A Novel Assessment of Peripheral Tissue Microcirculatory Vasoreactivity Using Vascular Occlusion Testing During Cardiopulmonary Bypass

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Objective: Cardiac surgery and cardiopulmonary bypass are associated with release of inflammatory mediators and microcirculatory alterations that result in organ dysfunction. Near-infrared spectroscopic measurement of tissue oxygen saturation (StO_2) and the vascular occlusion test (VOT) were utilized in a study of elective cardiac surgical patients as a novel, noninvasive method of assessing microcirculatory vasoreactivity during nonpulsatile cardiopulmonary bypass (CPB). The objective of this pilot study was to determine whether differences in microcirculatory function and vasoreactivity could be measured in cardiac surgery using StO_2 and VOT.

Design: A prospective, observational trial.

Setting: Tertiary care teaching hospital.

Participants: Thirteen patients undergoing elective cardiac surgery using tepid, nonpulsatile cardiopulmonary bypass.

Interventions: Patients had continuous regional oxygen saturation monitoring using near-infrared spectroscopy and vascular occlusion tests performed in the perioperative period before, during, and after cardiopulmonary bypass.

Measurements and Main Results: Occlusion slope and hyperemic area did not vary significantly. Mean reperfusion slope was significantly lower during cardiopulmonary bypass (2.4%/second) compared to before and after bypass (4.1 and 3.5%/second, respectively). Reperfusion slope decreased as a function of CPB duration.

Conclusions: This pilot study demonstrates a significant difference in reperfusion slopes during cardiopulmonary bypass when compared to prebypass and postbypass, suggesting impaired peripheral microvascular reactivity. Reperfusion slopes also exhibited a successive decline with duration of CPB, implying worsening microcirculatory dysfunction that returned to baseline values in all patients within 1 hour of separation from CPB. This noninvasive technique has potential to optimize circulatory parameters during cardiopulmonary bypass.

KEY WORDS: cardiopulmonary bypass, near-infrared spectroscopy, microcirculation

CARDIAC SURGERY and cardiopulmonary bypass (CPB) are associated with microcirculatory alterations[1] and release of inflammatory mediators[2] that are similar to severe sepsis. Microcirculatory dysfunction has been detected during and after cardiac surgery using sidestream dark field imaging[3,4]; however, it is a relatively cumbersome apparatus, and obtaining reliable intraoperative measurements is difficult. Well described in septic and hypovolemic shock,[5–7] near-infrared spectroscopic (NIRS) measurement of tissue oxygenation (StO_2) and vascular occlusion testing (VOT) are novel technologies for assessing the microcirculatory function of peripheral tissues specifically in cardiac surgery patients during CPB.

NIRS uses computer analysis of spectra in the near-infrared range (680-800 nm) to determine regional tissue hemoglobin oxygen saturation.[5] Commercially available monitors (Somanetics INVOS 4100 and Hutchinson InSpectra) calculate tissue perfusion and express it as a percentage of oxygen saturation. According to Beer's law, the spectrophotometric signal is limited to vessels with a diameter less than 1 mm (arterioles, capillaries, and venules),[7] and because NIRS is limited to monitoring only small vessels, it has been used to assess oxygen balance in the microcirculation of skeletal muscle.[8] The advantages of NIRS measurement of global tissue oxygenation include ease of use, reliability, noninvasiveness, real-time measurements, and avoidance of diagnostic phlebotomy.[5,7]

NIRS measurement of peripheral StO_2 combined with a reproducible ischemia-reperfusion challenge to induce reactive hyperemia has been described as a practical method for assessing tissue perfusion and vasoreactivity of the peripheral microcirculation.[6] A short period of ischemia followed by reperfusion stimulates release of endogenous nitric oxide (NO) from the microvascular endothelium resulting in hyperemia that appears subsequently to be modulated via alterations in NO bioavailability. Measurement of this ischemic/hyperemic response in the thenar muscle using NIRS has been validated as a noninvasive method of quantifying the integrity of microcirculatory vasoreactivity that demonstrates strong correlation with the gold standard of strain gauge plethysmography.[9] In patients with microcirculatory dysfunction, reactive hyperemia is impaired, and the slope of StO_2 recovery during VOT can be used to quantify such impairment.[8] As it has been demonstrated that prolonged exposure to CPB is associated with abnormal vasomotor responses and subsequent end-organ dysfunction,[1] the authors used continuous StO_2 and VOT as novel, noninvasive measures to evaluate the impact of CPB on vasoreactivity as an index of microcirculatory perfusion. The objective of this pilot study was to determine whether differences in microcirculatory function and vasoreactivity could be measured during cardiac surgery using StO_2 and VOT.

