Optical Bedside Monitoring of Cerebral Blood Flow in Acute Ischemic Stroke Patients During Head-of-Bed Manipulation

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Background and Purpose—A primary goal of acute ischemic stroke (AIS) management is to maximize perfusion in the affected region and surrounding ischemic penumbra. However, interventions to maximize perfusion, such as flat head-of-bed (HOB) positioning, are currently prescribed empirically. Bedside monitoring of cerebral blood flow (CBF) allows the effects of interventions such as flat HOB to be monitored and may ultimately be used to guide clinical management.

Methods—Cerebral perfusion was measured during HOB manipulations in 17 patients with unilateral AIS affecting large cortical territories in the anterior circulation. Simultaneous measurements of frontal CBF and arterial flow velocity were performed with diffuse correlation spectroscopy and transcranial Doppler ultrasound, respectively. Results were analyzed in the context of available clinical data and a previous study.

Results—Frontal CBF, averaged over the patient cohort, decreased by 17% (P=0.034) and 15% (P=0.011) in the ipsilesional and contralesional hemispheres, respectively, when HOB was changed from flat to 30°. Significant (cohort-averaged) changes in blood velocity were not observed. Individually, varying responses to HOB manipulation were observed, including paradoxical increases in CBF with increasing HOB angle. Clinical features, stroke volume, and distance to the optical probe could not explain this paradoxical response.

Conclusions—A lower HOB angle results in an increase in cortical CBF without a significant change in arterial flow velocity in AIS, but there is variability across patients in this response. Bedside CBF monitoring with diffuse correlation spectroscopy provides a potential means to individualize interventions designed to optimize CBF in AIS. (***Stroke***. 2014;45:1269-1274.)

Key Words: perfusion ■ spectroscopy, near-infrared ■ stroke

Optimization of cerebral blood flow (CBF) in an effort to salvage as much of the ischemic penumbra as possible is a major goal in the management of acute ischemic stroke (AIS). Cerebrovascular autoregulation is thought to be impaired after AIS.[1,2] Accordingly, interventions such as withholding antihypertensive medications, intravenous hydration, and the use of a flat head of bed (HOB) are typically used to maximize CBF.[2–4] However, CBF is rarely measured in AIS, and the effects of such interventions on CBF remain largely unknown.

Quantification of CBF is challenging. The current gold standard is ^{15}O-PET,[5] but this modality is complicated, expensive, and exposes patients to ionizing radiation. Other techniques such as MRI[6,7] and CT perfusion[8] are available but only provide isolated measures rather than continuous monitoring. Furthermore, all of these modalities are restricted to supine patients and are hence unable to measure the responses to HOB manipulations. Serial measurements are challenging with these methods because of radiation exposure, cost, and logistical considerations.

Transcranial Doppler (TCD) monitoring, which quantifies blood flow velocity in large vessels such as the middle cerebral artery (MCA), has been used as a surrogate measure of CBF. The coefficient of proportionality between flow and velocity is the vessel cross-sectional area, but a constant arterial diameter may not apply in AIS.[9,10] More importantly, TCD measures velocity through the MCA trunk, but local microvascular flow to brain parenchyma also includes potential collateral sources, particularly in the setting of AIS. Despite these limitations, TCD-based mean flow velocity (MFV) has been used for bedside CBF assessment, and MFV has been observed to increase with lowering HOB angle.[3,11]

Recently, diffuse correlation spectroscopy (DCS) has been demonstrated as a noninvasive transcranial optical method for measuring microvascular cortical CBF.[12–14] Although DCS provides limited depth penetration into brain parenchyma and, to date, has been limited to measurements over the frontal lobe, the methodology is noninvasive and holds promise as a real-time bedside CBF monitor.[15,16] Importantly, DCS has been validated against other measures of CBF, such as arterial spin labeling MRI,[17] Xenon CT,[18] TCD,[19] phase-encoded velocity mapping MRI,[20] and fluorescent microspheres.[21]

Preliminary work has shown that DCS is sensitive to changes in frontal CBF with HOB angle manipulation in AIS patients.[22] The current study aims to replicate these preliminary results and to correlate CBF changes with TCD and clinical data.

Methods

Patients

Eighteen patients with unilateral AIS affecting large cortical territories in the anterior circulation were enrolled at the Hospital of the University of Pennsylvania. One patient lacked temporal windows for TCD and was excluded. The study protocol was initiated <72 hours after symptom onset. National Institutes of Health Stroke Scale, demographics, vascular risk factors, modified Rankin Scale, and stroke cause were recorded. The protocol was approved by the local institutional review board. Written informed consent was signed by each participant or surrogate.

