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Anesthetics influence the incidence of acute kidney injury following valvular heart surgery

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Propofol has been shown to provide protection against renal ischemia/reperfusion injury experimentally, but clinical evidence is lacking. Here we studied the effect of propofol anesthesia on the occurrence of acute kidney injury following heart surgery with cardiopulmonary bypass. One hundred and twelve patients who underwent valvular heart surgery were randomized to receive either propofol or sevoflurane anesthesia, both with sufentanil. Using Acute Kidney Injury Network criteria, significantly fewer patients developed acute kidney injury postoperatively in the propofol group compared with the sevoflurane group (6 compared with 21 patients). The incidence of severe renal dysfunction was significantly higher in the sevoflurane group compared with the propofol group (5 compared with none). The postoperative cystatin C was significantly lower in the propofol group at 24 and 48 h. Serum interleukin-6 at 6 h after aorta cross-clamp removal, C-reactive protein at postoperative day 1, and segmented neutrophil counts at postoperative day 3 were also significantly lower in the propofol group. Thus, propofol anesthesia significantly reduced the incidence and severity of acute kidney injury in patients undergoing valvular heart surgery with cardiopulmonary bypass compared with sevoflurane. This beneficial effect of propofol may be related to its ability to attenuate the perioperative increase in proinflammatory mediators.

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Acute kidney injury (AKI) following cardiac surgery, even when mild and transient, undoubtedly poses the patients to increased risk of prolonged intensive care unit (ICU) stay, morbidity, and mortality.[1,2] Yet, its prevention proves to be difficult as the reported incidence of AKI reaches up to 40% depending on the type of surgery and the adopted definition of it.[1–3] The underlying mechanisms involved in the pathogenesis of AKI after cardiac surgery are multifactorial and are not completely understood, currently. Still, apart from the patient-related factors, cardiopulmonary bypass (CPB), which inevitably causes oxidative stress, ischemia–reperfusion (I/R) injury, and systemic inflammatory response, has been constantly incriminated as a major factor in causing AKI.[4,5] Even in the absence of a surgery-related overt ischemic insult by vascular clamps, CPB invariably causes injury to the renal medulla as it is prone to ischemic damage for having a unique blood supply with a limited oxygen reserve.[4]

Propofol is a widely used intravenous anesthetic agent, which bears structural similarity with the endogenous antioxidant α-tocoferol.[6] Propofol also has been shown to possess anti-inflammatory and immune-modulatory properties.[7,8] While volatile anesthetics have been well known to exert organ-protective effect against I/R injury experimentally, several animal studies suggested that propofol was more effective in attenuating the development of AKI after exposure to anoxic circumstances when compared with the volatile anesthetic agents.[7,8]

Considering the putative mechanisms leading to AKI, the antioxidant and anti-inflammatory properties of propofol may theoretically be able to attenuate renal injury in patients undergoing cardiac surgery with CPB. Although cumulative evidence suggests the lack of renoprotective effect by volatile anesthetics in cardiac surgical patients despite their solid experimental background,[9,10] a trial validating the efficacy of propofol as an anesthetic agent on preventing AKI after cardiac surgery would be worth noting.

The aim of this prospective, randomized, and controlled trial was to investigate the effect of propofol anesthesia on renal protection in patients undergoing CPB for valvular heart surgery, which comprises a high risk for AKI.

RESULTS

Valvular heart surgery was performed as planned in all patients, and complete follow-up data until discharge from the 112 patients were analyzed without any missing data. No relevant clinical problem occurred with either of the two anesthetic methods. Patients' demographics, preoperative characteristics including Cleveland Clinic score and EuroSCORE, and surgeries performed were similar between two groups (Table 1).

Operative data including durations of anesthesia, aortic cross-clamp (ACC) and CPB, fluid balance including the amounts of ultrafiltration, and packed erythrocyte transfusion requirement were similar between the two groups. The amount of norepinephrine required during the operation was significantly greater in the sevoflurane group (Table 2). In the propofol group, the infusion rates of propofol were 106 ± 36 and 125 ± 38 μg/kg/min during CPB and the entire operation period, respectively. Intraoperative hemodynamic variables including cardiac index were comparable between the groups (Table 3).

The total amount of infused fluid, blood loss, and urine output until 72 h after the operation was comparable between the groups. However, furosemide requirements during the first 24 h ($P = 0.035$) and 48–72 h ($P = 0.029$) after the operation were significantly higher in the sevoflurane group compared with the propofol group (Table 4).

Postoperatively, AKI occurred in 21 patients (37.5%) of the sevoflurane group compared with only 6 patients (10.7%) of the propofol group ($P = 0.001$). The number of patients with urine output of <0.5 ml/kg per hour continuously over 6 h but within 48 h after the operation was 9 (16.1%) in the sevoflurane group and 2 (3.6%) in the propofol group, respectively ($P = 0.026$). Five (8.9%) patients were diagnosed with AKI classified as Acute Kidney Injury Network stage 2 or 3 and two of these patients received dialysis in the sevoflurane group, while none in the propofol group ($P = 0.022$). The interaction of group and time in the creatinine, cystatin C, and creatine kinase-MB (CK-MB) levels ($P = 0.027$, 0.009, and 0.031, respectively) were significant between the groups in the linear mixed-model analysis. *Post hoc* analysis with Bonferonni correction revealed that cystatin C levels at 24 and 48 h postoperatively and creatine kinase-MB (CK-MB) levels at 48 h postoperatively were significantly lower in the propofol group compared with the sevoflurane group. The number of patients in whom estimated glomerular filtration rate (eGFR) declined $>30\%$ from the baseline value was significantly greater in the sevoflurane group compared with the propofol group (18 (32.1%) vs. 5 (8.9%), $P = 0.002$). The number of patients showing an increase in cystatin C levels $>25\%$ from the baseline value was greater in the sevoflurane group than in the propofol group (22 (39.3%) vs. 11 (19.6%), $P = 0.023$) (Table 5).

