

RESEARCH ARTICLE

Cortical hemodynamics of electrographic status epilepticus in the critically ill

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Abstract

Objectives: The pathophysiological mechanisms of status epilepticus (SE) underlying potential brain injury remain largely unclear. This study aims to employ functional near-infrared spectroscopy (fNIRS) combined with video-electroencephalography (vEEG) to monitor brain hemodynamics continuously and non-invasively in critically ill adult patients experiencing electrographic SE. Our primary focus is to investigate neurovascular coupling and cerebrovascular changes associated with seizures, particularly during recurring and/or prolonged episodes.

Methods: Eleven critically ill adult patients underwent simultaneous vEEG-fNIRS with large cortical coverage. Data from seven patients with identified electrographic SE were analyzed. The timing of recorded seizures was marked using standardized critical care EEG terminology. A general linear model was employed to extract the hemodynamic response to seizures from the fNIRS recordings. Linear mixed-effects models were utilized to correlate hemodynamic responses with seizure characteristics.

Results: A total of >200 h of monitoring and >1000 seizures were recorded. In most patients, an increase in oxyhemoglobin (HbO) and a decrease in deoxyhemoglobin (HbR) were observed during shorter-duration seizures. Although a similar response could also be seen initially for longer-duration seizures, this hemodynamic change was often followed by a progressive decline in HbO concentration and an increase in HbR. At the systemic level, no significant difference in peripheral oxygenation occurred during seizures, and only small changes in

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mean arterial blood pressure and heart rate occurred in four and two patients, respectively.

Significance: We demonstrate the feasibility of using multichannel vEEG-fNIRS to measure the hemodynamic changes associated with electrographic seizures in critically ill adult patients. Our findings suggest that disrupted neurovascular coupling is more prevalent during prolonged seizures compared to recurrent short-duration seizures. This research provides valuable insights into the dynamic interplay between neuronal activity and hemodynamics during critical care seizures.

KEYWORDS

electroencephalography, electrographic seizures, functional near-infrared spectroscopy, hemodynamic response, status epilepticus

1 | INTRODUCTION

Status epilepticus (SE) is defined as “a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures.”¹ These recurrent and/or prolonged seizures can manifest with overt jerking movements (i.e., electroclinical status epilepticus [ECSE]) or without prominent motor activity (i.e., electrographic status epilepticus [ESE]). ESE represents the form of SE most frequently seen in critical care patients and can only be identified using electroencephalography (EEG).²

It is well established that ECSE can cause widespread acute neuronal injury and death, even in the absence of systemic complications.^{3–7} Key mechanisms of ECSE-induced neuronal injury (and death) are multifactorial,⁸ including hypoxia, overproduction of reactive oxygen species caused by excessive activation of *N*-methyl-D-aspartate (NMDA) receptors⁹ and overaccumulation of intracellular calcium.¹⁰ In contrast, fewer studies have focused on cerebral hemodynamics and systemic changes during ESE.^{11–13} Notably, it remains unclear how “clinically silent” recurrent and/or prolonged seizures influence cerebral perfusion, oxygen delivery, and cardiovascular stability.

Functional near-infrared spectroscopy (fNIRS) is a noninvasive imaging technique that uses near-infrared light to assess cortical hemodynamics. Like EEG–functional magnetic resonance imaging (EEG–fMRI), the simultaneous fusion of EEG and fNIRS allows for capturing both sides of the neurovascular response (i.e., electrophysiological and hemodynamic activity), providing a unique opportunity to investigate neurovascular coupling (NVC) mechanism safely during interictal epileptiform discharges¹⁴ and seizures in patients with refractory epilepsy.¹⁵ However, using simultaneous video-EEG and fNIRS (i.e., vEEG–fNIRS) is challenging, especially when

Key points

- Functional near-infrared spectroscopy (fNIRS) combined with video-electroencephalography (vEEG) was used to explore large-scale hemodynamic changes from more than 1000 seizures in seven critically ill patients with electrographic status epilepticus (SE).
- Although both short seizures and prolonged seizures were initially associated with increased oxyhemoglobin (HbO) and decreased deoxyhemoglobin (HbR), prolonged seizures were later followed by a decline in HbO and an increase in HbR.
- Disrupted neurovascular coupling was found to be more common during prolonged recurrent seizures than during short recurrent seizures.

long recordings over the entire head are performed at the patient's bedside.^{16,17} Indeed, only a few pediatric cases have documented cerebral hemodynamics during seizures (including SE) in the critically ill using fNIRS.^{18–20} (See Table S1 for a brief review.)

Over the past decade, our group has focused on using vEEG–fNIRS for long-term bedside monitoring in various clinical settings.^{16,17} We previously demonstrated the feasibility of performing long-term vEEG–fNIRS recordings in critically ill adults presenting with diverse electrographic patterns¹⁶. However, in that study, we could not fully explore the neurovascular dynamics associated with ESE, as only two patients had a limited number of recurrent seizures during the monitoring period. In this study, we document the systemic and cortical hemodynamic changes associated with ESE by performing long-term whole-head

vEEG-fNIRS recordings while simultaneously monitoring systemic physiology in a larger cohort of critically ill comatose patients.

2 | MATERIALS AND METHODS

2.1 | Study design and clinical data collection

Patients admitted to the intensive care unit (ICU) of the University of Montreal Hospital Center (CHUM) were recruited for this study. Our study was approved by the research ethics boards of the research center of the CHUM; written informed consent was obtained from each legally authorized representative. Inclusion criteria were: (1) patients admitted with a confirmed or suspected diagnosis of ESE, or (2) any patient in the ICU with at least one confirmed “electrical” seizure on scalp EEG. All included patients underwent continuous long-term whole-head vEEG-fNIRS monitoring. Brain MRI (Philips, 3 Tesla) was performed during the management of these patients at the discretion of the attending physicians.

2.2 | EEG interpretation and event marking

Two certified epileptologists (D.H.T. and D.K.N.) independently reviewed the vEEG recordings. Abnormal patterns or discharges were identified and subcategorized using the standardized critical care EEG terminology of the American Clinical Neurophysiology Society.²¹

2.3 | Long-term whole-head vEEG-fNIRS monitoring protocol

2.3.1 | vEEG-fNIRS data collection and synchronization

vEEG data were recorded using the BrainAmp EEG amplifier and BrainVision Recorder software (BrainVision Recorder, Brain Products GmbH, Germany). Twenty-one EEG electrodes sampling at 500 Hz were positioned following the International 10–20 layout and 10–10 (FT9/FT10) systems. Two additional electrodes were used for electrocardiography (ECG) and two for electrooculography (EOG).

fNIRS data were recorded using the Brainsight Continuous-Wave (CW)-NIRS system (Rogue Research Inc., Canada). A total of 48 optodes, 16 laser diode emitters (wavelength: 685 nm and 830 nm), 16 standard photodiodes

for short-distance detectors, and 32 avalanche photodetectors for long-distance detectors were used in all patients. The 48 optodes provided a minimum of 100 channels covering the whole head (Figure S1). The optodes were glued using collodion to minimize sensitivity to motion artifacts and to improve fNIRS signal-to noise ratio (SNR).²² The distance between the sources and long-distance detectors and sources and short-distance detectors was ≈ 3 –4 cm and ≈ 8 –10 cm, respectively. fNIRS data were sampled at 20 Hz. E-Prime 2.0 (Psychology Software Tools, USA) was used to synchronize vEEG and fNIRS data.

