MULTIMODALITY MONITORING AND EVALUATION OF NEURO-FUNCTION IN MODERN NICU

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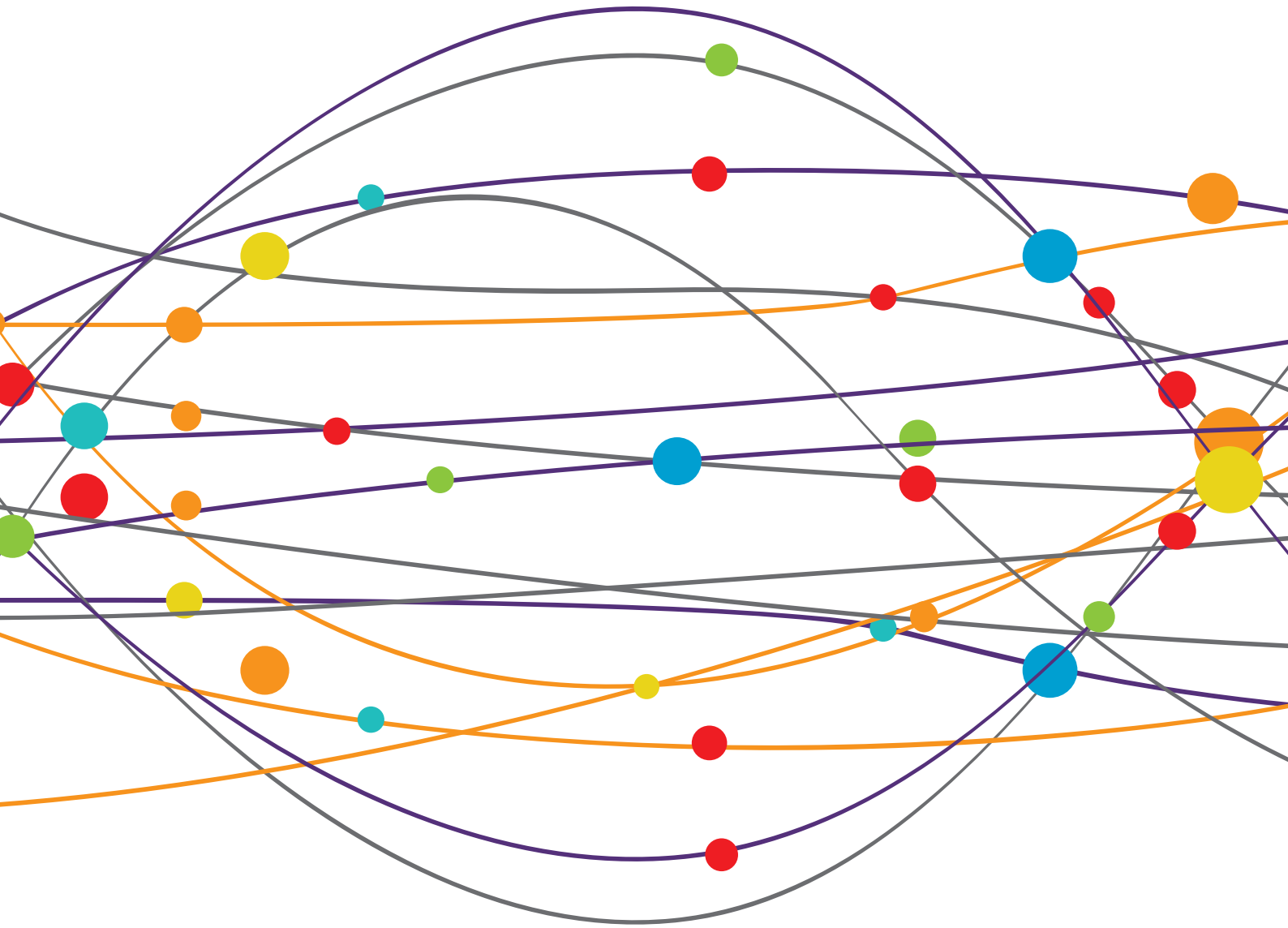

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MULTIMODALITY MONITORING AND EVALUATION OF NEURO-FUNCTION IN MODERN NICU

Topic Editors:
Liping Liu, Beijing Tiantan Hospital, Capital Medical University, China
Wengui Yu, University of California, Irvine, United States

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EDITORIAL
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Editorial: Multimodality Monitoring or Evaluation of Neuro-Function in Modern NICU

Liping Liu[1] *and Wengui Yu*[2]*

[1] Department of Neurology and Stroke Center, Beijing Tiantan Hospital, Capital Medical University, China National Clinical Research Center for Neurological Diseases, Beijing, China, [2] Department of Neurology, University of California, Irvine, Irvine, CA, United States

Keywords: acute ischemic stroke, anoxic brain injury, encephalitis, multi-modality monitoring, outcome, prognostication, status epilepticus

Editorial on the Research Topic

Multimodality Monitoring or Evaluation of Neuro-Function in Modern NICU

There have been significant advances in the management of acute ischemic stroke (AIS), autoimmune encephalitis, and anoxic brain injury in recent years. This Research Topic, Multimodality Monitoring and Evaluation of Neuro-Function in Modern Neurological Intensive Care Unit (NICU), presents eight original research articles and two mini reviews to highlight the applicability of novel multimodality monitoring and clinical evaluation in the management and prognostication of severe neurological disorders.

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Edited and reviewed by:
Sean Ruland,
Loyola University Medical Center, United States

***Correspondence:**
Wengui Yu
wyu@hs.uci.edu

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NON-INVASIVE MONITORING FOR ACUTE ISCHEMIC STROKE

Non-invasive electroencephalography (EEG) can capture sensory cortical neurons' entrainment to rhythmic sound stimuli known as the auditory steady-state response. The 40-Hz steady-state response (SSR) reflects early sensory processing and has the potential to differentiate disease severity. Wang et al. investigated the predictive value of 40-Hz SSR in patients with large hemispheric infarction. Bilateral abnormal 40-Hz SSRs were found to have a high specificity and positive predictive value for 30-day mortality and 90-day poor prognosis.

Neurovascular coupling is a dynamic physiological process that adjusts cerebral blood flow (CBF) to match neuronal activity needs. Liu et al. used continuous EEG and CBF velocity monitoring to investigate neurovascular coupling in patients with stroke from large vessel occlusion (LVO). A phase-amplitude cross-frequency coupling (CFC) algorithm was applied to assess how CBF velocities interact with the EEG amplitude. The degree of hemispherical asymmetry of CFC was found to correlate with the degree of arterial stenosis.

Huang et al. investigated the correlation between hyperchloremia and outcome in patients with severe stroke. Out of 405 study patients, 35 (8.6%) and 69 (17.0%) were found to have hyperchloremia at NICU admission and within 72 h, respectively. New-onset hyperchloremia and every 5 mmol/L increment in Cl^- were associated with increased 30-day mortality and poor 6-month outcome. However, hyperchloremia was not an independent predictor of poor outcome in multivariate models.

Taken together, EEG has great potential for evaluating LVO and outcomes from large hemispheric infarction. In contrast, hyperchloremia may be iatrogenic from the use of hypertonic saline in the NICU and is not an independent predictor of poor outcome.

DEFINING BLOOD PRESSURE GOALS DURING AND AFTER RECANALIZATION THERAPY

Extreme blood pressure (BP) and hemodynamic instability in stroke patients are associated with worse outcome. Vitt et al. provided an excellent overview of stroke pathophysiology and current BP management. Ideal BP target after recanalization therapy depends on the degree of reperfusion and extent of infarction. Following complete recanalization, lower BP target [i.e., systolic BP (SBP) < 140 mmHg] is reasonable to prevent reperfusion injury. However, randomized clinical trials are warranted to define optimal BP goals during and after recanalization therapy.

CONTINUOUS VITAL SIGN ANALYSIS TO PREDICT NEUROLOGICAL DECLINE AFTER TRAUMATIC BRAIN INJURY

In patients with traumatic brain injury (TBI), one of the major goals is to identify and prevent secondary neurological decline (ND). Melinosky et al. analyzed beat-to-beat variation of electrocardiogram (ECG) and photoplethysmogram (PPG) as well as waveform features during the first 15–60 min to identify physiologic parameters associated with future ND. Among 191 patients, 33 (17%) developed ND. Both ECG and PPG analyses during the first 15 min predicted ND better than did clinical characteristics. Predictive probability for ND by a PPG analysis at 15 min ($p = 0.03$) was independently associated with inpatient mortality. Early vital sign variation appears to be a promising biomarker of outcome prognostication in TBI.

TARGETED TEMPERATURE MANAGEMENT AND MULTIMODALITY MONITORING

Nguyen et al. provided an excellent review of targeted temperature management (TTM) and multimodality monitoring in modern NICU. TTM is neuroprotective for patients with anoxic brain injury. Current guidelines recommend the use of TTM for comatose survivors after out-of-hospital cardiac arrest from a shockable rhythm. Neurointensivists are central in the patient evaluation, management, and prognostication. Established prognostic tools include clinical exam, somatosensory evoked potential (SSEP), EEG, and MRI. Currently, functional MRI and invasive monitoring are not validated in prognostication, and further studies on biomarkers of poor outcomes are warranted.

REGIONAL CEREBRAL OXIMETRY FOR ACUTE BRAIN INJURY

Regional cerebral oxygen saturation ($rScO_2$) measured by near-infrared spectroscopy (NIRS) can be used to monitor brain oxygenation and acute brain injury (ABI) in extracorporeal membrane oxygenation (ECMO). Khan et al. evaluated the association between $rScO_2$ and ABI in ECMO patients. Among 18 study patients, 11 (61%) experienced rScO2 desaturations and 6 (33%) exhibited ABI. All ABI patients experienced $rScO_2$ desaturation as compared with 42% patients without ABI ($p = 0.04$). The presence and burden of cerebral desaturations noted on NIRS cerebral oximetry are associated with secondary ABI in ECMO patients. Monitoring of $rScO_2$ may be applicable in ECMO and TBI patients.

OTOACOUSTIC EMISSIONS AS OUTCOME MARKERS IN ANOXIC BRAIN INJURY

Kondziella et al. assessed the usefulness of otoacoustic emissions as outcome markers for comatose patients after cardiac arrest. Distortion-product otoacoustic emissions (DPOAEs) and transient evoked otoacoustic emissions (TEOAEs) were measured in cardiac arrest patients and 10 patients with myocardial infarction as controls. Compared with controls, cardiac arrest patients had significantly less preserved DPOAE [9.2 vs. 40.8%; odds ratio (OR) 0.15 (CI 0.07–0.30); $p < 0.0001$]. TEOAEs were not statistically different between the two groups. Despite convenience, otoacoustic emissions were unreliable prognostic markers in cardiac arrest survivors.

PREDICTING OUTCOME FOR ACUTE ENCEPHALITIS

Status epilepticus (SE) is the most serious complication of acute encephalitis. Early progression to super-refractory SE (SRSE) is associated with poor outcome. Yuan F et al. reported a retrospective study of 94 patients with SE from autoimmune encephalitis. There were 23.4% SRSE and 76.6% non-SRSE. Cortical or hippocampal abnormality on neuroimaging ($p = 0.002$, OR 20.55, 95% CI 3.16–133.46) and Encephalitis-Non-convulsive Status Epilepticus-Diazepam Resistance-Image Abnormalities-Tracheal Intubation (END-IT) score ($p < 0.001$, OR 4.07, 95% CI 1.91–8.67) were found to be independent predictors of progression to SRSE. Recurrent clinical or EEG seizures, tracheal intubation, and emergency resuscitation predict poor functional outcome.

Jiang et al. reported the use of quantitative EEG (qEEG) to predict the outcome of anti-*N*-methyl D-aspartate receptor (anti-NMDAR) encephalitis. Twenty-six patients were divided into critically ill ($n = 14$) and non-critically ill ($n = 12$) group on the basis of ICU admission. All patients underwent 2-h 10-channel qEEG recordings at the acute stage. No difference in qEEG parameters was observed between the two groups. A logistic regression analysis revealed that a narrower parietal amplitude-integrated EEG bandwidth was associated with favorable long-term outcomes (OR 37.9; $p = 0.044$).

These studies suggest that neuroimaging and qEEG may be used together to predict outcome of acute encephalitis.

In summary, multimodality monitoring has been rigorously investigated in patients with TBI and subarachnoid hemorrhage in the last two decades. Although invasive multimodality

monitoring may provide evidence of pathophysiological changes in a local area near the implanted probe, it is associated with risk of periprocedural complication and low sensitivity for the detection of changes in other brain regions. The articles in this Research Topic collection have presented new insight on non-invasive multimodality monitoring and vital sign variability analysis in prognostication of patients with large hemispheric infarction, acute encephalitis, and acute brain injury. The collection has also included judicious appraisal of targeted temperature management after cardiac arrest and blood pressure goals after endovascular thrombectomy. Currently, it remains challenging to predict secondary brain injury and outcome. This Research Topic article collection will stimulate future research on the development of integrated and reliable non-invasive monitoring and clinical evaluation tools in modern NICU.

AUTHOR CONTRIBUTIONS

LL and WY contributed to the drafting of this Editorial for the Research Topic that they edited. WY made critical revision and finalized the editorial.

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

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ORIGINAL RESEARCH
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Hyperchloremia Is Associated With Poorer Outcome in Critically Ill Stroke Patients

*Kaibin Huang†, Yanhong Hu†, Yongming Wu, Zhong Ji, Shengnan Wang, Zhenzhou Lin and Suyue Pan**

Department of Neurology, Nanfang Hospital, Southern Medical University, Guangzhou, China

Background and Purpose: This study aims to explore the cause and predictive value of hyperchloremia in critically ill stroke patients.

Materials and Methods: We conducted a retrospective study of a prospectively collected database of adult patients with first-ever acute ischemic stroke (AIS) or intracerebral hemorrhage (ICH) admitted to the neurointensive care unit (NICU) of a university-affiliated hospital, between January 2013 and December 2016. Patients were excluded if admitted beyond 72 h from onset, if they required neurocritical care for less than 72 h, and were treated with hypertonic saline within 72 h or had creatinine clearance less than 15 mL/min.

Results: Of 405 eligible patients, the prevalence of hyperchloremia ($[Cl^-] \geq 110$ mmol/L) was 8.6% at NICU admission ($[Cl^-]_0$) and 17.0% within 72 h ($[Cl^-]_{max}$). Thirty-eight (9.4%) patients had new-onset hyperchloremia and 110 (27.1%) had moderate increase in chloride ($\Delta[Cl^-] \geq 5$ mmol/L; $\Delta[Cl^-] = [Cl^-]_{max} - [Cl^-]_0$) in the first 72 h after admission, which were found to be determined by the sequential organ failure assessment score in multivariate logistic regression analysis. Neither total fluid input nor cumulative fluid balance had significant association with such chloride disturbance. New-onset hyperchloremia and every 5 mmol/L increment in $\Delta[Cl^-]$ were both associated with increased odds of 30-day mortality and 6-month poor outcome, although no independent significance was found in multivariate models.

Conclusion: Hyperchloremia tends to occur in patients more severely affected by AIS and ICH. Although no independent association was found, new-onset hyperchloremia and every 5 mmol/L increment in $\Delta[Cl^-]$ were related to poorer outcome in critically ill AIS and ICH patients.

Subject terms: clinical studies, intracranial hemorrhage, ischemic stroke, mortality/survival, quality and outcomes.

Keywords: hyperchloremia, neurocritical care, mortality, poor prognosis, fluid management

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Edited by:
Liping Liu,
Beijing Tiantan Hospital, Capital Medical University, China

Reviewed by:
Rick Gill,
Hospital of the University of Pennsylvania, United States
Christoph Stretz,
Yale School of Medicine, Yale University, United States
Yuchuan Ding,
Wayne State University School of Medicine, United States

***Correspondence:**
Suyue Pan
pansuyue82@126.com

†These authors have contributed equally to this work.

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INTRODUCTION

Critically ill acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH) patients account for most admissions to the neurointensive care unit (NICU) (1). These diseases heavily burden the family and society, making treatment and outcome prediction particularly important. Fluid management aiming at maintaining adequate cerebral blood flow and oxygenation plays a

crucial role in the management of these patients (2). Because of the propensity to cause brain edema by hypo-osmolar balanced crystalloids, hypertonic saline or normal saline (0.9% saline solution) are more frequently used in brain-injured patients (3). However, concerns have been raised that both hypertonic saline (4, 5) and large-volume infusion of normal saline (6, 7) may raise the risk of hyperchloremia.

Hyperchloremia has been reported to be associated with increased hospital mortality and negative outcome in critically ill patients (8), with severe sepsis and septic shock (9, 10), as well as after surgery and trauma (11, 12). In patients with ICH, a recent study demonstrated higher rates of in-hospital mortality in those who developed moderate hyperchloremia during treatment with continuous intravenous infusion of 3% hypertonic saline, with moderate hyperchloremia independently predicting in-hospital mortality (13). Another study in patients with subarachnoid hemorrhage found a strong association between hyperchloremia and acute kidney injury (AKI) as well as AKI and mortality (14). However, whether routinely used normal saline raises the risk of hyperchloremia in critically ill stroke patients remains largely unknown. Besides, the cause and predictive value of hyperchloremia in these patients requires further evaluation.

In this study, we aimed to identify risk factors that related to the development of hyperchloremia in critically ill patients with AIS and ICH, with particular focus to the amount of normal saline infusion. The influence of hyperchloremia and chloride fluctuation on patient outcome was evaluated as well.

MATERIALS AND METHODS

Study Design and Participants

The data that support the findings of this study are available from the corresponding author upon reasonable request. We conducted a retrospective study of a prospectively collected database of adult patients with first-ever AIS or ICH admitted to the NICU of Nanfang Hospital, a university-affiliated academic hospital, between January 2013 and December 2016 (**Figure 1**). Patients were excluded if they were younger than 18 or older than 85, admitted beyond 72 h of the onset, required neurocritical care for less than 72 h, had premorbid disability [modified Rankin Scale (mRS) $>$ 1] or end-stage renal disease requiring hemodialysis or creatinine clearance less than 15 mL/min. To explore the association between normal saline infusion and hyperchloremia, we also excluded patients who received hypertonic saline (3% or 10%) or other types of crystalloids except 0.9% saline during the first 72 h of NICU admission. The study proposal was approved by the hospital's ethics committee for clinical research. Informed consent was waived by the review board, because this study was observational, retrospective, and all data were fully de-identified.

Study Variables

Electronic medical records were carefully reviewed to collect patient demographics, previous medical history, laboratory values, and ICD-10-based final diagnoses. Since the concentration of serum chloride ($[Cl^-]$) shifts constantly, we defined the $[Cl^-]$ at the time of NICU admission as $[Cl^-]_0$ (baseline chloride) and the following maximum $[Cl^-]$ in the first 72 h as $[Cl^-]_{max}$. Hyperchloremia was defined as $[Cl^-] \geq 110$ mmol/L (9). The increase in serum chloride ($\Delta[Cl^-] = [Cl^-]_{max} - [Cl^-]_0$) was calculated, and $\Delta[Cl^-] \geq 5$ mmol/L was regarded as a moderate increase in chloride (8).

Glasgow Coma Scale (GCS) scores were extracted from the first neurological examination at NICU admission. The total score of Sequential Organ Failure Assessment (SOFA) (15) was obtained according to its corresponding parameters in the first 24 h of NICU admission. The requirement of vasopressor agents and mechanical ventilation within 24 h of NICU admission were also recorded. Total fluid input within the first 72 h was measured, and cumulative fluid balance (CFB) was calculated based on total fluid input minus output during this period. In order to explore the correlation between hyperchloremia and AKI, we used the kidney disease improving global outcomes (KDIGO) as diagnostic criteria of AKI (16).

Study Outcomes

Primary end points were 30-day mortality and 6-month poor outcome, with the latter defined as mRS of 4–6. Information on survival and functional outcome were obtained through telephone review by a trained neurologist blinded to the study data.

Statistical Analysis

Categorical variables were presented as number (%) and were compared using the two-sided chi-square test or Fisher's exact test. Continuous data were presented as mean ± standard deviation (SD) or median [25–75% interquartile range (IQR)] and compared by Student's *t*-test or Mann–Whitney *U* test, as appropriate.

To explore risk factors associated with the development of hyperchloremia, patients with normal $[Cl^-]$ at the time of NICU admission but who developed hyperchloremia in the first 72 h of NICU stay were defined as new-onset hyperchloremia. The whole study sample was then divided into the new-onset hyperchloremia and non-new-onset hyperchloremia subgroups. Univariate analysis was first performed, and candidate variables that had a *p*-value less than 0.05 were drawn into multivariate logistic regression model. Candidate variables included demographic data (age, gender), comorbidity (baseline creatinine, diabetes, hypertension, heart failure), indicators of critical illness (AKI, NIHSS, GCS, SOFA, base deficit, vasopressors, mechanical ventilation), and fluid management (total fluid input and CFB in the first 72 h) (9). Only one of the two variables was included in the event of collinearity between variables. The 95% confident intervals (CIs) reported for the logistic regression odds ratios (ORs) were calculated by the Wald estimation. The risk factors of moderate increase in chloride ($\Delta[Cl^-] \geq 5$ mmol/L) were evaluated using similar statistical methods as well.

To evaluate the influence of hyperchloremia on patient outcome, the associations between 30-day mortality or 6-month

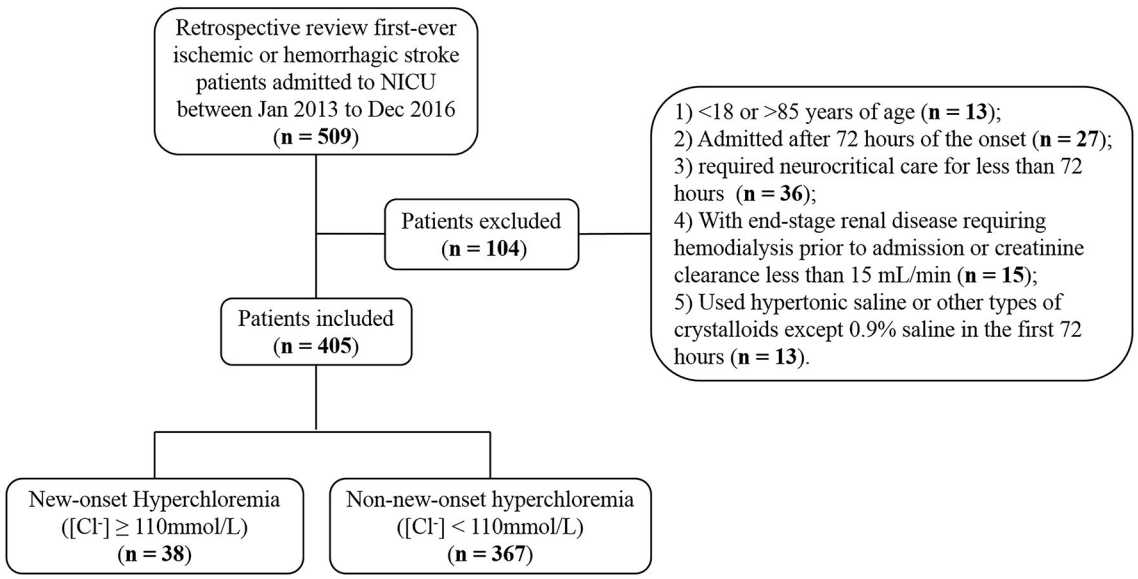

FIGURE 1 | Patient inclusion flowchart.

poor outcome (dependent variables) and (1) $[Cl^-]$ at the time of NICU admission ($[Cl^-]_0$), (2) maximum $[Cl^-]$ at the first 72 h of NICU stay ($[Cl^-]_{max}$), (3) $\Delta[Cl^-]$ ($\Delta[Cl^-] = [Cl^-]_{max} - [Cl^-]_0$), (4) new-onset hyperchloremia were examined using logistic regression analysis. The associations between patient outcomes and the independent variables of interest ($[Cl^-]_0$, $[Cl^-]_{max}$, $\Delta[Cl^-]$ and new-onset hyperchloremia) were further examined, separately, in multivariate logistic regression models that adjusted for confounders known to be associated with hospital mortality, as described in the above section. All analyses were performed using SPSS, version 23.0 (SPSS, Chicago, IL). A two-sided *p*-value less than 0.05 was considered to be statistically significant.

RESULTS

Of 509 patients screened for eligibility, 405 satisfied inclusion and exclusion criteria (**Figure 1**). Of those, 250 (61.7%) patients were diagnosed with AIS and 155 (38.3%) were ICH. There were 35 (8.6%) patients with hyperchloremia at the time of NICU admission ($[Cl^-]_0 \geq 110$ mmol/L), and the number increased to 69 (17.0%) within 72 h after admission ($[Cl^-]_{max} \geq 110$ mmol/L). Of note, 38 (9.4%) patients had new-onset hyperchloremia in the first 72 h after NICU admission (**Figure 1**). The median $[Cl^-]$ was 112 mmol/L (111−115 mmol/L) in the new-onset hyperchloremic subgroup and 104 mmol/L (102–107 mmol/L) in the non-new-onset hyperchloremic subgroup. Baseline demographics and clinical characteristics of these two subgroups were summarized in **Table 1**. The patients with new-onset hyperchloremia had lower GCS, higher NIHSS, and SOFA scores. Moreover, these patients required more vasopressors and mechanical ventilation when compared with those without new-onset hyperchloremia within 72 h of NICU admission. However, neither total fluid input nor CFB had significant association with new-onset hyperchloremia (**Table 1**).

Since GCS is included in SOFA and had collinearity with NIHSS, it was omitted from multivariate logistic analysis. In a multivariate model evaluating risk factors that related to the development of new-onset hyperchloremia, SOFA was identified as the only independent variable that associated with new-onset hyperchloremia (**Table 2**). Furthermore, SOFA and mechanical ventilation were found to be the risk factors of moderate increase in chloride ($\Delta[Cl^-] \geq 5$ mmol/L) in the first 72 h in both univariate and multivariate logistic analysis (Supplementary Tables S1, S2).

During follow up, 61 (15.1%) patients died within 30 days after admission and 236 (58.3%) patients achieved good outcome at 6 months. Results showed that patients with new-onset hyperchloremia were associated with a 158% increase in odds for 30-day mortality (OR = 2.58; 95% CI, 1.21–5.53; $p = 0.015$) (**Table 3**). In addition, each 5 mmol/L increase in $[Cl^-]_0$, $[Cl^-]_{max}$, and $\Delta[Cl^-]$ was associated with a 50, 66, and 55% increase in odds for 30-day mortality, respectively (**Table 3**). However, none of these changes of chloride showed independent association with 30-day mortality in multivariate logistic analysis, while age, base excess, SOFA, and mechanical ventilation were found to be significant (**Table 3**). In terms of 6-month functional outcome, new-onset hyperchloremia, $[Cl^-]_{max}$ and $\Delta[Cl^-]$ were all associated with increased risk of poor outcome, with an OR (95% CI) of 3.394 (1.660–6.941), 1.425 (1.205–1.685), and 1.383 (1.143–1.674), respectively (**Table 4**). Nevertheless, these three indicators were not independently related to 6-month outcome in multivariate models, where age, NIHSS, and SOFA were independent risk factors of poor outcome (**Table 4**). The detailed statistical results were summarized in Supplementary Tables S3, S4.

DISCUSSION

In this study, we showed that the prevalence of hyperchloremia in critically ill stroke patients increased from 8.6% at NICU admission to 17.0% in the first 72 h. The SOFA score was identified as an independent risk factor of both new-onset hyperchloremia and moderate increase in chloride ($\Delta[Cl^-] \geq 5$ mmol/L) after NICU admission. For the infusion of normal saline, neither total fluid input nor CFB was significantly related to new-onset hyperchloremia or moderate increase in chloride. Although no independent significance was found in multivariate models, both new-onset hyperchloremia and every 5 mmol/L increment in $\Delta[Cl^-]$ were associated with increased odds of 30-day mortality or 6-month poor outcome.

Chloride is the most abundant anion in the extracellular fluid, constituting approximately one-third of plasma tonicity, and plays an essential role in various body functions including the regulation of body fluids, electrolyte balance, acid-base status, muscular activity, osmosis, and immunomodulation (17). While the concentration of chloride shifts constantly during hospitalization, chloride receives much less attention than other routinely measured electrolytes until recent reports investigated the influence of hyperchloremia on hospital mortality and AKI (18).

TABLE 1 | Baseline demographics and clinical characteristics stratified by new-onset hyperchloremia ($[Cl^-] \geq 110$ mmol/L) or not ($[Cl^-] < 110$ mmol/L) within 72 h of NICU admission.

Variable	New-onset HC (*n* = 38)	Non-new-onset HC (*n* = 367)	*p*-Value
Demographics			
Age, year, median (IQR)	56 (46–69)	62 (50–72)	0.188
Male, *n* (%)	27 (71.1%)	251 (68.4%)	0.447
Chronic conditions			
Baseline serum creatinine, μmol/L, median (IQR)	90 (73–115)	82 (65–104)	0.135
Hypertension, *n* (%)	24 (63.2%)	236 (64.3%)	0.509
Diabetes mellitus, *n* (%)	8 (21.1%)	71 (19.3%)	0.471
Heart disease, *n* (%)	8 (21.1%)	63 (17.2%)	0.341
Critical indicators on NICU admission			
BE, mmol/L, median (IQR)	−1.3 (−4.0 to 1.65)	−0.2 (−2.0 to 1.7)	0.083
GCS, median (IQR)	9 (6–11)	11 (9–12)	0.001
NIHSS, median (IQR)	17 (11–22)	12 (7–17)	0.002
SOFA, median (IQR)	8 (4–10)	4 (2–6)	<0.001
Laboratory indicators			
Lactate, mmol/L, median (IQR)	2.8 (2.1–3.2)	2.3 (2.0–3.1)	0.392
Albumin, g/L, median (IQR)	38 (33–41)	39 (34–43)	0.240
Fluid indicators within 72 h			
Total fluid input (with enteral nutrition) within 72 h, L, median (IQR)	7.7 (6.0–9.6)	7.1 (6.1–8.2)	0.076
Total fluid input (without enteral nutrition) within 72 h, L, median (IQR)	4.2 (2.8–6.1)	3.6 (2.7–4.8)	0.074
Cumulative fluid balance within 72 h, L, mean ± SD	1.8 ± 1.6	1.7 ± 1.5	0.969
Vasopressor, *n* (%)	9 (23.7%)	22 (6.0%)	0.001
Mechanical ventilation, *n* (%)	17 (44.7%)	75 (20.4%)	0.001
Acute kidney injury, *n* (%)	7 (18.4%)	31 (8.4%)	0.052

HC, hyperchloremia ($[Cl^-] \geq 110$ mmol/L); SD, standard deviation; BE, base excess; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment; IQR, interquartile range.

TABLE 2 | Univariate and multivariate logistic regression analysis for risk factors of new-onset hyperchloremia ($[Cl^-] \geq 110$ mmol/L).

Variable	Univariate analysis			Multivariate analysis*		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
NIHSS	1.085	1.031–1.143	0.002	–	–	–
SOFA	1.259	1.146–1.384	<0.001	1.259	1.146–1.384	<0.001
Vasopressor	4.867	2.053–11.537	<0.001	–	–	–
Mechanical ventilation	3.152	1.584–6.271	0.001	–	–	–

*NIHSS, National Institutes of Health Stroke Scale; SOFA, Sequential Organ Failure Assessment; OR, odds ratio; CI, confidence interval. *In multivariate logistic regression, only parameter with statistical significance was shown.*

TABLE 3 | Univariate and multivariate logistic regression analysis of risk factors associated with 30-day mortality.

Variable	Univariate analysis		Multivariate analysis†	
	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
Age	1.026 (1.005–1.048)	0.016	1.035 (1.006–1.064)	0.016
Baseline serum creatinine	1.007 (1.003–1.012)	0.001	–	–
Base excess	0.788 (0.720–0.863)	<0.001	0.867 (0.782–0.960)	0.006
NIHSS	1.124 (1.075–1.176)	<0.001	–	–
SOFA	1.733 (1.526–1.969)	<0.001	1.540 (1.324–1.792)	<0.001
Albumin	0.925 (0.885–0.966)	<0.001	–	–
Vasopressors	17.535 (7.713–39.867)	<0.001	–	–
Mechanical ventilation	15.961 (8.438–30.191)	<0.001	2.705 (1.183–6.189)	0.018
Acute kidney injury	10.099 (4.921–20.722)	<0.001	–	–
New-onset hyperchloremia*	2.583 (1.206–5.533)	0.015	–	–
$[Cl^-]_0$ (per 5 mmol/L)*	1.502 (1.168–1.932)	0.002	–	–
$[Cl^-]_{max}$ (per 5 mmol/L)*	1.657 (1.368–2.007)	<0.001	–	–
$\Delta[Cl^-]$ (per 5 mmol/L)*	1.552 (1.235–1.951)	<0.001	–	–

**The indicators of chloride were drawn into multivariable logistic analysis separately.* †*Since age, base excess, SOFA, and mechanical ventilation were consistently found to be independent factors associated with 30-day mortality when each indicator of chloride was included, their odds ratio value and p-value were given when new-onset hyperchloremia was drawn in multivariate analysis only. GCS was not included in the multivariate model because of collinearity with the NIHSS. Serum creatinine was not included in the multivariate model because of collinearity with the acute kidney injury. CI, confidence interval.*

TABLE 4 | Univariate and multivariate logistic regression analysis of risk factors associated with 6-month poor outcome (mRS ≥ 4).

Variable	Univariate analysis		Multivariate analysis†	
	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
Age	1.032 (1.016–1.047)	<0.001	1.038 (1.019–1.057)	<0.001
Diabetes mellitus	1.669 (1.018–2.736)	0.042	–	–
NIHSS	1.143 (1.103–1.184)	<0.001	1.087 (1.041–1.136)	<0.001
SOFA	1.439 (1.323–1.565)	<0.001	1.308 (1.191–1.437)	<0.001
Albumin	0.926 (0.894–0.959)	<0.001	–	–
Vasopressors	11.028 (3.780–32.172)	<0.001	–	–
Mechanical ventilation	5.544 (3.307–9.293)	<0.001	–	–
Acute kidney injury	3.394 (1.660–6.941)	0.001	–	–
New-onset hyperchloremia*	3.394 (1.660–6.941)	0.001	–	–
$[Cl^-]_0$ (per 5 mmol/L)*	1.203 (0.995–1.453)	0.056	–	–
$[Cl^-]_{max}$ (per 5 mmol/L)*	1.425 (1.205–1.685)	<0.001	–	–
$\Delta[Cl^-]$ (per 5 mmol/L)*	1.383 (1.143–1.674)	0.001	–	–

**The indicators of chloride were drawn into multivariable logistic analysis separately.* †*Since age, NIHSS, and SOFA were consistently found to be independent factors associated with 30-day mortality when each indicator of chloride was included, their odds ratio value, and p-value were given when new-onset hyperchloremia was drawn in multivariate analysis only. GCS was not included in the multivariate model because of collinearity with the NIHSS. CI, confidence interval.*

In a retrospective study, hyperchloremia and moderate increase in serum chloride ($\Delta[Cl^-] \geq 5$ mmol/L) were both found to be independently associated with AKI in severe sepsis and septic shock patients (10). (9) revealed that hyperchloremia at 72 h of ICU stay (Cl_{72}) were related to all-cause hospital mortality and every 5 mmol/L increment in Cl_{72} or $\Delta[Cl^-]$ was, respectively, associated with a 27 or 37% increase in the odds for hospital mortality in those critically ill septic patients who were already hyperchloremic on admission to the ICU. (19) conducted a respective study on 76,719 hospitalized patients and found that both serum chloride alterations on admission and post-admission serum chloride increase predicted poor outcome. Similar to these studies, we observed that both new-onset hyperchloremia or every 5 mmol/L increment in $\Delta[Cl^-]$ were associated with increased odds of poor outcome in critically ill stroke patients, although these two variables did not show independent significance in multivariate models. The possible explanation could be that the prevalence of hyperchloremia in our subjects (17.0% in the first 72 h) was much lower than that in other patient groups [65.3% (13) in patients with ICH and treated with hypertonic saline; 40.8% ((10)) and 31.7% (9) in patients with septic shock].

Hyperchloremia may result from disease processes or clinical interventions (18). In the present study, we observed that the

main determinant of hyperchloremia in critically ill stroke patients was the disease severity, as reflected by the SOFA score. While previous studies have shown a strong association between hyperchloremia and administration of chloride-rich fluids (18), such as 0.9% saline (20), we did not find a significant association between normal saline infusion and new-onset hyperchloremia or moderate increase in chloride. The plausible explanation was that we only observed the chloride fluctuation within the first 72 h after NICU admission. Extending the observation period might result in different findings. Besides, we have excluded patients who had end-stage renal disease requiring hemodialysis or creatinine clearance less than 15 mL/min at the screening, which may decrease the risk of chloride retention. Finally, compared with the treatment in septic shock, the infused volume of normal saline was much lower in our study subjects, which might have weakened the association between normal saline infusion and chloride fluctuation. Although other balanced crystalloid fluid such Plasma-Lyte (Na, 140 mmol/L; Cl, 98 mmol/L) has been reported to cause less hyperchloremia (21), normal saline remains to be the first choice in most clinical scenarios (22). The encouraging findings from two recent trials that lactated Ringer's solution or Plasma-Lyte A reduced hospital death or adverse kidney events in contrast to saline in critically ill (23) and non-critically ill (24) adult patients may have the potential to change current practice.

Our results should be interpreted with caution. First, the retrospective nature of this study make it susceptible to selection and information bias. Second, we were unable to assess all potentially relevant variables. Still, the candidate variables selected in the present study were mostly in line with two representative studies (9, 14). Third, to explore the correlation between normal saline infusion and chloride disturbance, we have excluded patients who were treated with hypertonic saline within 72 h, which might have underestimated the prevalence of hyperchloremia in our study subjects. Fourth, the amount of chloride add through other chlorinated fluid such as potassium chloride and enteral nutrients were not evaluated. Nevertheless, the contribution of potassium chloride to serum chloride is far less than normal saline, and the supplement of enteral nutrients to patients were strictly conducted according to the operating guidelines (25, 26).

CONCLUSION

Hyperchloremia is not rare and tends to occur in patients more severely affected by AIS and ICH. While no independent association was found, new-onset hyperchloremia and every 5 mmol/L increment in $\Delta[Cl^-]$ within 72 h of NICU admission were associated with an increased odds of all cause 30-day mortality and 6-month poor prognosis in critically ill stroke patients. This study indicates that hyperchloremia has clinical importance as an indicator of prognosis in critically ill patients. Prospective study with rigorous design should be help to further explore the casual relationship between hyperchloremia and clinical outcome.

ETHICS STATEMENT

This study was approved by the Nanfang Hospital's ethics committee on clinical research. Informed consent was waived by the review board because of the pure observational and retrospective nature of the study.

AUTHOR CONTRIBUTIONS

SP contributed to study conception and design. KH participated in study conception and design, and helped to draft and revise the manuscript. YH collected data and drafted the manuscript. YW and ZJ performed statistical analysis. SW and ZL participated in patient follow up and helped to revise the manuscript. All authors made substantial contribution, and read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Targeted Temperature Management and Multimodality Monitoring of Comatose Patients After Cardiac Arrest

Peggy L. Nguyen, Laith Alreshaid, Roy A. Poblete, Geoffrey Konye, Jonathan Marehbian and Gene Sung*

Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States

Out-of-hospital cardiac arrest (CA) remains a leading cause of sudden morbidity and mortality; however, outcomes have continued to improve in the era of targeted temperature management (TTM). In this review, we highlight the clinical use of TTM, and provide an updated summary of multimodality monitoring possible in a modern ICU. TTM is neuroprotective for survivors of CA by inhibiting multiple pathophysiologic processes caused by anoxic brain injury, with a final common pathway of neuronal death. Current guidelines recommend the use of TTM for out-of-hospital CA survivors who present with a shockable rhythm. Further studies are being completed to determine the optimal timing, depth and duration of hypothermia to optimize patient outcomes. Although a multidisciplinary approach is necessary in the CA population, neurologists and neurointensivists are central in selecting TTM candidates and guiding patient care and prognostic evaluation. Established prognostic tools include clinal exam, SSEP, EEG and MR imaging, while functional MRI and invasive monitoring is not validated to improve outcomes in CA or aid in prognosis. We recommend that an evidence-based TTM and prognostication algorithm be locally implemented, based on each institution's resources and limitations. Given the high incidence of CA and difficulty in predicting outcomes, further study is urgently needed to determine the utility of more recent multimodality devices and studies.

Keywords: cardiac arrest, targeted temperature management, anoxic brain injury, EEG, prognosis, multimodality monitoring

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Wengui Yu,
University of California, Irvine,
United States

Reviewed by:
Cyrus Khurshed Dastur,
University of California, Irvine,
United States
Gunjan Parikh,
University of Maryland Medical System, United States

****Correspondence:***
Roy A. Poblete
roy.poblete@med.usc.edu;
roypoblete@gmail.com

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INTRODUCTION

Out-of-hospital cardiac arrest (CA) remains a leading cause of sudden morbidity and mortality. Based on recently published statistics from the American Heart Association, 1 of every 7.4 people in the United States will die of sudden cardiac death; however, in those who survive, outcomes have continued to improve over time (1). Enhanced recovery in CA-survivors is likely a product of multifactorial system-based changes, including the advent and evolution of targeted temperature management (TTM).

