulation assays include assessment of activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time (TT) (Feng et al., 2014). The assays are functional and evaluate the rate of clot formation when the coagulation cascade has been activated. Other commonly used markers of thrombogenicity are related to fibrin, which plays an essential role in the microstructure of the blood clot. Blood clots can be dissolved by the fibrinolytic system through degradation of fibrin. The key enzyme for degradation of fibrin is plasmin, which is converted from circulating plasminogen by plasminogen activators: tissue-plasminogen activator (t-PA) and urokinase-plasminogen activator (u-PA). The t-PA and u-PA can be inhibited by plasminogen-activator inhibitor-1 (PAI-1) and plasminogen-activator inhibitor-2 (PAI-2).

Although standard coagulation markers remain the mainstay of pathway analysis (PT, APTT), they have several limitations in assessing diseases and treatment thereof. The markers only indicate isolated parts of the plasma-based coagulation pathways. Furthermore, many of these pathway markers do not take into account the effect exerted by the cellular components in blood (such as platelets, and white and red blood cells). Furthermore, many of the tests are carried out in physiologically altered blood (in tubes with, e.g., heparin or sodium citrate). The testing process varies from laboratory to laboratory often with different reference ranges, making interpretation in various disease states difficult (Ebner et al., 2018). In addition, many of

the hypercoagulable disease states have a marked inflammatory component and response due to endothelial change and damage, which can neither be measured nor assessed with these tests. In most circumstances, this makes their overall utility in many diseases mainly an adjunct to clinical care.

Clot Microstructure

Due to the need for a global marker to assess hemostatic competency in hypercoagulable states and their treatment, recent studies have focused on the potential of clot microstructure and quality as a more global and accurate measurement. This has led to the development of a potential and exciting new marker, fractal dimension, which has been seen as an improved marker of coagulation that has the ability to assess the direct and indirect effect of coagulation in one simple and immediate test in unaltered whole blood (Kopytek et al., 2019).

Fractal dimension provides information about the structure of the fibrin network of a developing blood clot (Evans et al., 2010) and is thus a functional biomarker of hemostasis and clot microstructure. Fractal dimension provides a description of the incipient clot, which is the initial templating structure of the clot, which leads to its ongoing mechanical structure and strength (**Figure 1**) (Curtis et al., 2011, 2013). Low values of fractal dimension are equivalent to a weak and less dense clot with low number of branches, whereas high values are equivalent to a strong and dense clot with a high number of complex structured branches, which is more difficult to break down therapeutically (Evans et al., 2010; Sabra et al., 2017). In acute vascular inflammatory disease such as ischemic stroke and myocardial infarction, there is considerable over-production of mass and cross-linking at this templating phase, which leads to a very strong and abnormally structured clot, as compared to clot formation in healthy individuals (**Figures 1**, **2**). In contrast to standard and conventional coagulation measurements like PT or APTT, fractal dimension is performed in untreated blood within minutes after blood withdrawal and provides a rapid measurement of the integrated hemostatic property and thereby an immediate indication of the risk of cardiovascular events (Sabra et al., 2017). Limitations include the requirement of relatively expensive equipment, and as with platelet aggregometry, the measurement is made *in vitro* without physiological hemodynamic impact. Also, the method is still relatively new, and although the method has been used in a large number of subjects (Evans et al., 2010; Lawrence et al., 2014), normal ranges for gel point and fractal dimension in different populations have yet to be defined.

ACUTE EXERCISE AND ARTERIAL THROMBOSIS

Paradoxically, although regular exercise or a physically active lifestyle protect against cardiovascular disease (Albert et al., 2000; Lee et al., 2003; Sattelmair et al., 2011), a single acute bout of physical exertion might trigger an acute myocardial infarct or stroke (Lee et al., 2003). The increased risk is reported to last up to 30–60 min after termination of exercise (Röcker et al., 1986; Mittleman et al., 1993; Albert et al., 2000; Buckley et al., 2019), with one study reporting the effect to persist for up to 2 h (von Klot et al., 2008). However, an important aspect is that, whereas in a sedentary individual the risk of a myocardial infarct increases ∼ 50- to 100-fold with acute vigorous physical activity, in an individual accustomed to exercise the increased risk is much lower (∼2- to 5-fold) (**Figure 2**) (Bärtsch, 1999; Thompson et al., 2007). This would suggest that once an individual is accustomed to exercise, the susceptibility to thrombosis by acute exercise is substantially reduced. This aspect is further discussed below in the section on exercise training.

Exercise intensity is likely to influence the susceptibility to arterial thrombosis and may also affect the time required for returning to resting hemostasis (**Supplementary Table 1**) (Hegde et al., 2001; Menzel and Hilberg, 2011). As such, low to moderate intensity exercise elicits low or no increase in plasma thrombotic markers and platelet reactivity (Hegde et al., 2001; Davies et al., 2016; Lundberg Slingsby et al., 2018), whereas strenuous exercise leads to a substantial increase (Hegde et al., 2001; Davies et al., 2016). The increased risk of myocardial infarct correlates with high self-reported physical exertion, with a score representing vigorous exertion resulting in a >5-fold increase in the relative risk of onset of a myocardial infarct in the 1–2 h following exercise (Buckley et al., 2019).

One reason for the increased relative risk of arterial thrombosis with intense exercise could be elevated vascular shear stress (Badiei et al., 2015) due to the higher blood flows with intense exercise (Hathcock, 2006; Chen et al., 2010; Badiei et al., 2015). High shear stress levels can promote thrombosis as the frictional force may cause tearing or rupture of an atherosclerotic plaque (Hallqvist et al., 2000; Thompson et al., 2007). Also, many platelet activating factors are influenced by increased exercise intensities, such as catecholamines (Dimsdale and Moss, 1980; Lawrence et al., 2018), temperature (Meyer et al., 2013; Lawrence et al., 2016), blood osmolality (Lawrence et al., 2014), and central hypovolemia (Meyer et al., 2013). In addition, aspects such as endothelial alterations, which influence platelet adhesion and thrombin generation, may also be affected by exercise and lead to an increased susceptibility to thrombosis.

Catecholamines promote thrombosis by activation of platelets and an increase in clot microstructure (Mittleman et al., 1995; Thompson et al., 2007; Davies et al., 2016; Lawrence et al., 2018). In a recent study, tyramine infusion, leading to endogenous noradrenalin formation, was found to increase fractal dimension, indicating a denser incipient clot microstructure (Lawrence et al., 2018). Accordingly, compared to moderate intensity exercise, intense exercise with higher plasma norepinephrine concentrations was shown to be associated with significantly higher levels of thrombotic plasma markers (Menzel and Hilberg, 2011). Nevertheless, single leg knee extensor exercise, which has a limited impact on sympathetic activity, significantly increases fractal dimension suggesting that local hemodynamic changes such as shear stress can influence clot microstructure independently of catecholamines (Lawrence et al., 2018). Combined these studies provide support for that both catecholamines and hemodynamic changes during exercise

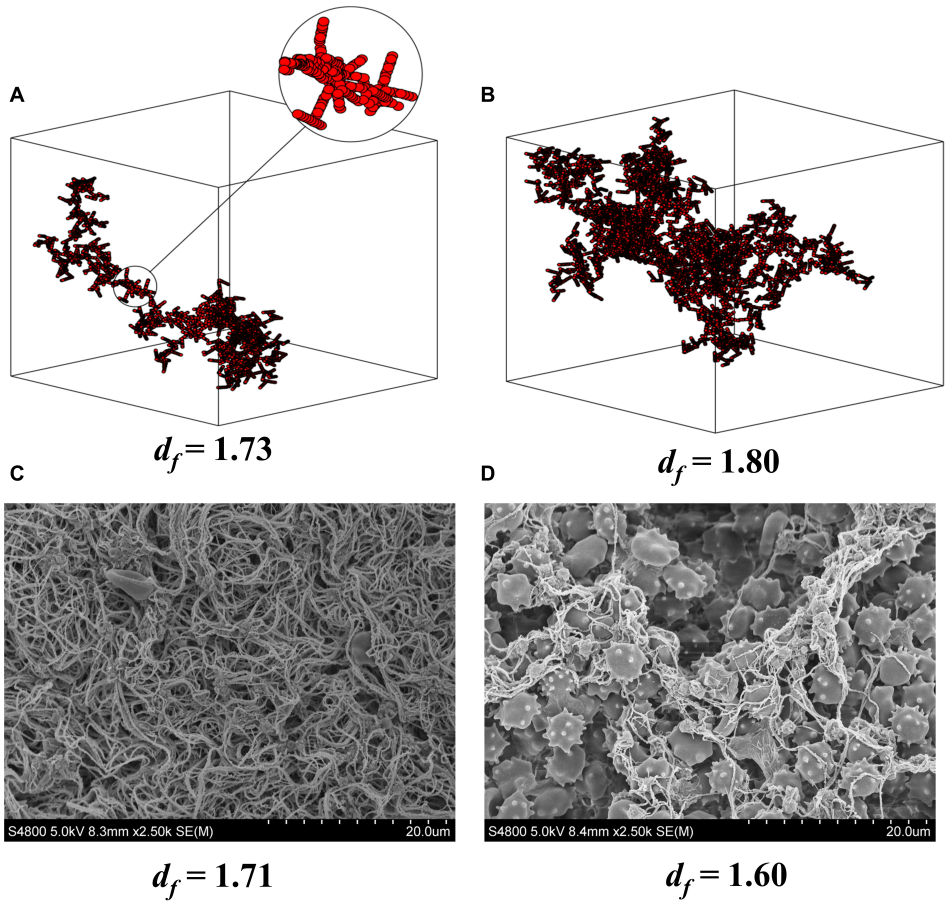

FIGURE 1 | d_f and clot microstructure. Computer modeling of fractal structures of blood clots at the gel point from **(A)** healthy individuals and **(B)** individuals with vascular inflammatory disease. Electron microscopy images of fractal dimension (d_f) and clot microstructure in whole blood **(C)** pre and **(D)** post 1 wk of oral dual antiplatelet therapy (75 mg Aspirin and 10 mg Prasugrel) in healthy individuals. The pictures **(C,D)** clearly show how inhibition of platelet activity alters clot microstructure and mass as indicated by d_f. Note that a small change in d_f results in a large increase in mass at the gel point for the developing clot. **(A,B)** are reproduced from Curtis et al. (2011).

can influence the microstructure of developing blood clots, but further studies elucidating their precise role are required.

Data on exercise-induced effects in healthy individuals may differ from data in patient groups for whom the exercise-induced thrombogenicity is likely to be more critical. For example, although patients with either hypertension or coronary artery disease do not seem to differ in basal platelet reactivity or markers of thrombosis compared to healthy controls (Petidis et al., 2008; Hong et al., 2009), these patient groups may present increased catecholamine levels during and after exercise (Petidis et al., 2008) with a potential impact on thrombogenicity. Nevertheless, findings on exercise-induced thrombogenicity in coronary artery disease patients are inconsistent (Mehta and Mehta, 1982; Pamukcu et al., 2005; Aurigemma et al., 2007; Petidis et al., 2008), likely due to variations in criteria for medication and co-morbidities of the populations.

It should be emphasized that despite the apparent immediate changes in thrombogenicity after exercise, the risk of hospitalization during clinical graded exercise testing is approximately one in 10.000 (Myers et al., 2009). In healthy adults, between 30 and 60 years of age, this risk of a cardiac event is estimated to be ∼0.2 and 0.3 per 10.000 person-hours of exercise for women and men, respectively (Gibbons et al., 1980). Moreover, in one of the few studies assessing platelet reactivity following acute low intensity one-leg knee extensor exercise, a significant decrease in epinephrine-induced platelet aggregation was observed in moderately and highly trained, but not sedentary, middle-aged male subjects (Lundberg Slingsby et al., 2018). This finding suggests that, in individuals accustomed to exercise, the risk of arterial thrombosis after exercise of lower intensities may even be lower than at rest. Also, plasma fibrinolysis has been shown to increase after acute exercise as a result of increased release of t-PA from endothelial cells in the vasculature (Rankinen et al., 1995; Gunga et al., 2002; Sumann et al., 2007). The increase in t-PA occurs with different exercise modalities but appears to be higher with higher exercise intensity (Handa et al., 1992; El-Sayed, 1993; Hegde et al., 2001; Menzel and Hilberg, 2011).

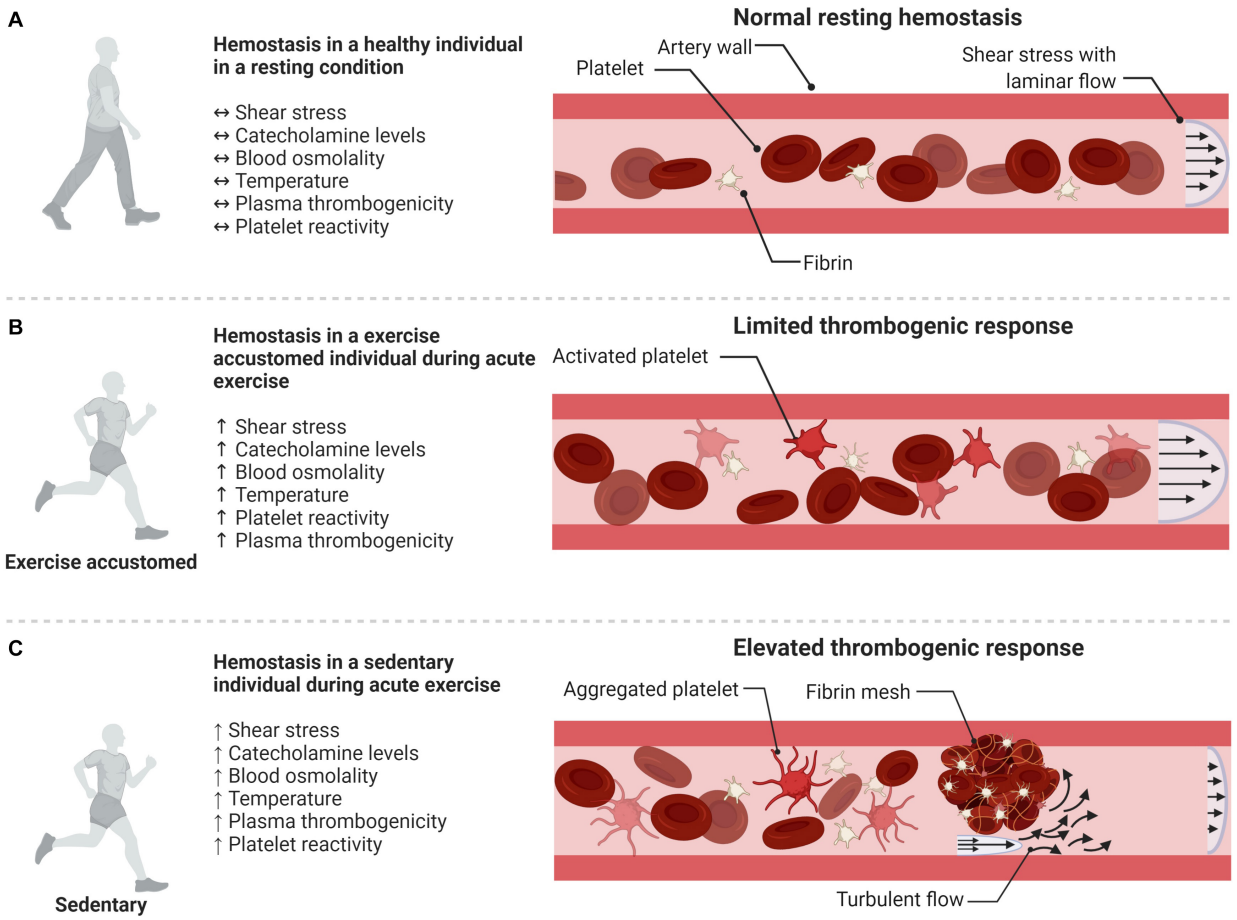

FIGURE 2 | Schematic illustration of the influence of acute exercise and habitually active lifestyle on hemostasis. **(A)** Resting hemostasis in a healthy individual. **(B)** Exercise accustomed individual: exercise-induced pro-thrombotic factors are counterbalanced by the release of anti-thrombotic and anti-aggregatory agents, e.g., prostacyclin and NO. **(C)** Sedentary individual: the exercise-induced increase in thrombogenic factors is not sufficiently counterbalanced by anti-thrombotic protection leading to a thrombogenic response. Illustration created with BioRender.

INFLUENCE OF EXERCISE TRAINING ON SUSCEPTIBILITY TO ARTERIAL THROMBOSIS

It is well established that regular physical activity protects against cardiovascular disease (Buckley et al., 2019), and physical activity for ≥ 30 minutes per day, 5 days a week, is advised (Arnett et al., 2019; Pelliccia et al., 2020). One of the beneficial effects of regular physical activity on arterial thrombi formation is likely through a reduction in basal platelet reactivity (Lundberg Slingsby et al., 2018; Heber et al., 2020). Whereas untrained individuals display an increased level of adrenaline-induced platelet aggregation in response to an acute bout of exercise, platelet aggregation remains unaffected in moderately trained or well-trained individuals (Lundberg Slingsby et al., 2018). Similar to that in healthy individuals, exercise training in patients with coronary artery disease has been found to decrease platelet reactivity, and inclusion of high intensity exercise sessions has been reported to be more beneficial than moderate exercise training alone (Heber et al., 2020). This effect of reduced platelet reactivity with the added high intensity exercise sessions is also present immediately after acute exercise (**Supplementary Table 3**) (Heber et al., 2020).

Currently, only a limited amount of data exists regarding the influence of exercise training on the thrombogenic clotting profile (**Supplementary Tables 2, 3**) (Stratton et al., 1991; van den Burg et al., 2000; Lundberg Slingsby et al., 2017, 2018; Heber et al., 2020). In these studies, exercise training consistently resulted in reduced platelet reactivity and a reduced level of plasma markers indicating thrombogenicity (Rauramaa et al., 1986; El-Sayed et al., 1995; Wang et al., 1995, 1997; van den Burg et al., 2000; Lundberg Slingsby et al., 2017; Heber et al., 2020). Interestingly, in late premenopausal women, a period of aerobic interval training by cycling, reduced platelet reactivity, whereas this effect was not observed in recently postmenopausal women (Lundberg Slingsby et al., 2017). The reason for this discrepancy is unclear. It should be noted that both groups of women were found to have improved endothelial function as well as enhanced sensitivity to platelet inhibition by prostacyclin. Improved endothelial function is associated with enhanced formation of prostacyclin

and nitric oxide (Taddei et al., 2006; Flammer et al., 2012) which both are potent inhibitors of platelet reactivity (Jin et al., 2005; Yau et al., 2015). Several studies, including studies on pre- and postmenopausal women, have shown that exercise training leads to increased expression of enzymes related to prostacyclin synthesis and nitric oxide formation as well as increased plasma levels of prostacyclin and nitric oxide metabolites (Hellsten et al., 2012; Cocks et al., 2013; Nyberg et al., 2017).

Thus, although numerous studies have examined the effect of regular physical activity on cardiovascular risk factors, the specific influence of physical activity on thrombogenicity has not been well investigated, and in particular, the role of exercise intensity and volume is lacking. Future studies should therefore aim to assess the impact of differentiated training modalities to evaluate the influence on plasma markers of hemostasis, platelet aggregation, and clot microstructure.

CONCLUSION

Exercise may be considered a double-edged sword since, on one hand, acute exercise can be a direct cause of a thrombotic event, and on the other hand, exercise training is a potent intervention for lowering the risk of cardiovascular events. Although further studies are required to unravel the influence of different exercise modalities, existing literature points at a greater risk of enhanced thrombogenicity with high, rather than light to moderate intensity exercise. Thus, for patients at risk, the safer recommendation would accordingly be to initiate exercise programs at low to moderate intensities. We propose that studies combining platelet reactivity assay, clinical measures of hemostatic markers, and the novel functional measure of clot microstructure will provide a new level of detailed prediction of the susceptibility to harmful arterial blood clots.

