Intraoperative Cerebral Autoregulation Assessment Using Ultrasound-Tagged Near-Infrared-Based Cerebral Blood Flow in Comparison to Transcranial Doppler Cerebral Flow Velocity: A Pilot Study

John M. Murkin, MD, FRCPC,* Moshe Kamar, MD,† Zmira Silman, MSc,† Michal Balberg, PhD,† and Sandra J. Adams, RN*

Objective: **This was a pilot study comparing the ability of a new ultrasound-tagged near-infrared (UT-NIR) device to detect cerebral autoregulation (CA) in comparison to transcranial Doppler (TCD).**

Design: **An unblinded, prospective, clinical feasibility study.**

Setting: **Tertiary-care university hospital cardiac surgical operating rooms.**

Participants: **Twenty adult patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).**

Interventions: **There were no clinical interventions based on study monitoring devices, but a continuous correlation analysis of digital data from transcranial Doppler (TCD) velocity was compared with a novel UT-NIR device and correlation analysis of change signals versus mean arterial pressure was performed in order to detect presence or absence of intact CA and for determination of the lower limit of cerebral autoregulation during CPB.**

Measurements and Main Results: **Similar and highly significant concordance ($\kappa = 1.00$; $p < 0.001$) was demonstrated between the 2 methodologies for determination of CA, indicating good correlation between the 2 methodologies. Intact CA was absent in 2 patients during CPB, and both devices were able to detect this.**

Conclusions: **To the authors' knowledge this is the first clinical report of a UT-NIR device that shows promise as a clinically useful modality for detection of CA and the lower limit of cerebral autoregulation. The utility of UT-NIR was demonstrated further during times at which extensive usage of electrocautery or functional absence of the transcranial window rendered TCD uninterpretable.**

KEY WORDS: cerebral blood flow, CBF, transcranial Doppler, TCD, ultrasound-tagged near-infrared device, UT-NIR, cardiopulmonary bypass, CPB, cerebral autoregulation

CARDIAC SURGERY employing cardiopulmonary bypass (CPB) has been associated with a variety of adverse neurologic and systemic outcomes.[1] Spontaneous and procedural variations in either cardiac output or pump flow rate during CPB, as well as changes in $PaCO_2$, mean arterial pressure (MAP), temperature, and cerebral metabolic rate, can produce alterations in regional and global cerebral blood flow (CBF) and may be etiologic in neurologic dysfunction.[2] A developing body of literature is demonstrating a strong correlation between perfusion below the lower limit of cerebral autoregulation (LLA) and associated major organ morbidity and mortality.[1,3,4]

Although posing technical challenges, relative changes in CBF can be quantified reliably using transcranial Doppler (TCD) via insonation of the middle cerebral artery (MCA) to detect alterations in MCA flow velocity (MCAFV) during conditions under which MCA diameter remains constant.[5,6] A recently introduced and commercially available near-infrared (NIR)-based device incorporating ultrasound (US) phase shifting of emitted NIR photons (UTLight Flowmetry, Ornim Medical Ltd., Kefar Saba, Israel) also allows monitoring of relative changes in cerebral microcirculatory perfusion (cerebral flow index [CFI]).[7]

As a "proof of concept" of the validity of CFI for continuous noninvasive monitoring of cerebral perfusion, the authors undertook a study employing time domain-based correlation analysis between MAP and CFI and MAP and MCACFV as a means of assessing cerebral autoregulation (CA) and the LLA in patients undergoing cardiac surgical procedures employing CPB.

Recognizing that TCD assesses flow velocity in major cerebral vessels whereas CFI monitors cerebral cortical microcirculatory flow, the authors hypothesized that indices of microcirculatory perfusion, including presence of cerebral autoregulation and LLA during CPB, would be detected by UT-NIR flowmetry during conditions under which CBF was expected to undergo large changes (eg, changes in MAP, CPB pump flow rate changes, circulatory stasis, etc) and would correlate with changes in MCAFV.