A multidisciplinary approach is necessary in the care of this complex and critically-ill population. Patients are managed by a team of physicians, nurses and ancillary staff. Neurologists and neurointensivists are often instrumental in the selection of TTM candidates and are central

to patient care and prognostication. Early consultation with neurologists might increase the use of therapeutic hypothermia (TH) (2). Despite advances in the medical management of out-of-hospital CA, predicting outcomes remains a challenging task. Established prognostic tools have needed to be re-visited with the advent of TTM (3), and the literature has been limited by heterogenous definitions, non-standardized study methods, small sample sizes, and publication bias. We therefore completed this review to highlight the clinical use of TTM, and to provide an updated summary of multi-modality monitoring and prognostication following CA in a modern neuroscience intensive care unit (ICU). Given the neuroprotective effect of TTM and its impact on prognostication, being familiar with current guidelines and literature is crucial to optimizing patient care.

PATHOPHYSIOLOGY OF ANOXIC INJURY FOLLOWING CARDIAC ARREST

Hypoxic-ischemic encephalopathy remains a primarily clinical diagnosis; however, the molecular pathophysiology has been studied in both animal and human models. Post-cardiac arrest syndrome, a term used to describe the resuscitative phase that follows return of spontaneous circulation (ROSC), encompasses four key processes: post-CA brain injury, post-CA myocardial dysfunction, systemic ischemia and reperfusion injury and a persistent precipitating pathology (4). Brain injury in the post-CA period is thought to be mediated by multiple pathways that result in ischemic injury, impaired cerebral autoregulation, and the development of diffuse cerebral edema (4).

During CA, the brain is exquisitely sensitive to global ischemia. Neuronal injury occurs when the severity and duration of ischemia is sufficient to cause depolarization of the neuronal plasma membrane. In animal models, this has been demonstrated to occur when blood flow falls below 10 mL/100 g per minute (5, 6). Animal studies have also demonstrated that loss of consciousness is experienced as early as 10 s following circulatory arrest, while an electroencephalogram (EEG) demonstrates isoelectric activity as early as 20 s after the event (7). When ischemic depolarization is brief with subsequent reperfusion, permanent glial injury may not occur; however, when the depolarization is more prolonged, a cascade of metabolic changes mediated by alterations in adenosine triphosphate (ATP), neurotransmitter pathways, mitochondrial dysfunction and calcium homeostasis occurs, which may lead to irreversible neuronal death. Ischemic depolarization >30 min most likely results in neuronal cell death regardless of reperfusion (5).

The exact mechanisms underlying ischemic injury following CA are poorly understood but are likely to involve multiple signaling pathways leading to disruption of cellular homeostasis. At a molecular level, global ischemia causes a depletion of intracellular ATP, with subsequent failure of ATP-dependent ionic channels. This results in accumulation of interstitial potassium with subsequent cell membrane depolarization. The eventual influx of sodium, chloride, and water into cells forms the basis of cytotoxic edema, which occurs during CA and other neurologic injuries. In addition, membrane depolarization results in the intracellular accumulation of calcium with activation of voltage gated calcium channels, as well as release of excitatory amino acid transmitters such as glutamate, perpetuating calcium and sodium influx into the neuron (5, 8).

If global ischemia occurs without subsequent reperfusion, failure of ATP production will lead to a final common pathway of cellular necrosis. Disruption of calcium homeostasis is thought to be one of the primary mechanisms of neuronal cell injury (9). Accumulation of calcium ions in the mitochondria increases free radical production and mitochondrial permeability transition (MPT), resulting in mitochondrial swelling, oxidative damage, loss of ATP production, and cell death. Cellular accumulation of calcium in the cytosol additionally triggers lipolysis, membrane destabilization, proteolysis, nitric oxide production, and endonuclease DNA degradation (5, 8). *In vivo* measurements of calcium demonstrate that in the acute ischemic period, cytosolic levels increase exponentially within 8 min of ischemia in vulnerable brain regions, although levels can return to baseline within 30–60 min if reperfusion occurs (5, 10).

In the setting of ROSC with cerebral reperfusion, additional ischemic injury can still occur. In particularly vulnerable neuronal subpopulations, including in the cortex, hippocampus, cerebellum, corpus striatum, and thalamus, degeneration can occur over hours to days (4). Secondary neuronal death is also mediated by disruption in calcium homeostasis, as levels of cytosolic calcium have been shown to increase up to 24 h after the primary insult in susceptible brain regions (5). Additional inflammatory processes involving cytokines are implicated in peripheral tissue ischemia. Cytokines such as interleukin-6 (IL-6) and tumor necrosis factors (TNF) perpetuate delayed ischemia in the reperfusion period. Animal models have demonstrated that rapid infiltration of neutrophil and pro-inflammatory T-lymphocytes into the brain occur as early as 3 h following ROSC, and last up to 3 days (11).

A PARADIGM SHIFT: TARGETED TEMPERATURE MANAGEMENT IN THE MODERN ICU

For the last two decades, TTM, previously referred to as therapeutic hypothermia, has been a growing research topic in the ICU literature. Currently, given its neuroprotective role after CA with improvement of neurologic outcomes, TTM is considered the standard of care for survivors of CA who present with coma after ROSC (12).

Mechanisms of Neuroprotection With Hypothermia

The manner that hypothermia acts as a neuroprotectant is still not fully understood. In animal models, hypothermia has been shown to limit several microscopic events, including the inhibition of inflammatory cytokine release (ex. interleukins, prostaglandins), that normally lead to apoptosis and cell death

(13–15). At a tissue level, hypothermia was found to reduce cerebral metabolic demand (approximately 6–8% per 1°C), cerebral edema, and intracranial pressure (ICP), while also increasing seizure threshold (16).

Targeted Temperature Management

TTM was first introduced in the 1950s and 1960s, primarily in animal models. Many of these early studies showed that both moderate systemic hypothermia (32–30°C) (17) and mild hypothermia (34°C) (18–20) cause decreased brain damage after CA in animals. The subject of TH somewhat faded until it was reintroduced in human subjects in the early 2000s by two important randomized trials (RCTs): a study by Bernard et al, and the Hypothermia after Cardiac Arrest Study Group (21, 22). These studies were the first to provide Class I evidence supporting the use of TTM for CA survivors to improve both survival and functional outcomes using mild hypothermia (32°-34°C for 12 or 24 h). Based on these findings, the International Liaison Committee on Resuscitation (ILCOR) recommended in 2003 that CA-survivors in coma should receive TH when the initial rhythm was ventricular fibrillation, with potential benefit with other rhythms (23).

These recommendations have since been under continuous review and change. Three major clinical trials and a meta-analysis by Kim et al failed to show definite improvement in outcomes in patients with non-shockable rhythm (24–27). Similarly, TTM does not appear to benefit patients who sustain in-hospital CA in terms of mortality or neurologic recovery (28). Regarding the timing and duration of TTM and depth of TH, best practices are unknown. Pre-hospital initiation of TTM has not been shown to improve outcomes (29, 30). Prolonged cooling also appears to have no important clinical effect. Kirkegaard et al compared 24 vs. 48 h of cooling to 33°C and found no significant differences in neurologic outcomes (31). While early guidelines recommend mild hypothermia, a recent RCT found no change in neurologic recovery or survival at 6 months when comparing 33° and 36°C (32).

Current guidelines do not recommend a specific cooling method for TTM; however, multiple methods are available for induction and maintenance, including both invasive and non-invasive devices (33, 34). Recent data suggest that endovascular cooling is more rapid and may be more effective in maintaining TTM, although surface cooling may be as effective during induction (35, 36); however, clinical trials to-date have not shown effect on overall mortality and neuro-sequelae between invasive and non-invasive methods. Alternative devices, including trans-nasal, peritoneal and esophageal cooling are under investigation, but no recommendations for their use can be made currently (37–39).

The current American Heart Association, Canadian TTM guidelines, and American Academy of Neurology practice parameters are considered the most evidence-based clinical recommendations and the standard of care for managing post-CA patients who remain in coma after ROSC (12, 40, 41) (**Table 1**). Further research is needed to study different aspects of these guidelines to achieve the best clinical results.

TABLE 1 | Summary of recent guidelines on targeted temperature management for out-of-hospital cardiac arrest patients.

Committee	Summary of recommendations
2015 American Heart Association (12)	• Induce hypothermia for unconscious adult patients with ROSC after OHCA when the initial rhythm was VF or pVT (class I, level of evidence: B-R) • Similar therapy may be beneficial for patients with non-VF/non-pVT (non-shockable) OHCA or with in-hospital arrest (class I, level of evidence: C-EO) • The temperature should be maintained between 32°-36°C (class I, level of evidence: B-R) • It is reasonable to maintain TTM for at least 24 h (class IIa, level of evidence: C-EO) • Routine prehospital cooling of patients with ROSC with IV rapid infusion is not advised (class III: no benefit; level of evidence A) • It is reasonable to prevent fever in comatose patients after TTM (class IIb, level of evidence C-LD) • Hemodynamically stable patients with spontaneous mild hypothermia (>33°C) after resuscitation from cardiac arrest should not be actively rewarmed
2016 Joint Statement from The Canadian Association of Emergency Physicians, the Canadian Critical Care Society, Canadian Neurocritical Care Society, and the Canadian Critical Care Trials Group (40)	• We recommend that patients who suffer out-of-hospital cardiac arrest are eligible for TTM (High quality, strong recommendation) • We recommend that TTM can be initiated in any medical environment with the necessary supports, including prehospital, ED and critical care unit (Moderate quality, strong recommendation) • We recommend that clinicians attempt to achieve target temperature as rapidly as possible (Low quality but strong recommendation) • We do not recommend a specific cooling method for TTM." • We recommend that patients undergoing TTM should receive sedation and analgesia • We suggest that paralytics be used during induction and rewarming phases of TTM, to facilitate tight temperature control and to prevent shivering
2017 American Academy of Neurology Practice Guidelines (41)	• Comatose patients after CA in whom the initial cardiac rhythm is VT or VF, TH is likely effective in improving neurologic outcome and survival (Level A) • Comatose patients after CA in whom the initial cardiac rhythm is VT/VF or PEA/asystole should not be offered prehospital cooling with 2 liters 4°C IV fluid or intranasal cooling (Level A) • Comatose patients after CA in whom the initial cardiac rhythm is either VT/VF or PEA/asystole, TTM (33°C for 24 h followed by 8 h of rewarming to 37°C and maintained below 37.5°C until 72 h) is likely as effective as TH in improving neurologic outcome and survival and is an acceptable alternative to TH (Level B) • In comatose patients after CA, the addition of coenzyme Q10 to TH possibly improves survival but does not improve neurologic status at 3 months and may be offered (Level C) • No recommendations are made on the following (Level U): TH when the initial cardiac rhythm is PEA/asystole Use of 32° vs. 34°C TH Use of invasive cooling instead of surface cooling Use of standardized protocols for TH Use of epoeitin alfa in addition to mild TH

ROSC, return of spontaneous circulation; OHCA, out-of-hospital cardiac arrest; VF, ventricular fibrillation; pVT, pulseless ventricular tachycardia; IV, intravenous; TTM, targeted temperature management; R, randomized; EO, expert opinion; LD, limited data; VT, ventricular tachycardia; TH, therapeutic hypothermia; PEA, pulseless electrical activity; IV, intravenous.

NEUROPHYSIOLOGIC TESTING AFTER CARDIAC ARREST

Use of EEG Studies

Beyond the clinical exam, EEG is one of the most widely used prognostic tools after anoxic brain injury from CA. Areas most susceptible to hypoxic-ischemic injury, including the cerebral cortex and hippocampus (42) are highly epileptogenic and are feasibly captured by surface EEG. From a practical aspect, it is an attractive study because it is non-invasive, can be performed rapidly, and is available at most hospitals managing CA patients. Clinical seizures are reported from TTM trials to occur in over 25% of patients (32), while malignant EEG features are recorded in up to 86% of patients who remain comatose after resuscitation and re-warming (43). Non-convulsive seizures are thought to occur in approximately one-quarter of comatose patients after cardiac arrest (44, 45).

Timing and Duration of EEG

The optimal timing for EEG recording after CA is unknown. Since sedation is required for TH and TTM, EEG is often reserved for those who fail to awake after rewarming; however, early monitoring may be indicated. In study populations undergoing TTM, most seizures on continuous EEG (cEEG) occur within 12 h of resuscitation and prior to achieving normothermia (44, 45). Malignant patterns in the first 8 h of cEEG have also demonstrated a high positive predictive value for poor outcome (46). Although this suggests utility in early cEEG, studies have shown that intermittent short-duration EEG has potentially similar diagnostic and prognostic yield, with no difference in clinical outcomes, and is associated with reduced per patient cost (47, 48). Given the lack of evidence to suggest treatment of seizures and malignant EEG findings improves outcomes (49, 50), the principal use of intermittent EEG as a prognostic tool is reasonable in centers where cEEG is not readily available.

Prognostic Value of EEG Findings

Electroencephalogram findings most thought to predict poor neurologic outcome includes absence of EEG reactivity, alpha coma, low-voltage recording, burst-suppression pattern, and status epilepticus (49). Several older and newer grading scales that account for TTM have been proposed to classify EEG findings after CA (50–54); however, none have achieved widespread adoption. This may in part be due to a difficulty of interpreting and understanding the clinical implications of complex EEG findings for non-electroencephalographers. A simplified system might differentiate between "benign" and "malignant" EEG patterns (43, 55).

EEG features in patients who do not undergo therapeutic hypothermia

A low-voltage EEG ($\leq$21 μV) reflects neuronal dysfunction and is a reliable predictor of poor outcome in those who do not receive TTM. In two larger studies, low-voltage EEG seen at 24–72 h after resuscitation was associated with poor outcome with a 0% false positive rate (FPR) (56, 57). Similarly, myoclonic status epilepticus (MSE) when differentiated from a benign form of chronic myoclonus, Lance-Adams syndrome, has been invariably associated with poor outcome in those who are not treated with TH (58). Although electrographic seizure other than MSE, alpha coma and burst suppression are considered useful prognostic findings, they are not invariably associated with poor outcome in the CA population (53, 57, 59, 60).

EEG features in patients treated with therapeutic hypothermia.

TTM improves neurologic outcomes following CA (32) but lowering intracranial temperature and the sedation necessary for TH confounds EEG interpretation. Its accuracy as a prognostic tool has had to be re-evaluated with the advent of TTM. Although early post-hypoxic myoclonus is associated with poor prognosis, since the publication of the 2006 American Academy of Neurology Guidelines on prognostication following CA (61), several authors have reported outcomes better than predicted in patients with myoclonic seizures (44, 50, 62–65). Cortical myoclonus or status myoclonus within 72 h from CA did not exclude a good neurologic recovery defined as Cerebral Performance Category (CPC) 1 or 2, with a 5% FPR (44, 50, 62–64). Some have suggested that "benign" and "malignant" myoclonus or MSE can be differentiated by the background EEG pattern (65, 66).

Status epilepticus (SE) other than MSE strongly predicts poor outcome (CPC 3–5) (45, 50, 67); however, good outcome in CA patients is possible. In one study of 106 comatose CA survivors, 2/33 SE patients achieved good neurologic outcomes (66). Like MSE, EEG background is an important factor. In a study of cEEG in TTM patients, those with SE arising from burst-suppression invariably had poor neurologic recovery, while good outcomes were possible in those with SE arising from an EEG with continuous background (4% FPR) (68).

A burst-suppression EEG background or low-amplitude recording alone does not predict poor outcome with 100% specificity (64, 68, 69). Similarly, a non-reactive EEG background is compatible with neurologic recovery with a 3% FPR when recorded during TH (50, 62, 67), while in one larger study, three patients with absence of EEG reactivity within 72 h of resuscitation achieved good outcomes (63). Although prognosis is not invariably poor in patients undergoing TTM with a single malignant EEG feature, the presence of multiple features significantly increases the likelihood of poor outcome. In a large cohort of patients enrolled in a TTM trial, a single malignant EEG feature had a low specificity for poor prognosis (48%), which increased to a 96% positive predictive value when two malignant EEG features were present (43).

Continuous EEG Using Depth Electrodes

In neurocritical care, EEG depth electrodes are inserted through small burr holes, often in combination with other multimodality brain monitors to capture electrographic activity below the cortex. Their use in the management and prognosis of CA survivors has not been extensively studied in any large trial. In one case report, authors demonstrated the feasibility of using multimodality monitoring, including depth EEG, to detect SE that was associated with reductions in brain tissue oxygen tension

and increase in cerebral blood flow and brain temperature (70). Future study is needed if invasive monitoring that includes depth EEG has additional prognostic value in CA.

Limitations

Beyond being confounded by hypothermia and sedative medications, EEG for prognostication after CA has other important limitations. The frequency of EEG and availability of cEEG is dependent on institutional resources and varies widely, with cEEG often only available at larger academic centers. Given the lack of evidence suggesting its superiority to intermittent EEG (49, 50), the American Clinical Neurophysiology Society and other committees have not made guidelines to standardize EEG after CA (71, 72).

EEG interpretation remains a specialized skill, with the large proportion of ICU providers unable to independently interpret studies. Recordings and terminology can be confusing to non-epileptologists. Even among experts, interrater agreement on EEG patterns can vary (73), resulting in many authors proposing standardization to classifying EEG in this population (43, 73). Use of automated, quantitative EEG techniques may find future utility in prognostication and is the subject of current study (51, 74, 75).

Somatosensory Evoked Potentials

Somatosensory Evoked Potentials (SSEPs) are often used for prognostication in CA survivors who have a poor neurologic exam after resuscitation and normothermia (76). In the most widely used test, small electrical stimulation ($<50\ \mu V$) is applied to the median nerve in the arm, followed by recording of post-stimuli waveforms over the primary somatosensory cortex by surface electrodes (76). The bilateral absence of the short-latency N20 waveform is highly specific for poor outcome after CA. In those who are not treated with TH, bilateral absence of the N20 response within the first 7 days showed a 0% FPR (95% CI 0–12] with only 1/432 patients achieving a good outcome (58). In TTM patients, this finding also showed high predictive value for poor outcome both during TH (64, 77, 78) and after rewarming (62, 64, 67, 77, 78), with exception of one case where reappearance of the N20 response corresponded with full neurologic recovery (79). Given these robust findings, early use of short-latency N20 SSEPs for prognostication after CA is endorsed by multiple expert committees (64, 72). The use of longer latency waveforms, such as the N70 response (80), requires further study.

Limitations

The optimal timing for SSEP is unknown. Given both peripheral and central conduction times are prolonged during hypothermia (81), most practitioners delay SSEP testing until after the rewarming phase. Using a dichotomous measure of absent vs. present SSEP also significantly limits its sensitivity in predicting poor outcomes. Determining prognostically useful N20 amplitude thresholds should be further studied in future cohorts (82). Importantly, SSEPs are not routinely performed at all hospitals that treat CA survivors, further limiting its adoption in standardized prognostication algorithms.

IMAGING MODALITIES AFTER CARDIAC ARREST

CT Imaging

Brain CT is typically the first neuroimaging study obtained in out-of-hospital CA survivors, as it can be performed quickly and identifies patients who may not benefit from TTM. The primary finding in moderate to severe hypoxic-ischemic injury is cerebral edema characterized by attenuation of affected gray and white matter (83). In a study of TTM trial patients, generalized edema was seen in 9.6% of CT images within 24 h of ROSC and predicted poor outcome (CPC 3–5) with 97.6% specificity (95% CI 91.8–9.4) but only 14.4% sensitivity (95% CI 9.4–21.4) (84). Between days 1 and 7, generalized cerebral edema predicted poor outcome with a 0% FPR. In this study, other CT findings were infarct in 18.9% and intracranial hemorrhage in 6.3% (84).

The Role of Standard MRI

Despite MRI being more sensitive for detecting neuronal injury compared to CT, because of longer acquisition times and more necessary resources, its early use during the pre-TH and TH phase is limited. The optimal time window for MRI imaging is unknown; however, prognostic accuracy may be greatest between 2 and 5 days, with reduced sensitivity if done within 24 h (85, 86).

Brain areas most susceptible to hypoxic-anoxic injury include the cerebral cortex and deep brain nuclei that include the caudate, basal ganglia and thalamus. Diffusion restriction involving these areas, characterized by hyperintensity on diffusion-weighted imaging (DWI) and hypointensity on apparent diffusion coefficient (ADC) images, predicts poor outcome with high specificity (85, 87, 88). In a study correlating MRI findings with neuron-specific enolase, a biomarker with high prognostic value, levels $>33\ \mu g/ml$ after CA was associated with extensive DWI changes in both deep nuclei and the cortex (89). These patients had invariably poor outcome. More recently, quantitative measures of diffusion restriction burden on MRI has been proposed to standardize post-CA prognostication (86, 87, 90, 91); however, the most appropriate thresholds have not been established. In one multi-centered study, an ADC value $<650 \times 10^{-6} m^2/s$ in $\geq$10% of the total brain volume independently predicted poor outcome with a specificity of 91% (95% CI 75–98) and sensitivity of 72% (95% CI 61–80), with >22% of brain volume needed to achieve 100% specificity (90). In another study, <15% total brain volume with significant diffusion restriction was predictive of good neurologic recovery (91). As part of multimodality monitoring, combining MRI findings with EEG features, biomarkers and clinical exam may result in the highest accuracy in predicting outcomes (89, 91). Currently, the implementation of MRI in post-CA prognostication algorithms has not been strongly recommended by consensus guidelines (72).

Other Imaging Modalities

Functional Imaging

There are a limited number of studies with small sample sizes that have investigated the use of functional MR imaging (fMRI) in the management and prognosis of CA survivors (92). In a positron

emission tomography (PET) pilot study of 7 post-CA patients, all initially demonstrated a low cerebral metabolic rate of oxygen metabolism (CMR02) and cerebral blood flow; however, at day 7, those with persistent coma had lower CMR02 compared to those who regained consciousness (93). More recently, fMRI connectome imaging has demonstrated potential as a prognostic tool in CA, where patients who achieved favorable outcome have higher default-mode network connectivity (94, 95). It is unclear if fMRI is more accurate in predicting outcome in comparison to other MRI modalities (94), and they have not been compared directly with more established prognostic tools (92). Validation of PET imaging and other fMRI techniques may be a field of future research.

Transcranial Doppler Ultrasound

Transcranial Doppler ultrasound (TCD) is a useful bedside, non-invasive tool for monitoring characteristics in cerebral blood flow and intracranial vascular resistance. Early TCD studies suggested that higher vascular resistance indices and post-resuscitation hyperemia predicted poor outcome (96, 97); however, subsequent larger studies have not found correlation between TCD measurements and outcomes during both the TH phase and after rewarming (98, 99). TCDs in CA survivors is not part of routine practice in most hospital centers.

OTHER MULTIMODALITY MONITORING OF COMATOSE PATIENTS AFTER CARDIAC ARREST

Use of Invasive and Noninvasive Multimodality Monitors

Following CA, global anoxia leads to derangements of cerebral oxygenation and metabolism. Multimodality monitoring, including invasive ICP monitors, microdialysis catheters, jugular bulb catheters, near-infrared spectroscopy (NIRS) and monitors of brain oxygen tension, discussed here, aim to provide the clinician with physiologic parameters that reflect cerebral perfusion, tissue oxygenation and degree of metabolic derangement to help guide treatment and minimize secondary brain injury. Its use in other forms of neurologic injury, including traumatic brain injury and subarachnoid hemorrhage, have been studied extensively, but its use in survivors of CA remains poorly established in clinical practice.

Brain Oxygen Tension Monitors

Direct measurement of brain oxygen tension (PtiO2) or brain tissue oxygenation (PbtO2) is performed using a catheter similar in size to an ICP monitor, often through a burr hole or craniotomy site. Currently, it is primarily utilized in traumatic brain injury (TBI) populations, where studies have demonstrated its use may help guide treatment; however, the evidence for PbtO2 monitoring improving outcomes is inconsistent and its recommendation was removed from the most recent Brain Trauma Foundation Guidelines (100). PbtO2 monitors have the disadvantage of being limited to measuring focal ischemia, which may not be adequate in CA patients, and requiring daily calibration (101).

In animal models, mostly porcine, brain tissue oxygenation has been measured during CA and cardiopulmonary resuscitation (CPR). In one model, PbtO2 decreased to near zero during arrest, but increased with initiation of CPR and, if ROSC was achieved, exceeded pre-arrest values by 4-fold (102). Similar findings were seen in another animal model, although PbtO2 did not increase during CPR and only recovered with achievement of ROSC (103). In a recent porcine model of CA, hemodynamic-directed CPR was compared to depth-targeted CPR. In the study, a higher PbtO2 was achieved with hemodynamic-directed care that utilized vasopressors to maintain a target coronary perfusion pressure >20 mmHg (104). In humans, one case report demonstrated that feasibility of PbtO2 monitoring during CPR in an adult patient who achieved ROSC (105). Theoretically, PbtO2 monitoring would provide accurate and real-time measurements of brain oxygenation to ensure cerebral perfusion is maintained during CPR, ROSC, and TTM. Larger case series and trials are needed.

Near-Infrared Spectroscopy

NIRS is a non-invasive method of monitoring regional oxygenation in the cerebral cortex (rSO_2). Near-infrared light emitted by one surface probe passing through the cortex is absorbed by biological molecules including oxyhemoglobin, deoxyhemoglobin, and less commonly cytochrome-c oxidase (CCO), at different wavelengths. Differences in absorption by the receiving probe are used to quantifythe proportion of oxygenated hemoglobin or other molecule, which is reflective of perfusion (101). Advantages of NIRS are that it is non-invasive and can be performed at bedside.

Higher values of rSO_2 on NIRS have been demonstrated in patients achieving ROSC compared to those who do not achieve ROSC (106). Studies have also demonstrated higher values of rSO_2 using NIRS in post-CA patients with good neurologic outcome, although specific thresholds or cut-offs have not been established. In one study, post-CA patients with good neurologic outcome had higher rSO_2 values compared to those who with poor outcome ($55.6 \pm 20.8\%$ vs. $19.7 \pm 11.0\%$, $p < 0.001$, respectively), with a threshold rSO_2 value of >42% for predicting good outcome yielding a sensitivity of 0.79, specificity of 0.95, PPV 0.41 and NPV 0.99 (107). In comparison, another prospective study found that although post-CA patients with a good outcome had significantly higher median rSO_2 levels compared to those who had poor outcome (median rSO_2 of 68% vs. median rSO_2 of 58%, respectively) there was significant overlap in the range of rSO_2 between the two groups, limiting its use as a prognostic tool (108).

Microdialysis Catheters

Microdialysis catheters allow frequent assessments of cerebral metabolism and ischemic injury by utilizing a thin dialysis probe that is inserted into brain interstitial tissue. The catheter can measure extracellular solutes that diffuse through the membrane of the probe. Measurable solutes include markers of cerebral metabolism such as CSF lactate, pyruvate, glucose, and markers

of excitotoxicity such as glutamate, and cellular damage such as glycerol (109, 110). Additional values of importance, including markers of metabolic crisis such as lactate:pyruvate ratio (LPR), can be calculated autonomously.

During CA, the brain becomes oligemic, leading to diffuse ischemia. Patterns of ischemia are characterized by a decrease in cerebral glucose and an increase in cerebral lactate, which may reflect a state of anaerobic metabolism. These findings, along with increased glutamate and LPR have been demonstrated in animal models of CA (111, 112). Microdialysis results may have additional prognostic value. In rats, survivors of CA after CPR showed significantly higher cerebral lactate and glucose concentrations within 8 min compared to non-survivors, as well as increased lactate, glucose and pyruvate beyond 8 min (111). One small patient series of 4 human subjects with microdialysis catheters who underwent TTM demonstrated elevated LPRs that persisted despite achieving a neurologically intact exam (113). Although glutamate was initially high, values normalized in all 4 patients. Another patient series of CA survivors who underwent TTM found that LPRs progressively increased in those with poor outcomes with significantly higher values on days 2–3 compared to patients with favorable outcomes (114).

These preliminary studies establish the feasibility of microdialysis catheter monitoring in CA patients undergoing TTM. Although it has been demonstrated that neurochemical markers of cerebral ischemia are found after CA, further studies are needed to determine if they have a role in predicting outcome.

Jugular Bulb Catheters

Indirect measurements of cerebral oxygenation using jugular bulb catheters have been used in brain injured patients to assess the balance of cerebral oxygen supply and consumption, and to estimate cerebral perfusion (101). The catheters are placed in the internal jugular vein and are directed cranially to measure venous oxygen saturation (SjvO2], with a normal range of 55–70%. In CA, SjvO2 is reduced, reflecting decreased oxygen delivery and increased oxygen utilization in a stress state (101). Disadvantages of jugular bulb catheters are that it is an invasive monitor, with risk of carotid puncture, hematoma formation, or venous thrombosis during prolonged monitoring (101).

In a study of 30 comatose post-resuscitation patients, all subjects had an initial SjvO2 that was lower than the measured mixed venous oxygen saturation (SmvO2) within 6 h of CA, but in 12/20 non-survivors, SjvO2 increased significantly to values higher than the SmvO2 (115). The significance of this finding is unclear. Other studies have demonstrated higher SjvO2 in comatose non-survivors of CA, which was thought to reflect a decrease in cerebral oxygen consumption due to loss of functional brain tissue and may be an indicator of poor neurologic outcome (116). Although it involved a small sample size, the study found that the positive predictive value of a difference between SmvO2 and SjO2 of ≤ 0 for predicting irreversible brain damage at 24 h following CA was 93%, while the negative predictive value of SmvO2–SjO2 > 0 was 53%. Another study of 34 patients found that having a SmvO2 $>$ SjvO2 between 24 and 48 h after ROSC had a positive predictive value of 100% and a negative predictive value of 92% for predicting recovery of consciousness (117). Unfortunately, these results have not been reliably duplicated with TTM patients. In the TTM era, one study of 75 patients found no difference in SjvO2 between patients with good and poor outcome at 6 months (118).

External Ventricular Drain and ICP Catheters

ICP monitoring devices are typically categorized based on their location of placement, often either ventricular or intraparenchymal, with extradural and subdural monitors being less common. Intraventricular catheters are both diagnostic and therapeutic, allowing clinicians to drain cerebrospinal fluid if ICP rises. Intraparenchymal monitors have the advantage of lower infection rates compared to ventricular catheters; however, they are more prone to drift and technical complications that limit its usability (119).

Following CA, cerebral edema occurs as early as the first 24 h, with CT imaging demonstrating diffuse loss of gray-white differentiation in up to 12% of scans performed and global cerebral edema in as many as 6% (120). ICP monitoring is frequently used when cerebral edema is diagnosed in brain injured patients, including those with traumatic brain injury, intracerebral hemorrhage, or subarachnoid hemorrhage. Uncontrolled intracranial hypertension is associated with poor outcomes in the TBI literature, and although its impact in CA patients is not well defined, ICP elevations can result in cerebral herniation and may serve as a trigger for monitoring and augmenting cerebral perfusion pressures (CPP) (8).

Elevations in ICP have been identified in post-CA patients during the resuscitation period, which may be due to delayed hyperemia (97). In one post-resuscitation study of ICP monitoring performed on 84 patients, peak ICP $>$ 25 mmHg was associated with poor outcomes. Additionally, non-survivors consistently had higher ICPs and lower CPP than survivors (121). This association has been noted in more recent studies following the advent of TTM. Increases in ICP have been noted during both TH and the rewarming period, and at least in one study, all cases of ICP $>$ 25 mmHg were associated with mortality (113, 122). Even when CPP did not differ between groups, studies have shown elevated ICPs are associated with poor outcome (114). The evidence suggests that elevated ICP can occur after CA and during rewarming in patients who undergo TTM; although, to date, no large studies have used ICP monitors to guide management of the post-CA patient.

DISCUSSING PROGNOSIS AFTER CARDIAC ARREST

Despite the use of multiple prognostic tools, prediction of outcomes after CA is difficult. Registries such as the International Cardiac Arrest Registry (INTCAR), a prospective multinational registry of treatment and outcomes in post-CA patients who achieve ROSC, have been developed with the intention of furthering research on CA outcomes (123). The ongoing clinical trial, Multimodal Outcome Characterization in Comatose Cardiac Arrest Patients Registry and Tissue Repository

(MOCHA), proposes to develop a multimodal prediction model for outcomes in post-CA patients (124). Currently, given the available evidence in the literature, it is reasonable to discuss pertinent clinical exam, EEG, SSEP, biomarker, and CT and MRI findings with family members and surrogate decision makers to help guide their expectations and inform their decisions. Further validation is needed before fMRI and invasive multimodality monitoring devices are used in standardized prognostication algorithms.

The timing of outcome prediction is crucial in CA. The 72 h clinical exam remains the most informative; however, in patients receiving TTM, the earliest time for prognostication using the clinical exam may be 72 h after achieving normothermia and after other confounding factors, such as paralysis and sedation are safely excluded (12, 64). Similarly, the accuracy of other prognostic tools may be affected by TH, with MRI at day 2–5 being reasonable for prognostication (85, 86).

The accuracy and limitations of prognostication should be shared with all family members and decision makers. Caution must be taken to avoid propagation of a self-fulfilling prophecy in withdrawing life sustaining therapy in this patient population. Studies on prognostication post-CA may suffer from bias as patients with poor neurologic prognosticators may receive limited intensive care or may have had recommendations for withdrawal of treatment (125). Often, goals of care established by family members or decision makers do not align with a patient's prognosis (126), where patient age, comorbidities, prior patient wishes, and cultural aspects factor in to a decision. Establishing and implementing a protocol and expected practice, based on each institution's resources and limitations may help clinicians and families navigate this difficult course.

CONCLUSION

Neurologists and neurointensivists are central to guiding TTM, ICU care and prognostication in survivors of CA. Given the neuroprotective effects of TTM and their influence on prognostication and multimodality monitoring, providers should be familiar with the most recent guidelines and literature. We recommend that an evidence-based TTM and prognostication algorithm be locally implemented, based on each institution's resources and limitations. Given the high incidence of CA and the difficulty in predicting outcomes, further study is urgently needed to determine the utility of more recent multimodality devices and studies.

AUTHOR CONTRIBUTIONS

RP, JM, and GS conceived the manuscript topic and outline. PN, LA, RP, and GK were the primary authors of the manuscript with input from all authors. PN, RP, and JM were involved in critical manuscript revisions. RP, JM, and GS directed manuscript preparation. All authors read and approved the submitted version.

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Continuous Vital Sign Analysis to Predict Secondary Neurological Decline After Traumatic Brain Injury

*Christopher Melinosky[1,2], Shiming Yang[1,3], Peter Hu[1,3], HsiaoChi Li[3], Catriona H. T. Miller[4], Imad Khan[1,2], Colin Mackenzie[1,3], Wan-Tsu Chang[1,5], Gunjan Parikh[1,2], Deborah Stein[1,6] and Neeraj Badjatia[1,2]**

[1] Program in Trauma, University of Maryland School of Medicine, Baltimore, MD, United States, [2] Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, United States, [3] Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, MD, United States, [4] Enroute care Division, Department of Aeromedical Research, U.S. Air Force School of Aerospace Medicine, Wright Patterson AFB, Dayton, OH, United States, [5] Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, MD, United States, [6] Department of Surgery, University of Maryland School of Medicine, Baltimore, MD, United States

Background: In the acute resuscitation period after traumatic brain injury (TBI), one of the goals is to identify those at risk for secondary neurological decline (ND), represented by a constellation of clinical signs that can be identified as objective events related to secondary brain injury and independently impact outcome. We investigated whether continuous vital sign variability and waveform analysis of the electrocardiogram (ECG) or photoplethysmogram (PPG) within the first hour of resuscitation may enhance the ability to predict ND in the initial 48 hours after traumatic brain injury (TBI).

Methods: Retrospective analysis of ND in TBI patients enrolled in the prospective Oximetry and Noninvasive Predictors Of Intervention Need after Trauma (ONPOINT) study. ND was defined as any of the following occurring in the first 48 h: new asymmetric pupillary dilatation (>2 mm), 2 point GCS decline, interval worsening of CT scan as assessed by the Marshall score, or intervention for cerebral edema. Beat-to-beat variation of ECG or PPG, as well as waveform features during the first 15 and 60 min after arrival in the TRU were analyzed to determine physiologic parameters associated with future ND. Physiologic and admission clinical variables were combined in multivariable logistic regression models predicting ND and inpatient mortality.

Results: There were 33 (17%) patients with ND among 191 patients (mean age 43 years old, GCS 13, ISS 12, 69% men) who met study criteria. ND was associated with ICU admission ($P < 0.001$) and inpatient mortality ($P < 0.001$). Both ECG (AUROC: 0.84, 95% CI: 0.76,0.93) and PPG (AUROC: 0.87, 95% CI: 0.80, 0.93) analyses during the first 15 min of resuscitation demonstrated a greater ability to predict ND then clinical characteristics alone (AUROC: 0.69, 95% CI: 0.59, 0.8). Age ($P = 0.02$), Marshall score ($P = 0.001$), penetrating injury ($P = 0.02$), and predictive probability for ND by PPG analysis at 15 min ($P = 0.03$) were independently associated with inpatient mortality.

Conclusions: Analysis of variability and ECG or PPG waveform in the first minutes of resuscitation may represent a non-invasive early marker of future ND.

Keywords: traumatic brain injury, machine learning, heart rate variability, photoplethysmogram, predictive model

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Wengui Yu,
University of California, Irvine, United States

Reviewed by:
Sara Stern-Nezer,
University of California, Irvine, United States
Syed Omar Shah,
Thomas Jefferson University, United States

***Correspondence:**
Neeraj Badjatia
nbadjatia@som.umaryland.edu

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INTRODUCTION

One and a half million Americans incur a traumatic brain injury (TBI) each year (1) and approximately 5.3 million individuals have enduring disabilities as a direct result of a TBI (1). In the acute resuscitation period, one of the goals is to identify those at risk for secondary neurological decline, represented by a constellation of clinical signs that can be identified as objective events related to secondary brain injury and independently impact outcome (2). In moderate to severe TBI, the incidence of secondary neurological decline is approximately 20% (3), and the negative impact of many of these events, e.g., rise in intracranial pressure or need for decompressive craniectomy, can be potentially minimized if identified early. In mild TBI populations, while delayed neurological decline is a relatively rare event [estimated to be 5–10%(4)], patients often require a lengthy observation and stays to rule out the possibility of secondary decline. Currently, initial risk stratification after injury is based on clinical judgment, clinical examination, and assessment of static vital signs (5), which only provide partial guidance in the acute resuscitation period.

Additional essential information can be derived from the analysis of continuous vital sign data and waveform analysis. Specifically, autonomic nervous system (ANS) function can be monitored non-invasively and continuously by analyzing variability and waveform features from routine electrocardiogram (ECG) or photoplethysmogram (PPG) monitoring (6–8).

We hypothesized that in combination with routine clinical assessments and neuroimaging in the first hour after injury, continuous vital sign monitoring for variability and waveform feature analyses from either the ECG or PPG can be utilized to reliably predict early (<48 h after injury) ND in a cohort patients with isolated TBI patients.

METHODS

Patient Selection and Study Design

This is a retrospective subgroup analysis using data collected for the project Oximetry and Noninvasive Predictors Of Intervention Need after Trauma (ONPOINT) project (FA8650-11-2-6D01) at the University of Maryland Medical Center, R Adams Cowley Shock Trauma Center Trauma Resuscitation Unit (TRU). ONPOINT was a project designed to identify new noninvasive sensors and physiological features that may predict trauma patients' need for lifesaving interventions (9–11). Patients were included in ONPOINT if they had a shock index of 0.62 or greater based on VS radioed in from the field by the emergency medical service (EMS) provider, were designated EMS "Priority 1" (denoting a critically ill or injured person requiring immediate attention), or were unstable with a life-threatening injury but without an available prehospital VS. Patients who survived less than 15 min after admission to the trauma center were excluded, as were patients with neurological impairment due to cervical spine injury. In addition, this subset analysis was limited to patients with a head abbreviated injury score (AIS)>1 who had at least 2 CT scans done within the first 24 h and availability of PPG and ECG waveform data for the first hour of admission. Patients with significant systemic trauma, identified as abdominal or thoracic AIS>1 were excluded.

Charts were retrospectively reviewed for ND from the time of arrival in the TRU through the first 48 h of admission. Clinical data were gathered from recorded hourly bedside neurologic assessments of GCS and pupillary reactivity and neurosurgical notes for surgical intervention. Radiographic data was gathered from Marshall scores of the first three CT scans done in the first 24 h. Demographic and injury severity data were obtained from the institutional Trauma Registry. Continuous PPG and ECG 240 Hz waveforms were collected via BedMaster® (Excel Medical Electronics Inc., Jupiter, FL) vital signs collection system beginning at the time of arrival in the TRU.

Data Processing and Feature Design

Signal quality was evaluated based on R-peaks in ECG and the peaks in PPG, with the assumption that good quality signals have normal distributed R-R intervals. R-R intervals from segments of low quality were detected as outliers using the Z-test. An additional Figure shows this more detail **(Supplemental Figure 1)**.

