Comparison of Transcranial Doppler and Ultrasound-Tagged Near Infrared Spectroscopy for Measuring Relative Changes in Cerebral Blood Flow in Human Subjects

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BACKGROUND: Currently, no reliable method exists for continuous, noninvasive measurements of absolute cerebral blood flow (CBF). We sought to determine how changes measured by ultrasound-tagged near-infrared spectroscopy (UT-NIRS) compare with changes in CBF as measured by transcranial Doppler (TCD) in healthy volunteers during profound hypocapnia and hypercapnia.
METHODS: Ten healthy volunteers were monitored with a combination of TCD, UT-NIRS (c-FLOW, Ornim Medical), as well as heart rate, blood pressure, end-tidal Pco_2 ($PEtco_2$), end-tidal O_2, and inspired O_2. Inspired CO_2 and minute ventilation were controlled to achieve 5 stable plateau goals of $Etco_2$ at 15–20, 25–30, 35–40, 45–50, and 55–60 mm Hg, for a total of 7 measurements per subject. CBF was assessed at a steady state, with the TCD designated as the reference standard. The primary analysis was a linear mixed-effect model of TCD and UT-NIRS flow with $PEtco_2$, which accounts for repeated measures. Receiver operating characteristic curves were determined for detection of changes in CBF.
RESULTS: Hyperventilation (nadir $PEtco_2$ 17.1 ± 2.4) resulted in significantly decreased mean flow velocity of the middle cerebral artery from baseline (to 79% ± 22%), but not a consistent decrease in UT-NIRS cerebral flow velocity index (n = 10; 101% ± 6% of baseline). Hypercapnia (peak $PEtco_2$ 59.3 ± 3.3) resulted in a significant increase from baseline in both mean flow velocity of the middle cerebral artery (153% ± 25%) and UT-NIRS (119% ± 11%). Comparing slopes versus $PEtco_2$ as a percent of baseline for the TCD (1.7% [1.5%–2%]) and UT-NIRS (0.4% [0.3%–0.5%]) shows that the UT-NIRS slope is significantly flatter, $P < .0001$. Area under the receiver operating characteristic curve was significantly higher for the TCD than for UT-NIRS, 0.97 (95% confidence interval, 0.92–0.99) versus 0.75 (95% confidence interval, 0.66–0.82).
CONCLUSIONS: Our data indicate that UT-NIRS cerebral flow velocity index detects changes in CBF only during hypercarbia but not hypocarbia in healthy subjects and with much less sensitivity than TCD. Additional refinement and validation are needed before widespread clinical utilization of UT-NIRS. (Anesth Analg 2017;XXX:00–00)

KEY POINTS

- **Question:** How do changes measured by ultrasound-tagged near-infrared spectroscopy (UT-NIRS) compare with changes in cerebral blood flow as measured by transcranial Doppler in healthy volunteers during profound hypocapnia and hypercapnia?
- **Findings:** UT-NIRS cerebral flow velocity index detects changes in transcranial Doppler only during hypercarbia but not hypocarbia in healthy subjects and with much less sensitivity than transcranial Doppler.
- **Meaning:** Additional refinement and validation are needed before widespread clinical utilization of UT-NIRS.

Oxygen delivery is dependent on both the quantity of oxygen in the blood (arterial oxygen content, Cao_2) as well as the blood flow to a particular region. While measurement of arterial hemoglobin oxygen saturation (eg, pulse oximetry) or tissue hemoglobin oxygen saturation (eg, near infrared spectroscopy) is widely used, determination of global or regional blood flow, in particular cerebral blood flow (CBF), remains challenging in the clinical setting.

Radiologic methods for measuring CBF such as single-photon emission computed tomography, positron emission tomography, computed tomography perfusion imaging, and perfusion magnetic resonance imaging are expensive, not continuous, and some carry significant radiation exposure.[1] Direct methods such as thermal diffusion flowmetry are invasive, expensive, and not without significant risk, thus limiting utilization in clinical practice. As a result, clinical medicine more commonly employs noninvasive techniques such as transcranial Doppler (TCD) and cerebral near-infrared spectroscopy (NIRS) as surrogates for direct measurement of flow and tissue oxygen saturation, respectively. These methods have significant limitations.[2,3] Accurate TCD measurements and interpretation require

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the presence of adequate transcranial windows, a highly-trained technician to perform the study, and a physician who can interpret the study. Measurements cannot easily be done continuously and may be subject to interference from electrical noise. One relatively newer technology that is Food and Drug Administration cleared, although has not been widely validated or widely used in clinical practice, is ultrasound-tagged NIRS (UT-NIRS). The Ornim UT-light technology (Ornim Medical Inc, Kfar Saba, Israel) uses proprietary technology that incorporates ultrasound and NIRS to provide an uncalibrated, surrogate measurement of flow.[4–7] The device uses low-power ultrasound to modulate near-infrared light via adhesive transducers that are applied to the subject's forehead. "Tagged" photons undergo a Doppler effect within the target tissue due to movement of scattering particles (ie, blood cells).[4,7] The UT-NIRS device correlates detected light intensity to ultrasound signals and reports this as a surrogate measurement of microcirculatory flow (cerebral flow velocity index [CFVx]).

While UT-NIRS is relatively new, NIRS technology has been in existence for nearly 3 decades and has been evaluated in a variety of clinical settings (vascular and cardiac anesthesia as well as traumatic brain injury). Cerebral NIRS measures brain tissue oxygenation (in arbitrary units) and is dependent on arteriovenous hemoglobin concentration and oxygenation. Although cerebral tissue oxygenation (and NIRS measurements) can be influenced by factors such as cerebral metabolic oxygen consumption and CBF, NIRS does not directly measure flow. By "ultrasound tagging" the NIRS signal, UT-NIRS attempts to utilize the Doppler effect to directly measure velocity as a surrogate for flow. Although continuous and easy to use, NIRS has not gained widespread implementation due to several limitations including a lack of outcomes data, the inability to evaluate more than a small region of the brain, and the ongoing debate over what the measured NIRS values actually signify.[8–13] It remains uncertain whether UT-NIRS shares these limitations.