Because employment of a running correlation analysis between spontaneous changes in MAP and MCAFV has been demonstrated to detect presence or absence of CA in critical care and other clinical settings,[8] the authors further hypothesized that by using a similar analysis technique, UT-NIR flowmetry could be investigated to determine if MCAFV correlated with CFI the ability to evaluate CA and LLA during nonpulsatile CPB.[9,10]

MATERIALS AND METHODS

After receiving approval of the study protocol from the University Research Ethics Board (#17837; June 7, 2011) and obtaining written informed consent, 26 patients undergoing elective cardiac surgery with use of nonpulsatile CPB were enrolled in the study. Exclusion criteria included age < 18 years, emergency surgery, stroke within preceding 3 months, and off-pump coronary revascularization.

After induction of anesthesia using fentanyl, rocuronium, and sevoflurane, titrated to maintain the bispectral index (BIS) in a range between 40 and 60 throughout the intraoperative period, a

*From the *Department of Anesthesiology and Perioperative Medicine, Schulich School of Medicine, University of Western Ontario, London, Canada; and †Ornim Medical, Kfar Saba, Israel.*

Address correspondence to John M. Murkin, MD, Rm C3-112 University Hospital, 339 Windermere Rd, London, ON, N6A 5A5, Canada. E-mail: john.murkin@lhsc.on.ca

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single TCD probe (SonaraTek, Natus Medical Inc, San Carlos, CA) was placed over the right temporal bone window using a designated fixation device (ST3, Spencer Technologies, Seattle, WA) and focused at a depth between 45 mm and 55 mm to provide optimal signal acquisition from insonation of the MCA. A unilateral UT-NIR sensor was placed on each patient's forehead ipsilateral to the TCD probe, overlooking the territories of the middle and anterior cerebral arteries (MCA, ACA). Baseline measurements were obtained after induction of anesthesia before the commencement of surgery. All hemodynamic parameters, temperature, and respiratory gases were recorded continuously and stored on digital media (Datex-Ohmeda S/5 Collect, Version 5 Finland, FIN-00031), as were digital signal outputs from TCD and UT-NIR devices. All monitoring devices were time synchronized at the commencement of the study period.

Consistent with institutional clinical routine, relevant laboratory parameters (arterial blood gas, hematocrit), temperature, anesthetic gas concentration, cardiac output/pump flow rate, and MAP were recorded at specified measurement intervals onto a designated case record form.

After administration of heparin to achieve activated clotting time (ACT) >450 seconds, patients were cannulated with a single 2-stage venous cannula and ascending aorta cannula, and nonpulsatile, mild hypothermic (temperature 34°C) CPB commenced, employing a membrane oxygenator with a pump flow of 2.0-2.5 L/m^2/min with continuous BIS monitoring titrated to maintain the depth of anesthesia using sevoflurane. Alpha-stat pH management was employed during CPB to ensure maintenance of constant blood CO_2 content and minimize the impact on cerebral autoregulation.[2] After separation from CPB, protamine was administered for heparin reversal, and patients were returned to the intensive care unit (ICU) for postoperative mechanical ventilation until extubation several hours postoperatively. CBF monitoring was stopped upon completion of sternal closure prior to transfer to the ICU.

DATA ANALYSIS

Patients were monitored during 3 periods of surgery: pre-CPB, during CPB, and post-CPB. A comparison of CFI to TCD for detection of CA was made during CPB. This period is unique because it has no electrocautery signal interference, which greatly confounds TCD signal. To define CA, a nonoverlapping, moving Pearson's correlation coefficient was calculated between the MAP and CBF velocity to determine the mean velocity index (Mx), and between MAP and CFI to find the cerebral flow index correlation index (CFIx).[7,8] Consistent with previous studies,[9,10] consecutive, paired, 10-second averaged values of 300 seconds duration were used for each calculation, incorporating 30 data points for each index. When autoregulation is intact, there is a low correlation between CBF and MAP, and Mx and CFIx approach 0; whereas when autoregulation is impaired, Mx and CFIx values approach 1.[8,9] For each patient, Mx and CFIx values were categorized in 5-mmHg increments of MAP. Intact CA was defined as an Mx or CFIx value <0.35 for 2 consecutive MAP increments, corresponding to a minimum 10-mmHg change in MAP.[11] The agreement between Mx and CFIx in detecting CA was evaluated using κ agreement test. LLA during CPB was defined as the MAP level demonstrating an increase of CFIx or Mx above the predefined value of 0.35.[11] Comparisons between device LLA levels was assessed using the Wilcoxon paired test. The CA state of each patient during all 3 study periods was assessed based on CFIx. Changes in MAP and CFI during the 3 study periods were compared using Friedman's test followed by Dunn's test.