2.4 | fNIRS data analysis

2.4.1 | fNIRS data pre-processing

The recorded fNIRS data were pre-processed with the open-source MATLAB toolbox Homer2²³ and in-house developed scripts. For each data set, fNIRS channels without clear cerebral origin (e.g., with negative raw amplitude, no clear heartbeats, or saturated),²³ or with an intensity of <1000 photon counts or a SNR of <2 dB, were first removed. Motion artifacts were identified in the data with both visual identification and a Homer2 automatic motion detection algorithm based on signal standard deviation (SD) and amplitude changes,²⁴ and were reassessed by visual inspection simultaneously with the video feed. Recording segmentation was performed to remove time periods affected by excessive motion artifacts. Any EEG event within the period from 30 s prior to a motion artifact to 30 s after the artifact was excluded.

For each channel, the fNIRS optical data were first transformed into optical density changes by taking the logarithm of the time course. A third-order Butterworth low-pass filter with the cutoff frequency of .20 Hz was then applied to remove high-frequency physiological noises.^{25,26} The filtered optical density time courses were transformed into concentration changes in oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) concentrations using the modified Beer–Lambert Law with a partial path-length factor of 6.²⁷ Systemic physiological changes in the extracerebral layers²⁸ were then regressed out from all fNIRS channels within a general linear regression model framework²⁹ by using short-separation channel data that had the highest correlation as a regressor.³⁰ Signal detrending was conducted by adding polynomial regressors up to the third order to the model. In addition, concentration changes in total hemoglobin (HbT, calculated as HbO + HbR), and hemoglobin difference (HbD, calculated as HbO – HbR) were calculated and serve as representative markers of cerebral blood volume (CBV)³¹ and cerebral oxygenation, respectively.^{32,33}

2.4.2 | Extraction of hemodynamic response functions

Due to the large seizure duration variability in our recordings, the estimation of the hemodynamic response function (HRF) was performed using a bin analysis approach.³⁴ For each patient, seizures of comparable durations were grouped into the same bin, with an arbitrarily selected width of 10 s. For instance, seizures lasting <20 s were divided into two bins ([0–10 s] and [10–20 s]), and seizures lasting <80 s were divided into 8 bins: ([0–10 s], [10–20 s], ..., [70–80 s]). For each bin of seizures, we estimated the hemodynamic response (HbO, HbR, HbT, and HbD) from 10 s before the seizure onset to 10 s after its offset. We applied a spatial principal component analysis to the extracted hemodynamic response functions of all remaining fNIRS channels (after exclusion for motion artifacts and low SNR; see section 2.4.1) to generate a representative HRF for each bin using principal components that accounted for 80% of global variance. The same spatial principal component analysis procedure and the global variance threshold were employed in our previous study and shown to be effective in retaining the representative components of hemoglobin concentration changes across channels of different regions.¹⁶

To enable comparisons of the representative HRFs across bins, we extracted two HRF characteristics for each bin: the full width at half maximum (FWHM), which assesses response duration, and the normalized area under the curve (AUC), which evaluates response intensity. The FWHM was defined as the length of time during which the response was greater than half of the peak amplitude (or during which the response was lower than half of the nadir amplitude), whereas the normalized AUC was defined as the integral of the HRF with respect to time divided by the total HRF duration. We established a linear mixed-effects model to model seizure duration with fixed-effects for response FWHM or normalized AUC and uncorrelated random effect for intercept (grouped by patients) and residual. The goodness-of-fit was evaluated by examining the *p*-values from *F*-tests on the fixed-effect regression coefficients, as well as the adjusted *R*-squared values of the fit. More details of the linear mixed-effects model can be found in Data S1.1.

2.4.3 | Duration of seizures until occurrence of abnormal hemodynamic responses

Based on the bin analysis, we further employed time-to-event analyses to explore the seizure bin durations until the occurrence of seizure hemodynamic responses that potentially indicate disrupted NVC. For HbO, we defined the endpoint of

interest as the associated bin HRF showed a phase of HbO decrease. Similarly, the endpoint for HbR was defined because the associated bin HRF exhibited an HbR increase phase. For patients who did not exhibit those phases (e.g., Patient P01), right censoring was performed. The survival functions of HbO and HbR responses were estimated using the nonparametric Kaplan–Meier estimator and fitted with the Weibull distribution, as detailed in Data S1.2.

2.4.4 | Cortical projection of the hemodynamic response

To investigate the spatial characteristics of hemodynamic changes, we employed a forward model and Monte Carlo simulations to generate fNIRS sensitivity profiles and map the channel-wise hemodynamic changes onto the brain cortex. These analyses were conducted using the open-source Matlab toolbox AtlasViewer.³⁵ Further details are provided in Data S3. However, caution is advised when interpreting the spatial patterns of the hemodynamic responses, as the fNIRS channel layout may be unbalanced, different for each patient, and the detection sensitivity may be limited to certain brain regions.

2.4.5 | Systemic physiology and sedation level

Semi-continuous collection of vital signs, including mean arterial blood pressure ($_{sc}$ MABP, mmHg), oxygen saturation ($_{sc}$ SpO₂, %), heart rate ($_{sc}$ HR, bpm), end-tidal carbon dioxide ($_{sc}$ EtCO₂, mmHg), temperature ($_{sc}$ T, °C), and Richmond Agitation-Sedation Score (RASS), was undertaken every 15–30 min. In addition, continuous noninvasive systemic hemodynamic monitoring was conducted using the Finapres NOVA system (Finometer MIDI, TNO Biomedical Instrumentation, Amsterdam, Netherlands). Measured parameters included (1) MABP (mmHg); (2) SpO₂ (%); HR (bpm); and (3) respiration rate (RR). For continuous measurements, two periods were selected: (1) the preictal period (i.e., 30 s before each seizure), and (2) the ictal period (i.e., the period starting from seizure onset and ending with its respective offset). If the interval between two consecutive seizures was <60 s, both seizures were discarded.¹³ Finally, arterial blood gas, hemoglobin, lactic acid, sodium, and glucose concentrations were retrospectively collected from medical records.

We compared systemic physiological changes using the nonparametric Wilcoxon test. A *p*-value < .05 was considered statistically significant. Data are presented as mean differences with ranges (i.e., min/max). Statistical

analysis was performed using GraphPad Prism (GraphPad Software, Inc., USA).