There are 2 potential advantages of UT-NIRS over TCD: the ability for greater ease of use as probes can be applied to a patient's forehead with minimal training and probes can remain on a patient with little or no need for repositioning to perform continuous monitoring. Despite numerous scenarios where continuous CBF measurement could provide useful clinical information (eg, vasospasm in subarachnoid patients or flow monitoring during carotid endarterectomy), relatively few intensivists, anesthesiologists, or intensive care unit nurses are proficient with TCD. Furthermore, even where trained personnel are available to provide TCD, continuous measurements for prolonged periods remain technically challenging.

Limited animal data demonstrate changes in UT-NIRS values correspond to periods of change in mean arterial blood pressures.[14] Recent, small studies in humans have used Xe-single-photon emission computer tomography, tissue oximetry (Licox Integra, Plainsboro, NJ), and jugular venous bulb saturations to demonstrate that changes in UT-NIRS correlate with physiologic perturbations that alter CBF.[6,15] One case report of the 24-hour experience in a patient with subarachnoid hemorrhage and diffuse vasospasms found that UT-NIRS decreased before 80% of brain tissue desaturations as measured concurrently by tissue oximetry (Licox Integra).[16] Another recent study found that UT-NIRS measurements indicated an increase in CBF with hyperventilation, the opposite of what should occur based on well-known effects of CO_2 on CBF.[17,18] In a study of patients undergoing general anesthesia, propofol induction and intubation were found to cause significant decreases and increases in UT-NIRS measurements.[19]

Given the limited data for this new technology and the great potential for clinical application, we sought to measure if and how strongly UT-NIRS correlates with CO_2-induced changes in CBF measured by a widely validated standard (TCD) in healthy volunteers.

METHODS

This study was approved by the University of California at San Francisco Committee on Human Research, and written informed consent was obtained from all subjects. Ten healthy, adult, paid volunteer subjects were studied during a total of 13 separate study sessions. Subjects were excluded if they reported a history of smoking, asthma or other pulmonary disease, obesity, cardiovascular disease, or any other significant medical illnesses.

Study subjects were semisupine (30° head up) with a nose clip, breathing air/carbon dioxide mixtures (F_{IO_2}, 0.21) via a mouthpiece from a partial rebreathing circuit. All subjects were continuously monitored with pulse oximetry; noninvasive blood pressure by upper arm cuff; end-tidal P_{CO_2} (PE_{tCO_2}), end-tidal P_{O_2}, and inspired P_{O_2} (O_2 and CO_2 analyzers, S3-A and CD3-A; Applied Electrochemistry Inc, Pittsburgh, PA).

All subjects were monitored with bilateral UT-NIRS probes (c-FLOW, Ornim Medical Inc) placed on the subjects' foreheads according to the manufacturer's recommendations 2–3 cm above the supraorbital ridge. An operations manager from the company was present for the initial 5 study subjects to ensure appropriate probe placement and device operation. Neither the representative nor the manufacturer participated in subsequent review of the data or preparation of this manuscript.

Mean flow velocity of the middle cerebral artery ($MCAv_{mean}$) was measured by placing bilateral 2 MHz transcranial Doppler probes (Viasys Companion III; Carefusion, Franklin Lakes, NJ) over the temporal window by an expert technician using an adjustable headset that holds the TCD transducers to the subjects' transtemporal windows. The depth of insonation ranged from 46 to 50 mm to measure $MCAv_{mean}$ in our subjects. After transtemporal windows were identified, a headset was used to immobilize probes. TCD was continuously monitored by an expert technician to ensure probes did not become displaced during the study protocol.

Subjects were initially observed while breathing room air (F_{IO_2}, 0.21) for 5 minutes or until stable TCD and UT-NIRS plateau readings were recorded for 3 consecutive minutes to establish baseline measurements. Subjects were then asked to voluntarily increase minute ventilation, and 10–20 L/min of fresh gas inflow (F_{IO_2}, 0.21) was applied until a goal PE_{tCO_2} of 15–20 mm Hg was achieved and maintained for at least 3 minutes. Inspired and expired air–nitrogen–carbon dioxide mixtures were monitored breath by breath and recorded using LabVIEW 2013 (National Instruments, Austin, TX). After this nadir

hyperventilation measurement, subjects were instructed to breath comfortably, while inspired Pco_2 was increased as needed to achieve 4 additional plateau goals of $PEtco_2$ at 25–30, 35–40, 45–50, and 55–60 mm Hg. Minute ventilation and $PEtco_2$ were then returned to baseline. Each plateau was maintained for a goal of at least 3 minutes or until stable UT-NIRS and TCD measurements were obtained. The target time of 3 minutes was selected based on primarily on concerns for patient comfort with our protocol. We also reviewed data from previously published studies that used 3–5 minutes of equilibration as well as piloting of our protocol that produced grossly stable plateaus after 3 minutes.[20]

All 10 study subjects went through the protocol described above; however, for study subjects 1–5, the UT-NIRS was paused for approximately 5 seconds at each plateau until TCD $MCAv_{mean}$ values were recorded, and then UT-NIRS measurements resumed. This modification of the protocol was done to eliminate observed interference from the UT-NIRS on the TCD, which resolved instantly with pausing UT-NIRS (as shown in Supplemental Digital Content, Appendix 1, http://links.lww.com/AA/C112). For study subjects 6–10, both the UT-NIRS and TCD were left to continuously record to eliminate the possibility that frequently pausing the UT-NIRS impacts CFVx accuracy. Three of the study subjects (1, 9, and 10) were reevaluated on a separate day with the same protocol as above but without the use of TCD. This was done to evaluate for possible TCD interference on UT-NIRS CFVx measurements.

