Tohoku J. Exp. Med., 2022, **258**, 129-141

Worsening Right Ventricular Function during Cardiac Surgery Is a Strong Predictor of Postoperative Acute Kidney Injury: A Prospective Observational Study

Yasuaki Tohi,[1] Yusuke Takei,[1] Kotaro Nochioka,[2] Hiroaki Toyama[1] and Masanori Yamauchi[1]

[1]Department of Anesthesiology and Perioperative Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
[2]Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

This prospective, observational study was conducted in a university hospital to verify that intraoperative worsening of right ventricular function causes cardiac surgery-associated acute kidney injury. Adult patients undergoing cardiac surgery under mid-sternal incision with cardiopulmonary bypass were included. Echocardiographic right and left ventricular function parameters were measured before and after bypass and compared using the Wilcoxon signed-rank test. Perioperative serum creatinine values at baseline and within the first 48 hours postoperatively were measured for the diagnosis of acute kidney injury. Spearman rank-order correlation (ρ) and receiver operating characteristic analysis were used to reveal relationships. Thirty-four patients were evaluated. Right ventricular ejection fraction (56.2 ± 7.0 vs. 51.6 ± 7.2%; P = 0.0002), right ventricular fractional area change (49.1 ± 6.4 vs. 46.6 ± 5.3%; P = 0.0201; mean ± standard deviation), and left ventricular ejection fraction (57.4 ± 6.1 vs. 51.7 ± 6.2%; P < 0.0001) were significantly decreased. Central venous pressure was significantly increased (7.2 ± 3.5 vs. 9.7 ± 3.7; P = 0.0001). Serum creatinine values increased from 0.82 [0.70-1.08] to 0.99 [0.82-1.54] mg/dL (P < 0.0001; median [interquartile range]). Changes in right ventricular ejection fraction, fractional area change, and right ventricular strain during cardiovascular surgery were significantly correlated with changes in serum creatinine values. Fractional area change exhibited the strongest correlation (ρ = −0.61, P < 0.0001). Change in fractional area change showed an area under the curve of 0.902 and a cutoff value of −2.1, which predicted acute kidney injury with 92% sensitivity, 73% specificity, and 79% accuracy. The functions of both ventricles were decreased after cardiopulmonary bypass. Worsening right ventricular function was independently correlated with postoperative renal dysfunction, and fractional area change was the strongest predictor of cardiac surgery-associated acute kidney injury.

Keywords: acute kidney injury; cardiac surgery; right ventricular fractional area change; right ventricular function; serum creatinine
Tohoku J. Exp. Med., 2022 October, **258** (2), 129-141.
doi: 10.1620/tjem.2022.J064

Introduction

Acute kidney injury (AKI) is associated with poor prognosis in patients in the intensive care unit (ICU) (Brochard et al. 2010). The incidence of cardiac surgery-associated acute kidney injury (CSA-AKI) is as high as 30% (Rosner and Okusa 2006). During cardiac surgery, careful circulatory management is performed by monitoring systemic and pulmonary arterial blood pressures, cardiac index (CI), and cardiac motion using an arterial catheter, a pulmonary arterial catheter, and transesophageal echocardiography. The cardio-renal connection that links cardiac and renal functions with each other through systemic congestion has been the focus of researchers (Herzog et al. 2011). However, a definite goal to inhibit CSA-AKI in the perioperative period has not yet been established. Recently,

Received May 31, 2022; revised and accepted July 22, 2022; J-STAGE Advance online publication August 4, 2022
Correspondence: Hiroaki Toyama, M.D., Ph.D., Department of Anesthesiology and Perioperative Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.
e-mail: h-toyama@umin.ac.jp

it was reported that postoperative right ventricular (RV) dysfunction was not associated with CSA-AKI (Yockelson et al. 2019). In contrast, the relationship between changes in RV function during cardiac surgery and postoperative renal function has not been elucidated. Therefore, we conducted an observational study to verify the hypothesis that intraoperative worsening of RV function contributes to the development of CSA-AKI. In this study, we analyzed the relationship between changes in RV function and renal function during the perioperative period of cardiovascular surgery.

Materials and Methods

This study was a prospective, observational, single-center study at Tohoku University Hospital that was conducted between August 2019 and July 2020. This study was approved by the Tohoku University Ethics Committee (2019-1-257), and registered at University Hospital Medical Information Network (UMIN000045617). Written informed consent was obtained from all the study participants.

Study setting and participants

The present study was conducted at a university hospital, and it included patients aged ≥ 20 years who underwent scheduled primary cardiovascular surgery involving a midsternal incision, cardiopulmonary bypass (CPB), and cardiac arrest without right heart surgery. The exclusion criteria of this study were as follows: on-pump beating surgery, cardiac pacing, use of cardiac assist devices such as left ventricular assist devices, veno-arterial extracorporeal membrane oxygenation, and intra-aortic balloon pumping, presence of chronic atrial fibrillation, intracardiac shunts, regional wall motion abnormality, moderate or severe tricuspid regurgitation, high suspicion of pulmonary hypertension in cases with a tricuspid regurgitation pressure gradient of over 45 mmHg, contraindications to transesophageal echocardiography and/or a pulmonary arterial catheter, and hemodialysis. Further, patients who underwent the following during the study were also excluded from the analysis: additional right heart surgery, conversion to off-pump surgery, pacing due to intraoperative atrioventricular block or sinus node syndrome, the abovementioned cardiac assist device, and monitoring failure of transesophageal echocardiography and pulmonary arterial catheter during surgery. Patients with preoperative RV dysfunction, such as a fractional area change (FAC) of less than 35% or a tricuspid annular plane systolic excursion (TAPSE) of less than 17 mm, and those with preoperative chronic kidney disease (CKD) were included.

Echocardiographic and hemodynamic measurements

In the operating room, the patient's electrocardiogram, non-invasive blood pressure, and pulse oximetry were monitored, and an intravenous line and arterial catheter were placed. After the induction of general anesthesia using intravenous anesthetics, a central venous catheter and pulmonary arterial catheter were placed via the internal jugular vein, and a transesophageal echocardiography probe was inserted (X9-2t probe, EPIC 7® ultrasound system, Philips Medical Systems, Andover, MA, USA). A circulatory monitoring system (Hemosphere™, Edwards Lifesciences, Irvine, CA, USA), a bedside monitor (BSM-6701™, Nihon Kohden, Tokyo, Japan), and an electronic anesthesia record (PrimeGaia™, Nihon Kohden) were used.

Intraoperative echocardiographic and hemodynamic parameters were measured shortly before pericardiotomy and after chest closure. A cardiovascular anesthesiologist certified by the board of echocardiography in Japan measured the transesophageal echocardiography parameters, following the recommendations for cardiac chamber quantification from the American Society of Echocardiography and the European Association of Cardiovascular Imaging (Lang et al. 2015). The cardiovascular anesthesiologist created images of the tricuspid valve annulus. The ultrasonic beam ran parallel to the contraction direction of the RV free wall in a deep trans-gastric view, and the M-mode images of the tricuspid valve annulus were acquired for the calculation of TAPSE. Thereafter, during cessation of breathing, three-dimensional full-volume datasets of both the RV and left ventricle were acquired in a mid-esophageal view with the six-beat mode setting of the ultrasound system to obtain high temporal resolution (≥ 15 Hz).

Subsequently, RV ejection fraction (RVEF), RV FAC, and RV strain were calculated offline from the three-dimensional images using a dedicated software (4D RV-FUNCTION©, TomTec Imaging Systems GmbH, Unterschleissheim, Germany) (Fig. 1). TAPSE was then determined using a basic measurement software (TomTec Imaging Systems GmbH). The RVEF was calculated from the RV end-diastolic volume and RV stroke volume (RVSV), which was measured from the RV end-diastolic volume and RV end-systolic volume; FAC was calculated from the RV end-diastolic area and end-systolic area; and RV strain was calculated by measuring the longitudinal length of the RV free wall by tracking the border of the cardiac chamber and endocardium using a software (4D LV-FUNCTION©, TomTec Imaging Systems GmbH). In this study, RV strain was expressed as an absolute value. The left ventricular ejection fraction (LVEF) was calculated by tracking the border of the left ventricular chamber and endocardium using the aforementioned software.

