Time–dose response of oxygen delivery during cardiopulmonary bypass predicts acute kidney injury

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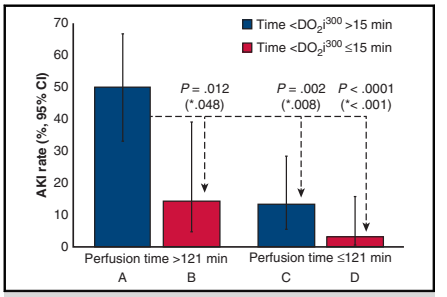
ABSTRACT

Objective: Previous studies have reported that nadir oxygen delivery during cardiopulmonary bypass is associated with the occurrence of postoperative acute kidney injury (AKI). However, these measurements only considered the bottom point of the oxygen delivery (DO_2) but did not consider the duration of DO_2. We aimed to examine whether the time–dose response of DO_2 during cardiopulmonary bypass can be used to estimate the risk for postoperative AKI.

Methods: We evaluated 112 patients who underwent cardiac surgeries with cardiopulmonary bypass. We analyzed the perfusion parameters recorded every 20 seconds. To obtain time–dose response of DO_2 index (DO_2i), the area under the curve was calculated as below the 300 mL/min/m^2 threshold, which accounts for depth and duration of cumulative oxygen debt. In addition, the cumulative time below DO_2i 300 mL/min/m^2 was also calculated. Receiver operating characteristic analysis, univariate regression analysis, and multivariate regression analysis were used to evaluate associations between perioperative variables and postoperative AKI.

Results: Patients who developed AKI had larger area under the curve below the 300 mL/min/m^2 threshold (1581 vs 632; $P < .01$) and cumulative time below DO_2i 300 mL/min/m^2 (34.7 vs 15.3 minutes; $P < .01$). Nadir DO_2i was not significantly different between the non-AKI and AKI groups (263.4 vs 247.0 mL/min/m^2; $P = .291$).

Conclusions: The time–dose response of DO_2i during cardiopulmonary bypass is a better indicator than nadir DO_2i in evaluating AKI risk. Maintaining DO_2i levels >300 mL/min/m^2 may result in decreased risk for postoperative AKI. (J Thorac Cardiovasc Surg 2019;158:492-9)



Acute renal failure rate based on the presence of 2 risk factors with respect to time.

Central Message

The time–dose response of DO_2i during CPB is associated with reduction in the incidence of AKI after cardiovascular surgery.

Perspective

The relationship between the time of exposure to a low DO_2 during CPB and the risk for postoperative AKI has been investigated. Patients who developed AKI had larger AUC below the 300 mL/min/m^2 threshold and longer cumulative time below the DO_2i 300 mL/min/m^2. Nadir DO_2i was not significantly different between the non-AKI and AKI groups. The time–dose response of DO_2i is better indicator than nadir DO_2i.

See Commentaries on pages 500 and 502.

Although the incidence of acute kidney injury (AKI) depends on preoperative renal function and the definition used or type of surgery,[1-4] AKI is a severe complication of cardiac surgery that occurs in up to 30% of patients (including 27.1%-33.2% of patients with preoperative estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2).[3,4] Higher mortality rates are shown even in patients with AKI stage 1 compared with those without postoperative AKI.[5-7] These facts suggest that a protective strategy for AKI is important in determining the prognosis of patients. Various risk factors for

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Abbreviations and Acronyms

AKI = acute kidney injury
AUC = area under the curve
AUC $<DO_2i^{300}$ = area under the curve below the oxygen delivery 300 mL/min/m^2 thresholds
AUC $<DO_2i^{280}$ = area under the curve below the oxygen delivery 280 mL/min/m^2 thresholds
AUC $<DO_2i^{260}$ = area under the curve below the oxygen delivery 260 mL/min/m^2 thresholds
BSA = body surface area
CPB = cardiopulmonary bypass
DO_2 = oxygen delivery
DO_2i = oxygen delivery index
eGFR = estimated glomerular filtration rate
GDP = goal-directed perfusion
Hct = hematocrit
ICU = intensive care unit
ROC = receiver operating characteristic
SvO_2 = venous oxygen saturation
Time $<DO_2i^{300}$ = cumulative time below the oxygen delivery 300 mL/min/m^2 thresholds
Time $<DO_2i^{280}$ = cumulative time below the oxygen delivery 280 mL/min/m^2 thresholds
Time $<DO_2i^{260}$ = cumulative time below the oxygen delivery 260 mL/min/m^2 thresholds
PvO_2 = partial pressure of venous oxygen

postoperative AKI include age,[8] sex,[9] preoperative renal function,[9] surgery type,[9,10] prolonged cardiopulmonary bypass (CPB) time,[8,10] and postoperative hypotension.[11] Although many of these risk factors are not modifiable, many studies have identified modifiable factors associated with CPB,[11-14] such as nadir oxygen delivery (DO_2) during CPB, which increases AKI risk at levels below the critical threshold of 225 to 272 mL/min/m^2.[11-13]

