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Arterial hyperoxia during cardiopulmonary bypass and postoperative cognitive dysfunction

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Abstract

Objective—To determine the effect of arterial normobaric hyperoxia during cardiopulmonary bypass (CPB) on postoperative neurocognitive function. We hypothesized that arterial hyperoxia during CPB is associated with neurocognitive decline at 6 weeks after cardiac surgery.

Design—Retrospective study of patients undergoing cardiac surgery with CPB.

Setting—A university hospital.

Participants—One thousand eighteen patients undergoing coronary artery bypass graft (CABG) or CABG + valve surgery with CPB who had previously been enrolled in prospective cognitive trials.

Interventions—A battery of neurocognitive measures was administered at baseline and 6 weeks post-surgery. CPB was managed by the anesthesia care team as clinically indicated.

Measurements and Main Results—Arterial hyperoxia was assessed primarily as the area under the curve (AUC) for the duration that PaO₂ exceeded 200 mmHg during CPB and secondarily as the mean PaO₂ during bypass, as a PaO₂ ≥ 300 mmHg at any point and as AUC > 150 mmHg. Cognitive change was assessed both as a continuous change score and a dichotomous deficit rate. Multivariable regression accounting for age, years of education, baseline cognition, date of surgery, baseline post-intubation PaO₂, duration of CPB, and percent change in hematocrit level from baseline to lowest level during CPB revealed no significant association between hyperoxia during CPB and postoperative neurocognitive function.

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Conclusions—Arterial hyperoxia during CPB is not associated with neurocognitive decline at 6-weeks in cardiac surgical patients.

Keywords

cardiopulmonary bypass; cardiac surgery; neurocognitive; hyperoxia

INTRODUCTION

Arterial hyperoxia during cardiopulmonary bypass (CPB) has long been used to safeguard against intraoperative hypoxic injury or to reduce the impact of gaseous embolization by denitrogenation; nevertheless, emerging evidence suggests that exposure to elevated oxygen tensions may be less protective than once thought and perhaps even harmful.¹ Exposure to oxygen at high partial pressures is an independent risk factor for mortality following cardiac arrest^{2, 3} and current guidelines for post-cardiac arrest care recommend the avoidance of hyperoxia.⁴ Hyperoxia has been shown to be toxic to the cardiovascular, respiratory, nervous, and gastrointestinal systems.⁵ The cellular response caused by hyperoxia exposure, specifically the increase of free-radical induced oxidative stress, is especially damaging to the brain.⁶ In comparison to other cells, neurons have increased susceptibility to free-radical damage due to their high oxygen consumption rate, large lipid content, and lower levels of antioxidant defenses.^{6–8} Oxidative stress is highly disruptive to neuronal homeostasis and can lead to decreased synaptic plasticity, increased blood-brain barrier permeability, and neuronal cell dysfunction and death.^{7, 8} Oxidative injury and the excessive formation of oxygen-free radicals have been implicated in the development of cognitive impairment and the pathogenesis of various neurodegenerative diseases.^{6, 8}

Patients undergoing cardiac surgery with CPB represent a distinct population in which risk of oxygen toxicity and postoperative neurocognitive dysfunction are high. Cardiac populations are routinely exposed to hyperoxic conditions and report frequent and persistent neurocognitive deficit with 30 to 65% of patients showing residual neuropsychological injury 6 weeks post coronary-artery bypass graft (CABG) surgery.^{9–11} Preoperative risk factors for postoperative neurocognitive decline have been identified and include level of education, age, and genetic predisposition.^{11–13} Potential surgical mechanisms for this neurocognitive decline include cerebral embolism, cell salvage, valve surgery, hypoperfusion, systemic inflammatory responses, hemodilution, hyperglycemia, and hyperthermia. However, recent data suggest that while some cognitive decline occurred immediately after CABG surgery, there were no significant differences in long-term cognitive decline between patients who had undergone CABG surgery and nonsurgical controls with diagnosed coronary artery disease.^{14–18} The many documented adverse effects of hyperoxia exposure and the high incidence of cognitive dysfunction in patients undergoing cardiac surgery warrant further investigation into the relationship between hyperoxia during CPB and neurocognitive outcome. Past examinations of hyperoxic conditions lack a consistent definition of hyperoxia with outcome assessment often occurring only 24 hours after exposure.^{2, 19} Our study sought to overcome such limitations by establishing a clinically relevant definition of hyperoxia and by determining the effect of hyperoxia during CPB on postoperative neurocognitive function. We hypothesized that

arterial hyperoxia during CPB is associated with neurocognitive decline at 6 weeks after cardiac surgery.

