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 (VT) 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 (VT) 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 VT (≤8 ml/kg) groups (intraoperative median VT 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 VT group (OR: 1.15, 95% CI: 0.80–1.66; \( P = .459 \)); however, subgroup analyses revealed that a high VT 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 VTs 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, VT = tidal volume.

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

1. Introduction
Using a low tidal volume (VT) for mechanical ventilation in critically ill patients is reported to confer clinical benefits.[1,2] Compared with a higher VT, a VT 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 VT can exert injurious effects on the lung by inducing the expression of inflammatory mediators and reactive oxygen species.[5–7] Theoretically, a high VT 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.[6,8–10] Several studies have investigated the use of a low VT 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 VT 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 VT 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 VT may be more prominent in off-pump cardiac surgery; therefore, we hypothesized that a high intraoperative VT would increase the risk of AKI after off-pump cardiac surgery.

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How to cite this article: Bae J, Lee SJ, Lee H-C, Lee S, Ju J-W, Cho YJ, Jeon Y, Nam K. Relationship between intraoperative tidal volume and acute kidney injury following off-pump coronary artery bypass grafting: A retrospective observational study. Medicine 2022;101:147(e31563).

Received: 22 July 2021 / Received in final form: 5 October 2022 / Accepted: 6 October 2022
http://dx.doi.org/10.1097/MD.00000000000031563
This study aimed to assess the relationship between intraoperative VT 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.11

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 VT data; a history of end-stage renal disease or renal replacement therapy prior to surgery; current 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

Anesthesia 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. VT 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 cmH2O, 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 cmH2O.

2.3. Data collection and statistical analysis

The primary outcome was the association between the level of intraoperative VT and the risk of AKI after OPCAB. Before the analysis, patients were divided into 2 groups based on their intraoperative VT standardized to PBW (VT/PBW): high VT (>8 mL/kg) and low VT (≤8 mL/kg) groups. The median values were selected as representative values for intraoperative VT measurements. PBW (kg) was calculated as 0.91 × (height [cm] – 132.4) + 50 (male) or 45.5 (female).12 A VT/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.12,20 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, nor-epinephrine 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 χ2 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 VT/PBW and the log-odds of postoperative AKI. With 3 knots set at the 10th, 50th, and 90th percentiles of VT measurements, patients were divided into 2 groups based on their VT standardized to PBW (VT/PBW): high VT (>8 mL/kg) and low VT (≤8 mL/kg) groups. The median values were selected as representative values for intraoperative VT measurements. PBW (kg) was calculated as 0.91 × (height [cm] – 132.4) + 50 (male) or 45.5 (female).12

![Figure 1. Study flowchart](image)

Excluded (n=165)
- Due to missing tidal volume data (n=60)
- End-stage renal disease/renal replacement therapy (n=88)
- Pre-operative mechanical ventilation (n=10)
- Minimally invasive surgery via thoracotomy with one-lung ventilation (n=6)
- Due to missing pre-operative ejection fraction (n=1)

Finally analyzed (n=1049)
VT/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 VT group, compared with the low VT 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 VT 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 VT group (n = 626) | High VT group (n = 423) | \(P\) |
|----------------------|-------------|------------------------|-------------------------|------|
| **Median VT (mL)**   | 440 (392–472) | 488 (424–544)          | <.001                   |
| **Median VT/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\%)               | .500                    |      |
| 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                    |      |
| eGFR (mL/min/1.73 m\(^2\)) | 78.3 (22.2) | 70.3 (21.2)             | .997                    |      |
| Serum creatinine (mg/dL) | 1.3 (0.4) | 0.9 (0.3)               | <.001                   |      |
| Number of diseased vessels | .846 |                        |                         |      |
| 1-vessel disease     | 17 (2.7\%)  | 14 (3.3\%)             | .718                    |      |
| 2-vessel disease     | 99 (15.8\%) | 65 (15.4\%)            | .792                    |      |
| 3-vessel disease     | 510 (81.5\%) | 344 (81.3\%)           | .500                    |      |
| 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       | 81 (13.3\%) | 51 (12.1\%)            | .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\(_2\)O) | 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; VT = 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 \( V_T/\text{PBW} \) was ≤4 mL/kg in 626 patients (low \( V_T \) group) and >4 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 \( V_T/\text{PBW} \) 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 \( V_T/\text{PBW} \) (Fig. 2). However, the risk of postoperative AKI was not significantly different between the high \( V_T \) (\( V_T/\text{PBW} \geq 8 \) mL/kg) and low \( V_T \) (\( V_T/\text{PBW} < 8 \) 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).

