A Multicenter, Randomized, Controlled Phase IIb Trial of Avoidance of Hyperoxemia during Cardiopulmonary Bypass

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ABSTRACT

Background: Cardiac surgery utilizing cardiopulmonary bypass (CPB) is one of the most common forms of major surgery. Cardiac surgery–associated multiorgan dysfunction (CSA-MOD) is well recognized and includes acute kidney injury (AKI), hepatic impairment, myocardial damage, and postoperative neurologic deficit. Pathophysiology of CSA-MOD involves numerous injurious pathways linked to the use of CPB including oxidative stress and formation of reactive iron species. During cardiac surgery with CPB, arterial return blood is oxygenated to supranormal levels. This study aimed to determine whether the avoidance of arterial hyperoxemia decreased oxidative stress and reduced the severity of the multiorgan dysfunction in patients undergoing cardiac surgery utilizing CPB.

Methods: The study was a multicenter, open-label, parallel-group, randomized controlled study of the avoidance of arterial hyperoxemia *versus* usual care in patients undergoing cardiac surgery involving CPB. Primary outcome was the incidence and severity of AKI. Secondary outcomes included serum biomarkers for CSA-MOD, duration of mechanical ventilation, and length of intensive care and hospital stay.

Results: A total of 298 patients were randomized and analyzed at two hospitals in New Zealand and Australia. Mean Pa_{O_2} was significantly different between groups during CPB. There was no difference in the development of AKI (intervention arm 72.0% *vs.* usual care 66.2%; difference, −5.8% [95% CI, −16.1 to 4.7%]; $P = 0.28$), other markers of organ damage, or intensive care unit and hospital length of stay.

Conclusions: Avoiding modest hyperoxemia during CPB failed to demonstrate any difference in AKI, markers of organ damage, or length of stay. **(Anesthesiology 2016; 125:465-73)**

CARDIAC surgery utilizing cardiopulmonary bypass (CPB) is one of the most common forms of major surgery, with more than 1.25 million patients undergoing this surgery worldwide each year.[1] Despite improvements to both surgical techniques and the equipment used for CPB, mortality and significant morbidity remain high. During CPB, it is common practice to oxygenate the arterial return blood to supranormal levels, in part because monitoring of the blood oxygen levels, and thus the function of the oxygenator, is commonly done intermittently using blood gas sampling. Oxygen is one of the most widely available and prescribed therapeutic drugs in medicine.[2] While the risks associated with hypoxemia are well recognized, there is growing concern that hyperoxemia could also induce detrimental systemic effects.[3–5]

Cardiac surgery–associated multiorgan dysfunction (CSA-MOD) is well recognized and includes cardiac surgery–associated acute kidney injury (CSA-AKI), acute hepatic impairment, myocardial damage, and postoperative neurologic deficit.[6] The etiology of CSA-MOD is complex but is thought to involve numerous injurious pathways including the development of oxidative stress and cellular damage caused by excess reactive oxygen species.[7] Animal

What We Already Know about This Topic

- Multiorgan dysfunction is a well-recognized and important potential complication of cardiac surgery with cardiopulmonary bypass
- Standard practice involves returning blood to the patient from the bypass machine with supranormal levels of oxygen
- The potential for arterial hyperoxemia during cardiopulmonary bypass to produce organ damage is an area of interest and has not been adequately addressed

What This Article Tells Us That Is New

- The authors provide the first multicenter, randomized control trial to address the potential of organ injury from perioperative hyperoxemia during cardiopulmonary bypass
- The authors show that avoiding hyperoxemia during cardiopulmonary bypass was safe but failed to demonstrate a difference in organ damage

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data suggest that these effects may be amplified by exposure to hyperoxemia, which is common during CPB.[7] Although there is a considerable overlap between them, the principal processes include exposure of circulating blood to nonbiocompatible surfaces and erythrocyte damage and hemolysis caused by mechanical stress from the blood circulating pumps and the blood–gas interfaces in cardiotomy suction. The subsequent activation of inflammatory pathways, ischemia–reperfusion injury, decreased end-organ perfusion, and hemolysis are contributors to CSA-MOD.[6] These complications result in significant morbidity and mortality, as well as in increased intensive care and hospital length of stay and consequential increases in healthcare costs.[8]