Comparisons between general characteristics of each group was assessed using the Kruskal Wallis test for continuous measurements and using χ^2 or Fisher exact test for categorical measurements. Significance level was defined as $\alpha = 0.05$. Statistical analyses were carried out using Statistical Package for Social Sciences (SPSS Statistics for Windows, Version 22.0. 2013, Armonk, NY: IBM Corp).

As a pilot study, the sample size was based in part on a previous study in which a similar UT-NIRS device was demonstrated to reliably detect change in CBF in 10 healthy volunteers.[12] Given that the current study represented the initial utilization of this device in an operating room setting and thus faced unknown logistic challenges and potential patient dropouts, a convenience sample of 12 patients evaluable for correlation analysis was deemed sufficient.

RESULTS

A total of 26 patients consented to this study, 6 of whom subsequently were excluded due to problems with the data acquisition system that resulted in loss of continuous MAP and other hemodynamic measurements, leaving 20 patients enrolled for analysis. Figure 1 represents the flow chart of data acquisition, and Table 1 gives patient and procedural characteristics for all consenting patients and indicates that there were no significant differences between those included or excluded from data analysis. Of these 20 enrolled patients, there were 8 in whom sufficient TCD data could not be obtained due to an inadequate temporal window or movement-induced loss of TCD signal during CPB. This allowed the primary analysis evaluating the agreement between CFIx and Mx to be calculated on 12 data sets, which provided validation of CFIx for detection of CA. A subset analysis describing the change in CA state (ie, autoregulation yes/no) during pre-CPB and post-CPB periods of the study was conducted on all 20 enrolled patients using the validated CFIx and MAP data.

Mean duration of surgery was 239 ± 100 minutes, whereas mean duration of CPB was 117 ± 74 minutes. Hemodynamic and biochemical parameters are shown in Table 2 as mean ± SD with comparisons among the 3 study periods. Importantly, there were no significant differences in $PaCO_2$, a key determinant of CBF, among study periods, and although MAP was lower significantly during CPB, it did not differ between pre- and post-CPB phases.

Comparison Between Mx and CFIx for Detection of CA During CPB

As shown in Table 3, of the 12 patients in whom both CFI and TCD data were analyzed for Mx and CFIx, 10 patients (83.3%) demonstrated intact CA (ie, Mx, CFIx correlation coefficient ≤0.35 for 2 or more intervals), whereas 2 patients demonstrated impaired CA (ie, Mx, CFIx correlation coefficient >0.35 for the majority of the MAP range). There was perfect agreement ($\kappa = 1.00$, $p < 0.001$) between the classification of CA (present or absent) based on CFIx compared with that derived from Mx. LLA was defined for each patient