Recently, goal-directed perfusion (GDP), which attempts to maintain adequacy of perfusion through pump flow adjustments, demonstrated a lower occurrence of postoperative AKI,[15] shorter length of hospital stay,[15] and lower costs.[16] Many of those GDP studies defined the thresholds of nadir DO_2 levels by measuring the DO_2 levels every 10 to 20 minutes. However, DO_2 level is always dynamically changing, increasing the possibility that DO_2 levels might not reflect a critical condition between the sampling points. Therefore, it is uncertain that proper DO_2 had been maintained throughout the CPB by evaluating nadir DO_2. Furthermore, patients with lower body size are prone to greater hemodilution effects during CPB, suggesting possible significant changes in hematocrit (Hct) and DO_2 levels. In this study, we tested the hypothesis that the time–dose response of DO_2 during CPB is a good indicator to predict postoperative AKI after cardiovascular surgery using CPB.

PATIENTS AND METHODS

The present study was approved by the Institutional Review Board of Juntendo University Hospital. Because this study is an anonymous and retrospective study, the need for patient consent was waived.

Patient Population

We enrolled 112 adult patients (age >20 years) with complete medical records who underwent cardiac surgeries with CPB at Juntendo University Hospital between April 2017 and March 2018. We excluded patients who had chronic renal insufficiency (baseline eGFR <60 mL/min/1.73 m^2 based on the Kidney Disease: Improving Global Outcomes[17] practice guideline), were on dialysis preoperatively, and those who required circulation arrest.

Data Collection and Definitions

The aim of this study was to determine whether the time–dose response of DO_2 during CPB is independently associated with the risk for AKI as defined by the Kidney Disease: Improving Global Outcomes guidelines.[17] Only the first 48-hour postoperative serum creatinine levels were analyzed to restrict our analysis to CPB-associated AKI. In this study, the assignment of patients to AKI criteria was based on creatinine changes only. Urine output was not considered because it has many variables, including the use of diuretic drugs. Baseline creatinine level was measured within a week before surgery.

Preoperative variables were collected, including age, sex, body surface area (BSA), history of hypertension, history of diabetes, baseline Hct, baseline eGFR, ejection fraction, and European system for cardiac operative risk evaluation II score.

Perioperative variables collected included reoperation, type of surgery, perfusion time, crossclamp times, nadir body temperature, nadir Hct, number of packed red blood cell units transfused, nadir venous oxygen saturation (SvO_2), nadir partial pressure of venous oxygen (PvO_2), nadir oxygen delivery index (DO_2i), and lactate at the end of CPB. These nadir points were defined as the lowest point during measurement. To obtain the time–dose response of DO_2i, the area under the curve (AUC) was calculated as below the 260, 280, and 300 mL/min/m^2 thresholds (AUC $<DO_2i^{260}$ AUC $<DO_2i^{280}$ and AUC $<DO_2i^{300}$, respectively), which accounts for depth and duration of cumulative oxygen debt. In addition, the cumulative time below the DO_2i 260, 280, and 300 mL/min/m^2 (Time $<DO_2i^{260}$, Time $<DO_2i^{280}$, and Time $<DO_2i^{300}$, respectively), and SvO_2 70% thresholds were also calculated. Using the published risk thresholds of DO_2i for AKI (225-300 mL/min/m^2) as references,[11-13,15] we chose those thresholds of 260, 280, and 300 mL/min/m^2. Those published risk thresholds were derived from results, including moderately hypothermic cases (28°C-34°C). Thus, because we performed normothermic perfusion, except for in circulation arrest cases, we analyzed from thresholds of 260, 280, and 300 mL/min/m^2, which were more than those of previous studies. The above perfusion parameters were collected using the LivaNova Connect data management system (LivaNova, Munich, Germany), which recorded data every 20 seconds. The DO_2i was calculated according to the equation: DO_2i (mL/min/m^2) = pump flow (L/min) × [Hct/2.94 (g/dL) × 1.36 × arterial oxygen saturation (%) + partial pressure of arterial

oxygen (mm Hg) × 0.003] × 10/BSA (m^2). Oxygen-related measurements, including partial pressure of arterial oxygen, arterial oxygen saturation, Hct, PvO_2, and SvO_2 were measured using the CDI blood parameter monitoring system 500 (Terumo, Tokyo, Japan) (Video 1).