Although the deleterious effects of CPB affect all body systems, they are most marked on the kidney, with renal damage occurring in up to 30 to 70% of patients, depending on the definition used.[9] Oxidative stress, the creation of oxygen free radicals and heme- or iron-containing reactive oxygen species, is recognized as an important factor in the development of CSA-AKI.[10–12] The production of these toxic molecules is in part dependent on arterial oxygen levels. There is also evidence suggesting that high levels of arterial oxygenation may exacerbate ischemic-reperfusion injuries, and this effect is attenuated by avoiding hyperoxemia.[13,14] Hyperoxemia has also been shown to have significant adverse hemodynamic effects after coronary artery bypass surgery.[15]

Current standard practice is to use supranormal arterial blood oxygen tensions during CPB; however, increasing availability of real-time continuous in-line blood gas analysis now provides the opportunity to safely use lower, more physiologic arterial oxygen tensions.

We hypothesized that the avoidance of perioperative arterial hyperoxia decreased the degree of oxidative stress and therefore the severity of the CSA-MOD after cardiac surgery utilizing CPB.

Materials and Methods

A prospectively randomized, open-label, parallel-group, phase IIb interventional study was undertaken in two metropolitan hospitals: one in New Zealand and one in Australia. The study was approved by the local ethics committees at each site (12/NTA/15 Northern A Health and Disability Ethics Committee, New Zealand, and Calvary Health Care Adelaide Human Research and Ethics Committee 13-CHREC-F001, Australia).

Patients were approached in hospital before surgery, the study was discussed, and written informed consent to participate was obtained by trained research staff from all study participants before enrollment. The trial was prospectively registered with the Australia and New Zealand Clinical Trials Registry: 12612000756820 (http://anzctr.org.au/).

Participants were eligible for inclusion if they were 16 yr of age or older and undergoing scheduled cardiac surgery utilizing CPB. Exclusion criteria were any of the following: acute renal failure (acute increase in serum creatinine more than 50% from baseline in the 6 weeks before surgery), preoperative end-stage renal disease (serum creatinine more than 3.4 mg/dl) or receiving any form of renal replacement therapy, preoperative hepatic dysfunction (aspartate aminotransferase [AST] more than 2× upper limit of normal), recent (less than 6 weeks) cerebrovascular event (including cerebrovascular accident, transient ischemic attack, or intracerebral bleed), pregnancy, planned hypothermic circulatory arrest, or preoperative intraaortic balloon pump.

After enrollment, patients were randomized 1:1 in blocks of 8 to the intervention or usual care, with the sequence generated by an independent statistician. To facilitate balance in severity between treatment arms, patients were further stratified according to risk of AKI using well-recognized criteria.[16]

Allocation concealment was maintained until the time of randomization by using opaque, sealed, sequentially numbered envelopes, prepared by a person independent of the study.

The intervention group received protocolized control of arterial oxygenation from induction of anesthesia until the end of surgery to maintain arterial oxygen tensions of 75 to 90 mmHg. It was recommended that hyperoxemia be avoided during anesthetic induction and the prebypass period to target peripheral oxygen saturation (Spo_2%) 92 to 95%. It was acknowledged that not all anesthetists would be comfortable with this approach and might wish to administer 100% FIO_2 (as opposed to the recommended target Spo_2 of 92 to 95%) during part or all of the pre- and post-CPB period. During CPB, the oxygen tension of the arterial return blood flow target was 75 to 90 mmHg using continuous, in-line, real-time blood gas monitoring (Terumo CDI 500, Terumo Corporation and Spectrum M4, Spectrum Medical, UK), providing arterial saturation more than or equal to 97% (if less than 97% then the Pao_2 was to be increased beyond 90 mmHg).

The control group received usual care, including selection of appropriate supplemental oxygen by the treating anesthetist and clinical perfusionist. Both the centers participating in this study do not routinely use a FIO_2 of 1.0 during CPB, rather FIO_2 is titrated to maintain a circuit arterial saturation of more than or equal to 99%.

The conduct of CPB followed normal clinical practice (crystalloid prime, mild hypothermia, ~34° to 32°C; target hematocrit, more than 0.23, flow index, 2.0 to 3.0 L min^{-1} m^{-2}; mean arterial pressure, more than 50 mmHg). Alpha-Stat blood gas management was used, and the oxygenator gas FIO_2 was titrated to meet the study protocol. All other anesthetic, CPB, and surgical care were provided at the discretion of the clinician.

