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Relationship between intraoperative tidal volume and acute kidney injury following off-pump coronary artery bypass grafting

A retrospective observational study

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Abstract

The effect of intraoperative tidal volume (V_T) on clinical outcomes after off-pump coronary artery bypass grafting (OPCAB) has not been studied. The aim of this study was to assess the relationship between intraoperative tidal volume (V_T) and acute kidney injury (AKI) after OPCAB. A total of 1049 patients who underwent OPCAB between January 2009 and December 2018 were analyzed. Patients were divided into high (>8 ml/kg) and low V_T (≤8 ml/kg) groups (intraoperative median V_T standardized to predicted body weight). The data were fitted using a multivariable logistic regression model. Subgroup analyses were performed according to age, sex, comorbidities, preoperative laboratory variables, operative profiles, and Cleveland score. The risk of AKI was not significantly higher in the high than the low V_T group (OR: 1.15, 95% CI: 0.80–1.66; $P = .459$); however, subgroup analyses revealed that a high V_T may increase the risk of AKI in males, patients aged < 70 years, with chronic kidney disease, a left ventricular ejection fraction < 35%, or a long duration of surgery. High intraoperative V_Ts were not associated with an increased risk of AKI after OPCAB. Nonetheless, it may increase the risk of AKI in certain subgroups, such as younger age, male sex, reduced renal and cardiac function, and a long surgery time.

Abbreviations: AKI = acute kidney injury, ARDS = Acute respiratory distress syndrome, CI = confidence interval, OPCAB = off-pump coronary artery bypass grafting, OR = odds ratio, PBW = predicted body weight, STROBE = Strengthening the Reporting of Observational Studies in Epidemiology, V_T = tidal volume.

Keywords: acute kidney injury; cardiac surgery; coronary artery bypass grafting; tidal volume; lung-protective ventilation

1. Introduction

Using a low tidal volume (V_T) for mechanical ventilation in critically ill patients is reported to confer clinical benefits.[1,2] Compared with a higher V_T, a V_T of 6–8 ml/kg predicted body weight (PBW) may decrease the duration of mechanical ventilation, as well as mortality rate in patients with acute respiratory distress syndrome (ARDS).[3,4] A high V_T can exert injurious effects on the lung by inducing the expression of inflammatory mediators and reactive oxygen species.[5–7] Theoretically, a high V_T can also damage other vital organs—such as the kidney—by reducing renal perfusion and inducing hormone secretion, thereby decreasing urine output and provoking inflammation and oxidative stress.[6,8,9] Several studies have investigated the use of a low V_T to prevent acute kidney injury (AKI) in various clinical settings, yielding conflicting results.[10,11]

The incidence of AKI after cardiac surgery is remarkably high, exceeding 40%.[12,13] Considering that cardiac surgery itself causes significant inflammation and oxidative stress,[14,15] a high V_T may further aggravate kidney damage during cardiac surgery. Indeed, a small, prior observational study demonstrated that the risk of postoperative AKI was significantly lower in patients who received a mean intraoperative V_T of ≤ 7 mL/kg PBW, than in those who received > 7 mL/kg PBW.[16] Notably, only 5% of the study population underwent off-pump cardiac surgery in this previous study.

While most patients do not undergo mechanical ventilation during cardiopulmonary bypass,[17] mechanical ventilation is performed throughout off-pump cardiac surgery without interruption. It can be inferred that the impact of intraoperative V_T may be more prominent in off-pump cardiac surgery; therefore, we hypothesized that a high intraoperative V_T would increase the risk of AKI after off-pump cardiac surgery.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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This study aimed to assess the relationship between intraoperative V_T level and the risk of postoperative AKI in patients who had undergone off-pump coronary artery bypass grafting (OPCAB).

2. Methods

2.1. Study design and population

This retrospective observational study's protocol was approved by the Institutional Review Board of Seoul National University Hospital (approval no. 2006-070-113), and the requirement for written informed consent was waived due to the retrospective nature. This study was reported in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[18]

All adult patients (≥18 years old) who underwent OPCAB in Seoul National University Hospital between January 2009 and December 2018 were consecutively included in the study, without an a priori sample size calculation. Exclusion criteria included missing intraoperative V_T data; a history of end-stage renal disease or renal replacement therapy prior to surgery; currently undergoing mechanical ventilation before surgery; having undergone minimally invasive cardiac surgery via thoracotomy with one-lung ventilation; and a lack of baseline or postoperative serum creatinine measurements.