Postoperative variables examined included AKI stages, intubation time (hours), days spent in the intensive care unit (ICU) and hospital postoperatively, predischarge eGFR, and hospital mortality.

Anesthesia and CPB Management

All patients underwent general anesthesia. General anesthesia was induced by administering midazolam and fentanyl. Orotracheal intubation was facilitated with rocuronium. Anesthesia was maintained with sevoflurane, propofol, and remifentanil. After the surgery, all patients were transferred to the ICU under sedation with propofol.

CPB was established via standard median sternotomy. Body temperature was maintained between 34°C and 36°C. The pump circuit was primed with 800 mL bicarbonated Ringer solution, 200 mL 20% mannitol, and 3000 IU heparin. Roller pumps (LivaNova) were used for CPB, with the institutional standard pump flow target of 2.6 L/min/m^2, and phenylephrine was dosed to achieve a mean arterial blood pressure of at least 60 mm Hg. Packed red blood cells were transfused when hematocrit fell below 20%. The CDI blood parameter monitoring system 500 was recalibrated every 20 minutes.

Statistical Analysis

Continuous and categorical data were expressed as mean ± standard deviation or median (quartiles), and numbers (percent), respectively. Patients were divided into 2 groups based on whether they developed postoperative AKI. The best cutoff values for significant predictors were further determined by receiver operating characteristic (ROC) analysis. Continuous variables were analyzed with unpaired Student *t* tests or Mann-Whitney *U* test, and categorical variables were analyzed with χ^2 test. Univariate regression analysis was used to comprehensively evaluate the associations between perioperative variables and AKI, and thus candidate predictors for AKI were selected. Subsequently, multivariate logistic regression analysis was performed to identify variables that could be significant predictors for AKI. The method of Holm was used to adjust the *P* values for multiple comparisons. To make the presentation simpler, we compared the *P* value adjusted with .05 to determine whether a particular test result was statistically significant after adjustment. Data analysis was performed using JMP12 software (SAS Institute Inc, Cary, NC).

VIDEO 1. Monitoring of oxygen delivery pump flow, and hematocrit level in a typical patient using a commercially available tool. Video available at: https://www.jtcvs.org/article/S0022-5223(18)32972-6/fulltext.

RESULTS

Patient Characteristics

The characteristics of 112 Japanese patients are shown in Table 1. There were no significant differences in preoperative renal function (baseline creatinine 0.70 ± 0.21 vs 0.65 ± 0.16 mg/dL [$P = .316$] and eGFR 80.4 ± 17.6 vs 75.3 ± 15.2 mL/min/1.73 m^2 [$P = .204$]).

Intraoperative Data

The results of the group comparisons between non-AKI and AKI are shown in Table 2. Patients who developed AKI had longer perfusion (135.3 ± 41.8 vs 115.2 ± 34.7 minutes; $P < .05$) and crossclamp times (110.1 ± 34.9 vs 92.1 ± 31.5 minutes; $P < .05$), larger AUC $<DO_2i^{300}$ (1581 [range, 483-4882] vs 632 [range, 145-1386; $P < .01$]), time $<DO_2i^{300}$ (34.7 minutes [range, 16.0-61.0 minutes) vs 15.3 minutes [range, 5.8-32.7 minutes); $P < .01$) and time $<DO_2i^{280}$ (7.7 minutes [range, 1.6-28.0 minutes] vs 2.7 minutes [range, 0.0-9.8 minutes]; $P < .05$). Nadir Hct, nadir DO_2i, mean DO_2i, nadir SvO_2, nadir PvO_2, and SvO_2 70% thresholds were not significantly different between the 2 groups.

Postoperative Outcomes

AKI occurred in 23 patients (20.5%) postoperatively. Of these patients, 17, 5, and 1 patients developed stage 1 (73.9%), stage 2 (21.7%), and stage 3 (4.4%) AKI. Although no significant differences were found in postoperative intubation time, ICU stay, hospital stay, and hospital mortality, patients who developed AKI had lower predischarge eGFR (62.4 mL/min/1.73 m^2 [range, 54.3-86.0 mL/min/1.73 m^2] vs 74.5 mL/min/1.73 m^2 [range, 63.4-88.6 mL/min/1.73 m^2]; $P < .05$] (Table 3).

