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ORIGINAL RESEARCH

A Better Predictor of Acute Kidney Injury After Cardiac Surgery: The Largest Area Under the Curve Below the Oxygen Delivery Threshold During Cardiopulmonary Bypass

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BACKGROUND: The aim of this study was to compare the predictive accuracy of acute kidney injury (AKI) after cardiac surgery using cardiopulmonary bypass for the largest area under the curve (AUC) below the oxygen delivery (DO_2) threshold and the cumulative AUC below the DO_2 threshold.

METHODS AND RESULTS: From March 2017 to October 2019, 202 patients who had undergone cardiac surgery with cardiopulmonary bypass were enrolled. The perfusion parameters were recorded every 20 seconds, and the DO_2 (10×pump flow index [L/min per m^2]×[hemoglobin (g/dL)×1.36×arterial oxygen saturation (%)+partial pressure of arterial oxygen (mm Hg)×0.003]) threshold of 300 mL/min per m^2 was considered to define sufficient DO_2. The nadir DO_2, the cumulative AUC below the DO_2^{300}, and the largest AUC below the DO_2^{300} were used to predict the incidence of AKI. Postoperative AKI was observed in 12.4% of patients (25/202). By multivariable analysis, the largest AUC below the DO_2^{300} ≥880 (odds ratio [OR], 4.9; 95% CI, 1.2–21.5 [*P*=0.022]), preoperative hemoglobin concentration ≤11.6 g/dL (OR, 7.6; 95% CI, 2.0–32.3 [*P*=0.004]), and red blood cell transfusions during cardiopulmonary bypass ≥2 U (OR, 3.3; 95% CI, 1.0–11.1 [*P*=0.041]) were detected as independent risk factors for AKI. Receiver operating curve analysis revealed that the largest AUC below the DO_2^{300} was more accurate to predict postoperative AKI compared with the nadir DO_2 and the cumulative AUC below the DO_2^{300} (differences between areas, 0.0691 [*P*=0.006] and 0.0395 [*P*=0.001]).

CONCLUSIONS: These data suggest that a high AUC below the DO_2^{300} is an important independent risk factor for AKI after cardiopulmonary bypass, which could be considered for risk prediction models of AKI.

Key Words: acute kidney injury ■ area under the curve ■ cardiac surgery ■ cardiopulmonary bypass ■ oxygen delivery

Acute kidney injury (AKI) is a common and serious complication with an occurrence rate ranging from 20% to 40% after cardiac surgery with cardiopulmonary bypass (CPB).[1–3] Several studies have shown that even minimal changes in postoperative creatinine values can predict early and long-term mortality after cardiac surgery.[4–6] Age, sex, obesity, preoperative renal function, preoperative anemia, diabetes mellitus, chronic lung disease, and postoperative hypotension were reported as risk factors of AKI.[7–15] Regarding CPB management, prolonged CPB duration, severe hemodilution, and low oxygen delivery (DO_2) were identified as predictors of AKI.[16–20] DO_2 is one of the few important modifiable parameters related to AKI. It is the amount of oxygen delivered to tissues throughout the whole body per minute and is expressed as the product of cardiac output and oxygen content of arterial blood. DO_2 during CPB is dependent on hemoglobin concentration, oxygen saturation, pump flow, and partial pressure of arterial oxygen. When either of these

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CLINICAL PERSPECTIVE

What Is New?

- The predictive accuracy of acute kidney injury after cardiac surgery using cardiopulmonary bypass was compared for the largest area under the curve (AUC) below the oxygen delivery (DO_2) threshold and cumulative AUC below the DO_2 threshold.
- The largest AUC below the DO_2 300 mL/min per m^2 threshold was detected as a more accurate predictor of postoperative acute kidney injury compared with nadir DO_2 and cumulative AUC below the DO_2 300 mL/min per m^2 threshold.

What Are the Clinical Implications?

- Potentially, these data suggest that avoiding a continuous or severe decrease of DO_2 (largest AUC below the DO_2 300 mL/min per m^2 threshold <880) could reduce the risk of acute kidney injury after cardiac surgery, and minimization of hemodilution and transfusion and adjustment of pump flow are important for preservation of DO_2 above 300 mL/min per m^2 in clinical practice.