2.2. Anesthetic management and perioperative mechanical ventilation

Anesthetic management and intraoperative mechanical ventilation were performed according to institutional protocols. Anesthesia was induced with intravenous midazolam (0.1–0.2 mg/kg) or etomidate (0.15–0.25 mg/kg), while sufentanil (1.0–2.5 μg/kg) was administered as an adjunct anesthetic. Tracheal intubation was facilitated by administering rocuronium (0.6–1.2 mg/kg), vecuronium (0.15–0.25 mg/kg), or cisatracurium (0.15–0.25 mg/kg). Cuffed endotracheal tubes with internal diameters of 7.0 and 7.5 mm were used for female and male patients, respectively. After tracheal intubation, volume-controlled ventilation (Primus®, Drägerwerk AG, Lübeck, Germany or S5 Avance®, GE Healthcare, Chicago, IL) was initiated. V_T was set at the discretion of the attending anesthesiologist. Positive end-expiratory pressure was not routinely applied. The initial fraction of inspired oxygen was 0.5; if arterial oxygen saturation decreased to < 94%, or arterial oxygen partial pressure to < 80 mm Hg during surgery, rescue therapy was performed in the following order: alveolar recruitment maneuver, positive end-expiratory pressure of 5–10 cmH_2O, and increasing the fraction of inspired oxygen. The respiratory rate was adjusted to maintain arterial carbon dioxide partial pressure between 35 and 45 mm Hg. A target-controlled infusion of propofol and remifentanil was administered to maintain a bispectral index between 40 and 60. Neuromuscular blockade was achieved by continuous infusion of vecuronium or cisatracurium at a rate of 0.5–1.5 μg/kg/min during surgery; after surgery, all patients were transferred to the intensive care unit without extubation. Mechanical ventilation was resumed with an initial fraction of inspired oxygen between 0.6 and 0.8. Patients were extubated at the discretion of the attending physician when arterial oxygen saturation remained > 94% and arterial oxygen partial pressure > 80 mm Hg at a fraction of inspired oxygen < 0.5, and positive end-expiratory pressure < 8 cmH_2O.

2.3. Data collection and statistical analysis

The primary outcome was the association between the level of intraoperative V_T and the risk of AKI after OPCAB. Before the analysis, patients were divided into 2 groups based on their intraoperative V_T standardized to PBW (V_T/PBW): high V_T (>8 mL/kg) and low V_T (≤8 mL/kg) groups. The median values were selected as representative values for intraoperative V_T measurements. PBW (kg) was calculated as 0.91 × (height [cm] – 152.4) + 50 (male) or 45.5 (female).[4] A V_T/PBW cut-off value of 8 mL/kg was selected, as it is the most commonly used value for a low-tidal volume ventilation strategy.[19,20] Postoperative AKI was defined according to the serum creatinine criteria of the Kidney Disease: Improving Global Outcomes: an increase in serum creatinine by ≥ 0.3 mg/dl within 48 hours, or to ≥ 1.5-fold the baseline within 7 days following surgery.[21] The baseline serum creatinine level was defined as the most recent value measured within 30 days prior to surgery.

The following perioperative patient data were obtained from electronic medical records: demographics (age, sex, and body mass index), past medical history (hypertension, diabetes, insulin-requiring diabetes, dyslipidemia, myocardial infarction, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, cerebrovascular disease, and chronic kidney disease), preoperative clinical variables (left ventricular ejection fraction, hematocrit, estimated glomerular filtration rate, serum creatinine level, number of diseased vessels, left main disease, and preoperative intra-aortic balloon pump), medication history (aspirin, β blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, diuretics, and statins), surgical profiles (surgery duration, emergent or urgent surgery, redo surgery, number of coronary anastomoses), intraoperative variables (red blood cell transfusion, hydroxyethyl starch use, epinephrine use, norepinephrine use, dobutamine use, and average mean blood pressure), and median peak inspiratory pressure. Continuous variables—expressed as mean (standard deviation) or median (interquartile range) after verifying the normality assumption—were compared using the *t*-test or the Mann–Whitney *U* test. Categorical variables were expressed as number (proportion) and compared using the χ^2 test or Fisher's exact test, as appropriate.

