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ORIGINAL ARTICLE

Continuous Optical Monitoring of Cerebral Hemodynamics During Head-of-Bed Manipulation in Brain-Injured Adults

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Abstract
Introduction Head-of-bed manipulation is commonly performed in the neurocritical care unit to optimize cerebral blood flow (CBF), but its effects on CBF are rarely measured. This pilot study employs a novel, non-invasive instrument combining two techniques, diffuse correlation spectroscopy (DCS) for measurement of CBF and near-infrared spectroscopy (NIRS) for measurement of cerebral oxy- and deoxy-hemoglobin concentrations, to monitor patients during head-of-bed lowering.

Methods Ten brain-injured patients and ten control subjects were monitored continuously with DCS and NIRS while the head-of-bed was positioned first at 30° and then at 0°. Relative CBF (rCBF) and concurrent changes in oxy- (ΔHbO_2), deoxy- (ΔHb), and total-hemoglobin concentrations (ΔTHC) from left/right frontal cortices were monitored for 5 min at each position. Patient and control response differences were assessed.

Results rCBF, ΔHbO_2, and ΔTHC responses to head lowering differed significantly between brain-injured patients and healthy controls ($P < 0.02$). For patients, rCBF changes were heterogeneous, with no net change observed in the group average (0.3 ± 28.2 %, $P = 0.938$). rCBF increased in controls (18.6 ± 9.4 %, $P < 0.001$). ΔHbO_2, ΔHb, and ΔTHC increased with head lowering in both groups, but to a larger degree in brain-injured patients. rCBF correlated moderately with changes in cerebral perfusion pressure ($R = 0.40$, $P < 0.001$), but not intracranial pressure.

Conclusion DCS/NIRS detected differences in CBF and oxygenation responses of brain-injured patients versus controls during head-of-bed manipulation. This pilot study supports the feasibility of continuous bedside measurement of cerebrovascular hemodynamics with DCS/NIRS and provides the rationale for further investigation in larger cohorts.

Keywords Diffuse correlation spectroscopy · Near-infrared spectroscopy · Diffuse optical spectroscopy · Head-of-bed · Cerebral blood flow · Neurocritical care · Cerebral hemodynamics

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Introduction

It is a common clinical practice in the neurocritical care unit to raise a patient's head-of-bed angle to 30° as a

strategy for lowering intracranial pressure (ICP) and increasing cerebral perfusion [1, 2]. The efficacy of head-of-bed manipulation for improving cerebral blood flow (CBF), however, is not well-understood. Reduction of ICP does not always lead to an increase in cerebral perfusion pressure (CPP) [1, 3–6], and even when CPP increases with head elevation, the link between CPP and CBF can depend on head-of-bed-position [5] and cerebrovascular resistance [7]. This complex relationship between ICP, CPP, and CBF may explain why no single optimal CPP has been defined for the severely brain-injured patient [8], and why ICP- and CPP-targeted interventions sometimes fail to improve outcome [9–11]. Since recovery of neurological function may depend more directly on tissue perfusion [12] than on ICP or CPP, it is desirable to develop new tools that directly measure CBF in the neurocritical care unit.

The current lack of understanding about the relationship between CPP and CBF is largely attributable to the absence of an effective and convenient method for measuring CBF at the bedside. Conventional imaging techniques capable of measuring perfusion such as computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI), are mainly suited for imaging in prone or supine positions, do not offer the possibility for continuous measurement of CBF, and are often unfeasible for single time-point perfusion measurements in clinically unstable patients. Similarly, current "bedside" techniques for monitoring CBF, which include transcranial Doppler (TCD) ultrasonography [13], thermal diffusion [14], and laser Doppler flowmetry [15], have significant limitations. TCD ultrasonography measures large vessel flow velocities that do not necessarily reflect microvascular perfusion [16]. TCD velocities may be used to calculate a pulsatility index reflecting more distal vasculature, but this measure is still considered only indirectly related to CBF [17]. Although thermal diffusion and laser Doppler flowmetry monitor microvascular perfusion, routine use of these techniques is limited by their invasive nature.

Diffuse correlation spectroscopy (DCS) is a novel optical technique for probing continuous changes in regional microvascular blood flow. DCS utilizes non-invasive near-infrared light sources and detectors to track rapid temporal fluctuations of light intensity in brain tissue that arise when light is scattered by moving red blood cells. The method derives a blood flow index (BFI) from these intensity fluctuations whose trends have been shown to correlate well with blood flow in both animals [18–24] and humans [25–30]. This BFI is readily used to calculate relative CBF (rCBF), i.e., blood flow variation relative to a baseline measurement. Validation of DCS-measured rCBF in adult patients with severe brain injury has been carried out with concurrent xenon-enhanced CT during induced manipulations of blood pressure and arterial CO_2 [25]. In addition, CBF responses during head-of-bed manipulation have been studied with DCS in both healthy [31] and ischemic stroke populations [32, 33]. In these early studies, DCS was combined with a more established optical technique called near-infrared spectroscopy (NIRS), also known as diffuse optical spectroscopy. NIRS uses wavelength-dependent light attenuation to measure concentration changes in oxyhemoglobin (ΔHbO_2), deoxyhemoglobin (ΔHb), and total hemoglobin (ΔTHC) concentrations. Our hybrid optical instrument employs both techniques concurrently.