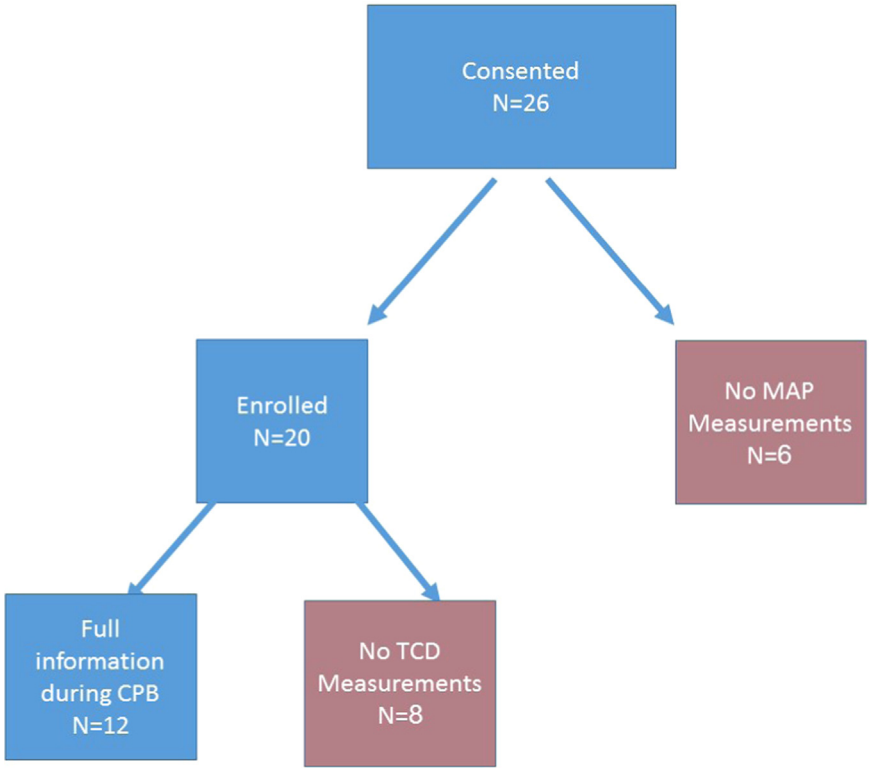

Fig 1. Flow chart of patient enrollment. CA, cerebral autoregulation; MAP, mean arterial pressure; CFI, cerebral flow index; TCD, transcranial Doppler.

as the value of MAP in which Mx or CFIx demonstrated an increase above the threshold of 0.35. In cases in which Mx and CFIx were below threshold (<0.35) for all examined MAP ranges, the minimal MAP bin was defined as LLA. Both the individual and group mean ± SD LLA detected by the Mx and CFIx methods during CPB were similar at 48.5 ± 11.1 and 48.0 ± 12.1 mmHg, respectively, and the range for both was 30 to 70 mmHg ($p = 0.785$, Wilcoxon test) and highly correlated ($r^2 = 0.828$, $p = 0.003$) as shown in Figure 2.

Autoregulation Based on CFIx for the Periods of Pre-CPB, During CPB, and Post-CPB

Given the concordance between Mx and CFIx in detecting the presence or absence of CA during CPB, further analysis of CA was conducted using CFIx for pre-CPB and post-CPB study periods as shown in Table 3. Of the 20 patients in whom complete hemodynamic and CFI data were obtained during all 3 phases, 6 patients (30%) demonstrated impaired CA whereas

Table 1. Demographic and Procedural Variables of All Patients

	CFI, TCD, MAP	CFI, MAP	No MAP	Total	p Value
Monitoring (n)	12	8	6	26	
Male N (%)	10 (83%)	4 (50%)	4 (67%)	18 (69%)	0.283
Age (y) mean ± SD	63.5 ± 11.3	65.5 ± 13.4	64.2 ± 14.3	64.9 ± 12.2	0.573*
Current smoking (N = 22)	6 (67%)	4 (50%)	2 (40%)	12 (55%)	0.603
Diabetes (N = 25)	6 (55%)	4 (50%)	3 (50%)	13 (52%)	0.977
Hypertension (N = 24)	8 (73%)	6 (86%)	4 (67%)	18 (75%)	0.711
CAD (N = 24)	8 (73%)	5 (71%)	4 (67%)	17 (71%)	0.965
Procedure					
CABG	4 (33%)	4 (50%)	3 (50%)	11 (42%)	
AVR	3 (25%)	3 (38%)	2 (33%)	8 (31%)	
CABG + AVR	3 (25%)	1 (13%)	0 (0%)	4 (15%)	
MVR	2 (17%)	0 (0%)	1 (17%)	3 (12%)	
Duration CPB (min) mean ± SD	99.1 ± 17.6	119.1 ± 25.1	149.2 ± 41.3	116.8 ± 74.1	0.547*
Duration surgery (min) mean ± SD	195.7 ± 17.5	260.5 ± 26.5	298.5 ± 63.5	239.3 ± 99.6	0.041*

NOTE. For categorical data, p values by χ^2 test; for continuous measurements.

Abbreviations: CFI, cerebral flow index; TCD, transcranial Doppler; MAP, mean arterial pressure; CAD, coronary artery disease; CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve repair or replacement; CPB, cardiopulmonary bypass.

*p values by Kruskal Wallis test.

