Impact of gender differences on optimal oxygen delivery thresholds to prevent acute kidney injury in cardiac surgeries with cardiopulmonary bypass

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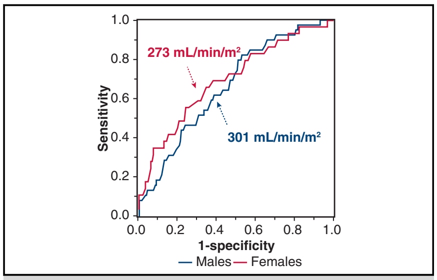
ABSTRACT

Background: The nadir oxygen delivery index (DO_2i) during cardiopulmonary bypass (CPB) is reportedly associated with acute kidney injury (AKI) in patients undergoing cardiac surgery. However, there are few reports on the relationship between patient sex and the nadir DO_2i threshold to prevent AKI. The aim of this study was to seek and evaluate the optimal DO_2i threshold differences between males and females to avoid AKI during on-pump cardiac surgery.

Methods: We retrospectively analyzed a total of 430 patients who underwent cardiac surgery between March 2017 and February 2023. A receiver operating characteristic analysis and univariable and multivariable regression analyses were performed to evaluate the association between perioperative variables, including the nadir DO_2i and incidence of AKI, in males and females.

Results: The nadir DO_2i was significantly lower (median, 294 [interquartile range (IQR), 272-317] mL/min/m² versus 277 [IQR, 262-295] mL/min/m²; $P < .001$) and cumulative time below the DO_2i of 270 mL/min/m² was longer (0.3 [IQR, 0-4.2] minutes vs 3.0 [IQR, 0-11.7] minutes; $P < .001$) in the female patients. However, the incidence rate of AKI was similar in males and females (15.2% [n = 39/256] vs 16.7% [n = 29/174]; $P = .68$). The best cut-off values of nadir DO_2i for AKI were <301 mL/min/m² (sensitivity, 82.1%; specificity, 39.5%) in males and <273 mL/min/m² (sensitivity, 69.0%; specificity, 61.4%) in females.

Conclusions: The optimal DO_2i to prevent AKI during cardiac surgery differs between males and females. Therefore, CPB management should be adjusted by sex based on the different cut-off values of nadir DO_2i. (JTCVS Open 2025;24:271-9)



Receiver operating characteristic analysis of nadir oxygen delivery index (DO_2i) by sex.

CENTRAL MESSAGE

The nadir oxygen delivery index (DO_2i) during cardiopulmonary bypass to prevent postoperative acute kidney injury differed by sex and was considerably lower in females.

PERSPECTIVE

This study validates the optimal oxygen delivery index (DO_2i) thresholds by sex for avoiding postoperative acute kidney injury (AKI) and demonstrates that the nadir DO_2i thresholds is lower in females compared to males. Considering the nadir DO_2i thresholds by sex as a goal-directed perfusion strategy may further reduce the risk of postoperative AKI.

Cardiac surgery–associated acute kidney injury (CSA-AKI) is a common and serious complication of cardiac surgery with cardiopulmonary bypass (CPB), with an incidence rate ranging from 20% to 40%.[1-3] Among patients with AKI, 1% to 2% require renal replacement therapy (RRT), after which the mortality rate increases to 25% to 50%.[4,5] Reported independent risk factors for AKI include age, obesity, renal function, anemia, diabetes, chronic lung disease, postoperative hypotension, and prolonged CPB.[6-14]

Over the past 2 decades, the nadir oxygen delivery index (DO_2i) on CPB has been studied as a modifiable parameter associated with AKI after cardiac surgery, and a critical DO_2i threshold (<262-272 mL/min/m^2) has been linked to an increased risk of AKI.[15,16] Additionally, Rasmussen and colleagues demonstrated that the cumulative time below the DO_2i threshold is associated with an increased

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Received for publication Oct 25, 2024; revisions received Dec 18, 2024; accepted for publication Dec 18, 2024; available ahead of print Feb 8, 2025.

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2666-2736

https://doi.org/10.1016/j.xjon.2025.01.001

Abbreviations and Acronyms

AKI	= acute kidney injury
BSA	= body surface area
CI	= confidence interval
CPB	= cardiopulmonary bypass
CSA	= cardiac surgery–associated
DO_2i	= oxygen delivery index
eGFR	= estimated glomerular filtration rate
KDIGO	= Kidney Disease: Improving Global Outcome
O_2ER	= oxygen extraction ratio
OR	= odds ratio
RBC	= red blood cell
RRT	= renal replacement therapy
SvO_2	= venous oxygen saturation
VO_2	= oxygen consumption

risk of CSA-AKI.[17] A recent randomized controlled trial showed that goal-directed perfusion aimed at maintaining $DO_2i > 280$ mL/min/m^2 significantly reduced the incidence of AKI compared to conventional CPB management based on body surface area (BSA) and body temperature.[18] Others reported that DO_2i should be maintained above 300 mL/min/m^2 to prevent AKI under normothermic CPB.[19,20]