The primary aim of this pilot study is to use DCS/NIRS to measure cerebral hemodynamic changes in severely brain-injured patients during a simple clinical intervention: head-of-bed lowering. Importantly, this patient group is different from those in the previous clinical studies of head-of-bed positioning described above. We compare postural CBF responses in brain-injured patients to those of healthy subjects, and we assess posture-induced correlations of DCS-measured rCBF and NIRS-measured ΔHbO_2, ΔHb, and ΔTHC versus other measured parameters such as ICP and CPP. We hypothesized that continuous optical monitoring during head-of-bed lowering would reveal differences in postural rCBF in the brain-injured patients versus the controls.

Methods

All subjects in the brain-injured cohort were adults ($\geq$18 years) receiving care in the neurointensive care unit at the Hospital of the University of Pennsylvania for subarachnoid hemorrhage or traumatic brain injury. Each study was performed at the patient bedside using protocols approved by the Institutional Review Board at the University of Pennsylvania. Written consent was provided by the subject (if able) or by a surrogate.

Comparison data in healthy controls were obtained from a previous study that included optical monitoring of head-of-bed positioning on 60 healthy volunteers [31]. Adult subjects were included in the healthy cohort if they had no history of hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, congestive heart failure, coronary artery disease, previous myocardial infarction, prior stroke or transient ischemic attack, carotid artery disease, smoking within the past 5 years, pulmonary disease, renal disease, or recent administration of vasoactive medications. Subjects were chosen to be gender-matched, since we previously found gender to have more of an effect than age on frontal cortical hemodynamics during posture change [31]. Written informed consent was provided by all control subjects, and the controls were studied at the Hospital of the University of Pennsylvania with protocols approved by the Institutional Review Board.

Optical Instrumentation

The optical instrument was a custom-built, hybrid device containing both DCS and NIRS modules. The DCS module uses two 785 nm lasers, two 4-channel avalanche photodiode arrays, and an 8-channel autocorrelator board to compute the temporal intensity autocorrelation functions. The NIRS module employs three laser sources, as well as two photomultiplier tubes for light detection. The data acquisition rate was one frame of DCS + NIRS every 7 s. Both modalities employ optical fibers that affix to a black foam probe pad with source-detector separations of 2.5 cm. This separation distance insures that light can penetrate to depths below the tissue surface of approximately 1.0–1.5 cm, a depth sufficient for light to reach the surface region of the adult human cortex [25, 34]. Further theoretical and technical details about diffuse optics can be found in recent reviews [35–37], and complete details about DCS and NIRS analyses have been previously published [38, 39].

Optical Protocol During Head-of-Bed Manipulation

Most often, two optical probes were affixed to both sides of the forehead equidistant from the midline, in order to measure hemodynamic changes in the frontal poles of the left and right hemispheres. Note, two of the early patients provided unilateral data only as a result of restrictions in optical probe size; later versions were more compact, and thus bilateral probes were used. For the unilateral measurements, a probe was placed on either the left or the right side of the forehead.

During the measurements, a black opaque cloth was placed over the probes to shield them from ambient light. Once adequate optical signal was confirmed, continuous measurements of rCBF, ΔHbO_2, ΔHb, and ΔTHC were made. The subject was initially positioned at a baseline head-of-bed elevation of 30°, wherein he/she rested quietly and still for 5 min. The head-of-bed was then lowered to the supine position (0°) over a period of 30 s, and the subject rested there for another 5 min. For the brain-injured patients, this intervention was repeated consecutively up to three times, and in order to examine longitudinal changes in frontal lobe hemodynamic response, for up to three measurement episodes usually on consecutive days. Data from these multiple days were averaged. The healthy subjects were monitored on a single day, all bilaterally, with the 30°–0° protocol performed once.

Monitoring of ICP, CPP, and $PbtO_2$ in Brain-Injured Patients

Cerebral and systemic physiological parameters were monitored as part of routine care for patients in the neurocritical care unit. ICP was monitored either by an external ventricular device (EVD) or using a fiberoptic intraparenchymal catheter (Camino-MPM1; Integra LifeSciences, Plainsboro, NJ). ICP transducers were zeroed at the level of the tragus, and in the case of ICP measurements via an EVD, the EVD was clamped at the time of measurement. CPP was then calculated as the difference between mean arterial pressure (MAP) and ICP. Prior to study enrollment, select patients underwent placement of a continuous brain tissue oxygen partial pressure ($PbtO_2$) monitor (Licox® CMP; Integra LifeSciences, Plainsboro, NJ) at the discretion of the treating clinician.

