Impact of Norepinephrine on Regional Cerebral Oxygenation During Cardiopulmonary Bypass

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Objectives: **Norepinephrine is used to increase mean arterial pressure during cardiopulmonary bypass. However, it has been suggested that norepinephrine could constrict cerebral arteries, reducing cerebral blood flow. The aim of this study, therefore, was to explore whether there was an association between doses of norepinephrine to maintain mean arterial pressure at ≈80 mmHg during cardiopulmonary bypass and cerebral oxygen saturation measured using near-infrared spectroscopy.**

Design: **Observational study.**

Setting: **University hospital.**

Participants: **Patients undergoing cardiac surgery (n = 45) using cardiopulmonary bypass.**

Interventions: **Norepinephrine was administered to maintain mean arterial pressure ≈80 mmHg during cardiopulmonary bypass.**

Measurements and Main Results: **From initiation of cardiopulmonary bypass to removal of the aortic cross-clamp, norepinephrine dose, mean arterial pressure, partial pressure of arterial carbon dioxide, partial pressure of arterial oxygen, hemoglobin, and pump flow values were averaged over 1 minute, giving a total of 3,460 data points entered as covariates in a linear mixed model for repeated measurements, with cerebral oxygen saturation measured using near-infrared spectroscopy as outcome. There was no statistically significant association between norepinephrine dose to maintain mean arterial pressure and cerebral oxygen saturation (p = 0.46) in this model.**

Conclusions: **Administration of norepinephrine to maintain mean arterial pressure ≈80 mmHg during cardiopulmonary bypass was not associated with statistically significant changes in cerebral oxygen saturation. These results indicated that norepinephrine could be used to increase mean arterial pressure during cardiopulmonary bypass without reducing cerebral oxygen saturation.**

KEY WORDS: oximetry, norepinephrine, cardiopulmonary bypass

CEREBRAL OXIMETERY is being used increasingly in cardiac surgery to monitor cerebral oxygenation. Reduced cerebral tissue oxygen saturation (rSO_2) during cardiac surgery has been associated with adverse outcomes,[1-3] and interventions based on monitoring of rSO_2 during coronary artery bypass grafting (CABG) have been shown to reduce major organ dysfunction.[4] Near-infrared spectroscopy (NIRS) is used to monitor rSO_2, and details about NIRS have been provided by Scheeren et al.[5]

There is insufficient evidence to recommend a specific mean arterial pressure (MAP) during cardiopulmonary bypass (CPB), but it has been recommended to maintain MAP >70 mmHg during CPB in high-risk patients.[6] Hypoperfusion resulting from impairment of cerebral autoregulation, hypotension, or anemia may lead to cerebral hypoxia. Autoregulation of cerebral blood flow (CBF) ensures delivery of oxygenated blood to the brain and protects the brain from ischemia caused by arterial pressure fluctuations.

One approach that aims to improve cerebral oxygenation during CPB is to increase cerebral perfusion pressure by increasing systemic MAP using a vasopressor[7] (eg, norepinephrine [NE]). According to departmental practice, the authors routinely administer NE during CPB, aiming for a MAP of 60 to 80 mmHg. However, the question has been raised whether vasopressors may induce cerebral vasoconstriction and thereby actually contribute to reduced cerebral oxygenation.[8-10] NE has been shown to reduce rSO_2 in healthy volunteers,[8] but potential effects of NE on rSO_2 during CPB have not been defined.

The aim of this study, therefore, was to explore whether NE administered during CPB to maintain MAP at ≈80 mmHg was associated with changes in rSO_2. The hypothesis was that there would be no such association when controlling for other factors with biologically plausible effects on rSO_2.

METHODS

Patients

Forty-five patients presenting for elective aortic valve replacement, CABG, or a combination of aortic valve replacement and CABG were included in the study. Exclusion criteria were age <18 or >80 years, patient included in pharmacologic study, vasoactive medication started before measuring baseline rSO_2, or any of the following medical conditions known at time of inclusion: frontal lobe pathology, intracranial vascular anomaly, neurologic disease, dementia, history of traumatic brain injury, cerebral insult, transient ischemic attack, or carotid artery stenosis (no study-specific examinations were performed). The study was approved by the Regional Committee for Medical and Health Research Ethics (REK sør-øst, 2010/823), and written informed consent was obtained. The study was registered in ClinicalTrials.gov (NCT01940874).

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Results from this study were presented, in part, at the Society of Cardiovascular Anesthesiologists annual meeting in Miami, FL, May 2013.

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Anesthetic Procedure

Patients were premedicated with intramuscular morphine/scopolamine. A 20-G arterial cannula was placed in the left radial artery and a 7-Fr triple-lumen catheter in the right internal jugular vein. Baseline rSO_2 was measured when patients were breathing room air. Anesthesia was induced with intravenous diazepam, fentanyl, and propofol, and endotracheal intubation was facilitated with intravenous cisatracurium. Patients were mechanically ventilated, and anesthesia was maintained with sevoflurane. Temperature was measured in the urinary bladder. Although core temperature affects cerebral oxygen consumption, temperature measurements were not used in the statistical model due to the poor agreement between bladder and core temperatures.