HRV and waveform morphology features were derived from the ECG. **Figure 1** shows a typical PQRST segment from ECG, with identified peaks and five items that were used for calculation. The normal-to-normal (NN) interval illustrated by item 1 is the time interval between two consecutive R peaks. HRV was measured beat to beat variability using standard definitions. HRV variables in time domain and nonlinear dynamics were calculated based on the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (12, 13). From items 2 and 4 in **Figure 1**, the rising time from Q to R and the falling time from R to S were calculated. Similarly, from items 3 and 5, the rising and falling amplitudes from Q to R and R to S were calculated. Statistical quantities, such as the 1st, 2nd, 3rd quartiles, minimum, maximum, and Shannon entropy were used to summarize each above variable in a selected time window.

PPG variability and waveform morphology features were also designed similarly with expansion based on PPG unique characteristics. **Figure 1B** subplot shows a normal PPG segment with identified peaks and valleys. Item 1 illustrates a peak-to-peak time interval, which is analog to the NN interval in ECG. PPGV variables and morphology features were calculated from items 1–4 as we did for ECG. PPG waveform also has unique dicrotic notch that its shape has been studied and shown to be related to arterial stiffness and aging (14). To measure the deceleration and acceleration near the dicrotic notch, the first and second derivatives of PPG were calculated through three-point central difference (15, 16).

We only utilized continuous vital sign data from the initial 15 and 60 min of arrival to the TRU to develop PPG and ECG derived models. The waveform and physiologic variables analyzed for both PPG and ECG are shown in **Supplemental Table 1**. Multiple models were created for analysis **(Table 1)**. The first set of models utilized clinical characteristics typically available within the first hour of patient arrival. The

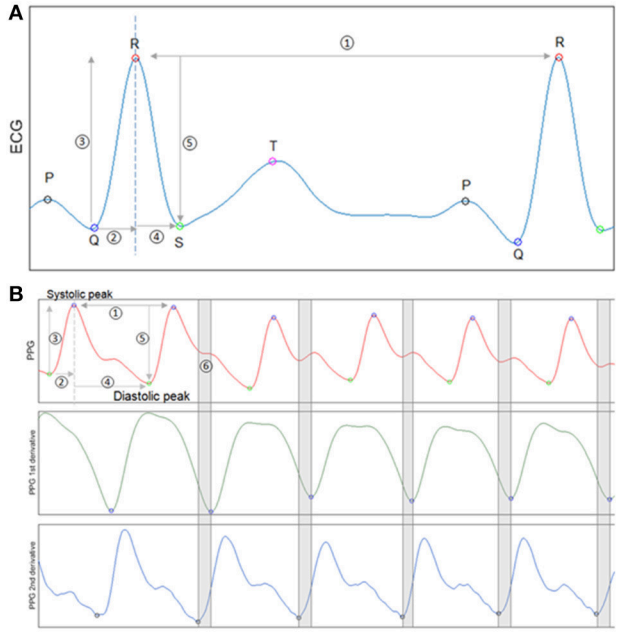

FIGURE 1 | Waveform feature analysis for ECG and PPG. **(A)** An exemplary ECG segment with identified P,Q,R,S,T peaks. Five items from the segment are used for ECG feature calculation. Item 1 is the NN interval. Items 2 and 4 are Q to R rising time and R to S falling time. Items 3 and 5 are Q to R rising amplitude and R to S falling amplitude. **(B)** An exemplary PPG segment with identified peaks and valleys (1st panel).The first derivative of PPG signal (2nd panel). The second derivative of PPG signal (3rd panel). The first and second derivatives of the PPG waveform were used to identify the diastolic notch indicated by segment 6.

second set of models utilized only physiologic data from the first 15 and 60 min after arrival in the TRU. The final set of models combined clinical characteristics with ECG and PPG analyses at 60 min after arrival to the TRU.

Outcome Measures

Neurological Decline (ND)

ND was defined using previously reported criteria as any of the following occurring in the first 48 h: new asymmetric pupillary dilatation(>2 mm), 2 point GCS decline not due to intubation for procedure, or analgo-sedation; interval worsening of CT scan as assessed by the Marshall score (17); treatment of cerebral edema by placement of intracranial monitoring (intracranial parenchymal pressure monitor or external ventricular drainage), or treatment by osmotherapy, hyperventilation, craniotomy or decompressive craniectomy. Two investigators (NB, GP) independently reviewed at least 2 CT scans during study period for each patient and provided a Marshall score for each scan. Changes in GCS and pupillary size were determined by assessing the hourly score and pupil size recorded in the nursing flowsheet. Influence of analgo-sedation was determined by reviewing medical records and eliminating any decline in exam that occurred within 2 h of medication administration. Decline not related to radiographic worsening was labeled as clinical ND, whereas interval worsening Marshall score was labeled as radiographic ND. Mortality within 48 h was abstracted from the chart.

TABLE 1 | Characteristics of models to predict neurological worsening.

Model	Variables
CLINICAL CHARACTERISTICS	
Model 1	Age, sex, first vital sign data recorded (HR, RR, SBP, DBP)
Model 2	Age, sex, first vital sign data recorded (HR, RR, SBP, DBP), and initial GCS recorded
Model 3	Age, sex, first vital sign data recorded (HR, RR, SBP, DBP), initial GCS, and Marshall score
PHYSIOLOGIC CHARACTERISTICS	
Model 4	ECG heart rate variability and waveform feature analysis for the first 15 min
Model 5	PPG variability and waveform feature analysis for the first 15 min
Model 6	ECG heart rate variability and waveform feature analysis for the first 60 min
Model 7	PPG variability and waveform feature analysis for the first 60 min
COMBINED CLINICAL AND PHYSIOLOGIC CHARACTERISTICS	
Model 8	Model 2 + Model 4
Model 9	Model 2 + Model 5

Statistical Analysis

Neurological decline was classified either present or absent, if any of the a priori criteria for ND were met. Multivariate stepwise logistic regression was used to establish the association between clinical, ECG, and PPG variables and neurological decline. The Wald Chi-square test was used to determine whether one variable should be included (forward step) or excluded (backward step). To test models' generalization capability on new data, 10-fold cross-validation repeated 10 times with stratified sampling was used (18). Area under the receiver operating characteristic curve (AUROC) was used as an overall performance metric. Lack of overlap in 95% confidence interval (CI) was considered statistically significant. Sensitivity, specificity, positive predicted value (PPV) and negative predicted value (NPV) were calculated from the optimal threshold based on the Youden index. All signal processing and feature extracting were analyzed with Matlab (2014b, Mathworks, Natick, MA). Multivariable models were built to determine whether the prediction probability of PPGV for ND was independently associated with in patient mortality.

Predictive models and statistical analysis were implemented with R software version 3.2.2 (R Development Core Team, Vienna, Austria).

Approval for this study was obtained from the University of Maryland School of Medicine and US Air Force Research Laboratory Institutional Review Boards.

RESULTS

There were 1191 patients admitted satisfying the age (≥18 years old) and pre-hospital SI (≥ 0.62) criteria for inclusion in the ONPOINT study between December 2011 and May 2013. There were 219 cases that met additional criteria for this subgroup analysis, and of those, 191 cases were found to

have complete data for analysis **(Figure 2)**. ND was found to have occurred in 17% of patients ($n = 33/191$) with baseline characteristics shown in **Table 2**. Clinical ND occurred in 19 (10%), radiographic worsening in 25 (13%). In the 11 (6%) patients that had both clinical and radiographic worsening only 1 ND event was counted for the final analysis. ND was associated with a longer hospital length of stay($P < 0.001$), admission to the intensive care unit ($P < 0.001$) and higher rates of in patient mortality ($P < 0.001$). These data are shown in more detail in **Supplemental Table 2.**

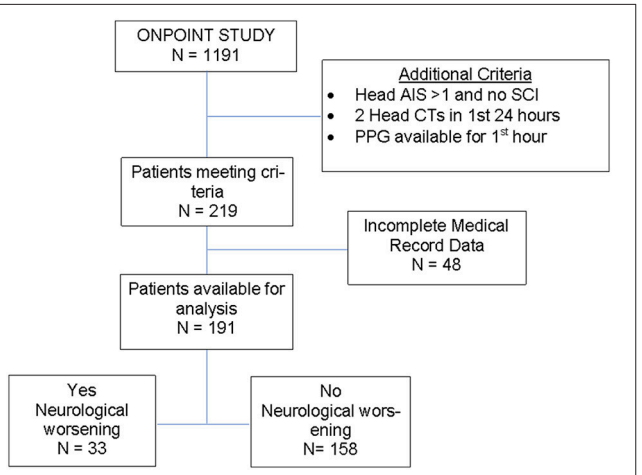

FIGURE 2 | Flow diagram of study cohort.

TABLE 2 | Baseline characteristics of study cohort.

Admission characteristics	Neurological decline		
	No	Yes	
	N = 158	*N* = 33	*P*-value
Age	41 (25, 54)	48 (26, 74)	0.19
Men	112 (71)	25 (76)	0.61
RACE			0.64
White	103(65)	23 (70)	
Black	40 (25)	10 (30)	
Other	15 (10)	–	
Injury severity score	5 (5, 14)	25 (16,29)	<0.001
GCS score	15 (15, 15)	7 (3, 14)	<0.001
Marshall score	1 (1, 1)	2 (1, 3)	<0.001
MAP(mmHg)	107 (98,118)	108 (102, 118)	<0.001
Heart Rate (bpm)	97 (82,106)	88 (75, 103)	0.39
Resp. Rate (bpm)	20 (17, 23)	18 (12, 24)	0.08
O_2 Saturation (%)	99 (98, 100)	100 (97, 100)	0.45
Mechanism of injury			0.21
Blunt	147 (93)	28 (85)	
Penetrating	11 (7)	5 (15)	

All continuous data shown at median (25th%ile, 75%thile). Categorical data shown as n(%). P-values obtained from Chi-Square test and Mann-Whitney U test for categorical and continuous data respectively.

ND Predictive Model Development and Performance (Table 3)

Clinical Characteristics

A model accounting for the initial VS measurements, age, and sex (Model 1) was the weakest model but able to predict ND within the next 48 h (AUC 0.69, 95% CI:0.59, 0.8 $P = 0.0002$); adding admission GCS to the model resulted in improvement (AUC 0.86, 95% CI: 0.77, 0.94, $p < 0.0001$). Incorporating Marshall scores to admission data further enhanced predictability (AUC 0.90, $p < 0.0001$).

Heart Rate Variability and Waveform Feature Analysis

ECG HRV and waveform feature analyses during the first 15 (model 4) and 60 min (model 6) post admission to the TRU demonstrated a strong ability to predict ND. Similarly, PPG variability and waveform feature analysis has a high AUROC at both 15 (model 5) and 60 (model 7) min for predicting ND. Both sets of models had high negative predictive values (NPV).

Combined Models of Clinical Characteristics and Physiologic Data

Combining clinical characteristics, including GCS, with physiologic data obtained from ECG (model 8) or PPG (model 9) yielded similar AUROC results, with a strong NPV of 0.97 and 0.98, respectively.

Prediction of in—hospital Mortality

The predictive probabilistic score of PPG feature analysis at 15 min for ND (PPG15) was entered into a multivariable logistic regression model determining factors associated with inpatient mortality. Older age (Odds Ratio (OR): 1.05, 95% CI: 1.01, 1.09, $P = 0.02$), Marshall CT score (OR: 4.2, 95% CI: 18.6, 9.47, $P = 0.002$), penetrating injury (OR: 2.9, 95% CI: 1.16, 7.22, $P = 0.02$), and PPG15 (OR: 3.26, 95% CI: 1.14, 9.4, $P = 0.03$) were found to be independently associated with a higher risk of inpatient mortality, after adjusting for sex, admission mean arterial pressure (MAP), heart rate, respiratory rate, and GCS.

DISCUSSION

Without regards to the patient age, sex, GCS or initial set of vital signs, the PPG and ECG analyses alone at 15 min (models 4 and 5) were better or as good as clinical models 1 and 2 (**Table 3**) to predict ND. Moreover, a combined model with the clinical and physiologic characteristics at 15 and 60 min after arrival yielded an improved prediction power for ND. These analyses reflect the great potential assessing the physiological state by utilizing continuous vital sign data to enhance the clinical assessment in the acute resuscitation period after TBI.

ECG and PPG sensors provide a wealth of information on the cardiovascular and respiratory systems through further waveform analysis. The ECG waveform can provide data on the heart rate variability (HRV) which has been used in studies of neurologic disorders (13, 19) as a marker of the function of the ANS (20) Specific to TBI, dysautonomia has been closely linked to increased ICP or decreased CPP (21). Baguley et al. (22) observed that in TBI, patients with and without

TABLE 3 | Predictive models of neurological decline.

Model	AUROC[a]	AUROC 95% CI		PPV[b]	NPV[c]
		Low	High		
CLINICAL CHARACTERISTICS					
Model 1	0.69	0.59	0.80	0.35	0.90
Model 2	0.86	0.77	0.94	0.67	0.94
Model 3	0.90	0.84	0.97	0.61	0.97
PHYSIOLOGIC CHARACTERISTICS					
Model 4	0.84	0.76	0.93	0.53	0.94
Model 5	0.87	0.80	0.93	0.47	0.95
Model 6	0.89	0.83	0.96	0.57	0.96
Model 7	0.83	0.74	0.91	0.47	0.94
COMBINED CLINICAL AND PHYSIOLOGIC CHARACTERISTICS					
Model 8	0.92	0.87	0.97	0.76	0.97
Model 9	0.92	0.86	0.98	0.68	0.98

[a] *AUROC, Area Under the Curve for Receiver Operator Curve.*
[b] *PPV, positive predictive value.*
[c] *NPV, negative predictive value.*

dysautonomia showed HRV differences compared to controls. The pulse oximeter is a commonly used sensor that can provide rich data by generation of a PPG waveform, which can provide information on heart rate, oxygen saturation, and respiratory rate (23). The PPG peaks correspond to the R peaks from ECG, therefore, the peak-peak interval from PPG can be used as an alternative to the NN interval calculated from ECG recordings. Lu et al. (24) found PPG variability (PPGV) was highly correlated to HRV and could serve as an alternative measurement. Several studies have correlated similar physiological measurements with autonomic changes in TBI patients with the severity of injury and, association with increased ICP (25–27) as well as overall morbidity and mortality (25, 27, 28).

Our results are novel given we only utilized continuous ECG and PPG data from the first minutes of arrival, prior to ICP monitoring and CT imaging, further signifying the viability of physiologic and waveform analysis as a robust early marker in the resuscitation phase. It is important to note that within 15 min of arrival, patients were still undergoing physical exam and assessment, and were not under the influence of sedatives or analgesics that may have confounded the signal from the continuous vital sign data collection. The ability to accurately discern a risk for ND early in the acute resuscitation phase could provide for an opportunity to develop targeted interventions to mitigate secondary injury, including rapid triage for timely, definitive treatment.

The results from this study also indicate that ND within the first 48 h after injury occurs commonly after isolated TBI, and that it is associated with a longer duration of hospitalization and higher rate of mortality. A recent analysis of mild TBI patients found a mortality rate of 23% in patients who had acute ND (4). Our study had a higher rate of inpatient mortality likely due to a higher baseline severity of injury.

ND prediction with admission VS, age, sex and GCS score was moderately accurate, confirming the importance of a thorough clinical assessment upon arrival to the hospital. GCS is a robust neurological assessment tool; however, early presentation can be deceiving, with many low energy falls resulting in brain hemorrhage and swelling, resulting in increased ICP and greater risk for severe disability and death (29–33). Additionally, the inter-rater reliability of GCS measurement is variable, and may be influenced by level of training and experience of the individual making the assessment (34–36). This further highlights the importance of utilizing metrics, such as ECG or PPG waveform feature analysis, that are resilient to factors that impact the reliability of the GCS assessment. Serial CT imaging provides additional information regarding clinically silent progression of injury (37–39) with the aim of capturing signs of neurologic worsening which can lead to early medical and surgical interventions even before the clinical symptoms manifest (40). Despite our results indicating additional benefit of scoring severity of injury by CT imaging, a multicenter prospective study as well as several large single center cohort studies have failed to find factors that reliably predicted the correlation between ND and serial CT imaging (41–44). Serial CT imaging is likely most useful as a practice for patients in whom examination is not reliable and/or as a confirmatory test for assessing structural reasons for ND. Moreover, serial imaging is often not practical in the rural areas, developing countries and combat fields with limited resources.

There are limitations to this study that are worth considering. This study was a retrospective analysis in which there may be reporting bias for ND. Due to this concern, we measured variables that we know are entered with high reliability, such as GCS score, change in pupil size, and radiographic changes. The timing of the imaging was not always consistent. However, most TBI patients at our institution receive a head CT within the hour of arrival. During CT, vital sign data is not able to be collected, however, our continuous data capture system was able to capture the majority of waveform data during the study period. Though we conducted a rigorous testing process by 10-fold cross-validation repeated 10 times with stratified sampling, the results here are from a single center and need validation in a prospective cohort. This was a population without polytrauma and a high initial GCS scores indicating mild TBI. We intentionally chose a population of relatively mild TBI without polytrauma in order to test our hypotheses; a broader population of TBI patients with polytrauma need to be tested in order to increase the generalizability of our findings. Sedation and analgesia may have played a role in exam features, though exam changes occurring following sedation was not labeled ND.

CONCLUSIONS

By coupling patient factors and continuous physiologic data, a non—invasive predictive model of neurological deterioration is feasible and may potentially lead to automated decision support algorithms and provide for earlier, targeted therapeutic interventions. This may be especially useful in rural or austere settings where acute triage decisions may be made without the benefit of neuroimaging or subspecialty expertise. Further

refinement in larger, more heterogeneous groups of TBI patients is necessary prior applying these findings in a prospective setting.

AUTHOR CONTRIBUTIONS

NB, ChM, SY, PH, and CaM made substantial contributions to conception and design, analysis and interpretation of data. GP, WC, HL, ChM, and IK made substantial contributions to the acquisition of data, analysis and interpretation of data. NB, ChM, SY, PH, GP, and DS were involved in drafting the manuscript or revising it critically for important intellectual content. All authors given final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00761/full#supplementary-material

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BRIEF RESEARCH REPORT
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Otoacoustic Emissions for Outcome Prediction in Postanoxic Brain Injury

Daniel Kondziella[1], Anne Marie Jensen[2], Thomas Hjuler[2], Michael Bille[2] and Jesper Kjaergaard[3]*

[1] Department of Neurology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [2] Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [3] Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Background: Non-invasive, easy-to-use bedside tools to estimate prognosis in unresponsive patients with postanoxic brain injury are needed. We assessed the usefulness of otoacoustic emissions as outcome markers after cardiac arrest.

Methods: Distortion product otoacoustic emissions (DPOAE) and transient evoked otoacoustic emissions (TEOAE) were measured in cardiac arrest patients whose prognosis was deemed to be poor following standard neurological assessment ($n = 10$). Ten patients with myocardial infarction without prior loss of consciousness served as controls.

Results: Compared to controls with myocardial infarction, cardiac arrest patients with poor neurological prognosis had significantly less often preserved DPOAE (9.2 vs. 40.8% positive measurements; OR 0.15 (CI 0.07–0.30); $p < 0.0001$). Partially preserved DPOAE were noted in 4 cardiac arrest patients. TEOAE were not statistically different between the two groups.

Conclusions: Despite their convenience, otoacoustic emissions cannot be used as reliable prognostic markers in cardiac arrest survivors. This is because we identified 4 cases with partially preserved otoacoustic emissions in a sample of 10 unresponsive post-cardiac arrest patients whose neurological condition was so poor that active treatment was withdrawn. However, we suggest that future research should address if decaying outer hair cell function over time may serve as a proxy for evolving ischemic brain damage.

Keywords: anoxic-ischemic encephalopathy, brain edema, cardiac arrest, prognostication, outcome

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Wengui Yu,
University of California, Irvine, United States

Reviewed by:
Benjamin Aaron Emanuel,
University of Southern California, United States
Cyrus Khurshed Dastur,
University of California, Irvine, United States

****Correspondence:***
Daniel Kondziella
daniel_kondziella@yahoo.com

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INTRODUCTION

Otoacoustic emissions are small sounds generated by the outer hair cell activity in the cochlear and can be measured in the ear canal of healthy people. These sounds are by-products of active processes in the cochlea, in which motility of the outer hair cells adjusts the basilar membrane and amplifies weak sounds. Although they do not contribute to hearing, otoacoustic emissions are clinically important because they allow evaluation of the integrity of outer hair cell function and the cochlea. They are therefore routinely assessed for evaluation of hearing, including screening in newborns.

A pre-neuronal phenomenon, otoacoustic emissions are unaffected by sedation; they can be assessed non-invasively at the bedside using an automated hand-held device; costs are low; and analysis does not require elaborate data post-processing (**Figure 1**) (1, 2). These are all features of a convenient candidate biomarker for prognostication following anoxic brain injury. However, the usefulness of otoacoustic emissions as prognostic markers after cardiac arrest is unknown.

The intention of this exploratory study was to compare otoacoustic emissions in patients from the extreme sides of the clinical spectrum, that is, cardiac arrest with poor neurological prognosis (fatal cerebral anoxic-ischemic injury) on one side and myocardial infarction without loss of consciousness on the other (no cerebral anoxic-ischemic injury).

We hypothesized that otoacoustic emissions would be absent in comatose cardiac arrest patients with irreversible anoxic-ischemic encephalopathy but relatively preserved in neurologically normal patients with myocardial infarctions and without prior loss of consciousness.

METHODS

We assessed distortion product otoacoustic emissions (DPOAE) and transient evoked otoacoustic emissions (TEOAE) in both ears of 10 consecutive unresponsive cardiac arrest survivors in whom a decision had been made to withdraw treatment based on standardized neurological assessment, including neuroimaging, electroencephalography, median nerve sensory evoked potentials, and serum biomarkers, $\geq$ 72 h after target temperature management and tapering of sedation. DPOAE and TEOAE, as well as auditory brainstem response audiometry, were assessed within 3 h prior to extubation and palliation. Ten age- and sex-matched patients with myocardial infarction without prior loss of consciousness served as controls.

Otoscopy and tympanometry was performed prior to testing of otoacoustic emissions in order to exclude obstruction of the ear canal and middle-ear effusion. Otoacoustic emissions were assessed using OAE Titan (®Interacoustics, Middelfart, Denmark) and TEOAE were recorded using AccuScreen (®Otometrics, Taastrup, Denmark), as described earlier (1). Briefly, a sensitive, low noise microphone is sealed in the external ear canal and an acoustic stimulus is delivered. The sound in the external ear canal that is elicited in response to the acoustic stimulus is recorded by the microphone (**Figure 1**).

Odds ratios were calculated and the level of statistical significance was set to $p < 0.01$. The Ethics Committee of the Capital Region of Denmark (De Videnskabsetiske Kommiteer—Region Hovedstaden, Hillerød, Denmark) approved the study and waived the need for written consent because risks were deemed negligible (reference j.nr. H-17038640).

RESULTS

Following cardiac arrest with severe anoxic-ischemic brain injury, TEOAE were present in 2 out of 20 measurements (i.e., 2 out of 10 cases; mean age 63.2 ± 12.6 years; 2 females). Following

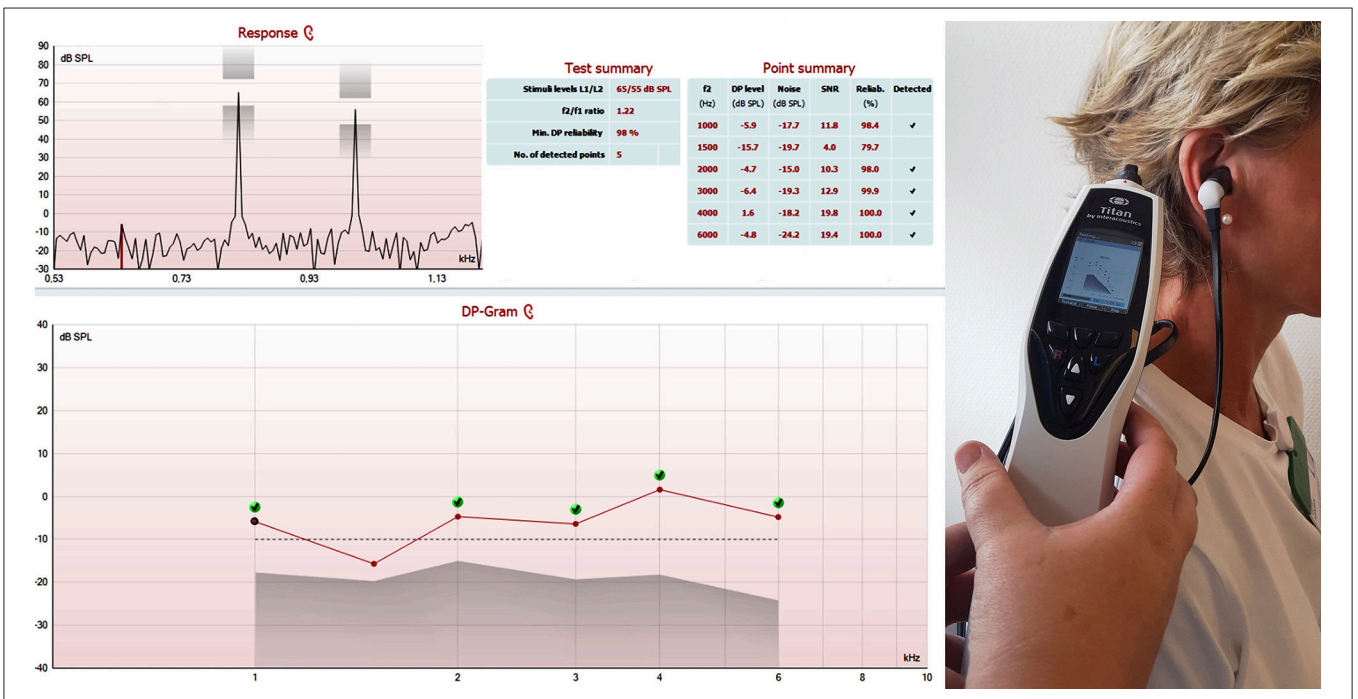

FIGURE 1 | This figure shows a screenshot depicting a schematic overview of distortion product otoacoustic emissions (DPOAE) of the right ear of a healthy volunteer. DPOAE were present at 1, 2, 3, 4, and 6 kHz (but not 1.5 kHz). Otoacoustic emissions were assessed with the OAE Titan (®Interacoustics, Middelfart, Denmark), an automated handheld device. The procedure takes less than 2 min. dB SPL – decibel sound pressure level; kHz –1,000 Hertz.

TABLE 1A | Contingency table showing the frequency of present vs. absent distortion product otoacoustic emissions (DPOAE) in patients following cardiac arrest (cases), respectively, myocardial infarction without loss of consciousness (controls).

	DPOAE present	DPOAE absent	Total	Percent
Cases Post-cardiac arrest patients ($n = 10$)	11	109	120	9.2%
Controls Myocardial infarct patients ($n = 10$)	49	71	120	40.8%

DPOAE were significantly less frequent after cardiac arrest (9.2 vs. 40.8%; OR 0.15 (CI 0.07–0.30); p < 0.0001).

TABLE 1B | Summary of individual results from cardiac arrest patients (cases) and patients with myocardial infarction but normal consciousness (controls).

	Preserved responses after cardiac arrest ($n = 10$ cases)	Preserved responses after myocardial infarction ($n = 10$ controls)
Auditory brainstem response audiometry 45 dB nHL	1r,l; 2l	3r,l; 5r,l; 6r,l; 7r,l; 8r,l; 10r,l
TEOAE	1r; 5l	2r,l; 3l,r; 6r,l; 8r; 10r,l
DPOAE 1 kHz	6l	2l; 5l,r; 7r; 8r; 10r,l
DPOAE 1.5 kHz	1r; 5l; 6l	2r,l; 3r,l; 5r,l; 6r,l; 8r,l; 9r; 10r,l
DPOAE 2 kHz	1r, 6l, 7r	2r; 3r,l; 4r; 5r; 6l,r; 8r,l; 9r; 10r,l
DPOAE 3 kHz	1r, l	3r,l; 6r; 7r,l; 8r,l; 9r;10r,l
DPOAE 4 kHz	1r; 6r	3r,l; 4r; 7r,l; 8r; 9r
DPOAE 6 kHz		

Only preserved responses are listed. Auditory brainstem responses could not be acquired in 3 controls due to excessive facial hair growth (patient 4), signal loss for technical reasons (patient 2), and complaints of lightheadedness (patient 9), respectively. DPOAE, distortion product otoacoustic emissions; l, left ear; r, right ear; TEOAE, transient evoked otoacoustic emissions; numbers denote individual patients. dB nHL, decibel normalized hearing level.

myocardial infarction without loss of consciousness, TEOAE were noticed in 9/20 measurements (5/10 controls; mean age 66.5 ± 8.3 years; 2 females).

DPOAE (which are frequency-specific) were present in 11/120 measurements after cardiac arrest (4/10 cases) and in 49/120 measurements following myocardial infarction (9/10 controls).

Compared to myocardial infarct patients with preserved consciousness, cardiac arrest patients had significantly less often preserved DPOAE [9.2 vs. 40.8%; OR 0.15 (CI 0.07–0.30); z statistic 5.24; $p < 0.0001$)].

Table 1 provides further details.

DISCUSSION

Outcome prognostication following cardiac arrest is essential, yet challenging (3). EEG is valuable but affected by levels of sedation and requires neurophysiological expertise (4, 5). Similarly, magnetic resonance imaging is promising but is associated with significant logistical challenges in the intensive care setting (6). Finally, new biomarkers such as serum tau appear to have good sensitivity and specificity but need further validation (7). A cheap point-of-care test that is easily interpretable, universally available and unaffected by sedation is clearly needed.

Otoacoustic emissions fulfill all criteria mentioned (1, 2) but previous studies have only assessed their role in perinatal anoxic-ischemic injury (8–10) and intracranial hypertension (11–13). Our study is the first to assess the potential of otoacoustic emissions for prognostication of adult cardiac arrest survivors. However, we conclude that otoacoustic emissions do not represent reliable outcome markers for neurological recovery after cardiac arrest because we identified 4 cases with (partially) preserved otoacoustic emissions in a sample of 10 unresponsive post-cardiac arrest patients whose neurological condition was so poor that active treatment was withdrawn (cases 1, 5-7; **Table 1b**).

While isolated measurements do not appear to add crucial information at the single-subject level, our results indicate, however, that otoacoustic emissions (i.e., DPOAE) are still affected by global anoxia following cardiac arrest ($p < 0.0001$). Thus, their usefulness as part of a multimodal approach, including serial measurements, should be further investigated. Decaying outer hair cell function over time may serve as a proxy for evolving ischemic brain damage.

AUTHOR CONTRIBUTIONS

DK: study concept, acquisition of data, analysis and interpretation, writing of the manuscript, critical revision for important intellectual content, and approval of final manuscript. AJ, TH, and MB: acquisition of data, critical revision for important intellectual content, and approval of final manuscript. JK: study concept, acquisition of data, analysis and interpretation, critical revision for important intellectual content, and approval of final manuscript.

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Features and Prognostic Value of Quantitative Electroencephalogram Changes in Critically Ill and Non-critically Ill Anti-NMDAR Encephalitis Patients: A Pilot Study

*Nan Jiang, Hongzhi Guan, Qiang Lu, Haitao Ren and Bin Peng**

Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

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Edited by:
Liping Liu,
Beijing Tiantan Hospital, Capital Medical University, China

Reviewed by:
Teneille Emma Gofton,
University of Western Ontario, Canada
Benjamin Aaron Emanuel,
University of Southern California, United States

***Correspondence:**
Bin Peng
pengbin3@hotmail.com

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Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a common cause of encephalitis in intensive care units. Until now, no reliable method has existed for predicting the outcome of anti-NMDAR encephalitis. In this study, we used quantitative electroencephalography (qEEG) to examine the brain function of anti-NMDAR encephalitis patients and assessed its predictive value. Twenty-six patients diagnosed with anti-NMDAR encephalitis were included and grouped according to whether they were treated in intensive care units (14 critically ill vs. 12 non-critically ill). All patients underwent 2-h 10-channel qEEG recordings at the acute stage. Parameters, including amplitude-integrated electroencephalogram (aEEG), spectral edge frequency 95%, total power, power within different frequency bands (δ, θ, α, and β), and percentages of power in specific frequency bands from frontal and parietal areas were calculated with NicoletOne Software and compared between groups. The short-term outcome was death or moderate/severe disability at 3 months after onset, measured with a modified Rankin Scale, and the long-term outcome was death, disability or relapse at 12 months. No differences in qEEG parameters were observed between the critically ill and non-critically ill patients. However, differential anterior-to-posterior alterations in δ and β absolute band power were observed. Logistic regression analysis revealed that a narrower parietal aEEG bandwidth was associated with favorable long-term outcomes (odds ratio, 37.9; $P = 0.044$), with an optimal cutoff value of 1.7 μV and corresponding sensitivity and specificity of 90.00 and 56.25%, respectively. In a receiver operating characteristic analysis, the area under the curve was 0.7312. In conclusion, the qEEG parameters failed to reflect the clinical severity of anti-NMDAR encephalitis. However, the parietal aEEG bandwidth may separate patients with favorable and poor long-term outcomes in early stages. The underlying mechanisms require further investigation.

Keywords: anti-NMDAR encephalitis, quantitative EEG, amplitude-integrated EEG, prognosis, intensive care unit

INTRODUCTION

Anti-N-methyl-D-aspartate receptor encephalitis is an autoimmune encephalitis involving antibodies directed against the NR1 subunit of the NMDA receptor (NMDAR), and is often associated with ovarian teratomas (1, 2). A considerable proportion of anti-NMDAR encephalitis patients fall into coma or develop status epilepticus and require intensive care. In one retrospective study, anti-NMDAR encephalitis accounted for 1% of all admissions of young adults to intensive care units (ICUs) (3).

Early identification of neurological outcomes is important in terms of therapeutic options. Several prognostic measures have been evaluated in anti-NMDAR encephalitis, including the Glasgow Coma Scale (GCS) score, number of complications, catatonia-predominant type, and electroencephalogram (EEG) (4–6). EEG is a commonly used monitoring tool at the bedside in the ICU, and an EEG "extreme delta brush" (EDB) pattern has been described in anti-NMDAR encephalitis and shown to be a marker of more severe disease and perhaps worse outcome (6). However, the identification of EDB on raw EEG requires experienced raters, which is inconvenient for the continuous monitoring of critically ill patients in the ICU. In addition, the prevalence of EDB is <30% in anti-NMDAR encephalitis patients; therefore, it may not be a sensitive prognostic factor (6–9). Hence, exploration for additional EEG markers to measure severity and predict the outcomes of anti-NMDAR encephalitis is needed, especially for cases where EDB is absent.

A variety of quantitative EEG (qEEG) parameters have been developed in neurocritical care practice, including some applied to the diagnosis of viral encephalitis (10). By applying fast Fourier transformation or other techniques, EEG can be quantified in terms of amplitude, power, frequency, and rhythmicity to generate numerical values, ratios, or percentages (11). Some qEEG parameters may provide quantitative information about short-term and long-term outcomes (11). In this study, we sought to explore features of brain background activity using quantitative analyses of EEG in anti-NMDAR encephalitis patients. The relationships of qEEG characteristics with disease outcomes were also assessed.

METHODS

Participant Enrollment, Data Collection, and Follow-Up

This single-center retrospective observational study was approved by the ethics committee of Peking Union Medical College Hospital. Eligible patients were enrolled from April 2014 to May 2017. Patient consent was not required because de-identified data were used in this study.

All enrolled patients met the diagnostic criteria for anti-NMDAR encephalitis introduced in 2016 (12). Exclusion criteria were as follows: (1) age at onset <12 years; (2) identifiable intracranial infections, other autoimmune encephalitis, or other etiologies causing admission to the ICU; (3) inability to cooperate with qEEG monitoring, due to issues such as agitation; (4) known medical history of a severe neurological deficit [modified Rankin Scale (mRS), ≥2] before onset of anti-NMDAR encephalitis; (5) lack of qEEG recording during the first week of hospitalization in our institute; and (6) missing data or loss to follow-up. According to the severity of disease, patients were further divided into critically ill or non-critically ill subgroups. Patients enrolled in the critically ill subgroup satisfied the following criteria: treated in the ICU for at least 48 h because of (1) GCS ≤8, (2) status epilepticus, or (3) hypoventilation or severe autonomic dysfunction. Patients who did not meet these criteria comprised the non-critically ill subgroup.

We collected the demographic, clinical and laboratory data of patients, including symptoms at the acute stage, serum and CSF studies, and therapeutic regimens. The short-term outcome for this study was death or degrees of disability, which was evaluated with the mRS at 3 months after onset. Patients were considered to have a favorable short-term outcome when their mRS scores were ≤2 without increasing compared with baseline, and poor short-term outcome if the mRS scores were ≥3 or had increased. Long-term outcomes were obtained from hospital medical records or face-to-face interviews 12 months after onset. Patients with mRS scores ≥3 for the whole experimental period or experienced relapse events and received another episode of first-line immunotherapy were defined as experiencing poor long-term outcomes. Patients were considered to have favorable long-term outcomes if their mRS scores were ≤2 with no relapse events.

In the final analysis, a total of 26 patients completed 1-year follow-up. Of these, 25 patients were diagnosed with definite anti-NMDAR encephalitis, and 1 patient met the diagnostic criteria for antibody-negative anti-NMDAR encephalitis. We also recruited 10 healthy volunteers with similar ages and collected their qEEG information as a control group.

EEG Recording and Interpretation

qEEG monitoring was performed for at least 2 h for each patient during the first week after admission to our center. Medication administrations during EEG recording were noted and intravenous anti-epileptic agents as well as sedatives were suspended before the start of qEEG monitoring. Silver-chloride disc electrodes were placed according to the International 10–20 System, with a 10-channel layout at the Fp1, F3, C3, P3, O1, and Fp2, F4, C4, P4, O2 sites. The reference electrode was located at Cz, and Fz was used as ground. A 1.0-Hz low- and 35-Hz high-frequency filter was used. Impedances were maintained below 10 kΩ. The qEEG recording was performed using a NicoletOne EEG monitor (VIASYS Healthcare Inc.), and both raw EEG and processed qEEG tracings were sampled simultaneously. The aEEG, spectral edge frequency 95% (SEF-95), total power, power within δ, θ, α, and β frequency bands, as well as relative percentages of power in specific frequency bands were calculated automatically and exported via NicoletOne system.

All qEEG recordings were analyzed off-line. For each patient, we selected one 30-min artifact-free epoch manually from the F3-F4 and P3-P4 montage for further quantitative analysis. We selected F3-F4 as the representative area of the anterior cross-cerebral EEG signal, and P3-P4 as

the representative area of the posterior cross-cerebral EEG signal. Because signals from Fp1-Fp2 and O1-O2 often contain more artifacts or higher impedances, we did not select these recordings for final quantitative analysis.

Statistical Analysis

Descriptive data are presented as mean ± standard deviation (SD) or median with interquartile ranges (IQR). We use Student's *t*-test or the Mann-Whitney *U*-test for group comparisons of continuous variables, and Fisher's exact test for categorical variables, as appropriate. The Kruskal-Wallis test with Bonferroni correction was used for multiple comparisons. Wilcoxon signed rank tests were performed to compare brain activity between anterior and posterior regions. Univariate and multivariate logistic regression with stepwise estimation method was performed to find the independent predictive ability of outcome predictors. Receiver operator characteristic (ROC) curves and areas under the curve (AUC) were constructed to study the ability of aEEG to predict outcomes. For these 2-tailed tests, $p < 0.05$ was considered statistically significant. Statistical analyses were performed using Stata software version 14.1.

RESULTS

Patient Characteristics

Of the 26 patients, 11 (42.3%) were male and 15 (57.7%) were female. The median age was 20 (IQR: 16–27) years. No tumor was found in any of the male patients. Eight (53%) female patients had underlying tumors, which were pathologically confirmed as ovarian teratomas. All patients received intravenous immunoglobulin (2 g/kg divided for 5 days), 25 (96.2%) treated with methylprednisolone (1 g/d for at least 3 days), and 14 (53.8%) patients received second-line immunotherapy. **Table 1** summarizes the comparison of demographic and clinical information between critically ill and non-critically ill patients.

TABLE 1 | Comparison of demographic, clinical, and CSF characteristics between critically ill and non-critically ill patients.

	Critically Ill subgroup	Non-critically Ill subgroup	*P*-value
DEMOGRAPHIC			
Gender(female)	8/14	7/12	1
Age	20(15,26)	20.5(17,31)	0.502
CLINICAL INFORMATION			
Fever	13/14	4/12	0.003*
Headache	10/14	4/12	0.113
Psychiatric behaviour	12/14	11/12	1
Cognition dysfunction	4/14	6/12	0.422
Memory impairment	4/14	9/12	0.047*
Speech dysfunction	4/14	8/12	0.113
Seizures	13/14	11/12	1
Movement disorder	9/14	6/12	0.692
Central hypoventilation	7/14	0/12	0.006*
Autonomic dysfunction	10/14	5/12	0.233
Decreased consciousness	11/14	3/12	0.016*
Glasgow Coma Scale	5(3,6)	11.5(7,15)	0.005*
Days till diagnosis	20(15,25)	17.5(13.5,34.5)	0.959
Days in hospital	61(54,120)	16.5(13,27.5)	0.0002*
Mechanical ventilation	10/14	0/12	0.0001*
Tumor	7/14	1/12	0.036*
Tumor in female	7/8	1/7	0.01*
Elevated CSF protein	2/14	5/12	0.19
CSF leukocyte			0.728
∼5	8/14	6/12	
6∼50	5/14	5/12	
51∼	1/14	1/12	
Oligoclonal band			0.642
Negative	6/13	3/10	
Suspected	0/13	5/10	
Positive	7/13	2/10	
Antibody titers in CSF			0.324
∼1:10	1/14	1/12	
1:32	3/14	5/12	
1:100∼	10/14	6/12	
Antibody titers in serum			0.040*
Negative	3/14	7/12	
1:10	2/14	1/12	
1:32∼	9/14	4/12	
SECOND-LINE IMMUNOTHERAPY			
MMF	9/14	4/12	0.238
MTX	4/14	0/12	0.100
CTX	1/14	0/12	1
RTX	1/14	1/12	1
No 2nd-line Immunotherapy	4/14	8/12	0.113

*$p < 0.05$.