HOB Manipulation Protocol

HOB angles of 0°, 15°, 30°, 0°, −5°, and 0° were sequentially evaluated for 5 minutes each. Measurements at 0° (supine) were recorded as the baseline, against which all subsequent angles were compared. HOB angle was manipulated using the adjustable hospital bed, so that the lower body remained flat whereas the angle of interest was applied to the upper body. Continuous noninvasive blood pressure was recorded with a Finapres (Finapres Medical Systems, Arnhem, the Netherlands).

Blood Flow Measurements

DCS provides a transcranial measurement of relative CBF. Briefly, temporal fluctuations of near-infrared light scattered by moving red blood cells in tissue are detected. These fluctuations are quantified by the intensity temporal autocorrelation function. Its decay rate is related to changes in CBF.[22] The instrument used two 785-nm lasers and 8 detectors.

The optical probes were coupled to the head via 2×5 cm foam pads placed bilaterally at the temporal margin of the forehead superior to the frontal sinuses to measure the anterior MCA distribution. The distance between the source and detector fibers was 2.5 cm, permitting light penetration to the cortical surface (≈1.25 cm). Data were collected from both hemispheres every 3 seconds. At each HOB angle, the median blood flow was calculated after discarding the first 30 seconds after a HOB change to avoid potentially spurious motion-induced signal fluctuations.

Blood Velocity Measurements

MFV was assessed on all patients using a Spencer Technologies ST3 TCD System. Probes were secured using a Marc 600 Headframe. MCA trunks were insonated bilaterally via transtemporal windows at a depth of 40 to 65 mm. For each HOB angle, MFV was calculated for both MCA trunks after discarding the first 30 seconds after a HOB change to avoid motion-induced signal fluctuations.

Statistical Analysis

Median flow and velocity values for each HOB angle were compared with baseline values (0°) in a paired fashion using the Wilcoxon signed-rank test. Spearman correlation was used to compare velocity and CBF changes across HOB angles. Mixed-effects linear regression was used to assess the relationship between HOB angle and both CBF and MFV using restricted maximum likelihood. Models incorporated a random slope, and the covariance was modeled as unstructured. Model results were compared across a range of assumptions and found to be insensitive to model specification. Regression diagnostics were performed, including evaluation of outliers and of model residuals.

In a post hoc analysis, data from this study were pooled with data from 17 patients from a previous study with a similar HOB protocol, but without TCD data.[22] This previous study had the same inclusion/exclusion criteria, and CBF was measured by DCS across the same HOB angles. The pooled patients (n=34) were dichotomously characterized as having an expected response to HOB manipulation, in which CBF increased with lower HOB position, or a paradoxical response, in which CBF decreased or did not change with lower HOB. Patient characteristics were compared between the 2 groups using Fisher exact test or Wilcoxon rank-sum as appropriate. The influence of large artery occlusion (identified by CTA) on CBF was examined using the Wilcoxon signed-rank test. Analyses were performed with Stata/SE version 10.0 (StataCorp, College Station, TX).

Results

HOB manipulation did not result in any transient worsening or improvement in neurological deficits. No side effects were reported, and probes were well tolerated in all patients. Cohort characteristics are described in Table 1. Figure 1 provides an example of raw CBF and MFV data from 1 patient.

Table 1. Demographics and Baseline Clinical Features

	Cohort (n=17)
Age, y	66 (9.8)
Male sex, %	59
White race, %	47
Left hemisphere, %	47
Days after stroke	2 (0.5)
NIHSS at presentation	12 (6.7)
NIHSS at time of study	10 (6.0)
NIHSS at time of discharge	9 (5.0)
Modified Rankin Scale	3 (1.2)
Stroke volume, cm³	22 (25.5)
ASPECT score	7 (2.0)
Distance (probe to infarct edge), cm	3.8 (1.6)
Ejection fraction	52 (16.6)
Medical comorbidities	
HTN	88%
CHF	35%
AF	41%
Previous stroke/TIA	35%
HLD	82%
Medications at time of study	
β-Blocker	41%
Nodal caclium channel blocker	0%
Digoxin	12%

All values are reported as mean (SD) or percentage for dichotomous variables. AF indicates atrial fibrillation; ASPECT, Alberta Stroke Program Early CT; CHF, congestive heart failure; HLD, hyperlipidemia; HTN, hypertension; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischaemic attack.
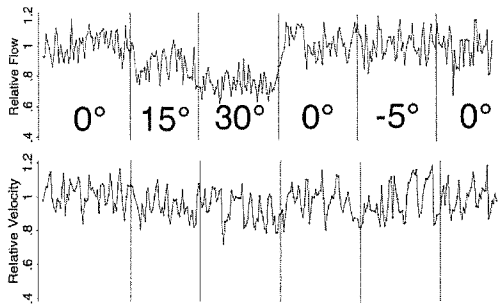
Figure 1. Cerebral blood flow (by diffuse correlation spectroscopy) and mean flow velocity (by transcranial Doppler) at each head-of-bed angle for an individual patient.