The TCD device did not have any digital or analog output of data, so readings were recorded manually throughout the protocol. The subjects' heart rate, UT-NIRS, $PEtco_2$, end-tidal Po_2, and inspired Po_2 data were monitored continuously although recorded for analysis at the same frequency as TCD data (every minute). Blood pressure was measured every 1 minute.

Statistical Analysis

Descriptive data are reported as mean ± standard deviation (SD). Slopes are reported with 95% confidence intervals (CIs). Linear regressions of TCD $MCAv_{mean}$ and UT-NIRS readings versus $PEtco_2$ were performed, accounting for repeated measures (linear mixed-effects model with the subject ID as a random effect). The slopes with 95% CIs were calculated using this model. The possibility of a nonlinear fit was examined by testing the significance of a quadratic (X^2) term for the independent variable ($PEtco_2$). Comparisons of left and right sides for the percentage changes in flow readings of TCD and UT-NIRS were performed using the original mixed-effects model, then adding an independent variable for the "side" (right or left), and including the interaction between "side" and $PEtco_2$. A statistically significant difference in slopes was assessed by a P value for the interaction term <.05. The comparison of slopes for UT-NIRS and TCD was similarly performed by combining all data, adding an independent variable for the device, and including the interaction term between the device and $PEtco_2$.

Data for TCD $MCAv_{mean}$ and UT-NIRS over the different $PEtco_2$ target levels were analyzed by repeated-measures analysis of variance. Two-way repeated measures analyses of variance were used to test differences between left and right sides and in the presence or absence of a second monitor. The model included the effect of the target CO_2 level, the term for the different conditions, and their interaction. The interaction term represents whether the changes over the CO_2 levels were different under the different conditions. Post hoc multiple comparisons were not performed because they were not deemed clinically relevant, although paired t-tests were performed for comparison of data at certain relevant steps, and uncorrected P values are reported as indicated.

Receiver operating characteristic (ROC) curves were created for changes in TCD and UT-NIRS readings at each step change in $PEtco_2$. CBF was categorized as "1" for the 4-step changes where $PEtco_2$ was increased relative to the prior step and "0" for the 2-step changes where $PEtco_2$ was decreased relative to the prior step. Data were analyzed after aggregating data obtained from right and left sides. Statistical significance was assessed using a hierarchical logistic regression model that compensates for repeated measures. Area under the curve (AUC) and 95% CIs were calculated using clustering by subject ID.

The change from baseline was determined for both TCD and UT-NIRS for construction of a 4-quadrant plot. A central exclusion zone was set at 4 for the TCD by 1 for the UT-NIRS, in a ratio approximating the range of values. The percent agreement (concordance) was calculated for left, right, and combined measurements.

The study size was selected based on experience with volunteer studies using a repeated measures study design and an estimation that CBF measured by TCD and UT-NIRS would change by approximately 15% between the different experimental treatments. We expected the SD of such a step change to be about 10%, which is to say that CBF changes are fairly consistent among subject. This would give a 90% power to detect these changes using 7 subjects. The adequacy of the sample size for statistical analysis was confirmed post hoc by the finding that there was a more than 50% difference in the slope of the $CBF/PEtco_2$ relationship between the UT-NIRS device and the TCD.

A $P < .05$ was considered statistically significant. Statistical analysis was performed with JMP 11.0 (SAS Institute, Cary, NC) and Stata 14 (Statacorp, College Station, TX).

RESULTS

All study subjects completed the protocol. The age of the subjects (mean ± SD) was 30 ± 4 years, with 6 men and 4 women. Baseline values for $PEtco_2$, TCD, UT-NIRS, Spo_2, hazard ratio, and blood pressure are shown in Table 1.

For the 10 study subjects where UT-NIRS and TCD were recorded concurrently, $PEtco_2$ dropped from the baseline (mean ± SD) of 34.5 ± 5.0 to 17.1 ± 2.4 mm Hg with hyperventilation, $P < .0001$. With hypercapnia, the highest CO_2 plateau was 59.3 ± 3.3. The step changes in $PEtco_2$, Spo_2, and blood pressure are summarized in Table 1.

Hypercapnia and hypocapnia resulted in significant decreases and increases, respectively, for $MCAv_{mean}$. Regressions of $PEtco_2$ versus TCD for left and right values combined are shown in Figure 1A, with Figure 2A showing the regression as a percent of baseline. Both left

Table 1. Data at Different CO_2 Step Changes for the 10 Subjects Who Had TCD and UT-NIRS Performed Simultaneously

