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Low Oxygen Delivery as a Predictor of Acute Kidney Injury during Cardiopulmonary Bypass

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Abstract: Low indexed oxygen delivery (DO_2i) during cardiopulmonary bypass (CPB) has been associated with an increase in the likelihood of acute kidney injury (AKI), with critical thresholds for oxygen delivery reported to be 260–270 mL/min/m^2. This study aims to explore whether a relationship exists for oxygen delivery during CPB, in which the integral of amount and time below a critical threshold, is associated with the incidence of postoperative AKI. The area under the curve (AUC) with DO_2i during CPB above or below 270 mL/min/m^2 was calculated as a metric of oxygen delivery in 210 patients undergoing CPB. To determine the influence of low oxygen delivery on AKI, a multivariate logistic regression model was developed including AUC < 0, Euroscore II to provide preoperative risk factor adjustment, and incidence of red blood cell transfusion to adjust for the influence of transfusion. Having an AUC < 0 for an oxygen delivery threshold of 270 mL/min/m^2 during CPB was an independent predictor of AKI, after adjustment for Euroscore II and transfusion [OR 2.74, CI {1.01–7.41}, $p = .047$]. These results support that a relationship exists for oxygen delivery during CPB, in which the integral of amount and time below a critical threshold is associated with the incidence of postoperative AKI. **Keywords:** cardiopulmonary bypass, oxygen delivery, acute kidney injury. *J Extra Corpor Technol. 2017;49:224–230*

Acute kidney injury (AKI) is a recognized and serious complication of cardiac surgery that increases in-hospital mortality, morbidity, length of stay, and hospital costs after surgery (1). Low indexed oxygen delivery (DO_2i) and low ratio of oxygen delivery/carbon dioxide elimination (DO_2/VCO_2) during cardiopulmonary bypass (CPB) have been associated with an increase in the likelihood of AKI (2,3) together with a number of modifiable factors including hemodilution and red blood cell transfusion (4,5), mean arterial pressure (6,7), and hyperthermic perfusion (8,9). Critical thresholds for oxygen delivery metrics associated with AKI have been reported to be 260–270 mL/min/m^2 for DO_2i and a ratio of 5 for DO_2/VCO_2 (2,3). The peak lactate during CPB has also been reported to increase below a DO_2i of 260 mL/min/m^2 (10); however, further data supporting a critical threshold of oxygen delivery are lacking. This study aims to explore whether a time-dose relationship exists for oxygen delivery during CPB, in which below a critical threshold, is associated with the incidence of postoperative AKI.

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METHODS

Data Source and Collection

This was a single center observational study of prospectively collected data during CPB procedures from January to July 2015 in which the M4 monitor (Spectrum Medical, Gloucester, UK) was routinely used which provided calculated DO_2i and DO_2i/VCO_2i parameters. The study was approved by our Institutional Ethics Review Committee (332.14). Average DO_2i for each minute of bypass was calculated from data stored on the M4 monitor, from which 10 minute rolling averages were calculated for DO_2i and DO_2/VCO_2 ratios. NADIR values for each patient were the lowest 10 minute rolling average values for DO_2i and DO_2/VCO_2. The area under the curve (AUC) with DO_2i during CPB above or below 270 mL/min/m^2 was calculated as a metric of oxygen delivery. The AUC represents the integral of amount and duration of oxygen delivery above or below 270 mL/min/m^2; therefore, for

each patient if the AUC was negative then they were exposed to a greater integral of amount and duration of oxygen delivery below 270 mL/min/m^2 than above 270 mL/min/m^2. Data for each entire case from initiation to end of bypass were included. All oxygen delivery and hematocrit data were obtained from the M4 monitor.

Continuous intraoperative variables were collected at 20 seconds intervals during CPB from either an Intellivue (Koninklijke Philips, Amsterdam, The Netherlands) or Datex (GE Healthcare, Chicago, IL) physiological monitor. Nadir hemoglobin data were collected every 20–30 minutes using an ABL700 analyzer (Radiometer, Copenhagen, Denmark). Monitoring and blood gas data were stored using the CONNECT™ software (LivaNova, London, UK). Patient risk factors, perioperative data, and outcomes were collected using the Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) which integrates electronic data from CONNECT™ software as previously described (11).