We used dedicated research nurses to collect data using paper case report forms. Data included demographic data (*i.e.*, age, ethnicity, body mass index, comorbidities), intraoperative data (*i.e.*, surgery type, CPB, and aortic cross-clamp time), postoperative data (*i.e.*, requirement for renal replacement therapy, length of mechanical ventilation, and

length of stay in intensive care unit [ICU] and hospital), and biochemical data (arterial blood gas measurement, serum creatinine, urea, hemoglobin, selenium, C-reactive protein, high-sensitivity troponin T, AST, and amylase were all measured immediately before surgery and at 6 and 24 h after commencement of CPB). Serum creatinine was also recorded, if measured, on postoperative days 1 to 5. Hourly urine output measures were performed up to day 5 if the patient remained catheterized and in the ICU. All patients were contacted 28 and 90 days after randomization to ascertain mortality and requirement for renal replacement therapy.

The primary outcome was the difference in CSA-AKI during hospital admission as determined by the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Work Group guidelines.[17] Secondary outcomes included changes in multiple markers of end-organ damage (troponin, AST, amylase, C-reactive protein) and length of mechanical ventilation, intensive care, and hospital stay. Process of care data was collected to determine the actual difference in arterial oxygen tension between the two groups and amount of inspired oxygen (FIO_2%) used by the anesthetist before commencement of CPB.

As a phase IIb equivalent study of a novel therapeutic intervention, we were seeking to provide proof of concept, evidence of potential efficacy, and sufficient information to enable rigorous design of a definitive phase III study.

Sample size calculations were based on the findings of a previous study of CSA-AKI in which a 20% reduction in the prevalence of AKI was observed.[18] Using our hospital database, the baseline incidence of CSA-AKI using KDIGO criteria was 67%. Sample size calculations were based on the desire to have an 80% power to reduce this incidence from 2 in 3 to 1 in 2 with a two-sided P value of 0.05. This equates to a raw difference of 17% (67 *vs.* 50%) and a relative risk reduction of 25%. A relative risk reduction of 25% is considered clinically significant and is less than that used in previous studies of CSA-AKI.[19,20] To facilitate this, 286 patients were required. To account for possible loss to follow-up, 298 patients were enrolled. When considering secondary variables, these 298 patients further enabled an 80% power to detect a difference in continuous outcomes equivalent to one third of a standard deviation with a two-sided P value of 0.05. A difference of this magnitude was perceived to be of clinical importance.

Statistical Analysis

All analysis was performed according to the intention-to-treat principle using SAS version 9.4 (SAS Institute Inc., USA). Group comparisons in the primary outcome were made using chi-square tests for equal proportion (or Fisher exact tests where numbers were small), Student's t tests for normally distributed data, or Wilcoxon rank sum tests otherwise. Results are presented as n (%), mean (SDs), or median (interquartile range). Repeated measures data were analyzed using mixed linear models fitting main effects for treatment, time, and an interaction between treatment and time to determine if the groups behaved differently over time, with results present as least square means (SEs). Risk stratification was not utilized for analysis nor were center effects included in the model. A two-sided P value of 0.05 was considered to be statistically significant.

Results

During the period from December 2012 to May 2014, 305 patients were enrolled, of which 298 patients were randomized at two hospitals (fig. 1).

Seven patients were not randomized before surgery due to changes caused by alterations in the operative schedule. Of those randomized, 148 were allocated to usual care and 150 to intervention. No subjects were lost to follow-up, and all had the primary and secondary outcomes available for analysis. Data were available for analysis of primary outcome for all 298 participants. Baseline characteristics of study participants are described in table 1.

No adverse events or side effects of treatment were recorded in study participants. A total of nine participants (3%) died: eight died postoperatively in the ICU and one died after discharge from hospital but before day 28 postoperative.

Treatment Administered

Excellent treatment separation was achieved between the two groups during the bypass phase, but Pa_{O_2} values pre- and post-CPB were similar in both groups (fig. 2).

The pre-CPB value was measured immediately before commencement of CPB. The post-CPB value is an average of the values recorded every 10 min from the end of CPB to the completion of surgery. The ICU value is the average of values recorded for 6 h from admission to ICU. Values are presented as means, and error bars show SEM. Both groups had FIO_2 titrated to meet the protocol (intervention arm) or as per usual practice (control arm; fig. 3).