Table 2. Intraoperative Hemodynamic and Biochemical Variables

Mean ± SD	Pre-CPB	On-CPB	Post-CPB	p value*	p value pre to CPB	p value pre to post
Hgb (g/dL)	12.5 ± 1.5	9.2 ± 1.2	9.7 ± 1.3	<0.001	<0.001	0.004
MAP (mmHg)	77.2 ± 6.4	61.8 ± 6.5	75.0 ± 6.3	<0.001	0.001	0.952
CFI (AU)	8.6 ± 2.5	6.6 ± 2.3	9.0 ± 3.4	<0.001	0.001	1.000
PaCO2 (mmHg)	43.8 ± 3.9	41.7 ± 3.5	40.8 ± 4.3	0.078	N/A	N/A
TCD† (cm/sec)	N/A	28.4 ± 11.8	N/A	N/A	N/A	N/A
Temperature (°C)	35.4 ± 0.4	35.1 ± 0.6	36.6 ± 0.5	0.008	1.000	0.073
pH	7.4 ± 0.04	7.4 ± 0.03	7.42 ± 1.7	0.504	N/A	N/A

NOTE: Pre-CPB, on-CPB, and post-CPB refer to the 3 study periods.

Abbreviations: Hgb, hemoglobin concentration; MAP, mean arterial pressure; CFI, cerebral flow index; TCD, transcranial Doppler.

*Comparison among 3 study periods based on Friedman's test followed by Dunn's post hoc test.

†TCD was available only during CPB.

14 (70%) demonstrated intact CA during the CPB period. As shown in Table 3, there were 9 patients in whom CA was impaired before CPB, of whom 5 demonstrated intact CA during and 4 after CPB. There were no significant differences in age or sex between patients with or without CA ($p = 0.281$, $p = 1.000$, respectively); however, among patients who were diagnosed with coronary artery disease, there was a trend for a higher rate of nondetectable CA of 50% versus 10% ($p = 0.07$, 1-sided Fischer exact test).

DISCUSSION

The present study was a feasibility study investigating the efficacy of a new UT-NIR device for monitoring CFI and determining CA and LLA in the operating room environment, and as such faced several challenges. As TCD is the only other continuous and noninvasive technique for assessment of CA, the authors sought to employ it for cross-validation of UT-NIR detection of CA. However, TCD is limited by the need to find and maintain an acoustic window, is highly operator dependent, and is very susceptible to interference from electrocautery and other noise transients. This was demonstrated in the current study as insufficient TCD data were obtained during electrocautery-free intervals to permit calculation of Mx during pre-and post-CPB intervals and in which a stable and continuous TCD signal could not be maintained in a further 8 of 20 patients during CPB. Of note, while a 40% failure rate for TCD monitoring may appear excessive, it is not inconsistent with other such clinical studies. In a study of 239 patients, it was reported that TCD was unsuccessful in 46% of female patients even at highest ultrasound intensity, and another study of 176 carotid endarterectomies reported an inability to monitor TCD hemodynamics in >40% of patients.[13,14]

Because agreement was demonstrated between Mx and CFIx in determining the presence or absence of CA during CPB, and given the high correlation ($r^2 = 0.828$; $p = 0.003$) between LLA determined independently by each device, as show in Figure 2, a further analysis of CA employing only CFIx data during pre- and post-CPB study periods was undertaken. The agreement in determination of CA between the 2 modalities of Mx and CFIx in patients monitored during CPB demonstrated that the UT-NIR device could detect CA and provided continuous monitoring of CBF intraoperatively independent of electrocautery usage.

The resulting observation that 15% of patients demonstrated impairment of CA during CPB, as represented in Figure 3B, was similar to the 20% incidence found in the study of Ono et al.[1] Although very preliminary, the further observation that 1 patient in whom intact CA was present before CPB, but who subsequently demonstrated impaired CA during and after CPB, and 5 patients in whom CA was impaired pre-CPB, all of whom demonstrated CA during CPB (Figs 3A and 4) of whom showed intact CA post-CPB, was provocative and suggested that nonpulsatile perfusion or other unknown factors during CPB may be etiologic in altering cerebrovascular vasoreactivity in the perioperative period. Also, while the mean LLA detected during CPB was 48 mmHg and was compatible with generally accepted perfusion parameters of MAP >50 mmHg during CPB, it should be borne in mind that 2 of 10 patients had LLA ≥60 mmHg and at least 2 further patients had nonintact CA, consistent with other reports.[1] This was further evidence

Table 3. Presence or Absence of Cerebral Autoregulation (CA) in Individual Patients