Nonstandard Abbreviations and Acronyms

AKI	acute kidney injury
AUC	area under the curve
CaO_2	oxygen content of arterial blood
CPB	cardiopulmonary bypass
DO_2	oxygen delivery
DO_2^{300}	oxygen delivery 300 mL/min per m^2
eGFR	estimated glomerular filtration rate
KDIGO	Kidney Disease: Improving Global Outcome
RBC	red blood cell

factors drop and DO_2 falls below critical levels, oxygen consumption cannot be maintained using aerobic energy production, activating the anaerobic mechanism to supply energy to the cells and increasing lactate levels. Previous retrospective studies have shown the association between nadir DO_2 during CPB and postoperative AKI, and the DO_2 level to prevent AKI must be maintained at >262 to 272 mL/min per m^2 under moderate hypothermia (>32°C).[21–23] However, in these studies, the nadir DO_2 level was defined by using an intermittent measurement value at 10- to 20-minute intervals. Since DO_2 level is constantly changing during CPB, nadir DO_2 level may not be accurately reflected depending on the timing of measurement. Moreover, DO_2 level should be >262 to 272 mL/min per m^2 under mild hypothermia (>34°C).

In recent years, Mukaida et al[24] evaluated the cumulative area under the curve (AUC) below the DO_2 threshold in patients receiving mild hypothermic (35°C) CPB. The AUC represents the area integrated with the time and depth from below the DO_2 threshold to return to above the DO_2 threshold, the cumulative AUC below the DO_2 threshold represents the accumulation of all AUCs (Figure 1). They concluded that a cumulative AUC below the DO_2 300 mL/min per m^2 (DO_2^{300}) threshold was a good indicator to predict postoperative AKI compared with nadir DO_2.[24] However, for cumulative AUC below the DO_2 threshold, it was not possible to accurately assess whether the time and depth below the DO_2 threshold persisted for a long time. We hypothesized that evaluating the magnitude of the time and depth of continuously falling below the DO_2 threshold would be important to predict AKI development after cardiac surgery compared with cumulative AUC below the DO_2 threshold. In this study, the largest AUC below the DO_2 threshold was evaluated as an indicator of the continuous time and depth below the DO_2 threshold during CPB. The largest AUC below the DO_2 threshold represents the one with the largest area among all AUCs (Figure 1). DO_2, hemoglobin, pump flow rate, arterial oxygen saturation, and partial pressure of arterial oxygen were measured at 20-second intervals during CPB. Based on this background, the aim of this study was to compare the predictive accuracy of AKI after cardiac surgery using CPB for the largest AUC below the DO_2 threshold and cumulative AUC below the DO_2 threshold.

METHODS

Patient Population

This retrospective, case-controlled study was approved by our institutional ethics committee. 015566-T3 for using patients' data was obtained from all patients. The data that support the findings of this study are available from the corresponding author upon reasonable request. Between March 2017 and October 2019, 244 patients (≥20 years) underwent cardiac surgery under CPB support at the Sakakibara Heart Institute of Okayama. Of these, 202 patients were enrolled, excluding patients with preoperative moderate renal insufficiency (preoperative estimated glomerular filtration rate [eGFR] <45 mL/min per 1.73m^2) and emergent operation. The procedures included 22 isolated coronary artery bypass grafting, 125 isolated valve surgery, 46 coronary artery bypass grafting+valve surgery, 2 ascending aorta replacement+valve surgery, 5 adult congenital surgery, and 2 myxoma resections. Postoperative AKI occurrence was evaluated, and we

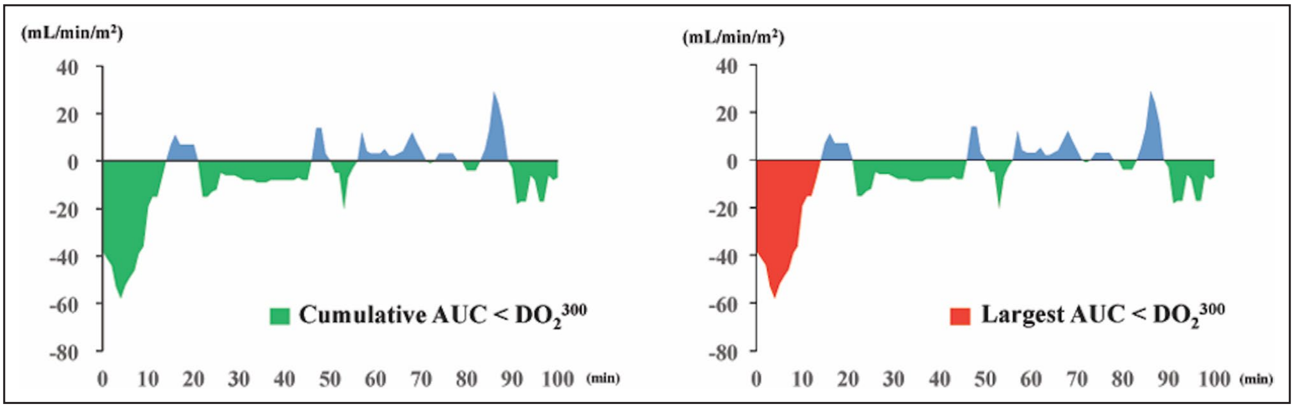

Figure 1. Typical case of oxygen delivery (DO_2) change during cardiopulmonary bypass based on DO_2 300 mL/min per m^2 threshold.
The green area shows the cumulative area below the DO_2 threshold=300 mL/min per m^2 and the blue area shows the cumulative area above the DO_2 threshold=300 mL/min per m^2. The red area shows the largest area below the DO_2 threshold=300 mL/min per m^2. AUC indicates area under the curve.