In the subgroup analyses, a high intraoperative \( V_T/\text{PBW} \) 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 \( V_T/\text{PBW} \geq 8 \) 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,[24] 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[25]; 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.[26] Likewise, lung-protective ventilation strategies, including a low \( V_T \), were also tested in non-ARDS or perioperative settings[27]; however, whether a low \( V_T \) improves clinical outcomes remains controversial.[20,26–31] While some studies have shown that low, protective \( V_T \) mechanical ventilation attenuates inflammatory response[26,27] and reduces the incidence of pulmonary complications[29,30] or mortality,[3] others have not.[25,28,29]

The effect of mechanical ventilation on other peripheral organs—such as the kidneys—has also gained recent attention,[21] and the underlying mechanism has been described in several ways.[31] 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.[6,24,31] 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[23,32]; additionally, vasoconstriction and sodium and water retention occur as the sympathetic nervous system is activated for compensation.[33] Third, in response to a decrease in atrial stretch due to relative intravascular volume depletion, the secretion of antidiuretic hormone increases,[34] while atrial natriuretic peptide decreases.[35] 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 \( V_T \)s 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.[31]
Regarding cardiac surgery, only one small observational study has previously evaluated the relationship between Vₜ and AKI as a primary outcome. Tojo et al investigated 338 patients, demonstrating that the risk of AKI was significantly lower in patients with a Vₜ ≤ 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, the impact of a high Vₜ 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 Vₜ 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 Vₜ may be linearly associated with the risk of AKI. Moreover, a higher Vₜ 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).

### Table 2
Logistic regression for acute kidney injury after cardiac surgery.

|                          | Total cohort | Unadjusted | Adjusted |
|--------------------------|-------------|------------|----------|
|                          | OR (95% CI) | P          | OR (95% CI) | P |
| Low Vₜ group             | 1.00 (Reference) | 1.00 (Reference) |          |
| High Vₜ group            | 1.00 (0.75–1.34) | .980 | 1.15 (0.80–1.66) | .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/m²)  | 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 (0.98–2.31) | .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 (0.78–1.61) | .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 (1.84–10.10) |          |          |  |
| 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                  | 0.67 (0.47–0.98) | .375 |          |  |
| β blocker                | 0.90 (0.65–1.23) | .498 |          |  |
| Calcium channel blocker  | 1.00 (0.76–1.33) | .901 |          |  |
| ACEi/ARB                 | 1.17 (0.88–1.55) | .288 |          |  |
| Diuretics                | 1.59 (1.10–2.29) | .014 |          |  |
| Statin                   | 0.71 (0.56–0.94) | .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 |
| Reo surgery              | 2.37 (0.81–6.69) | .114 | 1.77 (0.53–5.97) | .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 (0.95–1.01) | .080 |          |  |
| Median intraoperative PIP (cmH₂O) | 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, Vₜ = tidal volume.
which may have masked the renal protective effect of a lower VT. This is consistent with a similar trend observed in the subgroup of patients with a Cleveland score < 3 (OR: 1.41, 95% CI: 0.99–2.01; P = .060; Table 3 and Fig. 3). In addition, a higher VT 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 VT,[40] the proportion of females was disproportionately greater in the high VT group (40.0%) than in the low VT 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 VT and postoperative AKI in the total and female subgroups. The effect of VT 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 VT 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 VT 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. VT, as well as parameters related to airway pressure, should be controlled in future randomized trials.

In conclusion, a higher intraoperative VT (reflected by the median VT/PBW) was not significantly associated with postoperative AKI in patients undergoing OPCAB. However, a high VT 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.

Acknowledgements

This study used clinical data retrieved from Seoul National University Hospital Patients Research Environment (SUPREME) system. We would like to thank Editage (www.editage.co.kr) for English language editing.

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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)       | .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 m² (n = 973) | 1.52 (0.49–5.14)       | .479 |
| <45 mL/min/1.73 m² (n = 76)    | 1.33 (0.97–1.84)       | .082 |
| Anemia 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 |

*Defined as a preoperative hematocrit < 36% and < 39% in women and men, respectively.
CI = confidence interval, eGFR = estimated glomerular filtration rate, OR = odds ratio.
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.