Monitoring of MAP and Heart Rate (HR) in Brain-Injured and Control Subjects

In brain-injured subjects, MAP and HR were measured continuously via a radial arterial-line that was zeroed at the phlebostatic axis throughout the study. All hemodynamic measurements were performed with the arterial-line transducer at the level of the heart. In healthy controls, continuous measurements of MAP and HR were monitored using a non-invasive plethysmographic device (FinaPres Medical Systems, Finometer Pro Model 1; Amsterdam, The Netherlands) whose probe was secured to each subject's right third finger. An adjustable armrest was used to keep the subject's right third finger at the level of the heart at each head-of-bed position, and a continuous height-correction factor was applied to the MAP measurements to account for any inadvertent hand movements. Non-invasive measurements of MAP and HR by the FinaPres device have been shown to correlate with invasive intra-arterial measurements of these systemic hemodynamic parameters [40].

Statistical Analysis

Mean changes in each cerebral and systemic physiological parameter due to head lowering were computed from continuous time-series data by taking the average ($< >$) during the 5-min time period ($t_{30°}$) at head-of-bed 30° as baseline for comparison against the 5-min supine time period ($t_{0°}$). Periods were defined as those data measured after the optical signal had stabilized, with all data during the head-of-bed transition and all motion artifacts excluded from the analysis. Differential values for NIRS data (ΔHbO_2, ΔHb, ΔTHC) as well as for systemic vitals (HR, MAP, ICP, etc.) were defined as

$$\Delta Y = <Y(t_{0°})> - <Y(t_{30°})>,$$

with Y representing the parameter of interest. For DCS data, a percentage change from baseline was employed to compute rCBF:

$$rCBF = [<rCBF(t_{0°})> - <rCBF(t_{30°})>]/<rCBF(t_{30°})>.$$

A two-tailed Student's t test was used to determine whether the observed changes were different from zero,

and a one-way ANOVA was used to test whether the cerebral hemodynamic responses of brain-injured patients differed from those of healthy subjects. When both left and right frontal pole data were available, a Pearson's coefficient was used to assess correlations between bilateral measurements of rCBF, ΔHbO_2, ΔHb, ΔTHC. A Pearson's coefficient was also used to assess correlations between rCBF, CPP, and ICP. P values less than 0.05 were considered to indicate statistical significance.

Results

Patient and Control Characteristics

Table 1 summarizes all clinical and study data for the brain-injured cohort. A total of ten patients (seven males/three females) were included in the study, with a mean age of 46 years (range, 18–62 years). Five patients were admitted for subarachnoid hemorrhage (SAH) due to ruptured aneurysm, four for traumatic brain injury (TBI), and one for an arteriovenous malformation (AVM)-associated intracerebral hemorrhage (ICH) and SAH. For the TBI patients, the median admission Glasgow Coma Scale (GCS) [41] score was 9 (range, 3–15), while the median study day GCS score was 5 (range, 3–7). For the aneurysmal SAH patients, the Hunt Hess classification grade [42] was 1 ($n = 2$), 2 ($n = 1$), 3 ($n = 1$), or 4 ($n = 1$). The timing of optical data acquisition for the patient cohort ranged from post-injury day 2 to 12 and the GCS score for patients on the day of data acquisition ranged from 3 to 11. One patient was studied on 3 separate occasions, five patients on 2 occasions, and four patients were studied once. Data from all episodes of measurements were included in analysis. ICP was monitored for all patients (seven via EVD, three via intraparenchymal catheter), and eight patients had a brain tissue oxygen monitor in place during the study. The mean age for the ten healthy controls was 39 years (range, 24–55 years; seven males/three females).

Physiologic Responses to Head-of-Bed Manipulation

For the brain-injured cohort, ICP changed significantly ($P = 0.002$) as the head-of-bed was lowered from 30° (11.2 ± 4.3 mmHg) to 0° (16.8 ± 9.5 mmHg), but CPP, $PbtO_2$, MAP, and HR did not. Measurements of ICP, CPP, $PbtO_2$, MAP, and HR in the brain-injured cohort at each head-of-bed position are summarized in Table 2. None of the systemic vital signs, including HR and MAP, changed significantly for the healthy controls (Table 3).

The population-averaged DCS and NIRS results for the healthy and brain-injured cohorts are reported in Table 4. Positional changes in rCBF (18.6 ± 9.4 %, $P < 0.001$), ΔHbO_2 (2.3 ± 1.8 μM, $P < 0.001$), ΔHb (0.5 ± 0.7 μM, $P = 0.005$), and ΔTHC (2.8 ± 2.0 μM, $P < 0.001$) all reached significance for the healthy controls, with head-of-bed lowering causing an increase in each physiological parameter. ΔHbO_2, ΔHb, and ΔTHC increased for the brain-injured group as well ($P < 0.001$); however, no net change in rCBF was observed, and there was a large inter-subject variance (0.3 ± 28.2 %, $P = 0.938$). Figure 1 shows box plots comparing postural changes in rCBF and ΔTHC between the two groups.