Females generally have a similar cardiac index but a lower preoperative hemoglobin level compared to males,[21,22] and thus the DO_2i before CPB initiation (depending on the hemoglobin level and cardiac index) is estimated to be lower in females. Furthermore, because of their smaller BSA, females are frequently exposed to more severe hemodilution on CPB, which may cause a lower nadir DO_2i and prolonged duration of low DO_2i. Given the relationship between low DO_2i during CPB and the risk of AKI, it could be hypothesized that the risk of AKI may be higher in females compared to males because of lower nadir DO_2i during CPB; however, the sex-based difference in AKI incidence with cardiac surgery remains controversial.[23,24]

Additionally, there are few reports on the relationship between sex and required DO_2i on CPB. We hypothesized that the optimal DO_2i thresholds to prevent AKI may be lower in females compared to males. Based on this background, the present study investigated the difference between males and females in the optimal DO_2i threshold to avoid AKI with on-pump cardiac surgery.

MATERIALS AND METHODS

Patient Population

This retrospective case-control study was approved by our institutional Ethics Committee (approval B201707-63, dated June 19, 2017). Between March 2017 and February 2023, 542 patients (age $\geq$20 years) underwent cardiac surgery with CPB support at the Sakakibara Heart Institute of Okayama, Japan. After excluding patients with chronic renal insufficiency (preoperative estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), emergent operation, and procedures with circulatory arrest, 430 patients were enrolled in this study. Consent for the use of patient data was obtained from all patients. Patients or the public were not involved in the design, conduct, reporting, or dissemination of this research.

Definition of AKI

AKI was defined according to the serum creatinine level changes specified in the Kidney Disease: Improving Global Outcome (KDIGO) classification.[25] AKI stage 1 was defined as an absolute increase in serum creatinine of 0.3 mg/dL within 48 hours or an increase of 150% to 200% of baseline within the previous 7 days. AKI stage 2 was defined as an increase in serum creatinine >200% of baseline within the previous 7 days, and AKI stage 3 was defined as an increase in serum creatine >300% of baseline within the previous 7 days or the introduction of RRT. The eGFR was calculated using the following equations:

$$\text{eGFR (male)} = 194 \times \text{sCr}^{-1.094} \times \text{age}^{-0.287}\ (\text{mL/min/1.73 m}^2)$$

$$\text{eGFR (female)} = \text{eGFR (male)} \times 0.739\ (\text{mL/min/1.73 m}^2)$$

Anesthesia and CPB Management

All patients were treated by the same group of anesthesiologists, surgeons, perfusionists, and intensivists. Anesthesia induction was performed with dexmedetomidine hydrochloride, fentanyl, and propofol, followed by rocuronium for skeletal muscle relaxation. Sevoflurane, desflurane, propofol, and supplemental doses of remifentanyl were used for maintenance of anesthesia, based on clinical criteria. The pump circuit was primed with 700 mL of bicarbonate Ringer solution, 300 mL of 20% mannitol, and 4000 U of heparin. A 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 every hour. The institutional standard pump flow target was 2.5 L/min/m^2. Phenylephrine or noradrenaline was administered to maintain a mean blood pressure >50 mm Hg. Red blood cell transfusion was considered when hemoglobin concentration could not be maintained at 8 g/dL during CPB. Body temperature was maintained at 32°C to 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 left ventricular ejection fraction (<30%). Protamine was administered to neutralize the heparin after CPB. All remaining perfusate was used in an intraoperative blood salvage system (Xtra; LivaNova).

Monitoring of Oxygen Delivery During CPB

The DO_2i was calculated according to the following equation:

$$DO_2i\ (\text{mL/min/m}^2) = 10 \times \text{pump flow index (L/min/m}^2) \times [\text{hemoglobin (g/dL)} \times 1.36 \times \text{arterial oxygen saturation (\%)} + \text{partial pressure of arterial oxygen (mm Hg)} \times 0.003].$$

Hemoglobin concentration, arterial oxygen saturation, partial pressure of arterial oxygen, and venous oxygen saturation (S_VO_2) were measured every 20 seconds using the CDI Blood Parameter Monitoring System 500 (Terumo). The system was recalibrated every 30 minutes using a gas sample (ABL800FLEX; Radiometer). DO_2i during CPB was recorded every 20 seconds using the LivaNova Connect data management system. The nadir DO_2i was defined as the lowest value that lasted at least 2 minutes. To compare the duration of exposure to low DO_2i during CPB between males and females, the cumulative time of $DO_2i < 270$ mL/min/m^2 (time $DO_2i^{<270}$) was calculated. Additionally, to compare differences in DO_2i range during CPB with AKI and without AKI, DO_2i was divided into 8 categories ranging from <260 mL/min/m^2 to ≥320 mL/min/m^2: time $DO_2i^{<260}$, time $DO_2i^{260\text{-}270}$, time $DO_2i^{270\text{-}280}$, time $DO_2i^{280\text{-}290}$, time $DO_2i^{290\text{-}300}$, time $DO_2i^{300\text{-}310}$, time $DO_2i^{310\text{-}320}$, and time $DO_2i^{\geq 320}$). The cumulative times for each range were calculated as well.