The interaction of group and time in serum interleukin (IL)-6, C-reactive protein (CRP) levels, and segmented neutrophil counts ($P = 0.019$, 0.027, and 0.007, respectively) were significant between the groups in the linear mixed-model analysis. After *post hoc* analysis with Bonferonni correction, serum levels of IL-6 were significantly lower in the propofol group at 6 h after declamping of ACC, and serum concentration of CRP at postoperative day (POD) 1 and segmented neutrophil counts at POD 3 were significantly lower in the propofol group compared with the sevoflurane group (Figure 1).

The length of hospital stay was significantly shorter in the propofol group compared with the sevoflurane group, whereas other postoperative outcomes including duration of ventilator care, ICU stay, and in-hospital mortality were similar between the groups (Table 6).

None of the patients developed unexplained lactic acidosis, rhabdomyolysis, or dyslipidemia, indicating propofol infusion syndrome.

Table 1 | Patient demographics and preoperative clinical data

Variables	Sevoflurane ($n = 56$)	Propofol ($n = 56$)
Age (years)	58.8 ± 12.3	58.1 ± 12.2
Female gender	32 (57.1)	29 (51.8)
Body mass index (kg/m^2)	23.3 ± 3.3	24.1 ± 3.7
Operation		
Aortic valve replacement	18 (32.1)	18 (32.1)
Mitral valve replacement only	28 (50)	24 (42.9)
Mitral valve replacement with TAP	6 (10.7)	6 (10.7)
Double valve replacement	2 (3.6)	5 (8.9)
Bental	1 (1.8)	2 (3.6)
Redo	1 (1.8)	1 (1.8)
Diabetes mellitus	7 (12.5)	9 (16.1)
Hypertension	16 (28.6)	18 (32.1)
Cerebrovascular accidents	7 (12.7)	4 (7.1)
Congestive heart failure	5 (8.9)	4 (7.1)
Chronic obstructive pulmonary disease	2 (3.6)	1 (1.8)
NYHA classification		
I	24 (42.9)	27 (48.2)
II	28 (50)	27 (48.2)
III	4 (7.1)	2 (3.6)
Preoperative ejection fraction	63.1 ± 10.1	65.2 ± 11.3
Medications		
β-Blockers	20 (35.7)	16 (28.6)
Calcium channel blockers	14 (25)	11 (19.6)
Renin–angiotensin system antagonist	20 (35.7)	21 (37.5)
Diuretics	36 (64.3)	35 (62.5)
EuroSCORE	2.9 ± 1.7	3.2 ± 2.3
Cleveland Clinic score	1.8 ± 0.8	1.9 ± 0.7

Abbreviations: NYHA, New York Heart Association; TAP, tricuspid annuloplasty.
Values are mean ± s.d. or number of patients (%).

DISCUSSION

In spite of advances in CPB technology, the incidence of AKI after cardiac surgery has increased during the past decade.[11] The pathogenesis of AKI after cardiac surgery encompasses complex interplays among multiple factors, CPB-related I/R injury, oxidative stress, and activation of systemic inflammatory reaction have been regarded as major determinants.[4,5] Numerous strategies including pharmacologic and

Table 2 | Intraoperative parameters

Variables	Sevoflurane ($n = 56$)	Propofol ($n = 56$)	*P*-value
Anesthesia time (min)	187 ± 49	188 ± 46	0.978
Aortic cross-clamp time (min)	70 ± 24	68 ± 24	0.583
Cardiopulmonary bypass time (min)	96 ± 31	94 ± 29	0.598
Amount of ultrafiltration (ml)	816 ± 513	861 ± 638	0.630
Fluid balance			
Crystalloid (ml)	1345 ± 458.7	1269.8 ± 454.9	0.850
Colloid (ml)	439.2 ± 223	438.9 ± 157.2	0.995
Urine output (ml)	1145 ± 446.5	1005.9 ± 368.7	0.075
Transfusion			
Amount of cell saver (ml)	567 ± 189	558 ± 227	0.818
Amount of erythrocyte (unit)	0.4 ± 0.7	0.3 ± 0.5	0.500
Patients transfused with erythrocyte	18 (32.1)	17 (30.4)	0.838
Vasopressors needs			
Mean norepinephrine dose during cardiopulmonary bypass (μg/kg/min)	0.04 ± 0.02	0.03 ± 0.03	0.110
Mean norepinephrine dose during operation (μg/kg/min)	0.05 ± 0.03	0.03 ± 0.03	0.004
Patients needed vasopressin	45 (80.4)	37 (67.1)	0.088
Vasopressin dose during CPB (unit)	1.41 ± 1.44	0.96 ± 1.35	0.105
Vasopressin dose during operation (unit)	2.18 ± 2.35	1.41 ± 2	0.061