There was no difference between the intervention and control arms in respect to the management of blood flow (2.6 *vs.* 2.5 l m^{-2} min^{-1}: $P = 0.06$) and oxygen delivery index (320 *vs.* 324 ml min^{-1} m^{-2}, $P = 0.53$) during CPB. Both arterial (97.2 *vs.* 99.0%, $P < 0.001$) and venous (78.6 *vs.* 81.7%, $P < 0.001$) saturations of blood in the CPB circuit were lower in the intervention arm.

Primary Outcome

There was no significant difference in the occurrence of renal dysfunction between groups as measured by KDIGO and based on change in either urine output or creatinine (table 2).

Other Clinical Outcomes of Interest

There was no significant difference found between the two groups in the multiple biomarkers measured at baseline, 6 or 24 h after commencement of CPB (table 3). There was also no difference seen in ventilation hours, ICU or hospital

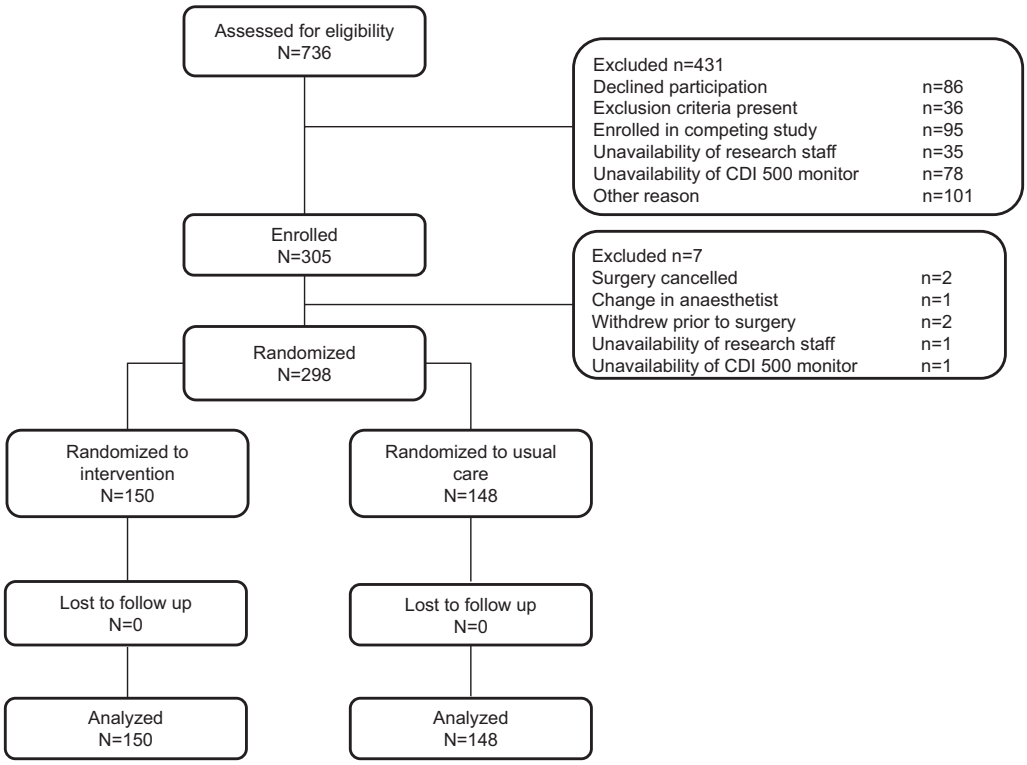

Fig. 1. Participant flow-through study.

Table 1. Baseline Characteristics of Study Participants

	Usual Care (n = 148)	Intervention (n = 150)
Gender, n (%)		
Male	110 (74)	108 (72)
Female	38 (26)	42 (28)
Ethnicity, n (%)		
European	113 (76)	113 (75)
New Zealand Maori	14 (9)	20 (13)
Pacific Island	9 (6)	6 (4)
Asian	2 (1)	0 (0)
Other	10 (7)	11 (7)
Age (yr), mean (range)	65.3 (30–90)	65.8 (20–88)
BMI (kg/m^2), mean (SD)	29.2 (6.3)	29.4 (6.2)
Euroscore II, median (IQR)	1.5 (0.9–2.5)	1.3 (0.9–2.1)
Surgery, n (%)		
Isolated CABG	63 (43)	72 (48)
Valve surgery	67 (45)	48 (32)
CABG + valve	14 (9)	23 (15)
Other cardiac surgery	4 (3)	7 (5)
Bypass time (min), mean (SD)	106 (40)	109 (46)
Cross clamp time (min), mean (SD)	78 (36)	80 (40)
Preoperative creatinine (mg/dl), mean (SD)	1.02 (0.27)	0.96 (0.23)

Data are presented as n (%), mean ± SD, or median (interquartile range [IQR]) as indicated.

