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Original Article

Factors for Acute Kidney Injury Following Total Arch Replacement and Association with Temperature Management During Cardiopulmonary Bypass: A Single-center Retrospective Observational Study

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Many patients develop acute kidney injury (AKI) after vascular surgery. In this retrospective observational study, we investigated the risk factors for AKI defined using the Kidney Disease Improving Global Outcomes criteria after total arch replacement (TAR). Additionally, we investigated the influence of temperature management during cardiopulmonary bypass (CPB) on postoperative renal function by propensity score-matched analysis. We retrospectively analyzed 161 consecutive patients who underwent TAR between 2016 and 2019. Postoperative AKI occurred in 48.7% of the patients. In the multivariate analysis, male sex (odds ratio [OR] 3.95, 95% confidence interval [95%CI] 1.56-8.27, $p=0.002$), ACE inhibitors/ARB medication (OR 3.19, 95%CI 1.49-6.82, $p=0.003$), preoperative chronic kidney disease (OR 2.47, 95%CI 1.17-5.23, $p=0.02$), prolonged CPB time (OR 2.36, 95%CI 1.05-5.34, $p=0.04$), and lower body ischemic time during CPB (OR 2.20, 95%CI 1.05-4.46, $p=0.04$) were identified as independent risk factors for AKI. Propensity score-matched analysis showed no significant difference in the risk of AKI following TAR between mild hypothermia or normothermia and moderate hypothermia (37.2% vs. 41.9%, $p=0.83$). In conclusion, modifiable risk factors for AKI included prolonged CPB time and lower body ischemic time. Temperature management during CPB had no clear effect on outcomes.

Key words: acute kidney injury, total arch replacement, cardiopulmonary bypass, lower body ischemic time

Acute kidney injury (AKI) after cardiovascular surgery is common [1], particularly after aortic surgery. However, there is wide variation in the reported incidence of AKI following aortic surgery due to the existence of different definitions of AKI and confounding patient factors [2]. Total arch replacement (TAR) is one of the most complex and challenging procedures for cardiovascular surgeons where many patients develop AKI afterwards. A recent study suggests that advanced age, elevated body mass index (BMI), elevated preoperative serum creatinine (sCr), and prolonged cardiopulmonary bypass (CPB) time are independent risk factors for AKI following aortic arch surgery [3]. However, the risk factors for AKI following TAR are not fully understood. Moreover, the definition of AKI differs greatly among studies, and data on AKI defined using the Kidney Disease Improving Global Outcome (KDIGO) criteria are scarce [4].

Over the past decades, TAR has been frequently performed under deep hypothermic circulatory arrest (DHCA) to provide a bloodless and still operative field,

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but it is a time-consuming process, and the potential side effect of coagulopathy is a great concern. In the 2010s, a protocol of moderate hypothermic circulatory arrest (MHCA), sometimes combined with selective antegrade cerebral perfusion (SCP), was widely accepted as a preferred alternative to DHCA since acceptably low rates of adverse neurological and renal events were reported using this modality [5]. Nonetheless, a few surgeons tried to push the limit by using mild rather than moderate hypothermia for TAR. Therefore, the debate about the optimal temperature for TAR remains unsettled.

Newland *et al.* reported that hyperthermic perfusion during CPB is an independent predictor of AKI following cardiac surgery [6]. In general, higher temperature is thought to risk harm to various organs including the brain and kidneys. On the other hand, previous studies suggest that MHCA with antegrade selective cerebral perfusion during complex aortic surgery is not associated with an increased risk of AKI [7]. At our institution, for example, the target temperature during CPB is often higher than 28°C, which establishes a condition called mild hypothermic circulatory arrest, and if the open distal anastomosis is unnecessary and the surgeon speculates that a neurological complication is unlikely to happen, normothermic (>34°C) circulatory arrest with SCP is sometimes performed. However, little is known about the influence of mild hypothermic or normothermic circulatory arrest on postoperative renal function or patient outcome.