3 | RESULTS

3.1 | Patient clinical and monitoring information

Among the 11 patients recruited and monitored, four were excluded from the analysis due to the absence of seizures during the monitoring period ($n=1$) and low signal quality ($n=3$). The clinical and vEEG-fNIRS monitoring profiles of the remaining patients ($n=7$, two women, age = 50 ± 13) are summarized in Table 1, and additional diagnostic and treatment information is included in Table S2.

3.2 | Temporal changes of cortical hemodynamic

Table 2 presents an overview of the bins of seizures for each patient and provides qualitative assessments of the representative HRFs for each bin in terms of increases ($\uparrow$) or decreases ($\downarrow$) of HbO, HbR, HbT, and HbD changes.

From most of the HRFs, a first phase of increases in HbO ($\approx 92\%$ of all bin HRFs), HbT (92%), and HbD ($\approx 85\%$) along with a decrease in HbR ($\approx 77\%$) was observed during seizures (phase 1). Among those HRFs, a subsequent decreasing phase in HbO, HbT, and HbD (phase 2) was observed in 39%, 36%, and 34%, respectively. Similarly, for HRFs exhibiting a decrease in HbR in phase 1, a subsequent phase 2 of HbR increase was observed in 30% of them, especially with seizures of longer durations.

The remaining HRFs ($\approx 8\%$ for HbO and HbT, $\approx 15\%$ for HbD, and $\approx 23\%$ for HbR) did not exhibit phase 1 changes but showed phase 2 changes immediately following seizure onset. This was most commonly observed in HRFs for HbR, where $\approx 23\%$ of bin HRFs presented an HbR increase without an initial HbR decrease phase.

Figure 1 and Figure 2 present two case studies (Patients P01 and P03, respectively) who exhibited uniphasic (phase 1) and biphasic (phase 1 + phase 2) hemodynamic responses to seizures. Details of the responses and spatial hemodynamic changes for these two patients are discussed in Data S2 and S3, respectively. For the other patients, spatial hemodynamic responses are provided in Data S3 and can be visualized in Figures S3–S7. Quantitative concentration changes for HbO and HbR are included in Table S3.

TABLE 1 Patient demographics.

Patient	Sex, age (BMI)	SE classification (etiology)	Admission			No. ASMs	No. anesthetics	Vasopressors	vEEG-fNIRS monitoring duration
			Dx	STESS	GCS				
P01	M, 63 (26.7)	ECSE $\rightarrow$ SRSE/NORSE (cryptogenic)	Graft-versus-host disease	6	3	3	2	Yes	144 h
P02	M, 34 (22.7)	ECSE $\rightarrow$ ESE with impaired consciousness (cryptogenic)	AMS	1	6	3	2	No	5 h
P03	M, 33 (23.0)	SRSE/NORSE (cryptogenic)	Seizure	3	3	4	3	Yes	36 h
P04	M, 40 (28.5)	ESE with impaired consciousness (postanoxic/hypoxia)	AMS	3	3	2	3	No	4 h
P05	M, 56 (34.5)	RSE with impaired consciousness (hepatic encephalopathy)	AMS	3	3	2	1	Yes	8 h
P06	M, 48 (24.7)	RSE with impaired consciousness (postanoxic/hypoxia)	Cardiac arrest	2	3	1	1	Yes	10 h
P07	M, 68 (24.9)	RSE with impaired consciousness (drug toxicity)	AMS	0	6	3	2	Yes	8 h

Abbreviations: AMS, altered mental status; ASMs, antiseizure medications; BMI, body mass index; Dx, diagnosis; ECSE, electroclinical status epilepticus; ESE, electrographic status epilepticus; F, female; GCS, Glasgow Coma Scale; M, male; NORSE, new-onset refractory status epilepticus; RSE, refractory status epilepticus; SRSE, super-refractory status epilepticus; STESS, Status Epilepticus Severity Score.

TABLE 2 Changes in directions for HbO, HbR, HbT, and HbD (for each seizure-duration bin).

	0–10s	10–20s	20–30s	30–40s	40–50s	50–60s	60–70s	70–80s	90–100s	100–200s	200–300s	1000–2000s	2000–3000s	3000–4000s	4000–5000s
P01	HbO	↑	↑	↑	↑	↑	-	-	-	-	-	-	-	-	-
P02	HbO	-	↓	↑	↑	↑	-	↑	-	-	-	-	-	-	-
P03	HbO	-	-	-	-	↑	↑	↑	↑	↑	↑↓	↑↓	↑↓	↑↓	↓
P04	HbO	-	-	↑	↑	-	↑↓	-	↑↓	-	-	-	-	-	-
P05	HbO	↑	↑↓	↓	-	-	-	-	-	-	-	-	-	-	-
P06	HbO	↑	↑	↑	↑↓	↑↓	↑↓	-	↑↓	-	-	-	-	-	-
P07	HbO	↑↓	-	↑↓	-	-	-	-	-	-	-	-	-	-	-
P01	HbR	↓	↓	↓	↓	↓	-	-	-	-	-	-	-	-	-
P02	HbR	-	↑	↑	↑	↓	-	↓	-	-	-	-	-	-	-
P03	HbR	-	-	-	-	↓	↓	↓	↓	↓	↓	↓↓	↓↓	↓↓	↓↓
P04	HbR	-	-	-	↑↓	-	↓	-	↑	-	-	-	-	-	-
P05	HbR	↓	↑↓	↑	-	-	-	-	-	-	-	-	-	-	-
P06	HbR	↓	↓	↓	↑↓	↑↓	↓	-	↓	-	-	-	-	-	-
P07	HbR	↑	-	↓↓	-	-	-	-	-	-	-	-	-	-	-
P01	HbT	↑	↑	↑	↑	↑	-	-	-	-	-	-	-	-	-
P02	HbT	-	↓	↑	↑	↑	-	↑↓	-	-	-	-	-	-	-
P03	HbT	-	-	-	-	↑	↑	↑	↑	↑	↑↓	↑↓	↑↓	↑↓	↑↓
P04	HbT	-	-	-	↑	-	↑↓	-	↑↓	-	-	-	-	-	-
P05	HbT	↑	↑↓	↓	-	-	-	-	-	-	-	-	-	-	-
P06	HbT	↑	↑	↑	↑↓	↑↓	↑↓	-	↓	-	-	-	-	-	-
P07	HbT	↑	-	↑	-	-	-	-	-	-	-	-	-	-	-
P01	HbD	↑	↑	↑	↑	↑	-	-	-	-	-	-	-	-	-
P02	HbD	-	↓	↑	↑	↑	-	-	-	-	-	-	-	-	-
P03	HbD	-	-	-	-	↑	↑	↑	↑	↑	↑↓	↑↓	↑↓	↑↓	↑↓
P04	HbD	-	-	-	↑	-	↑	-	↓	-	-	-	-	-	-
P05	HbD	↑	↑↓	↓	-	-	-	-	↑↓	-	-	-	-	-	-
P06	HbD	↑	↑	↑	↑↓	↑↓	↑↓	-	-	-	-	-	-	-	-
P07	HbD	↑	-	↑	-	-	-	-	-	-	-	-	-	-	-

Note: Graphical table depicting the direction of changes for each Hb biomarker. A single arrow signifies a uniphasic main increase (↑) or decrease (↓), whereas double arrows (↑↓ or ↓↑) refer to bi-phasic changes (i.e., an increase in the first phase followed by a decrease in the second phase, or a decrease in the first phase followed by an increase in the second phase). For some HbFs, an “initial dip” characterized by an initial, transient decrease of HbO and increase of HbR following the onset of a seizure was observed. The “initial dip” was not modeled as a phase as it was generally short in duration and was not present in all HbFs.

