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ORIGINAL ARTICLE

No renal protection from volatile-anesthetic preconditioning in open heart surgery

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Abstract
Purpose Acute kidney injury (AKI) is a common complication of open heart surgery (OHS). Preconditioning with volatile anesthetics is well proven to provide myocardial protection. Renal protection provided by volatile-anesthetic preconditioning has also been investigated; however, it is still controversial at the clinical level. This study aimed to investigate whether preconditioning with volatile anesthetics could mediate renal protection in OHS.
Methods A retrospective analytic study was designed. Medical records of patients (age ≥20 years) who had undergone OHS were reviewed. Types of anesthesia were classified as 'opioid-based anesthesia' (O group) and 'volatile-anesthetic-based anesthesia' (V group) according to the definitions given in the main text. Some medical records that had incomplete or ambiguous data were excluded. Renal protection was considered to be present if there was no clinical renal dysfunction as defined by the criteria given in the main text. AKI was considered to be present when there was a decrease of the postoperative estimated glomerular filtration rate (eGFR) that was >25 % of the preoperative eGFR. Also, postoperative 24-h oliguria (post-oliguria) and the provision of postoperative 48-h dialysis (post-dialysis) were considered. Differences between the O and V groups were tested by the appropriate statistics. A p value of <0.05 indicated significance.
Results A total of 1,122 patients (702 males) were included in this study. The O and V groups included 704 and 418 patients, respectively. AKI was present in 9.52 and 8.37 % of the patients in the O and V groups, respectively ($p = 0.532$). Post-oliguria was found in 36.08 and 37.79 % of the patients in the O and V groups; and post-dialysis was provided in 3.98 and 4.31 %, respectively, of these patients; these two parameters showed no significant differences between the groups.
Conclusions This study could not demonstrate volatile-anesthetic-mediated renal protection in OHS. Therefore, in practice, pharmacological preconditioning with volatile anesthetics did not seem to be beneficial.

Keywords Volatile-anesthetic preconditioning · Renal protection · Acute kidney injury

Introduction

Acute kidney injury (AKI) is a common complication of open heart surgery (OHS) with cardiopulmonary bypass (CPB) machines. Postoperative AKI events occur in up to 45 % of OHS patients [1]. But, importantly, postoperative renal impairment in OHS patients leads to a mortality as high as 60 % [2]. Therefore, prevention of AKI after OHS should be taken into consideration. Pharmacological preconditioning is one of the strategies for AKI prevention [3].

The preconditioning concept was originally derived from pioneering studies that demonstrated some extent of isolated myocardial protection after occlusion of the coronary arteries [4]. Subsequently, preconditioning by producing ischemia ('ischemic preconditioning') in the human myocardium has been abundantly investigated and it has been accepted that an episode of ischemia was associated with myocardial protection [5]. The mechanism of ischemic preconditioning was finally revealed to involve the activation of intracellular molecules and signaling

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pathways, which finally results in a decrease in the cellular demand for oxygen [4–7].

Interestingly, some pharmaceuticals have been found to also produce myocardial protection after an ischemic insult. In other words, the organ protection was conferred by pharmacological preconditioning. The mechanism of pharmacological preconditioning, especially that produced by volatile anesthetics, is claimed to mimic the mechanism of ischemic preconditioning [8]. Thus, the concept of preconditioning refers to an intracellular process of cellular protection that occurs by the modulation of intrinsic molecular signaling processes (preconditioning-related mechanism) arising from either ischemia or pharmacological preconditioning.