Statistical Analyses

Continuous data are presented as mean ± SD or median (interquartile range) were compared using the unpaired Student *t* test or Mann-Whitney *U* test. Categorical variables are given as count and percentage and compared using the χ^2 test. When any expected frequency was <1 or 20% of expected frequencies were ≤5, a Fisher exact test was used. Multivariable logistic regression analysis was used to identify the independent predictors of AKI using variables found to have an association ($P < .05$) on univariate analysis with these events. All continuous parameters were dichotomized at the best cut-off value obtained by receiver operating characteristic analysis as the thresholds for logistic regression analysis. The best cutoff values obtained by receiver operating characteristic analysis were calculated by the Youden index. $P < .05$ was considered to indicate statistical significance. All data were analyzed using JMP 10.0 (SAS Institute).

RESULTS

Patient Demographics and Preoperative Data for Males and Females

The percentage of females was 40.5% (n = 174/430 patients). Patient demographics and preoperative data are compared between males and females in Table 1. The females were significantly older (mean age: males, 70 ± 11 years; females, 73 ± 11 years; $P < .001$), had a significantly higher EuroScore II (mean, 2.9 ± 2.3 vs 3.4 ± 2.4; $P = .029$) and left ventricular ejection fraction (mean, 56 ± 14% vs 62 ± 12%; $P < .001$), and significantly lower BSA (mean, 1.66 ± 0.15 m^2 vs 1.42 ± 0.15 m^2; $P < .001$), incidence of diabetes mellitus (35.9% [n = 92/256] vs 24.7% [n = 43/174]; $P = .014$), and baseline hemoglobin concentration (mean, 13.8 ± 1.8 g/dL vs 12.5 ± 1.4 g/dL; $P < .001$). Although baseline creatinine was significantly lower in the females (mean, 1.02 ± 0.25 mg/dL vs 0.79 ± 0.21 mg/dL; $P < .001$), there was no significant difference in baseline eGFR between males and females (mean, 60.1 ± 15.8 mL/min/1.73 m^2 vs 58.6 ± 16.9 mL/min/1.73 m^2; $P = .37$).

TABLE 1. Patients' demographic and preoperative characteristics

Variables	Males (N = 256)	Females (N = 174)	P value
Age, y, mean ± SD	70 ± 11	73 ± 11	.002
Body surface area, m^2, mean ± SD	1.66 ± 0.15	1.42 ± 0.15	<.001
Euro Score II, mean ± SD	2.9 ± 2.3	3.4 ± 2.4	.029
Atrial fibrillation, n (%)	68 (26.6)	58 (33.3)	.13
Redo operation, n (%)	24 (9.4)	13 (7.5)	.49
Hypertension, n (%)	147 (57.4)	90 (51.7)	.24
Hyperlipidemia, n (%)	56 (21.9)	35 (20.1)	.66
Chronic lung disease, n (%)	37 (14.5)	16 (9.2)	.10
Brain natriuretic peptide, pg/mL, median (IQR)	110 (45-289)	102 (44-233)	.67
Diabetes mellitus, n (%)	92 (35.9)	43 (24.7)	.010
Serum creatinine, mg/dL, mean ± SD	1.02 ± 0.25	0.79 ± 0.21	<.001
eGFR, mL/min/m^2, mean ± SD	60.1 ± 15.8	58.6 ± 16.9	.37
LVEF, %, mean ± SD	56 ± 14	62 ± 12	<.001
Hemoglobin, g/dL, mean ± SD	13.8 ± 1.8	12.5 ± 1.4	<.001
Lactate, mg/dL, mean ± SD	9.9 ± 2.8	9.4 ± 2.9	.09

EuroScore, European System for Cardiac Operative Risk Evaluation; *IQR*, interquartile range; *eGFR*, estimated glomerular filtration rate; *LVEF*, left ventricular ejection fraction.

Comparison of Intraoperative Data in Males and Females

Intraoperative data, provided in Table 2, show no significant difference in CPB time between males and females (mean, 165 ± 55 minutes vs 157 ± 53 minutes; $P = .13$). The females had significantly greater red blood cell

TABLE 2. Perioperative data

Variable	Males (N = 256)	Females (N = 174)	P value
CPB duration, min, mean ± SD	165 ± 55	157 ± 53	.13
Mean perfusion pressure, mm Hg, mean ± SD	57 ± 9	56 ± 9	.13
Nadir bladder temperature, °C, mean ± SD	33.8 ± 0.8	33.9 ± 0.6	.13
Maximum lactate during CPB, mg/dL, mean ± SD	16.4 ± 4.6	15.9 ± 4.5	.33
RBC transfusions during CPB, IU, median (IQR)	0 (0-2)	2 (0-4)	<.001
Nadir SvO_2 during CPB, %, mean ± SD	70 ± 5	72 ± 6	<.001
Maximum O_2ER during CPB, %, mean ± SD	27.3 ± 5.6	25.8 ± 5.7	.002
Maximum VO_2 during CPB, mL/min/m^2, mean ± SD	80.7 ± 16.7	71.5 ± 16.9	<.001
Pump flow rate, L/min/m^2, mean ± SD	2.48 ± 0.15	2.53 ± 0.15	.046
Nadir hemoglobin during CPB, g/dL, mean ± SD	8.2 ± 1.0	7.5 ± 0.7	<.001
Nadir DO_2i during CPB, mL/min/m^2, median (IQR)	294 (272-317)	277 (262-295)	<.001
Nadir $DO_2i^{<270}$, n (%)	61 (23.8)	64 (36.8)	.004
Time $DO_2i^{<270}$, min, median (IQR)	0.3 (0-4.2)	3.0 (0-11.7)	<.001

CPB, Cardiopulmonary bypass; *RBC*, red blood cell; *IQR*, interquartile range; *SvO_2*, venous oxygen saturation; *O_2ER*, oxygen extraction ratio; *VO_2*, oxygen consumption; *DO_2i*, oxygen delivery index.