METHODS

This study was funded by an internal department research grant. After obtaining institutional review board approval and written informed consent, 13 patients undergoing elective cardiac surgery were enrolled. An initial bolus of heparin of 300 to 400 IU/kg was administered to maintain activated coagulation time above 480 seconds prior to cannulation of the ascending aorta using a no. 21 Sarns® cannula and a single two-stage atrial cannula for venous drainage. A 40-μm arterial line filter and a nonsurface-modified membrane oxygenator incorporating

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integrated venous and cardiotomy reservoir (Capiox®) was employed for CPB using a nonocclusive roller pump and in-line monitoring of venous saturation and hematocrit (Hct). During CPB, flow rates of 2.0 to 2.5 L/min/m^2 were used, with rectal temperature maintained at 34°C to 35°C during alpha-stat pH management. PaO_2 was maintained in the range of 150 to 200 mmHg. As per institutional protocol, lactated Ringer's solution was used for CPB pump prime and all intraoperative fluid administration.

After application of the aortic cross-clamp, both antegrade and retrograde cold blood cardioplegia were used for myocardial protection. To maintain anesthetic depth, the bispectral index was maintained in the range of 40 to 60 using a minimum concentration of inhaled sevoflurane titrated continuously by vaporizer during CPB. Best clinical practices aimed at maintenance of Hct $\geq$20%, blood glucose within the institutional normal range (3.4-11 mmol/L), MAP $>$50 mmHg, and central venous pressure $<$10 mmHg, were used specifically during CPB and throughout the intraoperative period for all patients. Arterial inflow temperatures did not exceed 37°C during rewarming.

Each patient had an InSpectra™ 650 (Hutchinson Technology Inc., Hutchinson, MN) NIRS StO_2 monitor with 15-mm probe spacing applied to the thenar eminence of the hand opposite the radial artery cannula. The published parameters for InSpectra™ 650 StO_2 indicate a range of 0% to 99%, a resolution of 1%, and accuracy of 1.63 StO_2 units between 70% and 99% and 2.94 StO_2 units from 0% to 70%. A series of VOT measurements were performed at the following clinically relevant time points: Immediately before induction of anesthesia, 15 minutes after induction of anesthesia, at initiation of CPB, every thirty minutes while on CPB, after weaning from CPB following protamine administration, and after chest closure. To monitor peripheral temperature, a thermistor also was placed on the same thenar eminence as the NIRS probe.

VOTs were performed by inflating a pneumatic tourniquet over the brachial artery of the same arm as the NIRS sensor to a pressure of 50 mmHg greater than systolic blood pressure while off CPB, or greater than mean arterial pressure during CPB, for a period of 3 to 5 minutes. Of note, after application and connection of the sensors and pneumatic tourniquet, the patient's arms were padded and tucked at their side as per clinical routine. InSpectra™ clinical research software (Hutchinson Technology Inc., Hutchinson, MN) was used to retrieve data, construct reactive hyperemia curves, and calculate the following vascular occlusion test parameters: Baseline StO_2 (%), occlusion slope (%/second), assessing metabolic demand, reperfusion slope (%/second), assessing microcirculatory responsiveness, hyperemic area (%●second), and increase of StO_2 over baseline during the hyperemic phase (ΔStO_2) (Fig 1). Baseline StO_2 was averaged over the 2 minutes preceding tourniquet inflation. Occlusion slope was calculated over a 1-minute interval commencing with StO_2 decreasing below baseline, and the reperfusion slope was calculated from the release of the tourniquet until 85% of baseline StO_2 was achieved. Physiologic parameters were recorded at the time of each vascular occlusion test.