This study aimed to investigate the clinical risk factors for AKI, as defined using the KDIGO criteria, following TAR, one of the most performed procedures in vascular surgery. In addition, we focused on the influence of temperature management during CPB on postoperative renal function by comparing the effects of mild hypothermia/normothermia to those of conventional MHCA.

Materials and Methods

Study design. This study was a retrospective analysis of a prospectively collected cohort. After institutional review board approval (approval number, 2019-126), we reviewed the electronic medical records and laboratory results of 161 consecutive patients who underwent TAR surgery with CPB at Hiroshima City Hospital, Japan, between January 2016 and March 2019. Patients who underwent both elective and emergent TAR were enrolled, in the study and those with chronic kidney disease who needed renal replacement therapy before surgery were excluded. The need for informed consent was waived because of the retrospective nature of the study.

In the first analysis, we investigated the risk factors for AKI following TAR, and in the second analysis, we compared the effect of temperature management on AKI following TAR.

Data collection. We retrospectively reviewed the clinical records and data on patient demographics, details of medical and surgical treatments and postoperative patient outcomes. Demographic variables included age, sex, BMI, underlying disease, comorbidities (diabetes, hypertension, pulmonary disease, coronary artery disease, cerebrovascular disease, chronic kidney disease and heart failure), medication history (angiotensin converting enzyme inhibitors [ACE inhibitors], angiotensin-II receptor blockers [ARBs], calcium channel blockers, β-blockers, and statins).

Preoperative laboratory variables included sCr, estimated glomerular filtration rate (eGFR), hemoglobin, and albumin levels. Preoperative hemodynamic information included left ventricular ejection fraction (via the modified Simpson method), and pulmonary hypertension detected by echocardiography. The eGFR rate was derived from the Modification of Diet in Renal Disease Equation: $eGFR\ (mL/min/1.73\ m^2) = 194 \times [sCr\ (mg/dL)]^{-1.094} \times [age\ (years)]^{-0.287}$ ($\times 0.739$ if female) [8].

Postoperative laboratory variables included hemoglobin at intensive care unit (ICU) admission, and maximum sCr within 7 days after surgery. Surgical details inrolved previous cardiac surgery, emergent or elective status, and type of combined surgery (Bentall procedure, coronary artery bypass grafting [CABG], and aortic valve replacement/plasty).

Operation-related variables were the durations of operation, CPB, and aortic cross-clamping, the lower body ischemic time, and the minimum core temperature during CPB. In addition, we analyzed the amount of blood products and the continuously administered drugs used (dobutamine, milrinone, norepinephrine, epinephrine, carperitide, landiorol, and nicardipine).

The outcome measures were postoperative variables including hemoglobin at ICU admission, and postop-

erative sCr for 7 consecutive days. Finally, patients' outcomes (ICU length of stay, intubation time, reintubation, severe infection, neurological complications, and redo operation) were also analyzed.

In the second analysis, patients were divided into 2 groups: a moderate hypothermia (MHCA) group, and a mild hypothermia/normothermia (non-MHCA) group. We investigated the effect of temperature management on AKI following TAR using propensity score (PS) matching.

Definitions. Preoperative chronic kidney disease (CKD) was defined as eGFR <60 mL/min/1.73 m^2. AKI was defined and staged for severity using the KDIGO criteria. Postoperative AKI was defined as an increase in sCr to more than 50% of the baseline within 7 days postoperatively or an increase of 0.3 mg/dL within 48 h postoperatively. In this study, we did not use urine output data because there are many confounding factors, such as diuretics, and the retrospectively collected data may have the potential to be inaccurate. Regarding temperature management during CPB, deep hypothermia was defined as a minimum core temperature below 20°C, moderate hypothermia was defined as a minimum core temperature between 20.1°C and 28°C, mild hypothermia was defined as a core temperature between 28.1°C and 34°C, and normothermia was defined as a core temperature between 34.1°C and 36°C [9].

Major adverse complications consisted of stroke, paraplegia, severe heart failure requiring mechanical support, redo surgery, the need for renal replacement therapy, and sepsis.