Condition ($PEtco_2$ Goal, mm Hg)	Baseline	Nadir, 15–20	25–30	35–40	45–50	Peak, 55–60	Return to Baseline	*P*
TCD								
Left (cm/s)	60.7 ± 12.2	48.9 ± 17.2	57.0 ± 14.8	65.8 ± 16.9	77.4 ± 15.0	91.1 ± 16.0 (9)	64.0 ± 11.4 (9)	<.0001
Right (cm/s)	66.5 ± 18.2	53.4 ± 22.5	67.9 ± 17.5 (9)	78.1 ± 11.9 (8)	86.1 ± 21.8	104.0 ± 25.7	64.7 ± 21.4	<.0001
Combined (cm/s)	63.6 ± 15.4	51.2 ± 19.6	62.2 ± 16.6 (19)	71.3 ± 15.8 (18)	81.8 ± 18.7	97.9 ± 22.1 (19)	64.4 ± 16.9 (19)	<.0001
Left (% of baseline)	100% ± 0%	80% ± 21%	95% ± 17%	108% ± 15%	129% ± 18%	146% ± 20% (9)	102% ± 8% (9)	<.0001
Right (% of baseline)	100% ± 0%	78% ± 24%	100% ± 9% (9)	121% ± 20% (8)	132% ± 24%	160% ± 29%	96% ± 11%	<.0001
Combined (% of baseline)	100% ± 0%	79% ± 22%	97% ± 14% (19)	114% ± 18% (18)	130% ± 21%	153% ± 25% (19)	99% ± 10% (19)	<.0001
UT-NIRS								
Left	49.0 ± 6.6	49.5 ± 8.3	49.1 ± 7.4	49.7 ± 6.7	53.4 ± 8.0	57.6 ± 7.4	53.3 ± 7.2	<.0001
Right	44.0 ± 5.6	44.7 ± 6.3	44.8 ± 5.9	46.6 ± 4.6	48.0 ± 6.1	52.5 ± 6.1	48.5 ± 6.7	<.0001
Combined	46.5 ± 6.5	47.1 ± 7.6	47.0 ± 6.9	48.2 ± 5.8	50.7 ± 7.5	55.1 ± 7.1	50.9 ± 7.2	<.0001
Left (% of baseline)	100% ± 0%	101% ± 7%	100% ± 7%	102% ± 8%	109% ± 8%	118% ± 10%	109% ± 8%	<.0001
Right (% of baseline)	100% ± 0%	102% ± 5%	102% ± 7%	106% ± 8%	109% ± 9%	120% ± 12%	111% ± 11%	<.0001
Combined (% of baseline)	100% ± 0%	101% ± 6%	101% ± 7%	104% ± 8%	109% ± 8%	119% ± 11%	110% ± 9%	<.0001
Spo_2 (%)	99.2 ± 1.1	98.1 ± 6.0	99.4 ± 1.1	99.4 ± 1.0	99.1 ± 1.1	99.5 ± 0.5	99.6 ± 0.7	.80
$PEto_2$ (mm Hg)	113 ± 7	134 ± 6	107 ± 8	108 ± 8	110 ± 8	112 ± 4	121 ± 9	<.0001
$PEtco_2$ (mm Hg)	34.5 ± 5.0	17.1 ± 2.4	30.2 ± 1.6	38.6 ± 1.7	48.9 ± 1.4	59.3 ± 3.3	32.1 ± 4.8	<.0001
Heart rate (/min)	67 ± 10	84 ± 12	64 ± 7	64 ± 9	71 ± 14	81 ± 14	73 ± 11	<.0001
Systolic blood pressure (mm Hg)	113 ± 10	118 ± 12	118 ± 8	118 ± 10	128 ± 13	136 ± 15	120 ± 13	<.0001
Diastolic blood pressure (mm Hg)	68 ± 7	73 ± 11	74 ± 7	76 ± 10	77 ± 7	85 ± 12	72 ± 9	.003
Mean blood pressure (mm Hg)	83 ± 6	88 ± 10	89 ± 6	90 ± 7	94 ± 8	102 ± 12	88 ± 10	<.0001

Data are represented as mean ± SD or mean ± SD (n) if n differs from total.

P values are from repeated measures ANOVA.

"Steps" are the staged changes in Pco_2.

Abbreviations: ANOVA, analysis of variance; $PEtO_2$, end-tidal oxygen partial pressure; $PEtco_2$, end-tidal CO_2 partial pressure; SD, standard deviation; Spo_2, pulse oximeter oxygen saturation; TCD, transcranial Doppler; UT-NIRS, ultrasound-tagged near-infrared spectroscopy.