ROC analysis for time $<DO_2i^{300}$ and AKI rate revealed an AUC of 0.700 (95% confidence interval [CI], 0.569-0.805; $P < .01$) and a cutoff value of 15 minutes (sensitivity, 87.0%; specificity, 49.4%) (Figure 1). ROC analysis of AUC $<DO_2i^{300}$ and AKI rate showed an AUC of 0.680 (95% CI, 0.546-0.789; $P < .01$) and a cutoff value of 2203 (sensitivity, 47.8%; specificity, 83.2%) (Figure 1). Although ROC analysis of nadir DO_2i and AKI rate revealed an AUC of 0.571 (95% CI, 0.459-0.676; $P = .283$) and a cutoff value of 271 mL/min/m^2 (sensitivity, 82.6%; specificity, 40.5%) (Figure 1). Time $<DO_2i^{300}$ and AUC $<DO_2i^{300}$ had higher accuracy with predicting postoperative AKI than nadir DO_2i (differences between areas, 0.129 [$P = .009$, adjusted $P = .027$] and 0.109 [$P = .012$, adjusted $P = .024$), respectively, but there was no significant difference between time $<DO_2i^{300}$ and AUC $<DO_2i^{300}$ (differences between areas, 0.020 [$P = .424$, adjusted $P = .424$]).

TABLE 1. Baseline characteristics of patients with and without acute kidney injury (AKI)

Variable	Total cohort n = 112	Development of AKI		
		Non-AKI n = 89 (79.5%)	AKI n = 23 (20.5%)	*P* value
Age (y)	65.2 ± 14.7	64.4 ± 15.1	68.3 ± 12.7	.258
Female	49 (43.8)	38 (42.7)	11 (47.8)	.659
BSA (m^2)	1.61 ± 0.19	1.63 ± 0.20	1.55 ± 0.16	.087
BMI	22.9 ± 3.6	23.2 ± 3.6	21.8 ± 3.3	.088
Hypertension	50 (44.6)	37 (41.6)	13 (56.5)	.199
Diabetes	19 (17.0)	16 (18.0)	3 (13.0)	.574
Baseline Hct (%)	38.2 ± 4.6	38.7 ± 4.7	36.1 ± 3.7	<.05
Baseline creatinine (mg/dL)	0.69 ± 0.20	0.70 ± 0.21	0.65 ± 0.16	.316
eGFR (mL/min/1.73 m^2)	79.3 ± 17.2	80.4 ± 17.6	75.3 ± 15.2	.204
LVEF (%)	64.9 ± 9.8	65.3 ± 9.0	63.5 ± 12.7	.444
Type of surgery				
CABG	1 (0.9)	1 (1.1)	0	
CABG + valve	8 (7.1)	8 (9.0)	0	
CABG + valve + TA replacement	1 (0.9)	1 (1.1)	0	
Valve	82 (73.2)	66 (74.2)	16 (69.6)	
Valve + TA replacement	12 (10.7)	8 (9.0)	4 (17.4)	
TA replacement	2 (1.8)	0	2 (8.7)	
Adult congenital	4 (3.6)	3 (3.4)	1 (4.4)	
Myxoma	2 (1.8)	2 (2.3)	0	
Redo operation	5 (4.5)	4 (4.5)	1 (4.2)	.976
Emergent operation	3 (2.7)	2 (2.3)	1 (4.4)	.578
EuroSCORE II	2.3 ± 2.0	2.08 ± 1.69	2.90 ± 1.79	.067

Continuous and categorical data are expressed as mean ± standard deviation and n (%), respectively. *AKI*, Acute kidney injury; *BSA*, body surface area; *BMI*, body mass index; *Hct*, hematocrit; *eGFR*, estimated glomerular filtration rate; *LVEF*, left ventricular ejection fraction; *CABG*, coronary artery bypass grafting; *TA*, thoracic aortic; *EuroSCORE*, European system for cardiac operative risk evaluation.

Some perioperative variables were significantly associated with AKI (Tables 1 and 2). The multivariate regression analysis for AKI was performed by entering significant ($P < .05$) univariates (baseline Hct: $P = .0143$, time < DO_2i^{300}: $P = .0026$, and perfusion time: $P = .0242$) into the model, other than crossclamp time ($P = .0206$), AUC <DO_2i^{300} ($P = .0088$), and time < DO_2i^{280} ($P = .0491$) mathematically related to perfusion time or time <DO_2i^{300}. This analysis revealed that baseline Hct, time <DO_2i^{300}, and perfusion time were significantly associated with AKI (odds ratio [OR], 0.877; 95% CI, 0.777-0.984; $P = .0249$ for baseline Hct), (OR, 1.024; 95% CI, 1.005-1.045; $P = .0136$ for time <DO_2i^{300}), and (OR, 1.013; 95% CI, 1.000-1.027; $P = .0439$ for perfusion time).