AUTHOR CONTRIBUTIONS

LO and MF drafted the manuscript. LG, PE, and YH critically revised and contributed to the content of the manuscript and approved its final version. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2021.636027/full#supplementary-material

Supplementary Table 1 | Influence of an acute exercise bout on biomarkers of thrombogenicity.

Supplementary Table 2 | The effect of different training protocols on biomarkers of thrombogenicity.

Supplementary Table 3 | Influence of an acute exercise bout on biomarkers of thrombogenicity in patient groups compared to healthy controls.

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MINI REVIEW
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Autonomic Function in Patients With Parkinson's Disease: From Rest to Exercise

*Jeann L. Sabino-Carvalho[1], James P. Fisher[2] and Lauro C. Vianna[1,3]**

[1] NeuroV̇ASQ̇ – Integrative Physiology Laboratory, Faculty of Physical Education, University of Brasília, Brasília, Brazil, [2] Manaaki Mānawa – The Centre for Heart Research, Department of Physiology, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand, [3] Graduate Program in Medical Sciences, Faculty of Medicine, University of Brasília, Brasília, Brazil

Parkinson's disease (PD) is a common neurodegenerative disorder classically characterized by symptoms of motor impairment (e.g., tremor and rigidity), but also presenting with important non-motor impairments. There is evidence for the reduced activity of both the parasympathetic and sympathetic limbs of the autonomic nervous system at rest in PD. Moreover, inappropriate autonomic adjustments accompany exercise, which can lead to inadequate hemodynamic responses, the failure to match the metabolic demands of working skeletal muscle and exercise intolerance. The underlying mechanisms remain unclear, but relevant alterations in several discrete central regions (e.g., dorsal motor nucleus of the vagus nerve, intermediolateral cell column) have been identified. Herein, we critically evaluate the clinically significant and complex associations between the autonomic dysfunction, fatigue and exercise capacity in PD.

Keywords: exercise, dorsal motor nucleus of the vagus nerve, parasympathetic activity, sympathetic activity, blood pressure

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***Correspondence:**
Lauro C. Vianna
lcvianna@unb.br

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INTRODUCTION

Parkinson's disease (PD) is currently the second most common neurodegenerative disorder (Alves et al., 2008; Rossi et al., 2018) and the worldwide prevalence is growing as age and life expectancy increases (Rossi et al., 2018). The disease is well-characterized by a dysfunction of dopamine-producing neurons in the substantia nigra pars compacta and was first described more than 200 years ago (Parkinson, 2002). This dopamine deficiency leads the classical motor dysfunctions (bradykinesia, rigidity, and resting tremor) featuring the disease (Braak and Braak, 2000). In addition, PD may include several non-motor impairments, including autonomic and cardiovascular dysfunction (Gallagher et al., 2010; Goldstein, 2014; Merola et al., 2018; Sabino-Carvalho et al., 2021). Furthermore, some aspects of the autonomic dysfunction can precede the motor dysfunction by more than a decade (Pont-Sunyer et al., 2015). Therefore, early detection of autonomic dysfunction may allow an early diagnosis (Kaufmann et al., 2004, 2017) and seem to make an important contribution to the PD pathophysiology (Goldstein, 2014; Greene, 2014).

Sympathetic and parasympathetic branches of the autonomic nervous system are crucial for homeostasis control (Billman, 2020) and are essential for ensuring that the appropriate cardiovascular and hemodynamic adjustments to exercise occur, such that the metabolic demands of working skeletal muscle are met. Conversely, autonomic dysfunction is associated with fatigue,

impaired exercise capacity, and poor quality of life in several patient populations, including PD (Chaudhuri and Behan, 2004; Gallagher et al., 2010; Nakamura et al., 2011; Vianna and Fisher, 2019; Pechstein et al., 2020). The present mini-review will critically evaluate the evidence for parasympathetic and sympathetic dysfunction in PD both at rest and during exercise, explore how such autonomic dysfunction may affect exercise capacity, and explore the therapeutic potential of exercise training.

Parasympathetic Dysfunction in PD

The parasympathetic preganglionic neurons are situated in the nucleus ambiguous (NA) and dorsal motor nucleus of the vagus nerve (DMV). The axons travel within the vagus nerve (tenth cranial nerve) and synapse at postganglionic neurons, such as those located at the cardiac plexus. While the NA contains vagal preganglionic neurons that inhibit the heart rate (Machado and Brody, 1988), the activity of the DMV vagal preganglionic neurons are responsible for tonic parasympathetic control of ventricular excitability (Machhada et al., 2015). Cardiac autonomic parasympathetic neurotransmission is accomplished through the release of acetylcholine and other substances onto receptors located in atrial and ventricular myocardium, modulating the chronotropic, inotropic and dromotropic properties of the heart (Degeest et al., 1964; Coote, 2013).

In patients with PD, a common pathological hallmark is the presence of Lewy bodies. These abnormal aggregates of α-synuclein protein are widely distributed in the hypothalamus, sympathetic [intermediolateral cell column (IML) and sympathetic ganglia] and parasympathetic centers (DMV, NA, and sacral parasympathetic nuclei), and may disrupt the central components of autonomic reflex arc involved in autonomic regulation (Braak and Braak, 2000; Del Tredici and Braak, 2016; Nakamura et al., 2016; Wang et al., 2020). Human studies and animal models of PD provide quantitative evidence for damage to brainstem parasympathetic neurons and in vagus nerves (Beach et al., 2010; Machhada et al., 2015; Walter et al., 2018). Post mortem studies of patients with PD have shown the presence of α-synuclein protein in the vagus nerve (Beach et al., 2010) and *in vivo* studies have reported significantly smaller vagus nerve axons in patients with PD (Pelz et al., 2018; Walter et al., 2018). With regards to animal models of PD, a reduced activity of DMV neurons is reported (Machhada et al., 2015). In fact, the DMV has been hypothesized by Braak et al. (2003) as being one of the first areas to be affected during the pathological progression of PD in humans, although this is not a universal finding (Kalaitzakis et al., 2008).

Heart rate variability (HRV) derived estimates of cardiac parasympathetic activity have been observed to be reduced in patients with PD (Kallio et al., 2000; Buob et al., 2010; Sabino-Carvalho et al., 2018; Li et al., 2020) independent of the measurement duration/experimental circumstance. However, this finding is not unanimous (Oka et al., 2011; Kiyono et al., 2012; Vianna et al., 2016). Intriguingly, Alonso et al. (2015) demonstrated that the lower the root mean square of successive differences in N–N intervals (RMSSD, a time domain marker of parasympathetic activity) and the standard deviation of N–N intervals (SDNN, the standard deviation of interbeat intervals), the greater the chances of PD developing during an 18-year follow-up period. However, Alonso's findings should be interpreted with caution, as the measurement duration (i.e., 2-min) is considered suboptimal for this purpose by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (i.e., ≥5-min) (Task Force, 1996). Altogether, these findings may suggest that aggregates of α-synuclein protein in the brainstem parasympathetic neurons might play a role in HRV alterations observed in patients with PD, however, this possibility remains to be tested.

Sympathetic Dysfunction in PD

Sympathetic preganglionic cell bodies are located in the IML of the spinal cord and the preganglionic fibers directed to the heart synapse at the stellate ganglion and upper thoracic ganglia (T1–T5). Postganglionic sympathetic fibers synapse in the heart (at the sinoatrial node, atrioventricular node, atria, and ventricles) and in the vasculature. The sympathetic preganglionic neurons in the IML receive strong excitatory drive from neurons of the rostral ventrolateral medulla (RVLM) (Dampney, 1994). Sympathetic preganglionic neurons at the IML also receive direct excitatory inputs from other regions of the central nervous system including the ventromedial medulla, caudal raphe nuclei, A5 noradrenergic cell group of the caudal ventrolateral pons, and the paraventricular hypothalamic nucleus (Dampney, 1994; Dampney et al., 2003). The sympathetic preganglionic neurotransmission is accomplished by the release of acetylcholine, whereas postganglionic neurons release norepinephrine (and other co-transmitters) onto α- and β-adrenergic receptors modulating both chronotropic and inotropic properties of the heart and the peripheral resistance in the vasculature (Drew and Whiting, 1979).

Orthostatic hypotension (OH) affects approximately 50% of the patients with PD and the prevalence may be higher when considering asymptomatic OH (Palma et al., 2015). Noteworthy, OH is often used as a clinical indicator of sympathetic nervous system dysfunction (Goldstein et al., 2015; Kaufmann et al., 2020; Palma and Kaufmann, 2020). Central lesions in the brainstem are thought to mediate the sympathetic dysfunction in PD (Metzger and Emborg, 2019), as showed by Braak and colleagues through analysis of the regional distribution of α-synuclein immunoreactive structures in the brain of 110 subjects (Braak et al., 2003, 2004; Braak and Del Tredici, 2010). This proposed model suggests that the PD process begins in the lower brainstem in the DMV, as well as in the anterior olfactory structures. Thereafter, the disease rostrally ascends from the DMV through regions of the medulla, pontine tegmentum, midbrain, and basal forebrain, reaching the cerebral cortex. Of note, as PD progresses upward from the brainstem, both the severity of the lesions and clinical manifestations of the PD symptoms increase (Braak et al., 2004). The mechanisms and precise neuronal profile damage responsible for the sympathetic dysregulation are not fully understood. However, studies have indicated that the abnormal aggregates of α-synuclein protein distributed in

the IML and sympathetic ganglia contributes to the sympathetic dysfunction (Braak and Braak, 2000; Del Tredici and Braak, 2016; Nakamura et al., 2016; Wang et al., 2020). Moreover, post mortem analyses of patients with PD also showed a selective loss of C1 and C3 neurons (Gai et al., 1993) providing quantitative evidence for brainstem damage of sympathetic neurons. Cardiac sympathetic denervation and lower norepinephrine spillover are also concomitant with the central lesions in patients with PD (Goldstein et al., 2003; Nakamura et al., 2014).

The microneurography technique provides a valuable tool for direct recording of muscle sympathetic nerve activity (MSNA) in humans (Carter, 2019). Shindo et al. (2003) demonstrated that resting MSNA was similar between patients with PD and control subjects. However, a negative association was observed between MSNA and both age and disease duration in PD, reflecting the impact of PD progression on sympathetic dysfunction (Shindo et al., 2003). Nevertheless, the inherent characteristics of PD (i.e., resting tremor and involuntary movements) makes it challenging to obtain and maintain MSNA recordings in this population, and thus only a few studies have attempted this (Shindo et al., 2003, 2005; Sverrisdóttir et al., 2014) and unfortunately not all compared their results with control subjects (Shindo et al., 2005; Sverrisdóttir et al., 2014). Sympathetic postganglionic neuronal function in the heart has been assessed in PD (Rascol and Schelosky, 2009). A myocardial concentration of metaiodobenzylguanidine (MIBG), a physical analog of noradrenaline that is transported into sympathetic terminals, has been used as a biomarker of cardiac sympathetic denervation in PD. Indeed, abnormal MIBG uptake has been reported in patients with PD both with (Nakamura et al., 2014) and without (Oka et al., 2011) OH. However, the cost and invasiveness of the MIBG technique have limited its use in the experimental assessment of cardiac sympathetic activity. Given this, alternative approaches, such as the analysis HRV, may provide important advancements in our understanding of sympathetic dysfunction in PD.

Despite the fact that most indices derived from HRV primarily reflect vagal function, the joint analysis of the low frequency (LF) component, expressed in normalized units, and the LF/HF ratio, has been suggested to be an acceptable marker of sympathetic modulation (Malliani et al., 1994) although this has been challenged (Parati et al., 2006). In this regard, a decreased LF (Li et al., 2020), LF/HF ratio at rest (Oka et al., 2011; Sabino-Carvalho et al., 2020) and a blunted increase in LF/HF ratio during tilt-table testing (Friedrich et al., 2010), has been identified in patients with PD compared to controls. However, this result is not unanimous, and other studies have not observed LF/HF ratio to be decreased at rest in PD (Bouhaddi et al., 2004; Friedrich et al., 2008; Vianna et al., 2016; Sabino-Carvalho et al., 2018). Notably, in patients with PD and OH both a lower resting LF/HF (Barbic et al., 2007) and a blunted LF/HF increase during an active standing test (Vianna et al., 2016) has been observed. This blunted response was also observed through analysis of the sympathetic component of HRV using symbolic analysis. Whereas, those patients without OH demonstrated only an attenuated response during an active standing test compared to controls (**Figure 1**, Vianna et al., 2016). Taken together, these data highlight the

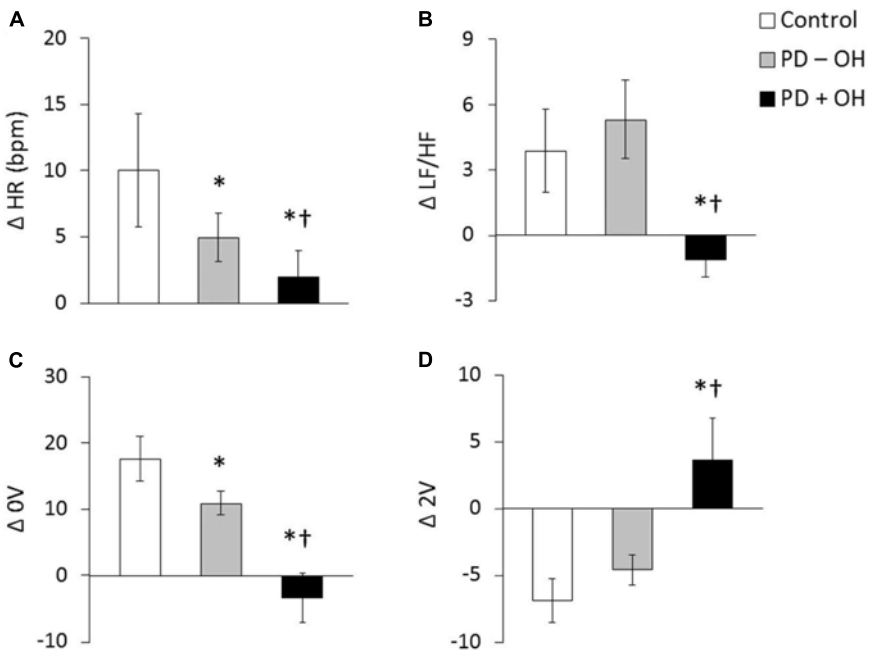

FIGURE 1 | Heart rate and LF/HF ratio in response to active standing in controls and in patients with PDwith (PD + OH) and without (PD – OH) orthostatic hypotension (**A** and **B**, respectively). Non-variable (0V – a proxy of sympathetic activity, **C**) and very variable (2V – a proxy of parasympathetic activity, **D**) category of symbolic dynamics analyses of heart rate variability. *$P < 0.05$ compared with control group. †$P < 0.05$ compared with PD – OH group. Mean data from Vianna et al. (2016).

presentation of sympathetic dysfunction in PD and suggest that the co-existence of OH, where a reduced vasoconstriction is thought to be a pathophysiological reason (van Wijnen et al., 2018), indicates a more severe condition.

Cardiovascular Responses to Exercise

During exercise, several neural mechanisms work in concert to precisely control cardiovascular and hemodynamic responses (Fisher et al., 2015). In neurodegenerative disorders, such as multiple system atrophy and pure autonomic failure, an abnormal cardiovascular responses to exercise is often observed (Low et al., 2012). These patients commonly have a blunted BP increase during isometric exercise (Khurana and Setty, 1996), and may even demonstrate a marked exercise-induced hypotension during dynamic exercise (Akinola et al., 2001). Considering the importance of the sympathetic contribution to the BP response to exercise, studies have suggested that sympathetic nerve activity is reduced during exercise in these patients (Kachi et al., 1988; Dotson et al., 1990; Donadio et al., 2010). Overall, this scenario is quite similar in PD, especially in those patients with OH (Marshall et al., 1961), where parasympathetic and sympathetic dysfunction together may interact to cause the abnormal cardiovascular responses to exercise.

The first evidence for an attenuated cardiovascular response to exercise in PD was provided in the late 80's by Sachs et al. (1985), Ludin et al. (1987), and Turkka et al. (1987) who demonstrated a blunted BP increase during isometric handgrip exercise. This finding was recently reproduced in dynamic exercise involving a large muscle mass (Reuter et al., 1999; Werner et al., 2006; DiFrancisco-Donoghue et al., 2009; Kanegusuku et al., 2016), resistance exercise (Miyasato et al., 2018) and isometric handgrip exercise (Sabino-Carvalho et al., 2018). Indeed, an inability to increase sympathetic activity to important compliant regions (i.e., splanchnic circulation), may impair the blood flow redistribution to the contracting muscles during exercise in PD (Sabino-Carvalho and Vianna, 2020) and, therefore, the reduced vasoconstriction in vascular beds will directly affect BP response to exercise. Consequently these impaired responses might contributed to metabolic distress, tissue/brain hypoperfusion, fatigue, cardiac autonomic dysfunction, and an lower exercise capacity, however, this hypothesis remains to be tested (**Figure 2**).

Sympatho-excitatory mechanisms are activated during exercise (e.g., exercise pressor reflex and central command), where both mechanically and metabolically sensitive sensory fibers provide feedback via the dorsal horn of the spinal cord to brainstem cardiovascular areas in response to mechanical (i.e., mechanoreflex) and metabolic stimuli (i.e., metaboreflex), respectively (Coote et al., 1971; McCloskey and Mitchell, 1972; Teixeira et al., 2020). The latter has a major role in regulating the sympathetically mediated increases in cardiac contractility, stroke volume, heart rate, peripheral resistance and, consequently, BP during exercise (Fisher et al., 2015; Teixeira et al., 2018). Sabino-Carvalho et al. (2018) assessed the contribution of the metabolic component of the exercise pressor reflex on cardiovascular responses to isometric handgrip exercise in patients with PD, using a experimentally approach

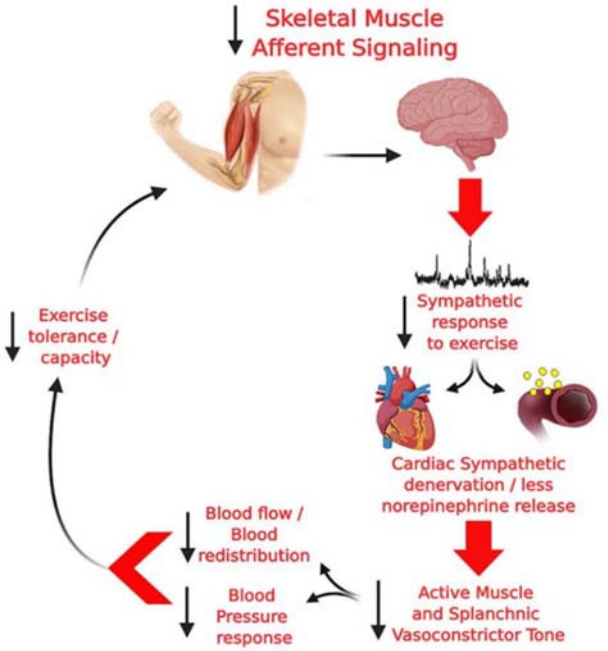

FIGURE 2 | Hypothetical model from Sabino-Carvalho and Vianna (2020) of the potential deleterious consequences of altered group III and IV skeletal muscle afferent activity in PD. Diminished skeletal muscle afferent signaling, together with central degeneration in PD, can result in a blunted sympathetic vasoconstriction leading to a blunted pressor response and, consequently, to lower increase blood flow to the active muscle, which may lead to metabolic distress, tissue/brain hypoperfusion, fatigue, cardiac autonomic imbalance, and an impaired exercise capacity.

described in a landmark study by Alam and Smirk (1937). As indicated in **Figure 3**, following isometric handgrip exercise performed at 40% of maximum voluntary contraction, a period of post-exercise ischemia was applied in the exercising arm to trap the metabolites generated during muscle contraction. The increases in BP were blunted during exercise and during the isolation of muscle metaboreflex in patients with PD when compared to control subjects. Responses to a non-exercise sympatoexitatory maneuver (i.e., the cold pressor test) did not differ between groups, which suggest no group differences in generalized sympathetic responsiveness. Therefore, this study suggests that attenuated BP responses to exercise observed in PD are partially explained by an altered metaboreflex in regulating the sympathetically mediated cardiovascular responses during exercise. However, this response does not exclude the involvement of a parasympathetic dysfunction in this altered response.