Figure 2A depicts the relationship, averaged across the study cohort (n=17), between HOB angle and CBF in each hemisphere. In the infarcted hemisphere, raising HOB angle by 15° resulted in a mean(±SD) decrease of 9(±15)% in CBF (P=0.036). Similarly, HOB 30° resulted in a decrease of 17(±19)% in CBF (P=0.034). In the contralesional hemisphere, a similar relationship was observed: 15° resulted in a 13(±16)% decrease in CBF (P=0.016), and 30° resulted in a 15(±19)% decrease in CBF (P=0.011). Velocity measured by TCD did not significantly change across the full range of HOB angles when averaged across the cohort (Figure 2B). In comparison to a flat HOB, mean arterial blood pressure (105 mm Hg) did not vary significantly at 15° (104 mm Hg; P=0.56), 30° (95 mm Hg; P=0.67), or −5° (103 mm Hg; P=0.15).

The mixed-effects linear regression confirmed that HOB angle is a predictor of CBF ipsilesionally and contralesionally, but HOB angle was not a predictor of MFV (Table 2). Spearman correlation further confirmed that HOB angle and CBF correlate ipsilesionally (ρ=−0.50; P<0.001) and contralesionally (ρ=−0.47; P=0.001) and confirmed the lack of relationship between HOB angle and velocity ipsilesionally (ρ=−0.070; P=0.65) and contralesionally (ρ=−0.070; P=0.64).

Variability in CBF responses to HOB angle was observed between individuals, suggesting heterogeneity in autoregulatory function. In 71% of patients, CBF decreased when the HOB angle increased (Figure 3A), as would be expected. By contrast, a paradoxical response was observed in 29% of patients (Figure 3B), with decreased CBF at lower HOB angles. Individual patient responses to HOB positioning are depicted in Figure IA in the online-only Data Supplement.

Variability was also seen in TCD-measured velocity changes, albeit to a lesser extent. However, although DCS identified changes in CBF among paradoxical responders, TCD failed to identify changes in MFV. In the contralesional hemisphere of patients with expected response to HOB manipulation, CBF also decreased when raising HOB to 30° (25%±28; P=0.002), but to a lesser extent than the ipsilesional hemisphere (Figure 3A). In paradoxical responders, contralesional CBF did not change significantly at 30° as compared with a flat HOB (P=0.51).

In a post hoc analysis, the 17 patients in this cohort were pooled with 17 patients from a previous study of HOB manipulation in AIS.[22] When compared with this cohort, the 17 patients from the previous study were similar with respect to age (P=0.82), National Institutes of Health Stroke Scale (P=0.33), stroke volume (P=0.13), Alberta Stroke Program Early CT score (P=0.62), and distance between stroke and DCS probe (P=0.24). Medical comorbidities were present in similar proportions. Five patients (29%) in each cohort showed a paradoxical response. These 10 subjects in the pooled analysis were compared with patients that demonstrated an expected response to HOB manipulation; however, no differences were found with respect to the clinical or radiological features (Table 3). Individual patient responses to HOB positioning for the combined cohort are depicted in Figure IB in the online-only Data Supplement.

An additional post hoc analysis of these pooled data dichotomized patients based on the presence or absence of ipsilesional large vessel occlusion. Patients with vessel occlusion (n=12) had a 40(±38)% increase in ipsilesional CBF at 0° as compared with 30° (P=0.004) and a 21(±34)% contralesional increase in CBF (P=0.13). Patients without vessel occlusion (n=22) had a 16(±36)% increase in ipsilesional CBF (P=0.08) and a 21(±34)% increase in contralesional CBF (P=0.003). Among those with TCD data available, no change in ipsilesional blood velocity was observed in patients with (n=8; 100% versus 95%; P=0.47) and without vessel occlusion (n=9; 100% versus 101%; P=0.75).