BMI = body mass index; CABG = coronary artery bypass graft.

length of stay, and requirement for renal replacement therapy or mortality to day 90.

Discussion

This study assessed the avoidance of hyperoxemia in adult patients undergoing cardiac surgery using CPB. We achieved excellent treatment separation once the participant was on CPB but failed to demonstrate any significant difference in the incidence of AKI, other measures of CSA-MOD, or ICU and hospital length of stay.

To our knowledge, this is the first study to utilize real-time in-line arterial blood gas analysis to avoid perioperative arterial hyperoxemia during CPB in an attempt to decrease oxidative stress and severity of CSA-MOD. Previously published work attempting to establish the most appropriate FIO_2 during CPB, which would result in normoxemia, found that to avoid hyperoxemia, FIO_2 should be kept at 0.35 during CPB.[21] Currently, there is no published evidence or consensus to inform clinical perfusionists as to where to target oxygen levels or what the ideal FIO_2 or PaO_2 is on bypass,[21] resulting in wide practice variation and results.

A pragmatic study design was used to ensure generalizability of study results to large numbers of patients presenting for cardiac surgery. This study enrolled a large sample

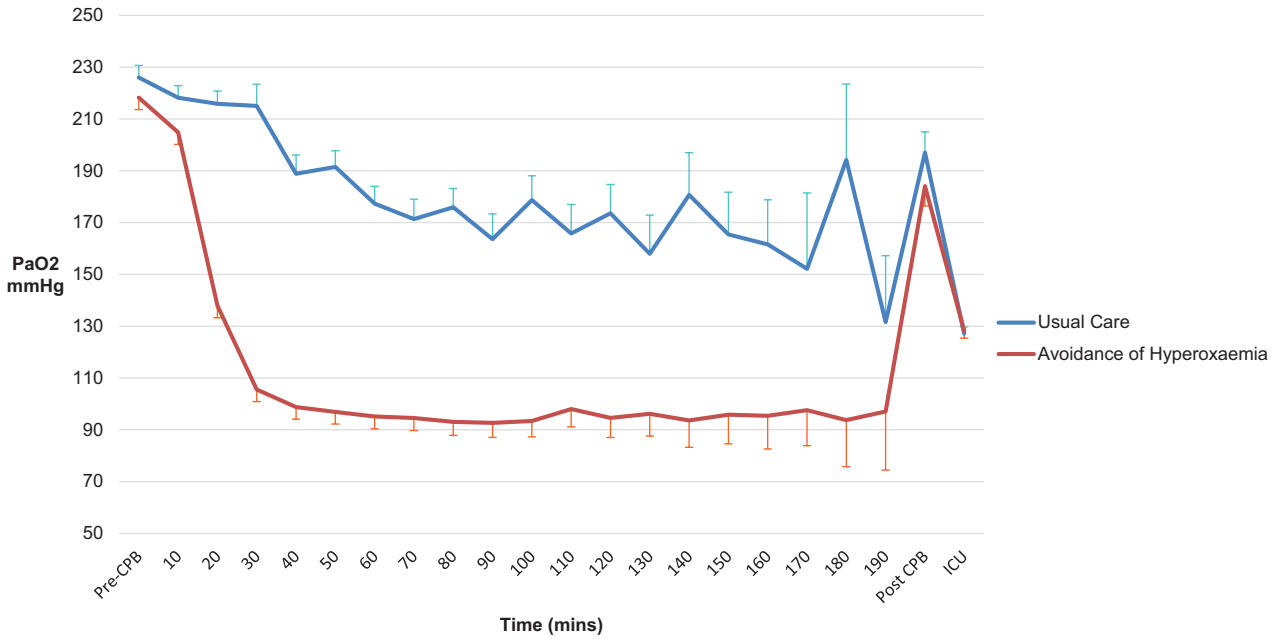

Fig. 2. Arterial oxygen partial pressure for oxygen (mmHg). The precardiopulmonary bypass (pre-CPB) value was measured immediately before commencement of cardiopulmonary bypass (CPB). The post-CPB value is an average of the values recorded every 10 min from the end of CPB to the completion of surgery. The intensive care unit (ICU) value is the average of values recorded for 6 h from admission to ICU. Values are presented as means, and *error bars* show SEM.