compared perioperative data between patients with and without AKI.

Definition of AKI

AKI was defined according to the creatinine changes specified in the Kidney Disease: Improving Global Outcome (KDIGO) classification.[25] AKI stage 1 is defined as an absolute increase of 0.3 mg/dL within 48 hours or an increase in serum creatinine level of 150% to 200% of baseline within the past 7 days, and AKI stage 2 is defined as an increase in serum creatinine level of >200% of baseline within the past 7 days.

The eGFR was calculated using the following equations, where sCr is serum creatinine:

$$\text{eGFR (men)} = 194 \times \text{sCr}^{-1.094} \times \text{age}^{-0.287} \left(\text{mL}/\mathit{min}\text{per}1.73\text{m}^2\right)$$

$$\text{eGFR (women)} = \text{eGFR (men)} \times 0.739 \left(\text{mL/min per}1.73\text{m}^2\right)$$

Anesthetic Protocol

Perioperative care was performed according to a standard protocol, to which all anesthesiologists adhered. Anesthesia induction was performed with dexmedetomidine hydrochloride, fentanyl, and propofol followed by rocuronium for skeletal muscle relaxation. Sevoflurane, propofol, and supplemental doses of remifentanil were used for maintenance of anesthesia, based on clinical criteria.

CPB Management

The pump circuit was primed with 800 mL of bicarbonate Ringer solution, 300 mL of 20% mannitol, and 4000 U of heparin. The hemoconcentrator was used for all patients. Anticoagulation was given at an initial dose of 300 U/kg to achieve a goal activated clotting time of at least 480 seconds and an additional dose of 4000 U was given per hour. Roller pumps were used. The institutional standard pump flow target was 2.5 L/min per m^2. Phenylephrine was administrated to maintain a mean blood pressure >50 mm Hg. Red blood cell (RBC) transfusion was considered when hemoglobin concentration could not be maintained at 8 g/dL during CPB. A CDI Blood Parameter Monitoring System 500 (Terumo) was recalibrated every 30 minutes, and an arterial blood gas sample was also checked every 30 minutes. Body temperature was maintained at 34°C. Cold crystalloid cardioplegia was given to all patients requiring cardiac arrest, and terminal warm blood cardioplegia was administered before declamping in the case of prolonged cardiac arrest (>3 hours) or low ejection fraction (<30%). After CPB, all remaining perfusate was used by an intraoperative blood salvage system (Xtra, LivaNova).

Monitoring of DO_2 During CPB

The DO_2 was calculated according to the equation: DO_2 (mL/min per m^2)=10×pump flow index (L/min per m^2)×(hemoglobin [g/dL]×1.36×arterial oxygen saturation [%]+partial pressure of arterial oxygen [mm Hg]×0.003).[26] Hemoglobin, arterial oxygen saturation, partial pressure of arterial oxygen, and venous oxygen saturation were measured using the CDI Blood Parameter Monitoring System 500 every 20 seconds. The DO_2^{300} threshold was considered to define sufficient DO_2.[24,27] Nadir DO_2, cumulative AUC below the DO_2^{300}, and the largest AUC below the DO_2^{300} were identified using the LivaNova Connect data management system (LivaNova), which recorded the data every 20 seconds. Figure 1 shows the respective parameters in a typical case.

Statistical Analysis

Continuous data are presented as mean±SD and were compared with a Mann–Whitney test. Categorical variables are given as count and percentage of patients and were compared using chi-square test. When any expected frequency was <1, or 20% of expected frequencies were ≤5, a Fisher exact test was used. All factors associated (P<0.1) with AKI were entered in a multivariable analysis. Univariate analysis was performed on all variables to detect potential risk factors for postoperative AKI. All continuous parameters were dichotomized at the best cutoff value obtained by receiver operating characteristic analysis as the threshold for logistic regression analysis. The best cutoff values obtained by receiver operating characteristic analysis were calculated by Youden index. The univariate predictors with a P<0.1 were selected by the stepwise method and entered into the multivariate analysis. To avoid multicollinearity, variables affected by mathematical coupling were separately entered into different models. P<0.05 was considered to be statistically significant. All data were analyzed using Statistical Analysis Systems software JMP 10.0 (SAS Institute Inc.).