Before analyzing the echocardiographic parameters, the cardiovascular anesthesiologist measured the aforementioned RV parameters of randomly sampled patients to verify intra-observer validity using a Bland-Altman plot. The correlation coefficient (r), mean difference, and standard error were as follows: RVEF—0.70, −0.70, and 1.60; FAC—0.83, −0.60, and 1.01; RV strain—0.85, −1.7, and 0.85; TAPSE—0.98, −0.003, and 0.18, LVEF—0.89, −0.66, and 0.81, respectively.

Hemodynamic data of CI, central venous pressure

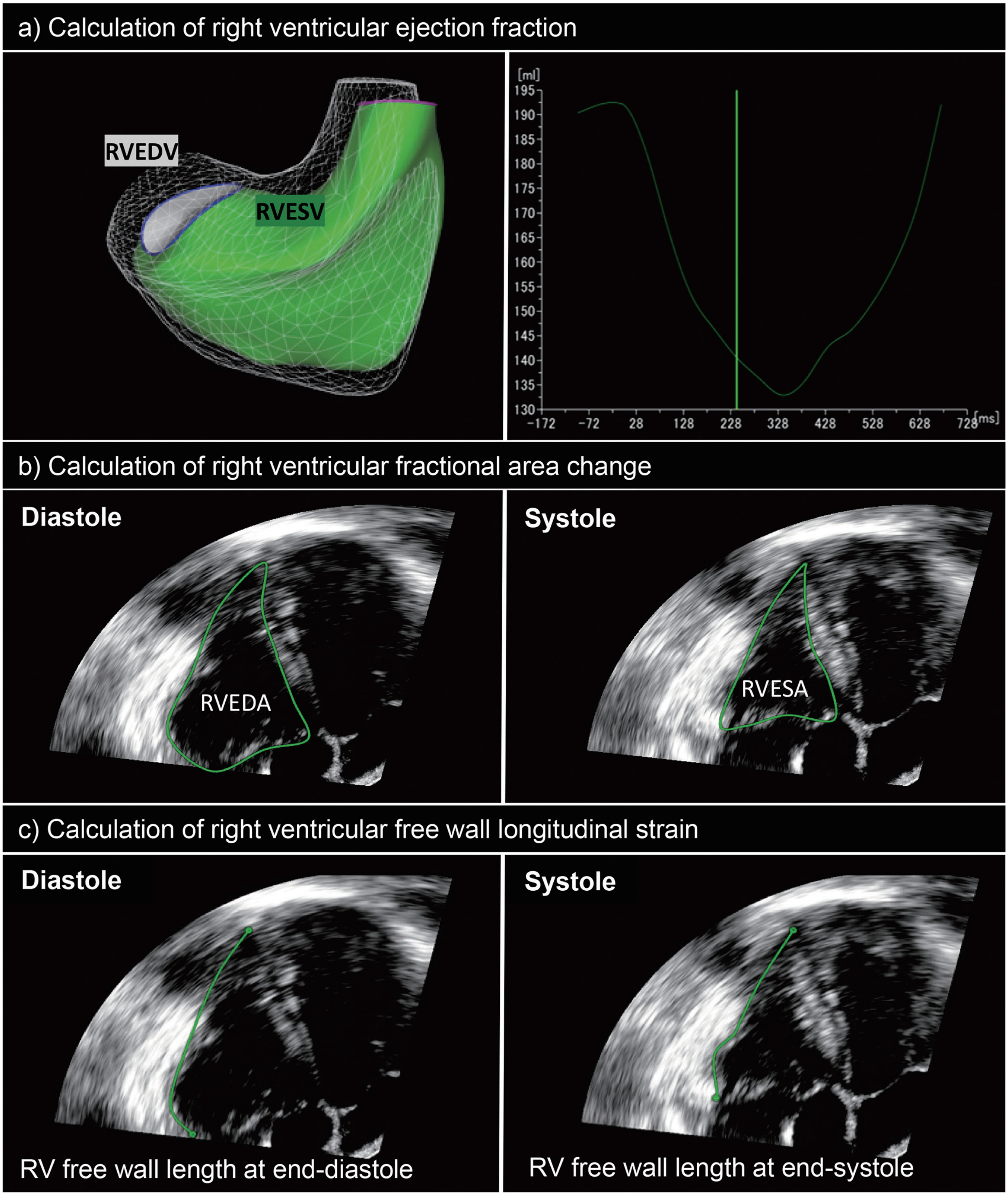

Fig. 1. Calculation of right ventricular ejection fraction (RVEF), right ventricular fractional area change (FAC), and right ventricular free wall longitudinal strain (RV strain).
a) Calculation of RVEF as the difference in volume. Right ventricular end-diastolic volume (RVEDV; white) and end-systolic volume (RVESV; green) were determined using a three-dimensional model of the right ventricle during the cardiac cycle. b) Calculation of FAC as the difference in area. The right ventricular end-diastolic area (RVEDA) and end-systolic area (RVESA) were calculated by tracking the right ventricle. c) Calculation of RV strain as the difference in free wall length. Right ventricular end-diastolic free wall length and end-systolic free wall-length were calculated by tracking the right ventricle.

(CVP), pulmonary arterial systolic pressure (PASP), and mean arterial pressure (MAP) were also recorded during the measurement period. Effective pulmonary arterial elastance (Epa) was calculated from the mean pulmonary arterial pressure using a pulmonary arterial catheter and the above-mentioned RVSV as follows:

Epa = mean pulmonary arterial pressure/RVSV

Measurements of renal function and definition of AKI

Age, sex, height, weight, underlying disease, preoperative medication, surgical indication, transthoracic echocardiographic data, serum creatinine values (sCr), and preoperative estimated glomerular filtration rates of the patients were extracted from their medical records.

We defined a preoperative estimated glomerular filtration rate of < 60 mL/min/1.73 m^2 (CKD stage G3a or higher) as preoperative CKD in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO)-CKD guidelines (Stevens et al. 2013). Regarding the evaluation of renal function after cardiovascular surgery, sCr was measured at ICU admission, on the first postoperative day, and on the second postoperative day (within the first 48 hours postoperatively). We extracted the peak sCr of the three measurements, and we defined an increase in sCr of ≥ 0.3 mg/dL or ≥ 1.5 times the baseline value at the postoperative period (AKI stage 1 or higher) as an AKI in accordance with the KDIGO-AKI guidelines (Khwaja 2012). Because most patients who underwent cardiovascular surgery were administered diuretics perioperatively and received hemofiltration during CPB, urine volume was not included for AKI diagnosis.

Extraction of other parameters

Other intraoperative information was extracted from the patients' anesthetic records, including CPB duration, intraoperative nadir hematocrit value, and vasoactive-inotropic score (VIS) (Gaies et al. 2010). The VIS was calculated based on intraoperative maximum dosing rates of inotropic and vasoactive agents as follows:

VIS = dopamine [µg/kg/min] + dobutamine [µg/kg/min] + milrinone [µg/kg/min] × 10 + epinephrine [µg/kg/min] × 100 + norepinephrine [µg/kg/min] × 100 + vasopressin [u/kg/min] × 10,000

Statistical analysis

All data analyses were performed using the JMP Pro 15 statistical software (SAS Instruments, Inc., Cary, NC, USA). Parametric data are expressed as the mean ± standard deviation. Nonparametric data are expressed as the median [interquartile range], and preCPB and postCPB values were compared using the Wilcoxon signed-rank test. Categorical variables are expressed as numbers and percentages. Spearman rank-order correlation (ρ) was used for correlation analyses between the differences of preCPB and postCPB values (Δ) in RVEF, FAC, RV strain, TAPSE, LVEF, CI, CVP, PASP, MAP, Epa, CPB duration, intraoperative nadir hematocrit value, and VIS, along with the difference between preoperative values and postoperative peak values (Δ) in sCr. Statistical significance was set at $P < 0.05$.