Clinical Management

General anesthesia was induced with fentanyl (10–30 g/kg) and supplemented with sevoflurane and/or propofol. All patients underwent cardiac surgery with CPB using a S5 roller pump (LivaNova). Arterial pressure was monitored via radial artery catheter. Cardiopulmonary bypass was instituted after positioning of either a single 36/51 Fr two-stage atrial cannula (Sarns™, Terumo Corporation, Tokyo, Japan), or 32–36 Fr bicaval cannulation (Sarns™), and a 22 or 24 Fr ascending aortic cannula (DLP, Medtronic, Minneapolis, MN). The CPB circuit included a hard-shell membrane oxygenator (Capiox® RX25, Terumo Corporation), biopassive tubing (Phisio, LivaNova) a 40 micron arterial line filter (AL40, Pall Corporation, Port Washington, NY) and a .2 micron prebypass filter (Prebypass Plus®, Pall Corporation). A ½″ diameter venous line was used routinely. The circuit was primed with 1 L Plasmalyte solution, 500 mL of Gelofusine (isolated CABG procedures) or 4% albumin (other procedures), 50 mL 8.4% sodium bicarbonate solution, 50 mL Hartmann's solution, and 10,000 iu heparin. Packed red blood cells (RBC) were added if required to provide a predicted hemoglobin level of >7 g/dL on initiation of CPB (determined by the algorithm of the CONNECT™ software). Before initiation of CPB retrograde autologous priming was performed with a target RAP volume of 250 mL if the predicted CPB hemoglobin level was <11 g/dL. The routine CPB protocol included arterial non-pulsatile target flow rate of 1.8–2.4 L/min/m^2, alpha-stat pH management with target pO_2 100–250 mmHg, gravity venous drainage, and tepid systemic temperature management (nasopharyngeal temperature 34–35°C) with no active cooling. After placement of the aortic cross clamp, cardioplegic arrest was induced with tepid (34°C) hyperkalemic blood cardioplegia (30 mmol/L) at induction and maintained with intermittent doses (16 mmol/L) delivered either anterograde or retrograde as required. Mean CPB arterial pressure was controlled using metaraminol, phentolamine or isoflurane to achieve a target of 40–80 mmHg. Target nasopharyngeal temperature for separation from bypass was >36°C with rewarming rate <.5°C per 2 minutes and arterial outlet temperature <37°C. Transfusion of red blood cells during CPB was triggered when hemoglobin level was measured to be <7 g/dL. Hemoconcentration was used in the setting of hyperkalaemia or fluid overload. Restrictive IV fluid administration was used routinely intraoperatively. For the four surgeons in our team, one used cardiotomy suction to collect shed mediastinal blood without cell salvage routinely. For the other three, shed mediastinal blood was collected using cell salvage (Xtra, LivaNova) in isolated coronary artery bypass graft (CABG) procedures, and cardiotomy suction and cell salvage in procedures other than isolated CABG. Salvaged blood was processed if sufficient volume was available for processing or when residual CPB circuit blood was processed (if last CPB hemoglobin was <9 g/dL), otherwise residual circuit blood was returned to the patient via IV infusion. Post-operative renal replacement therapy was initiated according to physician assessment based on oliguria unresponsive to fluid resuscitation measures, hyperkalaemia, severe acidemia, or clinically significant lung edema.

Acute Kidney Injury

AKI was defined according to the serum creatinine criteria of the RIFLE (renal Risk, Injury, Failure, Loss of renal function, and End-stage renal disease) classification at the risk or greater level as any increase in serum creatinine >50% from baseline to peak value postoperatively (12). Serum creatinine measurement was performed using the enzymatic method (Roche, Basel, Switzerland).