TABLE 3. Postoperative outcomes

Outcome	Males (N = 256)	Females (N = 174)	P value
Any AKI, n (%)	39 (15.2)	29 (16.7)	.68
KDIGO stage 1, n (%)	35 (13.7)	26 (14.9)	.71
Stage 2, n (%)	1 (0.4)	1 (0.6)	.78
Stage 3, n (%)	3 (1.2)	2 (1.2)	.98
CRRT, n (%)	4 (1.6)	2 (1.2)	.72
Creatinine increase from baseline, %, mean ± SD	16.0 ± 2.3	18.0 ± 2.4	.45
Intubation time, h, median (IQR)	13 (5-16)	14 (5-17)	.45
ICU stay, d, median (IQR)	2.8 (1.8-3.8)	2.8 (1.9-3.8)	.21
Hospital stay, d, median (IQR)	22 (17-28)	23 (18-31)	.43
In-hospital deaths, n (%)	1 (0.4)	0 (0)	.41

AKI, Acute kidney injury; *KDIGO*, Kidney Disease: Improving Global Outcomes; *CRRT*, continuous renal replacement therapy; *IQR*, interquartile range; *ICU*, intensive care unit.

(RBC) transfusion during CPB (median, 2 [IQR, 0-4] IU vs 0 [IQR, 0-2] IU; $P < .001$) and significantly higher mean pump flow rate (2.53 ± 0.15 L/min/m^2 vs 2.48 ± 0.15 L/min/m^2; $P = .004$). The females also had a significantly lower nadir hemoglobin concentration during CPB (mean, 7.5 ± 0.7 g/dL vs 8.2 ± 1.0 g/dL; $P < .001$) and nadir DO_2i during CPB (277 [IQR, 262-295] mL/min/m^2 vs 294 [IQR, 272-317] mL/min/m^2; $P < .001$). The percentages of nadir DO_2i < 270 mL/min/m^2 was significantly higher in females (vs 36.8% [64/174] vs 23.8% [61/256]; $P = .004$). Females had significantly longer cumulative time at DO_2i < 270 mL/min/m^2 (median time $DO_2i^{<270}$: 0.3 [IQR, 0-4.2] minutes vs 3.0 [IQR, 0-11.7] minutes; $P < .001$), significantly higher nadir SvO_2 (72 ± 6% vs 70 ± 5%; $P < .001$), lower maximum oxygen extraction ratio (O_2ER; mean, 25.8 ± 5.7% vs 27.3 ± 5.6%; $P = .002$) and lower maximum oxygen consumption (VO_2 max; mean, 71.5 ± 16.9 mL/min/m^2 vs 80.7 ± 16.7 mL/min/m^2; $P < .001$).

Comparison of Postoperative Outcomes in Males and Females

The incidence rate and severity of AKI were similar between males and females (15.2% [n = 39/256] vs 16.7% [n = 29/174], $P = .68$, KDIGO stage 1: 13.7% [n = 35/256] vs 14.9% [n = 26/174], $P = .71$; KDIGO stage 2: 0.4% [n = 1/256] vs 0.6% [n = 1/174], $P = .78$; KDIGO stage 3: 1.2% [n = 3/256] vs 1.2% [n = 2/174], $P = .98$). There were no significant differences in the rate of increased creatinine level (16.0 ± 2.3% vs 18.0 ± 2.4%; $P = .45$) and the rate of continuous RRT introduction (1.6% [n = 4/256] vs 1.2% [n = 2/174]; $P = .72$). Intubation time, durations of intensive care unit stay and postoperative hospital stay, and in-hospital deaths were equivalent in the 2 groups (Table 3).

Oxygen Delivery During CPB With and Without AKI

The nadir DO_2i during CPB was significantly lower in the AKI group for both males and females (males: AKI, 279 [IQR, 265-299] mL/min/m^2 vs non-AKI, 298 [IQR, 275-320] mL/min/m^2; $P = .002$; females: AKI, 266 [IQR, 248-281] mL/min/m^2 vs non-AKI, 279 [IQR, 267-296] mL/min/m^2; $P = .001$). Figure 1 compares the nadir DO_2i values of males and females with AKI and of males and females without AKI. The nadir DO_2i in both the AKI and non-AKI groups were significantly lower in females (AKI: 266 [IQR, 248- 281] mL/min/m^2 vs 279 [265 – 299] mL/min/m^2, $P = .001$; non-AKI: 298 [IQR, 275-320] mL/min/m^2 vs 279 [IQR, 267-296] mL/min/m^2; $P < .001$). Male patients who developed AKI had significantly longer cumulative time in the DO_2i range <300 mL/min/m^2, but there were no significant differences between the sexes in the time at DO_2i > 300 mL/min/m^2 (Figure 2, *A*). On the other hand, female patients who developed AKI had significantly longer cumulative time in the DO_2i range only below 280 mL/min/m^2, but there were no significant differences in more than DO_2i 280 mL/min/m^2 (Figure 2, *B*).