RESULTS

Comparison of Preoperative Characteristics

Postoperative AKI was observed in 12.4% of patients (25/202). The comparison of preoperative data between patients with and without AKI is shown in Table 1. There were no significant differences in age (72.5±8.7 years versus 70.0±12.0 years [P=0.49]) and percentage of women (40.0% [10/25] versus 37.3% [66/177], P=0.79) between patients with and without AKI, respectively. Preoperative hemoglobin concentration was significantly lower in patients with AKI (13.0±1.5 g/dL versus 13.7±1.3 g/dL, P=0.019) and percentage of diabetes mellitus was insignificantly higher in patients with AKI (44.0% [11/25] versus 26.6% [47/177], P=0.07). On the other hand, the baseline serum creatinine and the eGFR were equivalent between the AKI+ and AKI– groups (0.82±0.20 mg/dL versus 0.79±0.17 mg/dL [P=0.49] and 66.0±12.7 mL/min per 1.73 m^2 versus 70.2±14.7 mL/min per 1.73 m^2 [P=0.21]).

Comparison of Intraoperative Data Including CPB Management

Comparison of the intraoperative data is shown in Table 2. There were no significant differences in CPB duration and cross-clamp time between patients with and without AKI (170±50 minutes versus 165±50 minutes [P=0.51] and 123±39 minutes versus 117±41 minutes [P=0.27]). RBC transfusions during CPB were significantly greater (2 U [2–4] versus 0 U [0–2]; P<0.001) and nadir hemoglobin level during CPB was significantly lower (7.6±1.2 g/dL versus 8.0±0.9 g/dL, P=0.027) in the AKI+ group. Additionally, significantly lower nadir DO_2 during CPB (259±34 mL/min per m^2 versus 274±31 mL/min per m^2, P=0.015), greater cumulative AUC below the DO_2^{300} (2490 [261–5466] versus 441 [6–2085], P=0.002), and largest AUC

Table 1. Preoperative Characteristics of Patients With and Without AKI

Variables	All Patients (N=202)	AKI+ (n=25)	AKI– (n=177)	P Value
Age, y	70.3±11.7	72.5±8.7	70.0±12.0	0.49
Women, No. (%)	76 (37.6)	10 (40.0)	66 (37.3)	0.79
Body surface area, m^2	1.60±0.20	1.55±0.27	1.61±0.18	0.28
Body mass index, kg/m^2	23.2±3.4	24.2±4.2	23.1±3.3	0.27
Hypertension, No. (%)	103 (51.0)	13 (52.0)	90 (50.9)	0.91
Diabetes mellitus, No. (%)	59 (29.2)	11 (44.0)	47 (26.6)	0.07
Chronic lung disease, No. (%)	21 (10.4)	1 (4.0)	20 (11.3)	0.26
Preoperative atrial fibrillation, No. (%)	53 (26.2)	5 (20.0)	48 (27.1)	0.45
Redo operation, No. (%)	15 (7.4)	1 (4.0)	14 (7.9)	0.49
Serum creatinine, mg/dL	0.79±0.17	0.82±0.20	0.79±0.17	0.49
eGFR, mL/min per 1.73m^2	69.6±14.5	66.0±12.7	70.2±14.7	0.21
Hemoglobin, g/dL	13.6±1.4	13.0±1.5	13.7±1.3	0.019
Brain natriuretic peptide, pg/mL	74 (33–215)	111 (47–213)	69 (33–214)	0.19
LVEF, %	60.3±12.7	57.1±14.1	60.8±12.5	0.23
EuroSCORE II	2.5±1.7	2.5±1.9	2.5±1.7	0.98
Cleveland Clinical Foundation Score	2.7±0.9	2.7±0.8	2.7±0.9	0.66

AKI indicates acute kidney injury; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; and LVEF, left ventricular ejection fraction.

