原 著

Sevoflurane Anesthesia for Coronary Artery Bypass Graft Surgery Does Not Aggravate Renal Tubular Function in Patients with Preexisting Renal Dysfunction

Hiroshi Sakamoto*

Abstract

Background : Sevoflurane use is restricted because of potential fluoride induced renal problems. This study was designed to evaluate sevoflurane renal toxicity for coronary artery bypass graft (CABG) surgery in patients with preexisting renal dysfunction.

Methods : After obtaining written approval, 24 patients with renal dysfunction (creatinine clearance (Ccr) < 55 mL(min^{-1}) and 62 patients with normal renal function (Ccr ≧ 55 mL(min^{-1}) undergoing CABG surgery were enrolled. The patients with renal dysfunction were anesthetized with fentanyl 20 $\mu g \cdot kg^{-1}$ followed either sevoflurane 0.5 MAC or isoflurane 0.5 MAC. The patients with normal renal function were anesthetized with one of the same methods as patients with renal dysfunction, or sevoflurane 1.0 MAC or isoflurane 1.0 MAC. During cardiopulmonary bypass, volatile anesthetics were administered through a membrane oxygenator. Serum and urinary inorganic fluoride levels (SF^-, UF^-), blood urea nitrogen (BUN) and creatinine (Cr) were measured and Ccr, fractional clearanceof $\beta_2$microglobulin,urinary $\beta_2$microglobulin/urinary creatinine and urinary N-acetyl-β-glucosidase/urinary creatinine were calculated.

Results : Levels of SF^- during sevoflurane anesthesia were significantly higher than other anesthetic methods. The highest SF^- levels were 48.4 μM and 24.2 μM in the patients with normal and impaired renal function, respectively. Changes of BUN, Cr, clearances and other indices were not different among the groups.

Conclusions : Sevoflurane 0.5 MAC in patients with renal dysfunction did not aggravate preexisting renal dysfunction postoperatively. Sevoflurane 0.5 MAC can be safely used for CABG surgery in patients with impaired renal function.

Key words: sevoflurane; isoflurane; fluoride; cardiac surgery; kidney

Introduction

There are three main considerations in choosing anesthesia techniques for patients undergoing coronary artery bypass graft (CABG) surgery. They are the preservation of cardiac function, the desirability of early recovery and extubation, the adequate anesthesia depth to avoid awareness or recall and maintenance of stress free state.[1] Improvements in surgical techniques and refinements of equipment for cardiopulmonary bypass (CPB) have reduced the need for routine postoperative ventilatory support and shorten the stay in the intensive care unit (ICU).[2] This can reduce the costs and potential complications those are closely related to mechanical ventilatory care.[2]

Although high-dose fentanyl anesthesia provides hemodynamic stability, it frequently causes awareness or recall, evoked stress response and delayed recovery that necessitate prolonged postoperative ventilatory

*Staff in Anesthesia, Cardiovascular Center Hokkaido Ohno Hospital, Sapporo

support.[3] It was reported that 1 and 2 % isoflurane, given through an oxygenator during CPB, blunted the increase in plasma cortisol levels in a dose related manner.[4] And continuous administration of enflurane obtunded the norepinephrine response to CPB.[5] They demonstrate that the depth of anesthesia affects cortisol response to the stress of CPB.[6] The volatile anesthetic based technique which combines small doses of opioid for induction could potentially achieve the previously described three aims that the solo high dose opioid anesthetic technique could not.[7] Sevoflurane has a low solubility in blood that enhances a quick rise and subsequent decrease of alveolar concentrations to achieve rapid induction and recovery, a weaker cardiodepressant effect, a minimal change in the whole body oxygen consumption rate, a minimal arrhythmic response to epinephrine and a lesser tendency for tachcardia.[8] These are desirable characters that other potent anesthetics for CABG surgery patients do not have.[9] In spite of these potential usefulness of sevoflurane for cardiac surgery, renal toxicity of sevoflurane will be one of our serious concerns to apply in clinical practice, especially to the patients with impaired renal function. It has been recommended that the use of sevoflurane is acceptable only in patients without renal dysfunction, because of its nephrotoxic potency.[10] Although recent reports on sevoflurane in renal impaired patients for non-cardiac surgery demonstrated that sevoflurane did not show any deleterious effect of renal function during surgery and postoperative period,[11] it is well documented that renal function is certainly worsened after CABG surgery.[12] Preexisting renal dysfunction places the CABG surgery patients at increased risk of postoperative renal dysfunction. This renal dysfunction usually carries high morbidity and mortality.[13~15]

In this study, the author investigated whether the use of sevoflurane in CABG surgery might aggravate renal function in the patients with preexisting renal dysfunction and normal renal function. The author also compared the effects of sevoflurane with isoflurane and midazolam-fentanyl anesthesia in these settings.