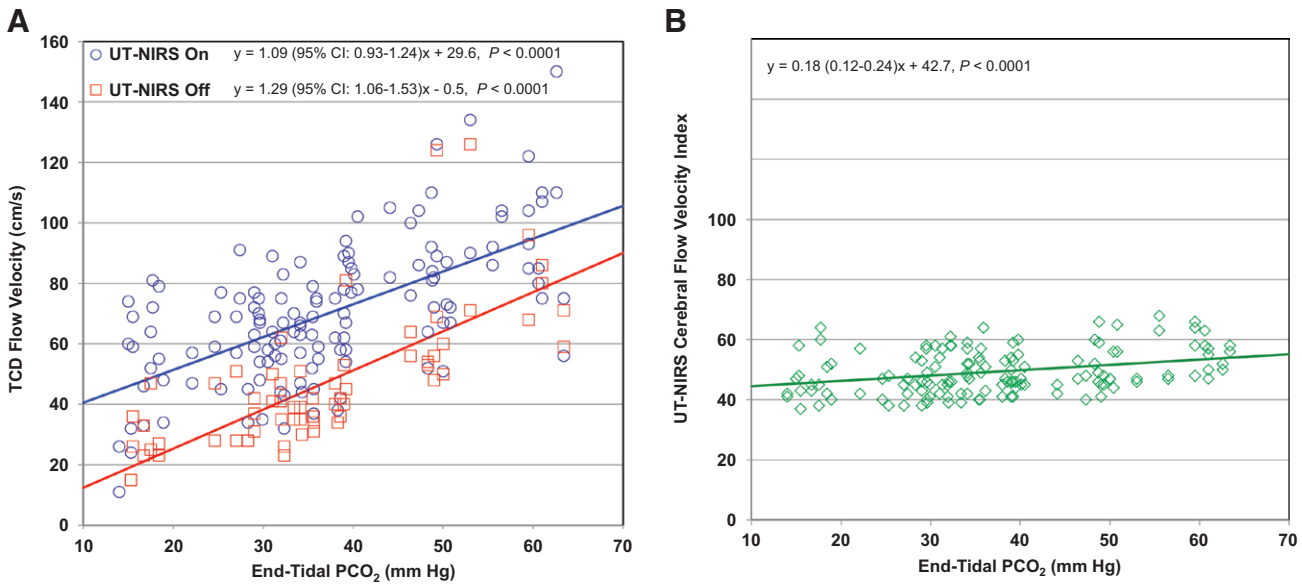

Figure 1. A, Transcranial Doppler (TCD) middle cerebral artery mean velocity is plotted versus end-tidal P_{CO_2}. In 10 study subjects (blue), TCD and ultrasound-tagged near-infrared spectroscopy (UT-NIRS) were measured concurrently. In 5 study subject (red), TCD was measured without UT-NIRS (A). Measurements from left and right sides are both shown as individual data points but not distinguished by different markers. The relationship was linear and the slope statistically different from 0, $P < .0001$. Concurrent measurement of UT-NIRS with TCD produced increased magnitude of reported values for TCD flow velocity. B, UT-NIRS cerebral flow velocity index versus end-tidal P_{CO_2}. The slope was also statistically different from 0, $P < .0001$. Equations are shown on the figures, with 95% confidence intervals for the slope.

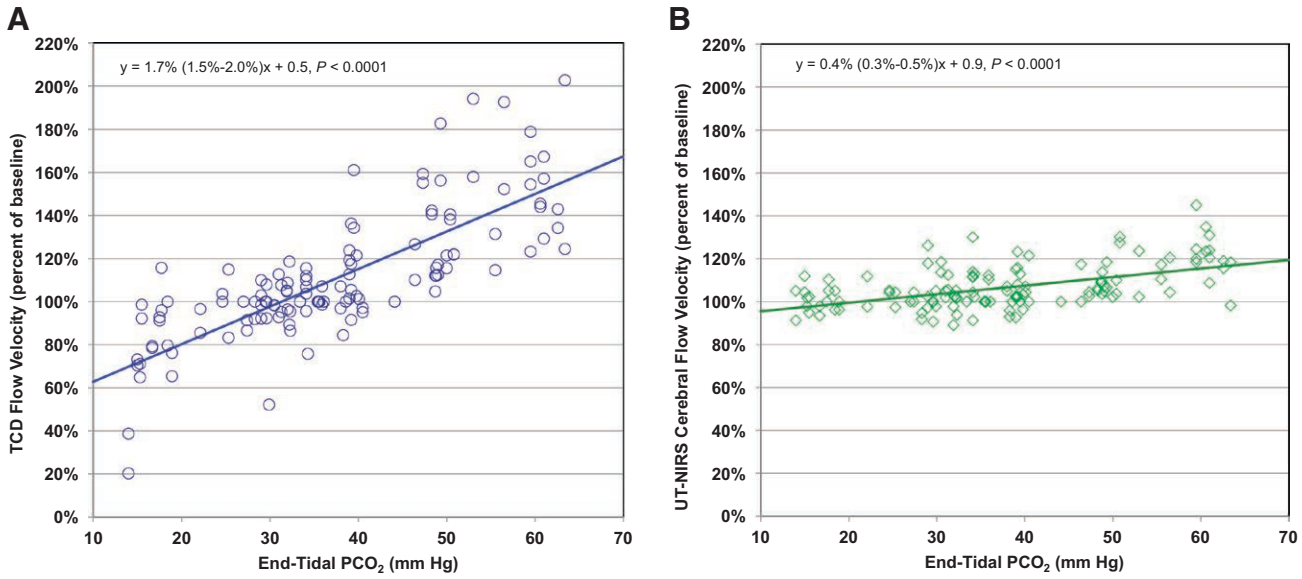

Figure 2. Transcranial Doppler (TCD) middle cerebral artery velocity as a percent of baseline is plotted versus end-tidal P_{CO_2} in 10 study subjects with concurrent ultrasound-tagged near-infrared spectroscopy (UT-NIRS) measurements (A). Both left and right sides are shown as individual data points but not distinguished by different markers. The relationship was linear and the slope statistically different from 0, significant, $P < .0001$. (B) UT-NIRS cerebral flow velocity index as percent of baseline versus end-tidal P_{CO_2}. The relationship was also statistically significant, $P < .0001$. Equations are shown on the figures, with 95% confidence intervals for the slope.

and right showed good linear fits (R^2; the quadratic term was not statistically significant [$P < .0001$]), 0.79 and 0.86, respectively. Flow was slightly higher on the right side, but slopes did not differ (P value for the interaction term 0.34). Data are also summarized at the different steps in Table 1.

UT-NIRS CFVx increased with hypercapnia (119% ± 110% of baseline) although there was no significant change from baseline with hypocapnia (101% ± 6% of baseline; uncorrected $P = 0.98$; Table 1).

Regressions for the UT-NIRS versus $PEtCO_2$ were made by aggregating data from left and right sides into a single regression curve as a percent of baseline, as shown in Figures 1B and 2B. The slopes were statistically different from 0, $P < .0001$. Right and left sides did not differ for raw data or for data expressed as a percent of baseline. Slight nonlinearity was found, with the P value for the quadratic term statistically significant (.004 and .003, respectively).

Comparing slopes as a percent of baseline for the TCD (1.7% [1.5%–2%]) and UT-NIRS (0.4% [0.3%–0.5]) shows that the UT-NIRS slope is significantly flatter, $P < .0001$.

ROC curves for TCD and UT-NIRS combining left and right sides are shown in Figure 3. The AUC (95% CI) for the TCD (0.97 [0.91–0.99]) were significantly better than for the UT-NIRS (0.71 [0.60–0.81]), although the UT-NIRS was still a statistically significant predictor ($P < .0001$).