Table 2. Perioperative Data of Patients With and Without AKI

Variables	All Patients (N=202)	AKI+ (n=25)	AKI− (n=177)	*P* Value
CPB duration, min	165±50	170±50	165±50	0.51
Aortic cross-clamp time, min	117±41	123±39	117±41	0.27
Nadir bladder temperature, °C	34 (34–34)	34 (34–34)	34 (34–34)	0.88
Maximum lactate level during CPB, mg/dL	15.9±4.2	16.8±4.9	15.7±4.1	0.42
RBC transfusions during CPB, U	0 (0–2)	2 (2–4)	0 (0–2)	<0.001
Phenylephrine administered during CPB, mg	0.8 (0.5–1.4)	0.7 (0.4–1.3)	0.9 (0.5–1.4)	0.25
Hemolysis during CPB, No. (%)	44 (21.8)	8 (32.0)	36 (20.3)	0.19
Mean arterial pressure during CPB, mm Hg	55.7±8.6	55.9±9.7	55.7±8.5	0.92
Urine output during CPB, mL/kg per h	1.9 (1.2–3.4)	2.3 (0.9–4.3)	1.9 (1.2–3.5)	0.89
Nadir hemoglobin during CPB, g/dL	8.0±1.0	7.6±1.2	8.0±0.9	0.027
Nadir DO_2 during CPB, mL/min per m^2	272±32	259±34	274±31	0.015
Maximum O_2ER, %	27.1±5.9	27.5±4.7	27.0±6.0	0.66
Nadir SvO_2, %	70.2±5.4	70.2±4.9	70.2±5.5	0.84
Cumulative AUC below the DO_2^{300}	549 (24–2472)	2490 (261–5466)	441 (18–2082)	0.002
Largest AUC below the DO_2^{300}	303 (21–1173)	1293 (222–4080)	273 (15–849)	<0.001

AKI indicates acute kidney injury; AUC, area under the curve; CPB, cardiopulmonary bypass; DO_2, oxygen delivery; O_2ER, oxygen extraction ratio; RBC, red blood cell; and SvO_2, venous oxygen saturation.

below the DO_2^{300} (1914 [621–4632] versus 237 [0–825], *P*<0.001) were observed in the AKI+ group. There were no significant differences in the maximum lactate levels, maximum oxygen extraction ratio, and nadir venous oxygen saturation between the groups.

Comparison of Postoperative Data

The results of the postoperative outcomes are shown in Table 3. AKI was diagnosed by using the maximum increase during the first 7 postoperative days based on the definition of the KDIGO classification. AKI occurred in 25 patients (12.4%) postoperatively. Of these patients, 23 developed KDIGO stage 1 (92.0%) and 2 patients developed stage 2 (8.0%). There was a case requiring continuous renal replacement therapy in the AKI+ group. The change in creatinine was significantly greater in the AKI+ group (0.43 [0.38–0.56] mg/dL versus 0.10 [0.03–0.19] mg/dL, *P*<0.001). Intubation time (17 [15–21] hours versus 7 [5–16] hours, *P*<0.001), intensive care unit stay (4.0 [2.6–5.8] days versus 2.8 [1.8–3.8] days, *P*=0.010), and postoperative hospital stay (28 [20–39] days versus 21 [16–27] days, *P*=0.024) were significantly prolonged in patients with AKI. There was no in-hospital death in either group.

Respective Parameters Regarding DO_2 as a Predictor of Postoperative AKI

Receiver operating characteristic analysis was performed to predict AKI in nadir DO_2, cumulative AUC below the DO_2^{300}, and largest AUC below the DO_2^{300}. The calculated AUC was 0.663 (95% CI, 0.534–0.772),

Table 3. Postoperative Outcomes of Patients With and Without AKI

Variables	AKI+ (n=25)	AKI− (n=177)	*P* Value
KDIGO stage, No. (%)			
Stage 1	23 (92.0)		
Stage 2	2 (8.0)		
Continuous renal replacement therapy, No. (%)	1 (4.0)		
Delta creatinine from baseline, mg/dL	0.43 (0.38–0.56)	0.10 (0.03–0.19)	<0.001
Creatinine increase from baseline, No. (%)	60 (49–66)	12 (4–24)	<0.001
Intubation time, h	17 (15–21)	7 (5–16)	<0.001
ICU stay, d	4.0 (2.6–5.8)	2.8 (1.8–3.8)	0.010
Postoperative hospital stay, d	28 (20–39)	21 (16–27)	0.024
Hospital mortality, No. (%)	0 (0)	0 (0)	1.00

AKI indicates acute kidney injury; ICU, intensive care unit; and KDIGO, Kidney Disease: Improving Global Outcomes.

0.693 (95% CI, 0.568–0.795), and 0.733 (95% CI, 0.608–0.829), respectively, and the largest AUC below the DO_2^{300} was more accurate to predict postoperative AKI compared with nadir DO_2 and cumulative AUC below the DO_2^{300} (differences between areas, 0.0691 [*P*=0.0061] and 0.0395 [*P*=0.0013]). There was no significant difference in the area between nadir DO_2 and cumulative AUC below the DO_2^{300} (differences between areas, 0.0297; *P*=0.25). According to the Youden index, the best cutoff values were the nadir DO_2 ≤265 mL/min per m² (sensitivity, 68.0%; specificity, 58.8%), the cumulative AUC below the DO_2^{300} ≥1555 (sensitivity, 60.0%; specificity, 67.8%), and the largest AUC below the DO_2^{300} ≥880 (sensitivity, 72.0%; specificity, 72.3%) (Figure 2).