Statistical Analysis

STATA® SE version 14.0 (StataCorp LP, College Station, TX) was used for the statistical analyses. Patient preoperative and intraoperative characteristics were compared in 210 patients with an AUC > 0 (greater proportion of CPB with DO_2 > 270 mL/min/m^2) or an AUC < 0 (greater proportion of CPB with DO_2 < 270 mL/min/m^2). The Kolmogorov–Smirnov test was used to check for normality of data before further analysis; *p*-values were calculated for continuous variables using the Student *t* test or the Wilcoxon rank sum test, as appropriate and the Pearson χ^2 test for categorical variables. Group differences were considered statistically significant with a *p*-value of <.05. To determine the influence of low oxygen delivery and AKI, a multivariate logistic regression model was developed. Because of the size of the study population, to avoid overfitting, covariates selected for inclusion in the model were Euroscore II to

provide preoperative risk factor adjustment, and incidence of red blood cell transfusion to adjust for the influence of transfusion on AKI. These covariates were tested for univariate association with AKI to confirm the assumption of their relevance to AKI. Logistic regression model discriminatory and fit indices included the Hosmer and Lemeshow χ^2 test and the c-index. A Lowess smoothing plot of the AUC DO_2i above or below 270 mL/min/m^2 was used to assess visually its relationship to the probability of AKI.

RESULTS

Data from 210 consecutive adult patients undergoing cardiac surgery were used. AKI was identified in 30 patients (14.3%). Having a greater integral of amount and duration of oxygen delivery during CPB above 270 mL/min/m^2 results in a positive value for the AUC and was observed in 42.4% (89/210) of patients. Conversely having a greater integral of amount and duration of oxygen delivery during CPB below 270 mL/min/m^2 results in a negative value for the AUC and was observed in 57.6% (121/210) of patients.

Patient baseline characteristics, intraoperative data, and outcomes collected using ANZCPR are displayed in Table 1. Patients with a negative AUC were significantly older, a greater proportion were female, had lower body mass index (BMI), a higher incidence of diabetes, cerebrovascular disease, preoperative myocardial infarction, lower preoperative hemoglobin, and greater predicted risk of mortality (Euroscore II). Intraoperatively, patients with a negative AUC underwent a greater proportion of coronary artery grafting and less proportion of other procedures, shorter CPB duration, lower CPB hemoglobin, and CPB flow. Postoperatively they received greater exposure to red blood cell transfusion and had a greater incidence of AKI.

Table 1. Baseline demographic, procedural, and outcome data obtained for patients undergoing cardiopulmonary bypass procedures with a positive or negative area under the curve for oxygen delivery index <270 mL/min/m^2.

	AUC+ (n = 89)	AUC− (n = 121)	*p*
Preoperative			
Age, years	64 (52–71)	68 (60–77)	.009
Female	7%	34%	<.001
BMI kg/m^2	29 (26–32)	28 (24–31)	.019
COPD	11%	19%	.126
Previous cardiac surgery	6.8%	3.4%	.252
Emergency surgery	2.3%	4.1%	.452
Hypertension	49%	57%	.276
Diabetes	15%	28%	.020
Dialysis	1.1%	2.5%	.478
Cerebrovascular disease	1.5%	13%	.009
Myocardial infarction	15%	32%	.003
Preoperative Hb, g/dL	148 (140–153)	131 (118–142)	<.001
Preoperative creatinine, μmol/L	90 (75–100)	88 (74–111)	.531
Euroscore II	.9 (.7–1.7)	1.7 (.9–3.4)	<.001
Intraoperative			
CABG	33%	56%	.001
Valve repair/replacement	12%	8%	.328
Valve + CABG	35%	26%	.148
Other procedure	20%	10%	.035
CPB duration, minutes	87 (72–111)	80 (62–101)	.026
Average CPB MAP, mmHg	64 (60–68)	62 (58–66)	.071
Nadir CPB Hb, g/L	106 (101–112)	89 (76–96)	<.001
Average CPB flow, L/min	4.0 (3.9–4.3)	3.8 (3.4–4.0)	<.001
Average CPB CI, L/min/m^2	2.0 (1.9–2.1)	1.9 (1.8–2.1)	.005
Nadir CPB Naso temperature, °C	33.2 (2.2)	33.2 (2.5)	.525
RAP	16%	50%	<.001
RAP volume	200 (200–400)	200 (200–300)	.988
Maximum lactate, mmol/L	1.7 (1.5–2.1)	1.6 (1.3–2)	.137
Postoperative			
Baseline creatinine %	107 (92–121)	110 (96–135)	.076
Received RBC transfusion	8%	38%	<.001
Postoperative renal dialysis	2.3%	4.9%	.310
Postoperative stay, days	6 (5–9)	7 (5–10)	.252
Acute kidney injury	7%	20%	.007