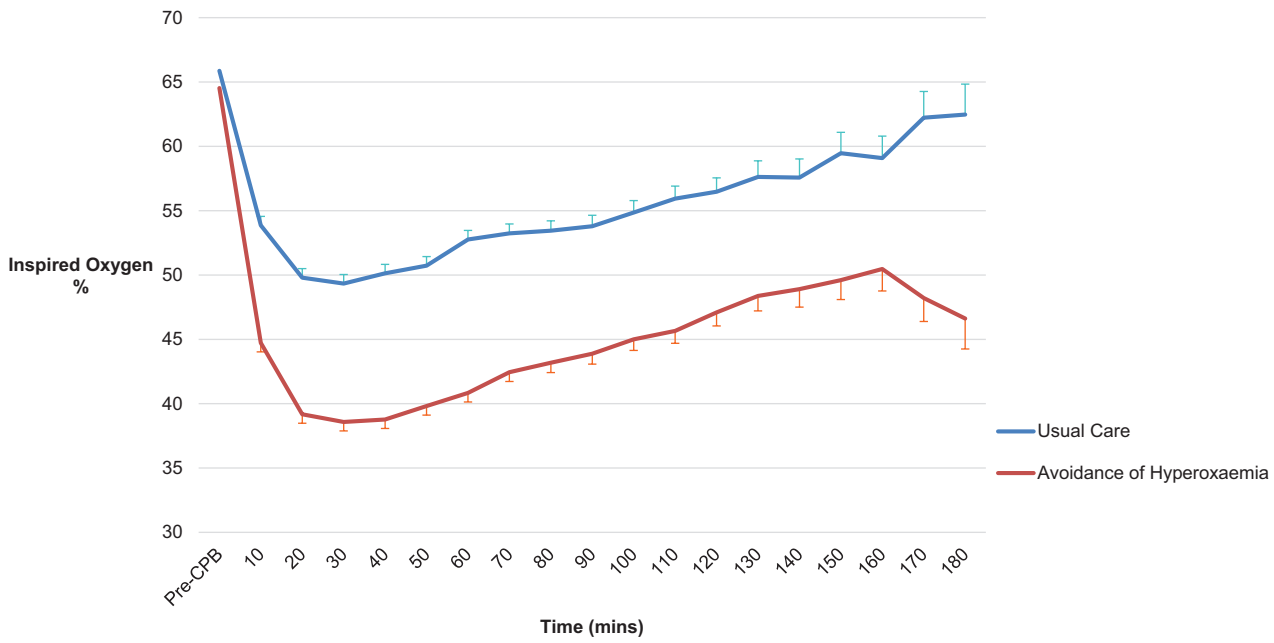

Fig. 3. Inspired oxygen administered before and during cardiopulmonary bypass (CPB). The pre-CPB value was measured immediately before commencement of CPB.

size, there was no loss to follow-up, and the study was undertaken over 17 months. Some delay to recruitment was experienced due to availability during the trial of the continuous in-line blood gas monitoring system, which was not present on all bypass machines. This meant that not all patients available could be recruited due to the inability to provide intervention treatment.

Treatment separation was easily achieved by clinical perfusionists using the continuous in-line real-time blood gas monitoring. The moderate degree of hyperoxemia (mean Pao_2, 178 mmHg) observed during CPB in the control arm reflects the current clinical practice in both our study sites and many other centers in New Zealand and Australia. A mean arterial oxygen saturation in the intervention arm of 97.2% demonstrated

Table 2. Incidence of Acute Kidney Injury as Measured by KDIGO Using the Full Criteria or the Creatinine-only Criteria