Multivariable Analysis for Risk of Postoperative AKI

The multivariable analysis was performed with AKI as dependent variables. For each model, the largest AUC below the DO_2^{300} and cumulative AUC below the DO_2^{300} were separately analyzed because of mathematical coupling between the 2 variables. By univariable analysis, diabetes mellitus, preoperative hemoglobin concentration, nadir hemoglobin during CPB, RBC transfusions during CPB, nadir DO_2, cumulative AUC below the DO_2^{300}, and the largest AUC below the DO_2^{300} were obtained as risk factors for AKI. In the multivariable analysis for AKI, we tested the following variables: diabetes mellitus, preoperative hemoglobin concentration ≤11.6 g/dL, RBC transfusions during CPB ≥2 U, nadir hemoglobin during CPB ≤7.4 g/dL, nadir DO_2 ≤265 mL/min per m² and largest AUC below the DO_2^{300} ≥880 (model 1), diabetes mellitus, preoperative hemoglobin concentration ≤11.6 g/dL, RBC transfusions during CPB ≥2 U, nadir hemoglobin during CPB ≤7.4 g/dL, nadir DO_2 ≤265 mL/min per m², and cumulative AUC below the DO_2^{300} ≥1555 (model 2). After multivariable analysis, in the multivariable model including the largest AUC below the DO_2^{300} ≥880, preoperative hemoglobin concentration ≤11.6 g/dL (odds ratio [OR], 7.6; 95% CI, 2.0–32.3 [*P*=0.004]), RBC transfusions during CPB ≥2 U (OR, 3.3; 95% CI, 1.0–11.1 [*P*=0.041]), and the largest AUC below the DO_2^{300} ≥880 (OR, 4.9; 95% CI, 1.2–21.5 [*P*=0.022]) were identified as independent risk factors for postoperative AKI. In the multivariable model including the cumulative AUC below the DO_2^{300} ≥1555, preoperative hemoglobin concentration ≤11.6 g/dL (OR, 8.2; 95% CI, 2.1–34.3 [*P*=0.002]) and RBC transfusions during CPB ≥2 U (OR, 3.2; 95% CI, 1.0–10.8 [*P*=0.048]) were identified as independent risk factors for postoperative AKI, but cumulative AUC below the DO_2^{300} ≥1555 was not identified as an independent risk factor for postoperative AKI (Table 4).

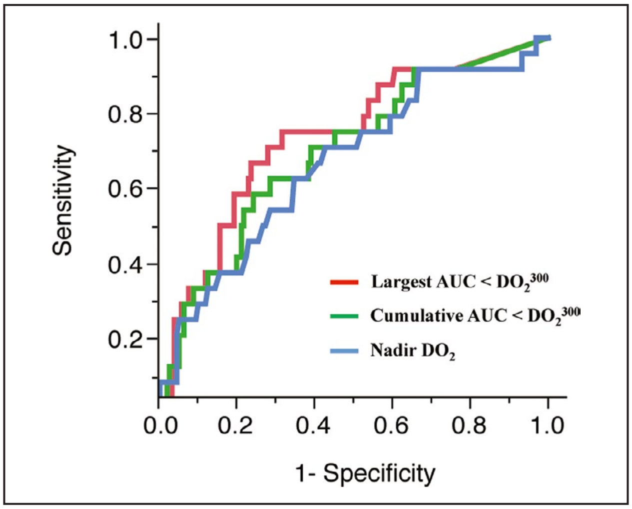

Figure 2. Comparison of receiver operating characteristic curve to predict acute kidney injury between the nadir oxygen delivery (DO_2), cumulative area under the curve (AUC) below the DO_2^{300}, and largest AUC below the DO_2^{300}. AUCs and *P* values are 0.663 (95% CI, 0.534–0.772) for the nadir DO_2, 0.693 (95% CI, 0.568–0.795) for the cumulative AUC below the DO_2^{300}, and 0.733 (95% CI, 0.608–0.829) for the largest AUC below the DO_2^{300}, respectively. Differences between areas are 0.0691 (*P*=0.0061) for the nadir DO_2 and the largest AUC below the DO_2^{300}, 0.0395 (*P*=0.0013) for the cumulative AUC below the DO_2^{300} and the largest AUC below the DO_2^{300}, and 0.0297 (*P*=0.25) for the nadir DO_2 and the cumulative AUC below the DO_2^{300}, respectively.