To reduce the influence of perfusion time to a minimum, the patient population was further divided into 4 groups based on the cutoff values for perfusion time (121 minutes) and time <DO_2i^{300} (15 minutes) derived from the ROC analysis (Figure 2). Group A had both variables higher than the cutoff values; and group B had perfusion time >121 minutes but time <DO_2i^{300} ≤15 minutes; group C had perfusion time ≤121 minutes but time <DO_2i^{300} >15 minutes; group D had both variables lower than the cutoff values. The AKI rate of group A (50.0% [15 out of 30]; 95% CI, 33.1-66.8) was a significantly higher than that of groups B (13.3% [2 out of 15]; 95% CI, 3.7-37.9; $P = .012$, adjusted $P = .048$), C (14.3% [5 out of 35]; 95% CI, 6.3-29.3; $P = .002$, adjusted $P = .008$), and D (3.2% [1 out of 32]; 95% CI, 0.5-15.7; $P < .0001$, adjusted $P < .001$). There were no significant differences between the other combinations (B vs C [$P = .929$, adjusted $P = .929$], B vs D [$P = .201$, adjusted $P = .402$], and C vs D [$P = .095$, adjusted $P = .284$]).

DISCUSSION

In this retrospective study, we tested the hypothesis that the time–dose response of DO_2 during CPB would be a good indicator to predict postoperative AKI after cardiovascular surgery using CPB. The AUC of DO_2i over time was constructed using data points collected every 20 seconds, other variables derived were nadir and cumulative time duration below the threshold. We found that the time–dose response of DO_2i with more frequent time point

TABLE 2. Operative data for patients with acute kidney injury (AKI) and without acute kidney injury (non-AKI)

Variable	Total cohort N = 112	Development of AKI		*P* value
		Non-AKI n = 89 (79.5%)	AKI n = 23 (20.5%)	
Perfusion time (min)	119.3 ± 36.9	115.2 ± 34.7	135.3 ± 41.8	<.05
Crossclamp time (min)	95.8 ± 32.9	92.1 ± 31.5	110.1 ± 34.9	<.05
Nadir rectal temperature (°C)	34.9 ± 0.7	34.9 ± 0.8	35.0 ± 0.2	.514
Nadir Hct (%)	23.1 ± 2.3	23.1 ± 2.4	22.9 ± 2.0	.599
RBCs transfusion during CPB (U)	1.3 ± 1.9	1.1 ± 1.9	1.8 ± 2.1	.107
Nadir DO_2i (mL/min/m^2)	262.1 ± 25.8	263.4 ± 27.8	247.0 ± 15.9	.291
Mean DO_2i (mL/min/m^2)	317.7 ± 23.5	319.6 ± 24.5	310.4 ± 17.8	.100
Nadir SvO_2 (%)	66.9 ± 4.8	66.7 ± 4.8	67.3 ± 4.7	.617
Nadir PvO_2 (%)	38.8 ± 4.0	39.1 ± 4.2	37.9 ± 4.2	.220
Post CPB lactate (mmol/L)	1.20 ± 0.48	1.20 ± 0.51	1.20 ± 0.36	.984
AUC $<DO_2i^{300}$	697 (172-2107)	632 (145-1386)	1581 (483-4882)	<.01
AUC $<DO_2i^{280}$	95 (0-542)	78 (0-448)	323 (14-323)	.100
AUC $<DO_2i^{260}$	0 (0-151)	0 (0-130)	33 (0-1117)	.190
Time $<DO_2i^{300}$ (min)	17.3 (6.8-36.8)	15.3 (5.8-32.7)	34.7 (16.0-61.0)	<.01
Time $<DO_2i^{280}$ (min)	3.7 (0.3-13.2)	2.7 (0.0-9.8)	7.7 (1.6-28.0)	<.05
Time $<DO_2i^{260}$ (min)	0.0 (0.0-3.0)	0.0 (0.0-2.7)	0.7 (0.0-9.3)	.227
Time $<SvO_2^{70}$ (min)	0.67 (0.0-3.3)	1.0 (0.0-3.3)	0.7 (0.0-3.3)	.362

Continuous data are expressed as mean ± standard deviation or median (interquartile range) and categorical data as n (%). *AKI*, Acute kidney injury; *Hct*, hematocrit; *RBC*, red blood cell; *CPB*, cardiopulmonary bypass; *DO_2i*, oxygen delivery index; *SvO_2*, venous oxygen saturation; *PvO_2*, partial pressure of venous oxygen; *AUC $<DO_2i^{300}$*, the area under the curve below the oxygen delivery 300 mL/min/m^2 thresholds; *AUC $<DO_2i^{280}$*, the area under the curve below the oxygen delivery 280 mL/min/m^2 thresholds; *AUC $<DO_2i^{260}$*, the area under the curve below the oxygen delivery 260 mL/min/m^2 thresholds; *Time $<DO_2i^{300}$*, the cumulative time below the oxygen delivery 300 mL/min/m_2 thresholds; *Time $<DO_2i^{280}$*, the cumulative time below the oxygen delivery 280 mL/min/m^2 thresholds; *Time $<DO_2i^{260}$*, the cumulative time below the oxygen delivery 260 mL/min/m^2 thresholds; *Time $<SvO_2^{70}$*, the cumulative time below the venous oxygen saturation 70% thresholds.

measurements was an accurate indicator to estimate postoperative AKI in this patient demographic.