Values denote median (25–75th percentiles), mean (SD), or proportion of patients in %. AUC, area under the curve; AUC+, greater integral of amount and duration of $DO_2i > 270$ mL/min/m^2; AUC−, greater integral of amount and duration of $DO_2i < 270$ mL/min/m^2; CABG, coronary artery bypass graft; BMI, body mass index; COPD, chronic obstructive airway disease; Hb, haemoglobin; CPB, cardiopulmonary bypass; CI, cardiac index; Naso, nasopharyngeal; MAP, mean arterial pressure; RAP, retrograde autologous prime; RBC, red blood cells.

Calculated parameters are shown in Table 2. Patients with a negative AUC had both lower CPB flow and hematocrit, resulting in lower average and nadir DO_2i. There was no difference in the nadir DO_2i/VCO_2i ratio between groups. By contrast, when comparing patients with or without AKI (Table 3), patients with AKI had lower average and nadir DO_2i, greater negative AUC; however, there was no difference in average CPB flow. There was no difference in the nadir DO_2/VCO_2 ratio for patients with or without AKI.

Figure 1 shows the LOWESS smoothing plot which allows visualization of the relationship between the time-dose relationship of oxygen delivery above or below 270 mL/min/m^2 (AUC) and the probability of the incidence of AKI. Figure 2, a contour interaction plot, indicates for patients with an overall negative AUC an increase in probability of AKI, and further increases in probability associated with each unit of red blood cells transfused.

Because the relationship between AUC and the probability of AKI was non-linear (as shown by the Lowess plot), AUC was categorized as above or below 0 and entered into the multivariate model. Both Euroscore II and RBC transfusion were found to have a significant univariate association with AKI and were also included in the model. Having a greater proportion of CPB with DO_2i $<$ 270 mL/min/m^2 was an independent predictor of AKI, after adjustment for Euroscore II and RBC transfusion [OR 2.74, CI {1.01–7.41}, $p = .047$]. Results of the multivariate model are summarized in Table 4.

DISCUSSION

The findings of this study support that for oxygen delivery during CPB, the integral of amount and time below a critical threshold (in this study a DO_2i of 270 mL/min/m^2) is associated with an increase in the incidence of postoperative AKI. The results of our multivariate model show that overall; patients that had an AUC that was negative (meaning that they had a greater integral of amount and duration of oxygen delivery during CPB below 270 mL/min/m^2) were 2.7 times more likely to experience AKI. These results support the previous work suggesting a critical threshold for oxygen delivery may be associated with an increase in the risk of AKI as previously reported (2,3). Ranucci et al. (2), in a study involving 1,048 patients undergoing coronary revascularization with CPB, reported a critical oxygen delivery threshold of 272 mL/min/m^2 for acute renal failure requiring renal replacement therapy and peak postoperative serum creatinine levels, within a multivariate model including serum creatinine, diabetes, and chronic pulmonary disease. More recently De Somer et al. (3) reported in 359 patients undergoing CPB that a nadir DO_2i level $<$262 mL/min/m^2 was independently associated with AKI within a model including EuroSCORE and CPB duration. Both studies were characterized by relatively small sample sizes (in the context of multivariate modeling) and non-linearity in the relationship between oxygen delivery and the outcome variables. The non-linearity between oxygen delivery and AKI, as demonstrated in the Lowess plot (Figure 1) provides visualization of how the relationship between AUC and the probability of AKI changes according to whether CPB was performed with an overall positive or negative AUC. The plot indicates a clear inflection point where the probability of AKI increases. This relationship is also evident in the contour interaction plot (Figure 2), which indicates for patients with an overall negative AUC an increase in probability of AKI, and further increases in probability associated with each unit of red blood cells transfused. Our results support previous findings that a threshold for critical oxygen delivery during CPB is relevant in the etiology of postoperative AKI; however, additional studies using larger datasets are warranted to confirm both the threshold value for oxygen delivery, its relationship to AKI, and the interaction of red blood cell transfusion.