The reperfusion slope was defined as the primary measurement in this observational study for the purposes of sample size calculation. Because no data reporting VOT reperfusion slope in patients during CPB had been published at the time of study design, unpublished data previously collected in the authors' institution measuring VOT reperfusion slopes in patients with septic shock were used to approximate the mean and standard deviation in this study population. A sample size of 12 was determined to be sufficient to measure Δ = 1.0 from a control mean of 3.1 %/s using a 2-sided test, with α = 0.05, power = 0.80, and standard deviation = 0.87.

Prism version 5.0 (GraphPad Software, La Jolla, CA) statistical analysis software was used to perform 1-way ANOVA of VOT parameters at each measurement time point and Tukey post-hoc comparisons within those groups demonstrating a significant difference (α = 0.05). Pearson correlation coefficients were calculated for reperfusion slopes and physiologic parameters.

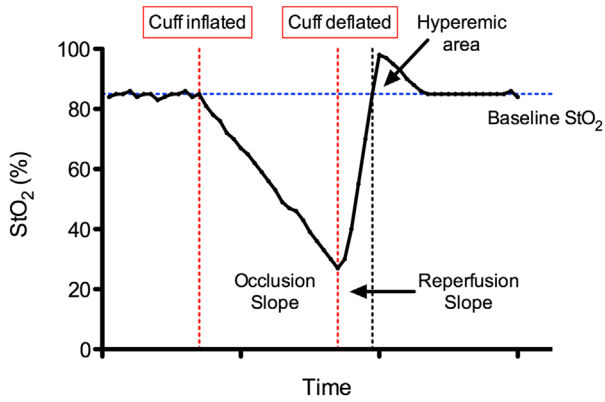

Fig 1. Vascular occlusion test measurement parameters. (StO_2 is tissue oxygen saturation.)

RESULTS

A total of 13 patients of mean age 68.5 years (SD = 11.6) underwent mean duration of CPB of 123 minutes (SD = 50.3). Patients underwent combined coronary artery bypass grafting and valve surgery (6 of 13; 46.2%), coronary artery bypass grafting alone (5 of 13; 38.5%) or valve surgery alone (2 of 13; 15.4%).

Mean baseline StO_2 before induction of anesthesia was 81.8% (SD = 8.5), and this did not vary significantly through the measurement period ($F(7,82) = 0.93$, $p = 0.49$). The occlusion slope did not vary significantly among measurement points ($F[7,82] = 0.66$, $p = 0.70$). Neither the mean hyperemic area (M = 23.6 %●s, SD = 16.4, $F[7,80] = 1.16$, $p = 0.33$) nor $\Delta StO2$ (M = 10.8, SD = 4.8, $F(7,82) = 1.28$, $p = 0.27$) exhibited significant differences among measurement points on or off CPB.

As shown in Figure 2, when stratified into 3 categories (pre-CPB, on-CPB and post-CPB), mean reperfusion slopes were significantly different (4.1 %/s v 2.4 %/s v 3.5 %/s, respectively, $F[2,87] = 7.80$, $p = 0.0008$) with a further progressive decrease in reperfusion slope with duration of CPB (Fig 3) ($F[7,82] = 2.70$, $p = 0.014$). There was no significant difference in reperfusion slope between pre- and post-CPB values, indicating partial recovery of microcirculatory vasoreactivity after discontinuation of bypass (Fig 2). Reperfusion slope during CPB was correlated weakly with mean arterial pressure ($r = 0.34$, $p < 0.001$), hematocrit ($r = 0.25$, $p = 0.010$) and lactate ($r = -0.18$, $p = 0.048$).

DISCUSSION

This pilot study demonstrated a significant difference in the VOT reperfusion slopes during CPB when compared to pre- and post-CPB intervals, suggesting impaired peripheral microvascular reactivity during bypass. Reperfusion slopes also exhibited a successive decline with duration of CPB, implying microcirculatory dysfunction that deteriorates with the duration of nonpulsatile perfusion. The similarity of pooled reperfusion