The pharmacological preconditioning provided by volatile anesthetics has become interesting for OHS, because volatile anesthetics are used in practice in OHS, and OHS is highly associated with organ ischemia. Therefore, based on the concept of preconditioning, the use of volatile anesthetics should lead to organ protection in OHS. As expected, a number of clinical investigations have indicated the existence of myocardial protection provided by volatile-anesthetic-induced preconditioning in OHS [9–12]. Therefore, it is possible that renal protection could be mediated by volatile-anesthetic-induced preconditioning [9]. In animal studies, some investigations initially demonstrated that renal protection after ischemia and reperfusion might be associated with a preconditioning-related mechanism [13–15]. In a clinical study, Julier et al. [16] reported that preconditioning with sevoflurane in patients undergoing coronary artery bypass grafting (CABG) could provide some renal protection. In spite of a special interest in myocardial protection, De Hert and colleagues (Lorsomradee et al. [17]) carried out a large-scale study regarding the protective effect provided by volatile-anesthetic-induced preconditioning in other organs. With serum creatinine as a biomarker, they found no significant difference in renal impairment between two groups of patients, one group who received anesthesia including sevoflurane and the other group who did not have any volatile anesthetic [17]. Thus, it seems that renal protection produced by volatile-anesthetic-induced preconditioning in OHS is still controversial.

Against this background, this study aimed to reveal whether or not preconditioning with volatile anesthetics leads to renal protection in OHS.

Methods

After approval for the study was received from the institutional review board (IRB) committee, this retrospective study was conducted at King Chulalongkorn Memorial Hospital. All patients who had undergone OHS between 2003 and 2009 were recruited (n=3,064). Inclusion criteria were age $\geq$20 years and that the operations were performed under cardiopulmonary bypass (CPB). All medical records of the recruited patients were reviewed by the researchers and their assistants.

Data that were planned to be collected included demographic data and perioperative characteristics, such as age, gender, underlying conditions, medications, preoperative laboratory data, CPB time, and postoperative cardiovascular instability (post-CVI). Post-CVI was defined either as an event of adrenalin and/or noradrenalin infusion, a new-onset atrial fibrillation (AF) and/or ventricular dysrhythmia, or intra-aortic balloon pump (IABP) support within 48 h postoperatively. The type of operation was recorded, and classified as CABG, valve surgery, aortic surgery, or combined surgery. The type of anesthetic technique and postoperative renal dysfunction were also extensively reviewed.

Postoperative renal dysfunction was reviewed through three parameters. The first parameter was the estimated glomerular filtration rate (eGFR), which was calculated by the Mayo quadratic formula from the preoperative serum creatinine level as a baseline (pre-eGFR), and the eGFR, calculated similarly from the serum creatinine on the first postoperative day (postoperative eGFR [post-GFR]). The second parameter was the accumulated urine output on the first postoperative day (total urine in 24 h) that was $<$12 ml/kg (termed post-oliguria). The third parameter was the need for dialysis in the 48-h postoperative period (post-dialysis), defined as new hemodialysis or peritoneal dialysis performed within 48 h postoperatively (not including patients who needed long-term dialysis).

The anesthetic techniques were classified as volatile-anesthetic-based anesthesia (V group) and opioid-based anesthesia (O group). The V group was defined as those patients who received sevoflurane or isoflurane (at least 1 minimum alveolar concentration [MAC]) for the accumulated delivery times over 30 min as complementary in the anesthetic technique [18]. The O group was defined as those patients who received fentanyl 20–30 μg/kg or morphine 0.5–1 mg/kg in total, as complementary in the anesthetic technique. Those patients who received any anesthetic technique that did not meet either of these two definitions, as well as those who received anesthetic techniques that met both definitions were excluded from this study.

All data were managed with SPSS version 14.0 software (SPSS, Bangkok, Thailand). Descriptive statistics such as percentages, means, and standard deviations were used, based on the characteristics of the variables. The t test, χ^2 test, and Fisher's exact test were applied as appropriate for testing differences in outcome between the two groups. The

paired *t* test was applied for testing the differences between the pre- and post-eGFR values. A p value of <0.05 indicated significance.

Results

The medical records of the 3,064 recruited patients were examined, and those that had incomplete necessary data and anesthetic records in which the anesthetic techniques were ambiguous were excluded. The medical records of 1,122 (36.62 %) patients remained for further analysis.