AKI is among the major complications of cardiac surgery and has been associated with increased morbidity and mortality rates.[5-7] In fact, although no significant difference was found in preoperative renal function, the AKI group showed more reduced predischarge renal function than the non-AKI group. Therefore, a protective strategy for AKI may be important in determining the prognosis of patients. Several studies have examined the risk factors associated with the development of AKI after cardiac surgery. The majority of these factors, such as age, preoperative renal function, and diabetes, are not modifiable. Many factors are implicated in the complex mechanisms leading to kidney injury after cardiac surgery.[1,2] More recently, the implementation of GDP to ensure adequate perfusion and

TABLE 3. Postoperative outcomes

Variables	Non-AKI (n = 89) (79.5%)	AKI (n = 23) (20.5%)	*P* value
AKI stage			
Stage 1	–	17 (73.9)	
Stage 2	–	5 (21.7)	
Stage 3	–	1 (4.4)	
Intubation time (h)	5.3 (4.0-8.0)	6.7 (4.7-10.4)	.103
ICU stay (d)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	.677
Postoperative hospital stay (d)	10.0 (8.0-12.3)	10.0 (10.0-14.0)	.242
Predischarge eGFR (mL/min/1.73 m^2)	74.5 (63.4-88.6)	62.4 (54.3-86.0)	<.05
Hospital mortality	0	0	1.000

Continuous data are expressed as mean ± standard deviation or median (interquartile range), and categorical data as n (%). *AKI*, Acute kidney injury; *ICU*, intensive care unit; *eGFR*, estimated glomerular filtration rate.

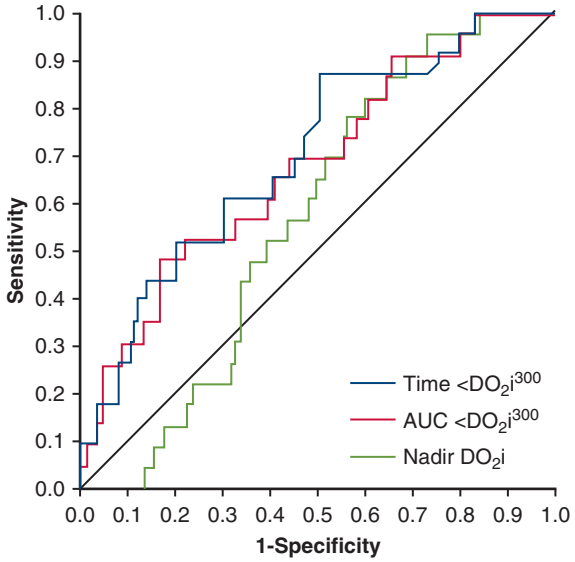

FIGURE 1. Results of receiver operating characteristic analysis of cumulative time below the oxygen delivery 300 mL/min/m^2 thresholds (*time* <DO_2i^{300}), area under the curve below the oxygen delivery 300 mL/min/m^2 thresholds (*AUC* <DO_2i^{300}), and nadir oxygen delivery index (*DO_2i*); AUCs and *P* values are 0.700 (95% CI, 0.569-0.805; $P < .01$) for the time <DO_2i^{300}, 0.680 (95% CI, 0.546-0.789; $P < .01$) for the AUC <DO_2i^{300}, and 0.571 (95% CI, 0.459-0.676; $P = .283$) for the nadir DO_2i, respectively. Differences between areas are 0.020 ($P = .424$, adjusted $P = .424$) for the time <DO_2i^{300} and the AUC <DO_2i^{300}, 0.129 ($P = .009$, adjusted $P = .027$) for the time <DO_2i^{300} and the nadir DO_2i, and 0.109 ($P = .012$, adjusted $P = .024$) for the AUC <DO_2i^{300} and the nadir DO_2i, respectively.