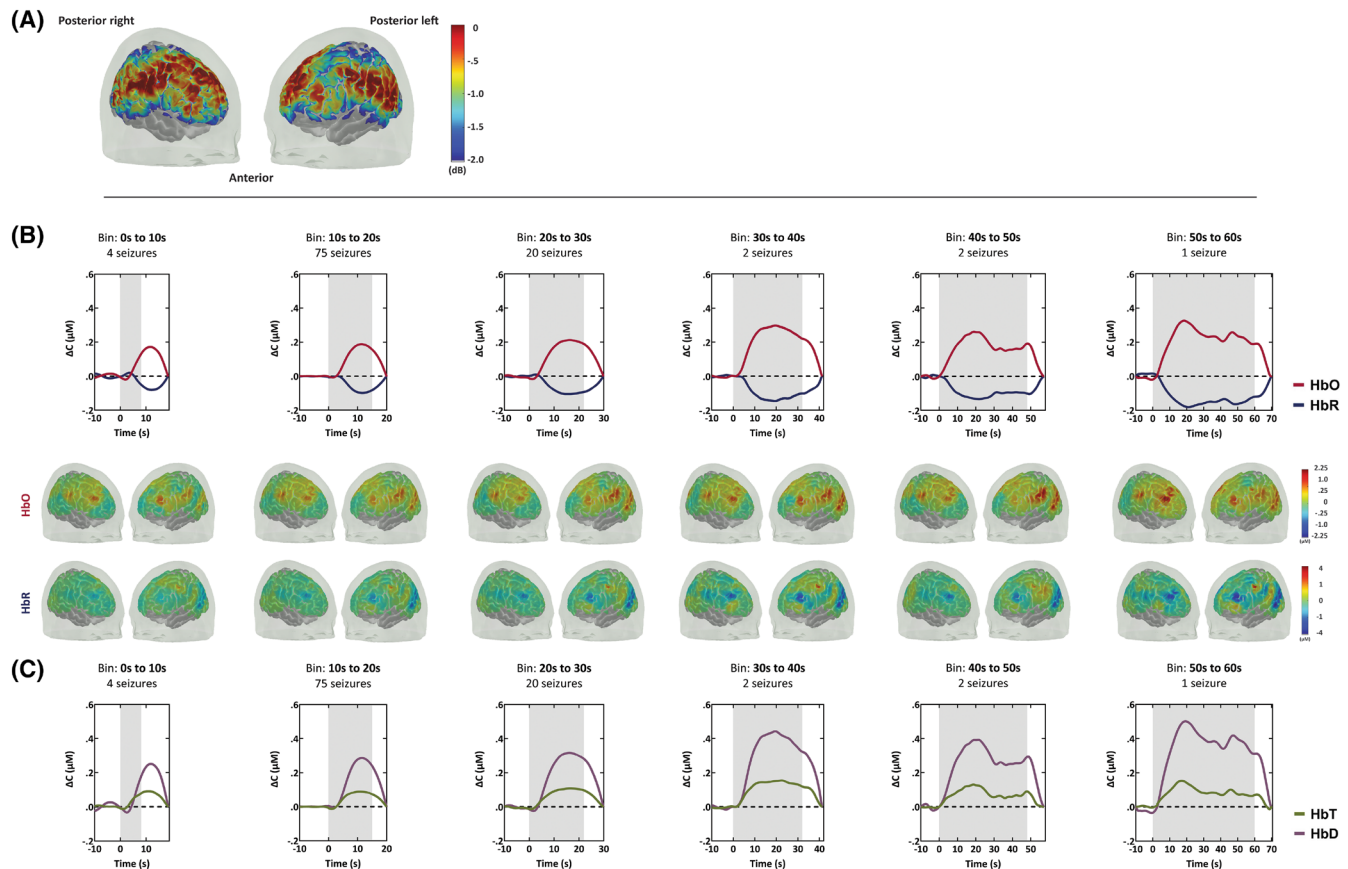


FIGURE 1 fNIRS results, Patient P01: Bin analysis of 181 seizures. Cortical sensitivity profile (A), each subplot of the figure shows the hemodynamic response functions (HRFs) of oxy- (HbO), deoxy- (HbR), the spatial projections of mean HbO and HbR changes (B), total hemoglobin concentration (HbT), and the difference between HbO and HbR (i.e., hemoglobin difference (HbD)) (C) associated with the seizures. The shadowed area indicates the average (mean) length of the seizures within a bin. Patient P01 exhibited mostly short-duration generalized seizures on electroencephalography (EEG), which were often seen to be the most significant in the bilateral frontotemporal regions. fNIRS showed global HbO increases and HbR decreases as seizure durations increased with the highest changes located in the bilateral frontal and fronto-temporo-central areas.

3.3 | Group analysis of cortical hemodynamic changes and seizure duration

All 39 bins from the seven patients were first divided into two groups, with the shorter seizure group containing the bins of the shorter-length seizures, which showed a uniphasic HbO increase (phase 1 or phase 2) and the longer seizure group consisting of the bins of longer-duration seizures with a biphasic HbO response (phase 1 + phase 2, i.e., $\uparrow\downarrow$). Linear mixed-effects model revealed a positive association between seizure length and response duration (assessed with the FWHM) in the *shorter seizures* of each patient for both HbO increase ($p = .0025$, adjusted R -squared = .66) and HbR decrease ($p = .031$, adjusted R -squared = .99) (Figure 3A). A positive association was also found between seizure length and response intensity, showing a higher normalized AUC for HbO ($p = .000013$, adjusted R -squared = .71) and a more negative AUC for

HbR ($p = .0045$, adjusted R -squared = .83) as seizure length increased (Figure 3B).

These associations were reversed in the *longer seizure* group, which exhibited a biphasic HbO response. We observed a negative association between the FWHM of the initial HbO increase ($p = .000049$, adjusted R -squared = .83) and the normalized AUC ($p = .00029$, adjusted R -squared = .51 for HbO and $p = .0018$, adjusted R -squared = .40 for HbR) of the HRF and seizure duration, indicating a shorter HbO increase period (phase 1) followed by a more prolonged and more significant HbO decrease and HbR increase periods (phase 2), with the further increase of seizure duration in this *longer seizure* group.