Parasympathetic activation produces negative inotropic, chronotropic and dromotropic effects on the heart (Armour, 2011; Coote, 2013). The activity of the DMV vagal preganglionic neurons is responsible for tonic parasympathetic control of ventricular excitability (Machhada et al., 2015, 2016, 2017). Machhada et al. demonstrated that silencing of DMV vagal preganglionic neurons provide parasympathetic control of left ventricular inotropy (Machhada et al., 2016), and that decreased

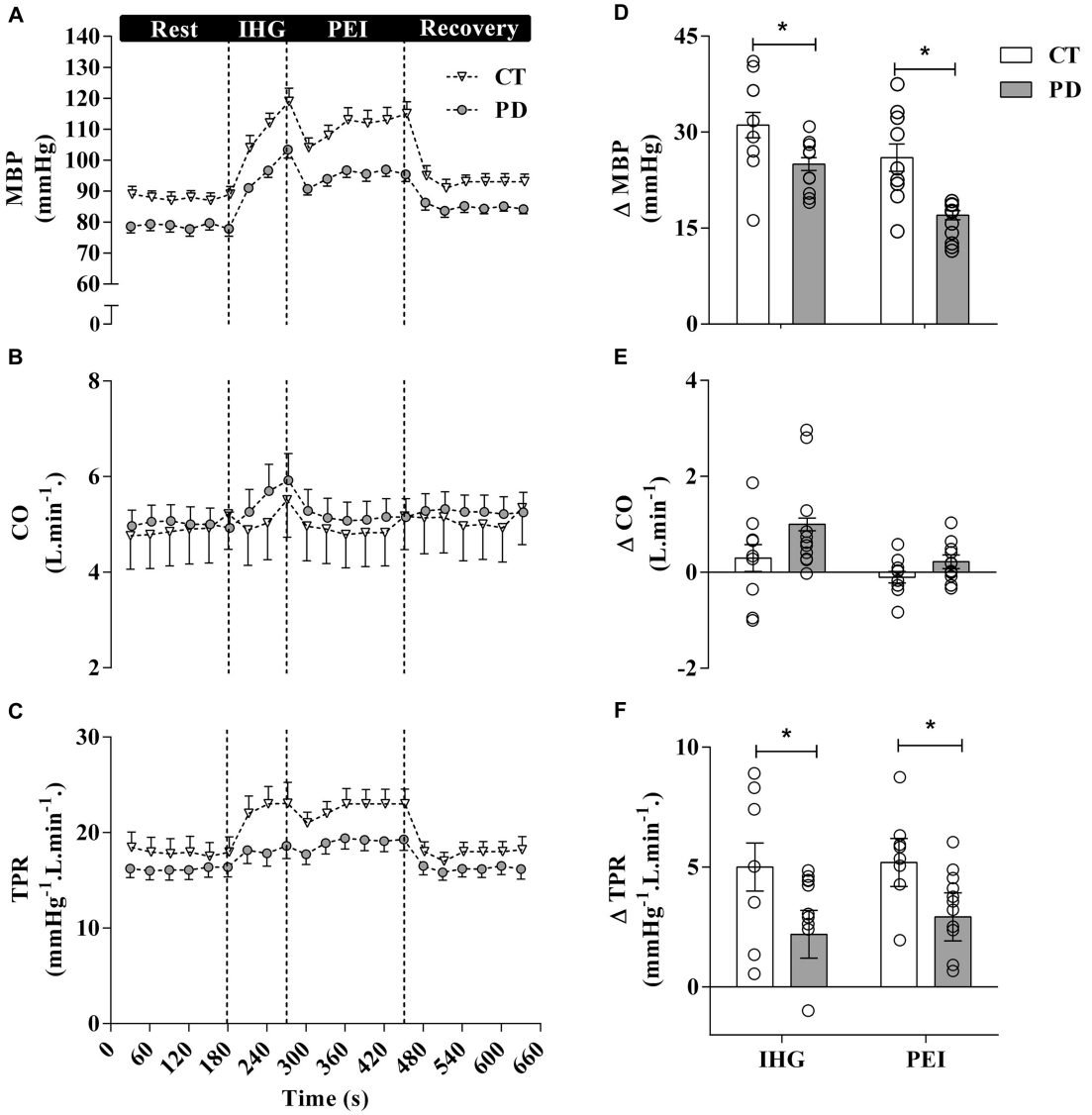

FIGURE 3 | Mean and individual data from Sabino-Carvalho et al. (2018) demonstrated that mean BP (MBP) responses to exercise and post-exercise ischemia (PEI) are attenuated in patients with PD compared to healthy control (CT) subjects. These blunted cardiovascular responses to isometric handgrip exercise in patients with PD are partially attributable to an altered metaboreflex. CO, Cardiac output; TPR, total peripheral resistance.

activity of DMV provides a neurophysiological basis for the progressive decline of exercise capacity with aging and in disease states (Machhada et al., 2017). By using an insect peptide (allatostatin) to inhibit DMV neurons the authors were able to show a dramatic reduction in exercise capacity. Noteworthy, along with this blunted exercise capacity, peak BP and heart rate during exercise were also blunted with DMV silencing, while DMV optogenetic recruitment enhanced the cardiac contractility and prolonged the exercise capacity (Machhada et al., 2017). Taken together, these results suggest that intact vagal activity generated by the DMV is required for proper cardiovascular adjustment to exercise.

Lowered vagal activity generated by the DMV might play a role in the attenuated cardiovascular responses, as well as, lowered exercise capacity presented by some patients with PD (Kanegusuku et al., 2016; Sabino-Carvalho et al., 2018). In an animal model of PD, Machhada et al. (2015) demonstrated that PD leads to a markedly reduction in DMV activity and this reduced activity led to changes in the electrophysiological properties of the ventricles, with a significantly shorter right ventricular effective refractory period than control animals and a QT prolongation. The attenuation was specifically in older animals (reflecting the PD progression), and that this reduced DMV neuron activity produced similar changes in ventricular excitability to that observed in control animals after DMV inhibition. Therefore, considering that the DMV neurons are affected by the pathological progression of PD (Braak et al., 2003) and intact DMV parasympathetic

activity seems to determine cardiac contractility and exercise capacity, in animal model (Machhada et al., 2017), this raises the hypothesis that DMV vagal preganglionic neurons might be also involved in the blunted cardiovascular responses to exercise, as well as, the exercise capacity observed in patients with PD. However, further studies are needed to explore this hypothesis.

Exercise Training in PD

There is currently no cure for PD, and although the primary resource for symptomatic control is pharmacologic-based, non-pharmacological low-cost approaches, such as exercise training, are being thought of as the universal prescription for PD (Alberts and Rosenfeldt, 2020; Lavin et al., 2020). Epidemiologic evidence suggest that moderate to vigorous exercise training might be protective against the developing of PD (Xu et al., 2010) and the growing body of evidence supports the beneficial effects of exercise on both motor (Silva-Batista et al., 2020a) and non-motor (Ganesan et al., 2014) symptoms. Furthermore, positive results regarding exercise training has been shown in PD animal models (Zhou et al., 2017). In addition to these positive effects, exercise has been employed as a coping resource to manage the quality of life (Corcos et al., 2013) and sleep (Silva-Batista et al., 2017), motor function (David et al., 2016; Vieira-Yano et al., 2020; Silva-Batista et al., 2020b), physical capacity (Kelly et al., 2014), fatigue (Santos et al., 2016) of patients with PD, and disease progression in a PD animal model (Zhou et al., 2017). Despite this, exercise training could be a challenging approach in this population, especially in those patients with OH (Roberson et al., 2019; Sabino-Carvalho et al., 2019; Sabino-Carvalho and Vianna, 2020), because of the impaired autonomic function (Goldstein, 2014; Vianna et al., 2016).

CONCLUSION

Optimal autonomic nervous system function is crucial for evoking appropriate cardiovascular and hemodynamic adjustments to exercise. Emerging evidence suggests that cardiac parasympathetic activity may be also a determinant of exercise capacity. In PD, the pathogenesis affects both parasympathetic and sympathetic nerve activity, which in turn seems to mediate the abnormal cardiovascular responses observed during exercise. These findings may be important in the understanding the complexity of the neural control of circulation in patients with PD. Further studies are needed to better understand the pathophysiological underpinnings on the exercise response in PD.

AUTHOR CONTRIBUTIONS

JS-C wrote the first draft of the manuscript. All the authors read and revised it critically for important intellectual content. All authors approved the final version of the manuscript.

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Neurovascular Dysregulation During Exercise in Type 2 Diabetes

*Ann-Katrin Grotle[1], Jasdeep Kaur[2], Audrey J. Stone[2] and Paul J. Fadel[1]**

[1] Department of Kinesiology, The University of Texas at Arlington, Arlington, TX, United States, [2] Department of Kinesiology and Health Education, The University of Texas at Austin, Austin, TX, United States

Emerging evidence suggests that type 2 diabetes (T2D) may impair the ability to properly adjust the circulation during exercise with augmented blood pressure (BP) and an attenuated contracting skeletal muscle blood flow (BF) response being reported. This review provides a brief overview of the current understanding of these altered exercise responses in T2D and the potential underlying mechanisms, with an emphasis on the sympathetic nervous system and its regulation during exercise. The research presented support augmented sympathetic activation, heightened BP, reduced skeletal muscle BF, and impairment in the ability to attenuate sympathetically mediated vasoconstriction (i.e., functional sympatholysis) as potential drivers of neurovascular dysregulation during exercise in T2D. Furthermore, emerging evidence supporting a contribution of the exercise pressor reflex and central command is discussed along with proposed future directions for studies in this important area of research.

Keywords: sympathetic nerve activity, blood pressure, blood flow, exercise pressor reflex, central command, baroreflex, functional sympatholysis

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***Correspondence:**
Paul J. Fadel
paul.fadel@uta.edu

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INTRODUCTION

Type 2 diabetes (T2D) negatively impacts cardiovascular health, contributing to a high risk of premature mortality (Raghavan et al., 2019). Notably, ∼60% of T2D patients also have hypertension, which suggests that alterations in blood pressure (BP) control are common in this population (Colosia et al., 2013). This is all very important because more than 34 million Americans currently live with T2D, a number projected to increase nearly 50% by 2050 (Boyle et al., 2010; Prevention, 2020). Notably, the prevalence of T2D and prediabetes in young adults is also increasing (Mayer-Davis et al., 2017; Prevention, 2020), which is alarming considering that an earlier disease onset is associated with high lifetime risk of cardiovascular disease (Song, 2016). These rates are, in part, attributable to the accelerated rates of sedentary lifestyle in our society (Mayer-Davis and Costacou, 2001). Indeed, physical inactivity has been shown to be an important modifiable risk factor that contributes to the development of T2D (Bowden Davies et al., 2019; Antwi et al., 2020). Although exercise is a well-recognized tool in the management of T2D due to its many cardiometabolic benefits, accumulating evidence suggests that T2D negatively affects cardiovascular responses to exercise. The most alarming consequence is an exaggerated exercise-induced BP (Scott et al., 2008; Regensteiner et al., 2009; Pinto et al., 2014; O'Connor et al., 2015; Holwerda et al., 2016a), a response associated with a heightened risk of acute adverse cerebral- and cardiovascular events (Kurl et al., 2001; Laukkanen et al., 2006). Furthermore, several studies also report reductions in contracting skeletal muscle blood flow (BF) in T2D, which likely hinders the ability to sustain exercise contributing to the well-known exercise intolerance in this population (O'Connor et al., 2012; Reusch et al., 2013; Sacre et al., 2015; Senefeld et al., 2019). Therefore,

understanding the underlying mechanisms contributing to altered cardiovascular responses to exercise in T2D is crucial to identifying strategies that can reduce the heightened cardiovascular risk in this population, while at the same time improving their ability to perform and sustain physical activity.

The sympathetic nervous system plays an integral role in controlling the cardiovascular adjustments to exercise. Increases in sympathetic nerve activity (SNA) to the heart facilitate increases in cardiac output and sympathetic outflow to periphery and viscera elicits vasoconstriction of inactive skeletal muscle and tissue beds, respectively. These actions contribute to elevations in BP while facilitating increases in BF to contracting muscles (Fisher et al., 2015). Moreover, within contracting muscles, the interaction between sympathetically mediated vasoconstrictor drive and local vasodilatory factors determines active skeletal muscle BF. In this regard, locally released vasoactive compounds attenuate sympathetically mediated vasoconstriction (i.e., functional sympatholysis) (Remensnyder et al., 1962) to further facilitate increases in active muscle BF. Several neural mechanisms work in concert to facilitate these adjustments. Feedback signals from the contracting skeletal muscle (i.e., exercise pressor reflex) and feedforward signals from higher brain centers (i.e., central command) both contribute to increase SNA during exercise (Alam and Smirk, 1937; Goodwin et al., 1972; McCloskey and Mitchell, 1972). These signals also contribute to the resetting of the arterial and cardiopulmonary baroreflex, which play important roles in modulating exercise-induced increases in BP via alterations in SNA (Scherrer et al., 1990; Fadel et al., 2001; Joyner, 2006). Thus, proper neural adjustments are essential to ensuring the appropriate sympathetic and thus cardiovascular responses to exercise.

Emerging evidence suggests that T2D impairs the ability to adjust the circulation during exercise, which is highlighted by reports of exaggerated muscle SNA (MSNA) (Holwerda et al., 2016a; Vranish et al., 2020), BP (Scott et al., 2008; Regensteiner et al., 2009; Pinto et al., 2014; O'Connor et al., 2015; Holwerda et al., 2016a), and attenuated increases in contracting skeletal muscle BF (Menon et al., 1992; Kingwell et al., 2003; Lalande et al., 2008; Mac Ananey et al., 2011; Kiely et al., 2014; O'Connor et al., 2015; Groen et al., 2019; Bock et al., 2020). Therefore, the purpose of this review is to provide a brief update on the current understanding of these altered exercise responses in T2D and the potential underlying mechanisms, with an emphasis on the sympathetic nervous system and its regulation during exercise. Furthermore, we discuss emerging evidence supporting a contribution of the exercise pressor reflex and central command along with proposed future directions for studies in this important area of research.

CARDIOVASCULAR RESPONSES TO EXERCISE IN TYPE 2 DIABETES

The first data identifying an exaggerated exercise-induced BP response in T2D patients came from studies assessing cardiovascular responses to maximal and submaximal exercise testing (Kingwell et al., 2003; Petrofsky et al., 2005; Scott et al., 2008; Regensteiner et al., 2009; Karavelioglu et al., 2013; Pinto et al., 2014; O'Connor et al., 2015). For example, Scott et al. (2008) reported an ∼50% greater prevalence of an exaggerated BP response to a graded maximal treadmill test in normotensive middle-aged T2D patients relative to controls. Furthermore, an augmented BP during submaximal steady-state and short-duration constant load cycling exercise has also been reported (Andresen and Kunze, 1994; O'Connor et al., 2015). Notably, these responses were also present at an early age in which studies have shown augmented BP responses to exercise in adolescents with T2D (Pinto et al., 2014; Yardley et al., 2015). Thus, these responses highlight that T2D patients are more likely to experience exaggerated exercise-induced BP responses, which is a prognostic indicator for an augmented risk of acute myocardial infarction and stroke (Kurl et al., 2001; Laukkanen et al., 2006). A recent study by Holwerda et al. (2016a) linked the augmented BP responses to exercise in T2D with elevated SNA demonstrating, for the first time, that T2D patients, independent of coexisting hypertension, had exaggerated MSNA responses to isometric handgrip exercise compared to nondiabetic controls (**Figure 1**).

Another common feature reported in studies examining exercise responses in T2D has been reductions in contracting skeletal muscle BF (Menon et al., 1992; Kingwell et al., 2003; Lalande et al., 2008; Mac Ananey et al., 2011; Kiely et al., 2014; O'Connor et al., 2015; Groen et al., 2019; Bock et al., 2020). For example, seminal work by Kingwell et al. (2003) showed attenuated leg BF responses to submaximal supine cycling exercise (60% VO_2 peak) in normotensive T2D patients. Consequently, leg vascular resistance was substantially greater in the T2D patients. Similarly, a more recent study (Groen et al., 2019) reported attenuated increases in leg BF and vascular conductance in T2D patients during single-leg knee extension exercise. However, it should be noted that conflicting findings have also been reported (Martin et al., 1995; Copp et al., 2010; Poitras et al., 2015). For example, Poitras et al. (2015) found similar increases in forearm muscle BF during a forearm critical force test in T2D patients and controls. Nonetheless, there are substantial data reporting that T2D significantly impacts the ability to properly adjust the circulation during exercise, leading to an augmented BP and reduced contracting skeletal muscle BF. For complementary details on exercise impairments in T2D, the reader is referred to other excellent reviews (Reusch et al., 2013; Green et al., 2015; Poitras et al., 2018; Kim et al., 2020; Nesti et al., 2020).