METHODS

Study Population and Procedure

After Institutional Review Board approval, 1,018 patients undergoing elective cardiac surgery (CABG or CABG + valve) with CPB from February 2000 to September 2010 who had previously been enrolled in prospective neurocognitive trials were evaluated.^{10, 12, 16, 20, 21} Patients with a history of symptomatic cerebrovascular disease with residual deficit, psychiatric illness (any clinical diagnoses requiring therapy), hepatic insufficiency (liver function tests > 1.5 times the upper limit of normal), or renal insufficiency (creatinine levels > 2 mg/dL) were excluded from the prospective cognitive studies. Patients who were unable to read and thus unable to complete the cognitive testing or who scored < 24 on a baseline Mini Mental State examination (identifying baseline cognitive impairment) or < 27 on the baseline Center for Epidemiological Studies Depression (identifying baseline severe depression) Scale had also been excluded from participation.

Anesthesia was induced and maintained with midazolam, fentanyl, propofol, and isoflurane or sevoflurane. All patients underwent nonpulsatile hypothermic (30°–32°C) CPB with a membrane oxygenator and an arterial line filter. The pump was primed with crystalloid and serial hematocrit levels were maintained at >21%. Perfusion was maintained at pump flow rates of 2–2.4 L • min¹ • m² throughout CPB to maintain mean arterial pressure at 50–80 mmHg. Arterial blood gases were measured every 15–30 minutes to maintain arterial carbon dioxide partial pressures of 35 to 40 mmHg, unadjusted for temperature (alpha-stat), and oxygen partial pressures of 150 to 250 mmHg.

Measures

To evaluate cognitive function, a battery of neurocognitive tests was administered preoperatively and six weeks after surgery. Assessments were conducted by trained psychometricians using a well validated battery that included the short story module of the Randt Memory Test, a reliable measurement of discourse memory (immediate and delayed) and oral language comprehension;²² the Modified Visual Reproduction Test from the Wechsler Memory Scale on which patients are required to reproduce from memory several geometric shapes both immediately and after a 30-minute delay, testing for short- and long-term figural memory;²³ the Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) exam, a measure of short-term auditory memory and attention that calls on subjects to repeat a series of digits that have been orally presented to them both forward and, in an independent test, in reverse order;²³ the Digit Symbol subtest of the WAIS-R, an evaluation of psychomotor processing speed, in which number-symbol pairs are transcribed under timed conditions;²³ and the Trail Making Test Part B, a timed test in which patients connect alternately letters and numbers in order to assess processing speed, attention, and mental flexibility.²⁴

Statistical Analysis

To reduce redundancy in the cognitive measures baseline raw test scores were subjected to a factor analysis. A principal components analysis was used to reduce the larger number of correlated dependent variables to a smaller number of uncorrelated outcome variables, thereby minimizing the likelihood of over-representing a single domain of neurocognitive functioning. Factor loadings of each test on each factor were calculated from the entire baseline population of 1,018 patients and used to construct analogous domain scores at each of the follow-up evaluations, thus allowing the domains to remain consistent across time.¹¹ Analysis generated independent scores representing four cognitive domains: 1) verbal memory and language comprehension; 2) attention, psychomotor processing speed, and concentration; 3) abstraction and visuospatial orientation; and 4) figural memory.