There were 702 males (62.57 %) and 420 females (37.43 %). The mean age was 60.94 ± 13.87 years (range 20–93 years). Hypertension (HT) was the most commonly found underlying disease (62.66 %). Ischemic heart disease (IHD) and diabetes mellitus (DM) were found in 40.29 and 30.48 %, respectively. A significantly higher percentage of patients in the O group than that in the V group had been diagnosed with IHD ($p = 0.001$). Regarding the anesthetic techniques, 704 patients had received opioid-based anesthesia (62.75 %) and 418 had received volatile-anesthetic-based anesthesia (37.25 %). The perioperative characteristics of the two groups were compared and the results are summarized in Table 1. There were no significant differences between the two groups in preoperative serum creatinine (pre-creatinine), pre-eGFR, or the number of patients who needed preoperative dialysis (pre-dialysis). Post-CVI also showed no significant difference between the two groups ($p = 0.286$). The mean total doses of morphine and fentanyl were significantly lower in the V group than the O group ($p = 0.001$).

Regarding the type of operation, there were 700 CABGs (62.39 %), 233 valve surgeries (20.77 %), 137 aortic surgeries (12.21 %), and 52 combined surgeries (4.63 %). The anesthetic techniques used differed significantly according to the operation (Table 2). Opioid-based anesthesia was used in significantly more patients than volatile-anesthetic-based anesthesia in CABGs and combined surgeries, while volatile-anesthetic-based anesthesia was used in significantly more patients than opioid-based anesthesia in aortic surgeries.

The pre-eGFR and post-eGFR values in the O group were 48.80 ± 17.83 and 48.88 ± 17.98 ml/min/1.73 m^2, respectively. The pre-eGFR and post-eGFR values in the V group were 46.72 ± 18.92 and 47.36 ± 18.91 ml/min/1.73 m^2. The pre-eGFR values in the two groups were compared, and no statistically significant difference was found ($p = 0.258$). Remarkably, the post-eGFR values in both groups showed small increases from the baseline (pre-eGFR) values, but there were no significant differences between the pre-eGFR and post-eGFR values in either group O ($p = 0.842$) or group V ($p = 0.227$). The post-eGFR values were compared between the two groups, and no statistically significant difference was found ($p = 0.505$) (Table 3). In patients who had a decrease in post-eGFR of more than 25 % of baseline AKI was regarded as having occurred (in 9.09 % of the total number of patients). The numbers of patients in the O and V groups who had postoperative AKI were 67 (9.52 %) and 35 (8.37 %) respectively, without a statistically significant difference ($p = 0.532$) (Table 3). Post-oliguria was found in 412 of

Table 1 Perioperative clinical characteristics in patients receiving the two anesthetic techniques

Characteristic ($N = 1,122$)	O group ($N = 704$; opioid-based anesthesia)	V group ($N = 418$; volatile-anesthetic-based anesthesia)	p value
Age (years)	60.05 ± 13.83	62.17 ± 14.59	0.156
Gender			
Male (62.57 %)	444 (63.07 %)	258 (61.72 %)	0.652
Female (37.43 %)	260 (36.93 %)	160 (38.28 %)	
DM (30.48 %)	224 (31.82 %)	118 (28.23 %)	0.207
HT (62.66 %)	451 (64.06 %)	252 (60.29 %)	0.206
COPD (2.67 %)	19 (2.70 %)	11 (2.63 %)	0.946
IHD (40.29 %)	315 (44.74 %)	137 (32.78 %)	0.001*
Atrial fibrillation (13.19 %)	83 (11.79 %)	65 (15.55 %)	0.072
Strokes (5.88 %)	45 (6.39 %)	21 (5.02 %)	0.346
Pre-IABP (4.46 %)	30 (4.26 %)	20 (4.78 %)	0.681
Pre-Hb (g/dl)	12.84 ± 1.20	12.41 ± 1.85	0.080
Pre-creatinine (mg/dl)	1.24 ± 1.04	1.32 ± 1.00	0.227
Pre-eGFR (ml/min/1.73 m^2)	48.80 ± 17.83	46.72 ± 18.92	0.258
Pre-dialysis (4.55 %)	28 (3.98 %)	23 (5.50 %)	0.703
CPB time (min)	114.55 ± 52.78	115.88 ± 51.42	0.935
Post-CVI (23.35 %)	181 (25.71 %)	81 (19.38 %)	0.286
Opioid usage			
Fentanyl (μg) ($n = 953$)	846.76 ± 576.71	425.67 ± 143.53	0.001*
Morphine (mg) ($n = 169$)	55.29 ± 22.02	14.73 ± 16.88	0.001*
Anesthesia time (min)	327.01 ± 108.09	280.07 ± 81.16	0.001*