The following statistical procedures were conducted for primary outcome analysis. First, restricted cubic spline regression analysis was performed to determine the relationship between continuous V_T/PBW and the log-odds of postoperative AKI. With 3 knots set at the 10th, 50th, and 90th percentiles of

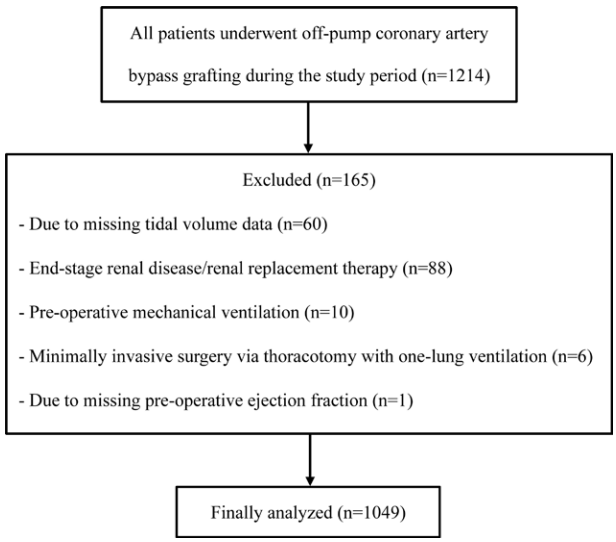

Figure 1. Study flowchart.

V_T/PBW, all variables included in the Cleveland score were adjusted for[22]: female sex, congestive heart failure, left ventricular ejection fraction < 35%, chronic obstructive pulmonary disease, insulin-requiring diabetes, previous cardiac surgery, preoperative use of intra-aortic balloon pump, emergency surgery, and preoperative serum creatinine (categorized as < 1.2, 1.2, <2.1, and ≥ 2.1). Second, logistic regression analysis was performed to estimate the relative risk of AKI in the high V_T group, compared with the low V_T group. After univariate analysis, the risk was adjusted for using the Cleveland score variables and the perioperative potential confounders listed above which showed a significant difference ($P < .05$) between the study groups.

Exploratory subgroup analyses of the primary outcome were also conducted to further address the potential confounders and to determine whether the effect of intraoperative V_T varied accordingly. Patients were classified according to their age at surgery (< or ≥ 70 years), sex, diagnosis of diabetes mellitus and chronic kidney disease, preoperative left ventricular ejection fraction (< or ≥ 35%), estimated glomerular filtration rate (< or ≥ 45 ml/min/1.73 m^2), hematocrit (< or ≥ 36% in females, and < or ≥ 39% in males), type of surgery (elective surgery or first cardiac surgery), duration of surgery (longer or shorter than the median), intraoperative hydroxyethyl starch use, intraoperative red blood cell transfusion, and the Cleveland score (< or ≥ 3 points; lower or greater risk category[22]). In each

Table 1

Patients' characteristics and perioperative data.

	Total cohort		
	Low V_T group (n = 626)	**High V_T group (n = 423)**	***P***
Median V_T (mL)	440 (392–472)	488 (424–544)	<.001
Median V_T/PBW (mL/kg)	7.10 (6.59–7.57)	8.77 (8.36–9.32)	<.001
Demographics			
Age (year)	66.6 (10.3)	66.3 (9.9)	.707
Female	72 (11.5%)	169 (40.0%)	<.001
Body mass index (kg/m^2)	24.0 (3.2)	25.4 (3.3)	<.001
Past medical history			
Hypertension	385 (61.5%)	276 (65.2%)	.241
Diabetes	295 (47.1%)	184 (43.5%)	.256
Insulin-requiring diabetes	63 (10.1%)	42 (9.9%)	>.999
Dyslipidemia	190 (30.4%)	164 (38.8%)	.005
Myocardial infarction	91 (14.5%)	40 (9.5%)	.017
Congestive heart failure	38 (6.1%)	23 (5.4%)	.689
Atrial fibrillation	44 (7.0%)	26 (6.1%)	.616
Chronic obstructive pulmonary disease	38 (6.1%)	22 (5.2%)	.590
Cerebrovascular disease	178 (28.4%)	81 (19.1%)	.001
Chronic kidney disease	175 (28.0%)	121 (28.6%)	.834
Preoperative clinical data			
LV ejection fraction (%)	56 (47-62)	58 (52–63)	.001
Hematocrit (%)	35.8 (4.4)	35.1 (4.5)	.009
eGFR (mL/min/1.73 m^2)	78.3 (23.2)	78.3 (21.2)	.997
Serum creatinine (mg/dL)	1.0 (0.4)	0.9 (0.3)	<.001
Number of diseased vessels			.846
1-vessel disease	17 (2.7%)	14 (3.3%)	
2-vessel disease	99 (15.8%)	65 (15.4%)	
3-vessel disease	510 (81.5%)	344 (81.3%)	
Left main disease	141 (22.5%)	100 (23.6%)	.708
Preoperative IABP	13 (2.1%)	13 (3.1%)	.318
Preoperative medication			
Aspirin	444 (70.9%)	303 (71.6%)	.835
β blocker	177 (28.3%)	116 (27.4%)	.779
Calcium channel blocker	290 (46.3%)	191 (45.2%)	.752
ACEi/ARB	268 (42.8%)	171 (40.4%)	.445
Diuretics	97 (15.5%)	62 (14.7%)	.726
Statin	378 (60.4%)	268 (63.4%)	.365
Surgery profiles			
Duration of surgery (min)	360 (325–395)	355 (317–400)	.434
Emergent or urgent surgery	18 (2.9%)	17 (4.0%)	.381
Redo surgery	11 (1.8%)	3 (0.7%)	.178
Number of coronary anastomoses	4 (3-4)	3 (3-4)	.007
Intraoperative data			
Red blood cell transfusion	441 (70.4%)	322 (76.1%)	.048
Hydroxyethyl starch use	209 (33.4%)	287 (67.8%)	<.001
Epinephrine use	8 (1.3%)	5 (1.2%)	>.999
Norepinephrine use	485 (77.5%)	270 (63.8%)	<.001
Dobutamine use	43 (6.9%)	56 (13.2%)	.001
Average mean blood pressure (mm Hg)	73.8 (5.2)	74.3 (5.6)	.134
Median intraoperative PIP (cmH_2O)	14 (12–16)	14 (12–17)	<.001