Additionally, receiver operating characteristic analysis was performed between RV function parameters and the presence of AKI to evaluate the accuracy of the prediction of AKI. The cutoff values were determined using the Youden index (J): the maximum value of sensitivity plus specificity minus 1. The goodness-of-fit of the model was evaluated using chi-squared statistics.

Power Calculations were performed using the G*power version 3.1 (Faul et al. 2009), which revealed that 26 patients were required to demonstrate a Spearman's correlation coefficient of > 0.5 when alpha and beta were set to 0.05 and 0.2, respectively. Additionally, considering an incidence of consent withdrawal of ~50%, our target sample size was set at 60 patients.

Results

Study population

During the study period, 64 patients were enrolled, of which 19 patients were excluded due to preoperative exclusion criteria, 1 patient did not consent to the study, and 10 patients were excluded according to the intraoperative exclusion criteria. Therefore, we analyzed the data of 34 patients (Fig. 2). The patients' characteristics are summarized in Table 1. Nineteen patients were hypertensive (55.8%), 13 patients had preoperative CKD (38.2%), and 0 patients had an FAC of less than 35% or a TAPSE of less than 17 mm. Aortic valve disease was the most common indication for surgery, and aortic replacement was the most frequently performed procedure.

Changes in echocardiographic and hemodynamic data

Intraoperative changes in RV function and hemodynamic parameters are shown in Fig. 3. Regarding RV function parameters, RVEF (56.2 ± 7.0% vs. 51.6 ± 7.2%; P = 0.0002), FAC (49.1 ± 6.4% vs. 46.6 ± 5.3%; P = 0.0201), TAPSE (20.3 ± 3.7 mm vs. 11.6 ± 3.6 mm; P < 0.0001), and LVEF (57.4 ± 6.1% vs. 51.7 ± 6.2%; P < 0.0001) were significantly decreased, but RV strain (25.7 ± 4.9% vs. 24.0 ± 5.9%; P = 0.1513) was not. For the hemodynamic parameters, CVP (7.2 ± 3.5 mmHg vs. 9.7 ± 3.7 mmHg; P = 0.0001) was significantly increased, and MAP (72.1 ± 8.4 mmHg vs. 64.7 ± 9.3 mmHg; P = 0.0003) was significantly decreased. However, the CI (2.71 [2.47-3.17] L/min/m^2 vs. 2.86 [2.56-3.59] L/min/m^2; P = 0.06), PASP (28.0 ± 8.1 mmHg vs. 26.5 ± 5.6 mmHg; P = 0.2950), and Epa (0.24 [0.17-0.31] mmHg/mL vs. 0.26 [0.22-0.33] mmHg/mL; P = 0.0651) did not significantly change.

Changes in renal function and incidence of AKI

The preoperative sCr of the study participants was 0.82 [0.70-1.08] mg/dL, which increased significantly to 0.99 [0.82-1.54] mg/dL at the peak within the first 48 h after surgery (P < 0.0001) (Fig. 4). AKI occurred in 35% of all patients (n = 12; stage 1 [n = 10], stage 2 [n = 2]), and the incidences of AKI in patients with and without preoperative CKD were 54% (n = 7) and 24% (n = 5), respectively. There were no patients who required hemodialysis and no deaths during the patients' hospital stays.

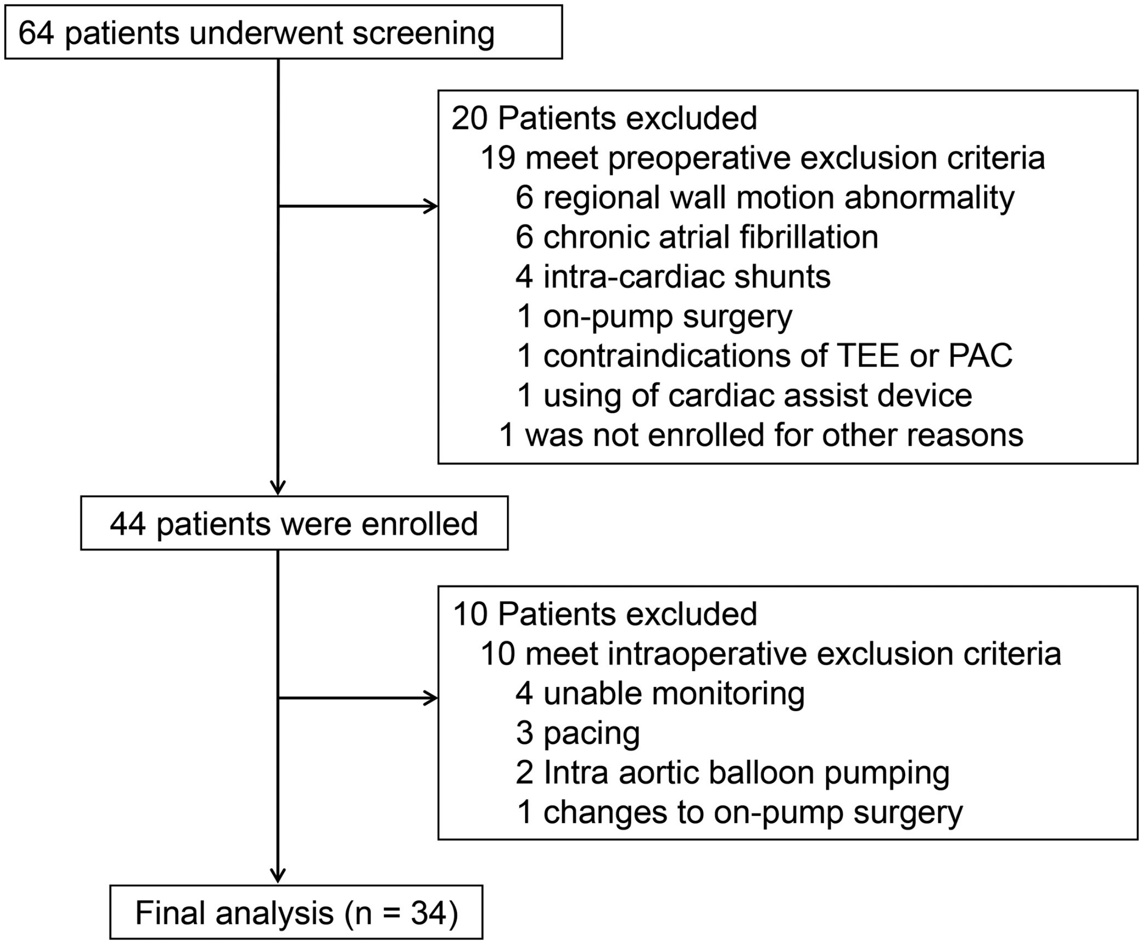

Fig. 2. The study population comprised 64 patients who underwent primary cardiovascular surgeries, which were performed between August 2019 and July 2020 in our facility.
Twenty patients were excluded during the preoperative screening. Furthermore, 10 patients were excluded in line with the intraoperative criteria. A final 34 patients were analyzed in our study.
PAC, pulmonary arterial catheter; TEE, transesophageal echocardiography.

Other parameters

The durations of CPB and aortic cross clamp were 231 ± 91 min and 152 ± 64 min, respectively, and the nadir hematocrit value was 24.9 ± 5.1%. The VIS was 0.94 [0-2.00].