CSF, cerebrospinal fluid; MMF, mycophenolate mofetil; MTX, methotrexate; CTX, cyclophosphamide; RTX, rituximab.

Patient Outcomes

Patient short-term outcomes were as follows: favorable outcome, 7 of 26 (26.9%); and poor outcome, 19 of 26 (73.1%). There was no significant difference between the two subgroups in terms of demographic information, CSF profiles, concomitant tumors, or immunotherapy regimens. All patients in the favorable short-term outcome subgroup had symptoms of impaired memory at admission (7/7 vs. 6/19, $p = 0.005$), and patients with impaired consciousness on admission were more likely to have poor short-term outcomes (1/7 vs. 13/19, $p = 0.026$). Short-term outcomes of the critically ill subgroup were worse than those of the non-critical subgroup (1/7 vs. 13/19, $p = 0.026$).

There were 10 (38.5%) patients experiencing poor long-term outcomes, including 5 with mRS ≥3 and 7 with relapse events within 12 months. One patient died because of complications due to infection. There were no significant differences between the favorable long-term outcome group and poor long-term outcome group in terms of sex, age, clinical symptoms, severity of onset, duration of hospital stay, profiles in CSF, concomitant tumors, or immunotherapy regimens during hospitalization.

TABLE 2 | Comparisons of qEEG parameters between patients and controls, critically ill patients and non-critically ill patients as well as patients with different outcomes.

		Patients group	Control group	*P*-value	Critically Ill subgroup	Non-critically Ill subgroup	*P*-value	Favorable short-term outcome	Poor short-term outcome	*P*-value	Favorable long-term outcome	Poor long-term outcome	*P*-value
Frontal area	aEEG Upper Margin (μV)	10.9(9.1,12.4)	10.8(10,11.4)	0.860	11.4(8.2,12.8)	10.8(9.7,11.9)	0.918	11(9.1,12.1)	10.7(8.8,12.8)	0.563	10.2(8.3,12.25)	11(10,12.5)	0.257
	aEEG Lower Margin(μV)	8.95(7.4,10.3)	8.9(7.9,9)	0.671	9.3(6.7,11)	8.8(7.9,9.8)	0.959	9(7.4,9.7)	8.9(7.2,11)	0.544	8.4(6.7,10.1)	9.2(8.2,10.3)	0.304
	aEEG Bandwidth(μV)	1.7(1.6,2)	1.9(1.8,2.1)	0.069	1.65(1.5,2)	1.7(1.65,1.95)	0.405	1.8(1.6,2)	1.7(1.6,2)	0.539	1.65(1.55,1.85)	1.8(1.7,2)	0.150
	SEF-95(Hz)	1.31(1.24,1.42)	1.39(1.35,1.4)	0.304	1.32(1.29,1.44)	1.31(1.21,1.41)	0.552	1.4(1.31,1.44)	1.31(1.17,1.4)	0.117	1.32(1.3,1.43)	1.3(1.15,1.4)	0.290
	Total Power(μV)	27.86(19.25,61.56)	18.92(16.88,26.01)	0.120	27.04(11.21,64.15)	29.58(20.85,48.95)	0.662	27.86(16.76,35.09)	27.86(19.41,64.59)	0.272	24.82(15.23,50.87)	31.475(25,66.96)	0.257
	δ RBP(%)	56.45(40.9,65.39)	54.54(41.08,55.98)	0.397	49.22(39.46,58.37)	61.46(52.31,69.94)	0.143	54.75(39.46,57.53)	58.05(40.9,68.09)	0.563	55.235(40.18,66.43)	57.615(49.86,65.39)	0.732
	θ RBP(%)	15.11(11.76,21.13)	16.21(15.32,20.44)	0.572	19.27(11.6,23.9)	14.28(12.54,19.18)	0.700	14.25(11.6,20.61)	17.74(11.76,23.9)	0.603	17.42(12.04,22.515)	14.28(11.21,20.61)	0.544
	α RBP(%)	6.18(4.31,10.08)	8.59(7.4,11.56)	0.072	6.59(5.25,11.16)	6.18(4.24,8.56)	0.625	7.86(6.11,10.08)	5.98(4.08,10.42)	0.203	6.03(4.195,8.84)	7.61(5.98,11.16)	0.236
	β RBP(%)	10.68(7.44,22.25)	16.38(11.55,18.34)	0.340	12.07(7.54,22.57)	10.60(6.52,16.15)	0.440	14.8(12.01,22.28)	8.34(7.34,22.25)	0.272	10.93(7.49,23.705)	10.175(5.43,20.77)	0.399
	δ ABP(μV)	15.01(8.71,24.34)	8.36(7.03,14.01)	0.148	10.83(6.45,37.88)	16.54(9.88,20.75)	0.520	9.39(8.71,21.6)	16.5(8.67,37.88)	0.418	12.92(7.9,22.97)	16.59(8.71,37.88)	0.510
	θ ABP(μV)	4.125(2.5,6.93)	3.575(2.39,4.36)	0.427	4.48(1.87,10.84)	4.13(2.58,6.17)	0.939	3.05(2.48,5.57)	4.23(2.5,10.84)	0.355	3.28(2.18,8.16)	4.30(3.06,5.57)	0.580
	α ABP(μV)	1.915(0.79,4.82)	2.03(1.34,2.64)	0.659	2.17(0.56,5.26)	1.92(0.89,2.51)	0.857	2.26(0.84,2.68)	1.08(0.78,5.26)	0.885	0.89(0.59,4.35)	2.43(1.08,4.82)	0.197
	β ABP(μV)	3.1(1.64,4.25)	3.01(2.01,4.27)	0.646	3.43(1.55,5.18)	2.14(1.70,4.11)	0.738	3.08(1.98,4.25)	3.12(1.55,5.18)	0.862	2.58(1.60,4.18)	3.37(1.98,5.18)	0.693
Parietal area	aEEG Upper Margin (μV)	10.2(8.8,12.4)	11.4(10.2,13.6)	0.223	9.1(8,12.1)	10.5(9.6,12.6)	0.537	10.8(8.9,12.8)	10.1(8,12.1)	0.506	9.35(7.8,12.4)	10.95(10.3,12.4)	0.108
	aEEG Lower Margin(μV)	8.45(6.8,10.2)	9.45(8.2,11.4)	0.244	7.25(6.5,10.2)	8.6(7.65,10.35)	0.589	9.1(7.2,10.7)	8.3(6.5,10.2)	0.623	7.45(6.35,10.45)	9.2(8.6,10)	0.170
	aEEG Bandwidth(μV)	1.7(1.5,2)	1.9(1.8,2.1)	0.130	1.65(1.5,2.1)	1.8(1.66,2)	0.393	1.9(1.6,2)	1.7(1.5,2)	0.398	1.6(1.5,1.8)	1.95(1.7,2.1)	0.030
	SEF-95(Hz)	1.29(1.19,1.4)	1.38(1.35,1.4)	0.082	1.36(1.24,1.4)	1.23(1.19,1.34)	0.104	1.33(1.22,1.4)	1.29(1.19,1.4)	0.622	1.36(1.21,1.43)	1.24(1.18,1.29)	0.057
	Total Power(μV)	18.88(10.58,33.86)	23.57(14.63,35.69)	0.698	16.51(10.58,43.39)	22.68(10.38,27.9)	0.857	13.84(10.13,28.43)	24.2(10.63,43.39)	0.470	10.68(9.33,26.47)	27.9(21.16,43.39)	0.022
	δ RBP(%)	49.75(41.61,65.05)	39.715(29.78,48.56)	0.024*	51.05(41.61,66.5)	49.75(38.29,61.95)	0.625	49.47(33.66,51.63)	53.04(42.91,67.91)	0.184	49.75(42.66,61.95)	57.11(39.87,67.91)	0.732
	θ RBP(%)	16.545(12.94,21.77)	15.72(14.95,17.62)	0.724	16.55(12.94,21.77)	16.69(13.31,21.06)	0.857	15.84(12.07,21.93)	17.04(13.44,21.77)	0.686	16.55(13.19,22.19)	16.69(12.07,20.18)	0.772
	α RBP(%)	7.995(5.26,14.93)	13.865(10.14,14.9)	0.066	7.09(4.91,11.94)	12.68(6.78,21.14)	0.143	13.02(10.5,27.48)	7.53(4.43,14.37)	0.073	7.66(4.84,14.65)	9.64(6.65,20.46)	0.414
	β RBP(%)	9.765(6.82,15.27)	17.44(14.79,26.7)	0.006*	11.9(8.79,16.62)	8.575(5.865,12.57)	0.165	10.83(6.82,14.89)	9.47(6.11,15.65)	0.644	10.68(8.09,18.48)	8.17(6.11,13.87)	0.114
	δ ABP(μV)	10.095(5.6,13.72)	7.015(3.63,13.56)	0.458	11.5(5.7,20.86)	8.46(5.39,12.73)	0.520	6.61(4.74,11.73)	11.26(5.7,17.38)	0.272	6.48(4.82,12.18)	11.76(9.73,20.86)	0.054
	θ ABP(μV)	2.89(1.47,6.32)	3.675(2.36,5.61)	0.778	2.39(1.35,6.45)	3.48(1.74,6.14)	0.857	2.83(1.35,7.68)	2.95(1.58,6.32)	0.908	1.95(1.34,6.39)	3.83(2.83,6.01)	0.257
	α ABP(μV)	1.755(0.67,4.95)	3.17(1.56,8.07)	0.148	1.16(0.55,4.38)	2.19(1.2,5.63)	0.396	2.38(1.4,6.31)	1.45(0.55,4.38)	0.355	1.17(0.5,4.67)	2.61(1.99,6.31)	0.133
	β ABP(μV)	1.75(1.04,3.05)	4.23(2.63,5.97)	0.008*	2.15(1.04,3.05)	1.33(1.04,2.77)	0.410	2.48(1.43,3.05)	1.58(1.03,3.05)	0.402	1.56(1.01,2.82)	2.24(1.22,3.1)	0.292

*$p < 0.05$.

aEEG, amplitude-integrated electroencephalogram; RBP, relative band power; ABP, absolute band power; SEF-95, spectral edge frequency 95%.

TABLE 3 | The anterior-to-posterior gradient of qEEG parameters in patients and control group.

	Patients group			Critically Ill subgroup			Non-critically Ill subgroup			Control group			Poor Long-term outcome			Favorable long-term outcome		
	Anterior area	Posterior area	*P*-value	Anterior area	Posterior area	*P*-value	Anterior area	Posterior area	*P*-value	anterior area	Posterior area	*P*-value	Anterior area	Posterior area	*P*-value	Anterior area	Posterior area	*P*-value
aEEG upper margin	10.85 (9.1,12.4)	10.2 (8.8,12.4)	0.341	11.4 (8.2,12.8)	9.1 (8,12.1)	0.245	10.8 (9.7,11.85)	10.5 (9.6,12.6)	1.000	10.8 (10,11.4)	11.4 (10.2,13.6)	0.103	11 (10,12.5)	10.95 (10.3,12.4)	0.959	10.2 (8.3,12.25)	9.35 (7.8,12.4)	0.224
aEEG lower margin	8.95 (7.4,10.3)	8.45 (6.8,10.2)	0.162	9.3 (6.7,11)	7.25 (6.5,10.2)	0.124	8.8 (7.9,9.8)	8.6 (7.65,10.35)	0.753	8.9 (7.9,9)	9.45 (8.2,11.4)	0.047	9.2 (8.2,10.3)	9.2 (8.6,10)	0.759	8.4 (6.7,10.1)	7.45 (6.35,10.45)	0.127
aEEG Bandwidth	1.7 (1.6,2)	1.7 (1.5,1.5)	0.918	1.65 (1.5,2)	1.65 (1.5,2.1)	0.777	1.7 (1.65,1.95)	1.8 (1.65,2)	0.811	1.9 (1.8,2.1)	1.9 (1.8,2.1)	1.000	1.8 (1.7,2)	1.95 (1.7,2.1)	0.603	1.65 (1.55,1.85)	1.6 (1.5,1.8)	0.498
SEF-95	1.31 (1.24,1.42)	1.29 (1.19,1.4)	0.258	1.32 (1.29,1.44)	1.36 (1.24,1.4)	1.000	1.31 (1.205,1.41)	1.23 (1.185,1.34)	0.091	1.39 (1.35,1.4)	1.38 (1.35,1.4)	0.959	1.3 (1.15,1.4)	1.24 (1.18,1.29)	0.240	1.32 (1.3,1.43)	1.36 (1.21,1.43)	0.569
Total power	27.86 (19.25,61.56)	18.88 (10.58,33.86)	0.059	27.04 (11.21,64.15)	16.51 (10.58,43.39)	0.433	29.58 (20.845,48.95)	22.68 (10.38,27.9)	0.050	18.915 (16.88,26.01)	23.57 (14.63,35.69)	0.959	31.475 (25,66.96)	27.9 (21.16,43.39)	0.285	24.82 (15.23,50.87)	10.68 (9.33,26.47)	0.070
δ RBP	56.45 (40.9,65.39)	49.75 (41.61,65.05)	0.638	49.22 (39.46,58.37)	51.045 (41.61,66.5)	0.158	61.46 (52.305,69.94)	49.75 (38.285,61.945)	0.060	54.535 (41.08,55.98)	39.715 (29.78,48.56)	0.005	57.615 (49.86,65.39)	57.11 (39.87,67.91)	0.721	55.235 (40.18,66.43)	49.75 (42.66,61.95)	0.756
θ RBP	15.105 (11.76,21.13)	16.545 (12.94,21.77)	0.409	19.265 (11.6,23.9)	16.545 (12.94,21.77)	0.778	14.28 (12.54,19.175)	16.685 (13.305,21.055)	0.136	16.21 (15.32,20.44)	15.72 (14.95,17.62)	0.333	14.28 (11.21,20.61)	16.69 (12.07,20.18)	0.799	17.42 (12.04,22.515)	16.55 (13.19,22.19)	0.255
α RBP	6.18 (4.31,10.08)	7.995 (5.26,14.93)	0.002	6.59 (5.25,11.16)	7.09 (4.91,11.94)	0.363	6.18 (4.235,8.56)	12.675 (6.78,21.14)	0.002	8.585 (7.4,11.56)	13.865 (10.14,14.9)	0.005	7.61 (5.98,11.16)	9.64 (6.65,20.46)	0.114	6.03 (4.195,8.84)	7.66 (4.84,14.65)	0.005
β RBP	10.675 (7.44,22.25)	9.765 (6.82,15.27)	0.228	12.07 (7.54,22.57)	11.9 (8.79,16.62)	0.470	10.595 (6.52,16.15)	8.575 (5.865,12.57)	0.388	16.38 (11.55,18.34)	17.44 (14.79,26.7)	0.075	10.175 (5.43,20.77)	8.17 (6.11,13.87)	0.241	10.93 (7.49,23.705)	10.68 (8.09,18.48)	0.501
δ ABP	15.01 (8.71,24.34)	10.095 (5.6,13.72)	0.025	10.83 (6.45,37.88)	11.495 (5.7,20.86)	0.363	16.535 (9.875,20.745)	8.46 (5.385,12.725)	0.015	8.36 (7.03,14.01)	7.015 (3.63,13.56)	0.169	16.59 (8.71,37.88)	11.76 (9.73,20.86)	0.169	12.92 (7.9,22.97)	6.48 (4.82,12.18)	0.049
θ ABP	4.125 (2.5,6.93)	2.89 (1.47,6.32)	0.086	4.475 (1.87,10.84)	2.39 (1.35,6.45)	0.198	4.125 (2.58,6.17)	3.48 (1.735,6.135)	0.272	3.575 (2.39,4.36)	3.675 (2.36,5.61)	0.799	4.30 (3.06,5.57)	3.83 (2.83,6.01)	0.799	3.28 (2.18,8.16)	1.95 (1.34,6.39)	0.063
α ABP	1.915 (0.79,4.82)	1.755 (0.67,4.95)	0.304	2.17 (0.56,5.26)	1.155 (0.55,4.38)	0.778	1.915 (0.89,2.505)	2.185 (1.195,5.63)	0.071	2.03 (1.34,2.64)	3.17 (1.56,8.07)	0.047	2.43 (1.08,4.82)	2.61 (1.99,6.31)	0.445	0.89 (0.59,4.35)	1.17 (0.5,4.67)	0.535
β ABP	3.1 (1.64,4.25)	1.75 (1.04,3.05)	0.020	3.43 (1.55,5.18)	2.15 (1.04,3.05)	0.300	2.14 (1.695,4.105)	1.325 (1.04,2.765)	0.019	3.01 (2.01,4.27)	4.23 (2.63,5.97)	0.114	3.37 (1.98,5.18)	2.24 (1.22,3.1)	0.093	2.58 (1.60,4.18)	1.56 (1.01,2.82)	0.088

aEEG, amplitude-integrated electroencephalogram; RBP, relative band power; ABP, absolute band power; SEF-95, spectral edge frequency 95%.

qEEG Findings

The detailed results for qEEG parameters are presented in **Table 2**. Compared with the healthy control group, the δ relative band power in the posterior area was significantly increased ($p = 0.024$) in the anti-NMDAR patient group, while β relative ($p = 0.006$) and β absolute ($p = 0.008$) band power in the posterior area were significantly reduced. The qEEG parameters in anterior area showed no significant differences between the patient group and the control group. There were also no significant differences in qEEG parameters between critically ill and non-critically ill subgroups, or between patients with favorable and poor short-term outcomes. However, in terms of long-term outcomes, the aEEG bandwidth in the parietal area was significantly lower in patients with favorable outcomes than those with poor outcomes (1.6 vs. 1.95 μV, $p = 0.030$). The parietal total power was also significantly lower in the favorable long-term outcome subgroup compared with the poor outcome subgroup (10.68 vs. 27.9 μV^2, $p = 0.022$).

We also investigated whether the differences in qEEG parameters between anterior and posterior areas were correlated with severities or outcomes (see **Table 3**). In the healthy control group, we found that the aEEG lower margin, δ relative band power, α relative band power, and α absolute band power differed statistically between the anterior and posterior areas. The aEEG lower margin, α relative band power, and α absolute power exhibited a decline from anterior to posterior areas, while δ relative band power showed the opposite trend. However, in the patient group, the differences in aEEG lower margin, δ relative band power, and α absolute power vanished. The gradient of α relative band power still remained, and new gradients of δ absolute band power and β absolute band power appeared in the patient group. The gradients of α relative band power, δ absolute band power and β absolute band power existed in the non-critically ill subgroup, whereas the differences in all parameters disappeared in critically ill subgroup.

Taking the long-term outcome as dependent variable, with univariate logistic regression we screened parietal aEEG upper margin, aEEG bandwidth, SEF-95, and β relative band power as independent variables. Subsequent multivariate logistic regression analysis yielded only one predictor: the parietal aEEG bandwidth (odds ratio, 37.9; 95% confidence interval, 1.11–1295.27; $p = 0.044$). The maximal index of Youden was 1.4625 for a cutoff value of 1.7 μV, with a sensitivity and specificity of 90.00% and 56.25%, respectively. ROC analysis of parietal aEEG bandwidth yielded an area under the curve of 0.7312 (95% CI: 0.572–0.891; **Figure 1**). Furthermore, using another univariate logistic regression analysis, we found that parietal aEEG bandwidth was associated with long-term moderate/severe disability (mRS score ≥3) at 12 months (odds ratio, 761.88; 95% confidence interval, 1.53–378836.40; $p = 0.036$), but not associated with relapse events ($p = 0.611$).

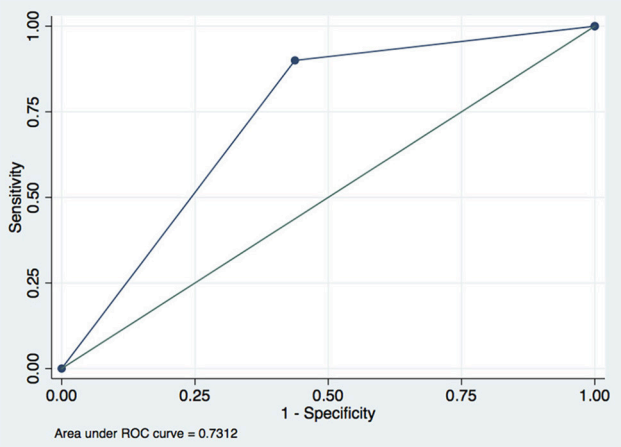

FIGURE 1 | Receiver operating characteristic curve of parietal aEEG bandwidth predicting long-term outcomes of anti-NMDAR encephalitis when cutoff point is 1.7.

DISCUSSION

Anti-NMDAR encephalitis has been recognized as a common cause of encephalitis in ICU. Despite its responsiveness to immunotherapy and tumor removal, the mortality rate of anti-NMDAR encephalitis in the ICU is 4–25% (4, 13–15). At present, there is no reliable tool for predicting outcomes of anti-NMDAR encephalitis. Most previous electrophysiological studies focused on raw EEG manifestations of anti-NMDAR encephalitis (6, 8, 9). In this study, we investigated the characteristics of qEEG in patients with anti-NMDAR encephalitis. To the best of our knowledge, this is the first study that depicts qEEG findings of patients with anti-NMDAR encephalitis. Our results indicate that most qEEG parameters, including aEEG background, total power, SEF-95, and power of various frequency bands of brain rhythms failed to measure the clinical severity of anti-NMDAR encephalitis. However, the widening of parietal aEEG bandwidth can be used as an objective marker to predict poor long-term outcomes with a good sensitivity.

aEEG is a type of processed EEG that is compressed with respect to amplitude and time, and the upper and lower margins of the aEEG reflect the maximum/minimum peak-to-peak amplitudes of the EEG signals (16). An abnormal aEEG, especially its lower margins, has been shown to be predictive of persistence of severe cerebral injury and poor neurologic outcome (17–19). However, aEEG bandwidth is not a commonly used monitoring marker. The prognostic value of parietal aEEG bandwidth in anti-NMDAR encephalitis is a novel finding and difficult to explain. Previous studies on aEEG have mainly concentrated on disorders that lead to neuron damage, such as stroke, traumatic brain injury, or hypoxic encephalopathy, which can be appraised by aEEG lower margins. However, anti-NMDAR encephalitis selectively reduces NMDAR function and changes the synaptic activities of neuronal networks without any impairment of other synaptic processes (20). Aberrant functioning of a single ion channel may result in various pathophysiological processes (20); therefore, the degree of NMDAR hypofunction may not have a linear

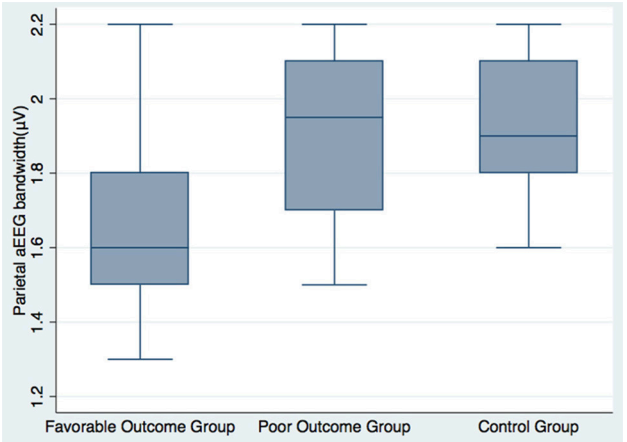

FIGURE 2 | Parietal aEEG bandwidth among favorable long-term patients, poor long-term patients, and healthy volunteers.

relationship with EEG discontinuity. Thus, the subsequent aEEG changes may be difficult to evaluate using traditional aEEG lower margin. On the contrary, unlike simply measuring the lower margin, aEEG bandwidth may play a diagnostic and predictive role in disorders that are pathogenic to synapses. Specifically, the parietal aEEG bandwidth in healthy controls was wider than in patients with favorable long-term outcomes, and narrower than in those with poor long-term outcomes (**Figure 2**). This opposite trend suggests that the long-term outcome of anti-NMDAR encephalitis may be determined by underlying, unexplained pathophysiological mechanisms, which might be reflected in electrophysiological parietal aEEG bandwidth. The molecular mechanism underlying this requires further investigation.

Interestingly, compared with healthy controls, the lower margins of the aEEG in both the critically ill and non-critically ill subgroup did not show any significant differences. One possible reason for this phenomenon is the small number of patients. Nevertheless, it may also suggest that brain function in anti-NMDAR encephalitis is relatively intact even in critically ill patients. This characteristic of qEEG is potentially consistent with the pathogenesis of anti-NMDAR encephalitis. NMDAR is an ionotropic glutamate receptor distributed in entire brain tissues. Antibodies directed at the NR1 subunit of the NMDA receptors act by mechanisms including the binding, capping, and cross-linking of NMDA receptors, leading to internalization from the cell membrane surface and a selective decrease in NMDA receptor currents with no effect on synapse number or other synapse proteins (2, 21). The NMDAR hypofunction is non-destructive and reversible, which may explain why the lower margins of aEEG did not decline in the patient group.

Compared with the healthy control group, there were specific anterior-to-posterior graded alterations of qEEG parameters in patients with anti-NMDAR encephalitis. In particular, there were alterations in δ and β absolute band power. δ absolute band power in the posterior area was lower than in the anterior area in the healthy control group and non-critically ill subgroup, but higher than in anterior area of the critically ill subgroup. However, this trend was reversed in the β absolute band power, which was higher in the posterior area in the healthy control group, and lower in the critically ill and non-critically ill subgroups. Increased power in slower frequency bands (δ and θ) and decreased power in faster frequency bands (α and β) are seen with reductions in brain metabolism (22). No previous studies have reported anterior-to-posterior gradient changes in electrophysiology in anti-NMDAR encephalitis; however, several FDG-PET/CT-based studies have observed specific anterior-to-posterior metabolic gradient changes in the active phase of NMDA encephalitis, and reported these to correlate with disease severity and renormalize with treatment and recovery (23–25). The observed anterior-to-posterior gradient may largely be driven by posterior hypometabolism rather than anterior hypermetabolism (25). Wegener et al. have identified a predominant pattern of frontotemporal hypermetabolism and parietal hypometabolism (26). However, they found that there were no consistent results regarding FD-PET results and impairment as indicated by the mRS (26), which is consistent with our study relative to the prognostic value of the anterior-to-posterior gradient. Another FDG-PET/CT-based study demonstrated marked posterior hypometabolism in patients with anti–NMDAR encephalitis with severe neurologic disability (mRS 4–5), which was more evident than in those less neurologically disabled (mRS 0–3) (25). In our study, the posterior δ absolute band power in non-critically ill subgroup is lower than the anterior area, and this discrepancy disappeared in the critically ill subgroup, which may indicate that more a significant posterior hypometabolism emerged in the critically ill subgroup and supports the research of Probasco et al.

The main limitation of our study is the small number of patients, which limits the power of the findings. In addition, patients requiring qEEG monitoring due to decreased consciousness or suspected seizures, but were not severe enough to require ICU admission, were enrolled as the non-critically ill subgroup. This might have led to a selection bias; however, it also enabled the analysis of the most challenging group of patients with this disease, in whom prognostic biomarkers are most needed. Additional analysis of temporal and occipital areas, as well as prolonged qEEG monitoring, are needed in the future. Furthermore, while critically ill patients are monitored, some were being administered with anti-epileptic drugs, sedatives, or antipsychotics at the same time. In our study, almost all patients in the ICU was administered at least one intravenous sedative, including midazolam, diazepam, or propofol, to control seizures and involuntary movements in the early course of the disease. Before the start of qEEG monitoring, we requested that these sedatives be suspended and restarted after the monitoring is over. However, these medications may still have an impact on EEG signals. In general, sedatives and antiepileptic medications depress the electrocortical activity and render the EEG background more discontinuous and depressed than expected; therefore, a continuous background may become slightly discontinuous (27). If the EEG background is considered normal there is typically no problem with interpretation. In this

study, the aEEG lower margins of all patients were continuous (>5 μV); therefore, sedatives and anti-epileptic medications were unlikely to have had a significant impact on our EEG results.

In conclusion, the qEEG pattern in anti-NMDAR encephalitis can offer better understanding of the pathophysiological mechanisms and prognostic possibilities. A wider parietal aEEG bandwidth was associated with worse long-term outcomes, and may serve as a useful biomarker in anti-NMDAR encephalitis. Further, well-designed studies are needed to confirm this novel finding, and elucidate the underlying mechanism.

AUTHOR CONTRIBUTIONS

NJ wrote the initial draft of the paper. HG and HR acquisitioned patients' demographic and clinical data from encephalitis database registration. QL guided for analyzing the EEG signals. BP guided for study designation and made critical revision of draft.

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Multimodal Predictions of Super-Refractory Status Epilepticus and Outcome in Status Epilepticus Due to Acute Encephalitis

*Fang Yuan, Fang Yang, Ruihua Jia, Wen Li, Yongli Jiang, Jingjing Zhao and Wen Jiang**

Department of Neurology, Xijing Hospital, Fourth Military Medical University, Xi'an, China

Objective: Status epilepticus (SE) is one of the most critical symptoms of encephalitis. Studies on early predictions of progression to super-refractory status epilepticus (SRSE) and poor outcome in SE due to acute encephalitis are scarce. We aimed to investigate the values of neuroimaging and continuous electroencephalogram (EEG) in the multimodal prediction.

Methods: Consecutive patients with convulsive SE due to acute encephalitis were included in this study. Demographics, clinical features, neuro-imaging characteristics, medical interventions, and anti-epileptic treatment responses were collected. All the patients had EEG monitoring for at least 24 h. We determined the early predictors of SRSE and prognostic factors of 3-month outcome using multivariate logistic regression analyses.

Results: From March 2008 to February 2018, 570 patients with acute encephalitis were admitted to neurological intensive care unit (N-ICU) of Xijing hospital. Among them, a total of 94 patients with SE were included in this study. The percentage of non-SRSE and SRSE were 76.6 and 23.4%. Cortical or hippocampal abnormality on neuroimaging ($p = 0.002$, OR 20.55, 95% CI 3.16–133.46) and END-IT score ($p < 0.001$, OR 4.07, 95% CI 1.91–8.67) were independent predictors of the progression to SRSE. At 3 months after N-ICU discharge, 56 (59.6%) patients attained good outcomes, and 38 (40.4%) patients had poor outcomes. The recurrence of clinical or EEG seizures within 2 h after the infusion rate of a single anesthetic drug >50% proposed maximal dose ($p = 0.044$, OR 4.52, 95% CI 1.04–19.68), tracheal intubation ($p = 0.011$, OR 4.99, 95% CI 1.37–11.69) and emergency resuscitation ($p = 0.040$, OR 9.80, 95% 1.11–86.47) predicted poor functional outcome.

Interpretation: Initial neuro-imaging findings assist early identification of the progression to SRSE. Continuous EEG monitoring contributes to outcome prediction in SE due to acute encephalitis.

Keywords: status epilepticus, encephalitis, super-refractory status epilepticus, neuroimaging, continuous electroencephalogram, multimodal prediction

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Capital Medical University, China

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Yale University, United States
Sebastian Pollandt,
Rush University, United States

****Correspondence:***
Wen Jiang
jiangwen@fmmu.edu.cn

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INTRODUCTION

Encephalitis is an inflammatory process of the brain, with an incidence of 3.5–12.6 cases per 100,000 patient-years worldwide (1, 2). Patients with acute encephalitis typically present with acute onset of fever, impaired consciousness, headache, seizures, or new onset of focal neurologic deficits (3). Acute encephalitis is a severe form of neurological illnesses that usually requires intensive care for monitoring and treatment. Reported mortality rates range between 7 and 18%, and up to 56% of survivors suffer from severe disability (4–7).

Status epilepticus (SE) is one of the most common neurological symptoms of encephalitis, occurring in 18.5% cases of acute encephalitis (5). Previous studies suggested that younger age, coma, cortical lesions on neuroimaging, and nonneurologic organ failure were risk factors for the incidence of SE in patients with encephalitis (8, 9). SE due to acute encephalitis is a critical condition that is strongly associated with higher refractoriness (10, 11). It often evolves to super-refractory status epilepticus (SRSE) and consequently results in higher mortality (5, 10, 11). Early identifications of the patients with higher risks of progression to SRSE and poor outcomes will help clinicians orient treatment strategies and may improve the outcomes of SE in acute encephalitis.

Given the current paucity of studies regarding the aforementioned problems, we conducted a 10-year retrospective study in the neurological intensive care unit (N-ICU) to investigate the contributions of brain magnetic resonance imaging (MRI) and electroencephalogram (EEG) monitoring in the multimodal predictions of progression to SRSE and 3-month poor outcome in SE due to acute encephalitis.

MATERIALS AND METHODS

Design and Setting

This study was based on a prospective database of acute encephalitis patients in N-ICU at Xijing hospital, China, a tertiary academic hospital. It was registered in ClinicalTrials.gov (NCT02278016) and approved by the ethics committee of the Xijing Hospital (KY20140916-3). We adhered to Chinese laws and the Declaration of Helsinki.

Patients

From March 2008 to February 2018, all consecutive patients with convulsive SE due to acute encephalitis and aged 13 years or older were included in this study. Acute encephalitis was defined as encephalopathy (altered mental status lasting $\geq$24 h with no alternative cause identified), and three or more of the following: documented fever $\geq$38°C within the 72 h before or after presentation; generalized or partial seizures not fully attributable to a preexisting seizure disorder; new onset of focal neurologic findings; CSF WBC count $\geq$5/cubic mm; abnormality of brain parenchyma on neuroimaging (suggestive of encephalitis); abnormal electroencephalogram (EEG) findings (consistent with encephalitis) (3). According to the operational definition proposed by International League Against Epilepsy, we defined convulsive SE as 5 min or more of continuous motor seizure activity or recurrent seizure activity without regaining full consciousness between episodes (12).

Management

The management of SE adhered to related guidelines (13–15). Benzodiazepines were administered as the first-line agents, followed by intravenous sodium valproate or phenobarbital sodium to treat persisting SE. In patients who were resistant to both first-line and second-line agents, midazolam or propofol was administered continuously as the third-line treatment. The initial loading dose of midazolam was 0.2 mg/kg, and the proposed maximal dose (PMD) of maintenance infusion rate for midazolam was 0.4 mg/kg/h (14, 15). The initial loading dose of propofol was 2 mg/kg, and the PMD of maintenance infusion rate of propofol was 10 mg/kg/h (14, 15). When a single anesthetic with PMD failed to control SE, simultaneous polytherapy of continuous infusion of anesthetics (CIVADs) was administered (16–19). All the SE patients received bedside video-EEG monitoring for at least 24 h with an array of 20 scalp electrodes (Solar 2000 N, Solar Electronic Technologies Co., Ltd., Beijing, China) to guide anti-seizure treatments and detect non-convulsive epileptic seizures.

Data Collection

The following measures were recorded and assessed: (1) variables before N-ICU admission including time from onset of encephalitis to N-ICU admission, time from onset of encephalitis until diagnosis of SE, seizures before admission, and history of epilepsy; (2) severity of illness including Glasgow Coma Scale (GCS), Status Epilepticus Severity Score (STESS) (20), and END-IT score (11); (3) encephalitis etiology diagnosed according to related guidelines and consensuses (21–26); (4) complication of non-convulsive status epilepticus (NCSE) in coma; (5) brain image (abnormal brain MRI findings were defined as hypointensity on T1WI and hyperintensity on T2WI and FLAIR); (6) N-ICU managements including length of EEG monitoring, number of intravenous antiepileptic drugs (IV AEDs), use of CIVADs, CIVAD > 50% PMD, CIVADs changed, immune therapies (including steroids, immunoglobulins, plasma exchange, and rituximab), tracheal intubation, use of vasopressors, and emergency resuscitation; (7) antiepileptic treatment responses including clinical or EEG seizures within 2 h after CIVAD, clinical or EEG seizures within 2 h after CIVAD >50% PMD, breakthrough seizures, and withdrawal seizures. NCSE in coma was defined as a type of SE, which happened in comatose patients, without motor movements or with manifestations of continuous and rhythmic phenomenon of more subtle motor twitches of the eyelid, jaw, face, trunk or extremities (12, 16). Emergency resuscitation was defined as administering emergency measures to sustain the vital functions of a person in severe respiratory and circulatory failure, malignant arrhythmia, or cardiac arrest. CIVAD was changed when a second CIVAD (monotherapy) was used because of the poor seizure control. Breakthrough seizures were defined as any clinical or EEG seizures occurring after the

first 6 h of the initial CIVAD treatment; withdrawal seizures were defined as any clinical or EEG seizures occurring within 48 h after initially discontinuing or tapering the CIVAD (27, 28). Clinical seizures were defined as any epileptic seizures with perceivable motor movements. EEG seizures were defined as any spikes, sharp waves, or sharp and slow wave complexes lasting for ≥10 s at either a frequency of at least three per second or a frequency of at least one per second with clear evolution in frequency, morphology, or location (28, 29).

Outcomes

Refractory status epilepticus (RSE) was defined as SE that continued despite treatment with benzodiazepines and one antiepileptic drug (30). SRSE was defined as SE that continued or recurred 24 h or more after the onset of anesthetic therapy (31). Three-month functional outcome was assessed via telephone interviews by a trained study assistant using Modified Rankin Scale (mRS), who was blind to the clinical data. A mRS >3 (severe disability and death) was considered as poor outcome, and a mRS ≤3 (normal, slight and moderate disability) was considered favorable outcome.

Statistics

Univariate comparisons of categorical variables were performed using χ^2-test analysis. For continuous variables, normal and non-normal distributions were distinguished by the Shapiro-Wilk test. The comparisons of normally distributed variables were performed using the Student *t*-test, and the comparisons of non-normally distributed variables were performed using the Mann-Whitney *U*-test. Age, gender, and potential risk factors with a significance level <0.05 in the univariate comparisons were included into univariate and multivariate (stepwise backward) logistic regression analyses to examine their associations with a certain outcome by estimating odds ratios (ORs) and associated confidence intervals (CIs). Two-sided $p \leqq 0.05$ were considered significant. Statistical analysis was performed with SPSS version 22 software (SPSS Inc., Chicago, IL, United States).

RESULTS

Demographics and Clinical Features

Between March 2008 and February 2018, 570 patients with acute encephalitis were admitted to N-ICU (**Figure 1**). Among them, a total of 94 patients with SE were included in this study. The median age of the study cohort was 26 years old (**Table 1**), and 55 (58.5%) patients were male. The median time from onset to SE was 5 days, and the median time from onset to N-ICU admission was 11 days. Eighty-nine (94.7%) patients had seizures before admission, and only eight (8.5%) patients had a history of epilepsy. Most patients had unknown causes (42.6%), followed by viral encephalitis (28.7%), autoimmune (22.3%), bacterial (4.3%), cryptococcosis (1.1%), and neurosyphilis (1.1%).

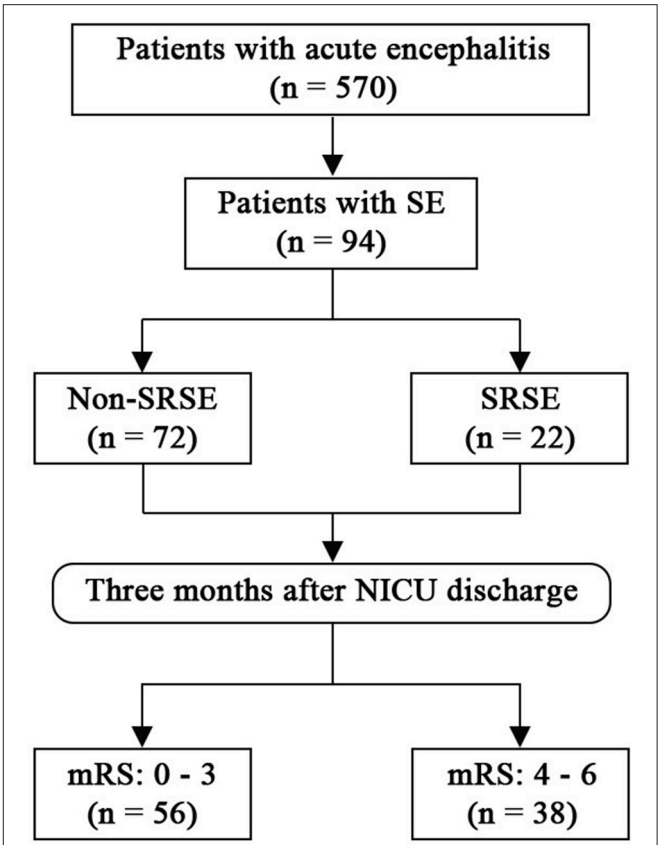

FIGURE 1 | Flow chart. mRS, modified Rankin Scale; SE, status epilepticus; SRSE, super-refractory status epilepticus.