Abbreviations: Amount of erythrocyte, number of units of erythrocyte transfused for the entire study group divided by the total number of subjects in that study group; CPB, cardiopulmonary bypass.
Values are mean ± s.d. or number of patients (%).

non-pharmacologic interventions have been attempted to prevent AKI associated with cardiac surgery without noticeable efficacy.[12,13]

Propofol is a widely used intravenous anesthetic agent with a proven antioxidant activity similar to α-tocoferol.[6] Propofol was also reported to modulate inflammatory reactions and oxidative stress in cardiac surgical patients.[7,8] The renoprotective effects of propofol against I/R injury has been demonstrated in animal experiments using renal artery or abdominal aorta clamping model,[14,15] and has also been reported to be superior to that of volatile anesthetics.[8] However, the renoprotective effect of propofol in cardiac surgical patients remains elusive and no comprehensive data exist in that regard.

In the current study, the incidence of AKI in the propofol group was 10.5% according to the Acute Kidney Injury Network criteria.[16] On the contrary, the incidence of AKI in the sevoflurane group was 37.5%, which was comparable to that of previous studies.[1,2] Moreover, AKI in the propofol group was confined to stage 1 of the Acute Kidney Injury Network criteria, whereas AKI in the sevoflurane group demonstrated various disease spectrum including dialysis requirement with significantly more number of patients having severe renal dysfunction. Also, significantly less patients in the propofol group developed eGFR decline of $>30\%$ and increase in serum creatinine level of $>25\%$ from baseline than in the sevoflurane group. Patients who developed a postoperative reduction in eGFR of $>30\%$ from baseline had a remarkably higher mortality,[17] and increase in serum creatinine level of $>25\%$ from baseline was associated with a hazard ratio of 1.63 for long-term mortality at 100 months after hospital discharge.[18]

In contrast to our results, one previous study comparing sevoflurane and propofol anesthesia reported no significant difference in the incidence of AKI.[19] The observed discrepancy may be explained by an inadequate target concentration of propofol. Although propofol concentrations producing renoprotection are unknown, that for cardioprotection has been reported to between 25 and 50 mmol/l (4.5–8.9 μg/ml) and the predicted infusion rate to achieve a mean plasma concentration of 5 μg/ml was 113 μg/kg per min during CPB.[20] Propofol at relatively low concentrations could not counteract oxygen free radical production, which is greatly increased during reperfusion or CPB.[21] In the previous study,[19] only a broad propofol target concentration of 1–8 μg/ml was presented and not the actual target concentration or the total consumption of propofol during surgery. In the current study, mean infusion rate of propofol was 125 ± 38 μg/kg/min during the surgery, which is comparable to the dose known to exert cardioprotection.

Notwithstanding the inherent limitations with regard to the definition of AKI based on the serum creatinine level, the serum cystatin C level was suggested to be a more reliable predictor of AKI after cardiac surgery.[22] Confirmation of AKI by cystatin C demonstrated a potential to predict high-risk patients for adverse outcome among patients who developed AKI detected by serum creatinine elevation.[23] In the present study, serum cystatin C levels were significantly lower in the propofol group compared with the sevoflurane group at POD 1 and POD 2. When defining AKI as an increase in cystatin C of 25% or more from the baseline value,[23] the incidence of AKI still remained to be significantly lower in the propofol group compared with the sevoflurane group in the current study.

Cardiac surgery with CPB is invariably associated with systemic inflammatory response.[4] Uncontrolled systemic inflammation may lead to tissue damage, or even organ failure.[24] In the current study, serum IL-6 levels were significantly lower at 6 h after declamping of ACC in the propofol group than in the sevoflurane group. Also, serum concentrations of CRP at POD 1 and segmented neutrophil counts at POD 3 were significantly lower in the propofol group. These results are in agreement with the results of previous experimental studies that showed propofol's ability to attenuate the release of proinflammatory cytokines including IL-1, IL-6, and tumor necrosis factor-α.[25–27] Serum IL-6 was suggested to be an early biomarker of AKI after cardiac surgery with CPB,[28] and to be related to severe acute renal dysfunction after cardiac surgery with CPB.[29] Moreover, high serum IL-6 levels are known to be associated with prolonged mechanical ventilation.[28] In the present study, the length of hospital stay was significantly shorter in the propofol group compared with the sevoflurane group. In addition, there was a trend toward a shorter duration of ventilator care and length of ICU stay in the propofol group.