De Somer et al. (3) identified a nadir DO_2/VCO_2 ratio $<$5.3 to be associated with AKI, supporting the results of a small earlier study which identified a DO_2/VCO_2 ratio $<$5 to be a predictor of hyperlactatemia (13). Our study

Table 2. Calculated parameters using data obtained from the Spectrum M4, for patients undergoing cardiopulmonary bypass procedures with a positive or negative area under the curve for oxygen delivery index $<$270 mL/min/m^2.

Calculated M4 Variables	AUC+ (89)	AUC− (n = 121)	p
Average CPB arterial flow, L/min	3.9 (3.7–4.2)	3.6 (3.3–3.9)	<.001
Nadir CPB hct, %	29 (3.6)	25 (3.4)	<.001
Nadir DO_2i, L/min/m^2	204 (179–232)	159 (125–182)	<.001
Average DO_2i, L/min/m^2	297 (24)	228 (28)	<.001
AUC DO_2i, 270 L/min/m^2	1,960 (681–3,507)	−3,080 (−4,968 to 1,299)	<.001
Nadir DO_2/VCO_2	4.4 (9.5)	3.6 (2.2)	.817

Values denote median (25–75th percentiles), mean (SD), or proportion of patients in %. AUC+, greater integral of amount and duration of DO_2i $>$ 270 mL/min/m^2; AUC−, greater integral of amount and duration of DO_2i $<$ 270 mL/min/m^2; Hct, hematocrit; CPB, cardiopulmonary bypass; DO_2, oxygen delivery; VCO_2, carbon dioxide elimination.

Table 3. Calculated parameters using data obtained from the Spectrum M4, for patients undergoing cardiopulmonary bypass procedures with or without acute kidney injury.

Calculated M4 Variables	AKI (30)	No AKI (n = 180)	*p*
Average CPB arterial flow, L/min	3.9 (3.4–4.3)	3.9 (3.6–4.2)	.475
Nadir CPB Hct, g/L	25 (4)	27 (4)	.002
Nadir DO_2i, L/min/m^2	170 (126–184)	180 (147–210)	.08
Average DO_2i, L/min/m^2	233 (40)	261 (42)	.001
AUC DO_2i, 270 L/min/m^2	−2,956 (−6,512 to −455)	−553(−3,273 to 1,835)	.001
Nadir DO_2/VCO_2	3.2 (3)	4.2 (7.8)	.258

Values denote median (25–75th percentiles), mean (SD). AKI, acute kidney injury; Hct, hematocrit; CPB, cardiopulmonary bypass; DO_2, oxygen delivery; VCO_2, carbon dioxide elimination.

did not explore the relationship between DO_2/VCO_2 ratio and AKI as we did not see a significant difference in the DO_2/VCO_2 ratio between patients with or without AKI (3.2 vs. 4.2, $p = .258$). A number of possible explanations may explain this difference, first the VCO_2 measurements in our study were obtained using the M4 monitor rather than a dedicated capnograph as described in the previous studies, second the formulae to calculate VCO_2 used by the M4 is different to that by De Somer, and third it has been widely reported that the design of the oxygenator contributes to the measurement of exhaust CO_2 (14–16). We did not observe a significant difference in lactate levels during CPB, between patients with an AUC above or below 0.

A consideration in the reporting and understanding of the role of oxygen delivery during CPB is variation in the measurement of oxygen delivery and carbon dioxide production parameters and also how we use these parameters in analyses. A published formula exists for the calculation of DO_2 and VCO_2; however, variation exists in the formula used by currently available monitoring devices. Variation can also be introduced through the devices used to measure the physiological parameters in the formula (see limitations). Equally important to consider is how we derive meaningful metrics that we can relate to outcome and how these metrics should be interpreted by the clinician. For example, in the studies reported by Ranucci et al. (2) and De Somer et al. (3) a metric of minimum DO_2i was used to relate oxygen delivery to outcome. In the Ranucci et al. (2) study, minimum DO_2i was calculated at the time when the lowest hematocrit was reached, with arterial oxygen tension recorded simultaneously to lowest hematocrit, and pump flow as the mean value during 30 minutes of CPB around the time when the lowest hematocrit was recorded. In the De Somer study, data were collected at 10-minute intervals with the nadir DO_2 level defined as the lowest DO_2 value registered for at least two consecutive measurements during CPB (3). These