3.4 | Time-to-event analysis of bin HRFs

We employed time-to-event analyses (“survival analyses”) based on the estimated bin HRFs of the seven patients

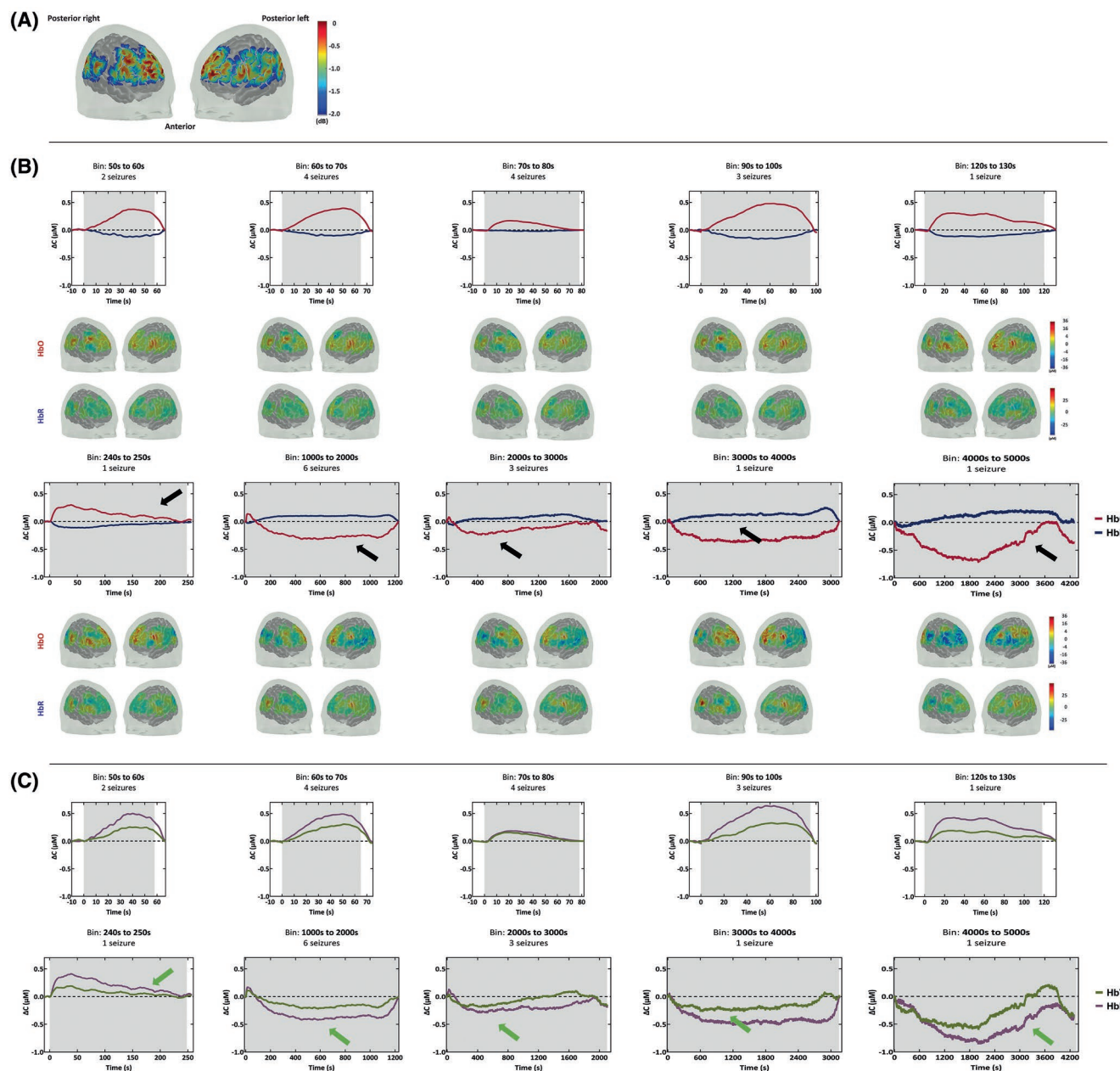


FIGURE 2 fNIRS results, Patient P03: Bin analysis of 26 seizures. Cortical sensitivity profile (A), each subplot of the figure shows the hemodynamic response functions (HRFs) of oxy- (HbO), deoxy- (HbR), the spatial projections of mean HbO and HbR changes (B), total hemoglobin concentration (HbT), and the difference between HbO and HbR (i.e., HbD) (C) associated with the seizures. The shadowed area indicates the average (mean) length of the seizures within a bin. Electroencephalography (EEG) recording on Patient P03 indicated generalized seizures and also focal activities in the bilateral central regions. fNIRS measurements revealed overall HbO increases and HbR decreases associated with shorter-duration seizures, but significant HbO decreases and HbR increases with longer-duration seizures (see black and green arrows). These second phases of the responses were mostly observed in the bilateral central regions.

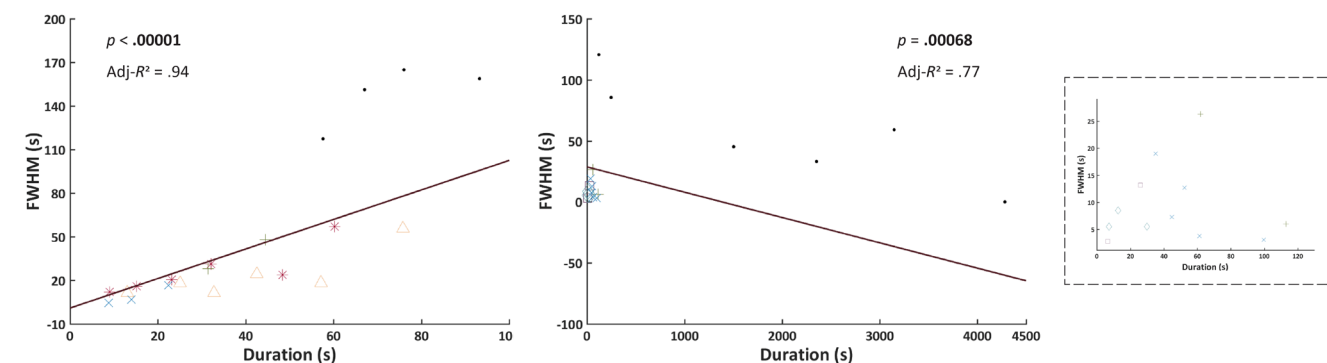
to analyze bin seizures durations until the occurrence of hemodynamic changes showing a phase of HbO decrease or HbR increase. Figure 4 depicts the survival functions using the descriptive Kaplan–Meier estimates and the fitted Weibull distributions for HbO and HbR responses, respectively.