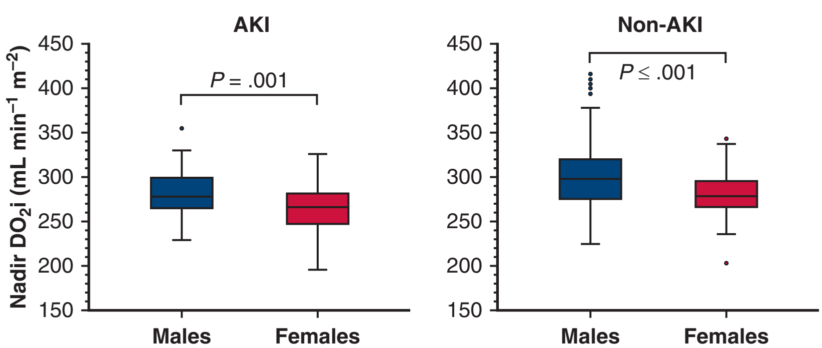

FIGURE 1. Comparison of nadir oxygen delivery index (DO_2i) during cardiopulmonary bypass (CPB) in males and females with acute kidney injury (AKI) and without AKI. The lower and upper borders of the boxes represent interquartile range (25th-75th percentiles), lines in the boxes represent the median, whiskers are the minimum and maximum values of nonoutliers, and extra dots are outliers.