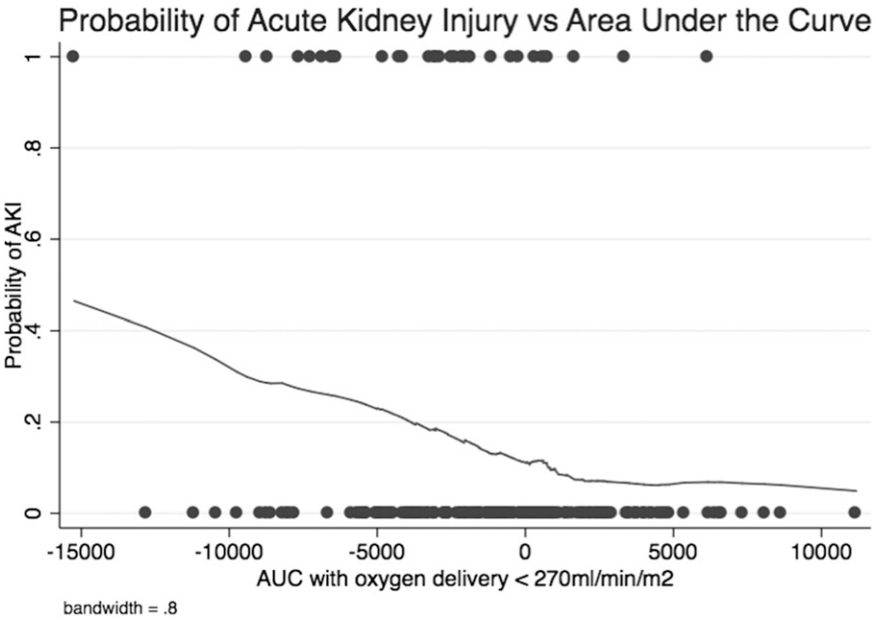

Figure 1. Lowess smoothing plot of the probability of AKI vs. AUC with DO_2i < 270 mL/min/m^2 during CPB. The Lowess is a smoothed scatterplot in which smoothed values are obtained by running a regression of the *y*-axis variable on the *x*-axis variable for each data point, and a few of the data near this point. In Lowess, the regression is weighted so that the central point gets the highest weight and points that are farther away receive less weight. The procedure is repeated to obtain the remaining smoothed values, which means that a separate weighted regression is performed for every point in the data. This plot indicates an increase in probability of AKI for AUC values <0 (greater integral of amount and duration of DO_2i < 270 mL/min/m^2 during CPB).