Two summary measures were calculated to represent cognitive function: (1) to quantify overall cognitive function and the degree of learning (i.e. practice effect from repeated exposure to the testing procedures), a baseline cognitive index was first calculated as the mean of the 4 preoperative domain scores. A continuous change score (the continuous outcome) was then calculated by subtracting the baseline from the follow-up cognitive index; (2) cognitive deficit (the binary outcome) was defined as a decline of 1 SD or more in at least 1 of the 4 domains. Hyperoxia was defined primarily as the area under the curve (AUC) for the duration that CPB PaO₂ exceeded 200 mmHg. To normalize the positively skewed distribution of this area, a log-transformed value was calculated. In secondary analysis, hyperoxia was further defined continuously as the mean PaO₂ during bypass, dichotomously as a PaO₂ during bypass > 300 mmHg at any time during CPB, and AUC for the duration that CPB PaO₂ exceeded 150 mmHg. We also examined the effect of excluding valve surgery patients from the analyses. We chose a cutoff of 300 mmHg for the dichotomous hyperoxia definition based on prior study.² For the AUC variable, which is a continuous value, we chose a lower value to ensure that the majority of patients would have a meaningful value for the AUC analysis. As < 50% of patients had any value over 300 mmHg, an analysis of AUC>300 would have resulted in more than half of the sample with a value of 0. The effect of hyperoxia on postoperative cognitive function was tested using linear and logistic regression modeling, accounting for age, years of education, baseline cognition, date of surgery, baseline post-intubation PaO₂, duration of CPB, and percent change in hematocrit level from baseline to lowest level during CPB. Interactions between age and bypass PaO₂ level, age and hematocrit level, and PaO₂ level and hematocrit level were also examined. A p-value <0.05 was considered significant; model p-values were Bonferroni corrected for multiple comparisons.

RESULTS

Baseline characteristics of the study population are shown in Table 1. Of the 1018 cardiac patients, the vast majority (94%) underwent CABG surgery. Although the cognitive change score at 6 weeks (continuous outcome) for the entire sample showed improvement (mean change score = 0.17 ± 1.45), cognitive deficit (binary outcome) was present in 45%. The mean area under the curve for PaO₂ exceeding 200 mmHg during CPB was 77.4 ± 93.9 mmHg.min while the mean PaO₂ during CPB was 257.3 ± 64.8 mmHg. The PaO₂ was

greater than 300 mmHg at least once during CPB in 42.2% (430/1018) of patients. During CPB, the hematocrit declined from baseline levels by an average of $40 \pm 12\%$.

The incidence of cognitive deficit (binary outcome) was 42% when AUC exceeded 200 mmHg compared to 43% when it was < 200 mmHg. Multivariable linear and logistic regression modeling adjusting for age, years of education, baseline cognition, date of surgery, baseline post-intubation PaO₂, duration of CPB and percent change in hematocrit level from baseline to lowest level during CPB revealed no significant association between the area under the curve for CPB PaO₂ > 200 mmHg and the cognitive change score ($p=0.23$) or the binary cognitive deficit ($p=0.65$) at 6 weeks after surgery. Similarly, no significant associations were detected between change in neurocognitive function at 6 weeks and the mean PaO₂ during CPB or PaO₂ > 300 mmHg at any time during CPB. The interactions between age and PaO₂, age and hematocrit, and PaO₂ and hematocrit were also not significant. Hyperoxia was not a significant predictor even after excluding valve surgery patients ($p=0.23$) or when utilizing a threshold of 150 mmHg for the AUC analysis ($p=0.26$).

Given our sample size, we had 80% power to detect an r^2 value of 0.0065 in a linear regression model. Our observed effect in a univariate linear regression model testing the association of PaO₂ AUC > 200 mmHg and 6 week cognitive change was 0.0013. A r^2 value of 0.0013 means that we were able to explain 0.13% of the variability in cognitive change with the AUC variable.

DISCUSSION

In this large study of 1018 patients undergoing cardiac surgery with CPB, we were unable to demonstrate a relationship between arterial hyperoxia during CPB and neurocognitive function at 6 weeks after surgery. Despite using multiple definitions of hyperoxia including the area under the curve for PaO₂ levels during CPB > 200 mmHg, mean PaO₂ during CPB, and PaO₂ during CPB > 300 mmHg, we found that none of these were associated with postoperative neurocognitive decline. A diminished or absent “classic” reperfusion injury in the brain following routine CPB (in contrast to deep hypothermic circulatory arrest) may explain this lack of association. Alternatively, the use of hypothermia during CPB may mitigate the deleterious effect of hyperoxia.^{25, 26}