NEUROVASCULAR REGULATION DURING EXERCISE IN HEALTH

In this section, we will provide a brief overview of appropriate neurovascular regulatory mechanisms during exercise to set the stage for future sections on what is known about the potential impairments in neurovascular control mechanisms in T2D. Several neural mechanisms work in concert to regulate BP and adjust the circulation during exercise. The exercise pressor

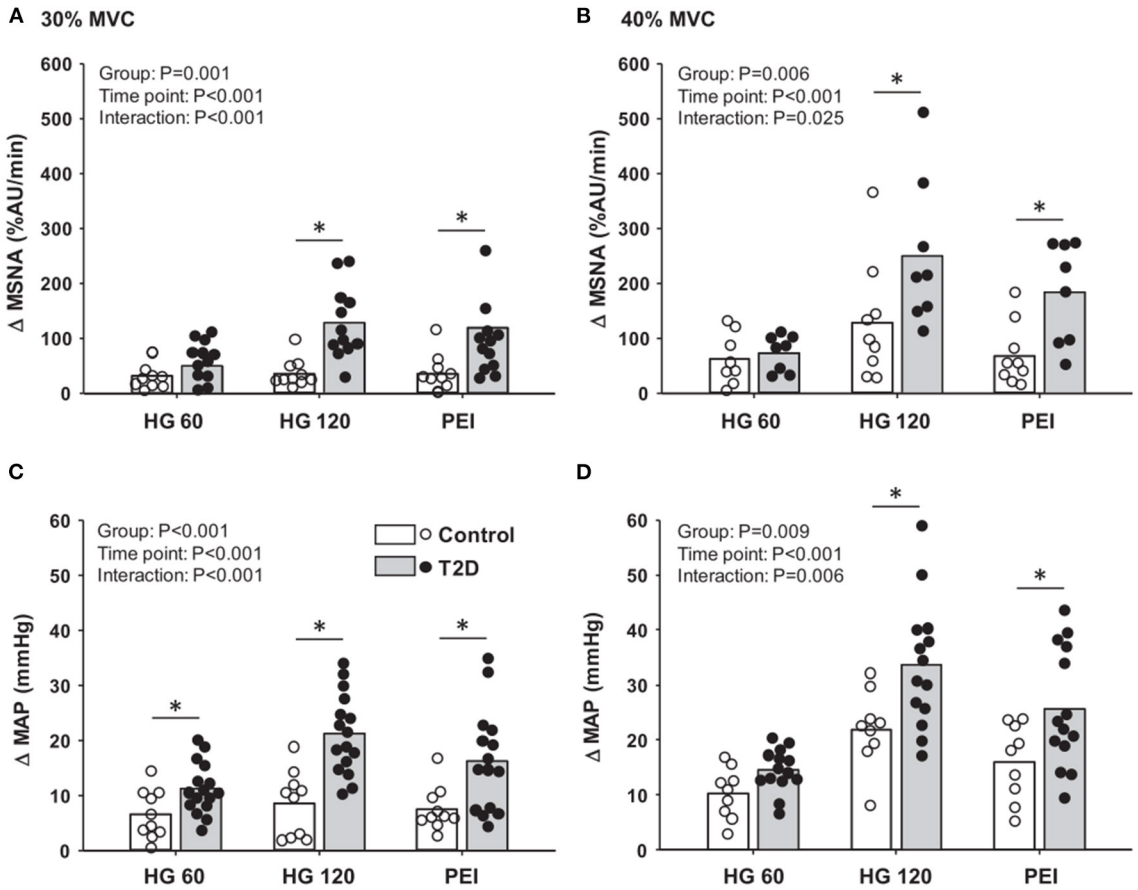

FIGURE 1 | Mean data and individual data showing changes in muscle sympathetic nerve activity (MSNA; **A,B**) and mean arterial pressure (MAP; **C,D**) at 60 and 120 s of 30 and 40% maximal voluntary contraction (MVC) handgrip followed by subsequent periods of post-exercise ischemia (PEI) in type 2 diabetes (T2D) patients and control subjects. $^{*}P < 0.05$ vs. control. Modified from Holwerda et al. (2016a) with permission.

reflex is a feedback mechanism that responds to mechanical (i.e., mechanoreflex) and metabolic (i.e., metaboreflex) stimuli produced by the contracting skeletal muscle and reflexively increases MSNA, BP, HR, and respiration (Alam and Smirk, 1937; McCloskey and Mitchell, 1972; Strange et al., 1993). The afferent arm of this reflex is comprised of thinly myelinated group III (predominantly mechanically sensitive) and unmyelinated group IV (predominantly metabolically sensitive) muscle afferents (McCloskey and Mitchell, 1972; Kaufman et al., 1983). However, these afferents exhibit polymodal characteristics (Rotto and Kaufman, 1988; Rotto et al., 1990). Central command is a feedforward mechanism referring to descending signals originating from higher brain areas that simultaneously increase motor efferent drive and autonomic neural outflow that, in turn, contributes to the cardiorespiratory responses to exercise (Goodwin et al., 1972; Eldridge et al., 1981, 1985). Furthermore, both the exercise pressor reflex and central command contribute to the resetting of the arterial and cardiopulmonary baroreflex (Bevegard and Shepherd, 1966; Papelier et al., 1994; Gallagher et al., 2006). The arterial baroreflex is a negative feedback mechanism that modulates BP at rest and during exercise by making rapid cardiovascular adjustments in response to beat-to-beat changes in BP. On the other hand, the cardiopulmonary baroreflex responds to changes in central pressure and volume by reflexively adjusting MSNA at rest and during exercise (Ray et al., 1993; Ogoh et al., 2007). These neural mechanisms all converge centrally in the nucleus tractus solitarius of the medulla oblongata (Andresen and Kunze, 1994; Potts et al., 2002) and ultimately adjust sympathetic outflow via neurons in the rostral ventral lateral medulla. It is worth noting that skeletal muscle afferents also increase SNA via direct projections to the rostral ventral lateral medulla (Potts, 2006). For more in-depth discussions on neurovascular control, we refer the reader to several comprehensive reviews (Fadel and Raven, 2012; Fisher et al., 2015; Holwerda et al., 2015; Michelini et al., 2015; Nyberg et al., 2015; Grotle et al., 2020).

The resultant increases in SNA directed to visceral and peripheral blood vessels have powerful vasoconstrictor and BP-raising effects during exercise (Fairfax et al., 2013). Indeed, sympathetic vasoconstriction of inactive tissue and skeletal muscle vascular beds increases to effectively redistribute cardiac output to active skeletal muscle (Joyner et al., 1992; Rowell, 1997; Saltin et al., 1998). At the same time, sympathetically mediated vasoconstriction is attenuated in active skeletal

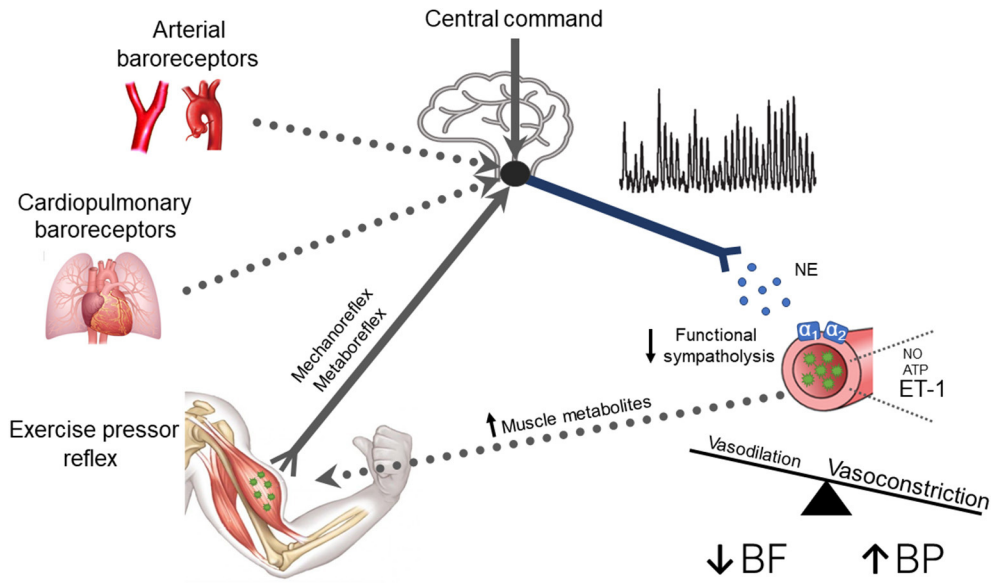

FIGURE 2 | A schematic of potential neural mechanisms responsible for neurovascular dysregulation in type 2 diabetes (T2D). Current evidence supports a contribution of the exercise pressor reflex and central command (solid lines), whereas the contribution of the arterial and cardiopulmonary baroreflex remains unclear (dotted lines). Briefly, T2D patients exhibit exaggerated muscle sympathetic nerve activity (MSNA) responses, which increases the release of norepinephrine (NE) binding to α_1 and α_2 adrenergic receptors causing constriction of peripheral vascular beds. T2D may also impair the normal ability to attenuate sympathetically mediated vasoconstriction in active skeletal muscle (i.e., reduced functional sympatholysis). Additionally, enhanced endothelin-1-mediated vasoconstriction and reduced nitric oxide (NO) and adenosine triphosphate (ATP) mediated vasodilation may also contribute to the reduced exercise hyperemia in T2D. These alterations favor vasoconstriction, leading to reduced active skeletal muscle blood flow and exaggerated BP responses to exercise. Thus, it is plausible that T2D leads to a positive feedback scenario where enhanced MSNA and reduced functional sympatholysis combined with other impaired local vascular control pathways augment metabolic distress, which in turn further enhances MSNA by stimulating the muscle metaboreflex.

muscle beds by local vasoactive compounds (i.e., functional sympatholysis) (Remensnyder et al., 1962) to further facilitate increases in contracting skeletal muscle BF. Although extensively studied, the sympatholytic compounds responsible for functional sympatholysis and their mechanism(s) of action are not well understood. Nevertheless, accumulating evidence supports a significant contribution played by ATP (Rosenmeier et al., 2004; Saltin and Mortensen, 2012), which appears to mediate its effect, in part, by attenuating the sensitivity of α-adrenergic receptors (Mortensen et al., 2009). Although less clear, NO also appears to contribute (Thomas and Victor, 1998), but its role may depend on the presence of other compounds such as prostacyclin (Dinenno and Joyner, 2004; Mortensen et al., 2007). Regardless, numerous studies demonstrate the presence of functional sympatholysis and its importance for increasing contracting skeletal muscle BF. Of note, functional sympatholysis does not mean complete "lysis" of sympathetic vasoconstriction but rather an attenuation that allows for increases in active skeletal muscle BF while still contributing to the maintenance of BP.

In addition to sympathetic control, non-adrenergic vasoconstrictor and vasodilatory compounds also contribute to the regulation of contracting skeletal muscle BF (Saltin and Mortensen, 2012; Holwerda et al., 2015). These can be released by skeletal muscle, endothelial cells, nerve terminals, and circulating erythrocytes in response to increased mechanical stimuli and metabolic activity during exercise. The interplay between these factors is complex and incompletely understood due, in part, to significant redundancy. Moreover, the participation of each pathway or compound may change from the onset to steady-state exercise (Clifford and Hellsten, 2004). Vasodilatory compounds include nitric oxide (NO), prostacyclin, adenosine, potassium, and ATP (Clifford and Hellsten, 2004; Clifford, 2007), which can act through endothelial-dependent or independent pathways. Additionally, non-adrenergic vasoconstrictors such as interstitial ATP, neuropeptide Y, endothelin 1, and angiotensin II also contribute to the vasoconstrictive influence during exercise (Holwerda et al., 2015); however, it should be noted that an attenuation of non-adrenergic vasoconstrictor pathways in active skeletal muscle has been reported (Brothers et al., 2006; Wray et al., 2007). Of note, the contribution of non-adrenergic vasoactive compounds to BF responses during exercise may not be as prominent in healthy individuals; however, it appears to increase with aging and disease (Schreuder et al., 2014; Barrett-O'Keefe et al., 2015; Nyberg et al., 2015).

NEUROVASCULAR DYSREGULATION DURING EXERCISE IN TYPE 2 DIABETES

Until recently, little was known regarding the underlying mechanisms for the impaired cardiovascular responses to exercise observed in T2D. In this regard, emerging evidence suggests that the exercise pressor reflex plays a prominent role in evoking exaggerated MSNA and BP responses to exercise

in T2D (**Figure 2**). For example, T2D rats have exaggerated renal SNA and BP responses to electrically evoked static muscle contractions in the absence of central command (Grotle et al., 2019; Kim et al., 2019). Both the mechanoreflex and metaboreflex have been shown to contribute to the exaggerated exercise pressor reflex in T2D. Indeed, T2D rats exhibit augmented BP responses to isolated mechanical stimuli (i.e., tendon stretch), suggesting an augmented mechanoreflex (Grotle et al., 2019). Furthermore, studies in humans suggest T2D also augments the metaboreflex (Holwerda et al., 2016a; Roberto et al., 2019). Specifically, Holwerda et al. (2016a) showed exaggerated MSNA and BP responses to postexercise ischemia (PEI) following isometric handgrip exercise (30 and 40% maximal voluntary contraction: MVC; **Figure 1**). This maneuver traps the metabolites produced during exercise and isolates the muscle metaboreflex. Interestingly, the magnitude of MSNA response to PEI was positively correlated with metabolic markers of disease severity (glucose, HbA1c, and HOMA-IR), which suggests that the severity of disease has significant impact on the enhanced expression of the exercise pressor reflex in T2D. In this regard, a recent study (Roberto et al., 2019) that reported a normal BP response to PEI following rhythmic handgrip exercise (30% MVC) had a cohort of T2D patients with relatively well-controlled blood glucose (106.41 ± 11.2 mg/dl; HbA1c 7.05 ± 0.10%). Although it is possible that the lower-intensity rhythmic exercise did not produce sufficient metabolic stimuli to unmask a difference in metaboreflex-induced BP responses between groups, notably T2D patients in this study exhibited exaggerated vasoconstriction during PEI. Interestingly, a recent study showed enhanced BP responses to ischemic rhythmic handgrip exercise (30% MVC) in nondiabetic individuals with greater insulin resistance than those with lower insulin resistance (Hotta et al., 2020). Overall, the existing literature supports that both components of the exercise pressor reflex (i.e., mechano- and metabo-reflex) may be enhanced in T2D (**Figure 2**).

The underlying mechanisms for an augmented exercise pressor reflex in T2D remain unknown. Specifically, it will be important to determine whether these mechanisms involve greater metabolite accumulation during skeletal muscle contraction, enhanced afferent sensitivity, or increased expression of mechanically or metabolically sensitive receptors and/or channels, or abnormal central integration of afferent feedback. It is possible that a slowed and attenuated hyperemic response to contracting skeletal muscle during exercise enhances muscle metabolite buildup, thereby increasing the activation of the metaboreflex and simultaneously sensitizing the mechanoreflex (Adreani and Kaufman, 1998; Holwerda et al., 2016a; Nesti et al., 2020). Additionally, there are reports of increased reliance on carbohydrate metabolism (Martin et al., 1995; Scheuermann-Freestone et al., 2003), reduced capillary density and recruitment, increased fast twitch muscle fiber type recruitment (Marin et al., 1994; Padilla et al., 2006; Womack et al., 2009), and increased leg lactate output during exercise (Martin et al., 1995) in T2D. These alterations may indicate a greater propensity for metabolite production during exercise in T2D. Furthermore, oxidative stress may also contribute as it is an important mediator of well-known complications of T2D (e.g., vascular dysfunction and peripheral neuropathy) (Giacco and Brownlee, 2010) and may directly influence thin fiber afferent activity (Delliaux et al., 2009). Indeed, studies have reported that reactive oxygen species may play a role in evoking the exaggerated exercise pressor reflex in common comorbidities of T2D (e.g., hypertension, peripheral artery disease, and heart failure) (Koba et al., 2009, 2013; Wang et al., 2009; Muller et al., 2012; Harms et al., 2017). Thus, it is plausible that the increased presence of metabolites and/or reactive oxygen species may contribute to the exaggerated exercise pressor reflex in T2D (Grotle and Stone, 2019). However, additional studies are needed.

Recent evidence suggests that insulin and glucose may also play a role in augmenting thin fiber afferent activity. Specifically, Hotta et al. (2019) used a whole-cell patch-clamp preparation to show that local application of insulin to small dorsal root ganglion in healthy mice decreased their mechanical threshold and augmented the amplitude of mechanically activated currents, whereas antagonizing insulin receptors attenuated this response. Furthermore, they used an isolated muscle-nerve preparation to show that application of insulin decreased the threshold, but not the magnitude, of mechanically evoked group IV afferent activity. In terms of glucose, a recent study showed that acutely infusing glucose into the hindlimb to concentrations observed in T2D rats did not affect the exercise pressor reflex or either of its two components (i.e., mechanoreflex and metaboreflex) in healthy rats (Huo et al., 2020). However, these responses may be different in T2D rats. Notably, Ishizawa et al. (2021) recently reported an augmented pressor and renal SNA response to capsaicin (chemically sensitive TRPV1 receptor agonist) administration in the hindlimb of T2D rats compared to controls. Furthermore, group IV muscle afferents isolated from T2D rats exhibited exaggerated capsaicin-induced discharge frequency, which was related to blood glucose concentrations. This aligns with findings in T2D patients showing a positive association between the MSNA response to isolated muscle metaboreflex activation and fasting blood glucose and HbA1c (Holwerda et al., 2016a). Thus, together these findings suggest that both insulin and glucose may play a role in augmenting the exercise pressor reflex in T2D. However, further studies are warranted.

Whether central command is impacted by T2D has received less attention. However, a recent study by Vranish et al. (2020) reported augmented MSNA and BP responses in T2D patients at the early onset of exercise, evident as early as 10 s into isometric handgrip. Although by no means direct evidence for central command involvement, these data at least suggest the possibility of heightened central command responses in T2D. A recent study (Kim et al., 2019) using a high-fat diet and streptozotocin-induced T2D model in rats supports a contribution of central command in evoking exaggerated SNA and BP responses to exercise (**Figure 2**). These investigators reported that neural stimulation of the mesencephalic locomotor region, a putative area for the central command pathway, resulted in greater renal SNA, HR, and BP responses in T2D rats compared to controls. The underlying mechanisms for these responses are not known but could involve direct alterations to brain areas responsible for central command, or the central integration of signals. Possible

contributors include enhanced central angiotensin II or oxidative stress-mediated reductions in NO within the NTS, both of which have been proposed as contributors to augmented SNA reactivity to exercise in hypertension, a common comorbidity in T2D (Song et al., 1994; Zimmerman et al., 2002; Leal et al., 2012, 2013). T2D also appears to impair dynamic cerebral autoregulation during exercise, which suggests the potential for direct cerebral vascular contributions (Vianna et al., 2015). For more information on the effects of T2D on cerebral vascular regulation during exercise, the reader is directed to a recent review (Kim et al., 2020).

It is also plausible that enhanced SNA responses during exercise in T2D include an altered interaction between central command and the exercise pressor reflex (Amann et al., 2008). Painful peripheral diabetic neuropathy is a common feature in T2D and affects similar sensory afferents as those evoking the exercise pressor reflex (Davies et al., 2006). Thus, considering that effort sense influences central command (Williamson et al., 2001), it is possible that activation of sensory afferents (i.e., ergoreceptors and nociceptors) evoking augmented SNA and muscle pain also increases central command by influencing one's perceived effort during exercise. Indeed, ischemia-induced muscle pain has been shown to increase effort sense during light resistance exercise in healthy individuals (Hollander et al., 2010). Moreover, attenuating afferent feedback during dynamic exercise lowers ratings of perceived exertion during exercise, a marker for central command activation (Amann et al., 2010). Notably, there is some evidence of higher perceived effort during exercise in T2D (Huebschmann et al., 2009; Kim et al., 2015). However, these interactions are complex and require further investigation.

Whether T2D impairs arterial and cardiopulmonary baroreflex function during exercise has not been directly tested (**Figure 2**). Several studies indicate that T2D attenuates cardiac baroreflex sensitivity at rest (Holwerda et al., 2016b; Cseh et al., 2020; Kuck et al., 2020). However, this may not be specific to T2D, as weight-matched controls also exhibit impaired cardiac baroreflex control at rest compared to lean controls suggesting that obesity rather than T2D impairs arterial baroreflex control of HR (Holwerda et al., 2016b). In contrast, arterial baroreflex control of MSNA appears to be preserved at rest in T2D (Holwerda et al., 2016b; Moura-Tonello et al., 2016). However, whether this is true also during exercise has not been directly tested. This is important because the arterial baroreflex plays an essential role in restraining sympathetic outflow during exercise (Joyner, 2006). Likewise, to our knowledge, no study has investigated the effect of T2D on cardiopulmonary baroreflex control of MSNA (**Figure 2**), which also has restraining effects on MSNA responses during exercise. There is a clear need for further studies.

In addition to an exaggerated MSNA response to exercise, recent research suggests T2D also appears to impair the ability to attenuate sympathetically mediated vasoconstriction in active skeletal muscle (i.e., functional sympatholysis; **Figure 2**). Specifically, Bock et al. (2020) demonstrated greater vasoconstrictor responses to intra-arterial infusion of α_1 and α_2–adrenergic receptor agonists in active muscle during rhythmic handgrip exercise in T2D patients compared to nondiabetic controls. It is important to note that these findings contrast with Thaning et al. (2011), demonstrating preserved functional sympatholysis in T2D. However, in this study, the T2D patients were relatively healthy and had normal vasodilatory responses to acetylcholine, suggesting normal endothelial function. This is interesting because recent work (Hearon et al., 2020) suggests that the degree of functional sympatholysis may be dependent on endothelial function and thus, could, in part, explain these disparate findings.

Non-adrenergic pathways may also contribute to the reduced BF responses in active skeletal muscle reported in T2D patients. Indeed, an imbalance favoring blunted endothelial-dependent vasodilation and enhanced non-adrenergic vasoconstrictors may be involved (**Figure 2**) (Mather et al., 2004; Malik et al., 2005; Frisbee et al., 2019). Although limited studies have been performed, there is some evidence that warrants discussion. For example, one study (Kingwell et al., 2003) showed that attenuated leg BF responses to dynamic exercise were significantly correlated with vasodilatory responses to acetylcholine but not to sodium nitroprusside infusion, suggesting that an impaired endothelial-dependent but not independent NO-mediated vasodilation may contribute. Furthermore, impaired ATP-mediated vasodilation, perhaps due to reduced ATP bioavailability or purinergic receptor sensitivity, may also be involved (Thaning et al., 2010; Groen et al., 2019). In terms of vasoconstrictors, blocking endothelin-1 receptors during rhythmic handgrip exercise has been shown to enhance muscle BF responses in T2D patients but not in healthy controls, indicating augmented endothelin 1-mediated vasoconstriction during exercise in T2D (Schreuder et al., 2014). Collectively, these findings suggest that attenuated vasodilation via reduced NO and ATP, in combination with enhanced vasoconstrictor influence via endothelin-1, may also impair the ability to appropriately regulate contracting skeletal muscle BF in T2D. Notably, these changes in non-adrenergic pathways, along with the heightened MSNA and impaired functional sympatholysis, likely also contribute to the exaggerated BP response to exercise reported in T2D patients. Additionally, recent work suggests that augmented exercise-induced increases in arterial stiffness may also contribute to the exaggerated BP response to exercise in T2D (Cooke et al., 2020).