Measure	CA status				LLA (mmHg)	
Monitor Type	CFIx			Mx	CFIx	Mx
Study Interval/Subject ID	Pre	CPB	Post	CPB	CPB	
1	CA	CA	CA		40	
2	CA	CA	CA		60	
3	CA	CA	CA	CA	70	70
4	CA	CA	CA	CA	40	40
5	CA	CA	CA	CA	40	50
6	CA	CA	CA	CA	30	30
7	CA	CA	CA	CA	50	50
8	CA	CA	CA	CA	55	45
9		CA	CA	CA	60	60
10	nCA	CA	CA		50	
11	nCA	CA	CA		50	
12	nCA	CA	CA	CA	35	40
13	nCA	CA		CA	50	50
14	nCA	CA	CA	CA	50	50
15	nCA	nCA	CA		40	
16	nCA	nCA	CA	nCA		
17		nCA	nCA		40	
18	nCA	nCA	nCA			
19	nCA	nCA	nCA	nCA		
20	CA	nCA	nCA		45	

NOTE. Pre is before CPB period; post is after CPB period; # indicates individual study patients.

Abbreviations: CFI, NIRS-derived cerebral flow index; TCD, transcranial Doppler; LLA, lower limit of cerebral autoregulation; nCA, nondetectable cerebral autoregulation; CPB, cardiopulmonary bypass period.

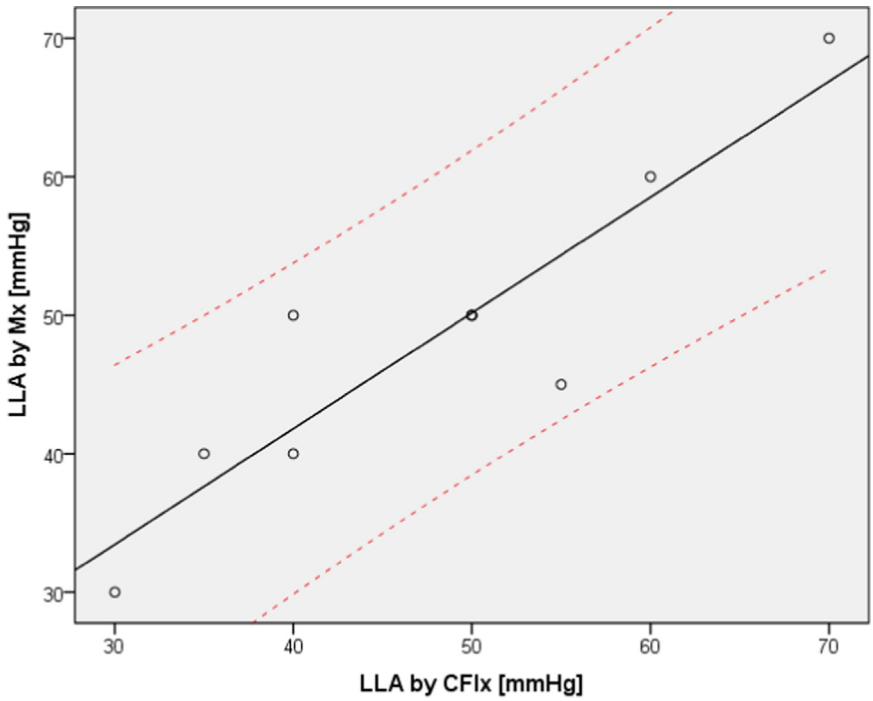

Fig 2. Correlation of LLA between TCD and UT-NIR. The figure demonstrates the correlation between LLA values as detected by both methods. LLA, lower limit of cerebral autoregulation UT-NIR, ultrasound-tagged near-infrared device; TCD, transcranial Doppler; CFIx, cerebral flow index correlation index; Mx, TCD flow velocity correlation index. ($r^2 = 0.828$; $p = 0.003$).

that monitoring and individualization of cerebral perfusion parameters is a requisite for maintenance of optimal perioperative cerebral perfusion.