All optical parameters except for ΔHb showed a significantly different postural response between the patient and healthy groups ($P < 0.02$). The most marked difference was seen for CBF responses ($P = 0.006$). Correlation analysis of left versus right hemisphere responses to postural change also revealed a difference between the cohorts. Specifically, left and right frontal cortex measurements showed strong correlation in healthy subjects for rCBF ($R = 0.94$, $P < 0.001$), ΔHbO_2 ($R = 0.85$, $P = 0.002$), and ΔTHC ($R = 0.75$, $P = 0.013$). In contrast, optical measurements in the left and right frontal lobe cortices did not correlate significantly for the brain-injured cohort (rCBF: $R = 0.27$, $P = 0.146$; ΔHbO_2: $R = 0.22$, $P = 0.249$; ΔHb: $R = -0.04$, $P = 0.817$; ΔTHC: $R = 0.09$, $P = 0.639$).

We also observed a moderate but significant correlation ($R = 0.40$, $P < 0.001$) between changes in CPP and rCBF, but no correlation with rCBF was seen for ICP ($R = -0.15$, $P = 0.213$). Also, $PbtO_2$ did not correlate with any NIRS parameters. While the magnitude (i.e., absolute value, disregarding sign) of rCBF change was found to have a negative association with patient GCS score on the day studied ($R = -0.42$, $P < 0.001$), this was not the case for the NIRS parameters (ΔHbO_2: $R = -0.19$, $P = 0.118$; ΔHb: $R = -0.01$, $P = 0.907$; ΔTHC: $R = -0.18$, $P = 0.152$).

We present one case example of a 40-year-old male SAH patient (No. 4) studied over three consecutive days. Cerebral angiography identified a ruptured aneurysm in his anterior communicating artery that was clipped on post-bleed day 1. Figure 2 shows time-series results, averaged over three head-of-bed lowering events on each day, for three consecutive days (days 8, 9, and 10). The patient's GCS was 7 on days 8 and 9, and 3 on day 10. On day 7, the patient had moderate right middle cerebral artery (MCA) and basilar artery vasospasm, as well as mild left MCA vasospasm. On days 8 and 9, the patient had moderate right MCA vasospasm and mild-to-moderate bilateral carotid siphon vasospasm. On day 9, the patient also had mild bilateral posterior cerebral artery (PCA) vasospasm. rCBF (Fig. 2a) in the left hemisphere decreased with position change to supine on all 3 days, while rCBF in the right hemisphere did not change on days 8 and 9, and then increased on day 10. Left frontal ΔTHC (Fig. 2b), on the other hand, showed no change or even a decrease on days 8 and 9, but then sharply increased on day 10. These THC findings are in contrast to the right frontal cortex, in which ΔTHC

Table 1 Patient clinical characteristics

No.	Gender	Age	Injury	SAH severity	Study day(s)	Admission GCS	Study GCS	Imaging findings
1	M	28	ICH + SAH	N/A	2, 3	7	7, 8	Arteriovenous malformation-associated left temporal ICH with SAH
2	M	58	TBI	N/A	11, 13	15	3, 5	Acute traumatic SAH, left subdural hemorrhage, and hemorrhagic contusion
3	F	52	SAH	HH2/F3 + 4	12, 13	14	10, 11	Left PCA aneurysm, diffuse vasospasm
4	M	40	SAH	HH3/F4	8, 9, 10	7	7, 7, 3	ACOMM aneurysm, intraventricular hemorrhage, left MCA/ACA vasospasm
5	M	60	TBI	N/A	2, 3	3	3, 4	Bilateral frontal and temporal contusions, multiple frontoparietal parenchymal hemorrhages
6	M	51	TBI	N/A	4, 6	14	6, 7	Contusions in bilateral frontal and left temporal lobes, traumatic SAH, parenchymal hemorrhage in frontal lobes
7	F	62	SAH	HH1/F3	9	15	8	Right MCA aneurysm, bilateral ACA and right MCA vasospasm
8	M	18	TBI	N/A	2	3	7	SAH along right cerebral convexity, subdural hemorrhages along bilateral frontal convexities
9	M	46	SAH	HH1/F3 + 4	9	14	6	ACA and left anterior choroidal artery aneurysms, diffuse vasospasm (right > left hemisphere)
10	F	44	SAH	HH4/F3 + 4	8	4	10	Posterior inferior cerebellar artery aneurysm, vasospasm of distal vertebral arteries bilaterally

ICH, intracerebral hemorrhage; *TBI*, traumatic brain injury; *SAH*, subarachnoid hemorrhage; *GCS*, Glasgow Coma Score; *AVM*, arteriovenous malformation; *HH*, Hunt-Hess Score; *F*, Fisher Grade; *N/A*, not applicable; *MCA*, middle cerebral artery; *ACA*, anterior cerebral artery; *PCA*, posterior cerebral artery; *ACOMM*, anterior communicating artery

Table 2 Effects of head lowering on cerebral and systemic vitals in brain-injured cohort