For HbO, the fitted Weibull distribution curve showed a 95% probability of “surviving” with an increased

concentration response for seizure durations of 5.7s, 75% probability for duration of 31.1s, 50% probability for duration of 74.0s, 25% probability for duration of 146.3s, and a <5% probability of retaining an increase for seizure durations longer than 312.6s. For HbR, the probabilities for HRFs to “survive” with a decreased concentration response at 95%, 75%, 50%, 25%, and 5% correspond to seizure durations of 2.9s, 18.5s, 47.9s, 101.4s, and 233.2s, respectively.

(A)

A) Seizure Duration vs. HbO Response Full-Width-at-Half-Maximum (FWHM)



B) Seizure Duration vs. HbO Response Area-Under-Curve (AUC)

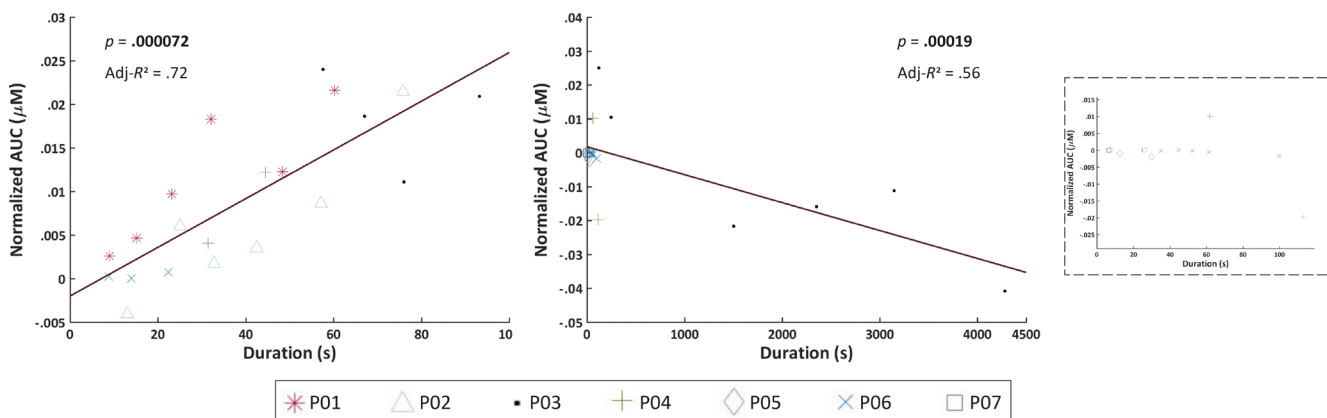


FIGURE 3 Group analysis. Correlation of seizure duration with (A) bin oxyhemoglobin concentration (HbO) response duration (FWHM of HbO increase) and (B) bin HbO response intensity (normalized AUC). Left panel: Shorter-duration seizures; right panel: Longer-duration seizures.

3.5 | Systemic physiological monitoring and laboratory results

Following seizure onset, mild but significant changes in MABP and HR occurred in four (57%) and two (29%) patients, respectively (Figure S8A,B). No significant SpO_2 changes were observed during seizures in any of the patients (Figure S8C). Sedation levels, semi-continuous systemic, and laboratory monitoring did not reveal any significant desaturation, anemia, acidosis, hyper/hyponatremia, or significant differences between patients (Table S4, Table S5 and Table S6).

3.6 | MRI changes and outcome

Pre-ictal MRI was performed in four patients, revealing findings such as leukoaraiosis, multiple siderosis foci, encephalomalacia, and diffuse cortical atrophy. Peri-ictal MRI was obtained in four patients, demonstrating increased diffusion-weighted imaging (DWI) and decreased

apparent diffusion coefficient (ADC) in 75% of cases, along with increased T2/fluid-attenuated inversion-recovery (FLAIR) signal in all patients (100%). MRI findings and outcomes for each patient are summarized in Data S1 and Table S7. De novo MRI changes were observed in all of the four Patients (P03, P05, P06, and P07) who had peri-ictal MRI, with only one exhibiting reversible changes (P07).

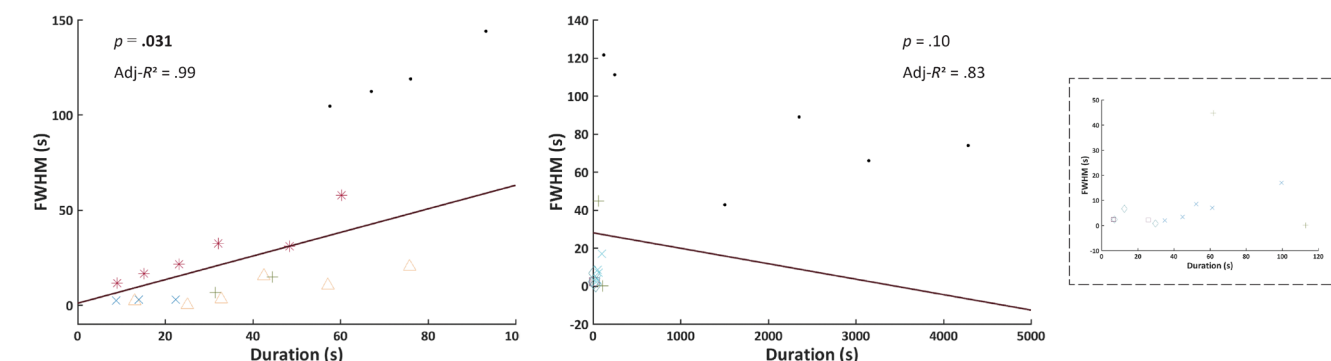
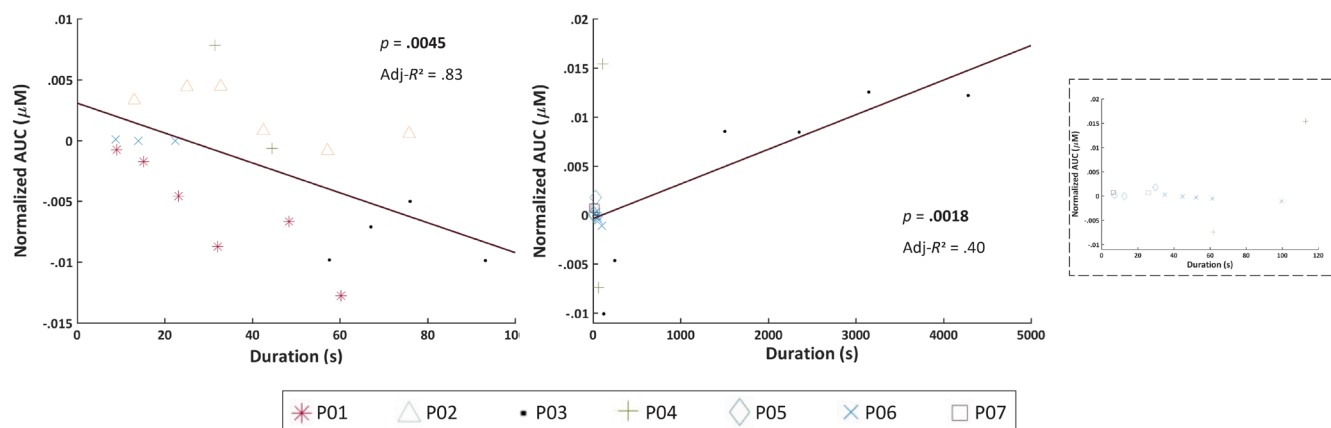
Three patients died and four patients showed improvements in their Glasgow Coma Scale (GCS) scores prior to discharge. The ICU length of stay ranged from 8 to 66 days.