CONSIDERATIONS AND FUTURE DIRECTIONS

T2D is a multifactorial disease with many potential contributing factors to the neural vascular dysregulation reported during exercise (e.g., diet, physical inactivity, aging, family history, sex, ethnicity, comorbidities, etc.). This likely contributes to variations in diabetic phenotypes (Stidsen et al., 2018) as well as potentially differential etiologies for exercise impairments (Nesti et al., 2020), making T2D a complex population to study. It is also important to note that differences in T2D characteristics (e.g., duration of diabetes, glycemic control, and varying medications), animal models used, and exercise modality employed (e.g., type, duration, intensity of exercise) may also influence the observed neural cardiovascular responses to exercise in T2D. In addition, the majority of studies discussed in this review

include relatively well-controlled T2D patients and exclude those with diabetic complications (e.g., neuropathy, uncontrolled diabetes, coronary heart disease etc.). Thus, examining neural cardiovascular responses to exercise in T2D patients with associated complications warrants future investigation. Likewise, although an augmented BP response to exercise is observed in several age groups and in both males and females, the influence of age and sex on neurovascular regulation during exercise in T2D has not been comprehensively assessed. It would be particularly interesting to determine the influence of sex hormones and menopausal status as estrogen has been shown to affect the cardiovascular responses to exercise (Schmitt and Kaufman, 2003; Fadel et al., 2004; Jarvis et al., 2011). Studies are also needed to further understand the contribution of factors such as insulin resistance, obesity, and physical inactivity. Notably, two studies indicate that insulin resistance may be a stronger predictor of an augmented metaboreflex than obesity in nondiabetic individuals (Milia et al., 2015; Hotta et al., 2020). However, others have demonstrated that obesity may drive negative effects on neural cardiovascular control mechanisms in T2D patients (Holwerda et al., 2016b). Moreover, the influence of physical inactivity on neural cardiovascular control in T2D is unclear and also warrants future investigation. Thus, overall, we have a lot more to learn about cardiovascular responses to exercise and underlying mechanisms in T2D and elucidating the role of the above mentioned factors in future studies will be important to consider as this field moves forward.

CONCLUSION

T2D patients are at a twofold higher risk of premature mortality, contributing to a significantly shorter life expectancy (Raghavan et al., 2019). Emerging evidence suggests that neurovascular dysregulation leading to enhanced SNA and BP reactivity to exercise or daily physical activities (e.g., carrying groceries, walking up stairs) may increase the already heightened risk for adverse cardiac events and stroke in this population. Although mechanisms for this are just starting to emerge, evidence supports a contribution of the exercise pressor reflex and central command. However, further studies are needed and elucidation of potential roles for the arterial and cardiopulmonary baroreflex requires investigation. Additionally, augmented α_1 and α_2 adrenergic receptor sensitivity, endothelin-1-mediated vasoconstriction and blunted NO, and ATP-mediated vasodilation may also contribute. Indeed, T2D may lead to a scenario where enhanced MSNA, via the exercise pressor reflex and central command, along with impaired local vascular control mechanisms (adrenergic and non-adrenergic) attenuates increases in exercising muscle BF and augments the BP response to exercise. Nonetheless, there is a clear need for future studies to investigate the impact of T2D on neural and vascular control mechanisms and their interaction during exercise.

AUTHOR CONTRIBUTIONS

A-KG drafted the manuscript, which was critically evaluated by JK, AS, and PF. All authors approved the submitted version. All authors contributed to the article and approved the final version.

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Breath-Hold Diving – The Physiology of Diving Deep and Returning

Alexander Patrician[1], Željko Dujić[2], Boris Spajić[3], Ivan Drviš[3] and Philip N. Ainslie[1]*

[1]Center for Heart, Lung & Vascular Health, University of British Columbia Okanagan, Kelowna, BC, Canada, [2]Department of Integrative Physiology, University of Split School of Medicine, Split, Croatia, [3]Faculty of Kinesiology, University of Zagreb, Zagreb, Croatia

Breath-hold diving involves highly integrative physiology and extreme responses to both exercise and asphyxia during progressive elevations in hydrostatic pressure. With astonishing depth records exceeding 100 m, and up to 214 m on a single breath, the human capacity for deep breath-hold diving continues to refute expectations. The physiological challenges and responses occurring during a deep dive highlight the coordinated interplay of oxygen conservation, exercise economy, and hyperbaric management. In this review, the physiology of deep diving is portrayed as it occurs across the phases of a dive: the first 20 m; passive descent; maximal depth; ascent; last 10 m, and surfacing. The acute risks of diving (i.e., pulmonary barotrauma, nitrogen narcosis, and decompression sickness) and the potential long-term medical consequences to breath-hold diving are summarized, and an emphasis on future areas of research of this unique field of physiological adaptation are provided.

Keywords: apnea, free-diving, hyperbaric, immersion, diving, nitrogen, breath-holding, spearfishing

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James P. Fisher,
The University of Auckland,
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Kay Tetzlaff,
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United States
Peter Lindholm,
University of California,
San Diego, United States

****Correspondence:***
Alexander Patrician
alexander.patrician@alumni.ubc.ca

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INTRODUCTION

Breath-hold diving is a ubiquitous activity for recreation, sustenance, military, and sport; it involves highly integrative physiology and extreme responses to both exercise and asphyxia during progressive elevations in hydrostatic pressure (Ferretti, 2001; Bain et al., 2018b; Fitz-Clarke, 2018). Since the famous anecdote of Giorgios Statti diving to 70 m in 1913; the attainment of 100 m by Jacques Mayol in 1976; and, more recently, Herbert Nitsch reaching a staggering 214 m in 2007, the human capacity for deep breath-hold diving has continually extended the physiological limits and refuted expectations. However, physiological limits do exist and adverse consequences readily occur when these limits are exceeded. The purpose of this review is to outline the basic physics that govern apnea diving, discuss the challenges, physiological responses, and associated clinical consequences of diving to depth.

GAS LAWS

Humans live in a pressurized air environment, with the pressure at sea level standardized to 760 mmHg or 1 absolute pressure in atmospheres (ATA). Upon diving, pressure increases proportionally with depth, due to the additive weight of the water column. Specifically, for every 10 m (33 ft)

of sea water, hydrostatic pressure increases by 1 ATA; therefore, as pressure doubles, the volume of the gas is halved (in accordance with Boyle's Law which states, in a closed system where temperature remains constant, the volume is directly and inversely proportional to the pressure) and the solubility of all gases increase [in accordance with Henry's Law which states that the amount of gas absorbed (at the same temperature in liquid) is proportional to the solubility coefficient of the particular gas and their partial pressure]. These concepts are illustrated in **Figure 1**, which outlines the role of Boyle's and Henry's Law on lung volume and circulating oxygen levels across a dive to 100 m.

PHASES OF A DIVE

To demonstrate the integrated nature of breath-hold diving to depth in humans, the physiological responses are presented as they occur during a dive and upon resurfacing.

The First ~20 Meters

Even before the dive, while floating at the surface, physiological changes are already occurring due to the partial state of immersion – consisting of fluid shifts, regional blood flow redistribution, altered cardiopulmonary hemodynamics, and autonomic activity (reviewed in; Pendergast et al., 2015). During the final inspiration, many divers perform glossopharyngeal insufflation (also known as lung packing). Lung packing has been shown to increase lung volume by 11–26% (up to +3 L; Lindholm and Nyrén, 2005; Loring et al., 2007; Chung et al., 2010; Walterspacher et al., 2011; Mijacika et al., 2017; Patrician et al., 2021a); however, too much packing can increase the risk of lung barotrauma (Chung et al., 2010) or pre-dive syncope, as lung hyperinflation alters cardiac mechanics (decreases end-systolic and diastolic volumes), reduces cardiac output (Mijacika et al., 2017; Kjeld et al., 2021), and facilitates cerebral hypoperfusion (Van Lieshout et al., 2003).

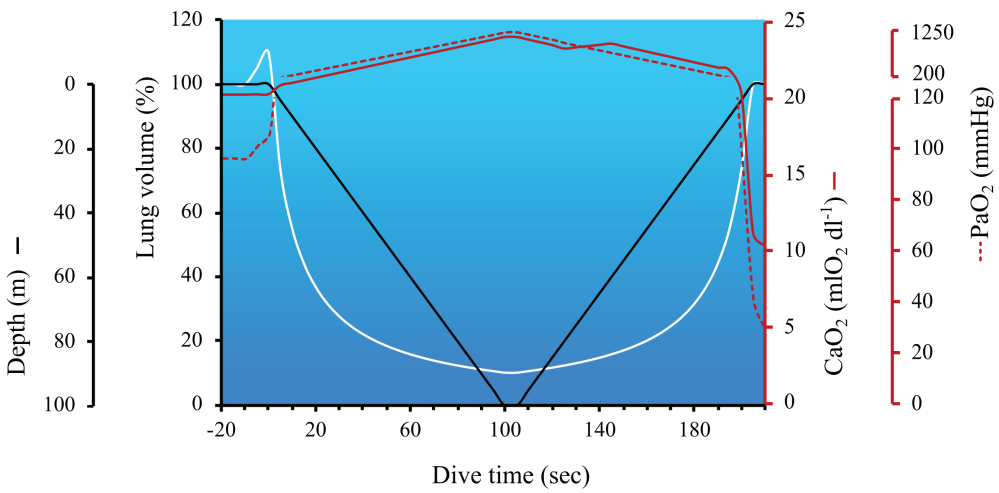

FIGURE 1 | The impact of hydrostatic pressure (also referred to as the absolute pressure in atmospheres; ATA) on lung volume and arterial hypoxia during a simulated dive to 100 m. The hyperbolic nature of lung volume across a dive is due to the nonlinear pressure-volume relationship (calculated in accordance with Boyle's Law). The temporary increase in lung volume immediately before the start of the dive coincides with lung packing, a maneuver employed by divers to increase the volume of oxygen in the lungs. In this example, with a total dive time of 205 s, the dive speed was set at 1 m/s, with a 5 s bottom time. The arterial oxygen content (CaO_2) and partial pressure of arterial oxygen (PaO_2) at the start of the dive were 20.3 mlO_2 dl^{-1} and 97 mmHg, respectively. Lung packing was performed prior to immersion, thereby increasing lung volume by 10% above TLC, and facilitating a 10 mmHg increase in PaO_2. CaO_2 was calculated to be the product of Hb × 1.36(SaO_2/100) + 0.003(PaO_2) – and consisted of the following considerations: (1) Hb was assumed to be 15 g dl^{-1}, until the early portion of ascent (i.e., ~2 min into dive), when a 5% increase in oxygenated Hb occurred in the circulation (i.e., +0.75 g dl^{-1}) *via* splenic contraction. As discussed in *the Ascent* section, splenic contraction is presumed to occur during the latter phase of the dive to coincide with the onset of exercise and growing hypercapnia; (2) SaO_2 was 98–100% until the last 15 s of the dive when PaO_2 dropped below 100 mmHg, and SaO_2 was estimated off a right-shifted O_2 dissociation curve (Hall et al., 2011); (3) the solubility of O_2 dl^{-1} of blood (i.e., 0.003) was assumed to remain constant and PaO_2 was calculated using the following steps – first the partial pressure of alveolar oxygen (P_AO_2) was calculated using a modified alveolar gas equation to account for hydrostatic pressure = $F_{ET}O_2$ (0.1444 during pre/post dive breathing and 0.16 during the dive due to lung packing) multiplied by the product of ATA × (760–47) – ($PaCO_2$/R). The partial pressure of arterial carbon dioxide ($PaCO_2$) pre-dive was 40 mmHg, and calculated to increase at a rate of 0.06875 mmHg sec^{-1} (derived from $PaCO_2$ data during a static apnea in an elite breath-hold diver; Willie et al., 2015 as reviewed in Bain et al., 2018b), resulting in an end-dive $PaCO_2$ of 54 mmHg. R was assumed to remain constant at 0.9. ATA increases by 1 every 10 m gain of depth (i.e., 1 ATA on the surface and 11 ATA at 100 m). Blood gases collected at 40 m in breath-hold divers support the notion of hydrostatic-induced hyperoxia – see section *Maximum Depth*; (Bosco et al., 2018). These data also align with predicted P_AO_2 across a simulated dive to 150 m (Ferretti, 2001). The metabolic uptake of oxygen during breath-holding was derived from data during static apneas (Willie et al., 2015; Bain et al., 2018b), and assumed to be steady across a dive, at a rate of 0.21205 mmHg sec^{-1}. This oxygen uptake was subtracted from P_AO_2. PaO_2 was assumed to mirror P_AO_2 until ascent, when an inefficiency of pulmonary gas exchange is expected to occur (Patrician et al., 2021b). In the latter portion of the dive, a widening of the a-A gradient was assumed to be 20 mmHg, which was based on measurements in divers diving beyond 100 m (Patrician et al., 2021a). PaO_2 within 5 s of surfacing was estimated to be 29.7 mmHg which, in trained breath-hold divers, is slightly above the theoretic limit of consciousness. However, most experienced divers are always conscious of the risk of shallow water blackout (see section: *The last 10 m*).

Mammalian Diving Response

To facilitate a reduction in oxygen consumption, the mammalian diving response initiates a vagally mediated increase in parasympathetic nerve activity that reduces heart rate (i.e., bradycardia; Olsen et al., 1962b; Craig, 1963) and sympathetically mediated vasoconstriction of peripheral vascular beds (i.e., transient reduction in blood flow to non-essential organs; Brick, 1966; Heistad et al., 1968). Both of these responses are augmented with facial immersion, especially with cool water (Hurwitz and Furedy, 1986; Schuitema and Holm, 1988; Schagatay and Holm, 1996). Even though there remains some ambiguity regarding quantifying the degree of bradycardia (i.e., when selecting the pre-dive baseline heart rate), heart rates have been reported to decrease to as low as 20–30 beats per minute (Ferrigno et al., 1997; Ferretti, 2001; Bain et al., 2018b), or even lower (Arnold, 1985).

Cardiac Dyssynchrony

An interesting, albeit less common phenomenon exhibited by divers is the presentation of cardiac arrhythmias (or dyssynchrony) during a dive. Such dyssynchrony has been demonstrated in both freely diving humans equipped with waterproof electrocardiographic (ECG) units (Olsen et al., 1962b; Scholander et al., 1962; Ferrigno et al., 1991; Hansel et al., 2009; Patrician et al., 2021a), including the Ama (Sasamoto, 1965; Hong and Rahn, 1967), and under experimental hyperbaric conditions (Ferrigno et al., 1997). The implications of such dyssynchrony are not clear, especially whether they infer a malignant or benign disposition. The mechanisms driving these dyssynchronous ECG signals are also not established, but likely reflect marked "autonomic conflict" between parasympathetically mediated bradycardia (i.e., diving response) and sympathetically driven tachycardia (i.e., cold shock and/or exercise response; Shattock and Tipton, 2012). Whether phenotypic predisposition is required or simply contributory in its genesis, the hydrostatically induced centralization of blood volume from the legs to thorax (Miyamoto et al., 2014), and concomitant mechanical release of hyperinflation-induced compression of the heart from lung packing (Mijacika et al., 2017) could alter baroreflex control (Chen et al., 2006) and chronotropic drive due to cardiac enlargement and activation of right atrial stretch receptors. Ultimately, further investigation and importantly the potential association with elevated myocardial infarction risk, has yet to be elucidated.

Passive Descent

Within the first 20 or so meters, the diver reaches a point of neutral buoyancy. In reality, however, the exact depth of neutral buoyancy depends on a variety of factors (e.g., body composition, neck/hip weights, wetsuit composition/thickness, surface lung volume, water density/salinity). At this depth, the weight of the water column exerted upon the diver equals the buoyancy of the diver – meaning the diver will not float or sink. Beyond this point, however, the hydrostatic force overcomes the buoyancy of the diver, and the diver becomes negatively buoyant and enters a state of continuous free-fall. At this stage (or earlier), peripheral vasoconstriction is likely maximized *via* elevations in sympathetic nervous system activity, which limits distribution of blood to non-essential organs (e.g., kidney and skeletal muscles; Fagius and Sundlöf, 1986; Heusser et al., 2009; Kyhl et al., 2016). This re-distribution has been well demonstrated in Weddell seals, where overwhelming vasoconstriction is evident in all organs, except in the brain (Zapol et al., 1979). In humans performing dry or facial immersion static apnea, the combined influence of (1) sympathetic excitation and chemoreflex engagement from combined inputs of hypoxia, hypercapnia, lack of ventilatory inhibition (Heusser et al., 2009; Steinback et al., 2010) and (2) peripheral vasoconstriction, likely drive the increases in mean arterial pressure; this has been measured to increase to 150 mmHg (Breskovic et al., 2011; Bain et al., 2015), and even reach 200 mmHg (during apnea at rest and with exercise; Bjertnaes et al., 1984; Ferrigno et al., 1997; Perini et al., 2010). However, blood pressure data during underwater diving are scarce. In an innovative study by Ferrigno et al. (1997), two participants with radial artery catheterization performed breath-holds in a hyperbaric chamber to simulate the hydrostatic load of a dive to 50 m. While there were substantial elevations in mean arterial pressure during descent (with occasional systolic peaks in one diver reaching 345 mmHg), mean arterial pressure appeared to slightly subside or even decrease during the latter portion of the dive (Ferrigno et al., 1997). These blood pressure responses in humans contrast to those in marine mammals, who demonstrate relatively stable blood pressure across a dive (Irving et al., 1942; Ponganis et al., 2006) due to an enhanced mammalian diving response (e.g., extreme bradycardia to 2–3 bpm; Williams et al., 2017; Goldbogen et al., 2019) and anatomical adaptations (e.g., hepatic sinus and venous vasculature; Harrison and Tomlinson, 1956; Ponganis, 2011).

Lung Compression

In accordance with Boyle's Law, and illustrated in **Figure 1**, lung volume decreases with increasing depth. Assuming the diver fully inspires at the surface, the hydrostatic-induced reduction in lung volume would reduce lung volume to approximately residual volume (RV) by 40–50 m. The RV-equivalent depth has certainly been theorized to represent a hurdle in deep diving, but since at least the 1960s, divers have successfully attained progressively deeper records (Fitz-Clarke, 2018). However, in studies of humans diving during both simulated and sea conditions, the RV-equivalent depth may still constitute a physiological threshold of lung injury risk (Lindholm and Lundgren, 2009; Patrician et al., 2021b). The risk of lung injury could be exaggerated when divers perform large thoracic movements at depth (e.g., an exaggerated swimming stroke), because the coincidingly elevated alveolar pressures proportionally dictate the degree of tissue strain (Hooke's Law). If severe enough, this tissue strain could overcome the structural capacity of lung tissue and contribute to capillary stress failure and pulmonary edema (see section: *Risk of lung squeeze*). However, even in the absence of overt barotrauma, divers diving to – or below – RV-equivalent depths, have been shown to present with transient impairments in pulmonary

gas efficiency and subtle alterations in lung compliance at ~2.5 h post-dive (Patrician et al., 2021b).