The 4-quadrant plot in Figure 4 shows only modest concordance between TCD and UT-NIRS in detecting the change in flow (63.1% overall concordance).

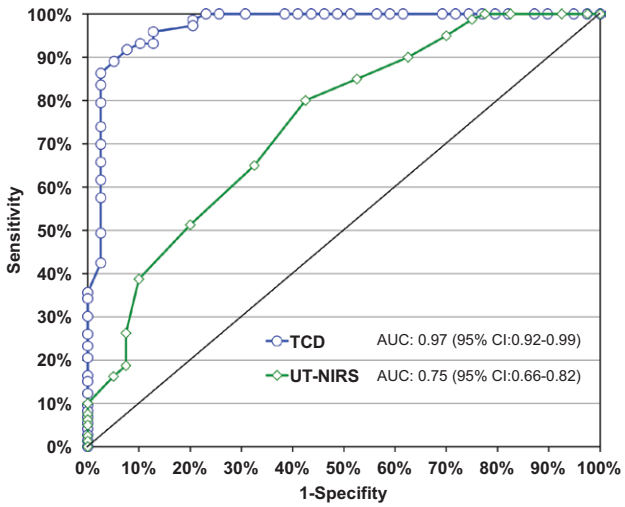

Figure 3. For the 6 CO_2 step changes, cerebral blood flow was categorized as increased for the 4-step increases in end-tidal P_{CO_2} and decreased for the 2 step decreases in P_{CO_2}. The change in the transcranial Doppler (TCD) velocity or ultrasound-tagged near-infrared spectroscopy (UT-NIRS) was determined at each step. The receiver operating characteristic curves for TCD (blue circles) and UT-NIRS (green diamonds) are shown, and the areas under the curve with 95% confidence limits are listed, with *P* values for the logistic regression. Left and right sides were combined for the analysis.

Interference

Data for the 5 subjects who had TCD recorded with both the UT-NIRS on and UT-NIRS off are shown in Table 2. Concurrent measurements of TCD and UT-NIRS consistently demonstrated significant and obvious interference on TCD in all subjects tested (Supplemental Digital Content, Appendix 1, http://links.lww.com/AA/C112). TCD values were significantly higher for both left and right sides ($P < .0001$) with concurrent UT-NIRS, but the changes over the different steps were not significantly different (*P* value for the interaction term left: .62, right: .77). By regression analysis, the values were significantly different, but the slopes were not.

Data collection for UT-NIRS was repeated for 3 subjects without simultaneous TCD. Absolute values were slightly different although the overall performance of UT-NIRS was otherwise unchanged.

DISCUSSION

In this study, we compared proxies for relative CBF as measured by TCD ($MCAv_{mean}$) and the relatively newer technology, UT-NIRS (CFVx). TCD was chosen in lieu of direct measurements of CBF because TCD is routinely used in clinical practice and has been extensively evaluated with high degrees of correlation with several methods of CBF measurement.[20,21] While TCD is not a direct measure of CBF, changes in TCD velocities are likely reflective of changes in flow rate through the middle cerebral artery, provided the angle of insonation is unchanged during the measurement period. For the current protocol, we used TCD velocities, with a fixed angle of insonation, as an estimate of blood flow through the middle cerebral artery in healthy subjects, the majority of whom are likely to have normal cerebral autoregulation.

With controlled hypercarbia and hypocarbia, we found a strong correlation between $PEtco_2$ and $MCAv_{mean}$ but less so with CFVx. Although the relationship between UT-NIRS CFVx and $PEtco_2$ was statistically significant, the

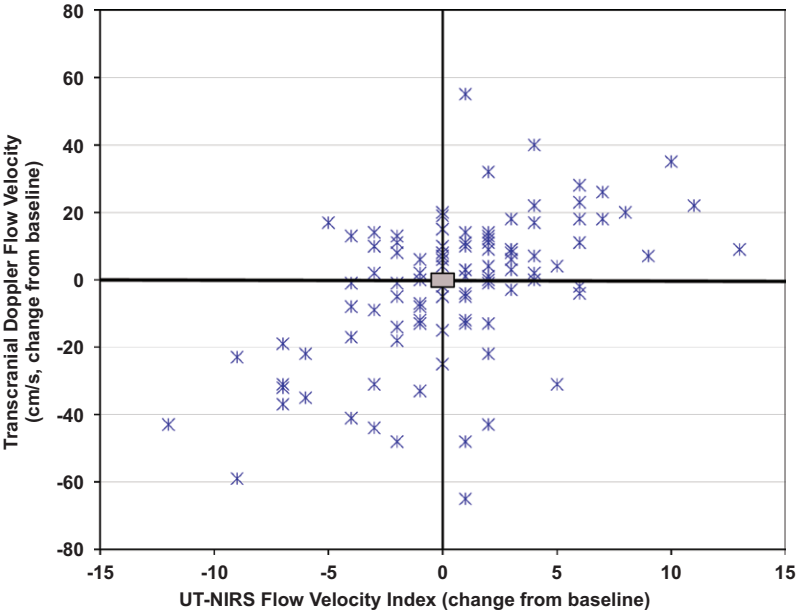

Figure 4. The 4-quadrant plot shows the absolute changes from baseline in transcranial Doppler (TCD) flow velocity and ultrasound-tagged near-infrared spectroscopy (UT-NIRS) flow index. Quadrants where changes are both negative or both positive show agreement. A central exclusion zone where changes are too small to be meaningful was set at 4 for TCD and 1 for the UT-NIRS, which is indicated by the gray box. This was a ratio in approximation to the range of values. The concordance between TCD and UT-NIRS was 63.1%.