Values are expressed as mean (SD), median (IQR), or number (proportion). ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blockers, eGFR = estimated glomerular filtration rate, IABP = intra-aortic balloon pump, LV = left ventricular, PBW = predicted body weight, PIP = peak inspiratory pressure, V_T = tidal volume.

subgroup, multivariable logistic regression analysis was performed by adjusting for the Cleveland score variables. Firth's penalized likelihood estimation was applied for subgroup analyses to reduce small-sample bias arising from sparse data and separation.[23]

R version 4.0.5 (R Development Core Team, Vienna, Austria) and SPSS version 25 (IBM, Armonk, NY) were used for all statistical analyses. Statistical significance was set at $P < .05$.

3. Results

Of the 1214 patients who underwent OPCAB during the study period, 60 patients with missing V_T data, and 88 patients with a history of end-stage renal disease or renal replacement therapy, were excluded from the study. Seventeen patients were further excluded due to the use of preoperative mechanical ventilation (n = 10), minimally invasive surgery via thoracotomy with one-lung ventilation (n = 6), and missing preoperative left ventricular ejection fraction (n = 1). The remaining 1049 patients were finally analyzed (Fig. 1). The median V_T/PBW was ≤ 8 mL/kg in 626 patients (low V_T group) and > 8 mL/kg in 423 patients (high V_T group); the baseline characteristics and perioperative data of the study groups are shown in Table 1. The median (IQR) intraoperative V_T and V_T/PBW was 440 (392–472) mL/kg and 7.1 (6.6–7.6) mL/kg in the low V_T group, and 488 (424–544) mL and 8.8 (8.4–9.3) mL/kg in the high V_T group, respectively. The median (IQR) intraoperative median peak inspiratory pressures were 14 (12–16) and 14 (12–17) in the low and high V_T groups, respectively. The proportions of females and hydroxyethyl starch use were 11.5% and 33.4% in the low V_T group, and 40.0% and 67.8% in the high V_T group, respectively.

Postoperative AKI occurred in 255 patients (24.3%). In the restrictive cubic spline model, the log-odds of postoperative AKI increased linearly with increasing intraoperative median V_T/PBW (Fig. 2). However, the risk of postoperative AKI was not significantly different between the high V_T (V_T/PBW > 8 mL/kg) and low V_T (≤8 mL/kg) groups in the multivariable logistic regression analysis of the total cohort (high V_T group; adjusted odds ratio [OR]: 1.15; 95% confidence interval [CI]: 0.80–1.66; $P = .459$) after adjustment for the Cleveland score variables and potential confounders (Table 2).

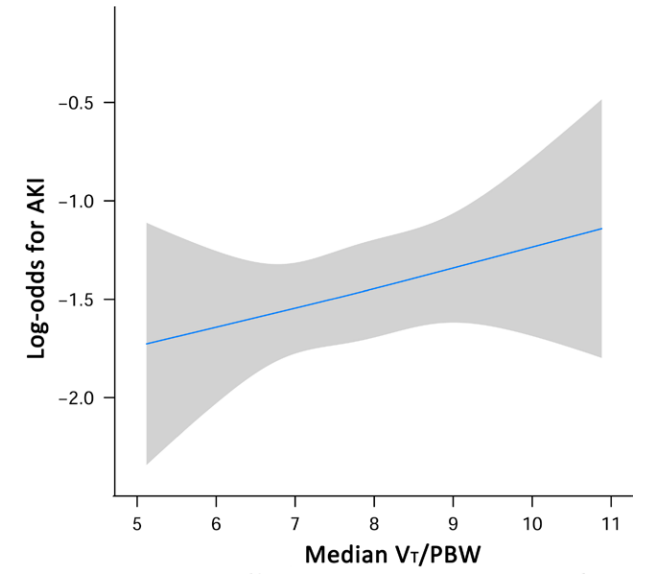

Figure 2. Adjusted restrictive cubic spline curves of postoperative acute kidney injury according to the median V_T/PBW. Shaded areas indicate 95% confidence interval. AKI = acute kidney injury; V_T = tidal volume; PBW = predicted body weight.