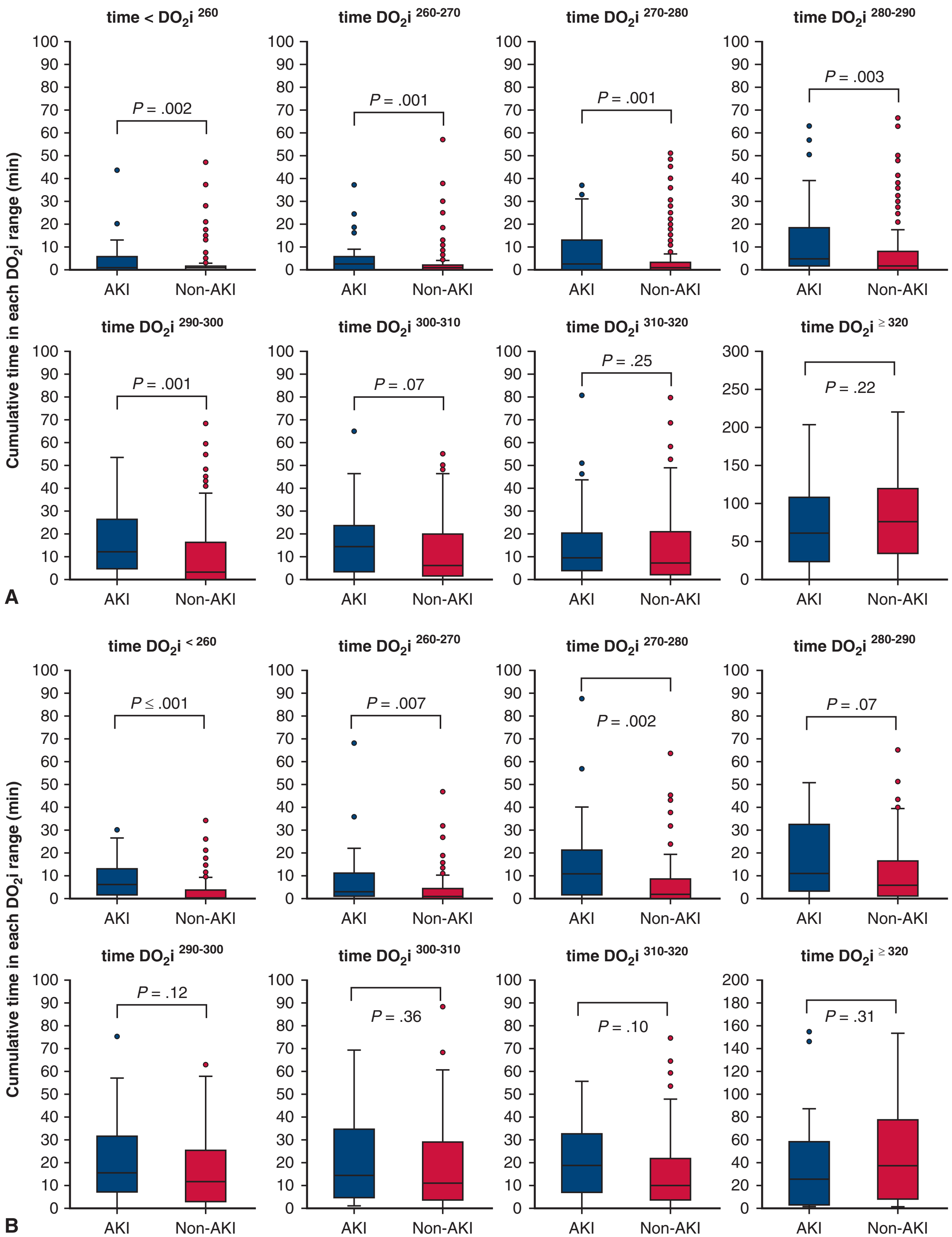

FIGURE 2. A, Cumulative time for each oxygen delivery index (DO_2i) range during cardiopulmonary bypass (CPB) in males with and without acute kidney injury (AKI). B, Cumulative time for each DO_2i range during CPB in females with and without AKI. The lower and upper borders of the boxes represent interquartile range, lines in the boxes represent the median, whiskers are the minimum and maximum values of nonoutliers, and extra dots are outliers.

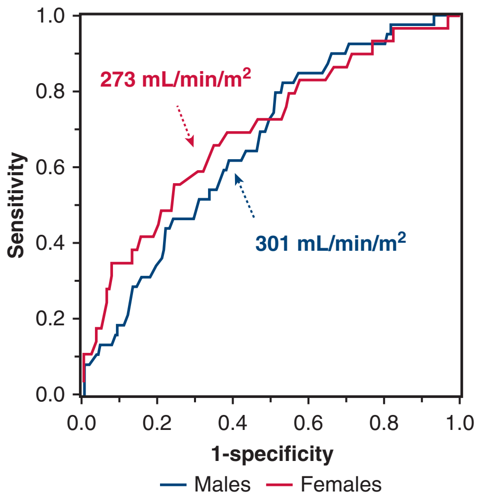

FIGURE 3. Receiver operating characteristic analysis of nadir oxygen delivery by sex.

A receiver operating characteristic analysis was performed to identify adequate cut-off values for the nadir DO_2i for each sex for AKI. The calculated area under the curve values were 0.69 (95% CI, 0.59-0.77) for males and 0.74 (95% CI, 0.64-0.83) for females. The best cut-off values by the Youden index were a nadir DO_2i < 301 mL/min/m^2 (sensitivity, 82.1%; specificity, 39.5%) in males and a nadir DO_2i < 273 mL/min/m^2 (sensitivity, 69.0%; specificity, 61.4%) in females (Figure 3).

Multivariable Analysis for Risk of AKI by Sex

The multivariable models were analyzed separately for males and females to determine the relationship of nadir DO_2i during CPB with AKI. On univariable analysis, preoperative hemoglobin, serum creatinine, eGFR, RBC transfusions during CPB, nadir hemoglobin, and nadir DO_2i were identified as risk factors for AKI in males, and preoperative hemoglobin, CPB duration, RBC transfusions during CPB, nadir hemoglobin, and nadir DO_2i were identified as risk factors for AKI in females. After multivariable analysis, preoperative eGFR <64.7 mL/min/1.73 m^2 (odds ratio [OR], 2.67; 95% confidence interval [CI], 1.15-6.99; P = .021), RBC transfusions during CPB >4 IU (OR, 2.75; 95% CI, 1.08-7.10; P = .034), and the nadir DO_2i < 301 mL/min/m^2 (OR, 2.46; 95% CI, 1.05-6.26; P = .038) were identified as independent risk factors for AKI in males. In the females, CPB duration >180 min (OR, 3.28; 95% CI, 1.37-8.02; P = .008) and nadir DO_2i < 273 mL/min/m^2 (OR, 2.96; 95% CI, 1.24-7.40; P = .014) were identified as independent risk factors for AKI (Table 4).

DISCUSSION

This retrospective study investigated the difference by sex in the optimal DO_2i thresholds during CPB to avoid AKI. The major findings of this study are (1) the nadir DO_2i was significantly lower in females, and the cumulative time and percentage in the lower DO_2i range (<270 mL/min/m^2) were significantly longer and higher in females; (2) although females had significantly lower DO_2i during CPB, the incidence and severity of AKI were equivalent to those in males; (3) the nadir DO_2i cut-off value for AKI differed substantially between males and females (males, 301 mL/min/m^2 vs females, 273 mL/min/m^2); and (4) nadir DO_2i was an independent risk factor for AKI in both males and females (Figure 4).

It is well known that oxygen cannot be consumed to maintain aerobic metabolism, and that anaerobic metabolism is activated for energy production in cells below the critical thresholds of DO_2i.[26,27] It is currently recommended to avoid a nadir DO_2i < 262 to 272 mL/min/m^2 and to maintain the DO_2i at >280 to 300 mL/min/m^2 to reduce the risk of CSA-AKI during CPB.[15-20] Lower preoperative hemoglobin concentration and higher hemodilution rate can cause lower DO_2i during CPB in females. This study reveals that females had a