Table 2. Data at Different CO_2 Step Changes for the 5 Subjects Who Had TCD With UT-NIRS Both On and Off

Condition ($PEtco_2$ Goal, mm Hg)	Baseline	Nadir, 15–20	25–30	35–40	45–50	Peak, 55–60	Return to Baseline	*P*
TCD								
Left, UT-NIRS on (cm/s)	55.4 ± 11.7	46.2 ± 12.8	54.2 ± 9.5	56.8 ± 13.7	70.4 ± 14.1	84.5 ± 21.2 (4)	56.8 ± 9.7 (4)	<.0001
Left, UT-NIRS off (cm/s)	33.8 ± 3.3	22.4 ± 4.3	35.2 ± 5.8	39.6 ± 3.9	55.4 ± 8.2	69.5 ± 8.7 (4)	30.0 ± 3.9 (4)	<.0001
Right, UT-NIRS on (cm/s)	62.6 ± 16.1	56.4 ± 21.7	66.2 ± 20.6	81.3 ± 12.4 (4)	85.4 ± 28.8	103.2 ± 27.1	61.8 ± 23.0	<.0001
Right, UT-NIRS off (cm/s)	41.0 ± 7.2	31.6 ± 11.8	44.8 ± 12.9	58.0 ± 15.5 (4)	71.4 ± 29.7	94.8 ± 23.2 (4)	36.2 ± 9.6	<.0001
Combined, UT-NIRS on (cm/s)	59.0 ± 13.8	51.3 ± 17.6	60.2 ± 16.4	67.7 ± 17.8 (9)	77.9 ± 22.8	94.9 ± 25.2 (9)	59.6 ± 17.6 (9)	<.0001
Combined, UT-NIRS off (cm/s)	37.4 ± 6.5	27.0 ± 9.7	40.0 ± 10.7	47.8 ± 13.9 (9)	63.4 ± 22.2	82.1 ± 21.1 (8)	33.4 ± 7.9 (9)	<.0001
Left UT-NIRS on (% of baseline)	100% ± 0%	83% ± 9%	98% ± 4%	102% ± 13%	128% ± 20%	143% ± 23% (4)	97% ± 5% (4)	<.0001
Left UT-NIRS off (% of baseline)	100% ± 0%	67% ± 17%	105% ± 18%	119% ± 24%	167% ± 45%	211% ± 37% (4)	91% ± 11% (4)	<.0001
Right UT-NIRS on (% of baseline)	100% ± 0%	87% ± 15%	104% ± 8%	118% ± 13% (4)	136% ± 28%	168% ± 30%	96% ± 15%	<.0001
Right UT-NIRS off (% of baseline)	100% ± 0%	75% ± 19%	108% ± 14%	132% ± 18% (4)	171% ± 42%	231% ± 11% (4)	88% ± 15%	<.0001
Combined, UT-NIRS on (% of baseline)	100% ± 0%	85% ± 12%	101% ± 7%	109% ± 15% (9)	132% ± 23%	157% ± 29% (9)	97% ± 11% (9)	<.0001
Combined, UT-NIRS off (% of baseline)	100% ± 0%	71% ± 17%	106% ± 16%	125% ± 21% (9)	169% ± 41%	221% ± 27% (8)	89% ± 12% (9)	<.0001
UT-NIRS								
Left	47.2 ± 7.8	46.6 ± 7.9	46.2 ± 7.3	47.0 ± 6.1	50.0 ± 6.5	56.2 ± 6.8	52.4 ± 7.6	.0008
Right	43.8 ± 4.2	43.4 ± 4.2	43.2 ± 3.3	45.6 ± 2.7	47.0 ± 3.9	51.8 ± 5.8	47.6 ± 2.5	<.0001
Combined	45.5 ± 6.2	45.0 ± 6.2	44.7 ± 5.5	46.3 ± 4.5	48.5 ± 5.3	54.0 ± 6.4	50.0 ± 5.9	<.0001
Left (% of baseline)	100% ± 0%	99% ± 4%	98% ± 6%	100% ± 8%	107% ± 7%	120% ± 13%	112% ± 9%	.001
Right (% of baseline)	100% ± 0%	99% ± 4%	99% ± 5%	105% ± 7%	108% ± 6%	119% ± 16%	110% ± 14%	<.0001
Combined (% of baseline)	100% ± 0%	99% ± 4%	99% ± 5%	102% ± 7%	107% ± 6%	120% ± 14%	111% ± 11%	<.0001
Spo_2 (%)	99.8 ± 0.4	100.0 ± 0.0	99.4 ± 1.3	100.0 ± 0.0	99.8 ± 0.4	99.8 ± 0.4	100.0 ± 0.0	.70
$PEto_2$ (mm Hg)	114 ± 5	136 ± 8	103 ± 10	109 ± 11	115 ± 6	114 ± 4	126 ± 5	<.0001
$PEtco_2$ (mm Hg)	34.0 ± 4.3	16.7 ± 1.3	30.4 ± 1.7	37.7 ± 2.1	48.6 ± 1.4	59.6 ± 3.9	30.9 ± 4.1	<.0001
Heart rate (/min)	65 ± 5	82 ± 13	65 ± 8	66 ± 9	76 ± 15	90 ± 13	77 ± 7	<.0001
Systolic blood pressure (mm Hg)	114 ± 11	118 ± 13	115 ± 9	120 ± 9	132 ± 17	140 ± 10	123 ± 6	<.0001
Diastolic blood pressure (mm Hg)	69 ± 8	69 ± 11	76 ± 6	82 ± 8	82 ± 8	90 ± 10	74 ± 6	.001
Mean blood pressure (mm Hg)	84 ± 8	86 ± 9	89 ± 6	94 ± 8	98 ± 9	106 ± 7	90 ± 5	<.0001

Data are represented as mean ± SD or mean ± SD (n) if n differs from total.