	Control (n = 148)	Intervention (n = 150)	Difference (Control – Intervention) (95% CI)	*P* Value
Full KDIGO criteria, n (%)				
Any AKI	98 (66.2)	108 (72)	–5.8% (–16.1 to 4.7%)	0.28
KDIGO stage 1	53 (35.8)	67 (44.7)	–8.9% (–19.9 to 2.2%)	0.12
KDIGO stage 2	43 (29.1)	36 (24.0)	5.1% (–5.0 to 15.1%)	0.32
KDIGO stage 3	2 (1.3)	5 (3.3)	–2.0% (–5.4 to 1.4%)	0.26
Surgical procedure				
Isolated CABG (n = 135)	39/63 (61.9)	50/72 (69.4)	–7.5% (–23.1 to 8.3%)	0.36
Other (n = 163)	59/85 (69.4)	58/78 (74.4)	–5.0% (–18.4 to 8.9%)	0.29
Creatinine-only KDIGO criteria				
Any AKI, n (%)	37 (25.0)	41 (27.3)	–2.3% (–12.2 to 7.6%)	0.65

AKI = acute kidney injury; CABG = coronary artery bypass graft; KDIGO = Kidney Disease: Improving Global Outcomes.

Table 3. Outcomes of Interest

	Control (n = 148)	Intervention (n = 150)	*P* Value
Biomarkers			
Creatinine (mg/dl), mean (SD)			
Baseline	0.96 (0.28)	0.93 (0.19)	0.24
6 h post-CPB commencement	0.89 (0.27)	0.84 (0.20)	0.09
24 h post-CPB commencement	1.03 (0.34)	0.99 (0.28)	0.39
Selenium (μmol/l), mean (SD)			
Baseline	1.18 (0.26)	1.22 (0.24)	0.08
6 h post-CPB commencement	0.96 (0.22)	0.94 (0.21)	0.49
24 h post-CPB commencement	0.88 (0.21)	0.89 (0.20)	0.62
CRP mg/l, median (IQR)			
Baseline	2 (1–5)	2 (1–5)	0.61
6 h post-CPB commencement	3 (2–6)	3 (1–5)	0.81
24 h post-CPB commencement	98 (69–122)	95 (68–124)	0.58
High-sensitivity troponin T (ng/l), median (IQR)			
Baseline	13 (8–22)	13 (8–20)	0.61
6 h post-CPB commencement	641 (345–1030)	535 (354–892)	0.23
24 h post-CPB commencement	379 (204–647)	336 (218–587)	0.53
AST (U/l), median (IQR)			
Baseline	21 (17–25)	21 (17–28)	0.77
6 h post-CPB commencement	43 (36–54)	40 (33–53)	0.10
24 h post-CPB commencement	44 (34–63)	41 (33–62)	0.50
Amylase U/l, median (IQR)			
Baseline	56 (44–73)	59 (43–78)	0.93
6 h post-CPB commencement	46 (33–64)	44 (32–62)	0.66
24 h post-CPB commencement	56 (37–100)	59 (37–100)	0.80
Other clinical outcomes			
Renal replacement therapy, n (%)	3 (2)	3 (2)	1.0
Renal replacement therapy at day 90, n (%)	0 (0)	0 (0)	1.0
Ventilation time (h), median (IQR)	7.2 (5.0–13.0)	7.2 (5.3–16.6)	0.35
ICU length of stay (h), median (IQR)	23.3 (19.9–47.3)	22.8 (20.6–48.5)	0.75
Hospital length of stay (d), median (IQR)	8.9 (6.7–13.5)	9.0 (7.1–13)	0.65
Alive at ICU discharge, n (%)	145 (98)	145 (97)	0.49
Alive at day 90, n (%)	144 (97)	145 (97)	0.75

Ventilation time is the number of hours from admission to intensive care unit (ICU) until extubation. ICU length of stay is the number of hours from admission to ICU until discharge to the ward or death. Hospital length of stay is the number of hours from admission to the hospital preoperatively to discharge home postoperatively.

AST = aspartate aminotransferase; CPB = cardiopulmonary bypass; CRP = C-reactive protein; IQR = interquartile range.

that we achieved the maximal possible reduction in hyperoxemia as it was considered clinically unacceptable to conduct CPB with arterial saturations lower than 97%.