Relationships between intraoperative parameters and postoperative renal function

Significant correlations were identified between ΔsCr and the changes in RV function parameters including ΔRVEF ($\rho = -0.39$, P = 0.0226), ΔFAC ($\rho = -0.61$, P < 0.0001), and ΔRV strain ($\rho = -0.40$, P = 0.0196), but this was not identified with ΔTAPSE ($\rho = 0.01$, P = 0.9514) (Fig. 5). Among these parameters, ΔFAC showed the strongest and most significant correlation with ΔsCr. Changes in other parameters were not significantly correlated with ΔsCr, including: ΔLVEF (P = 0.5522), ΔCI (P = 0.2925), ΔCVP (P = 0.1515), ΔPASP (P = 0.0672), ΔMAP (P = 0.8791), ΔEpa (P = 0.1032), preoperative sCr value (P = 0.0545), CPB duration (P = 0.1270), intraoperative nadir hematocrit value (P = 0.8955), and VIS (P = 0.7093). Additionally, multiple regression analysis between ΔsCr and ΔFAC, preoperative sCr value, and the CPB duration was performed, and this revealed that ΔFAC was most significantly correlated with ΔsCr (P = 0.0023). The receiver operating characteristic curves for the detection of AKI are shown in Fig. 6. ΔFAC showed the highest area under the curve (AUC) of 0.902 (95% confidence interval, 0.743-0.967), which was significantly higher than that of ΔTAPSE (AUC = 0.581, 95% confidence interval, 0.363-0.772) (P = 0.0191). The cutoff values of RV parameters were: ΔRVEF = −6.37, ΔTAPSE = −5.76, ΔFAC = −2.1, and ΔRV strain = −0.2. When the cutoff value of ΔFAC, −2.1, was applied to the patients in this study, the incidences of AKI in all patients, those with preoperative CKD, and those without CKD were 35%, 54%, and 24%, respectively (Fig. 7). For AKI diagnosis in all patients, those with preoperative CKD, and those without CKD, the sensitivities of ΔFAC ≥ −2.1 were 0.92, 0.86, and 1.0, respectively; the specificities of ΔFAC ≥ −2.1 were 0.73, 1.0, and 0.63, respectively; and the accuracies of ΔFAC ≥ −2.1 were 0.79, 0.92, and 0.71, respectively. Interestingly, post hoc analysis indicated that

Table 1. Characteristics of the participants.

Demographics	Mean ± SD, n (%), or median [interquartile range]
Age (years)	68.7 ± 12.0
Sex (male/female)	11/23
Body mass index (kg/m^2)	24.0 ± 3.5
Body surface area (m^2)	1.65 ± 0.16
Medical history	
Hypertension, n (%)	19 (55.8)
Dialysis, n (%)	0 (0.0)
Chronic obstructive pulmonary disease, n (%)	7 (20.6)
Diabetes mellitus, n (%)	4 (11.7)
Cerebrovascular disease, n (%)	9 (26.4)
Old myocardial infarction, n (%)	0 (0.0)
Treatments	
Beta-blockers, n (%)	7 (20.6)
ACEI or ARB, n (%)	23 (67.6)
Calcium channel-blockers, n (%)	23 (67.6)
Preoperative transthoracic echo findings	
IVST/PWT (mm)	10.0 [9.0-11.0]/10.0 [9.0-11.0]
LVDd (mm)	49.0 [43.8-54.5]
LVEF (%)	63.0 [59.8-69.3]
E/e’	9.5 [8.2-13.6]
RVD-mid (mm)	31.5 [28.8-34.3]
RVFAC (%)	43.2 [38.5-46.2]
TAPSE (mm)	19.8 [18.1-21.5]
Tr-PG (mmHg)	21.0 [16.5-24.0]
IVC (mm)	12.0 [10.0-15.0]
Renal function	
Blood urea nitrogen (mg/dL)	17.5 [15.8-23.0]
Serum creatinine (mg/dL)	0.82 [0.70-1.08]
eGFR (mL/min/1.73 m^2)	63.5 [51.8-81.5]
Chronic kidney disease, n (%)	13 (38.2)
Primary disease	
Aortic regurgitation, n (%)	12 (35.2)
Aortic stenosis, n (%)	11 (32.3)
Mitral regurgitation, n (%)	2 (5.9)
Mitral stenosis, n (%)	1 (2.9)
Angina pectoris, n (%)	8 (23.5)
Thoracic aneurysm, n (%)	10 (29.4)
Rupture of Valsalva sinus aneurysm, n (%)	2 (5.9)
Annuloaortic ectasia, n (%)	2 (5.9)
Tumor, n (%)	2 (5.9)
Type of surgery	
Aortic valve replacement, n (%)	15 (5.9)
Total arch replacement, n (%)	6 (5.9)
Complex procedure*, n (%)	6 (5.9)
Aortic root repair, n (%)	4 (5.9)
Cardiac tumor resection, n (%)	1 (5.9)
Mitral valve repair, n (%)	1 (5.9)
Coronary artery bypass grafting, n (%)	1 (5.9)

SD, standard deviation; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; E/e', The ratio of early trans-mitral flow velocity to early diastolic velocity of the mitral annulus; IVC, diameter of the inferior vena cava; IVST/PWT, interventricular septal thickness/posterior left ventricular wall thickness; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RVD-mid, right ventricular maximum mid transverse diameter; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; Tr-PG, tricuspid regurgitation pressure gradient.

*Complex procedure; Coronary artery bypass grafting with aortic valve replacement (2), Ascending aortic replacement with aortic valve replacement (2), Coronary artery bypass grafting and mitral valve repair with aortic valve replacement (1), Aortic root repair with aortic valve replacement (1).

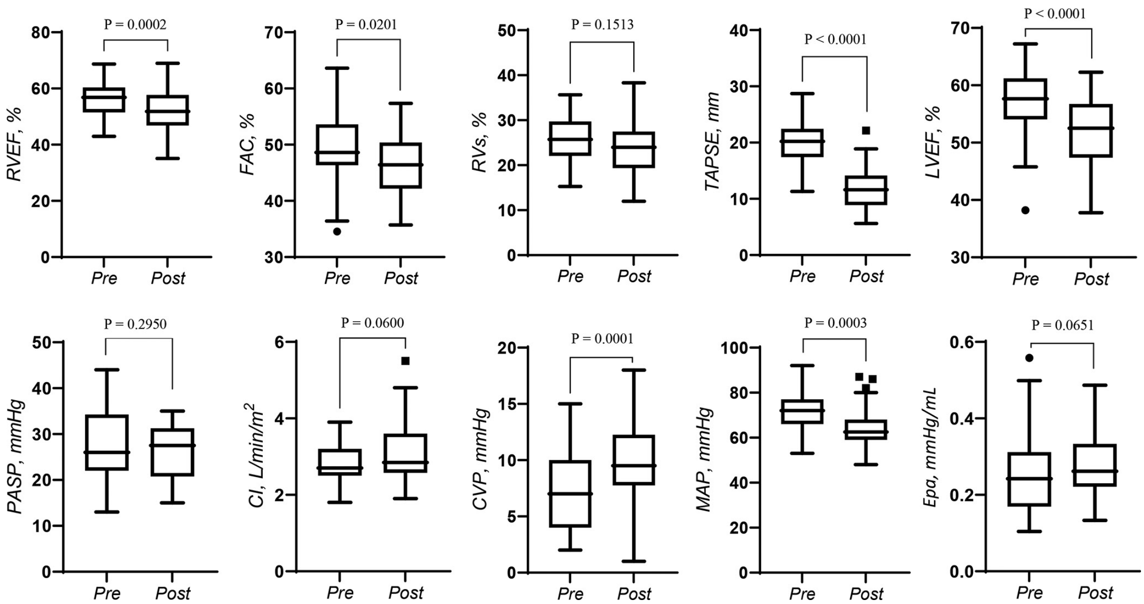

Fig. 3. Right ventricular and hemodynamic parameters before pericardiotomy (pre) and after chest closure (post).
The measured values at each time point are shown in a boxplot with the first quartile, median, third quartile, maximum, minimum, and outliers. Right ventricular free wall strain values are expressed by absolute values.
CI, cardiac index; CVP, central venous pressure; Epa, effective pulmonary arterial elastance; FAC, fractional area change; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PASP, pulmonary arterial systolic pressure; RVEF, right ventricular ejection fraction; RVs, right ventricular free wall strain; TAPSE, tricuspid annular plane systolic excursion.

the preoperative FACs of the patinets who had developed AKI (n = 12) were higher than those of the patients who had not developed AKI (52.3 ± 4.8 vs. 47.4 ± 6.6; P = 0.03). Additionally, the two patients with AKI that had progressed to AKI stage 2 had decreased FACs after the surgery (ΔFACs = −3.17 and −10.44), while only one patient had preoperative CKD.