Table 3 | Intraoperative hemodynamic change

Variables	Sevoflurane ($n = 56$)	Propofol ($n = 56$)	Estimate (95% CI)	*P*-value
Heart rate (b.p.m.)				0.772[a]
Before induction	75.5 ± 16.7	76.3 ± 12.9	−0.804 (−6.344 to 4.736)	>0.999
After induction	64.3 ± 11.7	65.1 ± 10.5	−0.875 (−4.992 to 3.242)	>0.999
Pericardium open	68.2 ± 12.4	67.8 ± 10.8	0.46 (−3.865 to 4.758)	>0.999
Postcardiopulmonary bypass	81 ± 13	80.7 ± 11.3	0.321 (−4.192 to 4.834)	>0.999
Sternum closure	89.9 ± 14.7	87.2 ± 14.2	2.804 (−2.560 to 8.167)	>0.999
Mean arterial pressure (mm Hg)				0.505[a]
Before induction	91.6 ± 12.2	93.6 ± 13.6	−2.036 (−6.821 to 2.750)	>0.999
After induction	78.5 ± 9.4	78.1 ± 11.1	0.357 (−3.459 to 4.173)	>0.999
Pericardium open	72 ± 9.6	75.2 ± 11.6	−3.321 (−7.273 to 0.631)	>0.999
Postcardiopulmonary bypass	69.8 ± 10.7	73.2 ± 12	−3.393 (−7.607 to 0.821)	>0.999
Sternum closure	69.5 ± 8.1	71.3 ± 9.1	−1.821 (−5.034 to 1.391)	>0.999
Pulmonary capillary wedge pressure (mm Hg)				0.733[a]
Before induction	17.7 ± 6	17.1 ± 6	0.768 (−1.416 to 2.951)	>0.999
After induction	16.1 ± 4.9	14.7 ± 4.8	1.482 (−0.306 to 3.270)	>0.999
Pericardium open	16.1 ± 5.3	15.2 ± 4.7	0.964 (−0.899 to 2.828)	>0.999
Postcardiopulmonary bypass	15.3 ± 3.8	14.8 ± 3.6	0.446 (−0.919 to 1.812)	>0.999
Sternum closure	16.3 ± 3.9	15.6 ± 3.5	0.679 (−0.683 to 2.040)	>0.999
Central venous pressure (mm Hg)				0.366[a]
Before induction	8.9 ± 2.6	8.9 ± 3.1	0.000 (−1.072 to 1.072)	>0.999
After induction	8.9 ± 2.4	8.8 ± 2.8	0.125 (−0.859 to 1.109)	>0.999
Pericardium open	8.6 ± 2.2	8.6 ± 2.6	−0.018 (−0.902 to 0.867)	>0.999
Postcardiopulmonary bypass	10.3 ± 2.8	9.4 ± 2.6	0.946 (−0.055 to 1.948)	>0.999
Sternum closure	11.1 ± 2.2	10.3 ± 2.5	0.821 (−0.045 to 1.688)	>0.999
Cardiac index (l/min/m^2)				0.725[a]
Before induction	2.5 ± 0.6	2.6 ± 0.6	−0.045 (−0.275 to 0.185)	>0.999
After induction	2.4 ± 0.7	2.5 ± 0.7	−0.129 (−0.387 to 0.129)	>0.999
Pericardium open	2.3 ± 0.5	2.5 ± 0.6	−0.146 (−0.340 to 0.047)	>0.999
Postcardiopulmonary bypass	2.7 ± 0.6	2.8 ± 0.8	−0.125 (−0.384 to 0.134)	>0.999
Sternum closure	2.8 ± 0.6	2.9 ± 0.7	−0.141 (−0.378 to 0.095)	>0.999

Abbreviations: CI, confidence interval; CPB, cardiopulmonary bypass; pericardium open, 5 min after pericardium opening; postcardiopulmonary bypass, 15 min after weaning from CPB; after induction, 15 min after anesthetic induction; before induction, before anesthetic induction.
Values are mean ± s.d.
[a]$P_{Group\times Time}$, *P*-value of the group and time interaction obtained by the linear mixed model.

In contrast to the results of the current study, numerous experimental studies reported the renoprotective effect of inhalation agents against renal I/R injury. In the recent study, isoflurane was reported to exert renoprotection through the induction of ecto-5′-nucleotidase,[30] while sevoflurane exerted protective effect through anti-inflammatory and antinecrotic effects during I/R injury in an *in vitro* study using proximal tubule cells of the human kidney.[31] Although propofol has been shown to be superior to sevoflurane in terms of modulating inflammatory markers and oxidative stress during suprarenal aortic clamping,[32] clinical studies comparing the renoprotective effects of propofol with inhalation agents in cardiac surgeries under CPB are scarce. Regarding the multifactorial causes of AKI, direct translation of the results of previous studies to clinical field needs caution and merits further studies.

Although propofol can decrease systemic blood pressure, its safety with adequate dosing and intravenous fluid supplementation in cardiac surgical patients has been proven already.[33] Paradoxically, the mean dose of norepinephrine administered during the surgery was significantly lower in the propofol group. This may be attributable to the anti-inflammatory property of propofol considering the significant influence of inflammatory response to the vascular tone. Less norepinephrine requirement may be a confounding factor in the development of AKI; however, as the norepinephrine dosage was well below 0.1 μg/kg/min in all patients, its influence should be negligible.

Of note, postoperative CK-MB levels were significantly lower in the propofol group compared with the sevoflurane group in the current study. Yet, it is beyond the scope of this study to draw a definite conclusion in that regard, as it was not sufficiently powered to address the cardioprotective effect of propofol.