Parameter	Head-of-bed position		Change from 30° to 0°	*P*-value
	30°	0°		
ICP, mmHg	11.2 ± 4.3 (3.8–19.5)	16.8 ± 9.5 (3.3–49.7)	5.6 ± 8.1 (−8.1 to 30.2)	**0.002**
CPP, mmHg	95.1 ± 22.8 (59.9–136.6)	88.2 ± 25.5 (42.0–137.8)	−6.9 ± 12.9 (−44.5 to 23.3)	0.218
$PbtO_2$, mmHg	47.5 ± 35.0 (8.5–196.5)	37.1 ± 19.8 (19.4–101.6)	−10.4 ± 18.0 (−94.9 to 11.5)	0.142
MAP, mmHg	106.7 ± 23.4 (67.8–151.0)	105.0 ± 23.3 (64.0–144.3)	−1.8 ± 8.3 (−15.5 to 26.9)	0.738
HR, bpm	84.3 ± 19.5 (54.2–118.4)	85.9 ± 18.7 (56.0–121.0)	1.6 ± 4.2 (−6.0 to 15.9)	0.712

Values listed as mean ± SD, with range in parentheses

P-values from one-way ANOVA test

Significant *P*-value is highlighted in bold

Table 3 Effects of head lowering on systemic vitals in healthy cohort

Parameter	Head-of-bed position		Change from 30° to 0°	*P*-value
	30°	0°		
SYS, mmHg	137.4 ± 11.4 (117.8–157.3)	134.6 ± 10.5 (113.3–144.9)	−2.8 ± 8.0 (−13.7 to 13.4)	0.581
DIA, mmHg	78.9 ± 9.9 (63.5–93.7)	75.8 ± 10.0 (58.5–86.7)	−3.0 ± 6.8 (−14.7 to 11.1)	0.505
MAP, mmHg	102.4 ± 9.8 (88.5–119.3)	99.4 ± 10.4 (83.9–112.2)	−3.0 ± 7.0 (−13.9 to 11.1)	0.513
HR, bpm	68.8 ± 9.6 (53.3–82.7)	68.5 ± 10.6 (50.9–82.2)	−0.2 ± 3.1 (−4.1 to 7.6)	0.957

Values listed as mean ± SD, with range in parentheses

P-values from one-way ANOVA test

Table 4 Effects of head lowering on rCBF, ΔHbO_2, ΔHb, and ΔTHC in brain-injured versus healthy cohorts

Parameter	Brain-injured ($n = 10$)	Healthy ($n = 10$)	*P*-value†, brain-injured	*P*-value†, healthy	Difference b/w groups††
rCBF, %	0.3 ± 28.2 (−49.2 to 90.0)	18.6 ± 9.4 (2.1 to 34.0)	0.938	**<0.001**	**0.006**
ΔHbO_2, μM	5.0 ± 4.5 (−6.3 to 14.2)	2.3 ± 1.8 (−0.2 to 5.3)	**<0.001**	**<0.001**	**0.010**
ΔHb, μM	1.3 ± 1.8 (−3.0 to 7.1)	0.5 ± 0.7 (−0.6 to 2.1)	**<0.001**	**0.005**	0.059
ΔTHC, μM	6.3 ± 6.0 (−9.3 to 20.4)	2.8 ± 2.0 (−0.2 to 7.4)	**<0.001**	**<0.001**	**0.012**

Values listed as mean ± SD, with range in parentheses

Significant *P*-values are highlighted in bold

† *P*-values from two-tailed student's *t* test

†† *P*-values from one-way ANOVA test

increased with head-of-bed lowering on all 3 days. Figure 2c shows ICP and CPP data for this case, with an ICP increase and CPP decrease on days 8 and 9, and an ICP decrease and CPP decrease of reduced magnitude on day 10.

Discussion

In this study, we employed a novel optical methodology that combines DCS and NIRS to measure cerebral hemodynamic changes during a simple intervention for altering CPP: head-of-bed manipulation. Our findings suggest that the effect of head-of-bed lowering on microvascular rCBF differs in brain-injured patients as compared to healthy adults. Whereas frontal cortical rCBF consistently increased in healthy subjects when lowering the head-of-bed from 30° to 0°, we found significant heterogeneity in cerebral hemodynamic responses to posture change in patients with severe brain injury. In addition, we observed substantial variation in hemispheric responses to posture change in the brain-injured cohort, possibly due to the spatial heterogeneity in their disease. This intersubject and