Statistical analysis. All statistics are presented as the mean ± standard deviation (SD) or median (interquartile range; IQR) for continuous variables as appropriate, and as numbers and percentages for categorical variables. The Mann-Whitney *U* test was used to compare continuous variables, and the χ^2 or Fisher's exact test was used to compare categorical variables. A logistic regression model was used to identify multivariate predictors of AKI. For all analyses, a *p*-value less than 0.05 was considered to be statistically significant. All data were analyzed using EZR version 3.4.1. (Saitama Medical Center, Jichi Medical University, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), a modified version of R commander designed to add statistical functions frequently used in biostatistics [10].

Results

Patient characteristics. In this retrospective cohort study, 158 patients were included after the exclusion of 3 patients with end-stage renal failure before surgery. As shown in Table 1, the median age was 69 ± 11.2 years (range: 22-88 years), and 107 (67.7%) of these patients were men. Among the 158 patients included, 122 patients (77.2%) were diagnosed with hypertension. Other comorbidities included diabetes (n = 24, 15.1%), pulmonary disease (n = 6, 3.7%), coronary artery disease (n = 32, 20.2%), and cerebrovascular disease (n = 18, 11.3%). All patients were hemodynamically stable before surgery, and preoperative echocardiography showed pulmonary hypertension in 8 (5.0%) patients, and apparent valvular disease in 26 (16.4%) patients. Preoperative laboratory data showed the mean sCr level was 0.95 ± 0.41 mg/dL, and the mean eGFR level was 62.0 ± 19.0 mL/min. Regarding surgical details, 25 (15.8%) surgeries were emergent, and combined surgery was as follows: Bentall procedure (n = 11, 6.9%), CABG (n = 12, 7.5%), and aortic valve replacement/plasty (n = 17, 10.7%). The mean operation time was 414.6 ± 97.4 min, and the mean CPB time was 183.0 ± 57.8 min. During CPB, the mean lower body ischemic time was 22.6 ± 16.1 min, and the mean minimum core temperature was 27.7 ± 2.4°C.

Analysis of risk factors for postoperative AKI. As shown in Table 1, the group of patients with AKI was significantly different from those without AKI with respect to each of the following: sex, BMI, coronary artery disease, CKD, ACE inhibitors/ARB medication, preoperative sCr, and eGFR. There were significant differences between the two groups in operation time and lower body ischemic time during CPB. The minimum core temperature was not significantly different between the 2 groups. Moreover, the amount of intraoperative blood product use and perioperative drug use were not significantly different.

The overall incidence of postoperative AKI defined using the KDIGO criteria was 48.7% (n = 77): 87% (n = 67) of these patients were classified as having stage 1, 7.7% (n = 6) as having stage 2, and 5.1% (n = 4) as having stage 3 AKI. Table 2 shows the outcome data of the patients who underwent TAR replacement. Postoperative AKI was associated with prolonged ICU stay, prolonged intubation time, and reintubation rate.