The limitations of this study are as follows. First, although the end points of this study were assessed by objective parameters, the attending anesthesiologist could not be blinded to the patients' group allocation. Second, even though the differences we observed were significant, our results have limited implications owing to insufficient sample size. Specifically, the incidence of AKI in the present study was lower than that of our previous study involving anemic

Table 4 | Postoperative fluid balance

Variables	Sevoflurane ($n = 56$)	Propofol ($n = 56$)	*P*-value
Crystalloid (ml)			
ICU arrival ~24 h	3555 ± 774	3313 ± 971	0.148
24–48 h	2054 ± 793	2168 ± 860	0.466
48–72 h	1287 ± 1080	1128 ± 767	0.401
Colloid (ml)			
ICU arrival ~24 h	301 ± 270	334 ± 274	0.533
24–48 h	35 ± 122	40 ± 96	0.804
48–72 h	2 ± 13	6 ± 27	0.271
Blood loss (ml)			
ICU arrival ~24 h	382 ± 338	394 ± 384	0.856
24–48 h	230 ± 169	218 ± 172	0.712
48–72 h	95 ± 92	98 ± 108	0.884
Urine output (ml)			
ICU arrival ~24 h	2802 ± 795	2862 ± 776	0.689
24–48 h	2543 ± 786	2716 ± 897	0.279
48–72 h	2082 ± 1105	2341 ± 1049	0.206
Diuretics usage (mg)			
0–24 h	13.1 ± 13.9	8.6 ± 7.8	0.035
24–48 h	29.7 ± 49.7	24.2 ± 31.9	0.485
48–72 h	11.3 ± 23.9	3.9 ± 7.4	0.029

Abbreviations: Diuretics usage, daily accumulated dose of furosemide; ICU, intensive care unit.
Between-group comparisons of the variables during corresponding periods were performed by the independent Student's *t*-test.
Values are mean ± s.d.

patients,[34] upon which the sample size of the current study was calculated. The relative risk of AKI occurrence in the propofol group compared with the sevoflurane group was 0.285 in our study. As noted by Chertow *et al.*,[35] such a large effect size is not plausible and likely overestimates the true effect. Owing to the small sample size and single-center design, our results must be confirmed in a larger multicenter trial before changes in practice can be recommended. Our results could contribute to a meta-analysis of previous[19] and any future comparisons of propofol and sevoflurane. Furthermore, as the current study was performed in a relatively low-risk group of patients with preoperatively normal renal function, the results should not be extrapolated to high-risk patients for AKI.

In conclusion, propofol anesthesia was associated with a significant reduction in the incidence and severity of AKI in patients undergoing valvular heart surgery with CPB compared with sevoflurane anesthesia, when used in conventional dosage for general anesthesia. This beneficial effect of propofol may be related to its ability to attenuate the perioperative increase in proinflammatory mediators.

MATERIALS AND METHODS

Patients

This trial was conducted at Yonsei University Health System, Seoul, Republic of Korea between May 2011 and February 2012. After the approval of Institutional Review Board (1-2011-0007) and registration at the clinicaltrial.gov (Unique Identifier: NCT01384643), this study was performed in full compliance with the Declaration of Helsinki Principles. Participants were recruited at the anesthesiology preoperative evaluation clinic and gave written informed consent. One hundred and twelve patients who were scheduled for valvular heart surgery and did not correspond to the following exclusion criteria were enrolled. Enrolled patients were immediately randomly assigned in a 1:1 ratio for parallel arms by means of a table of random numbers generated by a computer with sealed envelopes to either the propofol ($n = 56$) or the sevoflurane group ($n = 56$). There were no stratification and blocking on randomization. Study investigators except the anesthetist who took part in the operation were blinded to the group assignment. We excluded patients with pre-existing renal insufficiency (serum creatinine level $\geqslant 1.5$ mg/dl in men or $\geqslant 1.3$ mg/dl in women),[36] older than 80 years, coronary artery occlusive disease, hepatic or pulmonary disease, active infective endocarditis, left ventricular ejection fraction $< 30\%$, myocardial infarction within 4 weeks, or with a history of hypersensitivity to propofol. In addition, patients undergoing surgery requiring hypothermic circulatory arrest were also excluded.

This trial was overseen by an independent data safety monitoring board. The independent committee had reviewed our data when 15%, 33%, and 66% of the anticipated number of patients were accumulated to ensure safe and ethical treatment of research participants, data quality, and credibility of study findings, respectively.

Experimental protocol and anesthetic regimen

Patients in the propofol group received 1 mg/kg of propofol and 1.0–3.0 μg/kg of sufentanil for anesthetic induction. Anesthesia was maintained with continuous infusion of propofol 60–250 μg/kg/min and sufentanil 0.5 μg/kg/h to maintain the bispectral index score between 40 and 60 throughout the operation. Propofol 1 mg/kg and sufentanil 1 μg/kg were additionally given upon commencement of CPB.

In the sevoflurane group, the patients received 0.05 mg/kg of midazolam and 1.0–3.0 μg/kg of sufentanil for anesthetic induction. Anesthesia was maintained with sevoflurane (0.6–1.5%) and continuous infusion of sufentanil 0.5 μg/kg/h to maintain the bispectral index score between 40 and 60 throughout the operation. Midazolam 0.1 mg/kg and sufentanil 1 μg/kg were additionally given upon commencement of CPB (Figure 2).

In all patients, neuromuscular blockade was achieved with 0.9 mg/kg of rocuronium bromide followed by continuous infusion of vecuronium 8–10 mg/h.