Although arterial hyperoxemia has long been used to protect against potential side effects of CPB such as hypoxic injury and gaseous embolization, emerging evidence from diverse populations, such as those postcardiac arrest, suggests that exposure to high levels of oxygen tensions may in fact be harmful.[22,23]

Hyperoxemia has been associated with many side effects such as alterations in capillary blood flow, reduced cardiac index, increased systemic vascular resistance, hemolysis, and formation of micro air emboli.[24] We hypothesized that by controlling oxygen levels in a normal range while on bypass, these side effects would be negated in the intervention group. We utilized a wide range of biomarker-based endpoints to detect a treatment effect for organ damage between the groups but failed to show any difference. Although there are some newer biomarkers that may directly measure oxidative stress (*e.g.,* isoprostanes), we chose to measure commonly used and available measures of individual organ damage. We chose to use the incidence of AKI using the KDIGO definition as the primary outcome as it is well recognized that the development of AKI after cardiac surgery is associated with poorer outcomes. KDIGO has superseded earlier classifications of AKI and has been used in a number of clinical studies in this patient population; however, most previously published work has only used the creatinine component of KDIGO rather than both the creatinine and urine output components. We chose to use the full definition in accordance with guidelines, which yielded a much higher incidence of AKI than is found using creatinine criteria alone. However, even if only the creatinine component of the KDIGO definition is used, we found no difference between groups.

The lack of efficacy of the intervention may be explained by an absence of true ischemia-reperfusion injury after routine CPB as compared to that seen for instance in survivors of cardiac arrest whom have a "whole of body ischemia-reperfusion insult" as opposed to a more limited insult focused on the heart in CPB patients. It is plausible that routine hypothermia during CPB diminishes the effects of hyperoxemia, moderating the development of postoperative neurocognitive dysfunction and MOD.[25] Furthermore, there is recent evidence suggesting that exceeding a critical threshold of oxygen delivery might limit the incidence of postoperative AKI.[26] There was no difference in oxygen delivery index during CPB between the intervention and the control groups, and this was well in excess of the DO_2i threshold identified, possibly negating the impact of hyperoxemia on markers of renal outcome.

Limitations

We recognize some inherent limitations to our study. First, although attending anesthesiologists were encouraged to target a low normal level of arterial oxygenation pre- and post-CPB, there was only a small difference between groups at these time points. The explanation given by the anesthesiologists was that they were uncomfortable using low F_{IO_2} during these periods. The intervention, therefore, only occurred during CPB and thus there was significant hyperoxemia both pre- and post-CPB, and it is possible that these times represent "at-risk" periods for hyperoxemia-mediated cellular damage. In particular, it is theoretically plausible that the most critical time for hyperoxemia is when the blood is first exposed to the artificial surfaces of the bypass circuit. In our study, we did not achieve significant separation of oxygen levels immediately before initiating CPB. We also did not insist on the provision of normoxemia to patients in either the prebypass or postbypass period but left that to the discretion of the treating clinicians. Nevertheless, in our sample of cardiac surgery patients, we did not demonstrate any difference in outcomes with avoidance of hyperoxemia during CPB.

Although we successfully achieved normoxemia in the intervention group, the actual difference in Pa_{O_2} between the two groups was only moderate (approximately 80 mmHg), and it is plausible that greater degrees of hyperoxemia are required to cause organ damage. Greater hyperoxemia in the control arm could have been achieved by mandating a F_{IO_2} of 1.0 in these patients; however, this would have been contrary to usual care at the two participating sites.

This is an unblinded study in a group of all-comers rather than high-risk cardiac surgical patients. Perhaps if we had targeted only high-risk patients, results may have been different. CSA-MOD occurs through multiple injurious pathways, which may have differential effects in different subpopulations of patients. It is plausible that certain preoperative patient characteristics, surgical procedures, or time on CPB may identify a group of patients who are more likely to benefit from the avoidance of hyperoxemia. Although we have provided data on the primary outcome for isolated coronary artery bypass surgery and other patients, the sample size does not allow further meaningful analysis of other subgroups.

We chose to undertake indirect measures of oxidative stress and measured markers of organ dysfunction rather than attempting to quantify the degree of oxidative stress directly.

In summary, the avoidance of modest hyperoxemia (mean, 178 mmHg) during CPB appears safe and achievable but failed to demonstrate any difference in AKI, markers of organ damage, or length of stay. Future clinical studies in this area should consider extending the intervention to the pre- and post-CPB period and should also consider if

maximizing the treatment separation by using a FIO_2 of 1.0 is appropriate.

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Competing Interests

Research in the Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital, Auckland, New Zealand (Drs. McGuinness and Parke), is supported in part by an unrestricted grant from Fisher & Paykel Healthcare Ltd., Auckland, New Zealand. The other authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. McGuinness: shaymc@adhb.govt.nz. Raw data available from Dr. McGuinness: shaymc@adhb.govt.nz.

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Appendix

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