Discussion

DCS provides the means to assess microvascular cortical CBF at bedside in a safe, well-tolerated manner. Previous studies of DCS have quantitatively examined the penetration of DCS signals into the brain. At a source–detector separation of 2.5 cm, as used in this study, the optical signal is predominately a

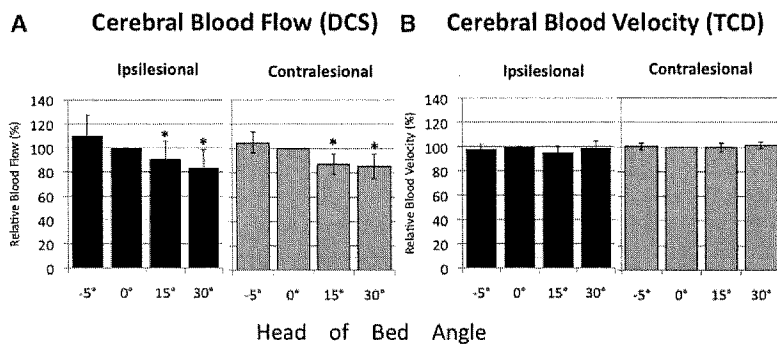**A   Cerebral Blood Flow (DCS)   B   Cerebral Blood Velocity (TCD)**

Figure 2. Average cerebral hemodynamic measurements for all patients across a range of head-of-bed angles. Cerebral blood flow (A) and mean flow velocity (B). Error bars represent standard deviation. DCS indicates diffuse correlation spectroscopy; and TCD, transcranial Doppler. *P<0.05 by Wilcoxon signed-rank test.

Table 2. Mixed-Effects Linear Regression: Head-of-Bed Angle

	Coefficient	Wald Z score	P Value
Cerebral blood flow			
Ipsilesional	−0.70	−2.13	0.033
Contralesional	−0.57	−3.21	0.001
Velocity			
Ipsilesional	−0.028	−0.24	0.81
Contralesional	0.036	0.68	0.50

reflection of brain hemodynamics.[12,23] The current study confirmed that DCS is sensitive to changes in CBF with HOB angle manipulation as previously observed.[12,17,22] Specifically, microvascular CBF increased with a lower HOB angle when averaged across the cohort. In contrast, MFV in proximal arteries measured by TCD did not change significantly. Substantial individual variability was also observed.

One previous study measured MCA velocity with TCD during similar HOB manipulation and found the velocity to increase with lower HOB among patients with large artery occlusion.[11] Another study similarly found that MFV increased at lower HOB angles in the setting of incomplete vessel recanalization, but with recanalization, CBF did not vary across HOB angles.[24] Note that although there has been some concern that recanalization is associated with hemorrhagic transformation, pooled data suggest that spontaneous recanalization does not carry such risk.[25] Our study failed to detect changes in flow velocity measured by TCD across HOB positions, even in patients with ipsilateral large artery occlusion at the time of admission, but recanalization was not addressed in the current study. The observed differences in flow relative to recanalization may be explained by differences in study timing. In this study, patients were examined 2 to 3 days after stroke onset, whereas previous studies measured blood velocity at earlier time points. The evolution of autoregulation impairment after stroke is poorly understood, but impairment is likely maximal in the acute setting.[26] Additionally, TCD-based assessments of CBF must be interpreted with caution as this assumes a constant arterial diameter.[26,27]

The results of the current study suggest that TCD MFV may not be an optimal surrogate for CBF. Several possible mechanisms may explain the discordance between MFV and CBF. First, MCA diameter may not remain constant with HOB manipulation. Second, collateral flow sources may contribute to cortical CBF not reflected in MCA MFV because DCS measures CBF in the microvasculature of the cortical surface, which TCD cannot detect. This finding is consistent with previous studies, wherein DCS correlated with TCD in healthy volunteers[19,28] but diverged in patients with severe carotid artery stenosis or occlusion.[29] The greater sensitivity of DCS underscores its potential value as a noninvasive bedside monitor of cortical CBF.[22]

Compared with healthy volunteers,[30] unilateral AIS patients experience larger CBF changes with HOB manipulation, which is consistent with previous reports and is thought to represent autoregulatory impairment.[3,22,31] Although HOB effects were most pronounced in patients with ipsilesional large artery occlusion, lowering the HOB can increase CBF irrespective of vessel occlusion. However, patients with severe arterial disease may be the most likely to benefit from flat HOB positioning.