TABLE 4. Univariable and multivariable analysis for predictors of AKI

Variable	Univariable analysis OR (95% CI)	Univariable analysis P value	Multivariable analysis OR (95% CI)	Multivariable analysis P value
Males				
Hemoglobin <12.4 g/dL	2.77 (1.33-5.74)	.005	1.12 (0.43-2.78)	.81
eGFR <64.7 mL/min/1.73 m^2	3.06 (1.29-7.24)	.008	2.67 (1.15-6.99)	.021
RBC during CPB >4 IU	4.47 (2.14-9.32)	<.001	2.75 (1.08-7.10)	.034
Nadir DO_2i < 301 mL/min/m^2	3.44 (1.51-7.82)	.002	2.46 (1.05-6.26)	.038
Females				
Hemoglobin <11.2 g/dL	2.66 (1.07-6.62)	.031	1.56 (0.53-4.50)	.41
CPB duration >180 min	3.73 (1.64-8.49)	.001	3.28 (1.37-8.02)	.008
RBC during CPB >4 IU	3.61 (1.56-8.35)	.002	2.18 (0.83-5.83)	.11
Nadir DO_2i < 273 mL/min/m^2	3.30 (1.43-7.62)	.004	2.96 (1.24-7.40)	.014

AKI, Acute kidney injury; *OR*, odds ratio; *CI*, confidence interval; *eGFR*, estimated glomerular filtration rate; *RBC*, red blood cell; *DO_2i*, oxygen delivery index; *CPB*, cardiopulmonary bypass.

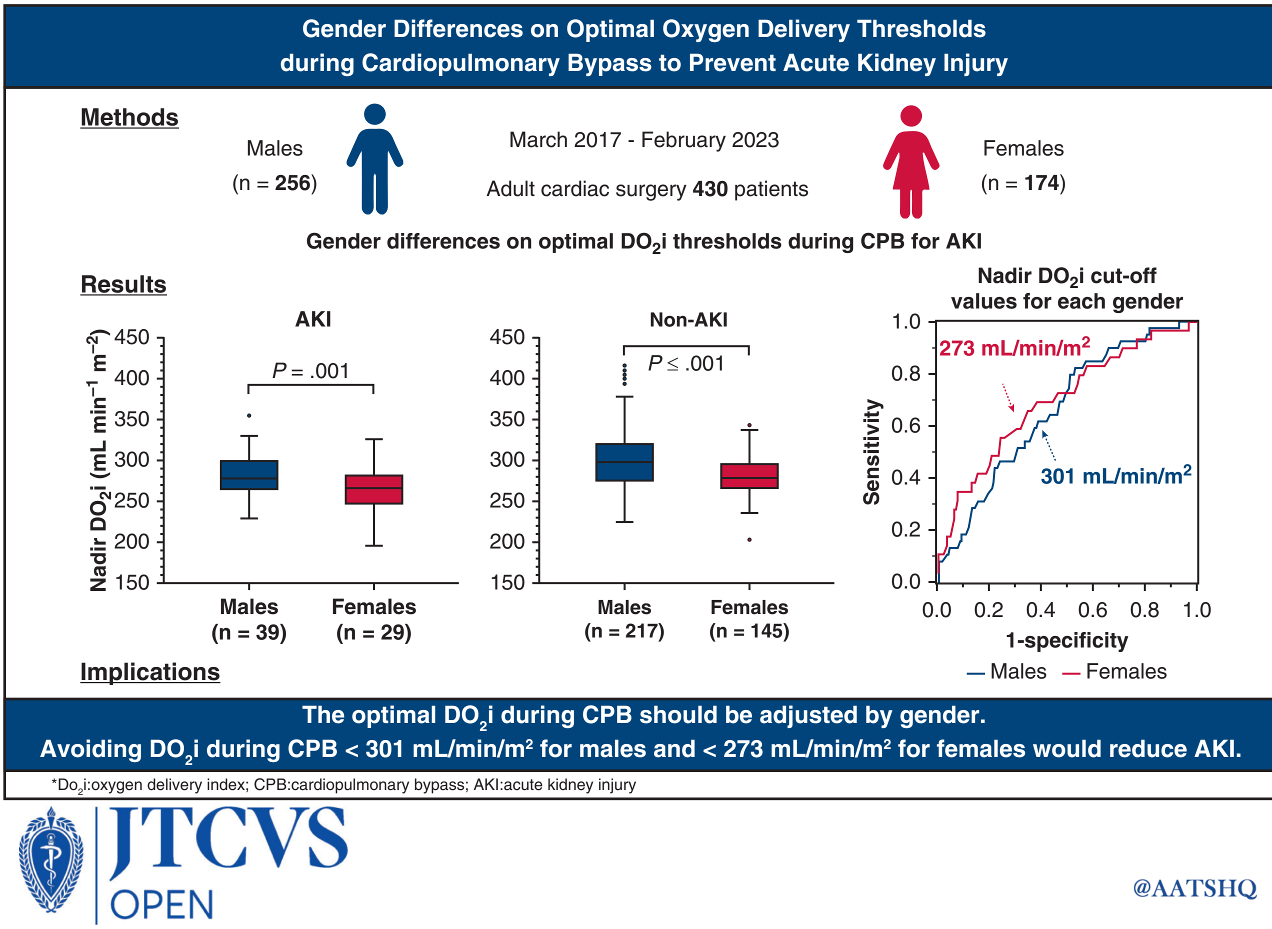

FIGURE 4. Graphical abstract summarizing the study findings. The nadir oxygen delivery index (DO_2i) during cardiopulmonary bypass (CPB) was significantly lower in females, but the incidence and severity of acute kidney injury (AKI) were similar in females and males. The nadir DO_2i cut-off value for AKI differed significantly between males and females (males: 301 mL/min/m^2; females: 273 mL/min/m^2). The results of this study shows that the optimal DO_2i thresholds during CPB differ by sex.

significantly lower nadir DO_2i and a longer cumulative time in the lower DO_2i range; however, the rate and severity of AKI development were similar to those in males. Furthermore, the DO_2i range associated with AKI was found to differ between males and females (males, DO_2i < 300 mL/min/m^2 vs females, DO_2i < 280 mL/min/m^2).