We selected candidate variables for multivariate

Table 1 Patients characteristics

	All patients	No AKI	AKI	*P*-value*
Patients Population (n)	158	81	77	
Demographic data				
Age (year), mean ± SD	66.9 ± 11.2	68.8 ± 11.8	69.8 ± 10.7	0.56
Sex, male (n)	107 (67.7%)	44 (54.3%)	63 (81.8%)	0.0003
Body mass index (kg/m^2), mean ± SD	23.6 ± 3.6	22.9 ± 3.4	24.3 ± 3.7	0.018
Comorbidities				
Diabetes (n)	24 (15.1%)	9 (11.1%)	15 (19.4%)	0.21
Hypertension (n)	122 (77.2%)	60 (74%)	62 (80.5%)	0.44
Pulmonary disease (n)	6 (3.7%)	5 (6.1%)	1 (1.2%)	0.23
Coronary artery disease (n)	32 (20.2%)	10 (12.3%)	22 (28.5%)	0.019
Cerebrovascular disease (n)	18 (11.3%)	8 (9.8%)	10 (12.9%)	0.71
Chronic kidney disease (n)	81 (51.2%)	32 (39.5%)	49 (63.6%)	0.003
Heart failure (n)	21 (13.2%)	10 (12.3%)	11 (14.3%)	0.81
Preoperative medications				
ACE inhibitors/ARB medication (n)	63 (39.8%)	22 (27.1%)	41(53.2%)	0.014
Calcium blocker (n)	24 (15.1%)	9 (11.1%)	15 (19.4%)	0.051
β blocker (n)	38 (24.0%)	18 (22.2%)	20 (25.9%)	0.71
Statin (n)	47 (29.7%)	18 (22.2%)	29 (37.6%)	0.051
Preoperative laboratory data				
Serum creatinine (mg/dL)	0.95 ± 0.41	0.83 ± 0.22	1.08 ± 0.52	0.0001
eGFR (mL/min/1.73 m^2)	62.0 ± 19.0	67.2 ± 18.8	56.6 ± 17.7	0.0003
Hemoglobin (g/dL)	13.0 ± 1.6	13.0 ± 1.4	13.0 ± 1.7	0.94
Albumin (g/dL)	3.9 ± 0.4	4.0 ± 0.3	3.9 ± 0.4	0.2
Preoperative hemodynamics				
Left ventricular ejection fraction (%), mean ± SD	65.7 ± 6.7	66.5 ± 6.0	64.9 ± 7.2	0.13
Pulmonary hypertension (n)	8 (5%)	4 (4.9%)	4 (5.1%)	1
Valvular disease (n)	26 (16.4%)	12 (14.8%)	14 (18.1%)	0.72
Surgical details				
Emergent operation (n)	25 (15.8%)	11 (13.5%)	14 (18.1%)	0.56
Previous cardiac surgery (n)	6 (3.7%)	3 (3.7%)	3 (3.8%)	1
Combined surgery (n)	45 (28.4%)	22 (27.1%)	23 (298%)	0.8
Bentall procedure (n)	11 (6.9%)	7 (8.6%)	4 (5.1%)	0.53
Coronary artery bypass grafting (n)	12 (7.5%)	2 (2.4%)	10 (12.9%)	0.015
Aortic valve replacement/plasty (n)	17 (10.7%)	10 (12.3%)	7 (9.0%)	0.61
Operation time (min), mean ± SD	414.6 ± 97.4	396.1 ± 79.0	434.0 ± 110.8	0.014
Cardiopulmonary bypass duration (min)	183.0 ± 57.8	174.5 ± 44.1	191.9 ± 68.4	0.059
Aortic cross-clamp time (min)	119.2 ± 44.8	114.0 ± 37.7	124.0 ± 51.0	0.18
Lower body ischemic time (min)	22.6 ± 16.1	18.9 ± 16.6	26.4 ± 14.6	0.003
Minimum core temperature (°C)	27.7 ± 2.4	27.9 ± 2.4	27.3 ± 2.2	0.07
Intraoperative blood product use (unit)				
Red blood cell (u)	6.1 ± 4.0	6.4 ± 4.0	5.7 ± 4.0	0.31
Fresh frozen plasma (u)	9.2 ± 3.8	8.6 ± 3.5	9.7 ± 3.8	0.067
Platelets (u)	16.5 ± 6.4	16.0 ± 7.0	16.8 ± 5.6	0.41
Perioperative drug use				
Dobutamine(n)	10 (6.3%)	3 (3.7%)	7 (9.0%)	0.28
Milrinone(n)	4 (2.5%)	2 (2.4%)	2 (2.5%)	1
Norepinephrine(n)	27 (17%)	14 (17.2%)	13 (16.8%)	1
Epinephrine(n)	2 (1.2%)	0 (0%)	2 (2.5%)	0.45
Carperitide(n)	65 (41.1%)	35 (43.2%)	30 (38.9%)	0.70
Landiorol(n)	48 (30.3%)	19 (23.4%)	29 (37.6%)	0.07
Nicardipine(n)	32 (20.2%)	13 (16.0%)	19 (24.6%)	0.25

AKI, acute kidney injury; SD, standard deviation.
*Comparing patients without AKI to patients with AKI.