Early Predictors for Progression to SRSE

Forty-one (43.6%) patients with SE due to acute encephalitis evolved into RSE, and 22 (23.4%) patients evolved into SRSE. Patients with SRSE had significantly lower GCS score ($p = 0.006$), higher STESS ($p < 0.001$) and END-IT score ($p < 0.001$; **Table 1**). There were significantly more patients with MRI abnormalities on the cortex or hippocampus in SRSE group ($p = 0.034$). Results from multivariate logistic regression analysis (**Table 2**) showed that END-IT score ($p < 0.001$) and cortical/hippocampal abnormality on MRI ($p = 0.002$) were independent predictors for progression to SRSE. The cut-off point of 4 in END-IT score produced the optimal sum of sensitivity and specificity for the prediction of the progression to SRSE.

NICU Management

Table 3 showed the managements in N-ICU for all the patients with SE due to acute encephalitis, including RSE and SRSE cases. The length of EEG monitoring for the whole cohort was 46 (28–81) hours, for RSE cases was 77 (47–171) hours, and for SRSE cases was 105 (69–274) hours. Forty-five (47.9%) patients with SE due to acute encephalitis received CIVADs, and 22 (23.4%) patients received CIVADs with more than 50% PMD. Immune therapies were used in 25 (26.6%) cases, tracheal intubation was

TABLE 1 | Demographics and clinical characteristics of patients with status epilepticus associated with acute encephalitis.

	Total ($n = 94$)	Non-SRSE ($n = 72$)	SRSE ($n = 22$)	*P* value
Age, year	26 (18–42)	32 (19–45)	22 (15–30)	0.017
Male (%)	55 (58.5)	44 (61.1)	11 (50.0)	0.355
Time from onset to NICU admission, day	11 (7–22)	10 (5–21)	13 (8–24)	0.264
Time from onset to SE, day	5 (3–11)	7 (3–14)	5 (3–7)	0.290
Seizures before admission (%)	89 (94.7)	67 (93.1)	22 (100.0)	0.204
History of epilepsy (%)	8 (8.5)	7 (9.7)	1 (4.5%)	0.446
GCS	9 (6–12)	9 (6–12)	6 (3–10)	0.006
STESS	4 (3–5)	4 (3–4)	5 (4–5)	<0.001
END-IT score	3 (3–4)	3 (2–3)	3 (3–4)	<0.001
Encephalitis etiology (%)				0.512
Viral	27 (28.7)	22 (30.6)	5 (22.7)	
Bacterial	4 (4.3)	4 (5.6)	0 (0.0)	
Cryptococcosis	1 (1.1)	1 (1.4)	0 (0.0)	
Neurosyphilis	1 (1.1)	1 (1.4)	0 (0.0)	
Autoimmune	21 (22.3)	17 (23.6)	4 (18.2)	
Unknown	40 (42.6)	27 (37.5)	13 (59.1)	
NCSE in coma (%)	53 (56.4)	33 (45.8)	20 (90.9)	<0.001
Brain image (%)				0.034
Normal	34 (36.2)	25 (34.7)	9 (40.9)	
Cortical or hippocampal involvement	27 (28.7)	17 (23.6)	10 (45.5)	
Exclusively abnormalities in other areas*	33 (35.1)	30 (41.7)	3 (13.6)	

*GCS, Glasgow coma scale; NCSE, nonconvulsive status epilepticus; NICU, neurological intensive care unit; SRSE, super-refractory status epilepticus; STESS, status epilepticus severity score. *Brain parenchyma except cortex and hippocampus.*
Data presented as n (%) or median (interquartile range).

TABLE 2 | Logistic regression analysis for predictors of SRSE in acute encephalitis.

Variables	Unadjusted analysis			Adjusted analysis**		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	0.96	0.92–0.99	0.021			
Male	0.64	0.24–1.66	0.356			
GCS	0.83	0.72–0.96	0.011			
STESS	5.36	2.19–13.14	<0.001			
END-IT score	2.36	1.45–3.86	0.001	4.07	1.91–8.67	<0.001
NCSE in coma	11.82	2.57–54.34	0.002			
Brain image			0.050			0.007
Cortical or hippocampal involment	5.88	1.42–24.35	0.015	20.55	3.16–133.46	0.002
Normal	3.60	0.88–14.75	0.075	4.30	0.87–21.33	0.074
Exclusively abnormalities in other areas*	1.00			1.00		

*GCS, Glasgow coma scale; NCSE, nonconvulsive status epilepticus; SRSE, super-refractory status epilepticus; STESS, status epilepticus severity score. *Brain parenchyma except cortex and hippocampus. **Hosmer and Lemeshow Test: $p = 0.935$.*

used in 51 (54.3%) cases, vasopressors were used in 32 (34.0%) cases, and emergency resuscitation was used in 12 (12.8%) cases. 35 (37.2%) cases, and withdrawal seizures occurred in 30 (31.9) cases.

Responses to Antiepileptic Treatment

Thirty-two (34.0%) patients with SE due to acute encephalitis had seizures within 2 h after the initial use of CIVAD, and 16 (17.0%) patients still had seizures within 2 h after the rate of CIVAD was raised to >50% PMD. Breakthrough seizures occurred in

Outcomes

Forty-one (43.6%) cases of SE in acute encephalitis were refractory status epilepticus (RSE), 22 (23.4%) cases are SRSE. Thirty-eight (40.4%) patients with SE due to acute encephalitis had a poor outcome 3 months after N-ICU discharge, 19 (46.4%)

TABLE 3 | NICU management and treatment responses of status epilepticus in acute encephalitis.

	SE ($n = 94$)	RSE* ($n = 41$)	SRSE ($n = 22$)
Length of EEG monitoring, h	46 (28–81)	77 (47–171)	105 (69–274)
Number of IV AEDs	2 (1–3)	3 (3–4)	4 (3–4)
Use of CIVADs (%)	45 (47.9)	41 (100.0)	22 (100.0)
CIVAD >50% PMD (%)	22 (23.4)	22 (53.7)	18 (81.8)
Seizures within 2 h after CIVAD (%)	32 (34.0)	30 (73.2)	19 (86.4)
Seizures within 2 h after CIVAD >50% PMD (%)	16 (17.0)	16 (39.0)	15 (68.2)
Breakthrough seizures (%)	35 (37.2)	33 (80.5)	21 (95.5)
Withdrawal seizures (%)	30 (31.9)	28 (68.3)	21 (95.5)
CIVADs changed (%)	20 (21.3)	20 (48.8)	17 (77.3)
Immune therapies (%)	25 (26.6)	11 (26.8)	6 (27.3)
Tracheal intubation (%)	51 (54.3)	30 (73.2)	20 (90.9)
Use of vasopressors (%)	32 (34.0)	19 (46.3)	15 (68.2)
Emergency resuscitation (%)	12 (12.8)	8 (19.5)	6 (27.3)

*CIVADs, continuous IV anesthetic drugs; PMD, proposed maximal dose; RSE, refractory status epilepticus; SE, status epilepticus; SRSE, super-refractory status epilepticus. *Includes SRSE cases.*
Data presented as n (%) or median (interquartile range).

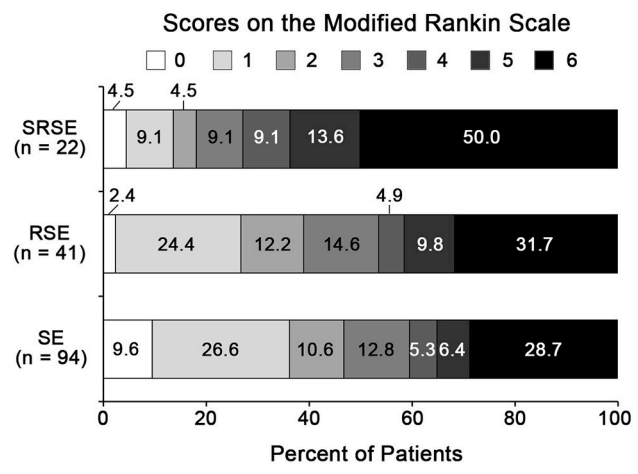

FIGURE 2 | Three-month functional outcomes of SE in acute encephalitis. 0, no symptoms; 1, no significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; 6, dead. RSE, refractory status epilepticus; SE, status epilepticus; SRSE, super-refractory status epilepticus.

RSE patients had a poor 3-month outcome, and 16 (72.7%) SRSE patients had a poor 3-month outcome (**Figure 2**).

Prognostic Factors for 3-Month Functional Outcome

Table 4 showed that patients with a poor outcome had significantly less time from the onset of encephalitis to SE ($p = 0.031$), significantly higher STESS ($p = 0.028$) and END-IT scores ($p = 0.001$). Patients with a poor outcome were administered with significantly more IV AEDs ($p = 0.031$). Significantly more patients had NCSE in coma ($p = 0.018$), CIVAD >50% PMD ($p = 0.042$), seizures within 2 h after CIVAD >50% PMD ($p < 0.001$), CIVADs changed ($p < 0.001$), tracheal intubation ($p < 0.001$), the use of vasopressors ($p < 0.001$), emergency resuscitation ($p < 0.001$) in the poor outcome group. Multivariate logistic regression analysis identified that the recurrence of seizures within 2 h after CIVAD >50% PMD ($p = 0.044$), tracheal intubation ($p = 0.011$), and emergency resuscitation ($p = 0.040$) were independent risk factors for 3-month poor outcome (**Table 5**).

TABLE 4 | Clinical characteristics of patients with favorable and unfavorable outcomes after status epilepticus associated with acute encephalitis.

	mRS: 0–3 ($n = 56$)	mRS: 4–6 ($n = 38$)	*P*-value
Age, years	25 (18–39)	33 (18–45)	0.282
Male (%)	29 (51.8)	26 (68.4)	0.108
Time from onset to NICU admission, day	11 (7–23)	10 (6–21)	0.685
Time from onset to SE, day	7 (3–14)	5 (1–9)	0.031
Seizures before admission (%)	54 (96.4)	35 (92.1)	0.359
History of epilepsy (%)	5 (8.9)	3 (7.9)	0.860
GCS on admission	9 (6–12)	7 (4–12)	0.188
STESS	3 (2–3)	3 (3–4)	0.028
END-IT score	3 (3–4)	4 (3–5)	0.001
NCSE in coma (%)	26 (46.4)	27 (71.1)	0.018
Abnormal MRI findings (%)	32 (57.1)	28 (73.7)	0.101
Number of IV AEDs	2 (1–3)	3 (1–4)	0.031
Use of CIVADs (%)	24 (42.9)	21 (55.3)	0.237
CIVAD >50% PMD (%)	9 (16.1)	13 (34.2)	0.042
Seizures within 2 h after CIVAD (%)	16 (28.6)	16 (42.1)	0.174
Seizures within 2 h after CIVAD >50% PMD (%)	3 (5.4)	13 (34.2)	<0.001
Breakthrough seizures (%)	17 (30.4)	18 (47.4)	0.094
Withdrawal seizures (%)	14 (25.0)	16 (42.1)	0.081
CIVADs changed (%)	5 (8.9)	15 (39.5)	<0.001
Immune therapies (%)	16 (28.6)	9 (23.7)	0.599
Tracheal intubation (%)	20 (35.7)	31 (81.6)	<0.001
Use of vasopressors (%)	9 (16.1)	23 (60.5)	<0.001
Emergency resuscitation (%)	1 (1.8)	11 (28.9)	<0.001

CIVADs, continuous IV anesthetic drugs; GCS, Glasgow coma scale; NCSE, nonconvulsive status epilepticus; NICU, neurological intensive care unit; PMD, proposed maximal dose; STESS, status epilepticus severity score.
Data presented as n (%) or median (interquartile range).

DISCUSSION

In this study, we investigated the values of brain MRI and EEG monitoring for the predictions of progression to SRSE and 3-month functional outcome in SE due to acute encephalitis. Our data demonstrated that cortical or hippocampal abnormality on MRI and END-IT score independently predicted the progression to SRSE, and the recurrence of clinical or EEG seizures within 2 h

TABLE 5 | Logistic regression analysis for three-month unfavorable outcome.

Variables	Unadjusted analysis			Adjusted analysis*		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	1.02	0.99–1.04	0.230			
Male	2.02	0.85–4.78	0.110			
Time from onset to SE	0.99	0.97–1.01	0.412			
STESS	1.98	1.08–3.62	0.027			
END-IT score	1.94	1.31–2.87	0.001			
NCSE in coma	2.83	1.18–6.80	0.020			
CIVAD >50% PMD	2.72	1.02–7.23	0.045			
Number of IV AEDs	1.57	1.10–2.25	0.013			
Seizures within 2 h after CIVAD >50% PMD	9.19	2.40–35.17	0.001	4.52	1.04–19.68	0.044
CIVADs changed	6.65	2.16–20.50	0.001			
Tracheal intubation	7.97	2.98–21.36	<0.001	4.99	1.37–11.69	0.011
Use of vasopressors	8.01	3.05–21.02	<0.001			
Emergency resuscitation	22.41	2.75–182.67	0.004	9.80	1.11–86.47	0.040

**Hosmer and Lemeshow Test: p = 0.970.*

after the infusion rate of a single anesthetic drug >50% PMD, the use of tracheal intubation, and the use of emergency resuscitation independently predicted 3-month poor outcome in patients with SE due to acute encephalitis.

SRSE is a life-threatening neurological emergency occurring in 4–16.9% of all cause SE (10, 32–37). The observed incidence rate of SRSE in our study of SE due to acute encephalitis was 23.4% which was much higher than the average incidence, and it was consistent with previous studies suggesting that encephalitis was the determinant of progression from SE to SRSE (10, 32). However, no particular etiology of encephalitis was found in our study to be associated with a higher incidence of SRSE.

Besides encephalitis, a lower premorbid mRS score and NCSE in coma were also indicated to be the independent predictors of SRSE (38). In our study, GCS, STESS, and END-IT score were chosen to assess the illness severity and investigated as the potential predictors of SRSE. GCS was initially designed to evaluate the level of consciousness. STESS includes consciousness, seizure type, age, and history of epilepsy. END-IT score encompasses etiology (encephalitis or not), NCSE, diazepam resistance, brain image, and use of tracheal intubation. The inclusion of measurements regarding more aspects of illness might be the reason why END-IT score was the independent predictor of SRSE in SE due to encephalitis.

Cortical regions and hippocampus have been demonstrated to be associated with epileptogenesis (39–46). In patients with acute encephalitis, cortical lesions on neuroimaging imply a high risk of early-onset status epilepticus (9). Our study also proved the predictive value of neuroimaging and found that the abnormality in cortex or hippocampus was an early predictor for the progression to SRSE in SE due to acute encephalitis. Further studies are needed to investigate whether a more aggressive anti-epileptic therapy will shorten the duration of SE and improve the outcome in those patients with a high risk of SRSE.

Compared to all cause RSE, patients with RSE due to acute encephalitis had higher rates of recurrent seizures within 2 h of the initial CIVAD treatment, breakthrough seizures, and withdrawal seizures (27). However, the recurrence of these seizures was not associated with a poor outcome. Only the recurrence of clinical or EEG seizures within 2 h after the initiation of a single CIVAD at a dose of more than half the proposed maximal dose predicted an unfavorable functional outcome at 3 months. The recurrent seizures under the CIVAD treatment are usually subtle or non-convulsive. Thus, continuous EEG monitoring not only plays an indispensable role in the monitoring and treatment of SE, but also contributes to the outcome prediction in SE due to acute encephalitis.

This study contained a larger sample size of SE due to acute encephalitis compared to previous studies, described the anti-epileptic treatment responses at length, and firstly identified early predictors of SRSE in SE due to acute encephalitis. However, this study had a retrospective observational design and was conducted in a single tertiary care center. Moreover, because our hospital is one of the largest hospitals in northwest China, many patients were referred from other hospitals. Some patients might have not received a timely and sufficient anti-epileptic treatment initially. In this study, we followed the Chinese guidelines on the management of SE (15), which were consistent with the European guidelines about the proposed maximal dose of CIVADs (14), but the maximal dose of midazolam we used was lower than the suggestions proposed in American guidelines (47). So far the treatment with high-dose midazolam for refractory SE has not been widely performed in China, future studies are needed to be conducted in China to investigate and validate the effects of different infusion doses of midazolam in SE patients.

CONCLUSIONS

This study investigated the values of neuroimaging and continuous EEG in the multimodal predictions in SE due to acute encephalitis. Cortical or hippocampal abnormality on

neuroimaging and END-IT score are independent predictors of SRSE. The recurrence of clinical or EEG seizures within 2 h after the infusion rate of a single CIVAD >50% proposed maximal dose predicts a poor outcome at 3 months after NICU discharge.

AUTHOR CONTRIBUTIONS

FYu: Study concept and design, drafting of the manuscript, critical revision, statistical analysis, study supervision. FYa: Study concept and design, critical revision, study supervision. RJ, WL, YJ, JZ: Acquisition, analysis, interpretation of data. WJ: Study concept and design, critical revision, obtained funding.

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Regional Cerebral Oximetry as an Indicator of Acute Brain Injury in Adults Undergoing Veno-Arterial Extracorporeal Membrane Oxygenation–A Prospective Pilot Study

Imad Khan[1], Mehboob Rehan[2], Gunjan Parikh[3], Christopher Zammit[1], Neeraj Badjatia[3], Daniel Herr[4], Zachary Kon[5], Charles Hogue[6] and Michael Mazzeffi[7]*

[1] Division of Neurocritical Care, Department of Neurology, University of Rochester School of Medicine, Rochester, NY, United States, [2] Department of Medicine, Eastern Idaho Regional Medical Center, Idaho Falls, ID, United States, [3] Section of Neurocritical Care and Emergency Neurology, Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, United States, [4] Division of Critical Care Medicine, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, United States, [5] Division of Cardiothoracic Surgery, Department of Surgery, University of Maryland School of Medicine, Baltimore, MD, United States, [6] Department of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [7] Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, MD, United States

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Wengui Yu,
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Northwestern University, United States

***Correspondence:**
Imad Khan
imad_khan@urmc.rochester.edu

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Background: Regional cerebral oxygen saturation (rScO2) measured by near-infrared spectroscopy (NIRS) can be used to monitor brain oxygenation in extracorporeal membrane oxygenation (ECMO). ECMO patients that develop acute brain injuries (ABIs) are observed to have worse outcomes. We evaluated the association between rScO2 and ABI in venoarterial (VA) ECMO patients.

Methods: We retrospectively reviewed prospectively-collected NIRS data from patients undergoing VA ECMO from April 2016 to October 2016. Baseline demographics, ECMO and clinical characteristics, cerebral oximetry data, neuroradiographic images, and functional outcomes were reviewed for each patient. rScO2 desaturations were defined as a >25% decline from baseline or an absolute value <40% and quantified by frequency, duration, and area under the curve per hour of NIRS monitoring (AUC rate, rScO2*min/h). The primary outcome was ABI, defined as abnormalities noted on brain computerized tomography (CT) or magnetic resonance imaging (MRI) obtained during or after ECMO therapy.

Results: Eighteen of Twenty patients who underwent NIRS monitoring while on VA ECMO were included in analysis. Eleven patients (61%) experienced rScO2 desaturations. Patients with desaturations were more frequently female (73 vs. 14%, $p = 0.05$), had acute liver dysfunction (64 vs. 14%, $p = 0.05$), and higher peak total bilirubin (5.2 mg/dL vs. 1.4 mg/dL, $p = 0.02$). Six (33%) patients exhibited ABI, and had lower pre-ECMO Glasgow Coma Scale (GCS) scores (5 vs. 10, $p = 0.03$) and higher peak total bilirubin levels (7.3 vs. 1.4, $p = 0.009$). All ABI patients experienced rScO2

desaturation while 42% of patients without ABI experienced desaturation ($p = 0.04$). ABI patients had higher AUC rates than non-ABI patients (right hemisphere: 5.7 vs. 0, $p = 0.01$, left hemisphere: 119 vs. 0, $p = 0.06$), more desaturation events (13 vs. 0, $p = 0.05$), longer desaturation duration (2:33 vs. 0, $p = 0.002$), and more severe desaturation events with rScO2 < 40 (9 vs. 0, $p = 0.05$). Patients with ABI had lower GCS scores (post-ECMO initiation) before care withdrawal or discharge than those without ABI (10 vs. 15, $p = 0.02$).

Conclusions: The presence and burden of cerebral desaturations noted on NIRS cerebral oximetry are associated with secondary neurologic injury in adults undergoing VA ECMO.

Keywords: NIRS (near infrared reflectance spectroscopy), cerebral oximetry, ECMO (extracorporeal membrane oxygenation), acute brain injury, neurological outcome, adults'

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is increasingly being used in adults with cardiac failure and cardiac arrest (1). While survival is improving, between 7 and 15% of adults undergoing ECMO are found to have potentially devastating and often debilitating neurological complications such as infarction, hemorrhage, and seizures (2, 3). In both veno-arterial (VA) and veno-venous (VV) ECMO patients, mortality is higher in patients with neurological injury than in patients without (1, 2).

Near infrared spectroscopy (NIRS) is a non-invasive tool that can be used to monitor regional saturation of cerebral oxygen (rScO2) and holds promise as a real-time bedside target for goal-directed ECMO therapy. This technology can demonstrate improvement in brain oxygenation in patients undergoing VV ECMO for acute respiratory distress syndrome (ARDS) (4), and has been used to titrate VA ECMO therapy in a patient with cardiac arrest (5). NIRS is also used intraoperatively to monitor patients undergoing cardiac surgery as desaturations in rScO2 can indicate post-surgical cognitive decline and stroke (6–8). However, it is unclear whether rScO2 desaturations associate with acute brain injury (ABI) in adults undergoing ECMO for acute cardiac failure. In this prospective cohort study, we sought to evaluate whether rScO2 desaturations were associated with radiographic brain injury in adult VA ECMO patients.

MATERIALS AND METHODS

Study Population

We conducted a retrospective analysis of prospectively collected data of consecutively-admitted adult patients at our medical center who received rScO2 monitoring during VA ECMO between April 1, 2016 and October 31, 2016. rScO2 monitoring was performed on all adult patients undergoing VA ECMO during that time period as an evaluation of a new NIRS device in the cardiothoracic ICU. Per institutional standard of care, patients with known pre-morbid neurologic injury or poor baseline level of function were not cannulated for ECMO. Patients who were on ECMO for less than 24 h were excluded because they underwent ECMO as a method of weaning from cardiopulmonary bypass after elective cardiac surgery, not for emergent cardiac failure typical of longer ECMO patients. The Institutional Review Board approved the study and informed consent was waived.

Patient and ECMO Data

Baseline demographic data and ECMO data were recorded prior to developing outcome of interest including indication for ECMO, cannulation type (peripheral vs. central), initial sweep gas flow, and initial ECMO blood flow. Comorbidities on admission were recorded. Lab values on admission, daily during admission, and during desaturations were recorded. The following organ failures during ECMO were recorded: acute renal failure requiring continuous renal replacement therapy (CRRT) and new onset liver dysfunction defined by *de novo* elevation of international normalized ratio (INR) >1.5 with transaminases >3× the upper limit of normal. The Glasgow Coma Scale (GCS) was used to define baseline neurologic function and was obtained from nursing documentation prior to the initiation of ECMO.

ECMO Management

Cardiothoracic surgeons performed ECMO cannulations in the intensive care unit or operating room. Either peripheral or central cannulation was used depending on surgeon preference. Initial sweep gas flows were set by the cannulating surgeon and were titrated according to the patient's arterial pH and partial pressure of carbon dioxide (pCO2). Initial ECMO blood flows were set by the cannulating surgeon and were adjusted to maintain goal MAP >65 mm Hg and cardiac index greater than 2 L/min/m^2. Patient temperature was managed using a heat exchanger attached to the ECMO circuit. Patient temperatures were maintained between 36 and 38C°. In patients who were placed on ECMO after cardiac arrest, temperature was strictly maintained at 36 C° for 24 h per institutional standard of care, after which they were rewarmed to 37 C° by 0.1 C°/h.

NIRS Monitoring

NIRS monitoring was performed using the Covidien INVOS 5100c Cerebral Oximeter (Medtronic, Minneapolis, MN, USA).

Monitoring was started within 24 h of cannulation and continued until ECMO decannulation. Sensors were attached to both sides of the forehead, each with one light-emitting diode emitting near-infrared wavelength light at 730 and 810 nm and two detectors (9). Sensors were routinely replaced every 5 days or if proper adhesion was lost. rScO2 was displayed on the INVOS monitor every 3 s, automatically recorded on a secure USB drive attached to it, and then uploaded to a computer for analysis. Patient care teams were blinded to rScO2 data as the medical center was conducting a pilot study of the device's feasibility during the period of data collection.

rScO2 values were analyzed using the INVOS Analytics Tool (Medtronic, Minneapolis, MN, USA) and visual inspection by two of the authors (IK and MR). Initial values were labeled as the baseline, and desaturations were defined as a drop in rScO2 > 25% below baseline or an absolute rScO2 <40%, based on a previous study that examined cerebral oximetry in adults undergoing ECMO (10). The start time of each desaturation was recorded at the beginning of a downward trend in rScO2 and the time point at which rScO2 began steadily increasing was labeled as the end time. An area under the curve (AUC, rScO2*min) value was automatically calculated by the Analytics Tool via a proprietary formula in order to quantify the degree of desaturation. The threshold below which rScO2 would be considered "under the curve" is set by the user in the Analytics Tool, and we set this threshold to be at 25% below the baseline rScO2. Each patient's total AUC was divided by the number of hours of rScO2 monitoring he/she underwent to devise an hourly AUC rate (rScO2*min/h), in order to account for differences in the duration of monitoring. An AUC, and AUC rate, was documented for both the right and left sensors and labeled correspondingly.

Study Outcomes

The study's primary outcome was acute brain injury (ABI) seen on radiographic imaging. Neuroimaging was obtained at the discretion of the medical team if there was clinical suspicion of brain injury. Brain injury was evaluated by review of available computed tomography (CT) scan and/or magnetic resonance imaging (MRI) scans that were conducted during or after ECMO. Two study authors independently adjudicated all injuries (IK and MR). As noted above, desaturations were never used as the sole indication for neuroimaging as they were not implicated in clinical decision-making. Patients who did not receive neuroimaging were added to the non-ABI group for statistical analysis. Secondary outcomes included good functional status at the time of discharge, defined by Cerebral Performance Category (CPC) 1 or 2 (11). This score was calculated by review of discharge, physical, and occupational therapy notes. The CPC score was utilized because of its prior validation in cardiac arrest populations, which was the most common indication for ECMO in our cohort. We also recorded the last nurse-documented GCS score prior to the patient's discharge, death, or withdrawal of care as a final assessment of the patient's neurologic status. This assessment could have been made during ECMO therapy or after its discontinuation if the patient survived to that point.

Statistical Analysis

Statistical analysis was performed using SPSS (Version 25.0, IBM Corp, Armonk, NY). Normality of variables were assessed using the Shapiro-Wilk test. Demographic, clinical, and rScO2 characteristics of patients were compared using Student's *T*-test (for normally distributed continuous variables), the Wilcoxon Rank Sum test (for non-normally distributed continuous variables), or Chi-Squared Test (for categorical variables). Characteristics were summarized as the mean ± 2 standard deviations, median (1st, 3rd quartiles), or n (%) depending on variable type and normality of distribution. Study outcomes were compared between patient groups using the Chi-Squared test or the Wilcoxon Rank Sum test. A p-value ≤ 0.05 was used to exclude the null hypothesis.

RESULTS

Twenty consecutive VA ECMO patients underwent rScO2 monitoring between April 1, 2016 and October 31, 2016. Two patients were excluded from the analysis because of poor data quality (missing data for >50% of ECMO time, due to disconnection of sensor pads), leaving 18 patients in the final analysis. High-quality data was available for >75% of the monitoring duration for all patients included in the analysis. Time periods with absent recorded rScO2 values were not included in the analysis. VA ECMO was performed for extracorporeal cardiopulmonary resuscitation (ECPR) for cardiac arrest in 9 patients, post-cardiotomy shock in 1 patient, massive or submassive pulmonary embolism in 3 patients, and acute cardiogenic shock from other causes in 5 patients. Other causes of cardiogenic shock included non-ischemic cardiomyopathy (1), ventricular septal defect (1), severe mitral stenosis (1), and ST-elevation myocardial infarction (2). Sixteen patients were cannulated peripherally and 2 patients were cannulated centrally.

rScO2 desaturations occurred in 11 of 18 patients (61%) (**Table 1**). Examples of cerebral oximetry graphs of patients with and without desaturations are displayed in **Figure 1**. Patients with rScO2 desaturations were more often female (73 vs. 14%, $p = 0.05$), had acute liver dysfunction (64 vs. 14%, $p = 0.05$), and had higher peak total bilirubin (5.2 mg/dL vs. 1.4 mg/dL, $p = 0.02$). ABI occurred in 6 patients (33%) (**Table 1**). These patients had lower pre-ECMO GCS scores (5 vs. 10, $p = 0.03$) and higher peak total bilirubin levels (7.3 vs. 1.4, $p = 0.009$).

Survivors had lower baseline rScO2 values than non-survivors (right: 57 ± 9 vs. 65 ± 6, $p = 0.04$; left: 57 ± 12 vs. 68 ± 8, $p = 0.05$) and had higher average hemoglobin values at the time of cerebral desaturation (10.9 vs. 8.5 mg/dL, $p = 0.02$) (**Table 2**). There was no significant difference in the number of desaturation events or area under the desaturation curve between survivors and non-survivors. All patients with ABI experienced a desaturation, while 42% of patients without ABI experienced a desaturation ($p = 0.04$) (**Table 2**). Both unilateral (4 vs. 0, $p = 0.02$) and bilateral (10 vs. 0, $p = 0.05$) desaturation patterns were seen more in ABI patients. ABI patients had significantly

TABLE 1 | Patient characteristics[a].

Characteristic	Desaturations ($n = 11$)	No desaturations ($n = 7$)	ABI ($n = 6$)	No ABI ($n = 12$)
Age	61 (24, 69)	67 (56, 73)	63 (57, 69)	57 (34, 71)
SEX				
Male	3 (27%)	6 (85%)	2 (33%)	7 (58%)
Female	8 (73%)	1 (14%)*	4 (67%)	5 (42%)
Pre-ECMO GCS[b]	7.5 (3–15)	10 (3–15)	5 (3–10)	10 (3–15)*
INDICATION FOR ECMO				
ECPR	4 (36%)	5 (71%)	2 (33%)	7 (58%)
Post-cardiotomy	1 (9%)	0	1 (17%)	0
PE[c]	2 (18%)	1 (14%)	0	3 (25%)
Cardiogenic shock	4 (36%)	1 (14%)	3 (50%)	2 (17%)
COMORBIDITIES				
Hypertension	4 (36%)	5 (71%)	3 (50%)	6 (50%)
Diabetes	3 (27%)	2 (29%)	1 (17%)	4 (33%)
Liver dysfunction	7 (64%)	1 (14%)*	4 (67%)	4 (33%)
Baseline lactate[f]	4.1 (2.7, 9.3)	2.6 (1.7, 9.2)	4.1 (3.2, 9.6)	2.7 (2, 9.2)
Baseline creatinine[g]	1.7 ± 0.7	1.5 ± 0.8	1.8 (1.4, 2.4)	1.1 (0.9, 2.5)
Peak total bilirubin[g]	5.2 (1.8, 10.4)	1.4 (1.3, 1.5)*	7.3 (2.9, 11.6)	1.4 (1.3, 2.3)*
Baseline EF[h]	20 (10, 50)	55 (15, 75)	40 (20, 55)	23 (15, 60)
CRRT[d]	5 (45%)	3 (43%)	4 (67%)	4 (33%)
Hemorrhage	2 (18%)	2 (29%)	2 (33%)	2 (17%)
Blood transfusions[e]	5 (0–11)	11 (5–13)	5 (0–11)	7 (0–13)
Duration of ECMO (days)	9 (6, 11)	8 (4, 14)	9 (6, 13)	9 (5, 11)
CANNULATION TYPE				
Peripheral	10 (91%)	6 (86%)	5 (83%)	11 (92%)
Central	1 (9%)	1 (14%)	1 (17%)	1 (8%)
Initial sweep gas flow[i]	5.5 ± 2	4.6 ± 2.3	6.3 ± 2.3	4.6 ± 1.9
Initial blood flow[i]	4.4 ± 0.5	4.4 ± 1.1	4.4 ± 0.5	4.4 ± 0.9

*[a]Normally-distributed variables are reported as mean ± SD, non-normally distributed variables reported as median (1st, 3rd quartiles); [b]GCS, Glasgow Coma Scale, median (range); [c]PE, pulmonary embolus; [d]CRRT, continuous renal replacement therapy; [e]Total units during ECMO, median (range); [f]in mmol/dL; [g]in mg/dL; [h]ejection fraction, in %; [i]in liters/min; *$p \leq 0.05$.*

more desaturation events (13 vs. 0, $p = 0.05$), higher right AUC rates (5.7 vs. 0, $p = 0.01$), more severe desaturation events with rScO2 <40 (9 vs. 0, $p = 0.05$), and had longer durations of desaturation (2:33 vs. 0, $p = 0.002$). The left AUC rate in patients with ABI trended toward significantly higher values than in those without (119 vs. 0, $p = 0.06$).

Fourteen of the 18 patients had neuroimaging (78%): 2 had MRIs after ECMO and 12 had CT scans during or after ECMO. Neuroimaging findings are detailed in **Table 3**. Five patients (35%) with neuroimaging had brain infarctions, consisting of 2 watershed infarctions, 2 embolic infarctions, and one patient with both. One patient (17%) with recent cardiac arrest had diffuse cerebral edema on CT scan. Microhemorrhages were noted on 2 (14%) images, both of which were MRI's. Four of the Eighteen patients (22%) did not clinically warrant neuroimaging. These patients were younger (36 vs. 60 years old, $p = 0.02$) and had higher pre-ECMO GCS scores (11 vs. 6, $p = 0.05$). The one patient who died before discharge and never received neuroimaging had a history of right ventricular failure, suffered a cardiac arrest warranting ECPR, and then developed septic shock with fungemia.

Acute brain injury was noted in 6 of the 18 patients (33%) and all 6 (100%) experienced rScO2 desaturations (**Table 4**). No significant differences were found in neurologic function at discharge, in-hospital death, or last recorded GCS scores between patients with or without desaturations (**Table 4**). All patients who died had life sustaining treatment withdrawn by their family due to poor prognosis. Non-survivors had lower median GCS scores prior to withdrawal of care compared to survivors at the time of discharge (4 vs. 15, $p < 0.001$). Patients with ABI also had lower last recorded GCS scores than those without ABI (10 vs. 15, $p = 0.02$).

DISCUSSION

In our single-center prospective cohort study of VA ECMO patients, we found that rScO2 desaturations were frequent, occurring in 11 (61%) of 18 patients. Six patients (33%) had confirmed brain injury. All patients with ABI experienced rScO2 desaturations during ECMO, and had more numerous, longer, and more severe events than those without ABI.

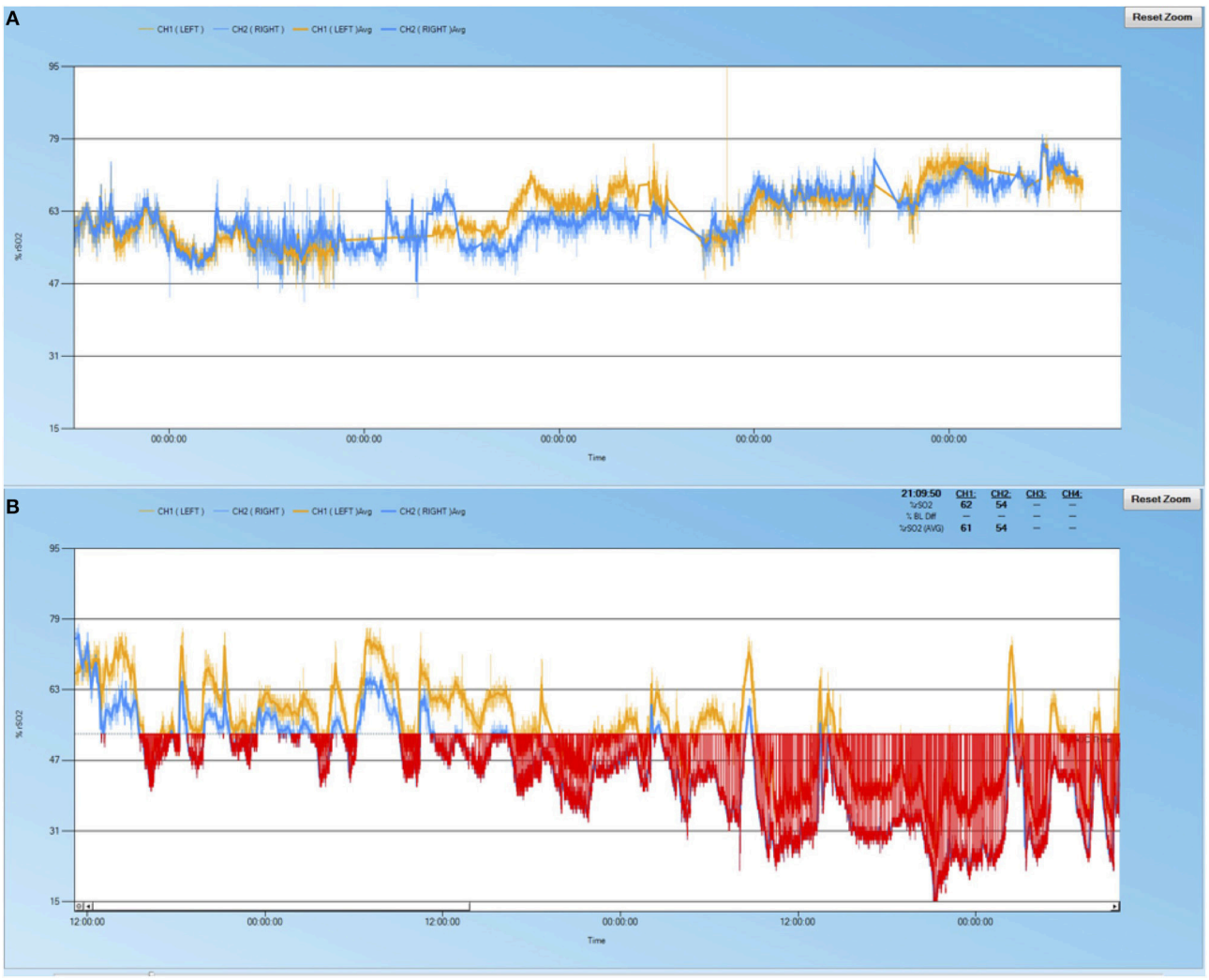

FIGURE 1 | Sample cerebral oximetry time course of patients. **(A)** 69 year-old male with pulmonary embolus, no acute liver injury, no rScO2 desaturations, normal neuroimaging, and survived to discharge. **(B)** 64 year-old male with cardiogenic shock, acute liver injury, significant rScO2 burden (red shaded area), watershed infarctions noted on neuroimaging, did not survive to discharge.

Establishing a method of monitoring the brain during ECMO is of key importance because the clinical exam, which is the gold standard for evaluating brain function, is often obviated by the requirement for sedation and/or neuromuscular blockade. Previous studies have evaluated cerebral oximetry with NIRS in ECMO patients, but most were in pediatric or neonatal populations (12–16). Three studies found that NIRS can detect cerebral hypoxia during carotid artery ligation in neonates (12, 13, 15). Another pediatric study used NIRS to demonstrate that autoregulation is impaired during periods of fluctuating ECMO blood flow (14). As NIRS allows for the continuous, non-invasive, portable monitoring of brain oxygen content, it is well-suited for monitoring for brain injury in the adult ECMO population (17). NIRS oximetry has also been shown to correlate closely with jugular bulb oximetry in pediatric patients undergoing cardiopulmonary bypass, a well-described monitoring technique in a population physiologically similar to VA ECMO (18, 19).

Patients who suffered acute brain injury appeared to have an overall higher burden of rScO2 desaturations than those without acute brain injury. This finding corroborates the two previous studies performed using NIRS to monitor rScO2 in the adult ECMO population (10, 20). In these studies, between 94 and 100% of the patients with confirmed neurologic injury experienced desaturations in rScO2, making cerebral oximetry with NIRS a highly sensitive screening tool. Our study differed from the prior two studies in that rScO2 values were blinded to patient care teams as the device was being tested in a pilot study. This allowed us to observe the natural history of cerebral oxygen saturation, and significant differences in desaturation duration and burden (AUC/h) became apparent between ABI and non-ABI groups.

TABLE 2 | Regional brain oxygenation values[a].