4 | DISCUSSION

4.1 | Summary of findings

This study reports relatively large-area electrophysiological and hemodynamic brain activity, along with systemic physiological changes during ESE in critically ill adult patients using long-term multimodal vEEG-fNIRS monitoring in the ICU. Overall, recurrent shorter electrographic seizures were more likely associated with a sustained

(B)

A) Seizure Duration vs. HbR Response Full-Width-at-Half-Maximum (FWHM)**B) Seizure Duration vs. HbR Response Area-Under-Curve (AUC)****FIGURE 3** (Continued)

increase in HbO, HbT, and HbD and a decrease in HbR. These changes contrasted with recurrent longer electrographic seizures, which were more frequently associated with a second phase of HbR increase, whereas the other hemoglobin biomarkers decreased. These cerebral hemodynamic changes could not be attributed to systemic hemodynamic changes, as evidenced by the lack of general significance in MAPB, HR, and SpO_2 changes. These observations may suggest that NVC mechanisms can adequately compensate for oxygen consumption during shorter seizures in a patient but appear insufficient during longer seizures.

4.2 | Cortical oxygen dynamics during recurring short and prolonged electrographic seizures

Previous animal and human studies using various neuromonitoring (e.g., oxygen-sensing probes, intrinsic optical imaging) and functional neuroimaging techniques (e.g., single-photon emission computed tomography [SPECT], positron emission tomography [PET])

have shown that the heightened metabolic demand and oxygen consumption associated with self-limiting (i.e., non-recurring, non-prolonged) seizures, including electrographic seizures, lead to an overall increase in the cerebral blood flow (CBF) intensive care unit and brain oxygen levels owing to a relatively well-preserved NVC mechanism.^{13,36} In contrast, fewer studies have utilized high temporal resolution neuroimaging methods to investigate brain hemodynamics during ESE, despite in vivo signs of metabolic impairment³⁷ and in vitro evidence of blood-brain barrier dysfunction following recurrent and/or prolonged seizures.³⁸

The most significant finding of our study was the influence of seizure duration in individual patients on the associated hemodynamic responses. Although an expected cortical hemodynamic response (i.e., decrease in HbR, and increases in HbO, CBV, and cerebral oxygenation) was associated with recurrent *shorter* duration seizures, *prolonged* seizures were more likely to exhibit a second phase of opposite hemodynamic response characterized by an HbR increase as well as decreases in HbO, CBV, and cerebral oxygenation, suggesting potential brain hypoxia.

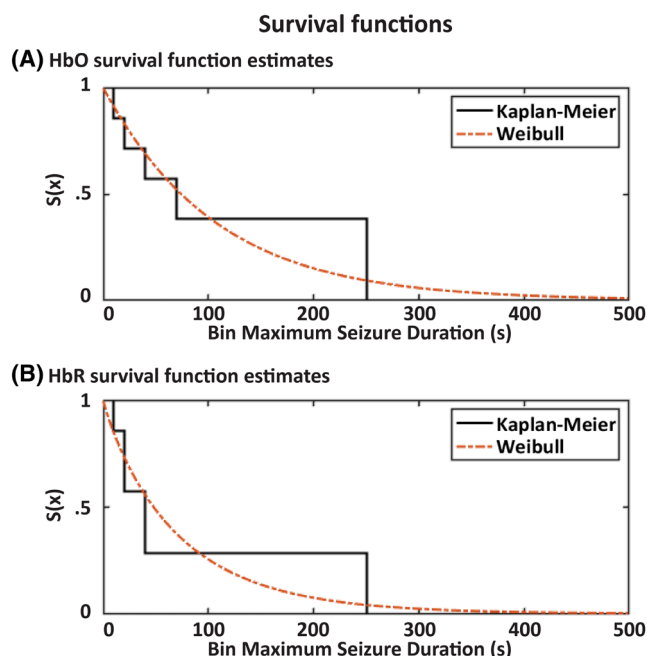


FIGURE 4 Survival functions using the Kaplan-Meier estimates and the Weibull model to predict the probability of HRFs “surviving” with uniphasic HbO increase (A) and HbR decrease (B).

Our findings align with previous experimental studies on animal models.^{39,40} In a recent study, an increase in partial brain tissue oxygenation was reported in sheep during relatively short recurring electrographic seizures lasting between 17.5 s and 59.6 s (average duration = 36.5 s).¹³ Another study focusing on spontaneous ictal episodes in anesthetized rats⁴¹ highlighted the contrast in brain hemodynamics (i.e., a decrease vs an increase in CBF and brain oxygenation) between short-duration bursts and long-duration seizures,⁴¹ although no clear definition was provided for the duration threshold.

In humans, multimodal invasive brain monitoring during ESE was performed in patients with traumatic brain injury¹¹ and subarachnoid hemorrhage (SAH).^{12,42,43} For example, a biphasic hemodynamic response characterized by a brief rise in brain tissue oxygenation ($PbtO_2$) followed by a pronounced and persistent drop in brain oxygenation was observed in 27 SAH patients with prolonged electrographic seizures (>10 min).¹² Non-invasive optical neuromonitoring studies in neonates during ESE revealed a similar impact of seizure duration on brain hemodynamics.^{32,44,45} Non-invasive optical neuromonitoring studies performed in neonates with only short-lasting seizures without SE (i.e., not recurrent) reported a monotonic increase in brain hemodynamics.⁴⁶ On the other hand, Alfonso et al. captured regional oxygen saturation

(rSO_2) changes during seven electrographic seizures in a 3-week-old newborn with tuberous sclerosis complex, and found a decrease in rSO_2 during (or shortly after) seizures that lasted more than 100 s, contrasting with seizures <63 s, which exhibited an rSO_2 increase.⁴⁴ Similarly, our previous fNIRS study in adult patients with drug-resistant epilepsy showed dichotomous hemodynamic responses, with isolated focal electroclinical seizures lasting 1–2 min, typically displaying (after an initial decrease in HbR) a relative increase in HbR as seizures progressed in time, as opposed to seizures lasting less than a minute.¹⁵

Overall, our findings, along with previous work, suggest that normal or partially intact NVC mechanisms are present during recurring short-duration seizures, as indicated by the “positive” uniphasic response or the initial ‘positive’ phase of the biphasic response. During longer seizures, the partially preserved NVC may persist until a duration threshold is reached, beyond which NVC may become disrupted, potentially leading to tissue hypoxia and brain injury. This form of injury is often reflected in peri-ictal MRI changes, as observed in three patients (75%), suggesting that longer seizures may pose a higher risk of developing peri-ictal MRI abnormalities.^{41,42}

4.3 | Potential of continuous vEEG-fNIRS monitoring of critical care seizures

Although this study observed an association between seizure duration and brain hemodynamic changes, we also identified significant individual variability in the critical duration threshold of seizures exhibiting biphasic vs uniphasic changes. For example, the ictal duration threshold ranged from 10 to 20 s in Patients P05 and P07 to 200–300 s in P03, whereas previous studies have suggested a broader duration cutoff window between 60 s and 10 min.^{12,15,44} This variability underscores the importance of conducting patient-specific monitoring and assessment, favoring (1) continuous EEG monitoring as opposed to discontinuous or routine EEG recordings in the management of ESE, and (2) the complement of a modality capable of measuring brain metabolism and/or hemodynamics with continuous EEG, such as fNIRS.