analysis of risk factors for AKI defined using the KDIGO criteria from previous reports and univariate analysis in this study [11]. The confounding factors included sex, BMI, use of ACE inhibitors/ARBs, preoperative CKD, coronary artery disease, CPB time, and lower body ischemic time. Table 3 shows the results of multivariate analysis of the risk factors. Male sex (odds ratio [OR] 3.95, 95% confidence interval [95%CI] 1.56-8.27, $p=0.002$), ACE inhibitors/ARBs (OR 3.19, 95%CI 1.49-6.82, $p=0.003$), preoperative CKD (OR 2.47, 95%CI 1.17-5.23, $p=0.02$), prolonged CPB duration (OR 2.36, 95%CI 1.05-5.34, $p=0.04$), and prolonged lower body ischemic time during CPB (OR 2.2, 95%CI 1.05-4.6, $p=0.04$) were identified as independent risk factors for AKI following TAR.

MHCA compared to normothermic or mild hypothermic circulatory arrest. Among all patients enrolled in this study, a total of 115 patients experienced MHCA, whereas 43 patients experienced non-MHCA. The propensity score (PS) model incorporated seven variables, *i.e.*, sex, age, BMI, ACE inhibitors/ARBs, cerebral disease, left ventricular ejection fraction, and preoperative creatinine clearance (CCR). The PS model was conducted using multivariate logistic regression, in which the probability of receiving non-MHCA was estimated for each patient. Table 4 shows the results of the multivariate logistic regression model for receiving non-MHCA. Finally, the MHCA cases were matched to non-MHCA cases using the nearest neighbor algorithm method.

A total of 43 matched pairs were obtained using 8 significant variables. As shown in Table 5, patients with MHCA showed a trend toward a significantly lower rate of female sex (MHCA 26.1% vs. non-MHCA 48.8%, $p=0.0008$), BMI (MHCA 24.2 ± 3.6 vs. non-MHCA 22.3 ± 3.3, $p=0.003$), and preoperative creatinine clearance (MHCA 59.8 ± 11.2 mL/min vs. non-MHCA 68.1 ± 20.0 mL/min, $p=0.015$). After PS

Table 2 Outcome data

	All patients	No AKI	AKI	*P*-value*
Patients Population (n)	158	81	77	
Outcomes				
ICU length of stay (days), median ± IQR	5.0 [4.0, 7.0]	5.0 [3.0, 6.0]	5.0 [4.0, 7.0]	<0.001
Intubation time (hours), median ± IQR	14 [6.0, 20.7]	12 [6.0, 17.0]	15.0 [8.0, 42.0]	0.012
Major complication (n)	14 (8.8%)	5 (6.1%)	9 (11.6%)	0.34
Neurological complication (n)	6 (3.7%)	3 (3.7%)	3 (3.8%)	1
Renal replacement therapy (n)	1 (0.6%)	0 (0%)	1 (1.2%)	0.48
Infection (n)	2 (1.2%)	0 (0%)	2 (2.5%)	0.24
Redo surgery (n)	3 (1.8%)	2 (2.4%)	1 (1.2%)	1
Reintubation (n)	5 (3.1%)	0 (0%)	5 (6.4%)	0.025
90-day mortality (n)	1 (0.6%)	0 (0%)	1 (1.2%)	0.48

AKI, acute kidney injury; ICU, intensive care unit; IQR, interquartile range.
*Comparing patients without AKI to patients with AKI.

Table 3 Multivariate analysis of risk factors for AKI following TAR

Variables	Odds ratio	95% Confidence interval	*P*-value
Sex male	3.95	1.56–8.27	0.002
BMI	1.04	0.94–1.16	0.45
ACE-I/ARB	3.19	1.49–6.82	0.003
CKD	2.47	1.17–5.23	0.02
Coronary artery disease	1.82	0.74–4.51	0.19
CPB time >180 min	2.36	1.05–5.34	0.04
Lower body ischemic time >25 min	2.20	1.05–4.46	0.04

BMI, body mass index; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CKD, chronic kidney disease; CPB, cardiopulmonary bypass.

matching, the significance of these differences disappeared (Table 5), and the lower body ischemic time was significantly different between the 2 groups (MHCA 23.0±14.0 min vs. non-MHCA 13.6±17.4 min, $p=0.007$). Table 6 shows the major outcome measures after PS matching, and the results showed that AKI was not significantly different between the 2 groups (MHCA 41.9% vs. non-MHCA 37.2%, $p=0.83$).