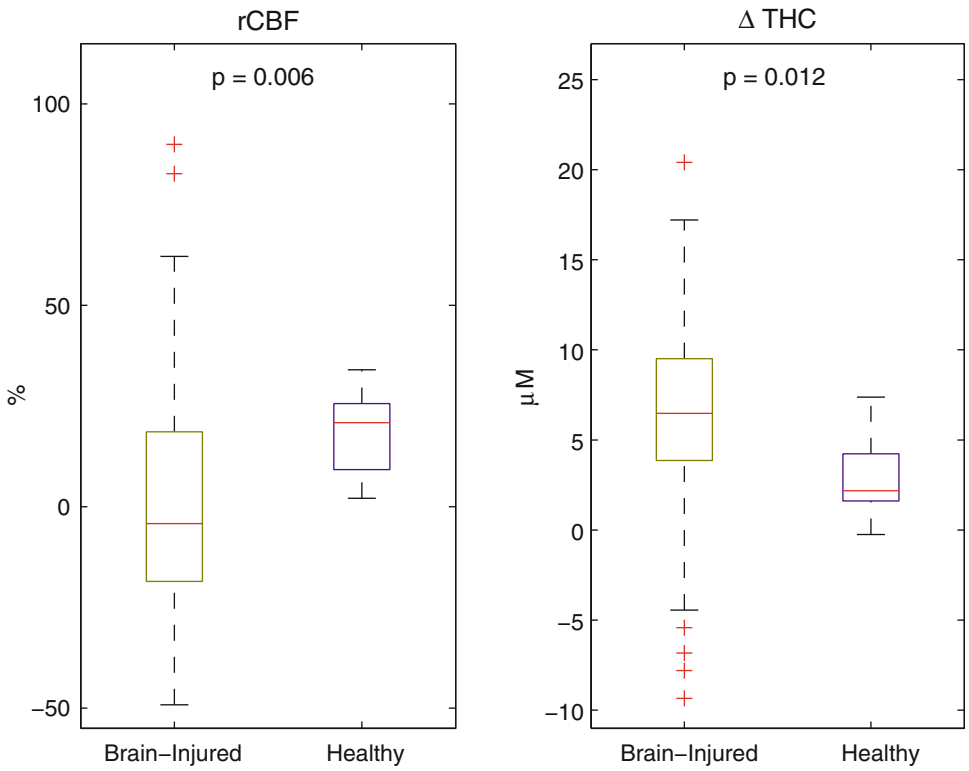

Fig. 1 Box plots showing (*left*) DCS-measured relative cerebral blood flow (rCBF) and (*right*) DOS-measured total hemoglobin concentration changes (ΔTHC) in a group of brain-injured patients versus gender-matched healthy controls during a head-of-bed lowering. *Note* the large spread of values around zero for the patient group is qualitatively different than the group response of the healthy subjects, e.g., a slight CBF increase. THC increases in both groups, with the patients' response again exhibiting significantly larger variance, and, on average, a greater magnitude

intrasubject (i.e., hemispheric) variability in rCBF responses to posture change suggests that optimization of cerebral perfusion for patients in the neurocritical care unit may require an individualized approach to CBF management. Our results provide also preliminary evidence that the DCS/NIRS hybrid device is well-suited to provide non-invasive, continuous hemodynamic monitoring that has the potential to optimize cerebral perfusion on an individualized basis.

The observed difference between positional rCBF changes in the brain-injured versus healthy cohorts is consistent with prior studies of cerebral hemodynamics that have demonstrated impaired cerebrovascular autoregulation in severely brain-injured patients [43–48]. Furthermore, the variability in frontal cortical cerebrovascular responses to posture change observed in the brain-injured cohort is consistent with similarly heterogeneous results in prior studies that examined the effect of head-of-bed position on CBF. Shenkin et al. [49] measured absolute CBF via the Kety-Schmidt N_2O technique at both 0° and 20° in six patients with elevated ICP due to brain tumors, finding that CBF was lower at 20° by an average of 30 %. These findings suggested that the head-up position was detrimental because of decreased cerebral perfusion. In contrast, Feldman et al. [6] recorded absolute CBF (also employing the Kety-Schmidt N_2O technique), CPP, and ICP in 22 head-injured patients at 0° and 30°, and found significantly lower ICP at head-of-bed 30° but no overall change in CPP and CBF. As in our study, they established that head-of-bed angle did not have a significant effect on group-averaged CBF (47.8 ± 16.9 ml/100 g/min at 30°, 48.9 ± 20.4 ml/100 g/min at 0°), and their subjects experienced heterogeneous CBF responses ranging from increased to decreased perfusion. Specifically, five patients had values of supine CBF that were 5 ml/100 g/min or more greater than their CBF at 30°, and this subgroup had significantly different changes in CBF, cerebral metabolic rate of oxygen, and cerebrovascular resistance than the other seventeen patients. Lastly, Moraine et al. [5] measured CBF with the continuous thermodilution method, CPP, and ICP in thirty-seven comatose patients at head-of-bed angles 0°, 15°, 30°, and 45°. CBF was higher at 0° (46.3 ± 4.8 ml/100 g/min) than at 30° (32.4 ± 2.8 ml/100 g/min), which constituted a relative difference of 43 %. ICP also decreased with raised head-of-bed, but again with no change in CPP. Our study thus adds to prior evidence and suggests that there may not be a single head-of-bed position that is optimal for maximizing cerebral perfusion in brain-injured subjects in the neurocritical care unit. With regard to the healthy cohort findings, several prior studies have similarly observed that CBF and cerebral blood flow velocity via transcranial Doppler increase as the head of a healthy individual is lowered [32, 50, 51].