The mechanics and geometry of hydrostatically induced lung compression are complex and likely determined by a number of factors. First, the compositional organization of collagen, elastin, and other lung tissue constituents in the lungs can dictate the mechanical behavior of tension and compression (Andrikakou et al., 2016). Humans lack many of the thoracic and lung adaptations found in diving mammals, which are designed to manage lung compression/collapse and reopening (reviewed in; Ponganis et al., 2003; Castellini, 2012). Second, airway modeling of head-up descent in humans (e.g., when using an underwater sled) suggests that airway collapse occurs early in descent (with basal segments collapsing as early as 18 m), and collapse occurs in a heterogeneric pattern (Fitz-Clarke, 2007). Third, there is evidence that the active centralization of blood into the thorax – referred to as the "blood shift" – alleviates the reduction in gas volume, and therefore provides some protection for the lungs against collapse. Using a non-invasive approach to estimate changes in regional blood volume (impedance plethysmograph), Schaefer and colleagues estimated that 850 ml of had translocated into the thorax in a diver diving to 40 m (Schaefer et al., 1968). Likewise, a 1.4–1.7 L increase in thoracoabdominal volume has also been reported in three divers performing simulated dives to 45–55 m (*via* wet hyperbaric chamber; Ferrigno and Lundgren, 2003). Given that head-out immersion induces translocation of blood to the thorax, such thoracic centralization during diving is not an unreasonable notion (reviewed in; Pendergast et al., 2015), and has long since been postulated to contribute to divers being capable of diving beyond RV, without ill-consequence (Craig, 1968).

Despite the numerous dangers of extreme diving, a recent report of two world-champion breath-hold divers, diving to 102 and 117 m, highlight the incredible tolerability of highly adapted individuals to extreme levels of hydrostatic-induced lung compression (Patrician et al., 2021a). These observations are consistent with the accomplishments of many highly trained divers who have performed dives to extreme depths (100–214 m), despite profound reductions in lung volumes [between 9 and 4.5% of surface volume (calculated in accordance with Boyle's Law), with modeling suggesting 55–85% of total airway collapse, respectively Fitz-Clarke (2007)].

Maximum Depth

Upon reaching maximum depth, the elevated hydrostatic pressure facilitates a peak in the partial pressure of arterial oxygen (PaO_2), due to the hyperbaric-induced increase in gas partial pressure and solubility (illustrated in **Figure 1**). In a recent study conducted at the "Y-40 THE DEEP JOY" pool in Italy, arterial blood gases were evaluated at a depth of 40 m in six breath-hold divers (Bosco et al., 2018). In four of the six divers, PaO_2 increased from 94 ± 6 mmHg on the surface to 263 ± 32 mmHg at 40 m. Intriguingly, two of the divers did not demonstrate the expected hyperoxia at depth (PaO_2 at 40 m was 68 ± 10 mmHg). The authors postulated that ventilation perfusion mismatching and right-left intrapulmonary shunt, due to atelectasis (i.e., airway closure) gave rise to these divergent findings in these two divers.

Nitrogen Narcosis

Depending on bottom depth and time at depth, the partial pressure of alveolar nitrogen (P_AN_2) will be inordinately elevated, and facilitate diffusion of nitrogen into the blood. Early work in diving mammals (Kooyman et al., 1972) and humans (Radermacher et al., 1992) have demonstrated that the nitrogen tension in the blood rises during breath-hold diving. Even in the normal upright lung, nitrogen uptake has been demonstrated to occur during rest (Canfield and Rahn, 1957; West, 1962). In fact, nitrogen narcosis is not an uncommon feature in breath-hold dives exceeding ~70–90 m, with transient amnesia being a prevalent symptom. In a recent report by Patrician et al. (2021a), two divers spent 26 and 42 s, respectively, beyond 90 m – with maximum depths of 102 and 117 m. As P_AN_2 (and therefore PaN_2) increases with depth, the total time exposed at these extreme depths evidently appears to play a crucial role in both divers reporting narcosis. However, despite its prevalence being higher than reported (potentially due to amnesia; Ferrigno and Lundgren, 2003), there are only a few published examples in the literature (Lindholm and Lundgren, 2009; Fitz-Clarke, 2018; Patrician et al., 2021a). Ultimately, the impact and physiological influence of nitrogen narcosis, and contributory role in pathogenesis of decompression sickness in breath-hold divers has not been thoroughly studied, and its awareness is important to reduce the risk for adverse incidents.

Ascent

To ascend, the diver must propel themselves toward the surface and overcome the negative buoyancy and exaggerated drag. With peripheral vasoconstriction already established, muscular contraction will likely rely heavily on anaerobic sources, and lead to an increase in lactate production. While early reports suggested that blood lactate only mildly increased following apneic exercise [i.e. foot-pedalling during apneas of 104 s in a hyperbaric chamber; Olsen et al., 1962a)], more recent assessments in divers performing horizontal underwater swimming (to 173 ± 25 m and 135 ± 23 m, either with and without using fins, respectively) have reported blood lactate concentrations of 10 ± 2mmol L^{-1} within 2–4 min of surfacing (Schagatay, 2010). Interestingly, from a comparative perspective, Weddell seals do not demonstrate a rise in lactate concentration until dives exceed 20 min (Kooyman et al., 1980); and lactate concentrations only reach comparable human values once dives exceed +40 min (Kooyman and Ponganis, 1998).

Depending on the dive duration, divers can experience involuntary breathing movements (IBMs). These IBMs are essentially diaphragmatic contractions, which signify the "physiologic break-point" and ensuing struggle phase (Schagatay, 2009; Bain et al., 2018b). The intensity of IBMs dramatically increase, coinciding with an amplifying drive to breathe, progressive hypoxemia, hypercapnia, and hypertension.

Interestingly, IBMs have been shown to help transiently alleviate the restrictions on cardiac output, especially at higher lung volumes (Palada et al., 2008) and improve cerebral oxygenation (Dujic et al., 2009). However, as lung compression alleviates with ascent, the onset of IBMs may conversely introduce exaggerated intrathoracic and transpulmonary pressure fluctuations. If such abrupt fluctuations in thoracic pressure were to occur below a diver's RV-equivalent depth, and/or coincided with instances of abrupt alveolar reopening (postulated to occur during ascent), the associated tissue strain (in accordance with Hooke's Law) could lead to pulmonary barotrauma/lung squeeze. In fact, hemoptysis following a dive, has been attributed to IBMs (Kiyan et al., 2001). The notion of abrupt alveolar reopenening is derived from modeling work by Fitz-Clarke (2007). This work suggests, that during ascent, disproportionate coordination between transpulmonary pressure and regional airway surface tension can arise in alveolar units that have collapsed. When the airway surface tension of a collapsed segment is eventually overcome, the widened transpulmonary pressure gradient leads to an abrupt compensatory airway equalization [referred to as airway/alveolar "popping"; Fitz-Clarke (2007)]. Ultimately, the physiological implication(s) of IBMs or alveolar "popping" on pulmonary barotrauma has yet to be elucidated.

Spleen Contraction

The spleen has for centuries been considered to act as a dynamic reservoir, capable of expelling blood into the circulation, with a hematocrit concentration higher than arterial blood (Barcroft and Poole, 1927) – intrasplenic hematocrit estimates of 64–78% in mice, 75% cats and 90% in dogs (Opdyke and Apostolico, 1966). In humans, a 18–35% decrease in spleen volume has led to an increase in hematocrit by 2–6% during breath-holding (Schagatay et al., 2001; Stewart and McKenzie, 2002; Baković et al., 2003; Schagatay et al., 2012). Interestingly, the Ama (an indigenous diving population) have demonstrated an increase in hematocrit by 10.5% following 1 h of repetitive diving to 5–7 m (Hurford et al., 1990). Certainly, such a splenic contraction may coincide with peripheral vasoconstriction and sympathetic activation during descent, as splenic contraction has been demonstrated to occur rapidly (within 3 s of apnea onset; Palada et al., 2007). However, the combined aspects of exertion and hypercapnia (Richardson et al., 2012), or developing hypoxemia during the last part of ascent, splenic contraction would certainly be timely during this phase of the dive. Ultimately, irrespective of when splenic contraction occurs during a dive, based on the calculations in **Figure 1**, the hemoconcentration *via* splenic contraction would increase CaO_2 (assuming all else remains equal) by ~5%, which may proffer a protective benefit immediately upon surfacing, to avoid hypoxic loss of consciousness.

The Last 10 Meters

The risk of shallow water blackout and hypoxic syncope is notoriously high within the last 10 m of ascent. Modeling conducted by Ferretti (2001) has estimated P_AO_2 of a diver returning from a dive at 150 m, to be as low as 25 mmHg, which lies close to the theoretic limit of consciousness – postulated to be when PaO_2 falls below 20 mmHg (Ernsting, 1963). This modeling aligns with **Figure 1** (where PaO_2 upon surfacing from a 100 m dive was estimated to be 29.7 mmHg), and is supported by static studies in trained breath-hold divers. For example, Lindholm and Lundgren (2006) showed that post-apnea $P_{ET}O_2$ values of 20.3 mmHg (range: 19.6–21.0 mmHg) coincided with loss of motor control, whereas $P_{ET}O_2$ values of only ~3 mmHg higher (mean 23.0 mmHg; range 22.4–23.6 mmHg) did not (Lindholm and Lundgren, 2006). Additionally, in elite apneists under "dry" laboratory conditions, a series of studies utilizing radial artery (Willie et al., 2015) and jugular venous catheterizations (Bain et al., 2016, 2017, 2018a) have demonstrated end-apnea PO_2's of 29.6 ± 6.6 mmHg and 25 ± 6 mmHg, respectively (including an extreme end-apnea PaO_2 of 23 mmHg following a 435 s breath-hold; Bailey et al., 2017), without syncope. Comparatively, PaO_2 in freely diving elephant seals has been measured as low as 12 mmHg (corresponding to an SaO_2 of only 8%) just prior to surfacing (Meir et al., 2009).

During severe hypoxemia, there is a reduction in oxidative metabolism of the brain (Bain et al., 2017), which complement the gradual rise in cerebral blood flow that occurs across an apnea, serving to sustain cerebral oxygen demands (Willie et al., 2015) – and ultimately prolong consciousness. It appears that diving (versus terrestrial) mammals have distinct neural adaptations (i.e., a different distribution of neuroglobins that are found in higher concentrations in glial cells/astrocytes than in neurons) which predispose tolerance to hypoxia and resistance to reactive oxygen species (Folkow et al., 2008; Mitz et al., 2009), and also have been found to have an enhanced tolerance to lactate and changes to exogenous substrate availability (Czech-Damal et al., 2014). For example, in early studies with restrained Weddell seals performing maximal effort apneas, surrogate indexes cerebral metabolism (i.e., abnormal electroencephalogram slow waves) suggest impairments only occur when arterial and cerebral venous PO_2 drop to 10 mmHg and 2.6 mmHg (Elsner et al., 1970; Kerem and Elsner, 1973).

Surface Protocol

If this was a competitive dive, the dive would only be considered successful by judges [from either the Association Internationale pour le Développement de l'Apnée (AIDA) or the World Confederation of Underwater Activities (CMAS)], if the diver demonstrated control upon surfacing. For example, AIDA requires divers to remove their facial equipment (i.e., goggles and nose clip), perform an "OK" hand-signal and verbally state "*I am OK*," in that order, all the while continuously maintaining airways above the water. Given risk of syncope (see section: *Last 10 m*), divers employ techniques upon surfacing to enhance cerebral perfusion (Fernández et al., 2019). However, we cannot stress with enough strength, or more strongly recommend against extreme diving, given the profound risk of drowning. Even though competitions employ vast safety protocols (including safety divers, winch and video/sonar systems)

to ensure diver safety, recreational incidents are unfortunately on the rise – with 52 fatalities in 2017 and the most injuries since 2004 (DeWitt et al., 2019).

Risk of Lung Squeeze

With a delicate pulmonary capillary interface (West et al., 1991), it is perhaps not surprising that lung injury can occur, due to the cumulative forces of hydrostatic-induced compression and decompression of both the lungs and thoracic cage, centralization of blood volume, hypertension, exertion, and hypercapnic hypoxia. Such an injury, commonly referred to as lung squeeze, is a form of pulmonary barotrauma that has been extensively reviewed (Ferrigno and Lundgren, 2003; Lindholm and Lundgren, 2009; Dujic and Breskovic, 2012; Mijacika and Dujic, 2016; Moon et al., 2016; Kumar and Thompson, 2019; Schipke et al., 2019). Lung squeeze manifests shortly after surfacing and is characterized by pulmonary edema and hemoptysis (Boussuges et al., 1999; Lindholm et al., 2008; Patrician et al., 2021a), and is often associated with productive cough, dyspnea, and chest tightness (Cialoni et al., 2012); decrements in lung function and reduced oxygen saturation (Linér and Johan, 2008); and an impairment in pulmonary gas efficiency (Patrician et al., 2021a). Certainly, any injury to the delicate pulmonary capillary interface is serious and requires the appropriate medical attention. But due to the elevated risk of drowning and/or meager accessibility to medical aid, it is potentially shortly upon surfacing when the consequences of barotrauma can be the most consequential, or even fatal (Vestin, 2015). The exact phase of a dive when the integrity of the pulmonary capillaries become compromised – and exact mechanisms involved – has been explored since the late 1950's (Carey et al., 1956; Craig, 1968; Ferretti, 2001; Fitz-Clarke, 2007; Lindholm and Lundgren, 2009; Ferretti et al., 2012). Yet, it is still not clear whether lung squeeze can be attributed to the compression and alveolar collapse during descent, the cumulative strain and capillary stress failure under compression, or the de-compression and alveolar reopening during ascent.

An important future direction that remains to be addressed in breath-hold divers, is the development of appropriate recovery strategies for breath-hold divers who suffer from a single bout or repetitive incidents of pulmonary barotrauma or lung squeeze. Abstinence from diving and rest is certainly a necessity, as the risk of swimming-induced pulmonary edema reoccurrence has been reported to be as high as 75% (reviewed in; Grünig et al., 2017). However, the nature and duration of such rest is unclear. The only available literature on future barotrauma risk is limited to SCUBA (self-contained underwater breathing apparatus) divers, and the findings are inconclusive (Calder, 1985; Russi, 1998).

Risk of Decompression Sickness

Decompression sickness (DCS) or "Taravana" can occur in breath-hold divers, especially those diving repetitively (e.g., spearfishing, safety divers, and/or use of underwater scooters) and those performing extreme depths (reviewed in; Cross, 1965; Paulev, 1965; Rahn and Yokoyama, 1965; Schipke et al., 2006; Fitz-Clarke, 2009; Lemaitre et al., 2009; Moon and Gray, 2010; Dujic and Breskovic, 2012). The pathology of DCS, including its manifestation and risk factors have been extensively reviewed elsewhere (Brubakk and Neuman, 2003); however, in breath-hold divers, symptoms can range from dizziness, nausea, thoracic/skin/joint pain, hemiplegia, paresis, dysarthria, vertigo, and unconsciousness, with short- to long-term prognoses (Cross, 1965; Schipke et al., 2006; Cortegiani et al., 2013; Tetzlaff et al., 2017). The consequences of DCS are related to the affinity of certain tissues and the rate at which they uptake nitrogen. For example, the brain, heart, and viscera saturate within a couple of minutes, whereas in fat tissues, nitrogen continuously rises (Schipke et al., 2006). Likewise, upon ascent, the half-life of nitrogen is less in neural tissues, followed by skin and muscle, and then joints, ligaments, and bones (Rusoke-Dierich, 2018). Even though the rapid uptake of nitrogen occurring in neural tissue and blood may only manifest as narcosis, the rate of nitrogen clearance is a serious concern for divers, since ascent cannot be feasibly or safely slowed. It is perhaps not surprising that intravascular bubbles have been reported following spearfishing, where short surface times and the repetitive dives occur with often insufficient times to allow nitrogen clearance (Cialoni et al., 2016). Although this observation is not a universal finding (Boussuges et al., 1997; Gargne et al., 2012), arterial gas embolism following breath-hold diving has been implicated in stroke risk (Tetzlaff et al., 2017). Ultimately, modeling has suggested that the risk of decompression sickness up to 100 meters is quite low, but increases non-linearly to 5–7% at 230 m, where total lung collapse is anticipated to occur (Fitz-Clarke, 2009). This aligns with reports of nitrogen narcosis in elite divers diving beyond 100 m (Patrician et al., 2021a).

ARE THERE LONG-TERM MEDICAL CONSEQUENCES TO EXTREME BREATH-HOLD DIVING?

There are indigenous diving populations, such as the Ama in Japan, the Haeyeno in Korea (Teruoka, 1932; Rahn and Yokoyama, 1965; Hong and Rahn, 1967; Vaneechoutte et al., 2011), and the Bajau in Indonesia (Abrahamsson and Schagatay, 2014; Ilardo et al., 2018) who still practice breath-hold diving as their primarily means of harvesting food. Early reports from the Ama seemed to limit occupational aliments to the ear, nose, and throat (e.g., hearing loss, stenosis of Eustachian tube, sinusitis; Harashima and Iwasaki, 1965). Oh and colleagues provide recent evidence to indicate an elevated prevalence of chronic kidney disease in Korean Haenyeo, based on a large cohort of Korean Haenyeo subsistence divers (n = 715) and controls (n = 715; matched for a variety of covariates, such as age, hypertension, cardiovascular disease, and circulatory parameters; Oh et al., 2017). However, the nature of this sustenance diving starkly contrasts the profound degrees of

hypoxemia, hyperoxia, and hypercapnia regularly experienced by modern competitive free-divers and spear-fishers who push their physiological limits. Therefore, whether chronic/lifelong extreme diving with profound exposures incurs any long-term consequences is an important future research topic.

Brain Biomarkers and Cognitive Function

It is perhaps not entirely surprising that increases in blood-brain barrier and astrocyte damage markers (i.e., S100β) have been shown immediately following maximal static apneas (Andersson et al., 2009), which can persist for >1 day following a blackout (Linér and Andersson, 2009). An elevated oxidative state following sustained diving (Theunissen et al., 2013) increased cortisol, copeptin, brain natriuretic peptide, and ischemia-modified albumin (Marlinge et al., 2019). However, in another study, there was an increase in another brain neuronal damage marker (i.e., neuron-specific enolase), yet without changes in other related brain and cardiac markers (Kjeld et al., 2015). At least with static apneas without blackout, the rise in some brain damage markers that suggest potential disruption of the blood-brain barrier seem to occur in the absence of neuronal-parenchymal damage (Bain et al., 2018a). However, with supramaximal performances during static and dynamic disciplines – which have moderate incidences of blackout – the risk is likely higher. With regards to cognitive function, however, the findings are mixed – with some reports suggesting normative scoring on neuropsychological tests (Ridgway and McFarland, 2006) and others showing slight decrements which were correlated with maximum static apnea duration (Billaut et al., 2018). More cross-sectional and longitudinal research is required on this topic.