Characteristic	Non-survivors ($n = 7$)	Survivors ($n = 11$)	ABI ($n = 6$)	No ABI ($n = 12$)
BASELINE RSCO2[b] (%)				
Left	68 ± 8	57 ± 12*	64 ± 11	60 ± 12
Right	65 ± 6	57 ± 9*	64 ± 9	58 ± 9
Experienced desaturation event	5 (71%)	6 (55%)	6 (100%)	5 (42%)*
Number of desaturation events	8 (0, 29)	4 (0, 15)	13 (8, 19)	0 (0, 14)*
AVERAGE AUC RATE[c]				
Left	0.5 (0, 236)	0.8 (0, 75.9)	119 (0.5, 327)	0 (0, 4.7)
Right	3.2 (0, 8.1)	0.6 (0, 2)	5.7 (0.7, 113)	0 (0, 1.4)*
No. events rScO2[b] <40	2 (0, 7)	0 (0, 10)	9 (2, 15)	0 (0, 4)*
Duration per patient[d]	0:47 (0, 3:51)	0:24 (0, 2:03)	2:33 (0:54, 3:51)	0 (0, 0:38)*
Average minimum rScO2[b] (%)	45 ± 11	41 ± 12	38 ± 10	45 ± 12
DESATURATION PATTERN				
No. of unilateral	2 (0, 5)	0 (0, 0)	4 (0, 6)	0 (0, 0)*
No. of bilateral	6 (0, 27)	4 (0, 10)	10 (6, 11)	0 (0, 11)*
Average Hb at time of desaturation[e]	8.5 (8.3, 8.4)	10.9 (8.8, 10)*	8.6 (8.4, 9.1)	9.7 (8.9, 9.8)
Events after blood flow change	1 (0, 2)	0 (0, 0)	0 (0, 1)	0 (0, 0)
Events after sweep change	1 (0, 3)	1 (0, 1)	1 (0, 3)	0 (0, 1)

*[a]Normally-distributed variables reported as mean ± SD, non-normally distributed variables reported as median (1st, 3rd quartiles); [b]rScO2, regional saturation of cerebral oxygen; [c]AUC, area under the curve, rate in rScO2*min/h; [d]in hours:minutes; [e]Hb, hemoglobin, in mg/dL; *$p \leq 0.05$.*

TABLE 3 | Characteristics of groups with and without neuroimaging.

Characteristic	Obtained imaging ($n = 14$)	Did not obtain imaging ($n = 4$)	p
Imaging result		N/A	N/A
Normal	8 (57%)		
Watershed infarction	3 (21%)		
Embolic infarction	3 (21%)		
Microhemorrhage	2 (14%)		
Diffuse cerebral edema	1 (7%)		
Age (years)	60 ± 14	36 ± 27	0.02
Pre-ECMO GCS[b]	6 (3–15)	11 (9–15)	0.05
Indication for ECMO			1
ECPR	7 (50%)	2 (50%)	
Non-ECPR	7 (50%)	2 (50%)	
Duration of ECMO (days)	8 (6, 13)	10 (7, 11)	0.9
Experienced desaturation	7 (50 %)	4 (100%)	0.1
BASELINE rScO2[c] (%)			
Left	60 ± 12	68 ± 12	0.3
Right	59 ± 9	62 ± 8	0.6
Last recorded GCS	14 (4–15)	15 (13–15)	0.07
FUNCTIONAL OUTCOME			
Good (CPC 1-2)[d]	8 (57%)	3 (75%)	0.6
Died before discharge	6 (43%)	1 (25%)	0.6

[a]Normally-distributed variables are reported as mean ± SD, non-normally distributed variables reported as median (1st, 3rd quartiles); [b]GCS, Glasgow Coma Scale, median (range); [c]rScO2, regional saturation of cerebral oxygen; [d]CPC, cerebral performance category.

The ABI group was noted to have a significantly higher AUC rate on the right hemisphere than the non-ABI group (**Table 2**). This may signify the presence of differential hypoxia, which is the partial perfusion of the brain with deoxygenated blood pumped from the patient's heart as it recovers and regains contractility while the lungs remain injured (21). This presents an intervenable moment, as possible treatment strategies to maintain the supply of oxygenated blood include increasing the ECMO circuit's flow rate, decreasing the heart's preload or inotropy, or introducing oxygen-rich blood via a second venous ECMO cannula (22). With the ability to monitor for differential hypoxia continuously at the bedside, NIRS may potentially provide a target for goal-directed ECMO therapy, which remains to be seen in future studies.

We found pre-ECMO GCS scores to be significantly lower in patients with ABI and lower in patients with desaturations, although this did not reach statistical significance (**Table 1**). This suggests the possibility that patients may have suffered ABI before the initiation of ECMO, which could confound the temporal relationship between desaturations and ABI. However, our study was not designed to determine a temporal relationship between desaturations and ABI, but merely an association between the two. Interestingly, although patients with ABI had lower pre-ECMO GCS scores, they did not appear to have lower baseline rScO2 values at the start of NIRS monitoring. Nevertheless, this group had a higher burden of desaturation. One possible explanation for this finding is that the ABI group may have had an underlying impairment of cerebral autoregulation making them prone to desaturation, although this remains to be elucidated in further studies.

A few baseline characteristics differentiated patients with desaturations vs. those without. First, female patients were more likely to experience desaturation (**Table 1**). This finding may be driven in part by sex differences in cerebral autoregulation (23, 24). Second, patients with desaturations had higher peak bilirubin levels and more often had acute liver dysfunction

TABLE 4 | Patient outcomes[a].

Characteristic	Desaturations ($n = 11$)	No desaturations ($n = 7$)	p	ABI ($n = 6$)	No ABI ($n = 12$)	p
Acute brain injury			0.04	N/A	N/A	
Absent	5 (45%)	7 (100%)				
Present	6 (55%)	0 (0%)				
Functional outcome						
Good (CPC 1-2)[b]	6 (55%)	5 (71%)	0.6	2 (33%)	9 (75%)	0.1
Died before discharge	5 (45%)	2 (29%)	0.6	4 (67%)	3 (25%)	0.1
Last recorded GCS[c]	13 (3–15)	15 (3–15)	0.5	10 (3–14)	15 (3–15)	0.02

[a]*All numbers reported as n (%) or median (1st, 3rd quartile);* [b]*CPC, cerebral performance category;* [c]*GCS, Glasgow Coma Scale, median (range).*

(**Table 1**). Patients with acute liver dysfunction can be at risk of cerebral hyper- or hypo-perfusion due to impaired cerebral autoregulation (25, 26). On the other hand, hyperbilirubinemia could falsely depress regional brain oxygenation values, as bilirubin can absorb near-infrared light (27). This confounding effect is challenged by the fact that bilirubin levels were also significantly elevated in the ABI group. The effect of acute liver dysfunction and hyperbilirubinemia on cerebral autoregulation in patients undergoing ECMO remains to be further described in future studies.

We found baseline rScO2 values to be higher in non-survivors than survivors in our study (**Table 2**), which was unexpected. This could be explained by the fact that patients with more severe brain injury, particularly anoxic injury, have lower cerebral oxygen consumption (28). Lower oxygen consumption increases venous oxygen saturation and subsequently could increase rScO2, which largely reflects the venous content of the brain (29). Cerebral ischemic preconditioning may offer another explanation for these findings, where the systemic ischemia experienced from cardiogenic shock may have lead to a vasodilatory state (30, 31). There were no other significant differences in rScO2 values between survivors and non-survivors including number of desaturation events and AUC, but our study was small and likely underpowered for these analyses.

In a recent retrospective review of an international ECMO registry, the survival rate for adults undergoing VA ECMO with radiographically-confirmed cerebral infarction or hemorrhage was 17.4 and 10.5%, respectively, vs. 57% for those without any neurologic injury (3). In our study, while the presence of desaturation was associated with radiographic brain injury, it did not correlate with survival and functional outcome. Our prospective pilot study was not adequately powered to determine a difference in these outcomes, and larger studies will be needed to determine if cerebral desaturation can independently predict functional outcome after ECMO.

We included the four patients who did not undergo neuroimaging into the non-ABI group because they did not clinically warrant neuroimaging. These patients had higher median pre-ECMO GCS scores and were significantly younger than those who received neuroimaging (**Table 3**). We did not find a significant difference in age between patients with or without ABI, or with or without desaturations (**Table 1**). Our study was not powered to be able to correlate age and occurrence of ABI, but it is notable that no age difference was noted in patients with or without acute cerebral complications in another recently published study examining cerebral desaturations in adults undergoing ECMO (20). However, the authors of that study did not describe the age of patients who underwent brain imaging vs. those without.

Our study has several limitations. First, it was a small prospective observational cohort study, which limits its generalizability and increases the possibility of Type 2 error. Our aim was to conduct a pilot study to evaluate the usefulness of NIRS technology to detect radiographic cerebral injury, and as such was not powered to detect differences in mortality or morbidity. Furthermore, as mentioned above, pre-ECMO brain injury could have confounded the association between cerebral desaturations and ABI, but this study was not intended to determine the causal relationship between the two. Second, rScO2 monitoring values can be skewed by elevated bilirubin levels, increased skull thickness, or superficial scalp deoxygenation, all of which could have affected our results (27, 32). Third, the system we used measures regional, not global cerebral oxygen saturation, and thus only a small portion of the cortex is evaluated. Thus, our device would not have detected deeper, subcortical pathology, or that of other regions of the cortex.

CONCLUSIONS

In summary, our study data suggest that amongst patients undergoing VA ECMO, acute brain injury is associated with the frequency, duration, and burden of desaturations noted on NIRS cerebral oximetry. rScO2 is a promising biomarker for future goal-directed ECMO therapy studies that deserves further validation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

IK and MM conceived the hypothesis and designed this study. IK and MR collected and reviewed data. IK was the primary author of the manuscript with input from all authors. IK performed statistical analysis. CH, GP, CZ, NB, DH, and ZK were involved in critical manuscript revisions. All authors read and approved the submitted version.

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Outcome Prediction by 40-Hz Steady-State Response After Large Hemispheric Infarction

*Yao Wang, Kaibin Huang, Shengnan Wang, Honghao Wang, Zhong Ji, Suyue Pan and Yongming Wu**

Department of Neurology, Nanfang Hospital, Southern Medical University, Guangzhou, China

Background and Purpose: The 40-Hz steady state response (SSR) reflects early sensory processing and has the potential to differentiate disease severity. This study aims to evaluate the predictive value of 40-Hz SSRs on the prognosis of patients with large hemispheric infarction (LHI).

Methods: We conducted a retrospective study in patients with LHI admitted to the neurological intensive care unit (NICU) of Nanfang Hospital, Southern Medical University, Guangzhou, China, between June 2008 and December 2014. Forty-hertz SSRs were recorded within 72 h of onset and categorized into 3 grades. The correlation between 40-Hz SSR grading and clinical outcome was examined.

Results: Of the 97 eligible participants, 41 (42.3%) died within 30 days and 68 (70.1%) exhibited a poor outcome (modified Rankin Scale of 5 and 6) at 90 days after the onset of LHI. We found that 40-Hz SSRs correlated significantly with NIHSS scores at admission and patient outcome. Moreover, Grade III 40-Hz SSR (bilateral sine waves that either disappeared or were not clearly identifiable) had a specificity of 97% and a positive predictive value of 94% in predicting 90-days poor outcome; Grade III 40-Hz SSR also had a specificity of 91% and a positive predictive value of 74% in predicting 30-days mortality.

Conclusions: 40-Hz SSR could be used as a simple and specific method in predicting poor prognosis after LHI.

Keywords: 40-Hz steady-state response, large hemispheric infarction, neurocritical care, mortality, poor prognosis

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****Correspondence:***
Yongming Wu
yongmingwucn@hotmail.com

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INTRODUCTION

Large hemispheric infarction (LHI) have the potential to cause severe cerebral edemas and cerebral herniations, leading to death and morbidity even when treated as conservatively as possible (1). Several methods have been developed to identify LHI patients at risk of progressing to a malignant stage (2, 3), given the growing body of evidence that suggests timely treatment with decompressive craniectomy may improve clinical outcomes (4). However, decompressive craniecto1my is not suitable for all patients and, although the procedure reduces mortality, it may also increase the number of severely impaired individuals (5, 6). The ability to reliably predict which LHI patients may develop an undesirable prognosis is an area of research that is significantly lacking. At present, the infarct volume under neuroimaging maintains a pivotal role for the estimation of prognosis, with robust associations of clinical relevance (7, 8). However, serial imaging might be difficult to perform in critically ill patients. The use of additional outcome parameters that could simply and

repeatedly be obtained and reflect different aspects of stroke damage may be able to help specify prognoses in the early phases of LHI.

Neuronal networks in the sensory cortices, comprised of sensory cortical neurons, have a unique capability of entraining faithfully to the driving stimuli when subjected to phasic inputs. This entrainment to rhythmic sound stimuli is often referred to as the auditory steady-state response (SSR) (9, 10). A maximum SSR to a driving frequency of approximately 40 Hz was first reported by Galambos et al. (11). The 40-Hz SSR was used to test hearing integrity in infants as well as in audiometric tests for people of all ages (12). It has been suggested as an index for monitoring anesthetic depth because of its sensitivity to most general anesthetics (13, 14), with the exception of ketamine (14–17). Changes in amplitude or in latencies of the response would be observed with the effects of lesions (18–21). Since a 40-Hz SSR represents simultaneous activation over widely spaced areas of the brain, the change in its amplitude or latencies can reflect dysfunction in the brain and thus, the 40-Hz frequency may be valuable in the evaluation of neurological function (13, 22, 23). In a study of comatose patients after severe head injury or intracerebral hemorrhage, the presence or absence of a 40-Hz SSR correlated closely with clinical course and outcome (24). However, few studies have addressed the application of 40-Hz SSR in patients with LHI.

The present study was designed to determine the predictive value of 40-Hz SSRs in clinical outcomes for LHI patients under the most conservative treatments.

METHODS

Study Design and Participants

The retrospective study was conducted in patients with LHI (8) admitted to the neurological intensive care unit (NICU) of Nanfang Hospital, Southern Medical University, Guangzhou, China, between June 2008 and December 2014. The inclusion criteria were: (1) a diagnosis of acute ischemic stroke affecting the total or subtotal territory of the middle cerebral artery (MCA), at least partially involving the basal ganglia and with or without involvement of the adjacent (i.e., anterior cerebral artery or posterior cerebral artery) territories, as confirmed by neuroimaging (8); (2) aged >18 years; and (3) a 40-Hz SSR test having been completed within 72 h of onset. Exclusion criteria included: (1) a pre-stroke score of ≥1 on the modified Rankin scale (mRS) or of <95 on the Barthel index; (2) suffering from end-stage malignant diseases that might confound the prognosis; (3) known diseases of hearing or peripheral nerves; (4) antiepileptic or sedative medications having been administered before the 40-Hz SSR assessment; and (5) endovascular treatment having been conducted during the study period.

According to national and international guidelines for the management of acute ischemic stroke (8), all participants received a maximum conservative treatment or a decompressive craniectomy, with the latter being performed in cases of increased intracranial pressure and herniation, and codetermined by the neurosurgeon and legal representatives independent of the study design.

40-Hz SSR Tests and Grading

40-Hz SSR tests were recorded within 72 h after the onset of LHI, according to standard techniques established for using the Viking Quest system evoked potential equipment (Nicolet Company, American). Briefly, silver-chloride electrodes were applied to the scalp at C_Z, A1, and A2 according to the international 10–20 system of electrode placement, and a ground electrode was placed on the forehead, at the Fpz position. To record 40-Hz SSR, repeated pips at a rate of 39.1 Hz were generated in standard inserted headphones. Monaural stimulation was used with 95 decibels (dB) nHL tone pips, and the ear contralateral to stimulation was masked with 70 dB white noise. We determined the interpeak amplitude between the first positive peak (P1) and the first negative wave (N1) as N1 amplitude with a 100 ms time base (11). Internal laboratory standards were established in an independent group of young healthy volunteers ($n = 80$) (**Supplementary Method**, **Supplementary Figure 1**).

Amplitudes of the 40-Hz SSR were considered abnormal when the side-to-side difference exceeded 50% when compared to the unaffected contralateral response or when the amplitude was below the 2.5-fold value of the established standard value (**Supplementary Table 1**). Accordingly, 40-Hz SSRs were classified as one of 3 grades (25) (**Figure 1**): Grade I (normal amplitude), with bilateral sine waves appearing clearly; Grade II (moderate abnormal amplitude), with unilateral sine waves not present, or an amplitude ratio lower than 50% of the unaffected side; and Grade III (severe abnormal amplitude), with bilateral sine waves not present or not clearly identifiable.

Clinical Data

Demographic, clinical, and neuroimaging data were collected from our prospectively organized database by a research associate (S.W.) and two neurologists (H.W. and Z.J.), all of whom were blind to the 40-Hz SSR data. All participants were followed up for 90 days after the onset of LHI by a trained neurologist blind to the study data via telephone interviews. The primary outcome was a functional prognosis at 90 days, which was classified as good (mRS of 0 to 4) and poor (mRS of 5 and 6) (26). The secondary outcome was mortality of all causes at 30 days.

Statistical Analysis

Continuous data were presented as the mean ± standard deviation (SD) or median (25–75% interquartile range [IQR]) and compared by Student's t-test or Mann-Whiney U test, as appropriate. Differences in proportion among categorical data were assessed using chi-squared test or Fisher's exact test. Correlations between the variables were determined with the Spearman correlation test. We calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of predefined thresholds with 40 Hz SSR Grade III to predict 90-days functional outcomes and 30-days mortalities, and reported the corresponding 95% confident intervals (CIs) (27). The level of significance was set to $p < 0.05$. All statistical analyses were performed with SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

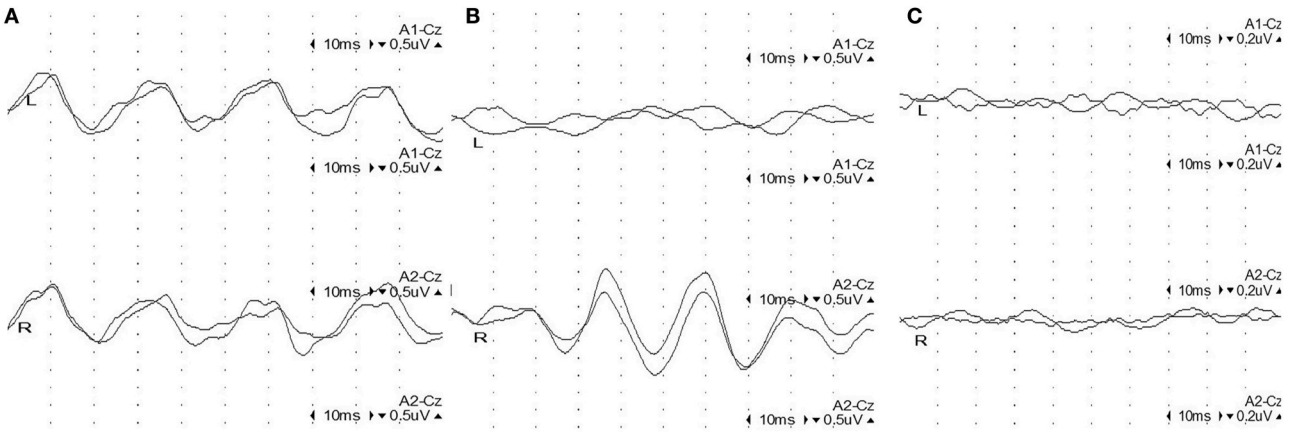

FIGURE 1 | Representative figures of 40-Hz steady-state responses (SSRs) in 3 grades. **(A)** Grade I: normal 40-Hz SSR: 4 sine waves appearing regularly in 100 ms with settled intervals, with a comparable amplitude on both sides. **(B)** Grade II: unilateral abnormal 40-Hz SSR: sine waves on the left side are extinct, while 4 sine waves appear regularly on the right side in 100 ms with settled intervals and normal amplitude. **(C)** Grade III: bilateral abnormal 40-Hz SSR: sine waves are extinct bilaterally.

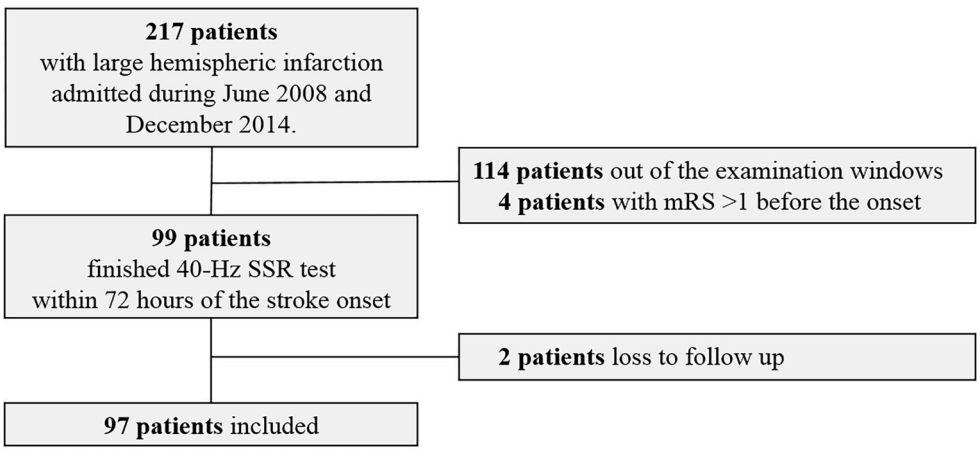

FIGURE 2 | Patient inclusion flowchart.

RESULTS

Between June 2008 and December 2014, 97 eligible LHI patients were recruited (**Figure 2**). Among them, 41 (42.3%) patients died within 30 days after the onset of LHI (**Supplemental Table 2**) and 68 (70.1%) patients had a poor outcome at 90 days (**Table 1**). The results showed that patients with poor outcomes had higher NIHSS scores at admission as compared to those with good outcomes. For the causes of the strokes, more patients in the poor outcome group could be attributed to cardioembolisms. However, beyond that, we did not observe significant difference between the good and poor outcome groups in age, gender, the ratio receiving intravenous thrombolysis or decompressive craniectomy, medical history or laboratory findings at admission. Similar results were observed between survivors and nonsurvivors at 30 days (**Supplementary Table 2**).

In terms of the 40-Hz SSR testing results, the median grade in the poor outcome group was higher than that in the good outcome group. Additionally, more patients in the poor outcome group received a Grade III classification than those in the good outcome group (**Table 1**). The correlation between 40-Hz SSR grades and 90-days prognoses remained when the functional outcome was treated as specific mRS scales (**Figure 3A**, **Table 2**). Correlation analysis also revealed a close correlation between NIHSS scores and 40-Hz SSR grades, indicating that the 40-Hz SSR could accurately reflect the severity of the LHI (**Table 2**).

To further evaluate the performance of 40-Hz SSRs in predicting patient outcomes, we categorized the 40-Hz SSRs into Grade I & II vs. Grade III (**Figure 3B**). It was found that 40-Hz SSRs that were Grade III had a sensitivity of 22%, specificity of 97%, PPV of 94%, and NPV of 35% in predicting 90-days poor outcomes (**Table 3**). Additionally, 40-Hz SSRs that were Grade III had a sensitivity of 34%, specificity of 91%, PPV of 74%, and NPV of 65% in predicting 30-days mortalities (**Table 3**).

TABLE 1 | Baseline characteristics between patients with good (mRS 0–4) and poor (mRS 5–6) outcome at 90 days.

Parameters	Good outcome (n = 29)	Poor outcome (n = 68)	P-value
Age [y], median (IQR)	67 (53, 76)	68 (57, 76)	0.611
Male, *n* (%)	18 (62.1)	41 (60.3)	0.870
NIHSS score on admission, mean ± *SD*	15.7 ± 6.0	20.5 ± 7.8	0.004
Intravenous thrombolysis, *n* (%)	4 (13.8)	8 (11.8)	0.953
Decompressive craniectomy, n (%)	1 (3.4)	7 (10.3)	0.472
Medical history, *n* (%)			
Hypertension	18 (62.1)	43 (63.2)	0.913
Diabetes mellitus	5 (17.2)	15 (22.1)	0.591
Atrial fibrillation	5 (17.2)	17 (25.0)	0.404
Myocardial infarction	1 (3.4)	2 (2.9)	1.000
Temperature [°C], median (IQR)	36.6 (36.5, 37.3)	36.9 (36.6, 37.6)	0.078
Systolic blood pressure [mmHg], mean ± *SD*	152.1 ± 26.1	144.6 ± 30.8	0.262
Stenosis or occlusion of the ipsilateral extracranial ICA, *n* (%)	0 (0)	4 (44.4)	1.000
Stenosis or occlusion of the contralateral extracranial ICA, *n* (%)	7 (25.9)	24 (36.4)	0.332
Vessel occlusion dichotomized, *n* (%)			0.205
Isolated MCA	21 (72.4)	40 (58.8)	
ICA + MCA	8 (27.6)	28 (41.2)	
Etiology (TOAST classification), *n* (%)			0.047
Large artery atherosclerosis	23 (79.3)	35 (51.5)	
Cardioembolism	6 (20.7)	27 (39.7)	
Small vessel disease	0 (0)	0 (0)	
Other determined etiology	0 (0)	5 (7.3)	
Undetermined origin	0 (0)	1 (1.5)	
Laboratory values			
Hematocrit [%], mean ± *SD*	39.5 ± 7.3	39.1 ± 7.1	0.829
White blood cell count [$\times 10^6$/mL], mean ± SD	10.9 ± 3.8	12.7 ± 4.8	0.075
Creatinine [μmol/L], median (IQR)	76 (59, 104)	80 (63, 105)	0.512
40 Hz SSR, median (IQR)	1 (1, 2)	1 (1, 2)	0.046
40 Hz SSR grade III, *n* (%)	1 (3.4)	15 (22.1)	0.034

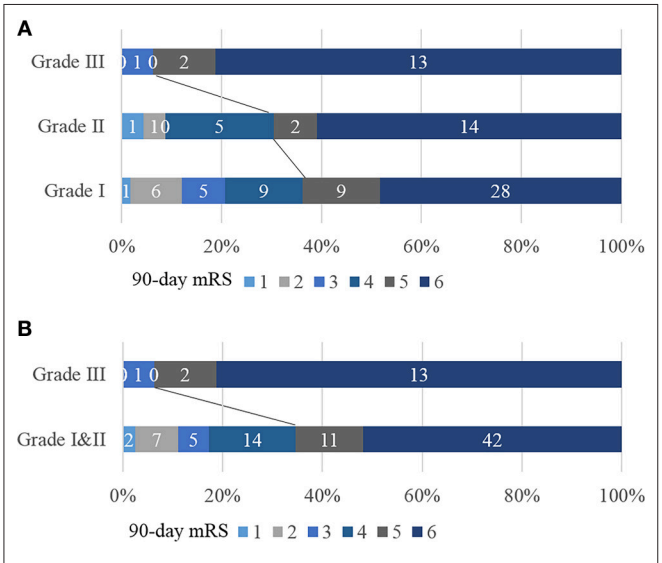

FIGURE 3 | Correlation between 40-Hz SSR grading and mRS scores. **(A)** 40-Hz SSRs were categorized into Grade I, II, and III. **(B)** 40-Hz SSRs were categorized into Grade I & II vs. Grade III.

TABLE 2 | Correlation between 40-Hz SSRs (Grade I & II vs. Grade III) and NIHSS, 90-days mRS and duration of hospital stay.

Parameters	*R*	*P*-value
NIHSS score on admission	0.244	0.016
90-days mRS	0.232	0.022
Duration of hospital stay	−0.181	0.108

DISCUSSION

The present study demonstrated the 40-Hz SSR as an outcome prediction tool for patients with LHI. The results showed that 40-Hz SSRs of Grade III had a high specificity and PPV in predicting both 90-days poor prognosis and 30-days mortality after LHI under the maximum conservative treatments, indicating that the 40-Hz SSR could be reliably used to assess a poor outcome after LHI.

Early prediction of clinical outcomes after an ischemic stroke is essential for the planning of acute and rehabilitative therapeutic strategies during the first days of hospital care. Early changes seen in cranial CT, MRI and angiography are all valuable for

TABLE 3 | The performance of 40-Hz SSR Grade III patients in prediction of 90-days poor outcome and 30-days mortality.

Outcome	Sensitivity	Specificity	PPV	NPV
90-days poor outcome	0.22 (0.13–0.34)	0.97 (0.80–1.00)	0.94 (0.68–1.00)	0.35 (0.25–0.46)
30-days mortality	0.34 (0.21–0.51)	0.91 (0.80–0.96)	0.74 (0.49–0.90)	0.65 (0.54–0.76)

PPV, positive predictive value; NPV, negative predictive value.

predicting malignant edemas after LHI (8). For instance, the presence of carotid T occlusions on angiographies predicted fatal outcomes with a positive predictive value of 47%, a negative predictive value of 85%, a sensitivity of 53%, and a specificity of 83% (28). However, neuroimaging might be difficult to complete for critically ill patients, especially when dynamic evaluation is required. Neuroelectrophysiology is an important part of neurological assessment in patients treated in the NICU, with great advantages in both bedside and dynamic evaluation. Current practice guidelines have suggested both brainstem auditory evoked potentials (BAEP) and EEG as complimentary methods to predict a malignant course within the first 24 h after LHI (8). Pathological response to BAEP exhibits a specificity of 79% and a PPV of 79% in the prediction of a malignant course in patients suffering from severe ischemic MCA syndromes (25). In stroke patients with initial paralysis of the upper extremities, the presence or absence of motor evoked potentials have a similar predictive value compared to early clinical assessment in regards to long-term motor recovery in the hands (29). Our study adds to the current knowledge that 40-Hz SSRs could be used to predict a fatal prognosis after LHI, with high specificity and PPV.

The 40-Hz SSR was proposed because an input frequency of approximately 40-Hz taps into the natural resonance frequency of auditory cortical neural assemblies, leading to a larger recruitment and a greater response in electroencephalograms (9, 30). The 40-Hz SSR represents a robust entrainment of auditory, cortical, and other networks involved in the auditory processing of sound that respond particularly well to click or tone stimuli presented in the gamma frequency. As previously reported, the 40-Hz SSR has, as its important source, the primary and secondary auditory cortices, while brainstem and forebrain structures also contribute to the scalp generated signal (22, 23, 31, 32). Therefore, if the occlusion of the MCA main stem impairs these structures, the 40-Hz SSR will represent a deficit response. Previous research has indicated that acute N-methyl-d-aspartate receptor seems to play an important role in the regulation of the 40-Hz SSR (33). In patients with Alzheimer's disease, the 40-Hz SSR power is significantly increased compared to mild cognitive impairment subjects and healthy controls, indicating that the 40-Hz SSR can reliably be used to measure disease progression (34).

Both clinical trials and animal models have demonstrated the high sensitivity of 40-Hz SSRs for consciousness level monitoring. As the severity of the disease progresses, the 40-Hz SSR amplitude decreases or disappears, and the results of 40-Hz SSRs are easier to read compared to traditional evoking potentials such as BAEPs. Neurologists simply need to recognize whether the 4 sine waves appear regularly and whether the amplitude ratio is lower than 50% of the referential range.

This study has several limitations. First, although all participants had completed 40-Hz SSR evaluation within 72 h, the exact time point differed among subjects. Thus, a further study with 40-Hz SSRs performed earlier after the stroke onset, possibly within 24 h, will be required to confirm the present findings. Second, this study was initially designed to evaluate the predictive value of 40-Hz SSRs in LHI patients with conservative treatment, before current evidence that supports the use of endovascular treatment in acute ischemic strokes. Therefore, another study utilizing a group of patients under endovascular treatment should be completed. Third, as a retrospective study, the potential selection and information bias in this study could not be completely avoided.

CONCLUSION

Our study initially indicates that the 40-Hz SSR can be used as a simple, reliable and specific tool in predicting early death and unfavorable prognosis in LHI under maximum conservative treatments.

ETHICS STATEMENT

This study was approved by the Nanfang Hospital's ethics committee on clinical research. Informed consent was waived by the review board because of the pure observational and retrospective nature of the study.

AUTHOR CONTRIBUTIONS

YoW contributed to study conception and design. YaW performed the 40-Hz SSR tests and drafted the manuscript. KH performed statistical analysis and helped to revise the manuscript. SW collected clinical data. HW and ZJ reviewed neuroimaging data and participated in patient follow up. SP participated in study conception and helped to revise the manuscript. All authors made substantial contributions. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.01093/full#supplementary-material

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REVIEW
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Management of Blood Pressure During and After Recanalization Therapy for Acute Ischemic Stroke

Jeffrey R. Vitt[1], *Michael Trillanes*[2] *and J. Claude Hemphill III*[1]*

[1] Department of Neurology, University of California, San Francisco, San Francisco, CA, United States, [2] Department of Pharmaceutical Services, University of California, San Francisco, San Francisco, CA, United States

Ischemic stroke is a common neurologic condition and can lead to significant long term disability and death. Observational studies have demonstrated worse outcomes in patients presenting with the extremes of blood pressure as well as with hemodynamic variability. Despite these associations, optimal hemodynamic management in the immediate period of ischemic stroke remains an unresolved issue, particularly in the modern era of revascularization therapies. While guidelines exist for BP thresholds during and after thrombolytic therapy, there is substantially less data to guide management during mechanical thrombectomy. Ideal blood pressure targets after attempted recanalization depend both on the degree of reperfusion achieved as well as the extent of infarction present. Following complete reperfusion, lower blood pressure targets may be warranted to prevent reperfusion injury and promote penumbra recovery however prospective clinical trials addressing this issue are warranted.

Keywords: acute ischemic stroke, cerebral autoregulation, hypertension, ischemic penumbra, embolectomy

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***Correspondence:**
J. Claude Hemphill III
claude.hemphill@ucsf.edu

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INTRODUCTION

Stroke is a common neurologic emergency worldwide with an overall growing incidence particularly in low to middle income countries where there has been over a 100% increase in stroke events over the past four decades (1). Approximately 85% are ischemic in origin and for the past two decades, intravenous tissue plasminogen activator (IV t-PA) has been the mainstay of treatment for patients with acute ischemic stroke (AIS) presenting within 3, and then expanded to 4.5, hours since last known well (2, 3). IV t-PA reduces the rate of functional dependence in up to one-third of individuals, but many AIS patients do not benefit from this treatment (2, 3). Over the past several years, multiple landmark studies have provided overwhelming evidence that intraarterial therapy (IAT) with mechanical thrombectomy, performed within 6 h of last known well in large vessel occlusion (LVO), leads to significantly improved functional outcomes and reduced mortality (4–7). More recently, the DEFUSE III and DAWN trials demonstrated that IAT can benefit patients treated out to 16 and 24 h if they have a favorable mismatch pattern on perfusion imaging (8, 9). While these breakthroughs have altered the paradigm of acute stroke management and can be considered as part of routine care, several unresolved issues remain regarding the optimal treatment of patients presenting with AIS, particularly regarding hemodynamic management. Though blood pressure (BP) elevation is common in AIS, the prognostic significance of this is unclear (10, 11). Some studies have found a correlation between hypertension and poor outcomes while others have reported inverse relationships (12–15). Furthermore, the guidelines for hemodynamic treatment following thrombolytic therapy in AIS are largely extrapolated from the IV t-PA trials as well as

retrospective analyses (16). Thus, high quality evidence to guide management after IAT is lacking. The purpose of this review is to discuss the physiology and available data regarding hemodynamics in AIS with particular focus on how blood pressure might be optimally managed throughout the revascularization process.

PATHOPHYSIOLOGY

In order to understand the principles of blood pressure management during AIS revascularization, it is useful to review fundamental aspects of blood flow in cerebral ischemia and infarction. Following complete cessation of cerebral blood flow (CBF) there is loss of normal neuronal electrical activity within seconds due to energy failure, disruption of ion homeostasis and membrane depolarization (17, 18). If perfusion is not restored within minutes, irreversible injury ensues leading to infarction (19). Ischemic stroke, however, is a focal process and there is rarely complete loss of CBF. Instead, surrounding the occluded vascular territory exist areas of mild hypoperfusion with intact function, ischemic tissue which remains salvageable but with dysregulated cellular processes (termed penumbra), and infarction with irreversible damage (17).

Early clinical studies using carotid clamping revealed that the risk of transitioning from ischemic to infarcted tissue depends on both the magnitude and duration of hypoperfusion (17). Furthermore, if CBF is reestablished in a timely manner the ischemic tissue may be salvaged and restored to normal function. Neurons within the penumbra are highly vulnerable to changes in local perfusion pressure, either from edema, alterations in systemic BP, or changes in cerebral vasoreactivity, and maintain a relatively preserved oxygen consumption despite lower CBF due to an increase in the oxygen extraction fraction (20, 21). While the infarction threshold largely depends on the duration and extent of hypoperfusion, individual factors including vascular compliance and collateral vessels between both intracranial and extracranial circulations can influence the resilience of the penumbra (17). Following acute vessel occlusion, the perfusion pressure distal to the clot falls leading to a pressure gradient in which retrograde flow commences through collaterals thereby achieving a sufficient level of CBF to maintain penumbra viability (22). In this setting, drops in BP or increases in tissue pressure from local mass effect can lead to an attenuation of the collateral gradient and exacerbate ischemia (23). This is demonstrated clinically in AIS as patients with more robust collaterals often have a lower BP, likely from adequate perfusion to the penumbra, and improved clinical outcomes relative to those with poor collateralization (24, 25). Furthermore, the presence of a robust collateral circulation predicts a higher likelihood of recanalization following IAT and, in cases where the procedure is unsuccessful, there is a reduced infarct volume compared to patients with poor collateralization (26, 27).

In the healthy brain, CBF is tightly regulated to meet regional metabolic demand and this is accomplished through the process of cerebral autoregulation whereby resistance-level blood vessels constrict or dilate across a range of systemic pressures (typically a mean arterial pressure [MAP] between 50 and 150 mmHg) in order to maintain a more constant flow (28). When pressures fall below the lower limit of autoregulation, surrounding brain parenchyma becomes ischemic and eventually infarcted unless CBF is rapidly restored. Conversely, when MAP rises above the capacity of cerebral autoregulation, a linear increase in CBF occurs leading to edema and hemorrhage. In AIS, the disruption of blood flow results in dysregulation of multiple cellular processes which may include autoregulatory mechanisms within the penumbra, thus making CBF directly dependent on systemic pressures (28, 29). Though early studies using radiotracer injection confirmed changes in CBF within the ischemic hemisphere in proportion to alterations in MAP, the resolution of these techniques did not allow for differentiation of penumbra from core infarct (28). Newer studies have had various findings, with reports of impaired autoregulation both globally and within the ischemic hemisphere contrasting with a recent study that found no change in regional CBF following alterations in MAP using high resolution positron emission tomography (PET) (30, 31). While these conclusions were derived from measures of static autoregulation, in which regional changes in CBF were assessed at a single time point after BP manipulation, recent focus has shifted toward dynamic autoregulation using techniques such as transcranial doppler to track instantaneous changes in blood flow in response to BP fluctuations (28, 30). In contrast to static autoregulation, which is often preserved in AIS, recent studies have revealed that dynamic autoregulation may be particularly vulnerable to ischemic insult and can remain abnormal for several weeks after presentation (30, 32). Though impairments in dynamic autoregulation appear common across a spectrum of stroke subtypes and may indicate selective damage to central autonomic control networks, the clinical relevance remains unclear and is the subject of ongoing investigation (30, 33).

While reestablishing CBF is essential for survival of ischemic tissue, reperfusion itself can contribute to significant neurologic injury in the form of infarction, edema and hemorrhagic transformation (34, 35). Reperfusion injury is a complex and incompletely understood process however several important underlying pathophysiologic mechanisms have been identified. Immediately following recanalization there often is a dramatic increase in CBF, likely as a result of impaired autoregulation as well as release of vasodilatory substances, which leads to hyperperfusion and the potential for secondary cellular injury (18, 36). The magnitude of cerebral hyperemia seems to be influenced in part by the duration of ischemia and in MRI studies, hyperperfusion following thrombolysis was most commonly observed in areas of pretreatment hypoperfusion and was an independent predictor of eventual infarction (36). After recanalization there can also exist a paradoxical hypoperfusion state, termed no-reflow phenomenon, which can lead to permanent infarction and is thought to result from microvascular dysfunction related to astrocyte and endothelial cell swelling as well as increased inflammation and platelet aggregation (37, 38). On a cellular level, reperfusion after prolonged ischemia leads to mitochondrial overproduction of toxic reactive oxygen species causing inflammation and

triggering the release of extracellular matrix metalloproteinases (MMP) which enzymatically degrade the endothelial basal lamina and increase microvascular permeability (39, 40). Loss of blood brain barrier (BBB) integrity in turn leads to vasogenic cerebral edema formation and in clinical studies is a strong predictor for hemorrhagic transformation and poor neurologic outcome following revascularization (41).

BLOOD PRESSURE IN ACUTE STROKE

Elevated BP is common in patients presenting with AIS, with one study involving more than 250,000 patients demonstrating a systolic blood pressure (SBP) > 140 mmHg in approximately three-fourths of patients (10). Severe hypertension is also relatively common with nearly 10% of patients presenting with SBP > 200 mmHg (42). Multiple observational studies have identified elevated BP as a risk factor for cerebral edema, hemorrhage and generally worse clinical outcomes following AIS (43–45). However, this association does not necessarily indicate a causative relationship. Instead, hypertension may be a marker of stroke severity, such as in the case of carotid terminus occlusion or poor collateralization, where spontaneously elevated blood pressure may serve as a compensatory mechanism to maintain cerebral perfusion (25, 46). Under which circumstances these mechanisms become maladaptive and contribute directly to cerebral injury remains uncertain and requires further clarification through clinical trials.