In the subgroup analyses, a high intraoperative V_T/PBW was associated with an increased risk of AKI in patients under 70 years of age (adjusted OR [95% CI]: 1.58 [1.03–2.42]; $P = .036$), males (1.44 [1.01–2.04]; $P = .042$), and patients with preexisting chronic kidney disease (1.86 [1.02–3.42]; $P = .042$), a preoperative left ventricular ejection fraction < 35% (2.79 [1.13–7.06]; $P = .026$), or a longer duration of surgery (1.65 [1.04–2.60]; $P = .033$) (Table 3, Fig. 3).

4. Discussion

In this study, a significant association was not observed between intraoperative V_T and the risk of postoperative AKI in patients undergoing OPCAB. The high V_T group (intraoperative median V_T/PBW ≥ 8 mL/kg) exhibited a similar risk of AKI when compared with the low V_T group (<8 mL/kg) after multivariable adjustment. However, extensive subgroup analyses revealed a significant association between a high V_T and an increased risk of postoperative AKI in several subgroups, including patients aged < 70 years, males, and patients with preexisting chronic kidney disease, a left ventricular ejection fraction < 35%, or a longer duration of surgery.

Since the ARDS Network investigators demonstrated in their landmark study that a low V_T (6 vs. 12 mL/kg PBW) increased ventilator-free days and reduced mortality rate,[4] numerous studies have sought to determine the potentially harmful effects of a high V_T on clinical outcomes in patients with ARDS.[3] One of the primary mechanisms includes inflammatory cytokine release caused by an overdistention injury[7]; based on these findings, leading societies strongly recommend that patients with ARDS receive mechanical ventilation using a V_T limited to 4–8 mL/kg PBW.[24] Likewise, lung-protective ventilation strategies, including a low V_T, were also tested in non-ARDS or perioperative settings[1]; however, whether a low V_T improves clinical outcomes remains controversial.[20,25–31] While some studies have shown that low, protective V_T mechanical ventilation attenuates inflammatory response[25–27] and reduces the incidence of pulmonary complications[20,30] or mortality,[31] others have not.[25,28,29]

The effect of mechanical ventilation on other peripheral organs—such as the kidneys—has also gained recent attention,[32] and the underlying mechanism has been described in several ways.[33] First, the production of cytokines—such as IL-6, IL-8, and TNF-α—or reactive oxygen species, may be induced by mechanical ventilation, causing renal tissue injury.[8,34,35] Second, the hemodynamic effects of mechanical ventilation may reduce renal perfusion. The left ventricular preload decreases due to an increase in intrathoracic pressure, whereas cardiac output and blood pressure decrease as the right ventricular afterload increases[33,36]; additionally, vasoconstriction and sodium and water retention occur as the sympathetic nervous system is activated for compensation.[37] Third, in response to a decrease in atrial stretch due to relative intravascular volume depletion, the secretion of antidiuretic hormone increases,[38] while atrial natriuretic peptide decreases.[39] Previous clinical studies have sought to determine whether mechanical ventilation causes renal dysfunction; however, this remains inconclusive.[10,11] In a prior observational study, a higher delivered intraoperative V_T was associated with an increased risk of AKI after noncardiac surgery.[10] However, a secondary analysis of a randomized controlled trial comparing V_Ts of 10 mL/kg and 6 mL/kg in non-ARDS patients failed to show any difference in the development of AKI, or plasma levels of neutrophil gelatinase-associated lipocalin and cystatin C.[11]

Table 2

Logistic regression for acute kidney injury after cardiac surgery.