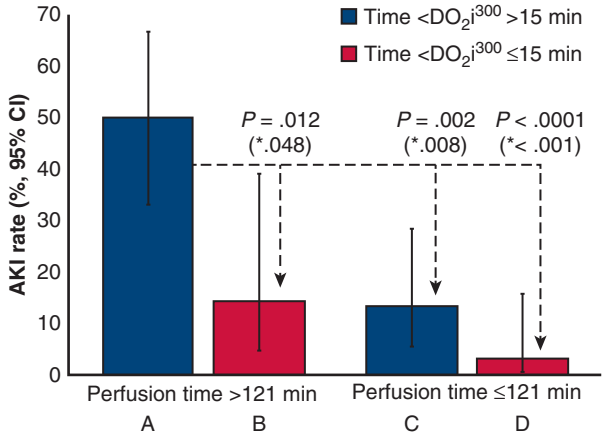

FIGURE 2. Acute renal failure rate based on the presence of 2 risk factors with respect to time. Group A has both variables higher than the cutoff values; group B has perfusion time >121 minutes but cumulative time below the oxygen delivery 300 mL/min/m^2 thresholds (*time* <DO_2i^{300}) ≤15 minutes, group C has perfusion time of ≤121 minutes but time <DO_2i^{300} of >15 minutes, and group D has both variables lower than the cutoff values. The acute kidney injury (*AKI*) rate of group A (50.0% [15 out of 30]; 95% CI, 33.1%-66.8%) is significantly higher than that of groups B (13.3% [2 out of 15]; 95% CI, 3.7%-37.9%), C (14.3% [5 out of 35]; 95% CI, 6.3%-29.3%), and D (3.2% [1 out of 32]; 95% CI, 0.5%-15.7%). *Adjusted *P* values using the Holm method for multiple testing. *CI*, Confidence interval.

prevent postoperative AKI has been proposed.[15] Previous reports of GDP have shown a relationship between low DO_2 during CPB and postoperative AKI with cutoff values of DO_2i at 262 to 272 mL/min/m^2.[12,13] However, in those studies, it should be noted that the cutoff values for nadir DO_2i during CPB were calculated based on data intermittently collected at 10- to 20-minute intervals. The DO_2 levels during CPB is always dynamically changing, increasing the possibility that DO_2 levels might vary depending on the sampling time. In fact, no significant differences were found in nadir DO_2i and mean DO_2i in our study. Measuring the DO_2 levels every 10 to 20 minutes cannot help accurately assess whether temporary or persistent decrease in DO_2i occurred (Video 1).

Recent studies[11,18] have shown a relationship between the time–dose response of mean arterial pressure and increased risk of AKI, and identified the critical time window between critical values and adverse outcomes. In addition, some studies[19,20] focused on the AUC to show the relationship between cerebral oxygen saturation and cognitive decline or delirium after cardiac surgery. The AUC of cerebral oxygen saturation accounts for both depth and duration of oxygen debt below threshold. Such results have presented the time–dose response as the AUC rather than the absolute values, which were more relevant in predicting organ ischemia.

In the present study, we demonstrated the time–dose response of DO_2i with thresholds of 260, 280, and 300 mL/min/m^2. We focused on a cutoff value of 300 mL/min/m^2, because the differences in the AUC and the cumulative time below the cutoff value (300 mL/min/m^2) between the non-AKI and AKI groups were significant. Although the nadir DO_2i was not significantly different between the non-AKI and AKI groups, significant differences were found in the AUC <DO_2i^{300} and time <DO_2i^{300} between the 2 groups. These findings demonstrate that nadir DO_2i identified by intermittent sampling cannot accurately evaluate the risk for AKI. The time–dose response of the DO_2i has been suggested to be a better predictor for AKI than nadir DO_2i. In addition, the lack of a significant difference in nadir DO_2i between the 2 groups in this study (compared with the previous studies[11-13]) can also be attributed to the hemodilution rate. In the present study, the mean values for BSA (1.61 m^2), body mass index (22.9), and nadir Hct during CPB (23.1%) were lower than those reported in previous studies.[11-13] Patients with lower body size are prone to greater hemodilution effects during CPB (due to lower circulating blood volume and

use of constant circuit-priming volume) leading to significant changes in Hct and DO_2 levels. Furthermore, significant changes were found in the Hct values obtained, depending on the sampling timing. The changes in Hct during CPB coupled with the difference in sampling interval might explain why no significant difference was found in nadir DO_2i in our study.

Novel results were shown regarding the time–dose response in the present study. Perfusion time has already been identified as a risk factor for AKI after cardiac surgery.[8,10] Similarly in this study, the AKI group had a significantly longer perfusion time than the non-AKI group. In addition, increased risk for postoperative AKI was significantly associated with time $<DO_2i^{300}$, baseline Hct, and perfusion time. To reduce the influence of perfusion time to a minimum, we performed subgroup analysis for perfusion time. We observed that even when perfusion time was >121 minutes, as long as the time $<DO_2i^{300}$ was ≤15 minutes, the AKI rate was almost equal to that for the group with perfusion time ≤121 minutes. This demonstrated that when perfusion time was long and delivery of oxygen was not sufficient, the AKI rate was remarkably increased. Sufficient delivery of oxygen during CPB may contribute to reduce AKI rate after cardiovascular surgery.