In several cohorts, a U-shaped relationship exists between BP and outcome in AIS in which both extremes of BP have prognostic significance for death and disability. In a retrospective analysis of the International Stroke Trial, patients presenting with SBP 140–179 mmHg had the lowest likelihood of death or dependency at 6 months with a nadir at around 150 mmHg (42). For every 10 mmHg above a SBP of 150 mmHg, patients had a 3.6% increase in the risk of death and a 4.2% increased risk of recurrent stroke within the next 6 months. For patients with a SBP > 200 mmHg there was more than a 50% increase in the risk of stroke. Conversely, relative hypotension was also detrimental with a 17.9% increased risk of death for every 10 mmHg drop below 150 mmHg; patients with SBP < 120 mmHg had the worst outcomes and a higher incidence of coronary events. Similar findings have been reported in other studies with slightly different BP thresholds conferring the most favorable outcomes. In work done by Vemmos and colleagues, the best outcomes were observed with SBP values around 130 mmHg while in a study from the Mayo Clinic, the optimal threshold for SBP seemed to be in the range of 156–220 mmHg with a nearly two-fold increase in risk of mortality with episodes of hypotension (47). Similarly, in work done by Castillo et al. patients had lower mortality and more functional independence when presenting with a SBP near 180 mmHg, with final infarct volumes being highest among patients with SBP well above or below this value (15). Interestingly, abrupt declines in SBP (>20 mmHg) were identified as the strongest predictor of poor outcome and were associated with a larger final infarct volume of over 60 ml, suggesting that dynamic BP changes may be particularly injurious to vulnerable ischemic tissue.

In clinical studies, dynamic fluctuations in BP have been identified as a strong prognostic marker in AIS and increase the risk of intracranial hemorrhage following IV t-PA (12). BP variability may be particularly harmful in the setting of large territory infarcts, where it has been independently linked to worse clinical outcomes (12, 48). In one study, patients with BP variability seemed to have worse outcomes in the presence of robust collaterals despite otherwise similar hemodynamic profiles (48). The reasons behind these findings are not entirely clear, however it may be related to increased transmission of fluctuating pressures to the ischemic penumbra. While the impact of BP variability seems to be more apparent in the initial stages of ischemia, one study found day-to-day variability over the course of 1 week was higher in patients with poor outcomes at 1 year (14). Overall, it appears that ischemic tissue may be particularly susceptible to fluctuations in systemic BP, likely as a result of impaired autoregulation and narrow ischemic thresholds, leading to either hypoperfusion with infarction or surges in perfusion with resulting edema (15, 28). **Table 1** summarizes results from several observational studies related to blood pressure and ischemic stroke outcome.

ACUTE ISCHEMIC STROKE HEMODYNAMIC MANAGEMENT

Current Practice Guidelines and Stages of Management

In the 2018 guidelines for management of AIS from the American Heart Association (AHA), BP may be permitted up to 220/120 mmHg in patients presenting with AIS who are not candidates for either IV t-PA or IAT and do not have another contraindication to an elevated BP (16). In patients where such a contraindication exists, such as an acute coronary event, decompensated heart failure or preeclampsia, lowering the BP should be individualized, with an initial decrease by 15% recommended. For patients who are eligible for IV t-PA therapy, it is recommended that the BP be maintained below 185/110 mmHg during the infusion and 180/105 mmHg for the following 24 h. These thresholds are largely extrapolated from thrombolysis trials in myocardial infarction as well as pilot data prior to the National Institute of Neurologic Disorders (NINDS) t-PA Trial and have subsequently been validated in retrospective studies where higher BP significantly increased the risk of hemorrhagic transformation (2, 16, 45, 50). In contrast, there is a paucity of prospective data to help guide the management of BP in IAT, particularly when considering the extent of post-procedural recanalization. Aside from the ESCAPE trial, all the pivotal thrombectomy trials used a BP cutoff of 185/110 mmHg, as patients were also potential candidates for IV t-PA, making it challenging to extrapolate the impact of different hemodynamic targets (4–7). As such, the current AHA guidelines recommend maintaining the BP below 185/110 mmHg, but acknowledge the lack of randomized controlled trials to substantiate this position (Class IIb recommendation) (16).

TABLE 1 | Observational studies examining impact of blood pressure in acute ischemic stroke.

References	Patients	Observed optimal blood pressure	Main findings
Leonard-Bee et al. (42)	17,398 patients with AIS enrolled in IST	SBP 140–179 mmHg	U-shaped relationship between baseline SBP and outcomes such that for every 10 mmHg below 150 mmHg there was an increase in early death by 17.9% and death or disability at 6 months of 3.6%. For every 10 mmHg above 150 mmHg there was a 3.8% increase in risk of early death. Low SBP independently associated with fatal coronary events.
Castillo et al. (15)	304 patients with hemispheric AIS	BP 180/100mmHg	U-shaped association with increase in poor outcome by 25% for every 10 mmHg below SBP 180 mmHg and 40% for every 10 mmHg below SBP 180 mmHg. Decrease in SBP > 20 mmHg associated with highest final infarct volumes.
Vemmos et al. (49)	1121 patients admitted for AIS or ICH and enrolled in "Athens Stroke Registry"	BP 121–140/81–90 mmHg	U-shaped relationship with 40% mortality for SBP<101 mmHg and 46.7% for SBP >220 mmHg. Mortality 45.8% for DBP<61 mmHg and 50% for DBP>120 mmHg. Low admission SBP associated with heart failure and coronary heart disease while high SBP was associated with lacunar stroke and history of HTN.
Stead et al. (47)	357 patients presenting to ED with AIS	BP 155–220/70–105 mmHg	U-shaped associated with worse outcomes noted for DBP < 70 mmHg or >105 mmHg and for SBP <155 mmHg and >220 mmHg. MAP 100–140 mmHg was associated with the most favorable outcomes.
Ishitsuka et al. (43)	1,874 patients with first ever AIS	BP <165/90 mmHg	Linear relationship between post-stroke BP and outcomes such that higher BP was associated with higher risk of neurologic deterioration and poor functional outcomes.

AIS, acute ischemic stroke; BP, blood pressure; SBP, systolic blood pressure; IST, International Stroke Trial; DBP, diastolic blood pressure; ICH, intracerebral hemorrhage; HTN, hypertension; ECASS, European cooperative acute stroke study.

The overall approach to AIS treatment is multifaceted and relies upon optimized systems of care to identify, triage and treat patients presenting with acute neurologic symptoms with the goal of reestablishing cerebral perfusion and minimizing secondary injury. In order to appreciate aspects of hemodynamic management in AIS, it is constructive to separate it into stages of treatment beginning with the initial assessment, during revascularization, and post-intervention (see **Figure 1**). Each stage presents slightly different considerations regarding hemodynamic management as well as physiologic optimization strategies aimed at maximizing the chances of good recovery.

Phase I: Initial Assessment

Hypertension is very common in AIS with 21–50% of patients presenting with blood pressure higher than the threshold eligible to receive IV t-PA (11, 42, 49). The largest concern regarding t-PA therapy is the risk of hemorrhage which was approximately 6% in the initial NINDS t-PA trial and has largely been validated in subsequent analysis when adhering to the same protocol BP thresholds (2, 51, 52). An analysis of the SITS-ISTR (Retrospective Analysis From Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register) trial demonstrated a linear relationship between SBP and symptomatic hemorrhage with the risk being four times higher for patients with a SBP >170 mmHg compared to those at 141–150 mmHg (53). In light of this data it is prudent to achieve the 185/110 mmHg threshold for patients who are deemed eligible for IV t-PA therapy. However, caution must be applied to avoid significant fluctuations in blood pressure which may be associated with adverse events. In the NINDS t-PA trial, patients treated with BP-lowering agents had more abrupt declines in BP and worse outcomes at 3 months compared to hypertensive patients not treated with medications (54). In subsequent analysis, an overall decline in SBP > 50 mmHg or an acute drop of > 30 mmHg was associated with poor functional outcomes while an acute drop of > 60 mmHg increased the risk of death by 2-fold (55).

For patients who are candidates for IAT there is considerably less data to guide management of initial blood pressure. However, several insights are apparent through retrospective analyses. In the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, patients presenting with SBP > 150 mmHg were less likely to achieve recanalization compared to those with lower pressures despite similar thrombus characteristics (56). Since higher BP is often associated with poor collaterals, these findings may signify that these patients have a maximal pressure gradient against the clot leading to impaction and more challenging retrieval (25). The impact of elevated SBP in IAT may not be related solely to revascularization success, however, as one cohort study found that lower admission SBP was independently associated with more favorable 3 month outcome even after statistical adjustment for complete revascularization (57). In the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial, a U-shaped relationship was apparent between SBP and poor functional outcome, with a nadir (most favorable BP) of 120 mmHg, and a 21% increase in the relative risk of hemorrhage for every 10 mmHg above this value (58). It should be noted that there was no interaction between BP and the benefit of IAT on clinical or radiographic measures, thus indicating that thrombectomy is safe and effective across a range of BP. Similar results were noted in the Endovascular Treatment in Ischemic Stroke registry, where there was a 3.78 and 1.81 times higher risk of mortality for SBP <110 mmHg and >180 mmHg respectively compared with 150 mmHg (59). Similar to other studies in AIS, the extremes of BP appear to have negative prognostic implications for patients eligible for IAT irrespective of recanalization success. Significant need exists for

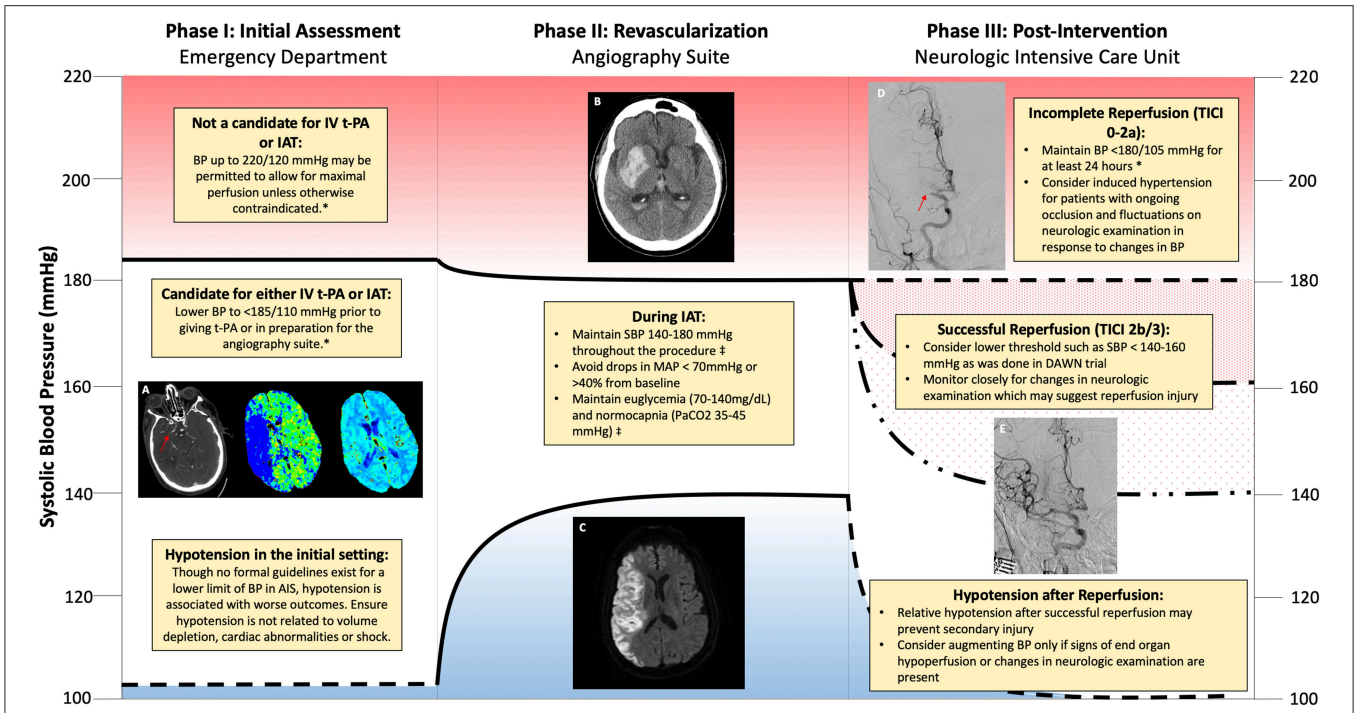

FIGURE 1 | Schematic of hemodynamic management during different phases of revascularization for acute ischemic stroke. **(A)** Computerized tomography (CT) angiogram demonstrating non-opacification (red arrow) of the right middle cerebral artery (R MCA) consistent with large vessel occlusion. Mean transit time increased within the territory of the R MCA with preserved cerebral blood volume consistent with penumbra. **(B)** CT revealing hemorrhagic transformation within the R MCA territory. **(C)** Magnetic Resonance Imaging (MRI) demonstrating increased signal on Diffusion Weighted Imaging (DWI) within the R MCA territory consistent with an acute infarction. **(D)** Absent reperfusion (red arrow) within the R MCA (Thrombolysis in Cerebral Infarction (TICI) Score of 0). **(E)** Complete Reperfusion within the R MCA (TICI Score of 3). *American Heart Association/American Stroke Association 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke. ‡Society for Neuroscience in Anesthesiology and Critical Care Expert Consensus Statement: Anesthetic Management of Endovascular Treatment for Acute Stroke.

prospective trials evaluating which patients may benefit from blood pressure augmentation prior to treatment. Based on the available trial data as well as observational studies demonstrating worse outcomes and less successful recanalization with higher BP, it is reasonable to lower the BP in the acute setting to less than 185/110 mmHg, particularly if patients may also be candidates for IV t-PA therapy.

Another important aspect to consider when evaluating AIS patients in the initial setting is intravascular volume status. In several observational studies, up to half of patients presenting with AIS are dehydrated (defined as an elevated BUN to creatinine ratio) and this has been correlated with increased in-hospital mortality and placement in institutional care at discharge (60, 61). Patients particularly at risk for dehydration include the elderly and women, who presumably have lower muscle mass, and those prescribed diuretics prior to presenting with stroke (60, 62). In AIS, hypovolemia may impair CBF to susceptible regions of ischemia and negatively influence collateral vessel development (63). While a 2015 Cochrane Review found no difference between colloid or crystalloid parenteral fluid regimens on outcome in AIS nor any data to guide the proper volume or duration of therapy, the studies were not designed to assess for treatment benefit in the acute setting or for patients who possessed serologic markers of dehydration (64). Further studies are warranted to evaluate the impact of fluid resuscitation regimens in patients presenting with AIS and dehydration. In the meantime it is reasonable to ensure patients are not volume depleted, particularly if there has been prolonged downtime, and treat with parenteral fluids as needed to target euvolemia.

Phase II: During Revascularization

For patients undergoing IAT, predictors of poor outcome include higher National Institutes of Health Stroke Scale (NIHSS) score, lower Alberta Stroke Program Early CT Score (ASPECTS), carotid terminus occlusion, and failed recanalization (65, 66). As in other aspects of AIS, elevated BP during IAT has been associated with worse outcomes with one large observational study identifying maximal intraprocedural SBP as the strongest hemodynamic predictor (66). In this study, patients who had favorable outcomes had an average maximal SBP of 164 mmHg compared to patients with unfavorable outcomes, who had an average maximal SBP of 181 mmHg. These findings highlight the vulnerable state that exists within reperfused tissue due to impaired autoregulation and BBB disruption with increases in systemic pressure contributing to secondary injury. However, caution must be applied before aggressively lowering elevated BP as intraprocedural drops in BP are strongly correlated with less favorable outcomes. In one study, drops in MAP of

greater than 40% were identified as a particular risk factor for persistent neurologic deficits (66, 67). Given the apparent detrimental effects of either extreme of intraprocedural BP, the Society of Neuroscience in Anesthesiology and Critical Care recommends SBP be maintained between 140 and 180 mmHg during IAT with careful investigation of any episodes of hypotension that may point toward end-organ injury, bleeding or volume depletion (68).

With the emergence of IAT as a prominent treatment for patients presenting with LVO, multiple questions have arisen regarding optimal treatment practices including whether general anesthesia (GA) or conscious sedation (CS) is preferable for patients undergoing thrombectomy. CS offers the advantages of allowing for neurologic assessment throughout the procedure and eliminating delays associated with anesthesia induction. GA on the other hand may reduce the risk of aspiration and eliminates patient movement thereby potentially making the procedure safer and more technically feasible (68). Early observational studies found a strong association between GA and increased time to intervention, procedural complications, ICU length of stay, and rates of tracheostomy (69–71). Furthermore, in the North American SOLITAIRE Registry, treatment with CS was associated with a 40% higher probability of good clinical outcome and a three-fold lower risk of death compared with GA (70).

While these studies seem to provide compelling evidence that CS is preferred over GA, several important methodologic issues must be addressed. First, these were all retrospective studies and possess significant selection bias as patients treated with GA were more likely to have higher NIHSS scores, lower ASPECTS, and were more likely to have carotid terminus and vertebrobasilar occlusions as well as premorbid coronary heart disease (69, 70, 72–75). In several studies, after controlling for baseline stroke severity with ASPECTS or NIHSS, the negative impact of GA was no longer statistically significant (72, 73). Second, a common observation in many of these analyses was that GA is associated with significant hypotension and fluctuations in blood pressure, particularly during the induction phase of anesthesia (70, 73, 75, 76). In a study by Davis et al., an intraprocedural SBP $>$ 140 mmHg was associated with good outcomes however this was only achieved in 4% of patients treated with GA compared with 60% receiving CS (75). Likewise in the MR CLEAN trial, GA use was associated with larger drops in MAP with longer episodes of hypotension despite increased use of vasopressors (76). These observations highlight the impact that anesthetic agents can have on vascular tone and the potential for precipitating hypotension in AIS. However, these risks are not isolated to GA alone. In a study evaluating patients treated with CS, lower MAP prior to recanalization was found to be an independent predictor of outcome such that for every 10 mm Hg decrease below 100 mmHg there was a 28% reduced probability of favorable outcome, while a MAP drop of $>$10% conferred the highest risk of death or disability (77).

Recently three randomized controlled clinical trials have been published comparing the impact of CS to GA in patients treated with IAT. In contrast to prior retrospective analyses, patients treated using CS did not have better outcomes compared to those who underwent GA and in both the Sedation vs. Intubation for Endovascular Stroke Treatment (SIESTA) and General or Local Anesthesia in Intra-arterial Therapy (GOLIATH) trials, GA was associated with higher rates of functional independence at 3-months (78–80). While the time to groin puncture was slightly prolonged for GA, the overall time to reperfusion was significantly decreased and rates of successful recanalization were improved in the GOLIATH study, highlighting the potential benefit of GA in improving procedural success (78). Another key insight from these trials is the importance of aggressive intraprocedural BP control with regard to patient outcomes. While GA was associated with more frequent drops in MAP $>$ 20% from baseline compared to CS, there was no significant difference in large falls in MAP (either defined as $>$40% decline or MAP $<$ 70 mmHg) between GA and CS (78, 80). The striking discrepancies of these findings compared to prior observational studies may be related to increased vigilance over intraprocedural hypotension and strict protocols to maintain a narrow SBP goal of 140–160 mmHg and MAP $>$ 70 mmHg (78, 79). These trials provide overwhelming evidence that both CS and GA are reasonable approaches in the management of patients undergoing IAT so long as there is strict control of BP and systems in place to ensure minimal delays are encountered while preparing patients for the interventional suite and throughout the recanalization procedure. Furthermore, in cases where potential contraindications for CS exist it may be more advantageous to start with GA rather than converting the type of anesthesia emergently in a less controlled environment. This is emphasized in the GOLIATH trial where four patients initially assigned to CS had to be converted to GA due to movement or loss of airway protection and ultimately sustained extensive infarcts (78).

Phase III: Following Revascularization

The AHA ischemic stroke guidelines recommend maintaining a BP $<$ 180/105 mmHg for at least 24 h in patients treated with either IV t-PA or IAT to promote perfusion to ischemic territories while mitigating potential risks of intracranial hemorrhage (16, 53). In patients treated with IV t-PA alone for LVO, these recommendations make sense from a pathophysiologic standpoint as individual recanalization status is often unknown in the clinical setting and in studies where angiography was performed the rates of early revascularization are only around 20% (81, 82). Conversely, IAT is associated with recanalization in 70–80% of cases and this can be readily confirmed during the procedure by complete anterograde reperfusion or reperfusion in more than half of the previously occluded territory (Thrombolysis in Cerebral Infarction [TICI] scores of 3 and 2b respectively) (83). In these patients, the risk of reperfusion injury with pressures approaching 180/105 mmHg could conceivably exceed that of hypoperfusion with lower BP targets.

After successful recanalization, there is often a significant spontaneous decline in BP over 12–24 h compared to patients with persistent occlusion (84, 85). For both recanalized and non-recanalized patients, sustained elevations in BP over the first 24–48 h after treatment have been identified as a risk factor for intracranial hemorrhage as well as worse functional

outcomes (86–89). Similarly, blood pressure variability is more common in patients with poor or incomplete recanalization and has been correlated with larger infarct size, intracranial hemorrhage, and worse outcomes following thrombectomy (85, 89–91). Since the majority of these studies are observational, questions remain regarding the causality of these relationships. For example, work done by Delgado-Mederos and colleagues found that blood pressure variability was associated with increases in DWI lesion growth, though this relationship was only present in patients with absent recanalization, calling into question whether blood pressure variability itself is a risk factor for cerebral injury or a marker of more severe stroke (85). Despite these limitations, several interesting observations have been made when comparing patients based on recanalization status. In a Portuguese study of patients following thrombolysis, individuals with poor recanalization exhibited a U-shaped relationship of BP and outcomes with a nadir of 120–130 mmHg, similar to other reports in AIS, while those with successful revascularization demonstrated a linear relationship with more favorable outcomes occurring at the lowest pressures (<110 mmHg) (88). These results indicate that the balance between hypoperfusion and reperfusion injury may be shifted in patients following good recanalization such that the risks of exacerbating ischemia is lessened under physiologic parameters while higher systemic pressures directly contribute to cerebral injury. Similar findings were reported in a large cohort of patients following IAT where the mean SBP for intracranial hemorrhage was lower following successful recanalization (170 vs. 196 mmHg) indicating a difference in thresholds for reperfusion injury depending on the degree of vessel recanalization (92).

Though randomized trials of BP control following IAT are lacking, Goyal et al. published a single center's experience with different BP targets following IAT over 4 years. Following good reperfusion, patients were either assigned to permissive (<220/110 mmHg or 180/110 mmHg if IV t-PA also administered), moderate (<160/90 mmHg) or intensive (<140/90 mmHg) BP targets in a non-randomized fashion (87). While patients in the moderate and intensive groups received antihypertensive agents more frequently, the 3-month mortality rate in these groups was significantly lower (6.5%) compared to those with a permissive threshold (28.7%). Due to the non-controlled retrospective study design, confounding between BP targets and cohort populations cannot be excluded and as such the results must be viewed with care. Regardless, this study provides evidence that a lower BP threshold may be beneficial in patients who have achieved good recanalization status. With the establishment of IAT as the standard of care for LVO, prospective multicenter studies are now warranted to better evaluate optimal BP targets in patients with complete, partial or absent recanalization status following attempted thrombectomy. In the meantime, it may be reasonable to target a lower BP goal for patients with excellent reperfusion (TICI 2b/3) and minimal infarct volume, as was the case in the DAWN trial where patients were assigned to an intensive (<140 mmHg) goal in order to prevent reperfusion injury (93). In cases where there is incomplete or poor reperfusion, substantially less data exists to help guide management. However, a higher BP target is reasonable in an attempt to prevent further ischemia particularly if there is evidence of a fluctuating neurological examination in the context of changes in systemic BP.

PHARMACOLOGY

Various agents are routinely used to manage hypertension in stroke however clinical trials utilizing BP agents in AIS have been inconclusive with some reports of marginal or no benefit while others suggest a risk of more severe disability in treated patients. Studies using angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers within the acute hypertensive phase of AIS have demonstrated significant acute reductions in blood pressure however this was not accompanied by changes in death or disability at 14 or 90 days (94–96). Moreover in the beta blocker stroke trial (BEST), the use of either atenolol or propranolol immediately following AIS was associated with a trend toward increased mortality, particularly among elderly individuals (97). In keeping with these disparate findings a 2014 Cochrane Review of 26 trials found insufficient evidence to support immediate resumption or routine administration of BP agents during the acute phase of stroke (98). It is important to note that many of these trials included participants with primary intracerebral hemorrhage and none were specific to patients treated either IV t-PA or IAT, further underscoring the need for trials specifically evaluating BP targets following revascularization therapy. One trial which may aid in bridging this gap in knowledge is the ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED) which is a 2 × 2 randomized controlled trial with one arm evaluating the impact of early intensive BP lowering to a SBP of 130–140 mmHg in patients who are eligible for thrombolytic therapy (99). Given the current clinical equipoise of different agents on outcomes, the selection is often driven by therapy-specific adverse reactions and availability. In general, agents with a fast onset of action and short duration are preferable in the acute setting to rapidly achieve hemodynamic goals and avoid prolonged periods of hypotension. **Table 2** summarizes the pharmacology of several of the most commonly used agents for acute blood pressure management.

Labetalol

Labetalol is a mixed α and β adrenergic blocker often used to control blood pressure post-AIS. Though it has less β-1 activity compared to other beta blockers, labetalol can exert negative chronotropic effects thereby limiting its utility in patients with significant bradycardia (100). However, it has minimal impact on either CBF or oxygen consumption making it a suitable agent for patients with AIS or other intracranial pathology (101).

Nicardipine

As a dihydropyridine calcium channel blocker, nicardipine is more selective for vascular rather than myocardial calcium channels and generally exerts a neutral effect on heart rate (102). When compared to labetalol, nicardipine allows for faster and more controlled reduction in BP with significantly less variability (100, 101). Despite these apparent advantages, head-to-head studies have found no differences in clinical outcomes between

TABLE 2 | Intravenous antihypertensives for AIS.

Drug	Dosing	Administration	Onset of action (min)	Duration	Clinical pearls
Labetalol	10–20 mg IV over 1-2 min	IV bolus, infusion	2–5	2–4 h	Bradycardia, contraindicated in >1st degree heart block and cardiogenic shock
Hydralazine	10–20 mg IV, repeat every 4–6 h PRN maximum 40 mg	IV bolus	10–20	Up to 12 h	Tachycardia, drug-induced lupus erythematosus, increased intracranial pressure
Enalaprilat	0.625–1.25 mg IV every 6 h	IV bolus	<15	Up to 6 h	Contraindicated in patients with history of angioedema related to an ACE inhibitor, caution in bilateral renal artery stenosis, caution in hypovolemia
Nicardipine	5 mg/h IV, uptitrate 2.5 mg/h every 5–15 min, maximum 15 mg/h	IV infusion	5–15	4–6 h	Contraindicated in advanced aortic stenosis
Clevidipine	1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	IV infusion	2–4	5–15 min	Hypertriglyceridemia, contains soy, avoid in patients with defective lipid metabolism, limited data with use > 72 h
Sodium Nitroprusside	0.3–0.5 mcg/kg/min IV (best to avoid doses above 2 mcg/kg/min)	IV infusion	1–2	2–3 min	Cyanide toxicity, increased intracranial pressure
Glyceryl Trinitrate	5 mg/day	Transdermal	30–60	Duration of application, typically 12–14 h	Contraindicated with phosphodiesterase-5 inhibitor, tachyphylaxis, possible increase in intracranial pressure
Urapidil	10–50 mg IV followed by 4–8 mg/h	IV bolus, infusion (also available oral for maintenance therapy)	2–5	Up to 4 h	Nausea, dizziness, headaches. Contraindicated in aortic isthmus stenosis or arteriovenous shunt

the two agents and the cost associated with nicardipine therapy is substantially higher (101, 103).

Clevidipine

Clevidipine is a newer dihydropyridine calcium channel blocker which is also included as a treatment modality in the AHA 2018 guidelines (16). Similar to nicardipine, clevidipine generally does not decrease heart rate and in retrospective analysis has similar efficacy in lowering BP though requires less volume to be administered which may be optimal in patients with volume overload (104, 105). Since clevidipine is formulated in a lipid emulsion, there is an inherent risk of hypertriglyceridemia and pancreatitis for which there is a recommended a daily maximum of 1,000 mL (or about 21 mg/h per day) (106).

Hydralazine

Hydralazine is a direct acting vasodilator that is often used for hypertensive emergencies (107). Despite its effectiveness in lowering BP, hydralazine can increase intracranial pressure (ICP) while simultaneously lowering MAP, leading to decreased perfusion pressure and increasing the risk of ischemia (108). Additionally, hydralazine has a prolonged and often unpredictable effect on BP which can contribute to precipitous drops in pressure and significant variability (109). For these reasons, hydralazine is less preferred in AIS however can be considered when other agents are not available.

Enalaprilat

Enalaprilat, the active metabolite of enalapril, is an intravenous angiotensin-converting enzyme (ACE) inhibitor which can lower BP without impacting cardiac chronotropy (107). Additionally, ACE inhibitors are thought to be neutral with respect to ICP making enalapril potentially beneficial in patients with intracranial pathology (110). A limitation however is the long duration of action, 12–24 h, which limits the ability to titrate the agent to specific BP goals (107). Furthermore, caution must be applied when using ACE inhibitors in the setting of tPA administration as there is an increased risk of orolingual angioedema which is uncommon though can be life-threatening (111).

Sodium Nitroprusside

Sodium nitroprusside is a potent venous and arterial vasodilator often used as an infusion in hypertensive emergency (112). However, due to its vasodilatory effects on cerebral vasculature, sodium nitroprusside can lead to increases in ICP in patients with impaired autoregulation by increasing the volume of blood within the intracranial vault (113, 114). Additionally, the sodium nitroprusside compound contains cyanide which can accumulate leading to toxicity (112). Patients at risk for this include those administered moderate to high doses as well as those with hypoalbuminemia or undergoing cardiopulmonary bypass (115). In summary, despite the potent anti-hypertensive properties of nitroprusside, the potential for impacting cerebral blood volume and ICP make it less ideal in AIS and other forms of intracranial pathology. However, it can be considered in cases where other agents are not available or are contraindicated due to patient-specific characteristics.

Glyceryl Trinitrate

Glyceryl trinitrate, or nitroglycerin, is a nitric oxide donor that primarily causes venodilation, as well as arterial dilation at high doses, thereby effectively reducing preload and BP (106). Glyceryl trinitrate is most commonly used for acute myocardial

infarction and unstable angina due to its ability to reduce cardiac oxygen demand, but there is recent literature evaluating its use in AIS. In the ENOS (Efficacy of Nitric Oxide in Stroke) Trial, which primarily took place in Europe and Asia, the investigators studied the use of transdermal glyceryl trinitrate patch in AIS or hemorrhagic stroke patients at a dose of 5 mg daily for 7 days compared to placebo. While transdermal glyceryl trinitrate was effective in lowering blood pressure, there was no significant improvement in functional outcome at 90 days (116). Of note, there is literature from primarily small observational studies that suggests nitroglycerin may increase ICP, although the clinical significance of this is uncertain (117).

Urapidil

Urapidil is an antihypertensive agent available throughout Europe and Asia and recommended by the European Stroke Initiative (EUSI) though it is not currently approved by the United States Food and Drug Association (FDA). Urapidil is a unique antihypertensive agent which exerts peripheral vasodilation through alpha-1-adrenoreceptor antagonism as well as sympatholytic effects via serotonin 5HT1A receptor stimulation (118). Animal studies have also demonstrated potential neuroprotective effects of urapidil thereby further increasing its potential for treating patients with AIS (119). While urapidil has generally be considered to have neutral effects on ICP, more recent studies including two patients with head injury as well as a cohort of normal volunteers suggest that administration of the agent may lead to increases in ICP (119, 120).

Induced Hypertension

In animal models of AIS, induced hypertension (IH) improves CBF to the ischemic territory and reduces final infarct volume compared to normotensive controls (121, 122). Phenylephrine is often utilized in this setting due to its pure α-1 receptor agonist properties which causes peripheral vasoconstriction without significantly impacting the cerebral vasculature thereby improving perfusion pressure (123). Though IH is sometimes used in clinical practice, particularly if there is evidence of changes in the neurologic exam across different blood pressures, little clinical data is available to substantiate its use. In a 2001 pilot study using phenylephrine in patients with AIS, targeting a BP of at least 160 mmHg or a 20% increase relative to admission was associated with short-term improvement in the NIHSS in over half of patients without any associated complications (124). A subsequent pilot clinical trial using IH in patients with large diffusion-perfusion mismatch demonstrated a significant improvement in NIHSS, cognitive scores, and hypoperfused tissue over 3 days compared to controls (125). In light of these findings, further studies are warranted to determine the clinical utility of IH. This is the focus of the randomized multicenter SETIN-HYPERTENSION phase III trial (NCT01600235) which aims to determine the safety and efficacy of phenylephrine in patients with non-cardioembolic stroke.

CONCLUSION

Hemodynamic management in AIS is an involved and complex process that aims to balance the competing interests of supporting CBF to the ischemic penumbra while avoiding reperfusion injury. Decades of observational studies have demonstrated a U-shaped association between BP and stroke outcomes. However, studies aimed at controlling hemodynamics have been inconclusive. In the setting of thrombolytic therapy, the pendulum may shift from a higher risk of hypoperfusion to that of reperfusion injury, therefore making BP control particularly paramount. This is especially relevant in IAT where rates of LVO recanalization are substantially higher than in other treatment modalities and revascularized patients could benefit from lower BP thresholds to prevent intracranial hemorrhage and cerebral edema. Well-designed prospective multicenter controlled clinical trials are now warranted to better understand the relationship between various BP goals during and post-embolectomy with particular focus on interactions with recanalization status. In the meantime, careful monitoring and management of hemodynamics is essential for prevention of significant hypo- or hypertension as well as minimizing BP variability in order to best promote tissue recovery while preventing secondary injury.

AUTHOR CONTRIBUTIONS

JH and JV manuscript concept and design. JV initial manuscript draft. MT and JH critical review of manuscript and addition of sections. All authors reviewed, edited, and approved the final version.

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Cross-Frequency Coupling Between Cerebral Blood Flow Velocity and EEG in Ischemic Stroke Patients With Large Vessel Occlusion

Xiuyun Liu[1], Yuehua Pu[2,3], Dan Wu[1,4], Zhe Zhang[2,3], Xiao Hu[1,5,6,7†] and Liping Liu[2,3†]*

[1] Department of Physiological Nursing, University of California, San Francisco, San Francisco, CA, United States, [2] Neurointensive Care Unit, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China, [3] China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China, [4] School of Computer and Information Technology, Beijing Jiaotong University, Beijing, China, [5] Department of Neurosurgery, School of Medicine, University of California, Los Angeles, Los Angeles, CA, United States, [6] Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, United States, [7] Institute of Computational Health Sciences, University of California, San Francisco, San Francisco, CA, United States

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***Correspondence:**
Liping Liu
liping_sister@163.com

† These authors share senior authorship

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Background: Neurovascular coupling enables a rapid adaptation of cerebral blood flow (CBF) to support neuronal activities. Whether this mechanism is compromised during the acute phase after ischemic stroke remains unknown. In this study, we applied a phase-amplitude cross-frequency coupling (PAC) algorithm to investigate multimodal neuro signals including CBF velocity (CBFV), and electroencephalography (EEG).

Methods: Acute ischemic stroke patients admitted to the Neurointensive Care Unit, Tiantan Hospital, Capital Medical University (Beijing, China) with continuous monitoring of 8-lead EEG (F3-C3, T3-P3, P3-O1, F4-C4, T4-P4, P4-O2), non-invasive arterial blood pressure (ABP), and bilateral CBFV of the middle cerebral arteries or posterior cerebral arteries were retrospectively analyzed. PAC was calculated between the phase of CBFV in frequency bands (0–0.05 and 0.05–0.15 Hz) and the EEG amplitude in five bands (δ, θ, α, β, γ). The global PAC was calculated as the sum of all PACs across the six EEG channels and five EEG bands for each patient. The hemispherical asymmetry of cross-frequency coupling (CFC) was calculated as the difference between left and right PAC.

Results: Sixteen patients (3 males) met our inclusion criteria. Their age was 60.9 ± 7.9 years old. The mean ABP, mean left CBFV, and mean right CBFV were 90.2 ± 31.2 mmHg, 57.3 ± 20.6 cm/s, and 68.4 ± 20.9 cm/s, respectively. The PAC between CBFV and EEG was significantly higher in β and γ bands than in the other three bands. Occipital region (P3-O1 and P4-O2 channels) showed stronger PAC than the other regions. The deceased group tended to have smaller global PAC than the survival group (the area under the receiver operating characteristic curve [AUROC] was 0.81, $p = 0.57$). The unfavorable outcome group showed smaller global PAC than the favorable group (AUROC = 0.65, $p = 0.23$). The PAC asymmetry between the two brain hemispheres correlates with the degree of stenosis in stroke patients ($p = 0.01$).

Conclusion: We showed that CBFV interacts with EEG in β and γ bands through a phase-amplitude CFC relationship, with the strongest PAC found in the occipital region and that the degree of hemispherical asymmetry of CFC correlates with the degree of stenosis.

Keywords: cerebral blood flow, EEG, cross frequency coupling, stroke, neurovascular coupling

INTRODUCTION

The brain is only able to withstand transient blood supply disruption. Adequate cerebral blood flow (CBF) must be maintained to ensure a constant delivery of oxygen and substrates and to remove the waste products of metabolism (1). This control system involves neurogenic, metabolic, myogenic, and endothelial mechanisms, but is still poorly understood (2, 3). Neurovascular coupling is an effective intrinsic vasoregulative mechanism that rapidly adapts CBF in accordance with neuronal activity (4). Its dysfunction has been implicated in serious neurological conditions, such as ventricular hemorrhage, ischemic stroke, hypertension, Alzheimer disease, subarachnoid hemorrhage, etc. (3, 5–7). With modern techniques in neuro critical care units (NCCU), monitoring of neuronal activity through electroencephalography (EEG) and cerebral hemodynamics through transcranial Doppler (TCD) has become available. In the late 1970s, Sharbrough et al. found a strong correlation between CBF and alterations in EEG during carotid occlusion (8); and Vespa et al. proved that the relative alpha variability of EEG was reduced with cerebral vasospasm in SAH patients (9); Additionally, Foreman and Claassen summarized that when normal CBF declines, the EEG first loses its faster frequencies, then activity with slower frequencies gradually increases, and if CBF continues to decline, the EEG ultimately falls silent, and cellular damage becomes irreversible (8, 10–12). Nevertheless, the precise mechanism of how neuronal activation interacts with CBF is still not fully understood. In particular, there is limited data of neurovascular coupling from stroke patients.

In the field of electroneurophysiology, there has been particular interest in how low frequency brain signal oscillations modulate high frequency oscillations, because recent evidence suggests a functional role for this type of cross-frequency coupling (CFC) (13, 14). The low frequency oscillations are associated with modulating activity in long range communication and long temporal windows (global process), while the high frequency rhythms modulate activity in small regions and short time windows (local process) (15, 16). This interaction of rhythms in different frequency bands mainly includes three types: amplitude-to-amplitude coupling (AAC), phase-to-phase coupling (PPC), and phase-to-amplitude coupling (PAC) (16–19). PAC, in which the phase of a low frequency rhythm from one signal regulates the amplitude of higher frequency activity (either from the same or another signal), is identified as the main communication mechanism of EEG in frequencies below 80 Hz (20).

In our daily recording of EEG and CBF velocity (CBFV), we have visually noticed an interesting relationship between the phase of slow waves of CBFV and the amplitude of high frequency EEG components, as shown in **Figure 1** (long duration). Therefore, we sought to find out whether PAC relationship exists between EEG and CBFV and whether the neurovascular coupling characteristics can be described using these two signals. In particular, we have three hypotheses: (1) there is a relationship between EEG and CBFV following ischaemic stoke, which might inform on the status of neurovascular coupling; (2) the degree of asymmetry of neurovascular coupling of the two brain hemispheres is positively related with the degree of occlusion on the patients with unilateral occlusion in major arteries; (3) neurovascular coupling is weaker in the deceased group than in the survival group.

METHODS AND MATERIALS

A total of twenty recordings from seventeen stroke patients admitted to Neurointensive Care Unit, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University (Beijing, China) were studied. Three patients were monitored twice on the 2nd day of admission and the 4th day of admission. The other patients were only monitored once. The inclusion criteria were as follows: (1) men or women aged $\geq$18 years; (2) acute ischemic stroke confirmed by computed tomography (CT), or magnetic resonance imaging (MRI) of the head; (3) stroke onset within 24 h of hospital admission; (4) stroke caused by cerebral large artery occlusion, including internal carotid artery (ICA), middle cerebral artery (MCA), and vertebral or basilar artery (BA), and (5) patient received recanalization therapy. We excluded the patients who had an insufficient or absent acoustic temporal bone window and who had scalp wounds or infections, as EEG was not tolerated in those cases. All the enrolled patients underwent continuous monitoring of 8-lead EEG, non-invasive arterial blood pressure (ABP), and CBFV of the bilateral MCA or posterior cerebral arteries (PCA). Written consent form was obtained from each patient or the next of kin. The study was approved by local Institutional Review Board (IRB). Patients' NIH Stroke Score (NIHSS) were recorded on admission and at discharge. Patients' Modified Rankin Scale (mRS) for neurologic disability was recorded at discharge. One stroke patient recording was excluded due to poor data quality.