	Total cohort			
	Unadjusted		Adjusted	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Low V_T group	1.00 (Reference)		1.00 (Reference)	
High V_T group	1.00 (0.75–1.34)	.980	1.15 (0.80–1.66)	0.459
Age (yr)	1.03 (1.01–1.04)	.001		
Female	0.61 (0.42–0.88)	.008	0.55 (0.36–0.85)	.007
Body mass index (kg/m^2)	0.99 (0.95–1.03)	.549	1.00 (0.95–1.06)	.927
Hypertension	1.49 (1.10–2.02)	.010		
Insulin-requiring diabetes	1.49 (0.96–2.31)	.074	1.16 (0.71–1.91)	.553
Dyslipidemia	1.02 (0.76–1.38)	.885	1.02 (0.74–1.42)	.894
Myocardial infarction	0.92 (0.59–1.41)	.688	0.85 (0.52–1.41)	.534
Congestive heart failure	1.69 (0.98–2.93)	.060	1.33 (0.67–2.63)	.411
Atrial fibrillation	0.77 (0.42–1.40)	.386		
Chronic obstructive pulmonary disease	0.72 (0.29–1.81)	.488	0.66 (0.32–1.35)	.253
Cerebrovascular disease	1.12 (0.81–1.54)	.500	1.29 (0.89–1.87)	.182
Chronic kidney disease	1.75 (1.30–2.37)	<.001		
LV ejection fraction < 35%	1.68 (1.10–2.56)	.017	1.00 (0.98–1.01)	.744
Hematocrit (%)	0.95 (0.92–0.98)	.002	0.97 (0.93–1.01)	.098
Serum creatinine (mg/dL)		<.001		
<1.2	1.00 (Reference)		1.00 (Reference)	
1.2 to < 2.1	3.26 (2.35–4.54)		2.71 (1.90–3.85)	<.001
≥2.1	45.17 (10.44–195.34)		38.04 (8.56–169.00)	<.001
Number of diseased vessels		.101		
1-vessel disease	1.00 (Reference)			
2-vessel disease	2.91 (0.84–10.10)			
3-vessel disease	3.10 (0.93–10.30)			
Left main disease	1.07 (0.77–1.50)	.679		
Preoperative IABP	2.34 (1.06–5.17)	.035	4.06 (1.24–13.25)	.020
Aspirin	0.87 (0.64–1.18)	.375		
β blocker	0.90 (0.65–1.23)	.498		
Calcium channel blocker	1.00 (0.76–1.33)	.991		
ACEi/ARB	1.17 (0.88–1.55)	.288		
Diuretics	1.59 (1.10–2.29)	.014		
Statin	0.71 (0.53–0.94)	.018		
Surgery duration (min)	1.00 (1.00–1.00)	.143		
Emergent or urgent surgery	1.08 (0.50–2.34)	.844	0.27 (0.08–0.90)	.033
Redo surgery	2.37 (0.81–6.89)	.114	1.77 (0.53–5.87)	.350
Year of surgery	0.90 (0.86–0.95)	<.001		
Number of distal anastomoses	0.96 (0.83–1.11)	.611	0.95 (0.81–1.12)	.529
Red blood cell transfusion	1.97 (1.38–2.80)	<.001	1.76 (1.19–2.62)	.005
Hydroxyethyl starch use	1.60 (1.20–2.12)	.001	1.32 (0.90–1.94)	.150
Epinephrine use	7.23 (2.21–23.67)	.001		
Norepinephrine use	0.85 (0.62–1.16)	.295	0.93 (0.64–1.35)	.711
Dobutamine use	1.82 (1.17–2.81)	.008	1.38 (0.83–2.30)	.213
Average mean blood pressure (mm Hg)	0.98 (0.95–1.00)	.080		
Median intraoperative PIP (cmH_2O)	1.02 (0.97–1.07)	.506	1.01 (0.95–1.08)	.682

ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blockers, CI = confidence interval, IABP = intra-aortic balloon pump, LV = left ventricular, OR = odds ratio, PIP = peak inspiratory pressure, V_T = tidal volume.

Regarding cardiac surgery, only one small observational study has previously evaluated the relationship between V_T and AKI as a primary outcome.[16] Tojo et al[16] investigated 338 patients, demonstrating that the risk of AKI was significantly lower in patients with a $V_{T \leq}$ 7 mL/kg PBW than > 7 ml/kg PBW. However, the types of surgery were heterogeneous, and most patients underwent surgery under cardiopulmonary bypass; only 18 (5.3%) patients underwent OPCAB. Considering that most clinicians do not perform mechanical ventilation during cardiopulmonary bypass,[17] the impact of a high V_T on the risk of AKI may be more pronounced in patients undergoing off-pump cardiac surgery where mechanical ventilation is performed throughout surgery without interruption.