Discussion

We investigated the correlation between RV function and renal function in the perioperative period of patients with cardiac arrest who underwent cardiovascular surgery without right heart intervention. We observed that RV parameters such as RVEF, FAC, and TAPSE were significantly decreased after CPB. ΔRVEF, ΔFAC, and ΔRV strain were related to an increase in ΔsCr, and ΔFAC was the most strongly related; furthermore, this correlation persisted even after adjusting for CPB duration and preoperative renal function. By applying the cutoff value of ΔFAC to patients undergoing cardiovascular surgery without right heart intervention, we can predict the incidence of CSA-AKI with a sensitivity of 0.92, a specificity of 0.73, and an accuracy of 0.79, and in patients with preoperative CKD, with a sensitivity of 0.85, a specificity of 1.0, and an accuracy of 0.92. These results suggest that changes in RV function during cardiovascular surgery can affect postoperative renal function, particularly in patients with CKD, and the deterioration of RV function is a strong predictor of CSA-AKI.

RV dysfunction after cardiovascular surgery is related to postoperative outcomes in various cardiac surgeries, such as valve replacement, heart transplantation, and implantation of a left ventricular assist device (Hosenpud et al. 2000; Lampert and Teuteberg 2015; Cremer et al. 2018; Magunia et al. 2018). RV failure after cardiovascular surgery can occur without right heart intervention (Cremer et al. 2018). Cardiovascular surgery itself causes RV dysfunction; therefore, evaluating the RV function by FAC and pre-

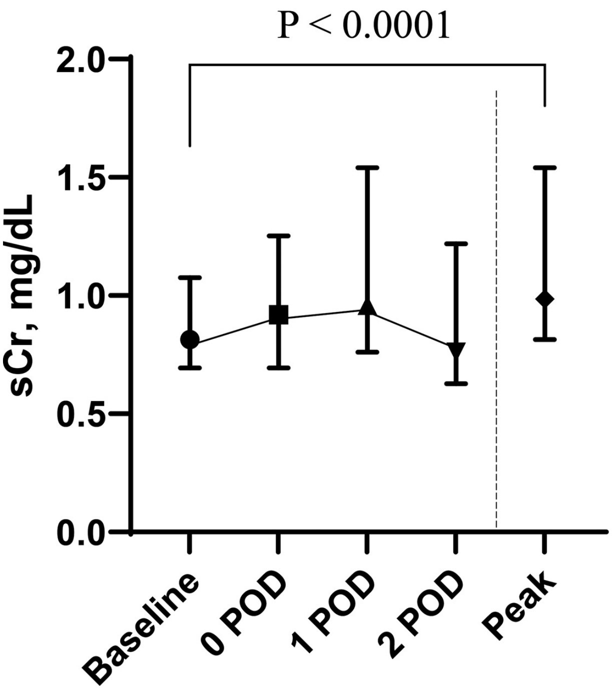

Fig. 4. Measured values of serum creatinine at each time point.
Baseline (preoperative), 0POD (intensive care unit admission), 1POD (first postoperative day), 2POD (second postoperative day), and Peak (peak values of postoperative measurements) are shown in a line with the first quartile, median, and third quartile. All postoperative measurements were performed within the first 48 h after surgery.

venting a decline in RV function might decrease the incidence of CSA-AKI and reduce mortality. Yockelson et al. (2019) showed that postoperative RV function and CSA-AKI were not related. Meanwhile, Cremer et al. (2018) reported that changes in RV function before and after cardiac surgery affected prognosis. Therefore, we hypothesized that changes in perioperative ventricular function, especially changes in RV function, affected postoperative renal function. The exclusion criteria of our study did not contain preoperative RV dysfunction because we considered the worsening RV function during surgery to be more important for AKI development than preoperative RV function. Moreover, Maffessanti et al. (2012) reported that preoperative RV function was not related to perioperative changes in indicators of RV function. We evaluated the relationships between changes in various indicators of RV function and renal function and found that intraoperative declines in FAC and RVEF were associated with the development of CSA-AKI. The result of our study was different from that of a previous study (Yockelson et al. 2019), which might be because the RV function indicators measured in the previous study could not accurately reflect the change in RV function. Additionally, Matsui et al. (2012) showed that renal tubular disorders occurred shortly after surgery and sCr subsequently increased. The previous study by Yockelson et al. (2019) evaluated RV function only after surgery, while our study evaluated RV function during surgery, which might help in determining the relationship between changes in RV function and renal function.

Thus far, RV function has not been well discussed because the detection of perioperative deterioration in RV function is difficult. Other reasons involve the detection of deterioration in RV function; the right ventricle has a complex three-dimensional structure, and the gold standard of volume analysis is magnetic resonance imaging (MRI), which is not possible during cardiac surgery. When using transesophageal echocardiography during cardiovascular surgery, long axis contraction of the right ventricle changes after pericardiotomy (Unsworth et al. 2010; Lindqvist et al. 2012; Maffessanti et al. 2012). Therefore, the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend the use of RV parameters, such as RVEF and FAC, to reflect the global RV function during cardiac surgery rather than TAPSE (Lang et al. 2015). According to the recommendations, we measured parameters that represented RV function, including RVEF, FAC, and RV strain, using three-dimensional analysis software, which has been reported to be in good agreement with MRI findings for the evaluation of RV function (Muraru et al. 2016). Singh et al. (2020) analyzed RV function during cardiac surgery and reported that TAPSE, FAC, RV strain at the septum, and average RV strain were decreased after CPB, whereas RV longitudinal strain at the free wall was not decreased. In our study, we found that the RV function parameters TAPSE, FAC, and RVEF declined after CPB, but RV longitudinal strain at the free wall (RV strain) did not. However, the difference in RV longitudinal strain change between the free wall and septum may have affected our results. Singh et al. (2020) also demonstrated that the FAC of patients undergoing coronary artery bypass grafting (CABG) was not decreased. Additionally, a study examining the intraoperative RV function only in patients undergoing CABG showed no change in FAC or RVEF (Sultan et al. 2019), whereas a study that compared RV function during surgical aortic valve replacement using cardiac MRI showed reduced RVEF (Musa et al. 2016), indicating that CABG has little impact on RV function and surgical aortic valve replacement can reduce RV function.

In our study, only 1 patient underwent isolated CABG (3%), and most of the participants were patients who underwent aortic valve surgery, which was believed to significantly affect our results on the changes in RV function. In our study, 35.3% of patients developed AKI (≥ stage 1) within the first 48 hours postoperatively, which was higher than that reported in previous studies (Karkouti et al. 2010; Vives et al. 2019). However, there were no deaths during hospitalization in our study. Preoperative renal dysfunction, anemia, minimum hematocrit, and duration of extracorporeal circulation have been suggested as risk factors for CSA-AKI (Hobson et al. 2009). It has also been reported that maintaining systemic arterial pressure and preventing body congestion are important to maintain renal perfusion