DISCUSSION

The rationale of the study was to investigate whether the prolonged and excessive decrease of DO_2 below the threshold of 300 mL/min per m² is superior in predicting AKI after cardiac surgery compared with the established parameters nadir DO_2 or cumulative AUC below the DO_2^{300} threshold. The major findings of this study are as follows: (1) postoperative AKI was observed in 12.4% of patients after cardiac surgeries with CPB support; (2) diabetes mellitus, preoperative hemoglobin concentration, nadir hemoglobin, RBC transfusions during CPB, nadir DO_2, cumulative AUC below the DO_2^{300}, and largest AUC below the DO_2^{300} were identified as risk factors for AKI; (3) the largest AUC below the DO_2^{300} ≥880, RBC transfusion ≥2 U, and preoperative hemoglobin concentration ≤11.6 g/dL were identified as risk factors of AKI by multivariate analysis; and (4) regarding management of DO_2 during CPB, the largest AUC below the DO_2^{300} was the most accurate assessment index compared with other valuation methods.

Even a slight increase in postoperative creatinine was reported to worsen short- and long-term prognosis.[4–6] Although there were only 2 cases of severe renal dysfunction (KDIGO stage 2), the intubation time,

Table 4. Univariate and Multivariate Analysis for Predictor of Postoperative AKI

Variables	Univariate Analysis		Model 1 Multivariate Analysis		Model 2 Multivariate Analysis	
	OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Diabetes mellitus	2.5 (1.1–5.9)	0.030	2.4 (0.9–6.6)	0.08	2.5 (0.9–6.7)	0.06
Preoperative hemoglobin ≤11.6 g/dL	13.4 (3.9–46)	<0.001	7.6 (2.0–32.3)	0.004	8.2 (2.1–34.3)	0.002
RBC transfusions during CPB ≥2 U	5.2 (1.9–13.7)	<0.001	3.3 (1.0–11.1)	0.041	3.2 (1.0–10.8)	0.048
Nadir hemoglobin ≤7.4 g/dL	3.0 (1.3–7.0)	0.009	1.4 (0.4–5.3)	0.58	1.0 (0.3–3.9)	0.99
Nadir DO_2 ≤265 mL/min per m^2	3.0 (1.2–7.4)	0.012	1.7 (0.4–7.7)	0.48	1.4 (0.3–5.3)	0.65
Largest AUC below the DO_2^{300} ≥880	5.4 (2.1–13.7)	<0.001	4.9 (1.2–21.5)	0.022		
Cumulative AUC below the DO_2^{300} ≥1555	3.3 (1.4–7.8)	0.006			1.0 (0.3–4.3)	0.95

AKI indicates acute kidney injury; AUC, area under the curve; DO_2, oxygen delivery; OR, odds ratio; and RBC, red blood cell.

intensive care unit stay, and postoperative hospital stay were significantly prolonged in the AKI group. Many factors are implicated in the complex mechanisms leading to postoperative kidney function impairment.[7–20] However, many of these risk factors were intrinsic to the individual patient. In the present study, preoperative anemia was detected as an independent risk factor by multivariate analysis. Administration of erythropoietin has been suggested as a way to promote erythropoiesis in anemic patients before cardiac surgery.[28] Although recombinant erythropoietin significantly increased preoperative hemoglobin levels and hematocrit, it has not been demonstrated to reduce the need for RBC transfusion in cardiac surgery.[29] In anemic patients, prophylactic RBC transfusion was reported by Karkouti et al[30] to be an effective option to reduce perioperative anemia and RBC transfusions and may reduce plasma iron levels. They demonstrated that perioperative RBC transfusions were directly related to postoperative transferrin saturation, and high transferrin saturation (>80%) was associated with AKI, implicating transfusion-related iron overload as a cause of AKI.

On the other hand, appropriate CPB management has been focused on to predict postoperative AKI as a modifiable approach. Nadir DO_2 during CPB was recognized as an important index and must be maintained higher than 262 to 272 mL/min per m^2 at moderate hypothermia.[21–23] However, in these studies, the nadir DO_2 level was defined using an intermittent measurement value at 10- to 20-minute intervals. Since DO_2 level is dynamically changing during CPB, the intermittently calculated nadir DO_2 level may be overestimated. Additionally, intermittent measurement of DO_2 levels cannot reflect the exposure time of low DO_2. In our study, the nadir DO_2 calculated every 20 seconds was significantly lower in the AKI group and the best cutoff value obtained by receiver operating characteristic analysis was 265 mL/min per m^2. This result confirms some important values identified in previous studies,[21–23] but had less accuracy with predicting postoperative AKI than largest AUC below the DO_2^{300}.