Values are numbers (with percentages shown in parentheses), except for age, pre-Hb, pre-creatinine, Pre-eGFR, CPB time, and opioid usage, which are means ± SD

Pre- preoperative, *IABP* intraaortic balloon pump, *Post- CVI* postoperative cardiovascular instability, *CPB time* duration under cardiopulmonary bypass machine, *DM* diabetes mellitus, *HT* hypertension, *COPD* chronic obstructive pulmonary disease, *IHD* ischemic heart disease, *Hb* hemoglobin, *eGFR* estimated glomerular filtration rate

* p value denotes significant difference between the groups

Table 2 Type of operation and anesthetic techniques

Operation ($N = 1,122$)	O group ($N = 704$)	V group ($N = 418$)	p value
Coronary artery bypass grafting (CABG) (62.39 %)	459 (65.20 %)	241 (57.66 %)	0.012*
Valve surgery (20.77 %)	138 (19.60 %)	95 (22.73 %)	0.212
Aortic surgery (12.21 %)	66 (9.38 %)	71 (16.99 %)	0.001*
Combined surgery (4.63 %)	41 (5.82 %)	11 (2.63 %)	0.014*

Table 3 Postoperative renal function parameters according to the anesthetic techniques

Parameters ($N = 1,122$)	O group ($N = 704$)	V group ($N = 418$)	p value
Post-eGFR (ml/min/1.73 m^2)	48.88 ± 17.98	47.36 ± 18.91	0.505
Postoperative AKI (9.09 %)	67 (9.52 %)	35 (8.37 %)	0.532
Post-oliguria (36.72 %)	254 (36.08 %)	158 (37.79 %)	0.418
Post-dialysis (4.10 %)	28 (3.98 %)	18 (4.31 %)	0.875

Values are numbers, (with percentages in parentheses), except for post-eGFR values, which are means ± SD

Postoperative acute kidney injury (AKI) = post-eGFR decrease of >0.25% of baseline

Table 4 Numbers of patients who had postoperative AKI according to specific operation and gender

Factors	Specific operation	O group ($N = 443$)	V group ($N = 257$)	p value
Type of operation	CABG ($n = 700$)	54	27	0.825
	Valve surgery ($n = 233$)	7	2	0.316
	Aortic surgery ($n = 137$)	4	4	0.616
	Combined surgery ($n = 52$)	2	2	0.193
Gender	Male ($n = 702$)	54	35	0.335
	Female ($n = 420$)	13	0	0.002*

the 1,122 patients (36.72 %). The numbers of patients with post-oliguria in the two groups were not significantly different (Table 3). Post-dialysis was newly performed in 46 patients (O group = 28, V group = 18), and the numbers in the two groups were not significantly different (Table 3).

Separate analysis of postoperative renal dysfunction, in terms of AKI events, was done for each type of operation. The results showed no significant differences in the numbers of patients who had postoperative AKI between the O and V groups (Table 4).

Analyses of postoperative renal condition according to gender were also undertaken (Table 4). Eighty-nine of the 702 male patients (12.68 %) and 13 of the 420 female patients (3.10 %) had postoperative AKI, showing a significant difference between the genders ($p = 0.001$). Another analysis was done to examine the incidence of postoperative AKI according to gender in the O and V groups; the findings showed a significant difference between the groups only in the number of females who had postoperative AKI ($p = 0.002$).