Lung Function

Another relevant question related to the long-term consequences of apnea diving pertains to the lungs, and in particular, the small airways. To enhance deep diving performance, divers regularly perform (1) passive thoracic stretches (e.g., static movements to elicit varying degrees of torsion and tension within the thorax, at elevated and minimal lung volumes) and (2) active lung stretches (*via* inspiratory and expiratory glossopharyngeal breathing, to alter lung volume >TLC and <RV respectively; Lindholm et al., 2009). These techniques aim to increase TLC and improve tolerance to hydrostatic-induced lung compression (i.e., to depths beyond RV-equivalent depth). However, any increase in lung compliance could come at the cost of exaggerated elastance and a premature closing pressure. Therefore, it is logical to hypothesize that the lungs of elite divers could become pendulous over time. Unfortunately, there is a scarcity of longitudinal data on lung function in breath-hold divers. However, some unique data exist in four male trained divers who were longitudinally tracked over 3 years (personal best depths ranging between 32 and 64 m; Walterspacher et al., 2011), and one well-trained male diver over 8 years (personal best depth of 88 m; Seccombe et al., 2013). Although it was concluded that there was not clear evidence of any long-term deleterious effects of diving or training on the lungs, elevations in TLC coincided with reductions in FEV_1/VC; however, these data should be confirmed in a lager sample size incorporating more sophisticated measures of pulmonary function. Cross-sectional reports indicate that the FEV_1/FVC ratio, at least in mostly recreational diving cohorts, does not appear markedly different from matched controls (0.79 for both groups; Ferretti et al., 2012), or is even improved (0.94 in elite divers vs. 0.84 in controls; Lemaître et al., 2010). However, mean FEV_1/FVC ratios of (1) 0.75 was demonstrated in competitive divers with a history of performing lung packing (Tetzlaff et al., 2008), (2) 0.74 was demonstrated in actively training and competing divers (Walterspacher et al., 2011), and (3) 0.76 was demonstrated in recreational to elite trained divers (Patrician et al., 2021b), where the highest trained divers (n = 8) had a mean FEV_1/FVC ratio of 0.71; and (4) 0.67–0.69 was demonstrated in the longitudinally tracked diver, after 5–8 years of diving/training (Seccombe et al., 2013). Certainly, FEV_1/FVC provides limited insight into lung function and most of these data do not conform to the classical criteria for obstructive impairment (i.e., <0.70%). Therefore, additional metrics need to be evaluated, especially given the difficulty in evaluating pre-clinical small airway disease. In the longitudinal study by Walterspacher et al. (2011), mean static and dynamic lung compliance was unaltered after the 3-year study, however the cohort was divided, with equal proportions of divers demonstrating an increase or decrease in compliance. In a more recent study by Patrician et al. (2021b) surrogate measurements of lung compliance (i.e., airway resistance and reactance *via* forced oscillation technique) appears mildly altered within 170 min post-dive, but were not outside the normative ranges at either baseline or post-dive. Ultimately, large scale longitudinal studies (with bronchodilator reversibility tests) are essential to support or refute the notion that diving – or the aggressive training strategies typically employed by divers to aid performance (e.g., inspiratory and expiratory glossopharyngeal breathing) – might incur any risk of pulmonary function decline.

CONCLUSION

Ever since the early diving studies in the Japanese Ama (Teruoka, 1932), our scientific exploration of human breath-holding capacity has advanced our understanding of human physiology and adaptation. In this review, we have discussed the physiological responses that occur across the phases of a dive, and highlighted the challenges driven by hyperbaria. Future longitudinal and cross-sectional studies are needed to fully elucidate the potential clinical consequences of apnea and diving.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the work. AP drafted the manuscript. All authors revised the manuscript critically for intellectual content, approved the final version, and agreed to be accountable for all aspects of the work.

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frontiers in Physiology

MINI REVIEW
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Central Hypovolemia Detection During Environmental Stress—A Role for Artificial Intelligence?

Björn J. P. van der Ster[1,2,3], *Yu-Sok Kim*[3,4], *Berend E. Westerhof*[3,5] *and Johannes J. van Lieshout*[1,3,6]*

[1] Department of Internal Medicine, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2] Department of Anesthesiology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands, [3] Laboratory for Clinical Cardiovascular Physiology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4] Department of Internal Medicine, Medisch Centrum Leeuwarden, Leeuwarden, Netherlands, [5] Department of Pulmonary Medicine, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam Cardiovascular Sciences, Amsterdam, Netherlands, [6] Medical Research Council Versus Arthritis Centre for Musculoskeletal Ageing Research, Division of Physiology, Pharmacology and Neuroscience, School of Life Sciences, The Medical School, University of Nottingham Medical School, Queen's Medical Centre, Nottingham, United Kingdom

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***Correspondence:**
Johannes J. van Lieshout
j.j.vanlieshout@amsterdamumc.nl
orcid.org/0000-0002-3646-212

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The first step to exercise is preceded by the required assumption of the upright body position, which itself involves physical activity. The gravitational displacement of blood from the chest to the lower parts of the body elicits a fall in central blood volume (CBV), which corresponds to the fraction of thoracic blood volume directly available to the left ventricle. The reduction in CBV and stroke volume (SV) in response to postural stress, post-exercise, or to blood loss results in reduced left ventricular filling, which may manifest as orthostatic intolerance. When termination of exercise removes the leg muscle pump function, CBV is no longer maintained. The resulting imbalance between a reduced cardiac output (CO) and a still enhanced peripheral vascular conductance may provoke post-exercise hypotension (PEH). Instruments that quantify CBV are not readily available and to express which magnitude of the CBV in a healthy subject should remains difficult. In the physiological laboratory, the CBV can be modified by making use of postural stressors, such as lower body "negative" or sub-atmospheric pressure (LBNP) or passive head-up tilt (HUT), while quantifying relevant biomedical parameters of blood flow and oxygenation. Several approaches, such as wearable sensors and advanced machine-learning techniques, have been followed in an attempt to improve methodologies for better prediction of outcomes and to guide treatment in civil patients and on the battlefield. In the recent decade, efforts have been made to develop algorithms and apply artificial intelligence (AI) in the field of hemodynamic monitoring. Advances in quantifying and monitoring CBV during environmental stress from exercise to hemorrhage and understanding the analogy between postural stress and central hypovolemia during anesthesia offer great relevance for healthy subjects and clinical populations.

Keywords: anesthesia, artificial intelligence, cardiovascular modeling, exercise, head-up tilt, hypovolemia, lower body negative pressure, POTS

INTRODUCTION

In 2021, six National Guard soldiers in officer training were hospitalized after suffering dehydration during a six-mile "ruck march" with 35-pound backpacks at a military training school in Connecticut (Koenig, 2021). In 2002, the Washington Times reported the death of a young woman after participating in the Marine Corps Marathon (Nearman, 2002). Her death was attributed to severe hyponatremia following excessive hypotonic fluid intake. Thirteen percent out of 488 runners participating in the 2002 Boston Marathon were presented with hyponatremia (serum sodium concentration <135 mmol/l); 0.6% had severe hyponatremia (<120 mmol/l). More than 70% of 716 (38% female) runners reported water loading prior to the marathon (Almond et al., 2005). The runners attempted to maintain their central blood volume (CBV) at the cost of water intoxication just trying to prevent what in Band of Brothers First Lieutenant Harry F. Welsh of 101st Airborne Division warned Pvt. Albert Blithe for: "dehydration's a soldier's worst enemy" (Ambrose, 2001). The CBV is defined as the fraction of thoracic blood volume directly available to the left ventricle. It declines in response to the assumption of the upright position, either passive head-up tilt (HUT) or active standing up with a gravitational displacement of blood away from the thorax to the lower part of the body with a fall in venous return (Van Lieshout and Secher, 1999). Capillary transmural pressure increases in the dependent parts of the body with a non-linear accumulation of blood volume in the small vessels of the leg resulting in continued filtration into the tissue spaces and a further fall in circulating volume (Smith and Ebert, 1990; Truijen et al., 2012). The hydrostatic load of 5 min of quiet standing induces a transcapillary loss of plasma volume of ∼400 ml (Lundvall and Bjerkhoel, 1994). The CBV may also become reduced in response to heat stress related to heavy physical exercise or to blood loss with the development of orthostatic intolerance (Wilson et al., 2006; Crandall et al., 2008, 2019; Gonzalez-Alonso et al., 2008; Lucas et al., 2013). Hemorrhage as a leading cause of death both in the military and civilian trauma casualty settings leads to a reduction in cerebral blood flow (CBF) and aggravates postural intolerance (Convertino et al., 2007, 2008, 2011; Crandall et al., 2019). Instruments to quantify CBV are not readily available, leaving decisions on fluid management based on the traditional parameters of blood pressure (BP) and heart rate (HR) (Jacobsen et al., 1986; Vincent and De Backer, 2013; van der Ster, 2019). Although these parameters are considered prime indicators of shock, they regularly do not reflect the loss of blood or fluid until syncope is imminent (Barcroft et al., 1944; McMichael, 1944; Secher et al., 1992; Bishop et al., 1993; Wo et al., 1993; Dabrowski et al., 2000; Harms et al., 2003). There is hardly a relationship between BP and oxygen delivery (Bartels et al., 2016) whereas tissues are in need of arterial blood flow rather than arterial pressure (Jarisch, 1928; Nichols and O'Rourke, 2005). In this mini-review, a perspective on central hypovolemia in humans is presented in relation to postural stress, exercise, and during anesthesia with a focus on early detection of central hypovolemia in the physiology lab and in the operating theater.

Abbreviations: AI, artificial intelligence; BP, blood pressure; CBV, central blood volume; CO, cardiac output; CO_2, carbon dioxide; CBF, cerebral blood flow; CVP, central venous pressure; DLCO, pulmonary diffusion capacity for carbon monoxide; EKG, electrocardiogram; HPI, hypotension prediction index; HR, heart rate; HUT, passive head-up tilt; LBNP, lower body 'negative' (sub-atmospheric) pressure; PEH, post-exercise hypotension; POTS, postural orthostatic tachycardia syndrome; SV, left ventricular stroke volume; TI, thoracic electrical (bio-) impedance; VO_2, volume of oxygen consumption.

POSTURAL STRESS AND EXERCISE

Obviously, in humans, the first step to exercise is preceded by the required assumption of the upright body position (Henry et al., 1951; Gauer and Thron, 1965; Wieling and van Lieshout, 1993). The act of standing itself involves physical exercise manifested by an increase in muscle sympathetic neural activity, ventilation, oxygen consumption, and carbon dioxide production (Bjurstedt et al., 1962; Wieling et al., 1996; Van Lieshout et al., 2001; Immink et al., 2006). The abrupt gravitational displacement of blood from the chest to the lower parts of the body upon standing elicits a fall in CBV and cardiac output (CO) (McMichael and Sharpey-Schafer, 1944; Harms et al., 1999, 2003). In parallel with this gravitational shift of blood, the sensitivity of the cardiac baroreflex decreases linearly, usually within 1 min (Westerhof et al., 2006; Truijen et al., 2012; Secher and Van Lieshout, 2013). Standing up creates a heart-brain hydrostatic gradient resulting in a reduction of CBF and a fall in CO by posture or cardiac disease contributes to it (Scheinberg and Stead, 1949; Hellstrøm et al., 1994; Ide et al., 1998; Pott et al., 2000; Van Lieshout et al., 2003; Bronzwaer et al., 2017b; Junejo et al., 2019, 2020; Vlastra et al., 2020; Claassen et al., 2021). Together with the acute vasodilatation in the active leg muscles, this sequence of events initiates autonomic cardiovascular reflex activity with an increase in HR and peripheral vascular resistance until an early steady state has been reached after ∼2 min in the upright position with slightly reduced CO, elevated HR, and increased diastolic BP and with an impact on CBF and brain cortical oxygenation (Piorry, 1826; Hill, 1895; Sjöstrand, 1952; Gauer and Thron, 1965; Blomqvist and Stone, 1984; Bode, 1991; Levine et al., 1994; Wieling et al., 1996; Pott et al., 2000; Shoemaker et al., 2001; Van Lieshout et al., 2001; Harms et al., 2003, 2010, 2020; Immink et al., 2006). The effects of exercising in the upright vs. seated position on cardiac preload are exemplified by a lower HR during ergometer rowing than during treadmill running (Yoshiga and Higuchi, 2002). In a similar vein, the transition to the upright posture accompanying the majority of exercise modalities affects both the arterial supply to and the venous drainage from the brain (Van Lieshout et al., 2003; Dawson et al., 2004; Gisolf et al., 2004). The postural reduction in CBV and its magnitude during standing are relevant for exercise capacity since CBV determines CO and relates directly to work capacity and maximal oxygen uptake during exercise (Higginbotham et al., 1986; Van Lieshout and Secher, 1999; Dawson et al., 2007; Levine, 2008; Bada et al., 2012; Halliwill et al., 2013). The HR response to exercise not only relates to the active muscle mass but also to body position during exercise (Bevegård et al., 1960; Wang et al., 1960; Thadani and Parker, 1978; Kramer

et al., 1982). In subjects presenting with what is designated as postural orthostatic tachycardia syndrome (POTS), standing upright has become an endeavor. The change of posture results in an excessive HR increment >30 with orthostatic intolerance but without orthostatic hypotension and a high HR response to a given level of exercise with reduced exercise capacity (Low et al., 1995, 1999; Joyner, 2012). POTS (Schondorf and Low, 1993) [also known as orthostatic tachycardia syndrome (Jacob et al., 1997) or orthostatic intolerance (Shannon et al., 2000)] is characterized by symptoms, such as fatigue, light-headedness, or dizziness, that come up as soon as the subject—free of orthostatic hypotension or evidence of cardiac or metabolic disease—assumes the standing position. POTS is heterogeneous in presentation and mechanisms involved are hypovolemia, deconditioning, and hyperadrenergic state with a reduced stroke volume (SV) (Masuki et al., 2007a,b; Low et al., 2009). Often a distant flu-like syndrome followed by a period of inactivity precedes POTS (Joyner, 2012). In 1871, Jacob Mendes Da Costa published the "Irritable Heart" which is considered as "a form of cardiac malady common among soldiers" (Da Costa, 1871). This concept of irritable heart was based on his observations during the Civil War with inspection, pulse rate, pulse quality, ventilatory rate, and auscultation as the measurement techniques available (Jarcho, 1959). Thomas Lewis recognized that what then was called the "effort syndrome" was, in fact, common among civilians and that of soldiers who suffered from it no less than 57% had been recruited from sedentary or light occupations before enlisting in the First World War (Lewis, 1919; Wood, 1941). The expression 'postural tachycardia syndrome' has replaced previous labels, such as Da Costa syndrome, soldier's heart, anxiety, exhaustion neuroses, and neurocirculatory asthenia (Oppenheimer and Rothschild, 1918; Wooley, 1976; Howell, 1985). Although psychological symptoms are common in POTS they usually are not causal (Masuki et al., 2007a). Nevertheless, heart and circulatory neurasthenia and soldier's heart continue to be considered as post-traumatic stress disorder by some (Dyde, 2011; Borges et al., 2020). Signs and symptoms of POTS resemble extreme deconditioning as observed following prolonged bed rest or spaceflight (Vernikos and Convertino, 1994; Levine et al., 1997; Gisolf et al., 2005; Joyner and Masuki, 2008) and most subjects suffering from this condition benefit from exercise training (Harms and van Lieshout, 2001; Shibata et al., 2012).

POST-EXERCISE HYPOTENSION AND RECOVERY

In 1898, Leonard Hill made evident that after exertion BP falls to normal far more rapidly than the pulse frequency and recognized that BP becomes depressed below the normal resting BP after severe muscular work (Hill, 1898). As soon as the exercise halts the leg muscle pump no longer contributes to maintaining venous return and thus CBV (Romero et al., 2017). The elevated CO quickly returns to baseline but the vasodilatation in the previously exercised muscles is rather sustained. This results in a temporary imbalance between a reduced CO and a still enhanced peripheral vascular conductance with the development of PEH. The decline in SV during recovery in the seated but not in the supine position indicates that the contribution of CO to the maintenance of arterial pressure is smaller in the standing position (Halliwill et al., 2013). Systolic BP is lower during seated and supine recovery post-exercise at 50% and 75% of VO_{2peak} vs. resting BP (Forjaz et al., 2004; Farinatti et al., 2009), and the lower peripheral resistance in the supine compared with the seated recovery position suggests resetting of the arterial baroreflex (Raine et al., 2001; White and Raven, 2014). An increased transfer function gain between diastolic BP and middle cerebral artery diastolic CBF velocity suggests a less effective dynamic cerebrovascular autoregulation in response to rapid decreases in BP during the initial 10 min of recovery from dynamic exercise (Ogoh et al., 2007). In addition, post-exercise pulmonary diffusion capacity for carbon monoxide (DLCO) is reduced with both membrane diffusion capacity and the capillary blood volume affected (Rasmussen et al., 1986; Hanel et al., 1994). Approximately 50% of the post-exercise reduction of DLCO has been attributed to a reduction in the pulmonary blood volume (Hanel et al., 1997). This, together with the reduction in venous return by loss of the muscle pump, more important in the upright vs. supine position, may be held responsible for symptoms of post-exercise orthostatic dizziness that regularly progresses to full vasovagal syncope (Holtzhausen et al., 1994; Van Lieshout et al., 2003; Takahashi et al., 2005; Roberts, 2007). A single bout of aerobic exercise is already sufficient to produce PEH, and attempts have been made to predict (Halliwill et al., 2013; Lacewell et al., 2014) and combat it (van Lieshout et al., 1992; Krediet et al., 2002, 2006). Across pre-hypertensive subjects, BP exhibits a strong positive correlation between the fall after a single session of aerobic exercise and the reduction observed after 8 weeks of aerobic training (Brito et al., 2018). A major precipitating factor for the development of PEH is prolonged exercise in the heat, resulting in hyperthermia and dehydration with bodyweight loss, and a significant reduction in CO, muscle, and skin blood flow (Gonzalez-Alonso, 1998; Hayes et al., 2000; Wilson et al., 2006; Luttrell and Halliwill, 2015; Dalmau, 2019). A recent meta-analysis suggests a larger PEH in men compared to women with an inverse association between PEH and age but a competitive half-marathon triggered PEH and a reduced cardiac baroreflex in men but not in women, leaving the physiology involved hitherto rather ill-understood (Carpio-Rivera et al., 2016; Brito et al., 2018; Mourot et al., 2020). In orthostatically intolerant athletes, recovery from postural dizziness related to PEH in the upright body position is facilitated by physical countermeasures, such as leg tensing and bending and contracting lower body muscles that engage the skeletal muscle pump to augment venous return after exercise (van Lieshout et al., 1992; Van Lieshout et al., 2001; Krediet et al., 2002, 2006). In healthy subjects, the leg-tensing maneuver lowers systemic vascular resistance with an elevation in central venous pressure (CVP), SV, and CBF. A similar effect was observed by Ray who demonstrated that in the first minute of 1-legged exercise in the upright position, CVP increased and sympathetic nerve activity became reduced (Ray, 1993). External counter measures, such as application of an impedance threshold device generating negative intrathoracic pressure to enhance venous

return (Rickards et al., 2007; Convertino et al., 2012; Poh et al., 2014) or lower limb compression garments, though less practical, may reduce pre-syncopal signs and symptoms after exercise as well (Privett et al., 2010; Lacewell et al., 2014).

ESTIMATION OF CBV

To express which magnitude the CBV in a healthy subject should have and how to quantify it remains complex (Matzen et al., 1991; Brengelmann, 2019; Dalmau, 2019; Moller and Berger, 2019; Moller et al., 2019). In the supine position, healthy humans are normovolemic in that a maximal venous oxygen saturation (S_vO_2) is established (Harms et al., 2003; Truijen et al., 2010). From supine to upright, S_vO_2 decreases and with a blood loss of ∼100 ml by gravitational relocation S_vO_2 is reduced by 1% (Harms et al., 2003; Secher and Van Lieshout, 2005). Thoracic electrical (bio-) impedance (TI) and its reciprocal admittance offer a non-invasive index of CBV changes in humans and animals (Patterson et al., 1978; Ebert et al., 1986; Matzen et al., 1990; Perko et al., 1991; Cai et al., 2000; Ogoh et al., 2003; van Lieshout et al., 2005). In the anesthetized pig, a change in the magnitude of TI appears to be an accurate non-invasive monitor of a blood volume deficit (Krantz et al., 2000). Comparisons have been made between TI and scintigraphy with technetium-99m labeled autologous red blood cells (Crandall et al., 2008). S_vO_2 requires a central venous line, scintigraphy is not practical during surgery and impossible to apply with changing body position, whereas TI is non-invasive but sensitive for postural movement of the liver to be avoided by careful electrode placement. A definition of normovolemia has been proposed as the CBV that ensures optimal CO and oxygen delivery to meet metabolic demand from rest to exercise (Secher and Van Lieshout, 2005; van Lieshout et al., 2005). Evidently, this does not offer a range of reference values or cut-off points, and the next best approach is by modifying the CBV by making use of environmental stressors, while quantifying biomedical parameters for thoracic blood volume (TI), systemic (CO), regional (cerebral) blood flow, and oxygen delivery. Accordingly, expanding the CBV (Ogoh et al., 2005, 2006, 2015) or reducing it is widely applied to study the cardio- and cerebrovascular effects of simulated bleeding in healthy humans. Graded central hypovolemia is created by postural stress, either active standing, HUT or simulated orthostasis by lower body "negative" (sub-atmospheric) pressure (LBNP) with or without adding HUT to aggravate the simulated gravitational load (Stevens and Lamb, 1965; Matzen et al., 1991; Rea et al., 1991; El-Bedawi and Hainsworth, 1994; Krediet et al., 2002; Hinojosa-Laborde et al., 2011, 2014; Truijen et al., 2012; Kay and Rickards, 2015; Rosenberg et al., 2021). Qualitatively comparable to the assumption of the upright position, LBNP induces venous pooling and enhances extravasation within the leg interstitial space deliberately reducing plasma volume and CBV (Matzen et al., 1991; Hinghofer-Szalkay et al., 1992, 1996; Jørgensen et al., 1993; Truijen et al., 2012). The hemodynamic responses to graded blood loss vs. LBNP are similar with the exception that the reduction in CBF represented by transcranial Doppler CBF velocity is larger during HUT (**Figure 1**, upper panel). This is likely attributable to the more pronounced reduction in end-tidal CO_2 partial pressure and the gravitational effect on cerebral perfusion pressure with HUT (Johnson et al., 2014; Bronzwaer et al., 2017a).