The present study included a much larger number of patients who underwent OPCAB. Unexpectedly, no difference was found between the high and low V_T groups in terms of postoperative AKI in the total cohort; however, in concordance with Tojo et al, our preliminary analysis—using a restricted cubic spline model—indicated that intraoperative V_T may be linearly associated with the risk of AKI. Moreover, a higher V_T was significantly related to an increased risk of postoperative AKI in patients with a longer duration of surgery in the subgroup analysis (Table 3 and Fig. 3).

A high V_T and postoperative AKI were also correlated in the other subgroups. An association was observed between a higher V_T and postoperative AKI in the < 70 years subgroup; however, older patients generally have more comorbidities,

Table 3

Subgroup analyses for acute kidney injury after cardiac surgery.

Subgroups		Adjusted OR (95% CI)	*P*
Age	<70 yr (n = 596)	1.58 (1.03–2.42)	0.036
	≥70 yr (n = 453)	1.19 (0.72–1.95)	.508
Sex	Male (n = 808)	1.44 (1.01–2.04)	.042
	Female (n = 241)	1.04 (0.49–2.35)	.913
Diabetes	Yes (n = 479)	1.27 (0.78–2.04)	.334
	No (n = 570)	1.47 (0.95–2.27)	.085
Chronic kidney disease	Yes (n = 296)	1.86 (1.02–3.42)	.042
	No (n = 753)	1.20 (0.82–1.77)	.345
Left ventricular ejection fraction	≥35% (n = 939)	1.22 (0.86–1.71)	.267
	<35% (n = 110)	2.79 (1.13–7.06)	.026
Preoperative eGFR	≥45 mL/min/1.73 m^2 (n = 973)	1.52 (0.49–5.14)	.479
	<45 mL/min/1.73 m^2 (n = 76)	1.33 (0.97–1.84)	.082
Anemia [a]	Yes (n = 772)	1.26 (0.88–1.80)	.212
	No (n = 277)	1.75 (0.85–3.61)	.129
Type of surgery	Elective surgery (n = 1014)	1.36 (0.99–1.89)	.062
	First cardiac surgery (n = 1035)	1.37 (0.99–1.89)	.055
Duration of surgery	Shorter than the median (n = 527)	1.16 (0.74–1.82)	.513
	Longer than the median (n = 522)	1.65 (1.04–2.60)	.033
Hydroxyethyl starch use	Yes (n = 553)	0.81 (0.44–1.46)	.484
	No (n = 496)	1.33 (0.87–2.05)	.195
Red blood cell transfusion	Yes (n = 763)	1.63 (0.83–3.19)	.154
	No (n = 286)	1.14 (0.58–2.17)	.706
Cleveland score	≥3 (n = 150)	1.27 (0.60–2.71)	.528
	<3 (n = 899)	1.41 (0.99–2.01)	.060

[a] Defined as a preoperative hematocrit < 36% and < 39% in women and men, respectively.

CI = confidence interval, eGFR = estimated glomerular filtration rate, OR = odds ratio.

which may have masked the renal protective effect of a lower V_T. This is consistent with a similar trend observed in the subgroup of patients with a Cleveland score < 3 (OR: 1.41, 95% CI: 0.99–20.1; *P* = .060; Table 3 and Fig. 3). In addition, a higher V_T was associated with an increased risk of postoperative AKI in the male subgroup. In line with a previous report that female sex predisposes patients to receiving a high V_T,[40] the proportion of females was disproportionately greater in the high V_T group (40.0%) than in the low V_T group (11.5%; Table 1). While female sex was included as a risk factor in the Cleveland score,[22] some studies have shown that female sex may reduce the risk of AKI.[41] This potential protective effect may have attenuated the association between a high V_T and postoperative AKI in the total and female subgroups. The effect of V_T on the development of AKI may thus differ according to sex. Further, in the subgroup of patients with chronic kidney disease, the adverse effect of a high V_T may have been more pronounced, as the kidneys were already vulnerable to injury.[22] There was also a statistically significant association observed in the subgroup where left ventricular ejection fraction was < 35%.[22] A low V_T may therefore be beneficial for patients with these predisposing factors.

The current study has several limitations. First, this was an observational study based on data obtained from electronic medical records, and some baseline characteristics were imbalanced between the study groups. Although multivariable and subgroup analyses were performed to offset this imbalance, biases may still be present. Second, we only included the creatinine criteria of the Kidney Disease: Improving Global Outcomes to define postoperative AKI, as we did not have accurate data on postoperative urine output; therefore, the incidence of AKI may have been underestimated. Third, the ventilation strategy was not protocolized in detail and was performed at the discretion of the attending anesthesiologist. V_T, as well as parameters related to airway pressure, should be controlled in future randomized trials.