P values are from repeated measures ANOVA.

"Steps" are the staged changes in Pco_2.

Abbreviations: ANOVA, analysis of variance; $PEtO_2$, end-tidal oxygen partial pressure; $PEtco_2$, end-tidal CO_2 partial pressure; SD, standard deviation; Spo_2, pulse oximeter oxygen saturation; TCD, transcranial Doppler; UT-NIRS, ultrasound-tagged near-infrared spectroscopy.

magnitude of this change was small, and the correlation was statistically significant only with hypercarbia, not with hypocarbia.

The overall trend we observed with TCD $MCAv_{mean}$ is consistent with previously reported relationships between $MCAv_{mean}$ and CO_2.[20,22,23] The magnitude of the change in $MCAv_{mean}$ we observed with changes CO_2 was statistically significant although less than might be expected based on prior reports. This could in part be explained by inadequate time to reach steady state in our study protocol. Although prior studies have reported approximately 5–8 minutes required to achieve steady state, the majority of change in $MCAv_{mean}$ occurs by approximately 3 minutes of exposure to new $Paco_2$ tension.[23,24] While this does not qualitatively alter our findings, as both devices tested should be equally impacted, it is possible that if given a longer period of time to equilibrate during hypocarbia, the UT-NIRS may have reported a significant change in CFVx.

Despite this possibility, the limited change of c-FLOW UT-NIRS measurements with hypocarbia (condition of acutely decreased CBF) is of particular relevance as many clinical applications (eg, cerebral vasospasm post subarachnoid hemorrhage) require sensitivity for detecting acute decreases in CBF. In the configuration tested here, UT-NIRS had relatively limited sensitivity to detect large changes in CBF.

The challenges with the small numerical changes with the UT-NIRS were more apparent in analyzing ROC curves. While the overall sensitivity and specificity of UT-NIRS could be considered fair with AUC in the 0.7–0.8 range, the sensitivity and specificity for detecting changes in CBF was much worse than with TCD, which was excellent. Smaller changes in CBF would be harder to detect with UT-NIRS.

There were several challenges and limitations encountered during the study protocol that warrant discussion and may be relevant to clinical application of the UT-NIRS technology in its current form.

The present study was not designed to help elucidate potential mechanisms responsible for our observation that UT-NIRS was less sensitive in detecting $PEtco_2$-related changes in CBF than TCD. Further studies are needed to explain this finding.

On study subjects where both TCD and UT-NIRS were used concurrently, a large amount of interference was easily visible on the TCD measurement (Supplemental Digital Content, Appendix 1, http://links.lww.com/AA/C112) and resulted in higher TCD values than when UT-NIRS was off. This finding was discussed with the UT-NIRS manufacturer, and although it is to be expected, we had not anticipated this limitation in our study design. It is relevant to note that previously published studies of concurrent TCD and UT-NIRS do not specifically comment on this interference.

To ensure accurate TCD measurements, the UT-NIRS device was paused for a period of <5 seconds to obtain an accurate TCD envelope and measurement and then restarted. This was done for study subjects 1–5. According to the manufacturer, this should not affect the CFVx accuracy. We observed prominent variability when turning on the UT-NIRS after these brief pauses in our protocol. This variability stabilized over a period of minutes and was not quantified in the present study. Nonetheless, to avoid the possibility that frequently pausing and unpausing the UT-NIRS impacts the quality of its measurements, in study subjects 6–10, the UT-NIRS was left to run continuously. A similar relationship between UT-NIRS CFVx and $Etco_2$ was found.

To eliminate the potential limitation that TCD could interfere with UT-NIRS measurements, 3 study subjects underwent repeat measurements with UT-NIRS alone, using the same protocol on a different study day. As expected, absolute values were slightly different although the overall performance of UT-NIRS was otherwise unchanged.

This study was designed to complete testing in each subject in <1 hour due to limitations in comfort while breathing on the experimental apparatus. As a result, despite efforts to achieve stable plateau values for $MCAv_{mean}$ and UT-NIRS, it is possible that true plateaus in CBF were not captured during the study.[25] In addition, appropriate positioning and repositioning of TCD probes during the protocol further limited time available for testing.

In several study subjects, the signal from the UT-NIRS on one side of the subject's head had a lower signal strength than the other side, as displayed in the signal strength indicator. Of note, signal strength was still greater than or equal to that recommended by the manufacturer in all subjects. Continuous data collection during the study was limited by the lack of such output from the TCD device. Data were collected manually at 1-minute intervals, thereby limiting the ability to detect transient changes in measurements.

A final limitation of the present study is the relatively small sample size of 10. Based on our hypotheses and findings, we believe that none of the issues reported would have been significantly changed with a larger sample size. Repeated measures regression and the ROC curves were robust, and only the ability to perform multiple comparisons on all data was limited, due largely to the number of step changes in $PEtco_2$.

CONCLUSIONS

Our data indicate a statistically significant trend in UT-NIRS CFVx that correlates with changes in TCD $MCAv_{mean}$ as induced by hypercarbia but not hypocarbia. Our data also demonstrate that the UT-NIRS appears less sensitive to changes in CO_2 than TCD. Thus, although applicability of UT-NIRS in real-time clinical scenarios may be relatively limited, this may potentially be overcome by changes in the uncalibrated scale used by the device. Additional refinement and validation are likely needed before widespread clinical utilization of UT-NIRS. ■

DISCLOSURES

Name: Michael S. Lipnick, MD.
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Contribution: This author helped design the study, collect the data, and prepare the manuscript.

Name: John R. Feiner, MD.
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