Regarding DO_2 in renal tissue during CPB, recent study has pointed out the renal oxygen supply–demand mismatch, which is caused by renal vasoconstriction in combination with dilution.[21] These findings supported the possibility that it can reduce risk of AKI due to the duration of low DO_2. Thus, risk factors for AKI related to CPB may not be evaluated accurately without considering the duration of low delivery of oxygen. The lack of significant differences in the nadir DO_2i, and mean DO_2i between the non-AKI and AKI groups suggest that it is important to monitor the delivery of oxygen during CPB, set the target value, and then maintain DO_2 to keep the renal tissue oxygenated.

We selected to divide the sample population into 4 groups based on the time $<DO_2i^{300}$ instead of AUC $<DO_2i^{300}$, owing to the need for an additional software program that could compute AUC in real time. By evaluating the time $<DO_2i^{300}$, we can ensure that the DO_2i will not decrease lower than the cutoff threshold. Because ROC analysis of time $<DO_2i^{300}$ and AUC $<DO_2i^{300}$ revealed AUCs without significant differences, the time $<DO_2i^{300}$ had accuracy in predicting postoperative AKI almost equal to AUC $<DO_2i^{300}$. In contrast, SvO_2, which is part of the traditional parameters for optimal perfusion, including nadir values and time–dose response, did not show any significant differences in the non-AKI and AKI groups. We suggest that the role of SvO_2 as an indicator of optimal perfusion is limited and does not reflect regional oxygen debt.

Our study has several limitations. First, because this relatively small study was conducted retrospectively, the measurement of DO_2 and other variables might be inconsistent and may have influenced the analysis. Because nadir DO_2i was defined as the lowest point during measurement (1 data per patient), nadir DO_2i may be more susceptible to small study size (power) than AUC $<DO_2i^{300}$ and time $<DO_2i^{300}$. Although statistical differences in the AUC $<DO_2i^{300}$ and time $<DO_2i^{300}$ between the non-AKI and AKI groups were demonstrated, given the low number of AKI stage 2 or 3, we cannot discuss serious renal injury (ie, AKI stage 2 or 3) after cardiovascular surgery. Second, the patient characteristics (baseline Hct, perfusion time, and complexity of surgical procedures) did not match between non-AKI and AKI groups. In addition, the multivariate analysis revealed that the baseline Hct, time $<DO_2i^{300}$, and perfusion time were significantly associated with AKI. Regarding Hct, there were no significant differences in intraoperative data (Nadir Hct and red blood cells transfusion during CPB). Next, to minimize the influence of perfusion effect, we excluded circulation arrest cases, as well as performed the subgroup analysis according to perfusion time. These results suggested that although baseline Hct and perfusion time affected the AKI incidence, it was unlikely that the differences in the baseline Hct or perfusion time between non-AKI and AKI groups may greatly influence the conclusion of this study. Conversely, regarding the surgical procedure, it was difficult to perform subgroup analysis because of the small number in each procedure group except for valvular heart disease. In addition, the standard procedure used for isolated CABG was the off-pump technique, and only 1 case of CABG underwent CPB in this study cohort. Therefore, it remains a possibility that the incidence and prognosis of AKI may be affected by the type of surgery or degree of urgency. Finally, this study also lacked data on patients treated under hypothermic conditions. However, because oxygen demand will change dramatically under hypothermic and circulatory arrest conditions (excluded in this study cohort), it may be more accurate to leave the index defined as the stated threshold derived from normothermic cases. A study focusing on diverse patient demographic characteristics and surgical situations, with sufficient power to move from association to predictive value of the indices, is under consideration. Moreover, we are planning a prospective randomized study to confirm these preliminary results and to assess the effect of the time–dose response in patients undergoing cardiac surgery with CPB. The important thing is how clinicians or perfusionists maintain DO_2. DO_2 depends on hemoglobin and/or pump flow (ignoring the minor contribution of partial pressure of oxygen); thus, it is important to assess whether increased pump flow is compensation for decreased hemoglobin level, and vice versa (for example, whether the AKI risk associated with hemoglobin level of 8 g/dL and pump flow rate of 3.0 mL/min/m^2 is the same as that associated

with hemoglobin level of 12 g/dL and pump flow rate of 2.0 L/min/m^2).

CONCLUSIONS

Although no significant differences were found in nadir DO_2i between non-AKI and AKI groups, the AUC $<DO_2i^{300}$ and time $<DO_2i^{300}$ were significantly different between those groups. The time–dose response of DO_2i during CPB is a better indicator than nadir DO_2 in evaluating AKI risk. A GDP strategy that maintains DO_2i levels to >300 mL/min/m^2 may result in decreased development of postoperative AKI.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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