Free Radical Biology and Medicine 103 (2017) 192–198

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Original article

Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery

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ARTICLE INFO

Keywords:
Brain oxygenation
Oxidative injury
Oxidative stress
Delirium
Oxygen
Hyperoxia
Ischemia reperfusion
Surgery
F2-isoprostanes
Isofurans

ABSTRACT

Background: Delirium affects 20–30% of patients after cardiac surgery and is associated with increased mortality and persistent cognitive decline. Hyperoxic reperfusion of ischemic tissues increases oxidative injury, but oxygen administration remains high during cardiac surgery. We tested the hypothesis that intraoperative hyperoxic cerebral reperfusion is associated with increased postoperative delirium and that oxidative injury mediates this association.

Methods: We prospectively measured cerebral oxygenation with bilateral oximetry monitors in 310 cardiac surgery patients, quantified intraoperative hyperoxic cerebral reperfusion by measuring the magnitude of cerebral oxygenation above baseline after any ischemic event, and assessed patients for delirium twice daily in the ICU following surgery using the confusion assessment method for ICU (CAM-ICU). We examined the association between hyperoxic cerebral reperfusion and postoperative delirium, adjusted for the extent of cerebral hypoxia, the extent of cerebral hyperoxia prior to any ischemia, and additional potential confounders and risk factors for delirium. To assess oxidative injury mediation, we examined the association between hyperoxic cerebral reperfusion and delirium after further adjusting for plasma levels of F_2-isoprostanes and isofurans at baseline and ICU admission, the association between hyperoxic cerebral reperfusion and these markers of oxidative injury, and the association between these markers and delirium.

Results: Ninety of the 310 patients developed delirium following surgery. Every 10%·hour of intraoperative hyperoxic cerebral reperfusion was independently associated with a 65% increase in the odds of delirium (OR, 1.65 [95% CI, 1.12–2.44]; P = 0.01). Hyperoxia prior to ischemia was also independently associated with delirium (1.10 [1.01–1.19]; P = 0.02), but hypoxia was not (1.12 [0.97–1.29]; P = 0.11). Increased hyperoxic cerebral reperfusion was associated with increased concentrations of F_2-isoprostanes and isofurans at ICU admission, increased concentrations of these markers were associated with increased delirium, and the association between hyperoxic cerebral reperfusion and delirium was weaker after adjusting for these markers of oxidative injury.

Conclusions: Intraoperative hyperoxic cerebral reperfusion was associated with increased postoperative delirium, and increased oxidative injury following hyperoxic cerebral reperfusion may partially mediate this association. Further research is needed to assess the potential deleterious role of cerebral hyper-oxygenation during surgery.

1. Introduction

Delirium is a manifestation of acute brain dysfunction and affects 20–30% of patients following cardiac surgery [1,2]. Delirium is associated with increased mortality, pulmonary dysfunction, and duration of hospitalization following cardiac surgery, and is an independent predictor of long-term cognitive decline in other medical and surgical patient populations [3–6].

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http://dx.doi.org/10.1016/j.freeradbiomed.2016.12.039
Received 11 October 2016; Received in revised form 16 December 2016; Accepted 26 December 2016
Available online 27 December 2016

During cardiac surgery impaired heart function, exposure to cardiopulmonary bypass, and rapid changes in temperature, intravascular pH, and arterial pressure lead to abrupt changes in cerebral perfusion, oxygen extraction, and oxygen consumption. These changes in brain oxygenation, along with exposure to anesthetics, systemic and cerebral inflammation, and microemboli may precipitate delirium following cardiac surgery, although precise mechanisms are poorly understood.

In preclinical studies tissue hypoxia, hyperoxia, ischemia, and hyperoxic reperfusion – all common in patients undergoing cardiac surgery – increase the production of reactive oxygen species and induce oxidative injury [7–10]. Intraoperative oxidative injury may contribute to postoperative brain injury, as it has been demonstrated that intraoperative oxidative injury contributes to postoperative kidney injury, another organ susceptible to ischemia reperfusion injury [11]. Hyperoxia may contribute to this phenomenon. Indeed, in other clinical scenarios of cerebral ischemia and reperfusion injury, including cardiac arrest and stroke, hyperoxia during reperfusion is a strong predictor of neurologic damage [12,13]. Hyperoxia during surgery remains standard clinical practice despite these potential deleterious effects.

We conducted this study to test the hypothesis that hyperoxic cerebral reperfusion is associated with the development of delirium following cardiac surgery and that increased oxidative injury may mediate this association.