Perioperative management

All patients received standardized anesthetic care and CPB management. CPB was instituted with a membrane oxygenator primed with 1.6 l priming solution consisting of 100 ml 20% human albumin, 20% mannitol (0.5 g/kg), sodium bicarbonate (20 mEq), heparin (2000 IU), acetated Ringer's solution (Plasma Solution A Inj.; CJ Pharma, Seoul, Korea), and experimental drugs. Body temperature was cooled to 32–33 °C. Acid–base management was conducted with α-stat methods. A non-pulsatile pump flow rate was maintained at 2.0–2.5 l/min/m^2. During the period before and after CPB, crystalloid solution was infused at a fixed rate of 6–8 ml/kg/h, whereas colloid solution (Voluven; Fresenius Kabi, Bad Homburg, Germany) was infused to compensate for the amount of blood loss at a maximal dose of 20 ml/kg per day. During the operation including CPB, mean arterial blood pressure was maintained between 60 and 80 mm Hg. For vasopressor support, norepinephrine and vasopressin were used. All patients received a loading dose of 1 g tranexamic acid followed by an infusion of 200 mg/h during the operation, and

Table 5 | Variables associated with renal and cardiac outcomes

Variables	Sevoflurane ($n = 56$)	Propofol ($n = 56$)	Estimate (95% CI)	*P*-value
Postoperative AKI[a]				0.007
No AKI	35 (62.5)	50 (89.3)		
Stage 1	16 (28.6)	6 (10.7)		
Stage 2	3 (5.4)	0 (0)		
Stage 3	2 (3.6)	0 (0)		
Oliguria within 48 h	9 (16.1)	2 (3.6)		0.026
Postoperative dialysis	2 (3.6)	0 (0)		0.154
Creatinine increased 25% or more[a]	28 (50)	17 (30.4)		0.034
eGFR declined 30% or more[a]	18 (32.1)	5 (8.9)		0.002
Cystatin C increased 25% or more	22 (39.3)	11 (19.6)		0.023
Creatinine (mg/dl)				0.027[b]
Baseline	0.85 ± 0.18	0.84 ± 0.18	0.011 (−0.057 to 0.078)	>0.999
ICU arrival	0.78 ± 0.18	0.76 ± 0.16	0.020 (−0.042 to 0.083)	>0.999
POD 1[c]	1.12 ± 0.46	0.95 ± 0.24	0.170 (0.033 to 0.306)	0.084
POD 2[c]	1.02 ± 0.40	0.88 ± 0.28	0.139 (0.011 to 0.267)	0.178
POD 3[c]	0.89 ± 0.28	0.78 ± 0.2	0.110 (0.018 to 0.201)	0.102
eGFR (ml/min per 1.73 m^2)				0.063[b]
Baseline	85.6 ± 19	85.9 ± 18	−0.270 (−7.116 to 6.577)	>0.999
ICU arrival	91.6 ± 18.9	92.8 ± 17.1	−1.185 (−7.871 to 5.501)	>0.999
POD 1[c]	71.9 ± 27.5	78.1 ± 21.2	−6.284 (−15.373 to 2.805)	>0.999
POD 2[c]	76.8 ± 26.8	84.1 ± 25.7	−7.336 (−17.059 to 2.388)	>0.999
POD 3[c]	84.6 ± 23.2	91.2 ± 18.9	−6.619 (−14.450 to 1.212)	>0.999
Cystatin C (mg/dl)				0.009[b]
Baseline	0.96 ± 0.20	0.92 ± 0.16	0.040 (−0.026 to 0.106)	0.965
ICU arrival	0.86 ± 0.17	0.84 ± 0.20	0.006 (−0.056 to 0.068)	>0.999
24 h	1.11 ± 0.41	0.92 ± 0.24	0.167 (0.040 to 0.294)	0.044
48 h	1.21 ± 0.43	0.93 ± 0.35	0.170 (0.045 to 0.295)	0.035
CK-MB (ng/ml)				0.031[b]
Baseline	2.3 ± 1.2	2.3 ± 0.7	0.194 (−0.407 to 0.796)	>0.999
24 h	43.4 ± 47.3	28.2 ± 20.4	14.729 (1.151 to 28.306)	0.108
48 h	26.2 ± 17.9	19 ± 8	7.376 (2.173 to 12.579)	0.019

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CK-MB, creatine kinase-MB; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; oliguria within 48 h, the patients with urine output of <0.5 ml/kg/h for >6 h continuously within 48 h after the operation; POD, postoperative days.
Values are number of patients (%) or mean ± s.d.
[a]Analyzed with highest creatinine value during postoperative 48 h.
[b]$P_{Group\times Time}$, *P*-value of the group and time interaction obtained by the linear mixed model.
[c]Analyzed with highest creatinine value during corresponding period.

another loading dose of 1 g upon commencement of CPB. Blood salvaged by the cell salvage device was reinfused into the patient before the end of operation. All patients were transferred to the ICU after the surgery, and sedated using remifentanil either with or without dexmedetomidine as appropriate.