In contrast to invasive neuromonitoring^{11,12,42,43} and conventional, non-portable neuroimaging modalities,^{16,18–20,32,44,45} our study demonstrated that fNIRS offers a safe and flexible approach to monitor brain metabolism and hemodynamics during both electroclinical and electrographic seizures at the bedside and over a relatively large portion of the cerebral cortex. Moreover, fNIRS can easily be combined with vEEG, enabling long-term, real-time neurovascular monitoring that may

provide additional insights into the peri-ictal changes detected via other imaging modalities (e.g., MRI) in patients with ESE. As technological and methodological advancements continue to enhance vEEG-fNIRS integration, this modality holds promise for broader application in critical care settings. It could pave the way for outcome studies and aid in establishing seizure duration thresholds that could guide individualized clinical management of patients with SE.⁴⁷

4.4 | Limitations

This study was conducted and reported in accordance with best practices for fNIRS publications⁴⁸; however, several limitations may remain. First, although this study includes more patients and seizures than any previously published work, it still represents a small sample study (seven patients analyzed) with respect to the critically ill and SE population. Specifically, the 11 seizures longer than 1000s came from a single patient (Patient P05). Therefore, the estimation of the correlation and the probability of response directionality of seizures might be biased and should be carefully interpreted. The actual probability or seizure duration threshold for normal or disrupted NVC may vary in practice, and different thresholds might exist for different patients or SE types. Second, significant heterogeneity exists in our study population regarding age, sex, anatomic differences, type of brain injury, comorbidities, and treatment procedures, which warrant further adjustments for confounding factors in future studies. Third, the extraction of a representative HRF across all measured brain regions using PCA did not account for region-specific changes or the influence of seizures on different regions. Future studies should consider more sophisticated modeling approaches, such as dynamic causal modeling, to capture these region-specific dynamics and better understand the network-level effects of seizures. Fourth, although the current study identified correlations between seizure duration and associated hemodynamic profiles, it should also be noted that other seizure characteristics, such as seizure load (number of seizures), inter-seizure interval, and frequency, may also significantly influence seizure-related brain hemodynamic changes. These factors should be further explored in future research. Fifth, there were no seizure-free “controls” in our analysis. These differences can potentially impact brain hemodynamic signals. For example, anesthetics can influence neuronal metabolism. However, their influence on NVC and brain perfusion remains unclear.⁴⁹ Sixth, this study was based on a bin approach that applied averaging to grouped hemodynamic responses of multiple seizures within a certain range of durations

(step size = 10s). This reduced the temporal resolution of our study to investigate the effect of seizure duration on the brain response. Seventh, although the choice of using a linear model and short-separation regression to filter out systemic physiological interferences (as applied in this study) is essential,⁴⁸ this method was validated primarily in short fNIRS recordings (e.g., 10 min)^{16,34} and its effectiveness has not been evaluated in data sets with the lengths comparable to those in our study (i.e., >6 h or even several days of continuous recording). Eighth, brain temperature, metabolism, cerebral blood flow, and intracranial pressure^{11,12,42,43} were not directly quantified in this study. Ninth, some changes in MABP and HR during seizures were noted in some patients. Cardiovascular changes are known to potentially influence brain hemodynamics and, consequently, seizure-induced cortical oxygenation changes.⁴⁵ However, we believe that the changes observed in our population are unlikely to have a significant influence on the direction of the hemodynamic response function for the following reasons: (a) changes observed in our population were closer to values commonly seen during cognitive tasks in healthy individuals (i.e., ≈ 2 to 5 mmHg),⁵⁰ and far less than what has been reported in neonates (range Δ MABP: -3 to 4 mmHg vs 8–17 mmHg)⁴⁵; (b) the employed short-separation regression approach has been shown to be effective in removing global hemodynamic variations from the measured brain signals.⁴⁸ Finally, although fNIRS offers several advantages for bedside monitoring in critically ill patients, there are important limitations to consider. First, its penetration depth is limited, restricting measurements to cortical regions and limiting access to deep brain structures,²⁹ which are frequently implicated in seizures and critical for comprehensive assessment of epileptiform activities. In the ICU setting, this can be a disadvantage compared to other imaging modalities like invasive probes, which provide higher depth resolution. In addition, the diffuse nature of near-infrared light as it travels through biological tissues results in lower spatial resolution, making it challenging to localize seizure-related activity precisely.²⁷ fNIRS signals can also be influenced by absorption and scattering in extracerebral tissues (e.g., scalp, skull), further complicating data interpretation.²⁸ This is especially relevant where factors such as skin pigmentation, hair density, skin edema, or cranial dressings may affect signal quality and reliability, potentially limiting the accuracy of monitoring seizures in these patients.^{29–31}

5 | CONCLUSION

In this study, brain electrophysiology and large-scale cortical hemodynamics were monitored concurrently

with systemic cardiovascular physiology in critically ill patients during ESE using vEEG-fNIRS. Our findings for individual patients were twofold: (1) shorter-duration recurrent seizures were generally associated with increased cortical hemodynamic and oxygenation responses, suggesting preserved normal NVC mechanisms; (2) recurrent seizures with longer duration were more likely to induce a subsequent decrease in cerebral hemodynamic and oxygenation changes, potentially indicating disrupted NVC and insufficient oxygen supply. Further studies are required to determine if such seizure-induced hypoxic states contribute to neuronal damage associated with ESE.

AUTHOR CONTRIBUTIONS

Ali Kassab: Acquisition and analysis of data; data curation; drafting the manuscript and figures. **Dénahin H. Toffa:** Analysis of data; writing-review. **Manon Robert:** Acquisition of the data. **Michaël Chassé:** Funding acquisition; writing-review. **Frédéric Lesage:** Conception and design of the study; funding acquisition; writing-review. **Ke Peng:** Funding acquisition, acquisition and analysis of data; data curation; writing-review. **Dang K. Nguyen:** Conception and design of the study; funding acquisition; supervision; writing-review.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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