Discussion

It is known that AKI after OHS is highly associated with CPB [19]. Ischemic and reperfusion (IR) injury is the main mechanism of postoperative renal impairment. The ischemic condition in OHS is caused by non-pulsatile circulation that occurs while CPB is applied. Moreover, reperfusion injury then occurs when pulsatile flows return after the CPB machine is switched off [2]. Physiological responses to IR injury are called inflammatory responses. Based on the myocardium model, the initial responses in the inflammatory processes to ischemia occur as aggregations of neutrophils and platelets in vascular lumens. Simultaneously, oxygen free radicals and a number of inflammatory cytokines are released [5, 6]. The leukocyte aggregations in vascular lumens lead to lower blood supply for the cells, which brings about further cellular ischemia. Of note, some of the released inflammatory cytokines play roles as activators that activate intracellular molecules and signaling pathways. Mitochondrial K_{ATP} receptors, which are the last of these molecules to be activated, modulate the cells themselves to enable them to survive under conditions of decreased oxygen supply during the ischemic period and also inhibit the process of intracellular Ca^{2+} influx during the reperfusion period [5, 6]. Therefore, IR has two distinct results: the first ischemic response of cell aggregation, which leads cells to have a compromised blood supply, and the second ischemic response of intracellular modulation under a preconditioning-related mechanism, which enables cells to tolerate the compromised blood supply. Nevertheless, the consequence of preconditioning-related intracellular modulation seems to overcome the consequence of cell aggregation. As a result, the preconditioning-related mechanism has been expected to play a major role in cellular protection from IR.

It is claimed that preconditioning by volatile anesthetics activates intracellular molecules and their signaling pathways by a mechanism that mimics preconditioning by ischemia. Volatile anesthetics predominantly activate intracellular molecules and their signaling pathways via K_{ATP} receptors, which are the keys of cellular modulation

in response to ischemic insults [8–11]. Therefore, against this background, in the present study, we intentionally recruited patients who received volatile-anesthetic-based anesthesia for the study group (V group). Actually, any type of volatile anesthetic could have been included in the study group. However, isoflurane and sevoflurane were the only two volatile anesthetics available at the study center. So, the study group was composed of patients who had received isoflurane and sevoflurane-based anesthesia. Based on previous studies, effective protection was observed when the subject was exposed to volatile anesthetics for at least 10 min either before, during, or after CPB with delivery at 0.5–1 minimal alveolar concentration (MAC) [18]. In order to provide effective preconditioning, we included only patients who had received isoflurane or sevoflurane of at least 1 MAC for at least 30 min in the study group. By this over-exposure, the effective roles of pharmacological preconditioning in the V group could be assured.

The group for comparison in our study consisted of patients with opioid-based anesthesia (O group). Although opioids are reported to have some degree of pharmacological preconditioning effect, their protective action is highly dependent on a high dose. Based on past investigations, the effective doses for protection were 3 mg/kg of morphine [20] or 30 μg/kg of fentanyl [21]. It is true that opioid-based anesthesia for OHS is such a high-dose opioid technique. However, the amounts of fentanyl or morphine given in the O group in our study were much lower than the amounts indicated as the above-mentioned effective doses. Therefore, the O group in this study could be assumed to have no preconditioning effect of opioids. Moreover, the amounts of fentanyl and morphine that were administered were significantly lower in the V group. This finding reassured us that opioid-induced preconditioning effects were unlikely to have confounded the results in the V group.

As a renal biomarker, GFR is preferable for indicating overall kidney function. However, in practice, serum creatinine is used because it is basic and inexpensive. But it is known that some individual conditions (for example, age, ethnic group, muscle mass, and medication) lead to poor correlations between serum creatinine and GFR. Therefore, in the present study the eGFR was intentionally used to monitor renal function. Although it is calculated from serum creatinine, eGFR is claimed to be more accurate than serum creatinine for detecting glomerular function [22]. Serum cystatin C is claimed to be a better biomarker of glomerular function, but it was found to show low correlation with GFR in patients with normal renal function [23], in chronic renal impairment [24], and inflammatory states [23]. Remarkably, all these conditions are very likely to be found in patients undergoing OHS. As a result, serum cystatin C might not be a good renal biomarker in OHS. On the contrary, eGFR is perhaps more suitable because it is easily applied in normal practice.