The heterogeneous frontal cortical rCBF responses to postural changes observed in the patients in this study are also consistent with a prior DCS/NIRS study in which

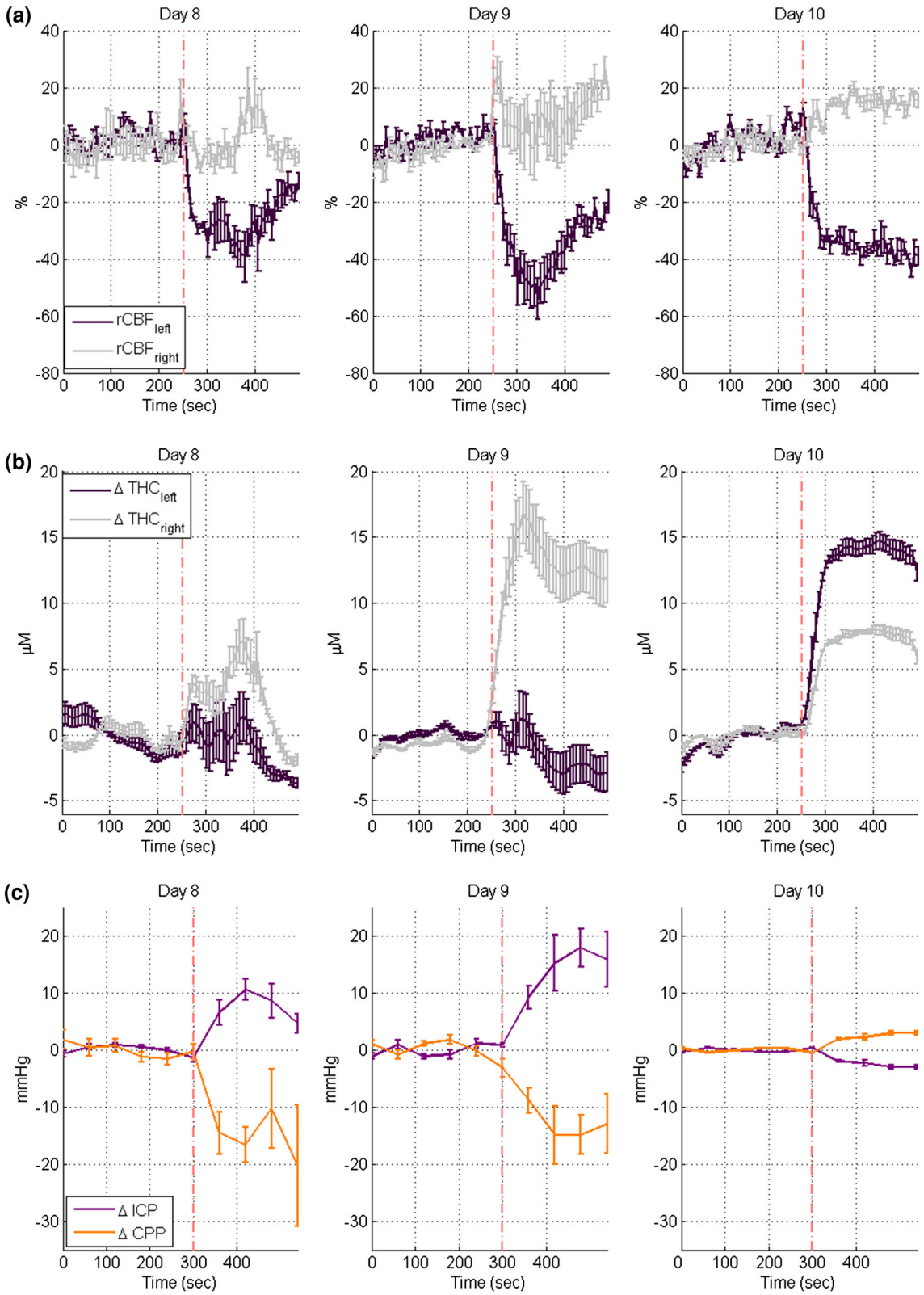

Fig. 2 Case example data over three consecutive days (8, 9, and 10 days after injury) for a 40-year-old male subarachnoid hemorrhage patient (No. 4) who suffered a ruptured aneurysm in his anterior communicating artery. The *vertical dotted line* indicates the moment at which the patient's bed was lowered from 30 degrees to flat. The Glasgow Coma Scale was 7 on days 8 and 9, and 3 on day 10. Each figure shows the averaged result of time-series data from three head lowering interventions for **a** rCBF, **b** ΔTHC, and **c** changes in ICP and CPP