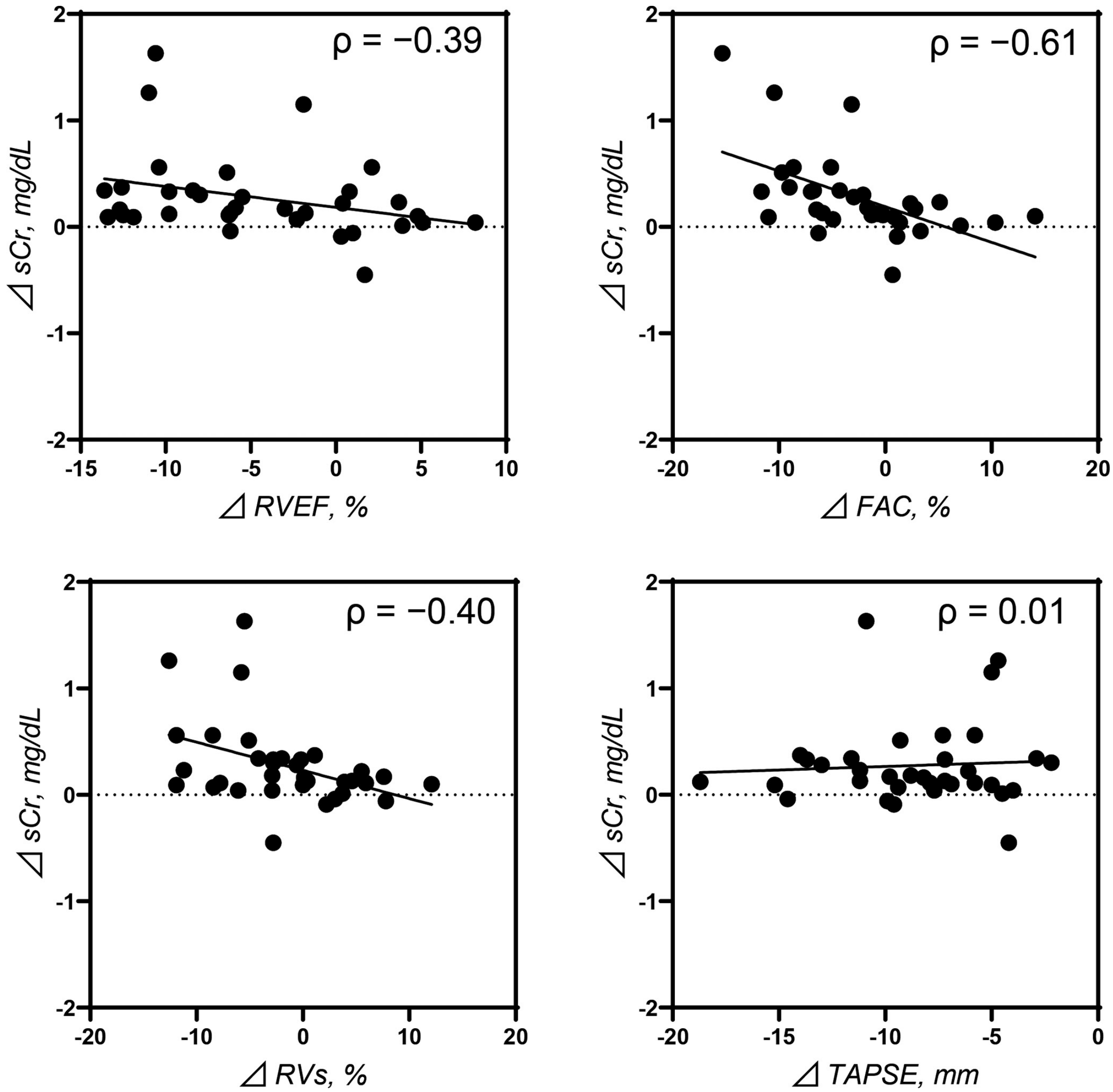

Fig. 5. Correlation between changes in serum creatinine value and changes in right ventricular function parameters of each patient in the perioperative period.
Regarding serum creatinine value, Δ indicates the difference in value between the postoperative peak within the first 48 h after cardiac surgery and the preoperative baseline. Regarding right ventricular function parameters, Δ indicates the difference in value between after chest closure and before the pericardiotomy.
FAC, fractional area change; RVEF, right ventricular ejection fraction; RVs, right ventricular free wall strain; sCr, serum creatinine; TAPSE, tricuspid annular plane systolic excursion.

and that RV dysfunction could cause organ congestion (Palomba et al. 2007; Gambardella et al. 2016; Saito et al. 2016). However, to our knowledge, there are no studies that have investigated these relationships using intraoperative parameters, including RV function. Our results showed that changes in RV function parameters during cardiac surgery, except TAPSE, were correlated with ΔsCr after adjusting for preoperative sCr and the duration of CPB, and ΔFAC had the strongest correlation with sCr. Our results also indicated that the intraoperative deterioration of RV function was associated with the deterioration of renal function after cardiac surgery, which has not been previously reported.

We considered maintaining renal function to be important, especially in patients with mild CKD, to prevent patients from requiring hemodialysis. Therefore, we included patients with CKD who had not undergone hemodialysis. The incidence of CSA-AKI in our patients with preoperative CKD was very high (54%) compared to those without CKD (24%). Fu et al. (2021) reported that more than half of patients with preoperative CKD who did not undergo hemodialysis developed CSA-AKI of KDIGO stages 1, 2, and 3. Both the mortality rate and the rate of permanent hemodialysis were higher in their patients with higher CSA-AKI grades. Although the number of our patients with preoperative CKD was small, using the ΔFAC ≥ -2.1 for AKI diagnosis in these patients yielded very high accuracy. These results suggest that worsening RV function

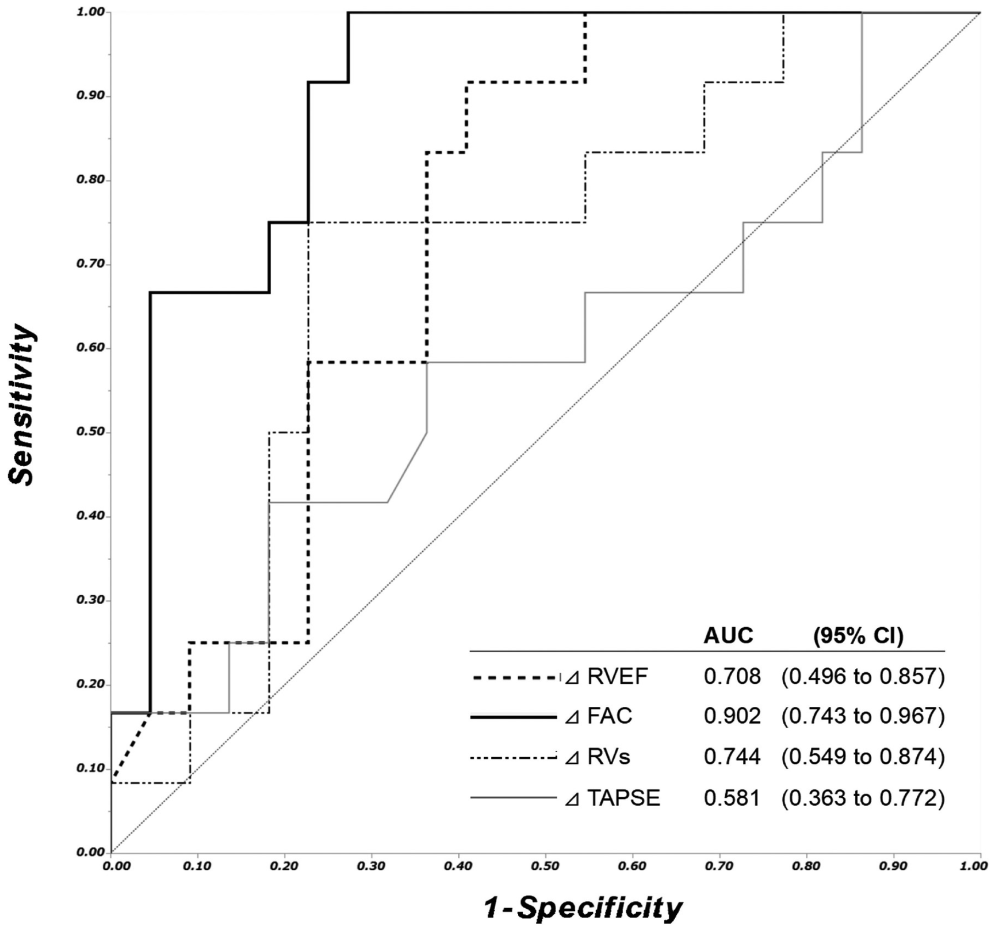

Fig. 6. Receiver operating characteristic curve illustrating the changes in right ventricular function parameters for the diagnosis of acute kidney injury.
The area under the curve (AUC) values and 95% confidence interval (CI) are shown together. Right ventricular free wall strain values are expressed by absolute values.
FAC, fractional area change; RVEF, right ventricular ejection fraction; RVs, right ventricular free wall strain; TAPSE, tricuspid annular plane systolic excursion.

during cardiovascular surgery, especially in patients with preoperative CKD, could cause postoperative renal dysfunction, and the deterioration of RV function is a strong predictor of CSA-AKI in these patients.