Discussion

In this retrospective observational study, the incidence of postoperative AKI defined using the KDIGO criteria following TAR was 48.7%. In the first analysis, we found that male sex, ACE inhibitors/ARBs, preoperative CKD, prolonged CPB time, and prolonged lower body ischemic time were independent risk factors for AKI following TAR. In the second analysis, *i.e.*, the investigation of temperature management during CPB, our study indicated that, compared with moderate hypothermia circulatory arrest, mild hypothermia and normothermia circulatory arrest were weakly associated with worsening renal function after TAR.

The incidence of postoperative AKI in our study was relatively high at 48.7%. The incidence of AKI after aortic surgery ranges from 18% to 53% [12]. In recent years, the definition of AKI has become more sensitive, since early detection of AKI is important. The RIFLE criteria and the Acute Kidney Injury Network (AKIN) criteria have been used to monitor the severity and progression of AKI [13, 14]. In 2012 the KDIGO criteria emerged as a more sensitive diagnostic tool for detect-

Table 4 Multivariate analysis of receiving non-MHCA for propensity score analysis

Variables	Odds ratio	95% Confidence interval	*P*-value
Sex female	2.03	0.92–4.48	0.48
Age	0.98	0.95–1.02	0.48
BMI*	0.87	0.76–0.98	0.03
ACE-I/ARB medication	0.98	0.44–2.19	0.96
Cerebral disease	1.00	0.29–3.45	0.99
Ejection Fraction*	0.98	0.93–1.04	0.57
Preoperative CCR*	1.01	0.99–1.03	0.26

*Odds ratio for increase of BMI of one kg/m^2, one percent of Ejection Fraction, and one ml/min /1.73 m^2 of CCR, respectively.
BMI, body mass index; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin-Ⅱ receptor blocker; CCR, creatinine clearance.

Table 5 Major results of Propensity-matched data

Variables	Overall data			Propensity-matched data		
	MHCA (n=115)	Non-MHCA (n=43)	*P*-value	MHCA (n=43)	Non-MHCA (n=43)	*P*-value
Sex, female (n)	30 (26.1%)	21 (48.8%)	0.0008	16 (37.2%)	21 (48.8%)	0.83
Age (year), mean±SD	69.8±11.1	68.1±11.7	0.419	69.2±12.1	68.1±11.7	0.67
Body mass index (kg/m^2), mean±SD	24.2±3.6	22.3±3.3	0.003	22.7±3.1	22.3±3.3	0.49
ACE inhibitors/ARB medication (n)	48 (41.7%)	15 (34.9%)	0.47	18 (41.9%)	15 (34.9%)	0.51
Preoperative CCR (ml/min/1.73 m^2)	59.8±11.2	68.1±20.0	0.015	68.4±21.1	68.1±20.0	0.72
Chronic kidney disease (n)	64 (55.7%)	17 (39.5%)	0.077	20 (46.5%)	17 (39.5%)	0.66
Cerebrovascular disease (n)	14 (12.2%)	4 (9.3%)	0.781	7 (16.3%)	4 (9.3%)	0.52
Coronary artery disease (n)	26 (22.6%)	6 (14%)	0.272	9 (20.9%)	6 (14%)	0.57
Left ventricular ejection fraction (%)	65.8±6.8	65.7±6.7	0.944	66.4±5.9	65.7±6.7	0.61
Emergency operation (n)	18 (15.7%)	7 (16.3%)	1	4 (9.3%)	7 (16.3%)	0.52

MHCA, moderate hypothermia circulatory arrest; SD, standard deviation; ACE inhibitors, angiotensin converting enzyme inhibitors; ARB, angiotensin-Ⅱ receptor blocker; CCR, creatinine clearance; CPB, cardiopulmonary bypass.