It also must be borne in mind, however, that these were preliminary observations and will need further validation because this investigation was undertaken as a feasibility study rather than as a primary assessment of cerebral physiology. Also, the cutoff threshold of 0.35 for the presence or absence of intact CA, while consistent with similar studies,[11] remained arbitrary and may have been predisposed toward a determination of nonintact CA; even the dichotomous categorization of CA as intact or nonintact may be a simplification because there is increasing evidence of even more subtle alterations in CA that reflect degrees of vasoreactivity more optimally characterized in head injury patients as "better or worse" cerebral autoregulation rather than an "all-or-none" phenomenon.[8]

In contradistinction to cerebral oximetry and related CFx indices, which reflect changes in cerebral tissue oxygen saturation and thus only indirectly reflect changes in CBF,[15,16] UT-NIR measures regional microcirculatory cerebral cortical perfusion in vessels <1 mm in diameter.[16,17] The degree to which current cerebral oximetry devices are susceptible to changes in cerebral venous/arterial blood partitioning and signal contamination from extracerebral tissue is a subject of increasing interest.[18,19] These issues largely are eliminated because of the novel use of ultrasound-tagged light as incorporated in the UT-NIR device, in which the phenomenon of acousto-optic coupling enables differential filtering of the CFI signal predominantly to reflect cerebral cortical capillary flow.[17]

The technology is based on the physical effect of *ultrasound-tagged light*: light is scattered (tagged/resonated) when photons interact with ultrasound waves in tissue. Localization is achieved by detecting the slight Doppler shift of light that was *tagged* (resonated) in a specific tissue volume. As the NIR laser light is scattered additionally by moving blood cells, it undergoes a further Doppler shift because tagged photons that encounter moving blood cells will show a slight Doppler shift relative to their original acoustic frequency. This shift affects the power spectrum of the tagged light at the acoustic frequency, enabling calculation of relative change in blood flow.

Although primarily a measure of cerebral microcirculatory flow, UT-NIR has been shown to correlate with changes in global CBF, as shown by Schytz et al when comparing UT-NIR to 133Xe single-photon-emission computed tomography in healthy volunteers in response to acetazolamide administration.[12] Transcranial Doppler assesses large-vessel (eg, MCA) flow velocities; therefore, as in this study, it was anticipated that both UT-NIR and TCD modalities would trend similarly but not necessarily correlate.

Increasingly, real-time detection of cerebral CA demonstrates a significant role in patient outcomes in various settings. In a series of 234 cardiac surgical patients, Ono et al reported impaired CA during CPB in 20%.[1] Of these patients, multivariate analysis demonstrated a significant correlation between impaired CA during CPB and perioperative stroke, with an occurrence in 6 of 47 (12.8%) patients with impaired CA compared with 5 of 187 (2.7%) in whom CA was intact.[3] Whether detection of CA will have similar prognostic importance in other high-risk clinical settings is yet to be determined. In severe traumatic brain injury, use of invasive intracranial pressure monitoring and MAP to calculate PRx and a low-frequency autoregulation index as comprehensive indices