Clinical evaluations

The primary end point was to compare the incidence of AKI. AKI was defined as an absolute increase in serum creatinine of 0.3 mg/dl or an increase to ⩾150% from the baseline value or a urine output of <0.5 ml/kg per hour for >6 h within 48 h after the operation using the modified Risk, Injury, Failure, Loss, and End-stage Kidney Disease classification by the Acute Kidney Injury Network[37] (stage 1 = serum creatinine of ⩾0.3 mg/dl or an increase to ⩾150–200% from the baseline value or a urine output of <0.5 ml/kg/h for >6 h; stage 2 = serum creatinine of >200–300% from the baseline value or a urine output of <0.5 ml/kg/h for >12 h; stage 3 = serum creatinine of >300% from the baseline value or a urine output of <0.5 ml/kg/h for >24 h or anuria for 12 h). To evaluate renal function, serum creatinine concentrations were assessed 1 day before the operation, upon ICU arrival, at least two times a day until POD 3, and additionally as needed according to clinical situations. We also monitored urine output hourly up to 72 h after the operation. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as $141\times\min(\text{serum creatinine}/\kappa, 1)^{\alpha}\times\max(\text{serum creatinine}/\kappa, 1)^{-1.209}\times0.993^{\text{Age}}\times1.018$ (if female), where κ is 0.7 for women and 0.9 for men, and α is −0.329 for women and −0.411 for men.[38] Serum cystatin C was measured 1 day before the operation, upon ICU arrival, and at 24 and 48 h after the operation.

The secondary end points were to compare perioperative changes in serum biomarkers of renal injury and inflammatory mediators, and occurrence of postoperative complications. To evaluate the degree of inflammation, IL-1, IL-6, and tumor necrosis factor-α were assessed at 15 min after anesthetic induction and after 1, 6, and 24 h after declamping of the ACC. CRP was measured 1 day before the operation and POD 1. Neutrophil counts were determined 1 day before the operation, upon ICU arrival, and POD 1, 2, and 3. CK-MB was measured 1 day before the operation, and at 24 and 48 h after the operation.

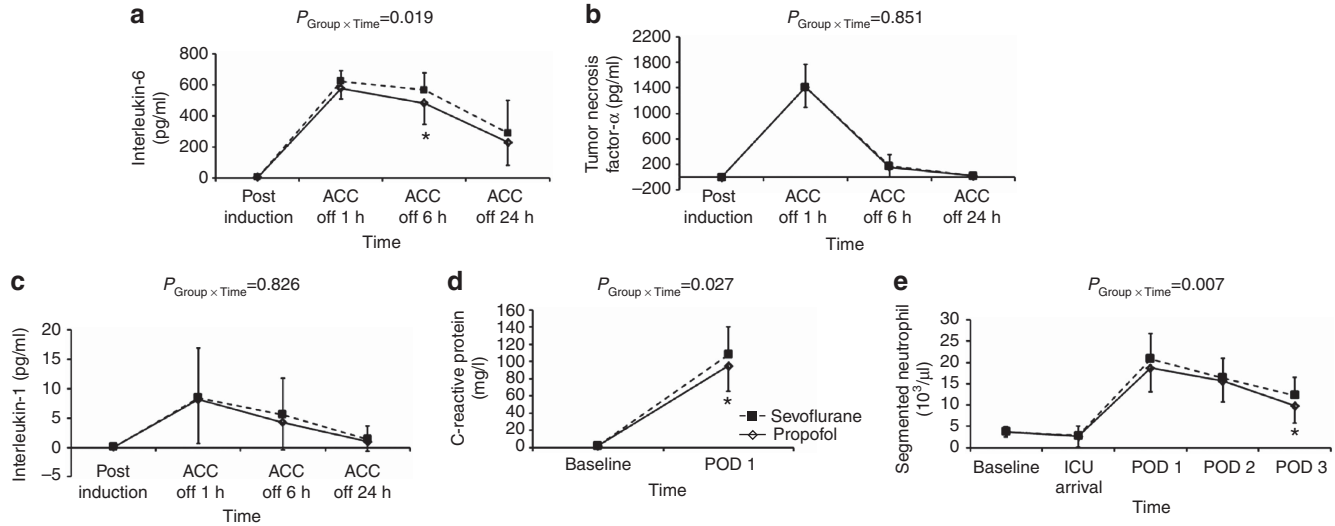

Figure 1 | Perioperative changes in inflammatory markers. ACC off, after declamping of the aorta cross clamping; ICU, intensive care unit; $P_{Group \times Time}$, *P*-value of the group and time interaction obtained by the linear mixed model; POD, postoperative days. * of **a**, mean difference and 95% confidence interval is 75.541 and 23.358–127.724, respectively, and *P*-value is 0.024 after Bonferroni correction; * of **d**, mean difference and 95% confidence interval is 13.108 and 1.483–24.733, respectively, and *P*-value is 0.050 after Bonferroni correction; * of **e**, mean difference and 95% confidence interval is 2.454 and 0.911–3.997, respectively, and *P*-value is 0.012 after Bonferroni correction. Values are mean ± s.d.

Table 6 | Postoperative outcome

Variable	Sevoflurane (*n* = 56)	Propofol (*n* = 56)	*P*-value
Reoperation for bleeding	1 (1.8)	0 (0)	0.315
Reintubation	0 (0)	0 (0)	0.999
Duration of ventilator care (h)	18.6 ± 9.5	16.8 ± 8.4	0.286
Duration of ICU stay (days)	3.1 ± 1.7	2.6 ± 0.6	0.051
Duration of hospital stay (days)	15.6 ± 7.5	12.3 ± 3.9	0.005
In-hospital mortality	0 (0)	0 (0)	0.999

Abbreviations: ICU, intensive care unit.
Values are mean ± s.d. or number of patients (%).