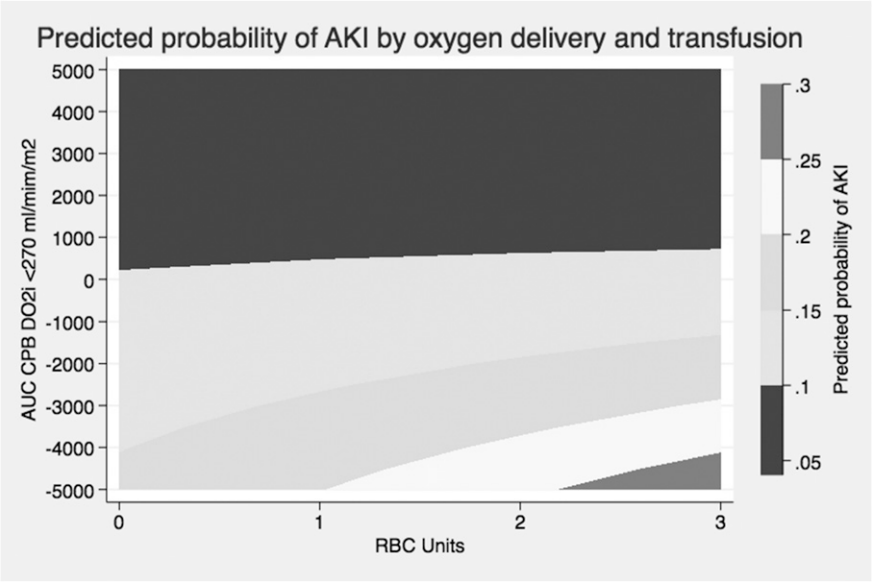

Figure 2. Contour interaction plot of the predicted probability of AKI, according to the interaction of the area under the curve for $DO_2i < 270$ mL/min/m^2 during CPB and the transfusion of 0–3 units of red blood cells peri-operatively. The plot indicates that there is lowest probability for AKI and no interaction between oxygen delivery and number of units transfused with AUC values >0 (greater integral of amount and duration of $DO_2i > 270$ mL/min/m^2 during CPB).

calculations of minimum DO_2i were able to identify a threshold of oxygen delivery associated with outcome but do not provide quantification of the duration or quantity of oxygen delivery below the threshold. This study was designed to generate an AUC metric similar to that presented by Justison (17) to support previous findings.

There are a number of limitations of this study; however, they provide insight into reporting studies in this field. First, this study is observational, from a single center with data from only one oxygenator. Second, we only evaluated one oxygen delivery threshold to base the calculation of AUC, whereas this was evidence-based, the inflection point in the Lowess plot occurs at a value around 2,000; therefore, the threshold at which oxygen delivery is associated with AKI may be higher than 270 mL/min/m^2. If a higher threshold were used the curve would move to the left. Third, the DO_2i value we report was calculated by the M4 monitor that measures the flow in the arterial line of the CPB circuit ultrasonically. The positioning of the flow probe distal to any arterial to venous shunts is important to avoid overestimation of DO_2i, which is highlighted in our data in the average arterial flow rates reported for the arterial pump (Table 1) and the M4 (Table 2). Previous studies used arterial pump flow values to calculate DO_2i and may not have taken such shunts into account (2,3). Calculating DO_2i using the arterial pump flow value would tend to shift the Lowess plot to the left and would result in the inflection point being closer to an AUC of 0. Fourth, we have found that using the M4 to calculate DO_2i consistently results in a DO_2i value approximately 20 units less than the CONNECT™ GDP system which may be attributed to differences in the formula used to calculate DO_2. The formula used by the M4 to calculate DO_2 (18) is;

$$DO_2 = 10 \cdot Q_{blood} \cdot \frac{SaO_2}{100} \cdot Hb \cdot 1.34$$

whereas the formula used by CONNECT (18) is;

$$DO_2 = Q_{blood} \cdot \left(\frac{Hct}{2.94} \cdot 1.36 \cdot SaO_2 + PaO_2 \cdot 0.003 \right) \cdot 10$$

Finally, the AUC value included the entire CPB period, and therefore, included periods of partial CPB at the initiation of bypass and weaning from CPB where actual DO_2i values may be less than the calculated value in the presence of native cardiac output. In our practice, these periods of partial bypass contribute only a small percentage of the

Table 4. Results of multivariate logistic regression modeling to identify predictors of acute kidney injury (n = 210).

	p Univariate	Adjusted OR (CI)	*p* Multivariate
AUC < 0 for $DO_2i < 270$ mL/min/m^2	<.001	2.74 (1.01–7.41)	.047
Euroscore II	<.001	1.06 (.96–1.18)	.247
RBC transfusion	<.001	1.4 (.56–3.51)	.468

Hosmer and Lemeshow goodness-of-fit test $\chi^2 = 7.34$, $df = 10$, $p = .5$. AUC, area under curve; RBC, red blood cell; OR, odds ratio; CI, confidence interval.

total bypass period for which DO_2 is reported. To date, clear consensus definitions of how oxygen delivery and carbon dioxide production parameters should be calculated during CPB have not been developed. Multicentre studies using larger datasets would improve the generalizability of studies evaluating oxygen delivery and exhaust carbon dioxide derived parameters.

CONCLUSION

Having an AUC < 0 for an oxygen delivery threshold of 270 mL/min/m^2 during CPB was an independent predictor of AKI. These results support that a relationship exists for oxygen delivery during CPB, in which the integral of amount and time below a critical threshold is associated with the incidence of postoperative AKI.

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