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

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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

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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