It has been reported that RV function parameters are load-dependent (Rudski et al. 2010; Lang et al. 2015). Considering the displacement of the heart and the effect of thoracotomy on hemodynamics (Reuter et al. 2004), we measured RV function and hemodynamic parameters at two time points: shortly before pericardiotomy and after the closure of the chest. Additionally, we measured the RV function indicators in the RV-centered cross-sectional view of the four heart chambers for the accurate evaluation of RV function. We observed that CVP was increased, but the PASP, Epa, and CI did not change. This suggests that the preload of the right side of the heart was increased, but the afterload showed little change. Therefore, the RV afterload was believed to have little influence on the RV function parameters in our study. Furthermore, although LVEF, CI, and MAP are considered the most important parameters in intraoperative circulatory management, these hemodynamic parameters did not correlate with sCr, unlike the RV parameters in our study. Even if CI and MAP can be maintained during surgery, intraoperative RV function parameters cannot always be maintained. In patients with normal RV function or a small RV, a change in FAC of −2.1% seems very small, and applying this cutoff value might be unreasonable. However, this suggests that any worsening of RV function after CPB can lead to CSA-AKI. Additionally, in a patient with an enlarged RV due to RV dysfunction, a FAC change of −2.1% can cause a large volumetric change in RV. Therefore, further investigations are required. Our findings suggest that careful monitoring of RV function parameters is important to prevent the development of CSA-AKI.

Our study has several limitations. First, it was a single-center study, and the study population was small. Second, pulmonary artery wedge pressure (PAWP) was not measured in this study. When PAWP is increased, it can decrease RV function due to an increase in afterload.

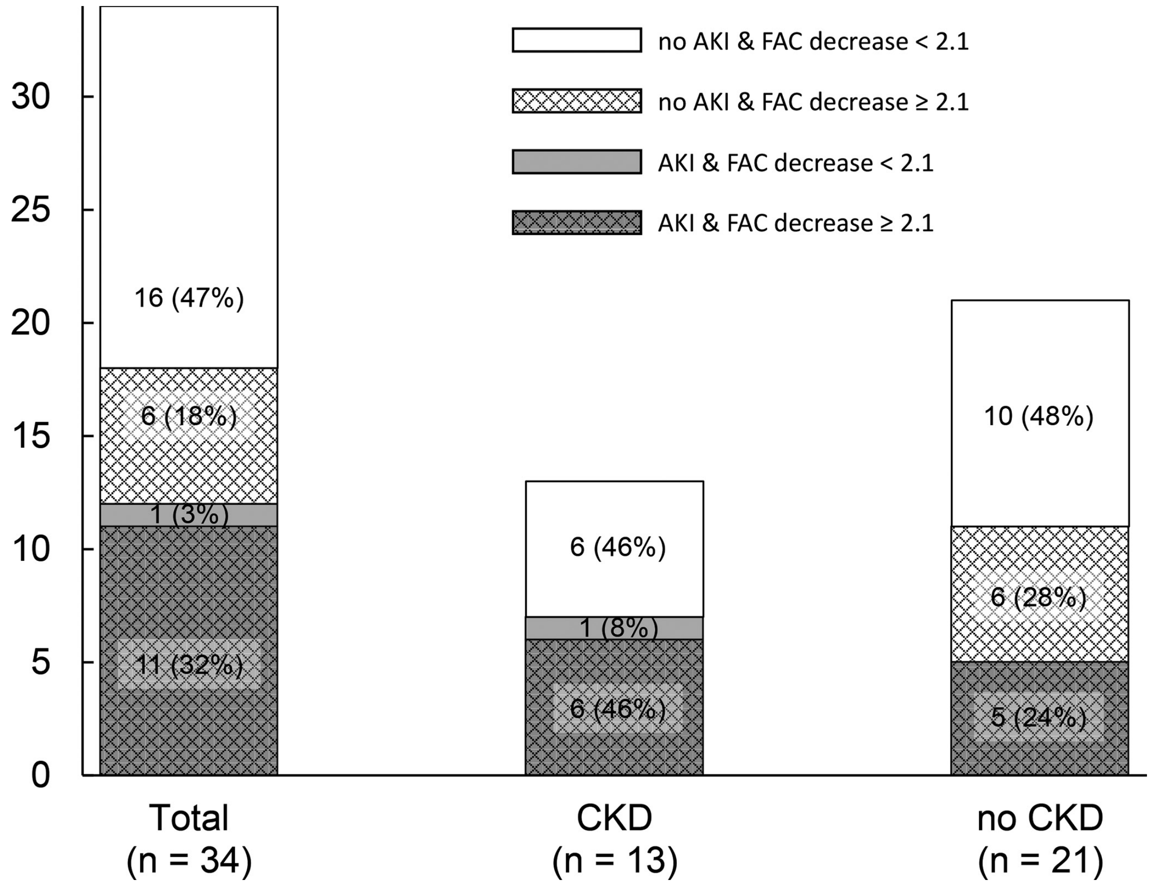

Fig. 7. Incidence rate and the number of patients who developed acute kidney injury (AKI) in the study.
In the total study patients (Total), patients with preoperative chronic kidney disease (CKD), and patients without CKD (no CKD), the white columns represent patients who did not develop AKI with a decrease in right ventricular fractional area change (FAC) of less than the cutoff value of 2.1 (no AKI & FAC decrease < 2.1); the meshed white columns represent patients who did not develop AKI with a decrease in FAC of 2.1 or more (no AKI & FAC decrease ≥ 2.1); the gray columns represent patients who developed AKI with a decrease in FAC of less than 2.1 (AKI & FAC decrease < 2.1); and the meshed gray columns represent patients who developed AKI with a decrease in FAC of 2.1 or more (AKI & FAC decrease ≥ 2.1).

However, other parameters that affect afterload, such as Epa and PASP, did not change in our patients. Third, this was an observational study; hence, the protocol of inotropic medications could not be unified, which could have affected both the RV contractility after CPB and postoperative renal function. However, all inotropic medications were initiated after CPB, irrespective of the situation, and RV function declined. In addition, the intraoperative VIS was not related to postoperative renal function. Fourth, it is impossible to deny the influences of perioperatively administered diuretics, such as carperitide and loop diuretics, on the renal prognoses of the study participants and on the cutoff values of RV function parameters for the detection of AKI. Because almost all participants were administered diuretics, we could not investigate the effect of diuretic administration on the ability of RV function indicators to predict CSA-AKI.

Our study indicated that intraoperative global RV function parameters declined after CPB, which was associated with a deterioration in renal function after cardiac surgery. Additionally, patients with preoperative renal dysfunction had a high incidence of CSA-AKI. Changes in RV function during cardiovascular surgery can affect postoperative renal function, particularly in patients with CKD, and a deterioration in RV function is a strong predictor of CSA-AKI. Further large studies are needed to determine whether careful intraoperative RV function monitoring and maintenance of RV function can improve the renal prognosis of patients with worsening RV function during surgery and patients with preoperative CKD.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Conceptualization: Yasuaki Tohi, Hiroaki Toyama; Methodology: Yusuke Takei, Kotaro Nochioka; Investigation: Yasuaki Tohi, Yusuke Takei, Kotaro Nochioka; Data analysis: Yasuaki Tohi, Kotaro Nochioka, Hiroaki Toyama; Writing - original draft preparation:

Yasuaki Tohi, Hiroaki Toyama; Supervision: Hiroaki Toyama, Masanori Yamauchi.

References

Brochard, L., Abroug, F., Brenner, M., Broccard, A.F., Danner, R.L., Ferrer, M., Laghi, F., Magder, S., Papazian, L., Pelosi, P. & Polderman, K.H.; ATS/ERS/ESICM/SCCM/SRLF Ad Hoc Committee on Acute Renal Failure (2010) An official ATS/ERS/ESICM/SCCM/SRLF statement: prevention and management of acute renal failure in the ICU patient: an international consensus conference in intensive care medicine. *Am. J. Respir. Crit. Care Med.*, **181**, 1128-1155.

Cremer, P.C., Zhang, Y., Alu, M., Rodriguez, L.L., Lindman, B.R., Zajarias, A., Hahn, R.T., Lerakis, S., Malaisrie, S.C., Douglas, P.S., Pibarot, P., Svensson, L.G., Leon, M.B. & Jaber, W.A. (2018) The incidence and prognostic implications of worsening right ventricular function after surgical or transcatheter aortic valve replacement: insights from PARTNER IIA. *Eur. Heart J.*, **39**, 2659-2667.