patients with acute ischemic stroke were found to experience variable changes in frontal cortical rCBF during posture change [32]. In this prior study, a rCBF reduction after head-of-bed lowering occurred in four out of seventeen acute stroke patients—a "paradoxical response" for which a definitive pathophysiological mechanism could not be determined. One possible explanation for rCBF reduction after head-of-bed lowering is increased ICP, but in the present study, we did not find a significant correlation between changes in ICP and rCBF response. CPP changes, however, were moderately correlated with rCBF responses. This observation is consistent with prior studies showing that CPP-guided management may be more effective than ICP-guided management at promoting tissue perfusion, and thus improving clinical outcomes [52]. Yet the absence of a strong correlation between CPP and frontal cortical CBF underscores the difficulty in predicting CBF from CPP measurements and reinforces the need for direct monitoring of microvascular CBF to guide therapies in the neurocritical care unit. Similar to our study, Moraine et al. [5] demonstrated that the correlation between CPP and CBF is not always strong, but rather varies depending on head-of-bed position. The authors found that the slope of absolute CBF versus CPP calculated with least-squares linear regression analysis changed from 1.71 at 0° to 0.76 at 30°. Ultimately, determination of which patients might experience predictable versus unpredictable changes in microvascular CBF during head-of-bed related CPP changes could be an important factor for optimizing cerebral perfusion in individual patients.

In considering the individualized nature of rCBF responses to posture change, it is also notable that the NIRS-derived parameters for cerebral tissue oxygenation—HbO_2, Hb, and THC—did not display the heterogeneous responses seen in rCBF. Rather, HbO_2, Hb, and THC all significantly increased in the brain-injured cohort ($P < 0.001$) with head-of-bed lowering. The observed increases may be the result of passive venous pooling that increases cerebral blood volume when the head is lowered to the supine position. Because of impaired autoregulation in some patients, this increase in cerebral blood volume could contribute to an increase in ICP, and thus a decline in CBF. The fact that DCS and NIRS results differed considerably in our study again highlights the advantage of hybrid DCS/NIRS instrumentation over NIRS monitoring alone.

Spatial resolution remains a major limitation of the current DCS/NIRS approach, since measurements of rCBF, ΔHbO_2, ΔHb, and ΔTHC are limited to approximately 1 cm^3 of cerebral tissue under the optical probes. This limitation could possibly explain any deviation from previous results in the literature, since CBF measurement techniques such as those used in Moraine et al. [5] and Feldman et al. [6] measured CBF more globally. In addition, interfacing the optical probes to the patient's head can be challenging and can be hampered by hair or hair follicles; overcoming these technical barriers is an area of active research. In the present application, flow measurements were limited to near the surface of the frontal cortex due to placement of the optical probes on the forehead. However, most other bedside monitoring methods have similar limitations, and brain-injured patients often have diffuse pathophysiological processes for which such measures remain useful. Another challenge in optical monitoring of cerebral physiology is accurate localization of signal changes measured by transcranial probes, which potentially detect signals from the scalp and other intervening tissues as well as the brain. Recent findings suggest the likelihood of some scalp contamination that can be suppressed by increasing probe pressure [53].

There are several further limitations of our study. First, timing of optical data acquisition ranged from day 2 to day 13 post-injury. As a result, patients were likely in different stages of their disease processes, during which cerebrovascular autoregulatory function may vary. For example, the data from the case example spanning three consecutive days demonstrated a change in cerebral hemodynamic responses to posture change from day 9 to day 10 post-injury. These longitudinal changes in rCBF were associated with changes in GCS and postural changes in cerebral perfusion pressure. Second, our cohort included three different types of brain injury: TBI, aneurysmal SAH, and AVM with associated ICH and SAH. Even within one of these injury categories, there is large variability with regards to the severity and neuroanatomic distribution of injury. Although our sample size was too small to determine the mechanisms that cause variability in CBF responses to posture change, our preliminary observations suggest that CBF responses may differ due to severity of injury (e.g., GCS score on day of study). We found that GCS on the day of study was negatively correlated with rCBF, indicating that as consciousness was more severely altered, postural changes in CBF were more pronounced. Finally, while studying individual patients on multiple days allowed for longitudinal analyses, such measurements could introduce bias toward data from these patients who were measured on more than one occasion. Nevertheless, the heterogeneity in our methods suggests that the DCS/NIRS protocol utilized in this study may be generalizable to multiple patient populations within the neurocritical care unit, with the potential to improve patient care by providing clinicians with the capability to monitor cerebrovascular hemodynamics longitudinally at the bedside.

In conclusion, this pilot study provides preliminary evidence that continuous, non-invasive bedside monitoring DCS/NIRS can be used to detect differences in cerebral hemodynamic responses of brain-injured patients to posture change in the neurocritical care unit. These cerebrovascular responses are not easily predicted by postural

ICP and CPP changes, highlighting the potential value of direct measurement of microvascular perfusion. The observed variability in postural CBF responses also suggests that there may not be a single head-of-bed position that optimizes cerebral perfusion in all patients. Larger studies are needed to reproduce these findings, to further validate transcranial monitoring of cerebral perfusion and metabolism with diffuse optics, and to test whether bedside monitoring with DCS/NIRS can be used to optimize head-of-bed positioning for maximizing cerebral perfusion in individual patients.

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