Surgical Procedure and Cardiopulmonary Bypass

After cannulation of the aorta and right atrium, CPB primed with Ringer's acetate was performed in a nonpulsatile manner. CPB flow was set to 2.4 × (height [cm] + weight [kg] – 60)/100 L/min, with partial pressure of arterial oxygen (PaO_2) 15 to 20 kPa and partial pressure of arterial carbon dioxide ($PaCO_2$) 5.2 to 5.7 kPa. Arterial blood gas analyses (α-stat) were performed intermittently. Temperature was measured in the urinary bladder. CABG procedures were performed with the patient in normothermia (35.0-37.0°C), whereas other or combined procedures were performed with the patient in mild hypothermia (32.0-35.0°C) or hypothermia (<32.0°C). Heparin was administered to maintain activated clotting time >480 seconds. Packed red blood cells were given routinely if hemoglobin (Hb) was <7 g/dL. Anesthesia was maintained with sevoflurane, 1.5% to 2% adminstered in the CPB circuit.

NE (Alaris CC Plus with Guardrails; CareFusion, San Diego, CA) diluted in glucose, 50 mg/mL to 20 μg/mL, was infused in the central venous catheter using a syringe pump (Alaris GH Plus with Guardrails; CareFusion, San Diego, CA). During CPB, NE was administered with the aim of achieving MAP ≈ 80 mmHg.

If rSO_2 was reduced by >20% relative to baseline or to <50% absolute, the following steps were taken to improve rSO_2: verification of CPB integrity and function/positioning of the cannulae; and controlling head position, $PaCO_2$, O_2, Hb, and CPB flow.[11] If the CPB circuit, position of the cannulae, and PaO_2 were adequate, $PaCO_2$, Hb, and/or CPB flow were increased. Unless intentionally altered as previously stated, PaO_2 and $PaCO_2$ were kept constant by continuous arterial in-line monitoring (BMU 40; Maquet, Rastatt, Germany).

Signal Acquisition and Analysis

Sensors (Adult SomaSensor; Medtronic, Minneapolis, MN) for the oximeter (INVOS 5100C Cerebral/Somatic Oximeter; Medtronic) were placed on the left and right forehead. Values were updated every 7 to 8 seconds and sampled with hemodynamic variables from the patient monitor (Solar 9500; GE Healthcare, Milwaukee, WI) at 1 Hz in a custom-made program in LabVIEW (National Instruments, Austin, TX). Dosage of NE was entered manually into this program. All rSO_2 values were relative to the preoperative baseline value, and the average of left and right measurements were used for analysis.

Data were analyzed from initiation of CPB to removal of the aortic cross-clamp. Offline, data were down-sampled to 1 value every minute by averaging (arithmetic means) after manually removing obviously erroneous data (eg, from flushing the arterial line), providing 3,460 observations. Results from arterial blood gas analyses were entered manually. To obtain continuous values for Hb, PaO_2, and $PaCO_2$, these values were interpolated linearly between the blood gas analyses performed. When packed red blood cells were transfused, the Hb value was changed at the time of transfusion (not linearly interpolated). In a subset of 12 patients, arterial blood gas analyses were performed every 10 minutes to increase the resolution of these variables. If CPB flow was altered, flow relative to baseline was entered (eg, a 5% increase giving a value of 1.05). If CPB flow was not altered, it always had a value of 1.

To explore autoregulation, as previously reported,[12] rSO_2 and MAP were averaged over 10 seconds from the raw data, giving a sampling frequency of 0.1 Hz. Pearson correlation coefficients between rSO_2 and MAP were calculated from 5 minutes (30 observations) in a moving, overlapping fashion, making each data point contribute to 30 correlation coefficients (except at the ends of the recording). The correlations were binned according to the average MAP in the 5-minute period of the correlation coefficient with bin size 10 mmHg. Lower and upper limits of autoregulation (LLA and ULA, respectively) were defined if there was a transition of bin mean correlation from <0.3 to >0.3 with a reduction or increase in MAP-bin, respectively.[12,13] For each bin, MAP was presented by its mean value (eg, 65 mmHg for the 60-70 mmHg-bin).

Statistics

Values are mean (standard deviation) or median (25th-75th percentiles) unless otherwise stated. The relation between NE dosage and rSO_2 was evaluated in a linear mixed regression model with rSO_2 as the oucome. The NE dose and other variables considered to have an effect on rSO_2 were entered as explanatory variables. These other variables were MAP, $PaCO_2$, PaO_2, Hb, and CPB flow. Because the study only sought to describe the possible effect of NE dose on rSO_2, the other varaibles (which were entered only to correct for their possible confounding effects) were included in the statistical model regardless of their p values. The model assumed a linear relation with the same slope between all explanatory variables and the outcome, rSO_2. The mixed model accounts for dependence of data within each patient (patient being a random effect), and in this model, with random intercept, allowed the regression line of each patient to have different intercepts. Model fit was assessed using the Akaike information criterion (AIC).[14] Due to the repeated nature of the data, the AIC was minimized by imposing an autoregressive-1 covariance structure to the residuals.

RESULTS

Forty-eight patients were included in the study. Two patients had incomplete data, and 1 underwent surgery in deep hypothermia. Thus, data from 45 patients were analyzed.