MONITORING CBV IN PATIENTS

Arterial hypotension in the emergency department and during surgery promotes progressive mismatching of oxygen delivery and demand with cardiac morbidity, renal impairment, and mortality (Jones et al., 2006; Brienza et al., 2009; Wesselink et al., 2018; Wijnberge et al., 2021). There are divergent opinions on which level of BP is indicative of arterial hypotension. In fact, given a lack of a universal definition of intraoperative hypotension, the reported incidence varies substantially with the chosen threshold (Davies et al., 2020). It has been argued that such definition is an individual cut-off value and has not accurately been derived from population-based data. It is obvious that a universally accepted standard definition of hypotension would facilitate further research into this topic (Brady and Hogue, 2013; Brady et al., 2020; Etemadi and Hogue, 2020; Wijnberge et al., 2021). Traditional patient monitoring in the emergency ward and the operating room includes HR, BP, electrocardiogram, and peripheral oxygen saturation but their use as predictors for incipient central hypovolemia is rather limited. Baroreflex control of BP makes it insensitive to blood loss up to about one liter, rendering assessment of volume status by BP monitoring not possible (Harms et al., 2003; van der Ster et al., 2018b). With the progression of central hypovolemia, cardiac preload declines until the tipping point where it has become too low to maintain a sufficient CO and when the limits of vasomotor reserve available for vasoconstriction have been reached BP drops (Schondorf and Wieling, 2000; Fu et al., 2004; Schiller et al., 2017). During World War II, the observation was repeatedly made that air raid victims in London City suffering from major blood loss presented with relative bradycardia rather than the expected tachycardia (Grant and Reeve, 1941). HR does change only minimally in the early stages, and when finally becoming beyond the "normal" range, the hypovolemic shock has already developed (Secher and Van Lieshout, 2010; Schiller et al., 2017; Suresh et al., 2018). Because of these limitations, several approaches, such as wearable sensors and advanced machine-learning techniques, have been suggested in an attempt to promote more sensitive metrics for the prediction of outcomes in civil patients and on the battlefield (Secher and Van Lieshout, 2005, 2010, 2013, 2016; Rickards et al., 2007, 2008; Convertino et al., 2011, 2020a,b; Ryan et al., 2011; Nadler et al., 2014; Schlotman et al., 2019; Rashedi et al., 2021).

MACHINE-LEARNING BASED CENTRAL HYPOVOLEMIA DETECTION

In the last decade, efforts have been made to apply artificial intelligence (AI) and develop algorithms in the field of hemodynamic monitoring both in the operating room and on the battlefield (Convertino et al., 2008, 2011, 2020a; Rickards

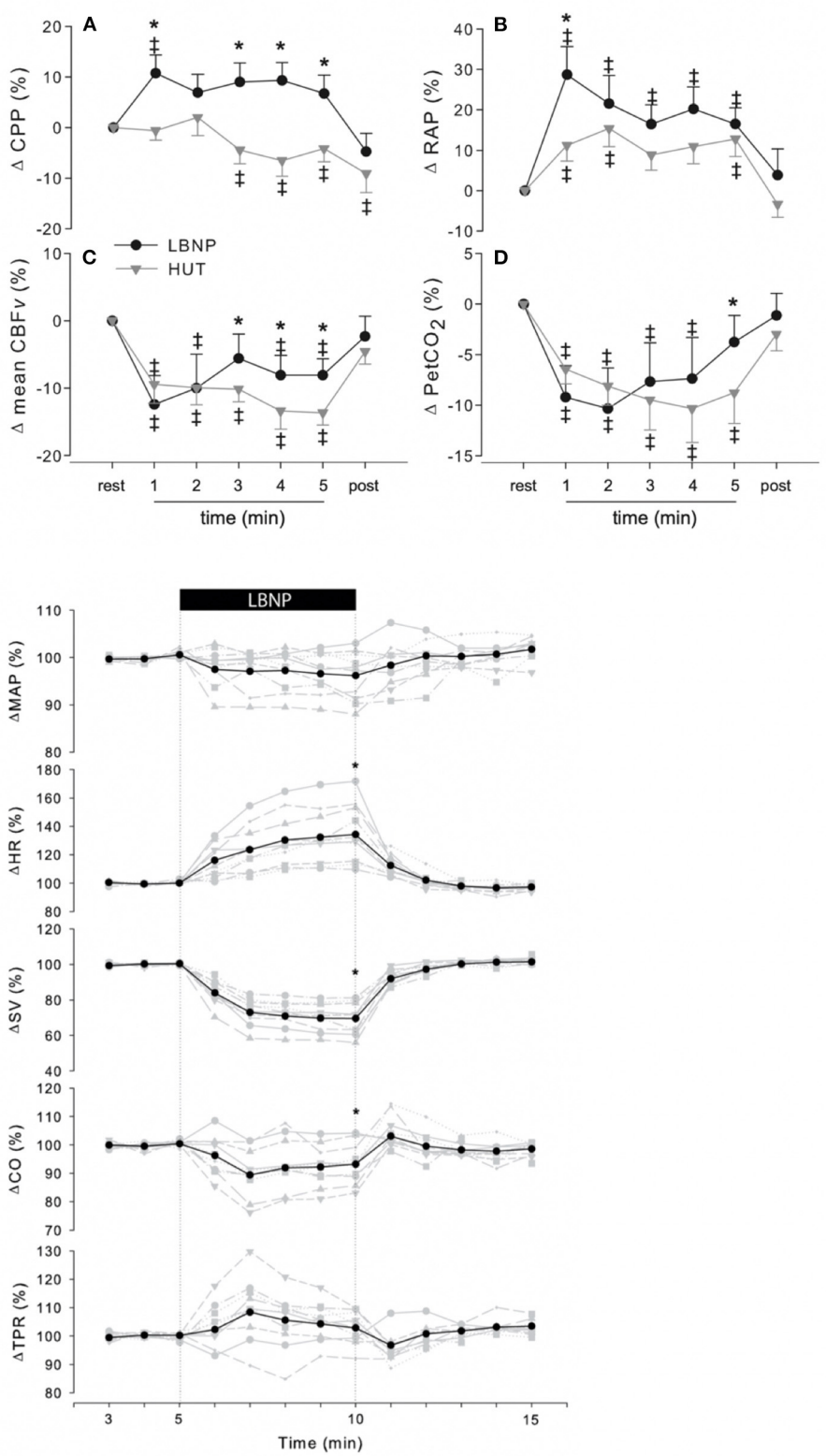

FIGURE 1 | (A–D) Change in cerebrovascular response to 5 min LBNP−50 mmHg−(black circles) or 70° passive HUT (gray triangles). CPP, cerebral perfusion pressure; RAP, resistance area product; CBFv, cerebral blood flow velocity; $PetCO_2$, end-tidal CO_2; LBNP, lower body "negative" or sub-atmospheric pressure.

(Continued)

FIGURE 1 | $p < 0.05$ vs. rest; $^{*}p < 0.05$ LBNP vs HUT; $^{\ddagger}p < 0.05$ vs. rest. Lower panel: In 10 healthy volunteers, a total of 60 LBNP−50 mmHg−trials were performed (3 trials per subject per measurement day). Individual (gray) and averaged (black) hemodynamic responses to LBNP. Data were normalized to the last 2 min of rest. MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; LBNP, LBNP, lower body "negative" or sub-atmospheric pressure. $^{*}p < 0.05$ last 2 min of LBNP vs. last 2 min of rest. From Bronzwaer et al. (2016) and Bronzwaer et al. (2017a).

et al., 2014; Hatib et al., 2018; Schenk et al., 2021; Wijnberge et al., 2021). Published data on machine-learning algorithms based on arterial pressure waveform analysis are expected to play a supportive role in distinguishing normal from reduced CBV and thus left ventricular preload in healthy subjects and patients with the purpose to predict and prevent the occurrence of arterial hypotension in the anesthetized patient (Hatib et al., 2018; Connor, 2019; van der Ster et al., 2020). The earliest work in medical AI dates to the early 1970s, when the field of AI was ∼15 years old. For the anesthesiologist, a monitoring system that assists in estimating the chance of developing intraoperative hypotension and predicting it would be of help (Watt et al., 1993; Mathis et al., 2018; Connor, 2019; van der Ven et al., 2020). Machine learning specifically for medicine is not new (Shortliffe, 1993; Patel et al., 2009; Convertino et al., 2011; Deo, 2015; Handelman et al., 2018), but the introduction of devices featuring models that have been trained using machine-learning algorithms has just started entering clinics. Randomized controlled trials in the field of AI-based applications of cardiovascular monitoring are as yet scarcely available (Angus, 2020; Kang et al., 2020) but progress is being made. As an example, the so-called hypotension prediction index (HPI), a machine-learning-based arterial hypotension predictive algorithm commercially available, has been proposed useful in the operating room environment (Maheshwari et al., 2020). It is based on arterial waveform features and has been claimed to predict intraoperative hypotension; the available evidence from recent clinical studies is summarized below (Davies et al., 2020; Maheshwari et al., 2020; Schneck et al., 2020; Wijnberge et al., 2020; Schenk et al., 2021). Maheshwari et al. reported a sensitivity of 88% (85–90%) and specificity of 87% (85–90%) to identify hypotensive episode 15 min in advance (area under the receiver operating characteristic curve 0.95). The fact that about 50% of the alerts were not followed by treatment was attributed to short warning time, complex treatment algorithm, or just clinicians ignoring the alert. HPI guidance did not reduce the incidence of hypotension <65 mmHg whereas that study did neither include episodes of hypotension caused by surgical manipulations (Etemadi and Hogue, 2020; Maheshwari et al., 2020). In an unblinded randomized clinical trial, patients were randomly assigned to receive either the HPI early warning system or standard care ($n = 34$ in each group), with a goal mean BP of at least 65 mmHg in both groups (Wijnberge et al., 2020). The median time-weighted average of hypotension was 0.10 mmHg [interquartile range (IQR), 0.01–0.43 mmHg)] in the intervention group vs. 0.44 mmHg (IQR, 0.23–0.72 mmHg) in the control group. The median time of hypotension per patient was 8 min (IQR, 1.3–26 min) in the intervention group vs. 33 min (IQR, 12–60 min) in the control group. In a 2-center retrospective analysis of 255 patients undergoing major surgery, the HPI predicted hypotension 5 min before a hypotensive event with a sensitivity and specificity of 85.8% (95% CI, 85.8–85.9%) and 85.8% (95% CI, 85.8–85.9%) (area under the curve, 0.926 [95% CI, 0.925–0.926]) (Davies et al., 2020). Intraoperative HPI-guided care did not reduce the time-weighted average of post-operative hypotension (Schenk et al., 2021). The warning for hypotension in these clinical studies generally appeared shorter than the 15 min previously reported in an offline validation study (Hatib et al., 2018). A reduction in CBV in the surgical patient is caused by insensible perspiration, hemorrhage, or by the accumulation of blood in the dependent parts of the body elicited or enhanced by regional anesthesia or surgery in sitting beach-chair position (Murphy et al., 2010; Larsen et al., 2014; Salazar et al., 2019). Accordingly, it represents a mimicry of the cardiovascular stress imposed by the assumption of the upright body position (Reithner et al., 1980; Secher and Van Lieshout, 2005; Hinojosa-Laborde et al., 2014; Larsen et al., 2014; Rickards et al., 2014; Schiller et al., 2017; Suresh et al., 2018). In a laboratory model of hemorrhage simulated by progressive central hypovolemia in healthy subjects by submitting them to either LBNP, HUT or both the global hypothesis tested was that AI-based methodologies may assist in monitoring and accordingly predict the progression from normo- to hypovolemia toward presyncope/cardiovascular collapse by extracting information of biomedical signals otherwise not routinely available. **Figure 2**, panel B, summarizes modeling of the non-invasive BP waveform (van der Ster et al., 2018b, 2020). During simulated hemorrhage in healthy subjects, volumetric parameters together with CBF velocity hemodynamics provided the most sensitive indication of the progression of central hypovolemia (**Figure 2**, panel C) (van der Ster et al., 2018a; van der Ster, 2019). One should realize that AI machine-learning algorithms do not entail a dynamic learning process evolving from use in clinical patient care (Schenk et al., 2021). In addition, the algorithm is unaware of the clinical situation and does neither provide any meaningful pathophysiological information. Inherently, there is no insight in the decisional process that leads to an early warning for intraoperative hypotension. Finally, it is up to clinicians to interpret and decide whether the predicted hypotensive episode can be ignored or requires intervention (Etemadi and Hogue, 2020). Another hurdle to overcome is to prove whether machine-learning-based prediction of hypotensive episodes actually does improve quality of care (Saugel et al., 2019; Etemadi and Hogue, 2020). In the laboratory model validation for larger reductions of CBV in humans is for obvious reasons not available. This constitutes a problem when realizing that in the second phase of impending shock when CBV has been reduced by about 30% a Bezold-Jarisch-like or vasovagal reflex may terminate sympathetic activity (Jarisch and Richter, 1939;

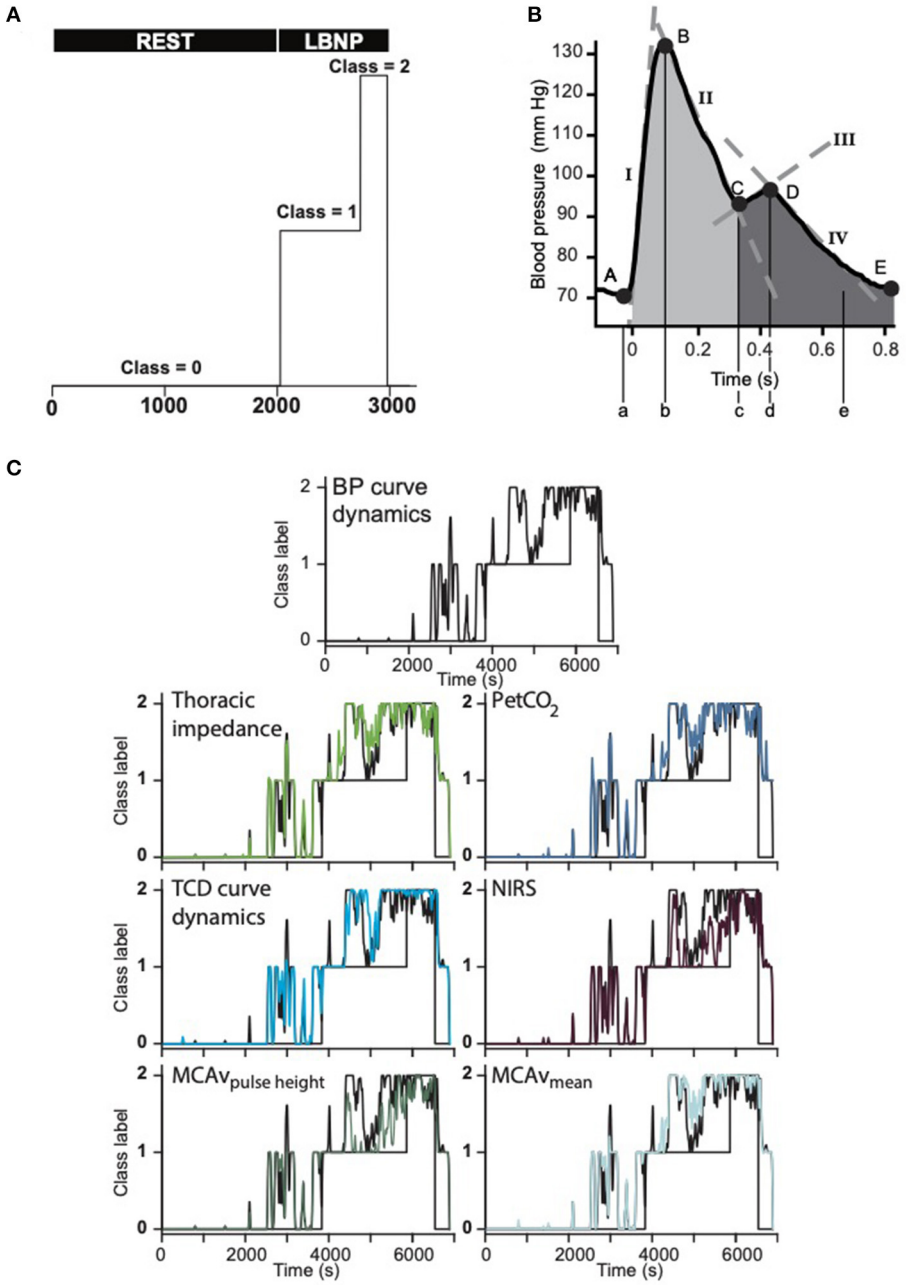

FIGURE 2 | (A) Class definitions: baseline rest—class 0. LBNP (50 mmHg) defined as class 1, of which the last 25% as end-stage LBNP before pre-syncope (class 2). LBNP, lower body "negative" or sub-atmospheric pressure. **(B)** Single arterial pressure curve with five primary points (A–E). From these points, model parameters were estimated. Their accompanying time points are described with lower case letters. Tangent lines are described with roman numerals. Areas of interest are shaded. **(C)** In 42 (27 female) healthy subjects CBV was progressively reduced by LBNP until the onset of pre-syncope. The figure represents the output of six models compared to the blood pressure curve dynamics model (#1, top) in a single subject. Each subsequent graph shows the modulation of the addition of the annotated feature(s). In this subject the model for MCAv pulse height (bottom left) had the lowest error. Note that all model outputs increase with increasing duration of lower body negative pressure. BP, blood pressure; PetCO2, end-tidal carbon dioxide partial pressure; NIRS, near infrared spectroscopy; TCD, transcranial Doppler; MCAv, middle cerebral artery blood flow velocity; LBNP, lower body "negative" or sub-atmospheric pressure. Modified from van der Ster et al. (2018a,b).

Sander-Jensen et al., 1986; Campagna and Carter, 2003). Under those conditions, the HR response deviates from the traditionally expected tachycardia (Sander-Jensen et al., 1986). From experiments on cardiovascular reflex activity in humans subjected to LBNP, it has become evident that cardiovascular reflex patterns in response to a similar degree of exposure to LBNP are diverse and unpredictable among subjects, varying from a predominant effect on HR to a consistent increase in peripheral vascular resistance (**Figure 1**, lower panel) (Bronzwaer et al., 2016). Clinicians need hypotension predicting algorithms that operate with more precision and earlier warning. This requires novel methods better equipped to identify the variation in vasodepression and cardio-inhibition, especially in the run-up to cardiovascular collapse when compensatory mechanisms have become exhausted (Saugel et al., 2019; van Dijk et al., 2020). Future AI modeling should take the non-linear relationships between a volume loss and the cardiovascular response into account as well as the substantial inter-individual variability in how human body systems respond to environmental stress (Murray et al., 1968; Sander-Jensen et al., 1986; Bronzwaer et al., 2016, 2017a,b).

AUTHOR CONTRIBUTIONS

BvdS and JJvL drafted the manuscript and Y-SK and BW helped in the literature search and edited the manuscript. All authors approved the submitted version.

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