In order to detect renal protection, we regarded postoperative AKI as present if post-eGFR showed a decrease of >0.25% of the baseline value [25]. Patients who had no postoperative AKI were assumed to have obtained renal protection. There were no significant differences between our O group and our V group in the numbers of patients diagnosed with AKI . Therefore, it could be assumed that there was no significant difference between the two groups in the number of patients who obtained renal protection; thus, one might say that the kidneys of both groups were similarly protected. The comparisons of the mean pre- and post-eGFR values in the two groups also indicated that postoperative glomerular function was similarly maintained in both groups. Moreover, the more specific indicators of renal impairment, i.e., post-oliguria and post-dialysis, also indicated no significant difference in postoperative renal impairment between the two groups. Therefore, regarding the assessment of renal function, the present study could not demonstrate significant renal protection arising from preconditioning by volatile anesthetics compared with another anesthetic technique.

It is surprising that preconditioning by volatile anesthetics is not effective for renal protection as it is for the myocardium. A basic explanation is that there are differences in the characteristics of physiological preservation between the heart and the kidney. Kidney functions are well preserved by complex autoregulatory processes [26]. Accordingly, renal impairment occurs less readily than myocardial impairment.

Secondly, it is possible that volatile anesthetics mediate renal protection by a preconditioning-related mechanism that is different from that in the myocardium. There have been some studies reporting that renal protection is not associated with K_{ATP} receptors. Lee and Emala [4] attempted to study the mechanisms of human renal protection in depth. Initially, they focused on renal molecular activation as indicated in an ischemia-preconditioning model of the myocardium reported by Tyagi and Tayal [4]. But they found that A_{2a} adenosine receptors were more significance in renal protection than K_{ATP} receptors [27, 28]. Because volatile anesthetics activate mainly K_{ATP} receptors, these findings might be important for explaining why preconditioning by volatile anesthetics does not obviously mediate renal protection.

Interestingly, it seems that the reno-protective effect of volatile anesthetics might come from other mechanisms in addition to a preconditioning-related mechanism. Since 2007, Kim et al. [29] and Lee et al. [30] have attempted to elucidate protective mechanisms for the kidney. They found that lymphocyte (T1) aggregation may be more

important than polymorphonuclear neutrophil (PMN) aggregation and found that these aggregations might be inhibited by volatile anesthetics. For example, isoflurane mediates renal protection via sphingosine kinase and sphingosine-1-phosphate-dependent pathways [29]; sevoflurane mediates renal protection via a transforming growth factor-β_1 pathway [30]. In agreement with to the investigations of Lee et al., Hashiquchi et al. [31] found a mechanism of isoflurane-mediated renal protection that occurred via mitogen-activated protein kinase (MAPK). Although the exact protective mechanism of MAPK in renal cells is not clearly known, MAPK was found to be associated with platelet aggregations in the vascular lumen [32]. As such, these findings seem to imply that volatile anesthetics play a greater role in the anti-inflammatory mechanism than in the preconditioning-related mechanism. Therefore, the cellular processes of enhancing tolerability to episodes of deprived oxygen do not seem to be predominantly activated by volatile anesthetics [33]. This explanation provides a third reason to explain why preconditioning by volatile anesthetics does not obviously mediate renal protection.