Assessed preoperative variables included demographic data, type of surgery, comorbid conditions (including presence of diabetes mellitus, hypertension, cerebrovascular accidents, congestive heart failure, and/or chronic obstructive pulmonary disease), New York Heart Association Functional classification, preoperative left ventricular ejection fraction, medications, and logistic EuroSCORE.[39] The Cleveland Clinic score was also evaluated to assess the estimated probability of AKI in each group.[40]

Assessed intraoperative variables included anesthesia time, duration of ACC and CPB, amount of ultrafiltration, fluid balance and urine output, and vasopressor requirements. Intraoperative hemodynamics including heart rate, mean arterial pressure, pulmonary capillary wedge pressure, central venous pressure, and cardiac index were recorded at 15 min after anesthetic induction, opened pericardium, weaning from CPB, and sternum closure.

Assessment of postoperative variables included the amount of bleeding measured by chest tube drainage, fluid balance and urine output, and diuretics usage for 72 h after surgery, and also application of renal replacement therapy. The indications of renal replacement therapy at our hospital include refractory fluid overload, hyperkalemia (plasma potassium concentration > 6.5 mEq/l) or rapidly rising potassium levels, signs of uremia, metabolic acidosis (pH < 7.1). Renal replacement therapy is considered to initiate before the development of symptoms and signs of renal failure due to AKI in the patients after cardiac surgery. The final decision to apply renal replacement therapy is based on the aforementioned policy of our hospital and expert opinion of the nephrologist. Also, the incidence of reintubation and hemostatic reoperation, duration of ventilator care, lengths of ICU stay and hospital stay, and in-hospital mortality were assessed. We also

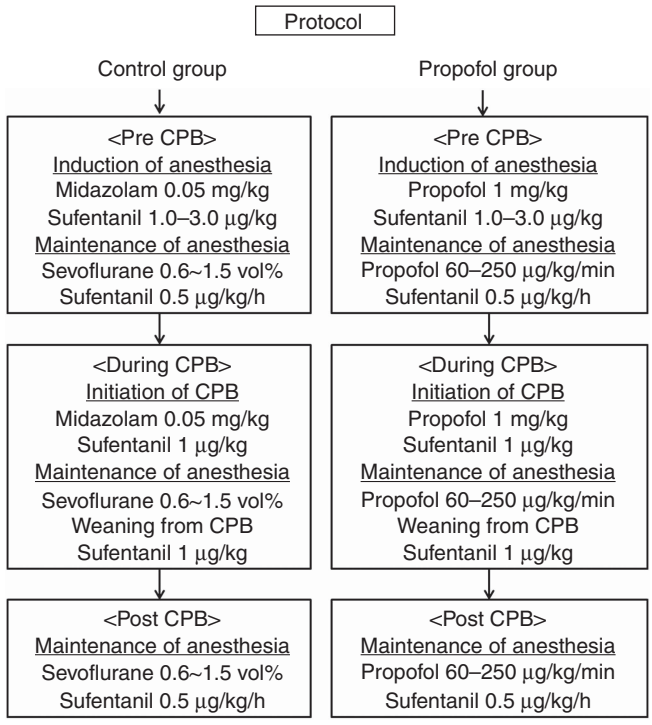

Figure 2 | Experimental protocol and anesthetic regimen. CPB, cardiopulmonary bypass.

monitored the occurrence of metabolic acidosis, rhabdomyolysis, and dyslipidemia within 3 days after the operation to monitor the occurrence of propofol infusion syndrome.

A physician who was blinded to patient's allocation assessed postoperative variables during study periods.

Statistical analysis

Continuous variables are shown as mean ± s.d. and dichotomous variables as numbers (percentages). Between-group comparisons of continuous variables were performed by independent Student's *t*-test. Dichotomous variables were compared using χ^2 or Fisher's exact tests, as appropriate. Repeated measure variables such as creatinine, eGFR, cystatin C, IL-1, IL-6, tumor necrosis factor-α, CRP, neutrophil counts, CK-MB, and intraoperative hemodynamics were analyzed using a linear mixed model with patient indicator as a random effect, and group, time, and group-by-time as fixed effects. When the interactions of group, time, group-by-time of the variables showed statistical significance, *post hoc* analysis was carried out with Bonferroni correction for the adjustment for multiple comparisons. All statistical tests were two-tailed. *P*-values <0.05 were considered statistically significant. This study was designed to determine the superiority of propofol on renal protection. In our previous study,[34] using the same anesthetic method as in the sevoflurane group, the incidence of AKI was 54%. A power estimation analysis of that study suggested that 56 patients per group would be required to obtain a power of 80%, considering a type I error of 0.05, and expecting a reduction of 50% in the incidence of AKI. All statistical analyses were performed using SPSS software version 19.0 (SPSS, Chicago, IL).

DISCLOSURE

All of the authors have participated in the design, execution, and analysis of this work and have approved the final version of the manuscript. All authors have no commercial associations that might pose a conflict of interest in connection with the submitted article. All the authors declared no competing interests.

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