In conclusion, a higher intraoperative V_T (reflected by the median V_T/PBW) was not significantly associated with postoperative AKI in patients undergoing OPCAB. However, a high V_T was related to an increased risk of AKI in certain subgroups, including patients under 70 years of age, males, and patients with chronic kidney disease, a low left ventricular ejection fraction, or long surgery time. Randomized controlled trials should therefore follow in selected subgroups of patients undergoing off-pump cardiac surgery.

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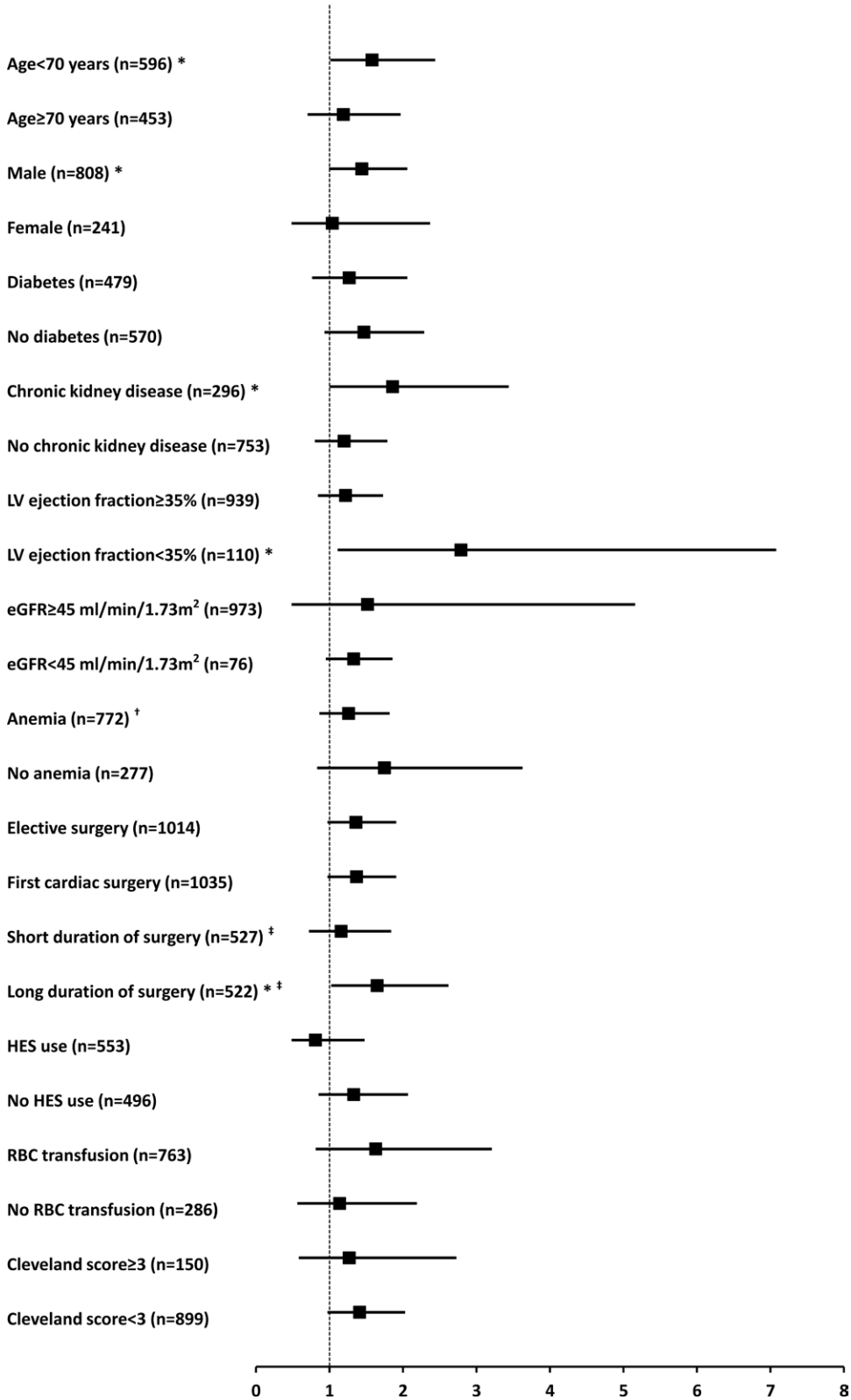

Figure 3. Subgroup analyses for postoperative AKI. LV = left ventricular; eGFR = estimated glomerular filtration rate; HES = hydroxyethyl starch; RBC = red blood cell. *Denotes statistical significance. †Defined as hematocrit < 36% and < 39% in female and male patients, respectively. ‡Short/long duration of surgery was defined as being less or greater than the median duration of surgery.

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