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.G. (2009) Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav. Res. Methods*, **41**, 1149-1160.

Fu, H.Y., Chou, N.K., Chen, Y.S. & Yu, H.Y. (2021) Risk factor for acute kidney injury in patients with chronic kidney disease receiving valve surgery with cardiopulmonary bypass. *Asian J. Surg.*, **44**, 229-234.

Gaies, M.G., Gurney, J.G., Yen, A.H., Napoli, M.L., Gajarski, R.J., Ohye, R.G., Charpie, J.R. & Hirsch, J.C. (2010) Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr. Crit. Care Med.*, **11**, 234-238.

Gambardella, I., Gaudino, M., Ronco, C., Lau, C., Ivascu, N. & Girardi, L.N. (2016) Congestive kidney failure in cardiac surgery: the relationship between central venous pressure and acute kidney injury. *Interact. Cardiovasc. Thorac. Surg.*, **23**, 800-805.

Herzog, C.A., Asinger, R.W., Berger, A.K., Charytan, D.M., Diez, J., Hart, R.G., Eckardt, K.U., Kasiske, B.L., McCullough, P.A., Passman, R.S., DeLoach, S.S., Pun, P.H. & Ritz, E. (2011) Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.*, **80**, 572-586.

Hobson, C.E., Yavas, S., Segal, M.S., Schold, J.D., Tribble, C.G., Layon, A.J. & Bihorac, A. (2009) Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation*, **119**, 2444-2453.

Hosenpud, J.D., Bennett, L.E., Keck, B.M., Boucek, M.M. & Novick, R.J. (2000) The registry of the international society for heart and lung transplantation: seventeenth official report-2000. *J. Heart Lung Transplant.*, **19**, 909-931.

Karkouti, K., Wijeysundera, D.N., Yau, T.M., McCluskey, S.A., Tait, G. & Beattie, W.S. (2010) The risk-benefit profile of aprotinin versus tranexamic acid in cardiac surgery. *Anesth. Analg.*, **110**, 21-29.

Khwaja, A. (2012) KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin. Pract.*, **120**, c179-184.

Lampert, B.C. & Teuteberg, J.J. (2015) Right ventricular failure after left ventricular assist devices. *J. Heart Lung Transplant.*, **34**, 1123-1130.

Lang, R.M., Badano, L.P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., Flachskampf, F.A., Foster, E., Goldstein, S.A., Kuznetsova, T., Lancellotti, P., Muraru, D., Picard, M.H., Rietzschel, E.R., Rudski, L., et al. (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J. Am. Soc. Echocardiogr.*, **28**, 1-39. e14.

Lindqvist, P., Holmgren, A., Zhao, Y. & Henein, M.Y. (2012) Effect of pericardial repair after aortic valve replacement on septal and right ventricular function. *Int. J. Cardiol.*, **155**, 388-393.

Maffessanti, F., Gripari, P., Tamborini, G., Muratori, M., Fusini, L., Alamanni, F., Zanobini, M., Fiorentini, C., Caiani, E.G. & Pepi, M. (2012) Evaluation of right ventricular systolic function after mitral valve repair: a two-dimensional Doppler, speckle-tracking, and three-dimensional echocardiographic study. *J. Am. Soc. Echocardiogr.*, **25**, 701-708.

Magunia, H., Dietrich, C., Langer, H.F., Schibilsky, D., Schlensak, C., Rosenberger, P. & Nowak-Machen, M. (2018) 3D echocardiography derived right ventricular function is associated with right ventricular failure and mid-term survival after left ventricular assist device implantation. *Int. J. Cardiol.*, **272**, 348-355.

Matsui, K., Kamijo-Ikemori, A., Sugaya, T., Yasuda, T. & Kimura, K. (2012) Usefulness of urinary biomarkers in early detection of acute kidney injury after cardiac surgery in adults. *Circ. J.*, **76**, 213-220.

Muraru, D., Spadotto, V., Cecchetto, A., Romeo, G., Aruta, P., Ermacora, D., Jenei, C., Cucchini, U., Iliceto, S. & Badano, L.P. (2016) New speckle-tracking algorithm for right ventricular volume analysis from three-dimensional echocardiographic data sets: validation with cardiac magnetic resonance and comparison with the previous analysis tool. *Eur. Heart J. Cardiovasc. Imaging*, **17**, 1279-1289.

Musa, T.A., Uddin, A., Fairbairn, T.A., Dobson, L.E., Steadman, C.D., Kidambi, A., Ripley, D.P., Swoboda, P.P., McDiarmid, A.K., Erhayiem, B., Garg, P., Blackman, D.J., Plein, S., McCann, G.P. & Greenwood, J.P. (2016) Right ventricular function following surgical aortic valve replacement and transcatheter aortic valve implantation: a cardiovascular MR study. *Int. J. Cardiol.*, **223**, 639-644.

Palomba, H., de Castro, I., Neto, A.L., Lage, S. & Yu, L. (2007) Acute kidney injury prediction following elective cardiac surgery: AKICS Score. *Kidney Int.*, **72**, 624-631.

Reuter, D.A., Goresch, T., Goepfert, M.S., Wildhirt, S.M., Kilger, E. & Goetz, A.E. (2004) Effects of mid-line thoracotomy on the interaction between mechanical ventilation and cardiac filling during cardiac surgery. *Br. J. Anaesth.*, **92**, 808-813.

Rosner, M.H. & Okusa, M.D. (2006) Acute kidney injury associated with cardiac surgery. *Clin. J. Am. Soc. Nephrol.*, **1**, 19-32.

Rudski, L.G., Lai, W.W., Afilalo, J., Hua, L., Handschumacher, M.D., Chandrasekaran, K., Solomon, S.D., Louie, E.K. & Schiller, N.B. (2010) Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J. Am. Soc. Echocardiogr.*, **23**, 685-713.

Saito, S., Uchino, S., Takinami, M., Uezono, S. & Bellomo, R. (2016) Postoperative blood pressure deficit and acute kidney injury progression in vasopressor-dependent cardiovascular surgery patients. *Crit. Care*, **20**, 74.

Singh, A., Huang, X., Dai, L., Wyler, D., Alfirevic, A., Blackstone, E.H., Pettersson, G.B. & Duncan, A.E. (2020) Right ventricular function is reduced during cardiac surgery independent of procedural characteristics, reoperative status, or pericardiotomy. *J. Thorac. Cardiovasc. Surg.*, **159**, 1430-1438. e1434.

Stevens, P.E. & Levin, A.; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members (2013) Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann. Intern. Med.*, **158**, 825-830.

Sultan, I., Cardounel, A., Abdelkarim, I., Kilic, A., Althouse, A.D., Sharbaugh, M.S., Gupta, A., Xu, J., Fukui, M., Simon, M.A., Schindler, J.T., Lee, J.S., Gleason, T.G. & Cavalcante, J.L.

(2019) Right ventricle to pulmonary artery coupling in patients undergoing transcatheter aortic valve implantation. *Heart*, **105**, 117-121.

Unsworth, B., Casula, R.P., Kyriacou, A.A., Yadav, H., Chukwuemeka, A., Cherian, A., Stanbridge Rde, L., Athanasiou, T., Mayet, J. & Francis, D.P. (2010) The right ventricular annular velocity reduction caused by coronary artery bypass graft surgery occurs at the moment of pericardial incision. *Am. Heart J.*, **159**, 314-322.

Vives, M., Hernandez, A., Parramon, F., Estanyol, N., Pardina, B., Munoz, A., Alvarez, P. & Hernandez, C. (2019) Acute kidney injury after cardiac surgery: prevalence, impact and management challenges. *Int. J. Nephrol. Renovasc. Dis.*, **12**, 153-166.

Yockelson, S.R., Heitner, S.B., Click, S., Geleto, G., Treggiari, M.M. & Hutchens, M.P. (2019) Right ventricular systolic performance determined by 2D speckle-tracking echocardiography and acute kidney injury after cardiac surgery. *J. Cardiothorac. Vasc. Anesth.*, **33**, 725-731.