We monitored bilateral CBFVs from the MCA for the anterior circulation stroke patients ($n = 13$) and CBFVs of PCA ($n = 3$) for posterior circulation stroke patients through 2-MHz probes mounted on a headband using transcranial Doppler (Doppler BOX, DWL, Singen, Germany or EMS-9PB Transcranial Doppler Ultrasound System, Delica, China). ABP was continuously monitored through non-invasive finger plethysmography (CNAP

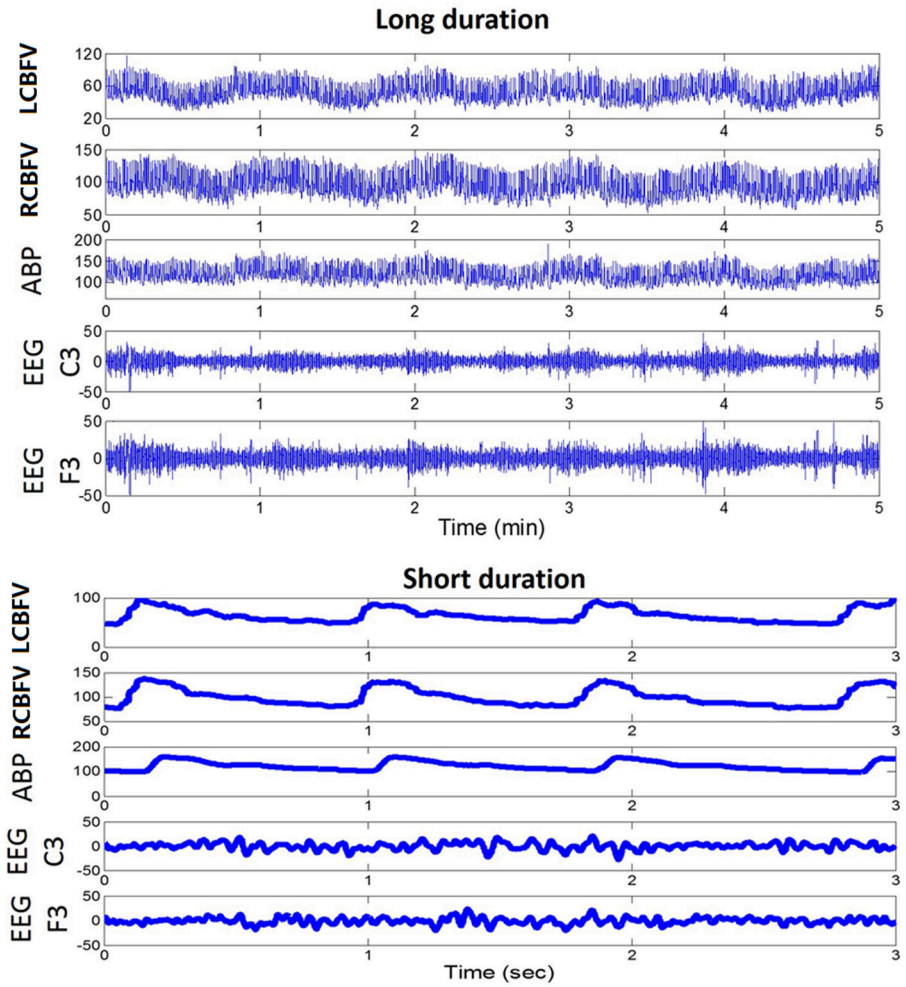

FIGURE 1 | An example of a daily recording of CBFV, ABP, and EEG in a neuro critical care unit. Upper panel: recordings of fast fluctuations (5 min). Lower panel: recordings of signal waveforms. CBFV, cerebral blood flow velocity; LCBFV, left CBFV; RCBFV, right CBFV; ABP, arterial blood pressure; EEG, electroencephalography.

Monitor 500, Graz, Austria or Finometer model 1, Finapres, Netherlands). Continuous EEG monitoring was performed using an 8 electrode longitudinal bipolar montage (Nicolet V44 EEG Monitor, Natus Neurology Incorporated, Wisconsin, USA or NSD-7101 Neuro Monitor System, Delica, China) with electrodes placed according to the international 10–20 system (F3-C3, T3-P3, P3-O1, F4-C4, T4-P4, P4-O2) (21). The CBFV, ABP, and EEG signals were saved simultaneously through the neuro monitor system at a sampling frequency of 500 Hz.

Estimation of Phase-Amplitude Cross-Frequency Coupling (PAC)

PAC was calculated between the phase of slow waves of CBFV (0–0.05 and 0.05–0.15 Hz) and the amplitude of five EEG bands (δ, θ, α, β, γ). We used the method proposed by Canolty et al. (17) to extract PAC through a complex valued signal: $A_{EEG}(t)\, e^{i\varphi_{CBFV}(t)}$, where $A_{EEG}(t)$ refers to amplitude of EEG in each frequency band, and $\varphi_{CBFV}(t)$ refers to the phase of CBFV. In order to calculate PAC, the raw EEG signal was first separated into bands with center frequencies ranging from 2 to 44 Hz, in 2 Hz steps, with 2 Hz bandwidths. This process created a set of real valued band-pass filtered EEG signals $\{EEG(t)\}$. Second, the Hilbert Transform was applied to each signal in $\{\varphi_{CBFV}(t)\}$ to create a set of complex-valued analytic signals $\{Z_{EEG}(t)\}$. The absolute value of each analytic signal was then obtained to produce the set of analytic amplitude time series $\{A_{EEG}(t)\}$. Next, the CBFV signals were separated into two bands: 0–0.05 and 0.05–0.15 Hz, and the phase information of CBFV in these two frequencies was extracted from the Hilbert Transform, resulting in $\{\varphi_{CBFV}(t)\}$. We then constructed a composite complex-valued signal by combining the amplitude of EEG of one frequency band and the phase series of CBFV of another frequency band: $z(t) = A_{EEG}(t)\, e^{i\varphi_{CBFV}(t)}$. This composite signal takes on some particular value in the complex plane at each time point. If the probability density function (PDF) of $z(t)$ is not radially symmetric, then it must be the case that either (1) A_{EEG} and φ_{CBFV} share mutual information, or (2) the distribution of φ_{CBFV} is non-uniform. Measuring the degree of asymmetry of this PDF,

which can be done by computing the mean or first moment M of $z(t)$, provides a useful metric of coupling between the two time series (14, 17).

Since the question of interest is the degree of coupling between A_{EEG} and φ_{CBFV}, rather than the statistical properties of either A_{EEG} or φ_{CBFV} examined alone, the mean M must first be normalized before it can be used as a metric of coupling strength (17). In other words, we were interested in the properties of the joint distribution of A_{EEG} or φ_{CBFV}. One way to accomplish this is to compare the actual mean M (M_{real}) to a set of surrogate means $\{M_{sur}\}$ created by offsetting A_{EEG} or φ_{CBFV} by some large time lag. That is, we can introduce a time lag τ between A_{EEG} and φ_{CBFV} such that the composite signal is a function of both time and lag: $z(t, \tau) = A_{EEG}(t+\tau)\, e^{i\varphi_{CBFV}(t)}$. Note that the dependence (if any) between A_{EEG} and φ_{CBFV} will be a function of the lag τ between them, decreasing for large τ, while τ has no effect on the distribution of φ_{CBFV} alone or A_{EEG} alone. Therefore, computing the distribution of $z(t, \tau)$ at large τ can maintain the statistics of the individual time series, and only the pairing of sample points between the two time series is changed. Any asymmetry in the distribution of $z(t, \tau)$ at large τ will be due to the non-uniformity of φ_{CBFV}, while the scale (how far points fall from the origin) will be determined by A_{EEG} alone. The modulus or length of M_{real}, compared to the distribution of surrogate lengths, provides a measure of the coupling strength, while the angle of M, compared to the distribution of surrogate angles, indicates the phase of CBFV associated with the largest EEG amplitudes (14). We can define a normalized or z-scored length $M_{norm} = (M_{real} - \mu)/\sigma$, where μ is the mean of the surrogate lengths and σ is their standard deviation. This normalization ensures that M_{norm} is insensitive to the marginal distributions of A_{EEG} and φ_{CBFV} and is sensitive only to their joint distribution, as desired. We define this normalized metric M_{norm} as the modulation index (MI) for PAC assessment in this paper. It is thus assumed that the existence of coupling leads to a larger MI (14).

After calculating the MIs between the phase of CBFV in two bands (0–0.05 and 0.05–0.15 Hz) and the amplitude of all the EEG bands (2 to 44 Hz, in 2 Hz steps, with 2 Hz bandwidths), the MIs were averaged in five EEG frequency bands: δ (1–4 Hz), θ (4–7Hz), α (7–13 Hz), β (13–30 Hz), and γ (30–45 Hz). Therefore, for each EEG channel, we obtained $5 \times 2 = 10$ MI values for CBFV of each side at every calculating time point, where 5 refers to the five EEG frequency bands (δ, θ, α, β, γ) and 2 refers to the two CBFV frequency bands. The MI was calculated using a 300 s window, updated every 2 min.

Global PAC

In order to assess the systematic coupling between CBFV and EEG, we introduced a parameter named global PAC. First, the MIs between each EEG channel (6 channels) and CBFV of each side were averaged across the whole recording time, which resulted in $6 \times 2 \times 10 = 120$ MI values for each patient (2 refers to the CBFV of two sides, 6 refers to six EEG channels and 10 refers to the MI values that each EEG channel can produce). The global PAC was calculated as the sum of all the 120 MI values.

Degree of Asymmetry of Bilateral PACs

In order to evaluate the degree of asymmetry of bilateral PACs, we first calculated the mean value of MIs between left CBFV (MI_{left}) and the 6 EEG channels ($n = 6 \times 10 = 60$), and the mean value of MIs between right CBFV (MI_{right}) and all the 6 EEG channels ($n = 6 \times 10 = 60$). The absolute difference between MI_{left} and MI_{right} was calculated to demonstrate the degree of asymmetry of bilateral PACs. We hypothesized that the degree of asymmetry of bilateral PACs is positively related with the degree of stenosis.

Collateral Flow Strength

We calculated the mean value of MI (MI_{ips}), between CBFV on the side contralateral to stroke and the EEG of the ipsilateral side (3 channels), and the mean value of MI (MI_{con}) between CBFV on the side contralateral to stroke and the EEG on the side of stroke (3 channels). The difference between MI_{ips} and MI_{con} was calculated to denote the collateral flow strength. We hypothesized that smaller difference between these two metrics might correspond to more efficient collateral flow. The difference was compared with the degree of stenosis.

Statistical Analysis

The statistical analyses were performed using Matlab software (ver. R2012A, MathWorks, Inc.). In order to determine which frequency band showed the strongest coupling relationship between EEG and CBFV, the mean MI across all the EEG channels (six channels) was calculated for each EEG frequency band (δ, θ, α, β, γ) individually, resulting in five MI values in each CBFV band at each side. Then in order to eliminate individual differences and make the comparison compatible, each MI was divided by the sum of the five MIs for each patient. Finally, all the patients' normalized MIs were separated into five groups with each group representing one EEG band. A One Way ANOVA was used to tell whether there is significant difference between at least two bands. If the p value of One Way ANOVA was smaller than 0.05, an additional multiple comparison test (Bonferronim) was used to find out where the significant difference was located.

In order to identify the region of the brain that showed the strongest PAC between CBFV and EEG, the average value of MIs across all EEG bands was calculated for each EEG channel, resulting in six MI values for each patient in each CBFV band at each side. Then each MI value was divided by the sum of the six MIs of each patient for normalization. Finally, all the patients' normalized MIs were separated into 6 groups with each group representing one EEG channel. A One Way ANOVA was used to tell whether there is significant difference between at least two channels. If the p value of One Way ANOVA was smaller than 0.05, an additional multiple comparison test (Bonferronim) was used to find out where the significant difference was located.

Patients were divided into a deceased (mRS = 6) and a survival group (mRS = 1 to 5), and into a favorable (mRS: 1 to 2) and an unfavorable group (mRS: 3 ∼ 6) (22). The mean global PAC in each group was calculated. The Wilcoxon rank sum test was used to calculate the difference in the global PAC between the deceased and survival groups, and between the favorable and unfavorable groups. $p < 0.05$ was considered to be significant. Receiver Operating Characteristic (ROC) curves were used to

compare the ability of PAC in distinguishing patient outcome, rendering an area under the ROC curve (AUROC). The patients were also divided into three groups according to NIHSS at discharge: NIHSS < 10, 10 ≤ NIHSS < 20 and 20 ≤ NIHSS. Mean global PAC was calculated in each group and a One Way ANOA was used to compare the difference among the three groups.

RESULTS

Patient Demographics

The mean age of the 16 (three males) patients enrolled in the study was 60.9 ± 7.9 (mean ± SD) years. Nineteen recordings were studied, with a mean duration of 100.0 ± 42.6 min, ranging from 15.3 to 172.9 min. Information about each patient's blocked artery, age, NIHSS on admission and at discharge, mRS at discharge, mean ABP, and mean CBFV of both sides are summarized in **Table 1**.

How CBFV and EEG Interact With Each Other

The MIs between the phase of CBFV (0–0.05 Hz and 0.05–0.15 Hz) and EEG amplitude in each band (five bands: δ, θ, α, β, γ) were calculated and averaged across the whole recording period for each EEG channel. **Figure 2** shows the MIs of all 16 patients, where the *x* axis represents six EEG channels, and the *y* axis represents five EEG bands. Each subfigure represents CBFV of one side in one frequency (A, C: 0∼0.05 and B, D:0.05∼0.15 Hz), and one dot represents one patient, with red color indicating strong PAC and blue color indicating weak PAC. In general, MIs between CBFV and EEG in β and γ bands show brighter belt, indicating stronger PAC in these two bands than the other three EEG bands (**Figure 2**). The One Way ANOVA and multiple comparison test of normalized MIs show that PAC is significantly stronger in EEG β and γ bands than in the other three bands (**Figure 3**).

The Brain Region That Shows Strongest PAC Between CBFV and EEG

We also investigated the brain region that shows strongest phase-amplitude coupling between CBFV and EEG. **Figure 4A** combines the MIs of all the 16 patients together, where the x axis represents the bilateral CBFV frequency bands (0–0.05 and 0.05–0.15 Hz), and the y axis represents six EEG channels (F3-C3, T3-P3, P3-O1, F4-C4, T4-P4, P4-O2). One point represents one patient. In general, P3-O1 and P4-O2 show brighter belts than the other four EEG channels (**Figure 4A**). The One Way ANOVA and multiple comparison test indicate stronger PAC in the occipital region (P3-01, P4-02) than the other regions (**Figures 4B,C**), with MI in P3-O1 channel significantly bigger than other channels (**Figures 4B,C**, $p < 0.05$). The relationship between PAC and outcome.

The patients were divided into a deceased ($n = 2$) and a survival ($n = 14$) group. The mean MI of the deceased group was 5.99 ±1.54 and the mean MI of the survival group was 7.36±1.19. No significant difference exists between these two groups (AUROC = 0.81, $p = 0.57$, **Figure 5A**). There is no significant difference between the mean MI of the favorable group ($n = 2$, mean MI was 7.8 ±1.55) and unfavorable group ($n = 14$, mean MI was 7.1 ± 1.27, AUROC = 0.65, $p = 0.23$, **Figure 5B**), either. The global PAC seemed to increase while NIHSS increased, but this relationship was not significant ($p = 0.50$, **Figure 5C**).

The relationship between the degree of asymmetry of the bilateral PACs and the degree of occlusion is interesting (**Figure 5D**). Greater degree of occlusion in unilateral main artery, demonstrated by higher degree of stenosis, was associated with greater asymmetry in the coupling relationship between the two brain hemispheres (mean difference of bilateral PACs was 0.27 ± 0.24, 0.46 ± 0.36, and 1.81 ± 1.21 at 0–20% stenosis, 30–40% stenosis, and >50% stenosis, $p = 0.01$).

No significant relationship was found between the collateral flow strength and the degree of stenosis (mean MI_{ips} - MI_{con} was 0.07 ± 0.08, 0.08 ± 0.23, 0.33 ± 0.32 at 0–20, 30–40, and >50% stenosis, p =0.19).

DISCUSSION

As the first leading cause of death in developing countries, stroke is the greatest cause of disability (23, 24). Strokes are classified as hemorrhagic and ischemic, with the majority falling into the latter category (25). Studies show that CBF decreases in the occluded artery which is the main etiology of ischemia (26). However, the effect of the occlusion in large intracranial arteries and the related hemodynamic changes are still not clear in stroke patients (27). The present work demonstrates that it is possible to link the degree of occlusion in unilateral main artery and the asymmetry of neurovascular coupling strength between the two brain hemispheres. In summary, we have shown strong coupling relationship between the phase of CBFV slow waves and the amplitude of EEG in β and γ bands. We also found the occipital region displayed the strongest PAC among the limited number of brain regions studied. In this cohort of stroke patients, the degree of stenosis was positively related with the asymmetry of the coupling relationship between the two brain hemispheres. Moreover, the deceased group and unfavorable outcome groups tended to have a weaker neurovascular coupling relationship than the survival or favorable group, though this was not significant.

A close correlation has been established between EEG and regional CBF in experimental animals and in humans under normal conditions (28–30). This relationship is reasonable because both EEG and CBF are closely related with neuronal metabolic states (31). Increased neurological activities, such as seizures and arousal, need more CBF and increased cerebral metabolism. It has been demonstrated that under normal conditions, local field potential activity, and in particular the γ-band component, is thought to be a more reliable predictor of perfusion based signals (32–34). However, how EEG and CBF interact with each other in stroke patients remains unknown. In this study, we found a close CFC relationship between EEG and CBFV in a cohort of ischemic stroke patients. In general, CBFV phase in low frequency interacts with EEG amplitude in high frequencies (β and γ bands). The present findings closely

TABLE 1 | Patients' demographic.

Patient	Sex	Blocked Artery	Age	NIHSS on admission	NIHSS at discharge	mRS at discharge	ABP (mmHg)	Left CBFV (cm/s)	Right CBFV (cm/s)
1	M	RICA	57	11	10	4	113.0 ± 32.1	55.7 ± 13.8	91.3 ± 18.0
2	F	LICA	85	20	35	6	52.3 ± 13.1	87.8 ± 35.8	44.9 ± 20.7
3	M	RICA	54	40	34	5	85.9 ± 26.4	64.4 ± 14.8	118.9 ± 30.4
4	M	BA	46	21	10	5	105.5 ± 24.8	54.3 ± 10.0	63.3 ± 17.5
5	M	LICA	75	26	19	5	111 ± 12.0	50.0 ± 20.6	99.2 ± 50.1
6	F	LICA	56	14	4	4	90.3 ± 16.7	22.8 ± 13.3	49.5 ± 15.4
7	M	LICA	62	18	11	4	120.4 ± 23.4	38.4 ± 9.5	61.4 ± 14.7
8	M	LICA	68	15	11	4	99.6 ± 23.9	75.2 ± 33.7	68.6 ± 19.2
9	M	RICA	58	13	9	4	104.2 ± 22.9	95.6 ± 36.4	61.1 ± 21.4
10	F	BA	64	37	35	5	98.0 ± 25.9	77.1 ± 19.0	73.9 ± 18.6
11	M	LMCA	66	15	1	1	99.3 ± 27.5	57.6 ± 18.5	38.0 ± 13.8
12	M	RICA	76	10	35	6	114.4 ± 41.1	23.5 ± 22.5	64.5 ± 18.6
13	M	LMCA	62	18	34	5	98.9 ± 29.1	51.2 ± 13.0	57.6 ± 17.7
14	M	RICA	56	13	2	1	97.2 ± 13.9	40.1 ± 10.0	69.7 ± 30.3
15	F	RMCA	57	15	16	5	115.8 ± 21.5	56.5 ± 17.4	52.2 ± 16.2
16	M	BA	45	NA	NA	NA	47.8 ± 11.7	67.4 ± 16.7	80.6 ± 20.7

NIHSS, NIH stroke scale; mRS, Modified Rankin Scale for neurologic disability; NA, not available; ICA, internal carotid artery; MCA, middle cerebral artery; BA, basilar artery; L, left side; R, rite side. ABP, arterial blood pressure; CBFV, cerebral blood flow.

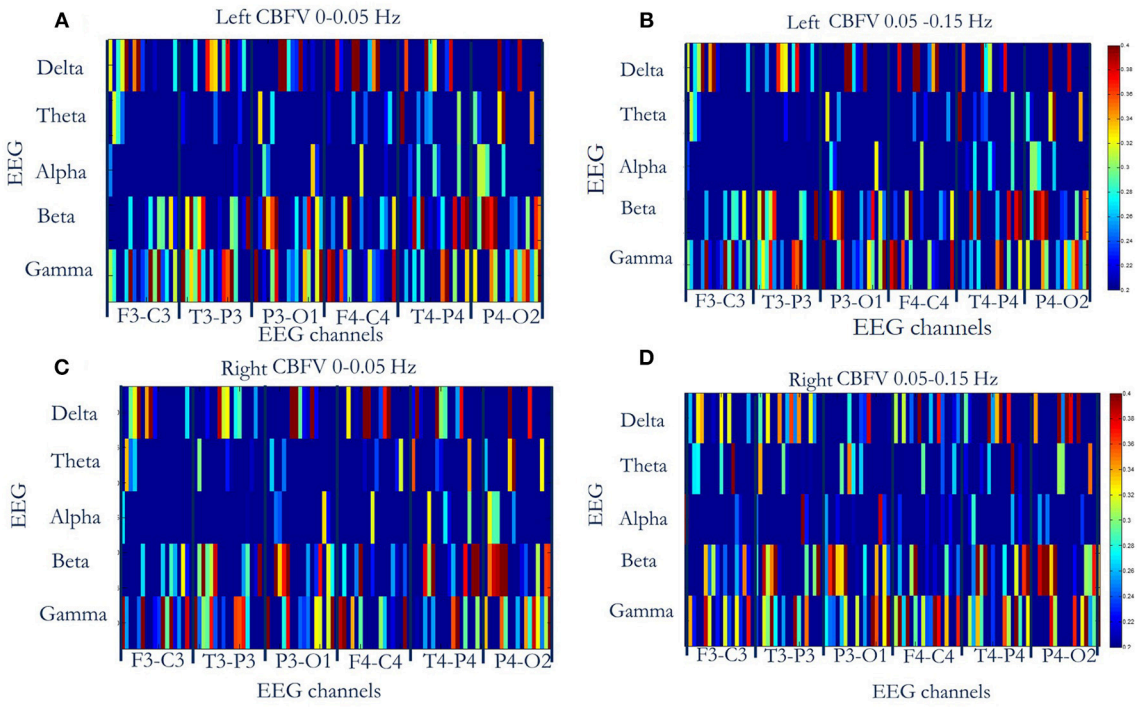

FIGURE 2 | Phase-amplitude cross-frequency coupling (PAC) between CBFV and EEG of six channels (F3-C3, T3-P3, P3-O3, F4-C4, T4-P4, P4-O2) of all the 16 patients. The *x* axis represents six EEG channels, and the *y* axis represents five EEG bands. Each subfigure represents CBFV of one side in one frequency (**A**,**C**: 0∼0.05 Hz and **B,D**:0.05∼0.15 Hz), and one dot represents one patient, with red color indicating strong PAC and blue color indicating weak PAC. In general, PAC between CBFV and EEG in β and γ bands show brighter belt, indicating stronger PAC in these two bands than the other three EEG bands. **(A)** PAC between phase of left CBFV (0–0.05 Hz) and amplitude of EEG (six channels, five bands). **(B)** PAC between phase of left CBFV (0.05–0.15 Hz) and amplitude of EEG. **(C)** PAC between phase of right CBFV (0–0.05 Hz) and amplitude of EEG. **(D)** PAC between phase of right CBFV (0.05–0.15 Hz) and amplitude of EEG. CBFV, cerebral blood flow velocity; ABP, arterial blood pressure; EEG, electroencephalography.

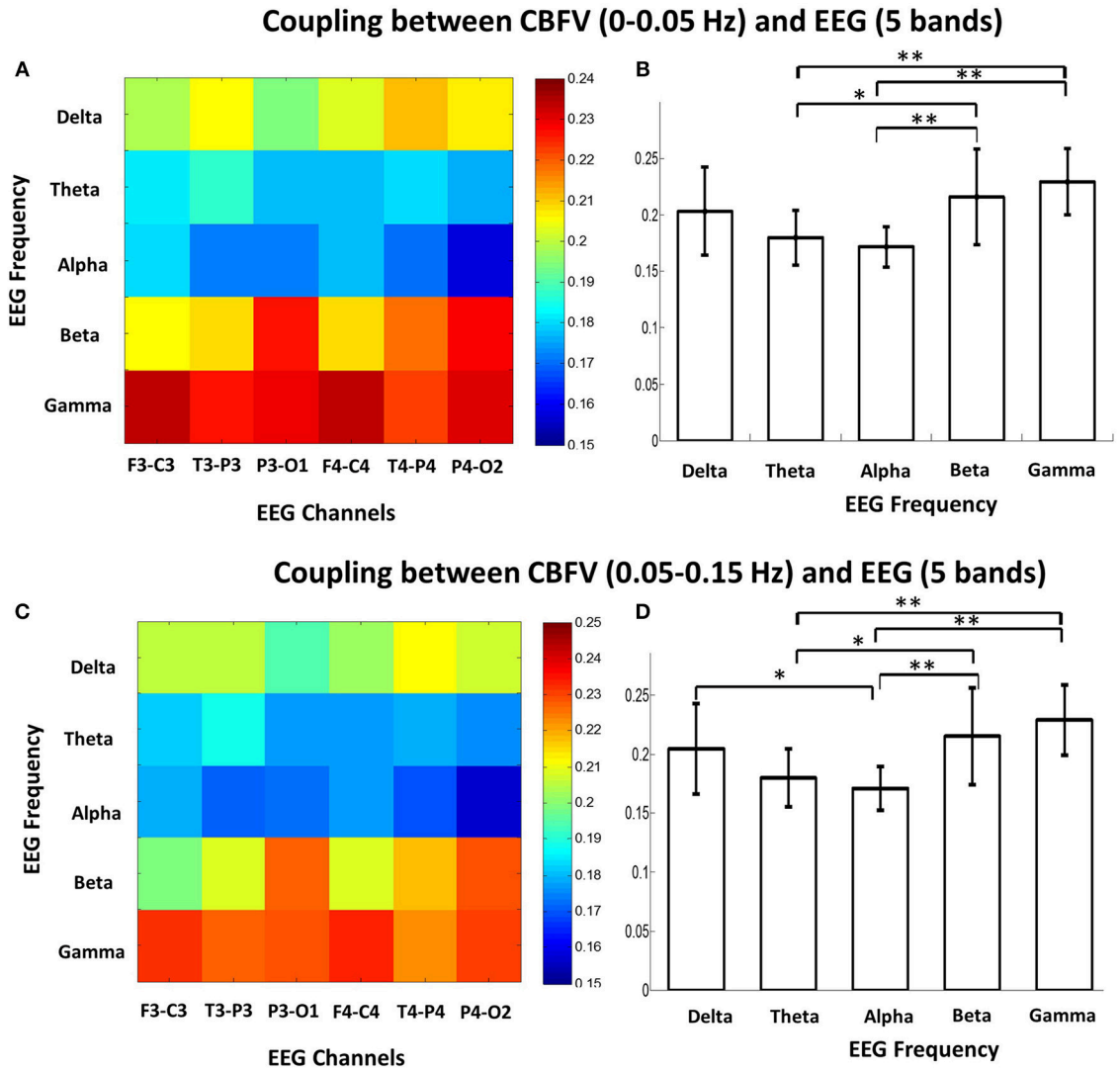

FIGURE 3 | (A) Mean phase-amplitude cross-frequency coupling (PAC) between CBFV (0–0.05 Hz) and EEG of six channels in five frequency bands (δ, θ, α, β, γ) of the 16 patients. **(B)** Statistical comparison of mean PAC between CBFV (0–0.05 Hz) and EEG in the 5 frequency bands (δ, θ, α, β, γ). The PAC in β and γ bands were significant higher than the other bands. One star means $p < 0.05$; two stars means $p < 0.01$. **(C)** Mean PAC between CBFV (0.05–0.15 Hz) and EEG of six channels in five frequency bands of the 16 patients. **(D)** Statistical comparison of mean PAC between CBFV (0.05–0.15 Hz) and EEG in the 5 frequency bands. The PAC in β and γ bands were significant higher than the other bands. CBFV, cerebral blood flow velocity; ABP, arterial blood pressure; EEG, electroencephalography.

link hemodynamic responses to the process of EEG oscillations in β and γ bands. Our results are compatible with previous findings (32–35). Scheeringa et al. found γ band EEG power correlates positively with the superficial layers' hemodynamic signal and that β power is negatively correlated to deep layer hemodynamics (36). A possible explanation of the relationship between γ band EEG and CBFV is that γ oscillations, mainly observed in granular and supragranular layers, are thought to be initiated by the firing of inhibitory interneurons and pyramidal cells (34, 36). At the same time, these interneurons contain enzymes for the synthesis of vasoactive compounds such as nitric oxide (NO) and vasoactive peptides (34, 37, 38). Thus, when cortical networks engage in γ oscillations, inhibitory interneurons are highly active, and as their discharges are phase-locked to the oscillations (23), their activity increases with oscillation frequency. Moreover, previous findings also found that β band EEG is inversely correlated to hemodynamic signals and is predominantly measured in deep layers (i.e., the infragranular layers) (39–41). The deep layers are therefore also a likely source for the β signal and vascular mediators. Moreover, since the feedforward connections of the brain target the granular layer (42) and the feedback connections originate preferentially in the infragranular layers (43), we hypothesize that the synchronization between CBF and EEG γ band might reflect feedforward influences, and the synchronization between CBF and EEG β band might reflect feedback influences of CBF control

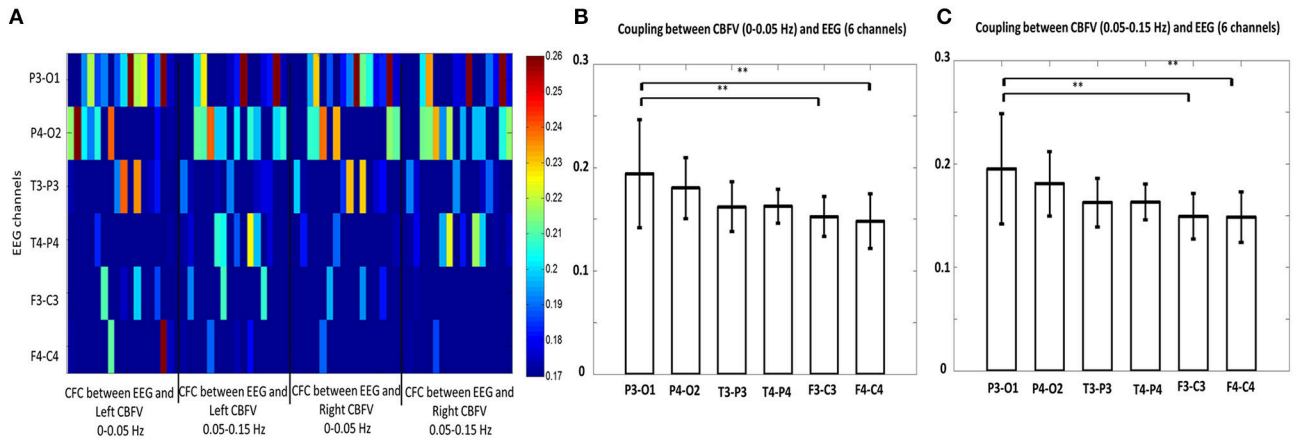

FIGURE 4 | (A) Phase-amplitude cross-frequency coupling (PAC) between bilateral CBFVs and EEG of six channels (F3-C3, T3-P3, P3-O3, F4-C4, T4-P4, P4-O2). The x axis represents the bilateral CBFV frequency bands (0–0.05 and 0.05–0.15 Hz), and the y axis represents six EEG channels (F3-C3, T3-P3, P3-O1, F4-C4, T4-P4, P4-O2). One point represents one patient, with red color indicating strong PAC and blue color indicating weak PAC. In general, P3-O1 and P4-O2 show brighter belts than the other four EEG channels. **(B)** Statistical comparison of mean PAC between CBFV (0–0.05 Hz) and EEG of 6 channels. **(C)** Statistical comparison of mean PAC between CBFV (0.05–0.15 Hz) and EEG of 6 channels. The PAC of P3-O1 channel was significant higher than the other channels. CBFV, cerebral blood flow velocity; ABP, arterial blood pressure; EEG, electroencephalography. Two stars indicates $p < 0.05$.

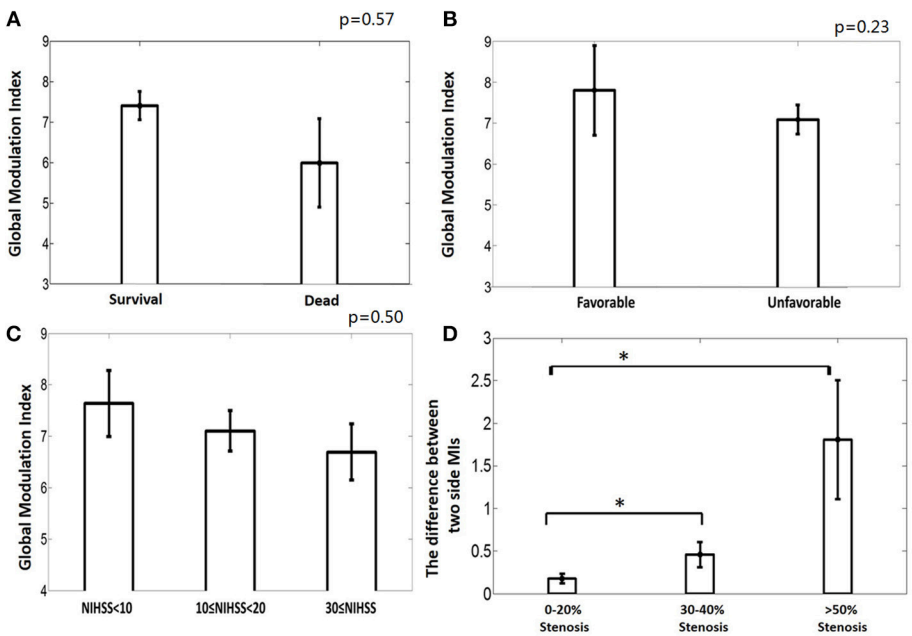

FIGURE 5 | (A) The deceased group tends to have weaker phase-amplitude coupling (PAC) relationship between CBFV and EEG than the survival group, though not significantly. **(B)** The unfavorable group tends to have weaker PAC than the favorable group, though not significantly. **(C)** The group with higher NIHSS has weaker global PAC; **(D)** Greater degree of occlusion in unilateral main artery, demonstrated by higher degree of stenosis, is associated with greater asymmetry in the coupling relationship between the two brain hemispheres. MI: modulation index, which is used to indicate the strength of PAC. One star means $p < 0.05$.

(44). However, these hypotheses are highly speculative given that we are studying this phenomenon at a super macro level.

Our data also shows that the strongest phase-amplitude coupling between CBFV and EEG is found in the occipital region. The occipital lobe, the cerebellum, and the medial aspects of the temporal lobe receive blood from the vertebrobasilar system, which is called the posterior circulation (36). It has already been noted that in human EEG, γ rhythms are prevalent in local visual response synchronization (45, 46). In his article, Scheeringa pointed out that γ band modulation dominated in posterior electrodes consistent with a source in the early visual cortex. Furthermore, Bastos et al. found that among primate

visual cortical areas, feedforward communication utilizes the θ and γ-bands and feedback communication relies upon the β band (44). These findings offer some possible explanations of why we observed stronger CFC in P3-O1 and P4-O2 channel in the present study.

Acute ischemic stroke is a leading cause of morbidity and mortality worldwide (47). It has been demonstrated that large vessel occlusion related acute ischemic strokes are associated with more severe deficits and have worse long-term outcomes (48). Stenosis or occlusion of the major arteries of the head and neck may cause hemodynamic impairment of the distal cerebral circulation (49). The key in reducing the high morbidity and mortality associated with stroke is to develop a method that can detect cerebral asymmetries and vessel occlusion. Several neuroimaging methods are currently available for the indirect assessment of the hemodynamic effect of atherosclerotic stenosis or occlusion on the distal cerebral vasculature. However, these methods are not continuous. It will be of great interest to develop a tool that can identify the degree of patient's stenosis continuously at bedside. Our study demonstrated the potential of using PAC between CBFV and EEG as an indicator of the degree of occlusive level in stroke patients. Higher stenosis is positively related with bigger difference between the bilateral PACs. For a patient with occlusion in the unilateral big artery, the blood supply will mainly rely on the contralateral, unblocked artery. If the artery cannot supply sufficient blood to both hemispheres, it will cause asymmetry of the coupling relationship between the two brain hemispheres. The more severely the artery is blocked, the more obvious this asymmetry is.

This study is a preliminary research to develop and validate metrics for neuro vascular coupling assessment using continuously available signals at the bedside. Our current focus on studying the relationship between EEG amplitude and CBFV phase was motivated by the observation as presented in **Figure 1** where one can appreciate the changes of EEG amplitude are related to changes in phase of slow waves of CBFV. Physiologically speaking, EEG activity is much faster than hemodynamic changes. Therefore, the time delay (or equivalently the phase relationship) would be a critical aspect of neurovascular coupling. However, coherence may be also of interest as a potential marker of neuro vascular coupling. One potential challenge in using coherence is that it only provides the strength of relationship at matched frequencies of two signals, which might be a disadvantage because relevant information in EEG is at a higher frequency than that of CBFV. Considering that CFC idea can be extended to study: phase-to-phase CFC, phase-to-amplitude CFC and amplitude-to-amplitude CFC, therefore other two forms of CFC not studied in this work can be further investigated and they both can use different frequency contents from two signals.

Since Brazilian physiologist Leao described the cortical spreading depolarization (CSD) in 1944, there has been significant progress in this area (50). The physiological haemodynamic response to CSD is the dilation of resistance vessels, in order to increase regional CBF to match the energy consumption during the neuronal depolarization phase (51, 52). However, with the dysfunction of local microvasculature, sever microvascular spasm instead of vasodilation is coupled to the neuronal depolarization phase, inducing cortical spreading ischemia, and/or inverse neurovascular coupling. Researchers already demonstrated cortical spreading ischemia in animal models, and in patients with stroke, aneurysmal subarachnoid hemorrhage (51–53), using electrocorticogram (ECoG). Cortical spreading ischemia probably represents a late consequence of prolonged impaired neurovascular coupling. Our current work can be considered as a preliminary and technology development toward providing capability for the first time to continuously monitor and detect impairment in neurovascular coupling—so that spreading ischemia can be predicted. However, this hypothesis remains speculative at the moment and will motivate the field to collaborate and share multimodality recordings to facilitate further development of the algorithms and recording technologies.

We also looked into the changes of CFC between CBV and EEG over time. We reviewed the results of the 16 stroke patients, and in most cases the CFC in gamma and beta bands were continuously higher than other bands, as shown in the **Figures S1A–C**; however, 5 out of 16 patients did not show continuously strong CFC in gamma and beta bands as shown in **Figures S1D–F**. Interestingly, two out these five patients died and this bears the speculation that consistently high CFC might be associated with good outcome. However, given the small number of patients studied in the present work, it is not feasible to provide robust statistical conclusion on this topic. More sophisticated study on the changes of CFC over time should be done in the future.

Finally, we acknowledge the following limitations of this study. First, the current study has limited EEG channels and limited spatial discrimination of TCD measured CBFV. Only six EEG channels were used in this cohort of patients. Although, the six EEG channels covered the frontal, occipital and parietal lobes, they were not enough to cover the whole brain hemisphere with adequate, spatial resolution. More channels need to be used to more precisely determine the brain region that shows strongest neurovascular coupling between hemodynamic signals and EEG. Secondly, a small cohort of ischemic stroke patients (only 16 patients) were recruited in this paper, and we did not get adequate ranges of outcome to robustly study the relationship between neurovascular coupling characteristics and patient outcome. A prospective study on a bigger cohort is needed to further establish the clinical values of the EEG-CBFV multimodality monitoring. Furthermore, the study lacks a metabolic assessment to define neurovascular coupling and uncoupling.

CONCLUSION

In this study, we found a strong coupling relationship between phase of CBFV slow waves and EEG amplitude in β and γ bands. We also found that the occipital region shows the strongest phase-amplitude coupling between CBFV and EEG. These findings are consistent with other studies. Moreover, we demonstrated the degree of stenosis of stroke patients correlated

with the asymmetry of the neurovascular coupling strength between the two brain hemispheres. The PAC metric has the potential for routine use to guide clinical management in patients with occlusive stroke, but further studies are needed.

AUTHOR CONTRIBUTIONS

The concept and study design were formed by XH, LL, and XL. Data acquisition was conducted by YP and ZZ. Data analysis was conducted by XL and DW. Drafting of the manuscript and figures was contributed by XL, XH, DW, LL, ZZ, and YP.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00194/full#supplementary-material

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