In a recent study, Lannemyr and associates[31] demonstrated that renal DO_2 during CPB is reduced by about 20% as a result of renal vasoconstriction and hemodilution, leading to renal oxygen supply/demand mismatch. Especially in the outer medulla, oxygen tissue partial pressure is as low as 10 to 20 mm Hg even under normal conditions compared with 50 mm Hg in the cortex.[32] Thus, as the outer medulla is on the border of hypoxia already under normal conditions, low renal DO_2 episodes are likely to cause ischemic conditions. Sustained ischemia causes subsequent ischemia-reperfusion kidney injury, resulting in impaired renal oxygenation and proximal tubular dysfunction.[33,34] Therefore, risk factors for postoperative AKI may not be assessed accurately without considering the continuous duration of low DO_2.

Recently, Mukaida et al[24] evaluated time and depth below the DO_2 threshold and reported that cumulative AUC below the DO_2^{300} and cumulative time below the DO_2^{300} were more sensitive indicators for predicting AKI after cardiac surgery with CPB compared with nadir DO_2. They concluded that the incidence of AKI significantly increased when the cumulative time below the DO_2^{300} exceeded 15 minutes. However, this parameter included both temporary and continuous decreases in DO_2, and the rates of temporary and continuous decreases in DO_2 were not accurately assessed. Studies on kidney ischemia have shown that repeated temporary renal ischemia (4 cycles of 4 minutes of ischemia with a cumulative ischemia time of 16 minutes) does not damage the kidneys. On the other hand, continuous ischemia for 20 minutes caused mild renal tubular injury as a result of ischemia reperfusion injury.[35] Therefore, it may be necessary to accurately assess the extent of continuous oxygen debt during CPB in predicting postoperative

AKI. In this study, the largest AUC below the DO_2^{300} was evaluated as an indicator of the degree of continuous oxygen debt during CPB. In multivariate analysis, the largest AUC below the DO_2^{300} was identified as an independent risk factor for postoperative AKI, but cumulative AUC below the DO_2^{300} was not identified as an independent risk factor.

Based on the findings of this study, the largest AUC below the DO_2^{300} is a modified index to reflect both the depth and duration of continuous decrease in DO_2. The largest AUC below the DO_2^{300} can be a good indicator to take intraoperative measures to avoid a continuous or severe decrease in DO_2. The largest AUC below the DO_2^{300} had a significantly larger area in the AKI group, and the highest accuracy of predicting postoperative AKI was obtained compared with nadir DO_2 and cumulative AUC below the DO_2^{300}. The cutoff value of the largest AUC below the DO_2^{300} was 880, and this value can be an improved index to avoid postoperative AKI. DO_2 during CPB mainly depends on hemoglobin concentration and pump flow (ignoring partial pressure of oxygen as it is only a minor contribution). Lannemyr et al[36] demonstrated that the renal oxygen supply/demand mismatch caused by CPB hemodilution and vasoconstriction was improved by increasing CPB flow rate above 2.7 to 3.0 L/min per m^2. On the other hand, it is known that RBCs undergo irreversible morphological and biochemical changes during storage. As a result, RBC transfusions can cause AKI as a result of impaired tissue DO_2 and exacerbate inflammatory responses and tissue oxidative stress.[37,38] Therefore, in clinical practice, we try to minimize hemodilution and RBC transfusion by reducing the priming volume and using a hemoconcentrator for preservation of DO_2 above 300 mL/min per m^2. Additionally, pump flow is adjusted according to the level of hemodilution.

Study Limitations

This study has several limitations. First, this study was a retrospective observational study in a single center. Therefore, our models need to be validated at multiple centers for broad applicability. Second, patients with preoperative chronic renal insufficiency were excluded, so the development rate of AKI and a number of cases presenting with severe renal injury was small. Thus, the clinical impacts of this index are still undetermined. Finally, although this study defined AKI only by the change in creatinine within 7 days after surgery, creatinine production is affected by muscle mass and can vary greatly depending on factors such as age, sex, and nutritional status. The effectiveness of DO_2 management should be evaluated using urinary tissue inhibitor of metalloproteinases-2/insulin-like growth factor–binding protein 7 as biomarkers for AKI.[39]

CONCLUSIONS

The present data suggest that the largest AUC below the DO_2^{300} during CPB is an important independent risk factor for AKI. Potentially, these data suggest that avoiding a continuous or severe decrease of DO_2 (largest AUC below the DO_2^{300} <880) could reduce the risk of AKI after cardiac surgery.

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