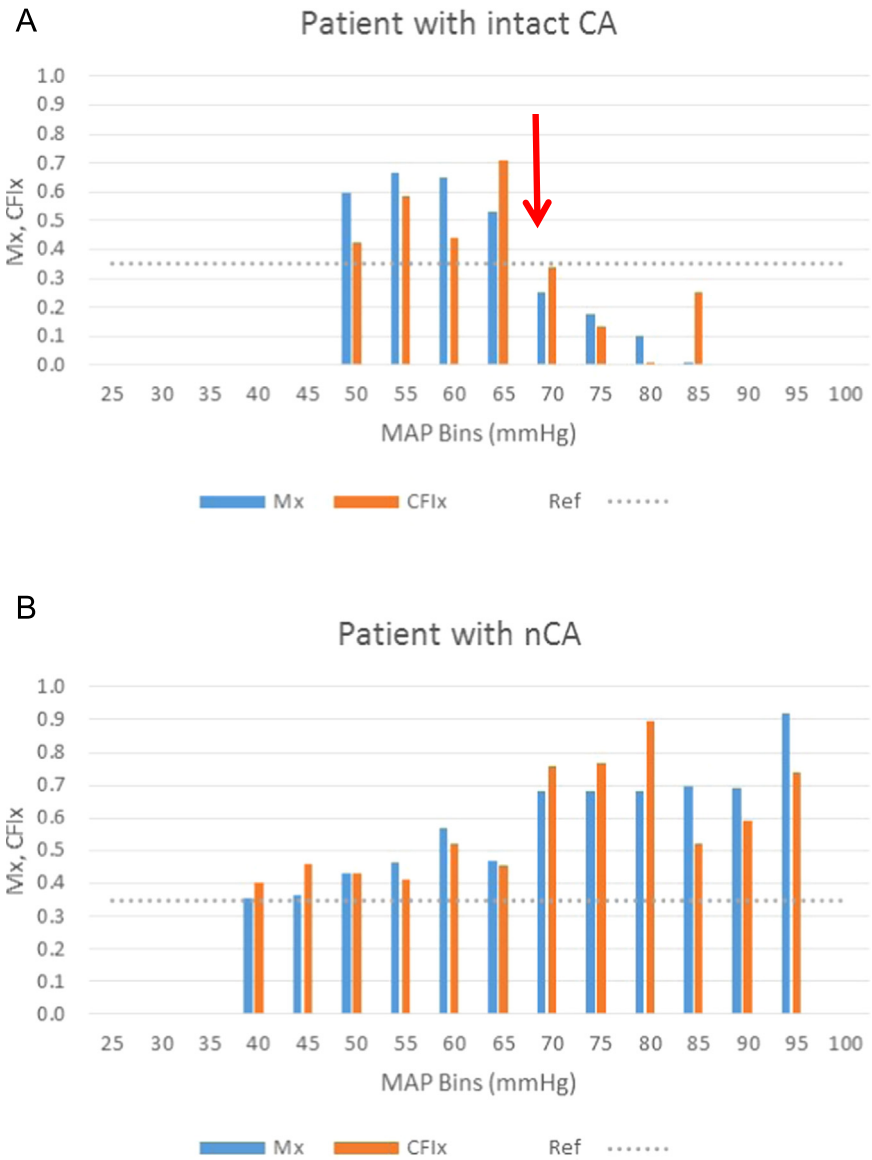

Fig 3. Example of patients with intact and nonintact cerebral autoregulation. CA, cerebral autoregulation; nCA, absent cerebral autoregulation; CPB, cardiopulmonary bypass; Mx, mean velocity index; CFIx, cerebral flow index correlation index; LLA, lower limit of CA as shown by vertical arrow (A). Ref is Mx/CFIx >0.35 and indicates absence of CA (B).

of cerebrovascular autoregulatory capacity increasingly are being advocated for clinical management guidelines, with a goal of optimizing cerebral perfusion without increasing and potentially lowering intracranial pressure.[20]

The associations that have been made to date between impairment of CA and duration of hypotension below LLA and various adverse cerebral and renal outcomes make optimal MAP and cerebral perfusion pressure management a dynamic and potentially titratable process in a variety of high-risk patients.[3,4,15]

The concept that cerebrovascular autoregulatory capacity is a dynamic physiologic phenomenon sensitive to perturbations in the brain milieu, as reflected in the temporally and procedurally variable results shown by several patients within the current study, is provocative. Whether the dynamic status of CA the

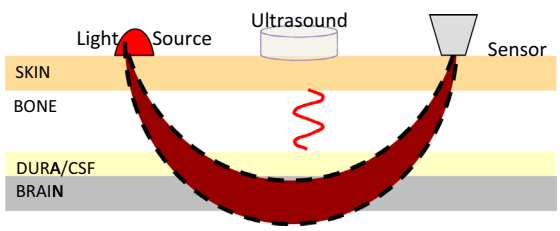

Fig 4. Schematic of US-tagged NIR device, in which light source indicates laser NIR, ultrasound indicates integral ultrasound crystal incorporated into the device and imparting Doppler shift to NIR light, sensor represents sensing component of UTLight Flowmetry NIR device, and skin, bone, dura/CSF and brain represent various tissue layers.

authors observed in some patients was related to alterations in autonomic tonus,[21] alterations in plasma volume,[22] or systemic inflammation and endotoxin release,[23] all of which can accompany CPB, or rather reflected other unknown mechanisms currently is unclear, but the demonstrated ability of CFIx to function as a noninvasive index of cerebral autoregulatory homeostasis is becoming increasingly clinically attractive.[24]

The current feasibility study demonstrated excellent concordance of CFIx with TCD-derived Mx for detection of CA and LLA, and the authors anticipated that it will be followed by a larger study based on data and experience gained from the current investigation.

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