It is possible that eGFR, as a marker for renal function, is not a sensitive tool. As knowledge of AKI has now been demonstrated on the molecular level, renal biomarkers are expected to be suitable for the detection of parameters beyond renal function itself, such as the detection of oxidative stress, structural and cellular injuries, and immune response or fibrosis [34]. Therefore, the previously used biomarkers of renal function have been criticized in that they cannot detect a small degree of renal protection. However, molecular renal biomarkers were claimed to be high-sensitivity indicators of AKI [25]. According to our basic knowledge, an organ that is protected or preserved is still normally functional after ischemic events. Moreover, in normal practice, treatment for kidney dysfunction is given only when biomarkers of renal function indicate an abnormality. Thus, the assessment of renal protection by biomarkers for renal function should not be considered a disadvantage [24], especially for a clinical study. To summarize, the employment of the renal biomarker eGFR in the present study provides another explanation for the observed lack of volatile-anesthetic-mediated renal protection. However, the renal biomarker eGFR was appropriate for a clinical study despite it being less sensitive for molecular detection than molecular renal biomarkers.

One advantage of the present study was that the number of patients included was more than that in past clinical studies of volatile-anesthetic-mediated renal protection. As previously mentioned, eGFR, which was the main indicator in this study, was more appropriate than serum creatinine, as reported from the study of Lorsomradee et al. [17] and more practical than serum cystatin C, as reported from the study of Julier et al. [16]. These two investigations studied only patients who received CABG, whereas this study also included patients with valve surgery, aortic surgery, and combined surgery. Therefore, this study served as a large-scale, multi-operation study regarding volatile-anesthetic-mediated renal protection. Importantly, renal protection in this study was clinically detected. Moreover, postoperative renal dysfunction was also demonstrated.

However, this study had some limitations. Because it was a retrospective study, many confounding aspects were not controlled. Intraoperative surgical and anesthetic management factors and hemodynamic optimization are mostly associated with perioperative AKI, in addition to CPB-induced ischemia [35]. The experience of surgeons and anesthesiologists also plays an important role. Therefore, because we could not control for these factors, this was also a limitation of this study. Additionally, selection bias might have seriously affected the outcome of this study. However, such bias was taken into consideration. Meticulous reviews were undertaken by the reviewers, and a different reviewer undertook repeated reviews of medical records with ambiguous data. The medical records that were still found to have ambiguous data were then excluded from the study. In fact, the high volume of exclusions in this study might have led to an imbalance in the distribution of exclusions between the two groups. However, with the high number of remaining samples, we considered that all these mentioned limitations would have a minimal effect on the results.

The patients' preoperative conditions were another confounding factor in this study; we note that IHD was found in a significantly higher number of patients in the O group. Additionally, opioid-based anesthesia was used significantly more often in patients with CABG than in the other operative groups. These findings were examined and could be explained by opioid-based anesthesia being a reasonable technique for CABG. Thus, it was necessary to perform separate analysis for each operation in order to exclude some possible affects of the operation itself. Nevertheless, the results regarding each operation also showed that volatile-anesthetic-mediated renal protection could not be observed.

Gender effects on renal function were not included in our study objective, but they were also analyzed because some past evidence has indicated the effects of gender [36, 37]. Surprisingly, fewer females than males had postoperative AKI. This finding might be explained by the protective effects of estrogen on renal ischemia and reperfusion injury. Although the mechanism is unclear, there is some evidence that estrogen can increase endothelial nitric oxide synthetase (eNOS) and decrease c-Jun N-terminal kinase (JNK) [36].

Regarding the fragmented knowledge of whether renal protection is provided by a preconditioning-related

mechanism or a non-preconditioning-related mechanism, further investigations should be promoted. Also, future clinical studies regarding volatile-anesthetic-mediated renal protection under specific ischemic conditions are strongly suggested. Moreover, appropriate renal biomarkers should be selected. Furthermore, the timing and duration of the monitoring of postoperative renal function should be examined [1, 25].

In conclusion, volatile-anesthetic-mediated renal protection in OHS was not observed in this study. The most likely explanation for this lack of renal protection is that volatile anesthetics have some effects of renal protection at the cellular level, but these effects do not effectively protect the overall renal function. Therefore, in practice, pharmacological preconditioning by volatile anesthetics did not seem to be beneficial.

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