Table 6 Major outcomes of Propensity-matched data

Variables	Overall data			Propensity-matched data		
	MHCA (n=115)	Non-MHCA (n=43)	*P*-value	MHCA (n=43)	Non-MHCA (n=43)	*P*-value
Operative information						
Operation time (min), mean ± SD	416.5 ± 102.4	409.5 ± 83.6	0.689	402.6 ± 76.3	409.5 ± 83.6	0.69
CPB time (min), mean ± SD	185 ± 61.3	177.7 ± 47.3	0.477	175.9 ± 40.0	177.7 ± 47.3	0.85
Aorta clamp time (min), mean ± SD	118.6 ± 46.3	120.9 ± 41.2	0.767	110.9 ± 33.7	120.9 ± 41.2	0.22
Lower body ischemic time (min), mean ± SD	26.2 ± 14.2	13.6 ± 17.4	0.001	23.0 ± 14.0	13.6 ± 17.4	0.007
Major complication (n)						
Acute kidney injury (n)	61 (53%)	16 (37.2%)	0.107	18 (41.9%)	16 (37.2%)	0.83
Neurological complication (n)	5 (4.3%)	1 (2.3%)	1	2 (4.7%)	1 (2.3%)	0.85

CPB, cardiopulmonary bypass; MHCA, moderate hypothermia circulatory arrest.

ing AKI. The strict definition of the KDIGO criteria may have been responsible for the high incidence of AKI in our study. On the other hand, the mortality rate and rate of major complications were lower in our study compared to previous reports [11]. As a result, we found that AKI following TAR was associated with prolonged ICU stay, and with the reintubation rate, but AKI was not associated with hard outcomes such as 90-day mortality, which is not consistent with the previous reports [15]. One possible explanation is that the mortality rate in this study was much lower than the average rate reported previously, and the difference was not statistically significant. However, patients with AKI experienced longer ICU stays in this study. These findings reinforce the notion that AKI has a significant impact on patient outcome, as well as a substantial impact in terms of medical costs and resources.

In our study, ACE inhibitors/ARBs were identified as risk factors for postoperative AKI. There is a lot of evidence of the benefits of ACE inhibitors/ARBs for the treatment of hypertension, heart failure, ischemic heart disease and proteinuric CKD. However, ACE inhibitors/ARBs are considered to be associated with AKI in various settings [16,17], particularly during acute hypovolemic illness. Therefore, patients with CKD should stop taking these agents if they become acutely ill [18]. The perioperative period is also clinically vulnerable and vascular surgery is one of the most invasive procedures for patients. Considering all the above, it is reasonable to stop ACE inhibitors/ARBs before surgery.

It should also be noted that, in this study, none of the intravenously administered drugs were associated with AKI following TAR. Numerous pharmacological agents including inotropes, statins and erythropoietin have failed to demonstrate any benefit in terms of AKI prevention following cardiac surgery [19,20]. There are currently no drugs that can help prevent AKI after cardiovascular surgery. For this reason, it might be important to focus not on the beneficial pharmacological strategies but on the avoidance of potentially harmful drugs, such as non-steroidal anti-inflammatory drugs or ACE inhibitors/ARBs.

Additionally, neither the amount of transfusion nor the perioperative hemoglobin level was a risk factor for postoperative AKI in this study. These results may indicate that the perioperative transfusion strategies should focus on oxygen delivery or the prevention of coagulopathy rather than AKI prevention.

In accordance with other studies, our findings demonstrated that preexisting CKD is a strong predictor for postoperative AKI, and care should be taken when treating patients with CKD during the perioperative period.

In this study, the lower body ischemic time affected the incidence of impaired renal function. Prolonged lower body ischemic time may cause postoperative AKI following TAR by promoting renal ischemia. Since the lower body ischemic time is determined based on the complexity of the distal anastomosis, prompt anastomosis is needed to restore and improve the renal perfusion. Amano *et al.* reported that lower body ischemic time is a risk factor for AKI following type A acute aortic dissection [21]. Similarly, the prolonged CPB time was associated with worsening renal function in this study. Importantly, the lower body ischemic time and CPB time are both modifiable risk factors, suggest-

ing the need to focus more precisely on these time-related parameters.