Patients and methods

Eighty six patients scheduled for elective CABG surgery were enrolled in this study. The Institutional Committee on Human Research approved the study protocol and written informed consent was obtained from each patient. Patients with known neurological, respiratory and hepatic diseases were excluded from this study. Cardiac medications such as nitrates and βblockers were continued until the night before surgery.

All patients were premedicated with intramuscular morphine 0.15 mg · kg^{-1} and scopolamine 5 μg · kg^{-1} 90 min prior to induction of anesthesia. Central and peripheral intravenous cannulas for infusion and drug administration, a radial artery catheter for continuous monitoring of arterial blood pressure and a pulmonary artery catheter for pulmonary arterial pressure, pulmonary capillary wedge pressure and cardiac output measurements were placed under local anesthesia. Multi-leads ECG, SpO_2 and $ETCO_2$ were routinely monitored. Then intravenous administration of nitroglycerin 0.1 μg · kg^{-1} · min^{-1} and diltiazem 0.5 μg · kg^{-1} · min^{-1} were started and titrated to keep mean blood pressure between 70 and 80 mmHg.

Patients were assigned to normal or impaired renal function groups according to the preoperative creatinine clearance (Ccr). A patient whose Ccr was above or equal to 55 mL · min^{-1} was considered to have normal renal function. A patient whose Ccr was below 55 mL · min^{-1} was considered to have impaired renal function.

All patients were induced anesthesia with midazolam 0.1 mg · kg^{-1} and fentanyl 6 μg · kg^{-1} followed by vecuronium 0.1 mg · kg^{-1} to facilitate tracheal intubation. Then we subdivided the normal renal function group into four groups (groups 1, 2, 3 and 4) and the renal dysfunction group into two groups (groups 5 and 6). Anesthesia was maintained with total fentanyl 20 μg · kg^{-1} and combined with either sevoflurane (0.5 MAC in groups 1 and 5 and 1.0 MAC in group 2) or isoflurane (0.5 MAC in groups 3 and 6 and 1.0 MAC in group 4). We did not use sevoflurane 1.0 MAC and isoflurane 1.0 MAC in patients with

impaired renal function to avoid possible aggravation of renal function. We started to administer either sevoflurane or isoflurane after tracheal intubation and continued to use until the end of surgery, including the CPB period. Vecuronium was supplemented as needed in all patients.

Fresh gas flow to the semi-closed circle system was 5 L · min^{-1} and carbon dioxide was absorbed through a canister with soda lime (Wako lime, Wako Pure Chemical, Osaka, Japan) before and after CPB. During CPB, the volatile anesthetic was administered through a membrane oxygenator and whole outflow was dumped. The MAC values used in this study were 1.7 % for sevoflurane and 1.2 % for isoflurane.

We kept Pa_{O_2} above 150 mmHg and Pa_{CO_2} between 35 and 40 mmHg. We monitored the anesthetic concentrations during whole anesthesia course using a routinely calibrated anesthetic gas monitor, Ultima (Datex Engstrom, Helsinki, Finland). Esophageal temperature was kept around 36℃ but it was about 34℃ during CPB.

The CPB circuit with a membrane oxygenator was primed with lactated Ringer's solution 1500-2000 mL, methylpredonisolone 1 g and mannitol 25 g. During CPB, flow rate was maintained at 2.2 L · min^{-1}. We gave a bolus dose of chlorpromazine 2 mg or phenylephrine 0.2 mg to maintain perfusion pressure between 50-70 mmHg and gave furosemide 5-10 mg to keep urinary volume more than 0.5 mL · kg^{-1} · h^{-1}, as necessary, during CPB.

Inorganic fluoride concentrations were determined by direct ion-sensitive potentiometry using a specific ion fluoride electrode in conjunction with a combination pH electrode (Microprocessor Ion Analyzer, Orion Research, Cambridge, MA, USA). Calibrations were made against standard solutions of sodium fluoride (0 to 100 μM) and we took care to avoid contamination from glassware. Interassay coefficients of variation were 2.5 % and 1.8 % at mean plasma fluoride concentrations of 2.4 μM and 40 μM, respectively. Serum and urinary inorganic fluoride levels were measured before induction of anesthesia, at the time of aortic cannula insertion, 0, 30 and 60 min after installation of CPB, 0 and 45 min after the release of the aortic cross clamp, at the end of surgery and on the first postoperative day. Volume of urine output excretion was counted at the above measuring points and urine excretion rate was calculated as the difference of volume of urine excretion between the measuring point and previous one divided by its time interval. Urinary inorganic fluoride excretion rate was calculated as urinary inorganic fluoride level multiplies urine excretion rate at the measuring point.