Based on these findings, we hypothesize that the critical DO_2i threshold differs between the sexes, and our results confirm that the nadir DO_2i thresholds were approximately 10% lower in females (males, 301 mL/min/m^2 vs females, 273 mL/min/m^2). Although our data do not provide any mechanistic insight into sex-based differences in nadir DO_2i thresholds, it can be speculated that thresholds are influenced by differences in metabolic rate between males and females. Arciero and colleagues[28] reported that resting metabolic rate (predicted by fat-free mass, fat mass, VO_2 max, and sex) was 3% lower in females compared to males. In addition, females tend to have lower fat-free mass and VO_2 max and higher fat mass.[28] In this study, VO_2 max during CPB was significantly lower in females, by approximately 13%. These differences show that females tend to have significantly lower nadir DO_2i and longer cumulative time in the lower DO_2i range and a significantly better oxygen supply–demand index (SvO_2 and O_2ER), but that maximal lactate concentration during CPB (an index of anaerobic metabolism) does not differ significantly by sex. These findings suggest that females have a lower metabolic rate and can maintain aerobic metabolism at lower DO_2i than males and are less likely to develop hypoxic damage to the kidneys. Ellis and colleagues[29] reported a sex-based difference in the relationship between CSA-AKI and the nadir hematocrit, which is a component of the DO_2i equation. Females had lower AKI incidence at lower nadir hematocrit (<23%) status, indicating greater tolerance of low hematocrit status. Metha and colleagues[30] suggested that as one of these mechanisms, menstruation and associated blood loss may provide females with the ability to optimize oxygen extraction and delivery to tissues at lower systemic hematocrit levels. The present study's finding of lower nadir DO_2i thresholds in females also may be compatible, considering these mechanisms.

Our data suggest that critical DO_2i thresholds vary by sex, and that the optimal DO_2i during CPB should be adjusted for each sex. DO_2i depends mainly on pump flow rate and hemoglobin concentration. A pump flow rate of 2.0 to 2.5 L/min/m^2 at a mean blood pressure of 50 to 80 mm Hg are considered appropriate to achieve systemic perfusion, but Lannemyr and colleagues[31-33] demonstrated that a higher perfusion flow rate (2.7-3.0 L/min/m^2) ameliorated renal oxygenation impairment in CPB. Especially for males, a higher perfusion flow rate should be considered, as pump flow rates as high as 2.8 to 3.0 L/min/m^2 (if the hemoglobin is 7-8 g/dL) may be required to be maintained above the critical DO_2i thresholds of 300 mL/min/m^2. On the other hand, it is known that RBCs undergo irreversible morphologic and biochemical changes during storage.[34] As a result, RBC transfusion may cause AKI due to impaired tissue oxygenation, exacerbating inflammatory responses and tissue oxidative stress.[35] Females tend to received more RBCs during CPB because they have a lower baseline hemoglobin concentration than males.[36-38] Considering the tolerance to low hemoglobin level and lower critical DO_2i thresholds shown by the data for our females, it is possible that females may be able to reach a DO_2i above the critical level without administering higher doses of RBC transfusions.

Study Limitations

This study has several limitations. First, this is a retrospective observational study in a single center, and thus our models need to be validated at multiple centers for broad applicability. Second, patients with a minimum body temperature <32 °C were excluded, and thus the critical DO_2i thresholds in hypothermia may differ from those used in this study. Third, this study excluded patients who had chronic renal failure preoperatively, and thus the clinical impacts of these patients are undetermined. Fourth, excessively low perfusion pressure could be associated with AKI, but the perfusion pressures recorded in this study were obtained every 10 to 15 minutes, and it was not possible to evaluate the time or depth over which perfusion pressure decreased. Fifth, although this study defined AKI as the change in creatinine within 7 days after surgery, creatinine production is affected by muscle mass and depends on several factors, including age, sex, and nutritional status. Different AKI biomarkers could be used to determine more accurate optimal DO_2i thresholds.[39,40] Finally, this is a retrospective review limited by the inclusion of many assumptions, and we are planning a prospective cohort study to further support our conclusions.

CONCLUSIONS

The optimal DO_2i during CPB should be adjusted by sex. Our data suggest that avoiding a DO_2i during CPB <301 mL/min/m^2 for males and <273 mL/min/m^2 for females will reduce CSA-AKI.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: oxygen delivery, sex, cardiopulmonary bypass, acute kidney injury, goal-directed perfusion