2. Methods

2.1. Patients

We performed a cohort study using participants from the Statin AKI Cardiac Surgery RCT, a randomized clinical trial conducted to test the hypothesis that perioperative atorvastatin treatment compared to placebo reduces acute kidney injury, intensive care unit (ICU) delirium, and additional organ dysfunctions following cardiac surgery [14]. We used the Statin trial cohort because study participants were assessed for delirium by research personnel twice daily while in the ICU, had detailed preoperative, intraoperative, and postoperative prospective data collected, and were phlebotomized at baseline and following surgery to quantify perioperative oxidative injury. Adults undergoing elective coronary artery bypass grafting, heart valve surgery, or ascending aortic surgery at Vanderbilt University Medical Center (Nashville, TN) were eligible to participate. Patients with acute coronary syndrome, liver dysfunction, prior statin intolerance, use of CYP3A4 inhibitors, current use of cyclosporine, current renal replacement therapy, history of kidney transplant, or pregnancy were excluded. Patients who had detailed measurements of intraoperative cerebral oximetry saved in the perfusionist database comprised the study cohort. The Vanderbilt Institutional Review Board approved the study, and all patients provided written informed consent.

2.2. Baseline assessments

Past medical history, vital signs, and baseline laboratory data were obtained. To characterize baseline mental function, each subject was administered the Mini Mental State Exam and scored from 0 to 30 [15]. The Charlson comorbidity index, a 17-component mortality prediction score, was calculated for each subject [16].

2.3. Standardized patient management

Anesthetic and surgical management were conducted according to institutional protocols as outlined below and previously described [17]. Pulse oximetry, electrocardiography, and cerebral oximetry (INVOS, Medtronic, Minneapolis, MN) probes were placed on the finger, chest, and both sides of the forehead, respectively, prior to induction of general anesthesia and remained until completion of surgery. Baseline pulse oximetry and cerebral oximetry measurements were recorded prior to supplemental oxygen administration. Following induction of anesthesia and tracheal intubation, patients were mechanically ventilated with a fraction of inspired oxygen (FIO_2) between 60–100%, tidal volumes of 8 ± 2 ml/kg ideal body weight, respiratory rate titrated to an end-tidal carbon dioxide partial pressure between 30 and 35 mmHg, and positive end expiratory pressure of 5 cm H_2O. Anesthesiologists did not use cerebral oximetry measurements to adjust patient ventilation.

Institutional protocol directed the perfusionist to set the oxygen/carbon dioxide blender on the cardiopulmonary bypass oxygenator to an FIO_2 of 80% and titrate the sweep rate to maintain a $PaCO_2$ between 45 and 50 mmHg during bypass. If cerebral oximetry values decreased below 80% of baseline during cardiopulmonary bypass the perfusionist performed the following sequence: requested the surgeon to check and adjust arterial and venous cannulas to confirm central cannulation and increase venous drainage, decreased sweep speed on oxygenator to increase patient partial pressure of carbon dioxide to 50–55 mmHg, increased arterial flow to as high as 3 L/min/m^2, increased FIO_2 to 100%, and requested the anesthesiologist to transfuse one unit of packed red blood cells if the hematocrit was less than 24%. If cerebral oximetry values rose above baseline prior to or following any decrease in values, perfusionists and anesthesiologist did not change patient management to reduce cerebral oxygenation.

2.4. Cerebral oxygenation measurements

Cerebral oximetry continuously measures regional cerebral tissue oxygenation using near-infrared spectroscopy. Sensors are designed to measure approximately one and a half cubic centimeters in the outer cortical layers of the brain [18,19]. Cerebral oximetry measurements were automatically recorded every 5 s and stored in the INVOS monitor, and the perfusionist saved the data in the clinical database after surgery. The cerebral oxygenation values used for analyses were taken as the average of the right and left probes. These values were used to quantify baseline cerebral oxygenation, ischemia, and the cumulative (over the course of surgery) levels of hypoxia, hyperoxia, and hyperoxic reperfusion. These levels were quantified using areas under the oxygenation-time curves (AUCs). Examples of these AUC oxygenation metrics are presented (Fig. 1).

Hyperoxic cerebral reperfusion was defined as any cerebral oxygenation greater than baseline that followed a period of cerebral ischemia, and we quantified hyperoxic cerebral reperfusion by calculating the oxygenation AUC above baseline after any period of ischemia. We chose a decrease to 80% of baseline as a threshold for cerebral hypoxia and ischemia because this value has been reported as the threshold for interventions to increase cerebral oxygenation during surgery [20,21], and we chose 5 min of cerebral hypoxia or an equivalent AUC for data less than 80% of baseline (e.g., 60% of baseline for 2.5 min) to define ischemia because this duration has been associated with neuron injury and poor neurologic recovery in other settings [22,23]. We quantified cerebral hyperoxia independent of hyperoxic cerebral reperfusion by measuring the oxygenation AUC above baseline throughout surgery prior to any ischemia or in patients that never experienced ischemia.

Because associations between cerebral hyperoxia and outcomes have not previously been investigated, criteria for cerebral oximetry hyperoxia are not established. Some degree of cerebral oxygenation above baseline may still be in the normal range. As a sensitivity analysis, we used a higher threshold (10% above baseline) to define and calculate AUC magnitudes of hyperoxic reperfusion and hyperoxia.

AUCs are reported as 10%·hours for ease of interpretation. For example, a 20% change for one half hour equals one 10%·hour.

2.5. Delirium assessment

Research personnel assessed delirium twice daily while patients were in the ICU using the Confusion Assessment Method for ICU delirium (CAM-ICU) and Richmond Agitation-Sedation Scale (RASS).