In the second analysis, in which temperature management during CPB was investigated, our results indicated that neither mild hypothermia nor normothermia circulatory arrest was associated with worsening of renal function after TAR compared to moderate hypothermia circulatory arrest. Historically, deep hypothermic temperature has been reported to be associated with coagulopathy, increased systemic inflammatory response, and increased risk of organ dysfunction. In response to this, several institutions have implemented warmer temperatures for aortic surgery. Our own institution also adopted normothermia or mild hypothermia circulatory arrest as a standard technique. Importantly, surgeons tend to adopt higher temperature management for their patients with normal cardiac function and no apparent preoperative neurological complications or CKD. The contributors to PS matching were determined based on these factors.

However, the ideal temperature for surgical repair of the aortic arch remains unclear. Previous studies have shown similar results regarding temperature management for postoperative AKI. Tian *et al.* reported that MHCA was not associated with a higher incidence of AKI than DHCA after aortic surgery for acute dissection [22]. Tsai *et al.* concluded that MHCA is a safe and effective technique for organ protection in aortic surgery with low mortality and morbidity [23]. Meanwhile, Fang reported that MHCA was not superior to DHCA in decreasing AKI following TAR in patients with type A aortic dissection [24]. These reports indicate that the incidence of AKI after vascular surgery is similar between DHCA and MHCA. This study investigated the effect of the higher temperature management compared with MHCA on renal function following TAR.

Our data demonstrated that mild hypothermia/normothermia was not associated with AKI following TAR. Additionally, the neurological outcomes were similar in both patients with and those without AKI. Our data suggest that we can choose temperature management depending on the predisposing factors of the individual patient. In general, the organ-protective effect of lower temperature management during CPB is partly produced by reducing oxygen consumption, but many factors during vascular surgery, such as postoperative inflammatory response and coagulopathy, may offset the organ protective effect. It is reasonable to focus on the most vulnerable organ on a case-by-case basis. In conclusion, temperature management during CPB did not necessarily affect the patient outcomes in our study.

Our study has several limitations. First, this study was a single-center retrospective study, and was not sufficiently powered to evaluate outcomes precisely. Because of its retrospective nature, there may have been biases that were not accounted for in the results. Furthermore, after PS matching, each group had only 43 patients in the second analysis, which is below the necessary power for generalization. Second, the patients' backgrounds, especially the miscellaneous underlying diseases, were not homogeneous. In additim, the TAR encompasses various surgical techniques, depending on accessibility, emergency status, and availability of cross-clamp sites. More importantly, lower body ischemic time, a modifiable risk factor in this study, was dependent on the skill of the surgeon, hence our results do not necessarily apply to the strategies at other facilities. In addition, we included 25 emergency cases in this study. All these patients were hemodynamically stable, but their preoperative laboratory data, including creatine levels, were extracted in an emergency setting, which may have caused some bias. In addition, CT contrast was used before all emergency cases, which may have had an adverse effect on renal function, although the univariate analysis revealed no statistically significant difference between patients undergoing emergent surgery and those who underwent elective surgery. Third, perioperative hemodynamic status was not considered in this study, that might have biased the results. Finally, lower body ischemic time was significantly lower in the non-MHCA group than in the MHCA group in the matched analysis, but the rate of postoperative AKI did not differ significantly between patients in the non-MHCA group and those in the MHCA group. This finding is not consistent with the multivariate analysis. This discrepancy needs to be examined in further studies.

In summary, we investigated the postoperative AKI following TAR using the KDIGO criteria. Our data indicate that the independent risk factors for AKI following TAR include ACE inhibitors/ARBs, male sex, preoperative CKD, prolonged CPB duration, and prolonged lower body ischemic time. A mild hypothermia/normothermia strategy during CPB was not associated with a higher incidence of AKI following TAR

compared to moderate hypothermia. Future studies may explore the modifiable risk factors for postoperative AKI such as lower body ischemic time and shortened CPB time.

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