The use of a flat HOB after stroke is not consistent at all stroke centers and should be considered in the context of the patient's ability to tolerate positioning safely with regard to aspiration risk, congestive heart failure, and intracranial pressure changes. Significant CBF changes were observed 2 and 3 days after symptom onset, indicating that a flat HOB has the potential to increase CBF long after the onset of symptoms. It is not yet known whether such flow changes influence long-term clinical outcomes given the potential rapid reduction in penumbral tissue after the first 24 hours,[32] and maintaining a supine position for several days may be impractical. Nonetheless, clinical responses to increased CBF with induced hypertension were reported up to 9 days after stroke,[33] suggesting that penumbra did persist for some patients. Although the evolution of penumbra over the first few days is not well understood, if the supine position is tolerated, our findings support the use of a flat HOB acutely after a stroke, consistent with American Stroke Association guidelines.[34] Future characterization of the evolution of CBF responses to HOB may help determine the optimal timing for liberalizing HOB restrictions, although this may ultimately be patient-specific.

Considerable individual variability in both DCS and TCD measurements with HOB manipulation was observed in patients with AIS. This extent of variability was not observed in healthy volunteers,[30] suggesting that it reflects underlying pathophysiology. Although we investigated the potential sources for such variability, we found no relationship between CBF changes and either stroke volume or stroke–probe distance. The proportion of patients with a paradoxical response to HOB manipulation was also consistent in 2 independent cohorts. A paradoxical response has been reported in other

A Patients with Expected Response (n = 12)

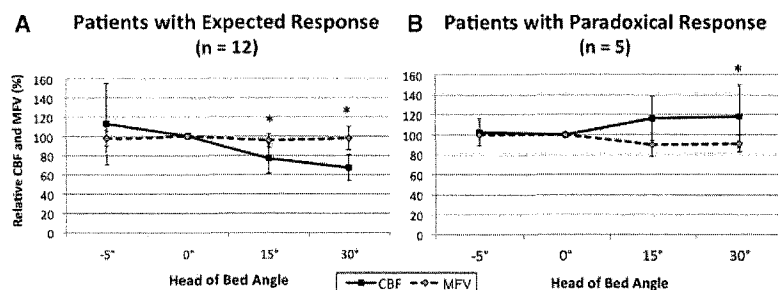**B Patients with Paradoxical Response (n = 5)**

Figure 3. Cerebral blood flow (CBF) and mean flow velocity (MFV) in a patient with (A) expected and (B) paradoxical response to head-of-bed manipulation. Error bars represent standard deviation. *P<0.05 by Wilcoxon signed-rank test.

Table 3. Features of Paradoxical Responders

	Paradoxical Response (N=10; 29%)	Expected Response (N=24; 71%)	P Value
Age, y	64 (13.0)	66 (12.9)	0.79
White race, %	50%	54%	0.82
Male sex, %	50%	50%	1.0
Admission NIHSS	14 (7.3)	13 (8.1)	0.58
Discharge NIHSS	11 (6.1)	10 (6.7)	0.68
Modified Rankin Scale	3 (1.1)	3 (1.6)	0.65
Infarct volume, cm³	54 (57.3)	51 (91.0)	0.29
ASPECT score	6 (2.9)	7 (1.8)	0.12
Ejection fraction, %	59 (21)	56 (18)	0.49
Distance (probe to infarct edge), cm	3.4 (1.2)	3.4 (1.5)	0.86
Proportion with MCA occlusion, %	20%	41%	0.23
Comorbidities, %			
CHF	20%	25%	0.75
AF	20%	38%	0.32
Previous stroke or TIA	20%	33%	0.44
Medications, %			
β-Blocker	20%	38%	0.32
Nodal calcium channel blocker	0%	4%	0.51

All values are reported as mean (SD) or percentage for dichotomous variables. AF indicates atrial fibrillation; ASPECT, Alberta Stroke Program Early CT; CHF, congestive heart failure; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischaemic attack.

brain injuries and confirmed by invasive monitoring.[35] We attempted to identify clinical covariates that related to the paradoxical response in stroke patients, but these patients appeared similar to the overall cohort with respect to baseline clinical, demographic, and radiographic features. Although neither the mechanism of a paradoxical response nor its effects on stroke outcome are currently known, this subgroup may present a challenge to clinicians attempting to optimize perfusion acutely after a stroke. In the absence of reliable clinical identifiers, paradoxical responders might only be identifiable by real-time cortical CBF monitoring, because this subgroup could not be identified by TCD.

Conclusions

DCS provides real-time continuous monitoring of cortical CBF at bedside. Raising HOB causes a measurable decrease in CBF in most AIS patients, but the response varies widely across patients. Clinical features do not predict CBF response, emphasizing the importance of direct CBF measurements to individualize treatments. Continuous bedside monitoring of CBF using DCS can also be applied to other therapeutic interventions, such as intravenous fluid boluses or pharmacological blood pressure augmentation, with the goal of individualized therapy to optimize perfusion and improve outcome after ischemic stroke.

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Disclosures

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