Studies have long shown cardiac surgical patients to be at risk for postoperative neuropsychological deficit;^{11, 18} the literature also highlights the brain’s hypersensitivity to insufficient cerebral blood flow, inadequate oxygen delivery, and excess oxidative stress products as mechanisms for neurological injury.^{6–8} The overproduction of reactive oxygen species (ROS) has been well established as the biochemical mechanism for hyperoxic toxicity.^{27, 28} ROS are chemically reactive molecules containing oxygen that are endogenously generated during the reduction of oxygen in the mitochondria.²⁹ These natural byproducts of cellular metabolism play a critical role in cellular communication or cell transduction; however, exposure to higher than normal concentrations of oxygen can result in the increased production of ROS such as hydrogen peroxide, nitric oxide, superoxide and the highly reactive hydroxyl radical.^{6, 28} As ROS generation exceeds the capacity of antioxidant defense mechanisms to neutralize them, reactive species, pro-oxidant/

antioxidant homeostasis is disrupted and the formation of unstable free oxygen radicals increases to unregulated, cytotoxic levels.^{6, 30} The resulting influx of oxidizing agents and the breakdown of regulatory processes, better known as oxidative stress, initiate a cascade of cellular reactions that generate even more reactive species, disrupting important cellular components and causing elevated levels of oxidized lipids, proteins, and nucleic acids.^{6, 7} The result of this oxidative surge propagates lipid peroxidation, disrupted protein synthesis, inactivation of enzymes and nucleic acids, DNA mutations, cytoskeleton abnormalities, impaired mitochondrial calcium homeostasis, increased membrane permeability and, finally, chemotaxis.^{6, 27, 28}

The induction of hypothermia, however, has been shown to protect against ischemic insult, thus serving as a potential neuroprotective strategy against hyperoxic injury.²⁶ Lowering brain temperature reduces cerebral metabolism, thereby decreasing oxygen demand and strengthening the brain's tolerance to ischemia and ability to safeguard against subsequent neuronal death.²⁵ Hypothermia further provides neuroprotection by moderating inflammatory immune responses, minimizing the production of injurious free oxygen radicals, decreasing excitatory neurotransmitter release and apoptosis, and reducing ion flux, vascular permeability, edema, and blood-brain barrier disruption.^{25, 31} Although the current study was not designed to evaluate the cellular effects of hypothermia, it is possible that the mild hypothermia routinely employed during CPB acts as a mitigating force against oxygen toxicity, moderating any detrimental effect on postoperative neurocognitive function.

Our study is limited by the fact that we have examined the effect of hyperoxia only during CPB. It is possible that hyperoxia in the post-CPB and postoperative period is of greater importance as reperfusion injury progresses. Nevertheless, in a large sample of cardiac surgery patients, we are unable to demonstrate a detrimental effect of hyperoxia *during* CPB. A second limitation is that we have assessed only arterial hyperoxia which may not reflect brain tissue oxygenation. Near-infrared reflectance spectroscopy can be used to measure regional cerebral tissue oxygen saturation but is currently limited to the frontal lobes and was not available in the majority of our subjects. Studies have suggested that brain desaturation may be associated with greater neurocognitive decline but the relationship between arterial oxygenation and these desaturation episodes are poorly described.^{32–35} Finally, we are limited by the lack of biochemical markers of oxidative stress. For example, it has been shown that lipid oxidation, a product of oxidative stress, causes increased beta amyloid (A β) deposition which in turn initiates the propagation of further lipid oxidation and neuronal degeneration.^{7, 30} Measuring lipid oxidation and elevated A β deposition may provide a more nuanced understanding of the relationship between oxidative damage and neurocognitive function in cardiac surgical patients.

To summarize, past research has suggested that while hyperoxia may protect against hypoxic injury, it may also initiate a sequence of cellular processes just as deleterious. In the largest study to date we found no association between hyperoxia and neurocognitive function at 6 weeks postoperatively. In the presence of hypothermia and without evidence of classic ischemia-reperfusion injury, arterial hyperoxia during CPB does not appear to have a detrimental effect upon neurocognitive outcomes.

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Table 1

Demographic characteristics of the study population.

Age in years (SD)	64.0 (10.3)
Gender (% female)	34.2
Race (% Caucasian)	84.0
Years of education (SD)	11.9 (4.0)
CABG surgery (%)	94
CABG + valve surgery (%)	6
Weight in kg (SD)	86.0 (20.9)
Diabetes (%)	26.8
Hypertension (%)	67.2
Prior smoker (%)	58.8
Number of grafts (SD)	2.7 (2.0)
CPB time in minutes (SD)	131.9 (50.0)
Hematocrit level (% drop)	39.8 (12.1)
PaO ₂ baseline level, mmHg (SD)	227.3 (125.3)
Baseline cognitive score (SD)	0.00 (1.30)
Cognitive change at 6 weeks (SD)	0.17 (1.45)

* CPB, cardiopulmonary bypass; PaO₂, partial pressure of oxygen in arterial blood; SD, standard deviation.