Urinary levels of N-acetyl-β-glucosidase (NAG), serum levels of $\beta_2$microglobulin ($S\beta_2MG$), urinary levels of $\beta_2$microglobulin ($U\beta_2MG$), blood urea nitrogen (BUN), plasma creatinine (Cr) and creatinine clearance (Ccr) were measured before surgery, at the end of surgery and on the first postoperative day. Thereafter, both BUN and Cr levels were measured every day until the third postoperative day.

NAG (normal laboratory range: < 7.6 U·L^{-1}) was measured by the synthetic ground substance method, and $S\beta_2MG$ (normal laboratory range: 0.8-2.4 ng·L^{-1}) and $U\beta_2MG$ (normal laboratory range: 5-253 μg·L^{-1}) were measured by the radioimmunoassay method.

Urinary NAG and β_2MG excretions were normalized to urinary Cr excretion to compensate for variation in urine flow (NAG/creatinine ratio and $U\beta_2MG$/creatinine ratio). $U\beta_2MG$ over $S\beta_2MG$ ($Fc\beta_2MG$) were also calculated to evaluate the renal tubular injury. They were measured preoperatively and after surgery till the third postoperative day.

Data were expressed as mean±SD. One-way ANOVA followed by Tukey's HSD was used to compare groups. Regression lines were determined with the least square method. Spearman rank correlation coefficient was calculated to examine correlation between two parameters.

Results

The clinical and demographic characteristics of patients including age, body weight, body surface area (BSA), left ventricular ejection fraction (LVEF), duration of aortic cross clamp (AXC), CPB, operation and anesthesia time, number of grafts, and blood loss were similar in all groups. Exposure to the volatile anesthetics did not differ among the groups with

respect to the duration of administration (Table 1). No patients received drugs during perioperative period that might promote enzyme induction or enhance anesthetic metabolism.

Preoperative values of Ccr had no significant difference among groups 1-4 and between groups 5 and 6, respectively. Preoperative values of Cr and BUN in groups 5 and 6 were significantly higher than those of groups 1-4. Other preoperative values including Hb, Na^+, K^+, alkaliphosphatase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase and total protein were not different in all groups. Almost the same duration of anesthesia made it possible to compare the MAC-hours of correspondent anesthetics among groups 1-6.

Changes of temperature in all groups during the CPB period showed the same trend. The lowest esophageal temperatures during CPB were 33.9±0.3, 34.1±0.3, 34.0±0.2, 33.2±0.8, 33.4±0.6 and 33.6 ±0.3℃ in groups 1-6, respectively.

We used the combination of dopamine and dobutamine at the time of weaning from CPB, and the dosages of these two drugs were not different among all groups.

(1) Serum inorganic fluoride levels in normal renal function groups (Fig. 1a)

Patients in groups 3 and 4, anesthetized with isoflurane 0.5 and 1.0 MAC and fentanyl, respectively, showed no significant increase of serum fluoride levels. Serum fluoride levels in groups 1 and 2, anesthetized with sevoflurane 0.5 and 1.0 MAC, were significantly higher than those in groups 3 and 4 at any measuring points except pre-anesthesia. Following rapid increase of serum fluoride levels after sevoflurane administration, at the aortic cross clamp,

Table 1. Demographic Data of Each group

group	1	2	3	4	5	6
N	19	16	15	12	15	9
Gender (F/M)	1 / 18	4 / 12	5 / 10	2 / 10	6 / 9	0 /9
Age (yr)	64.3±9.1 ‡	49.0±11.4 §	61.3±9.6	45.2±21.5 ‡	66.6±7.3 ‖	62.1±12.8 ‡
Weight (kg)	65.7±9.8	68.7±9.2	60.0±11.0	53.8±23.0	60.5±12.4	68.1±13.4
BSA (m^2)	1.70±0.15	1.76±0.16 ‡	1.63±0.19	1.44±0.60	1.60±0.17	1.74±0.18
LVEF (%)	61.8±11.8	66.6±14.0	62.1±12.1	54.7±23.7	53.7±15.4	60.6±12.6
CI ($L \cdot min^{-1}(m^{-2})$	3.0±0.6	3.3±(0.8	3.1±0.6	2.9±1.3	2.8±0.7	2.8±0.8
Number of bypass grafts						
Total	3.5±1.3	2.9±1.2	3.4±1.0	2.4±1.3	2.7±1.3	3.0±1.2
Arterial	1.7±0.8	1.9±0.7	1.5±0.5	1.4±0.7	1.2±0.6	1.3±0.8
Total bypass time (min)	144.1±43.6	134.8±40.5	145.8±34.2	109.7±60.4	141.1±87.4	131.3±37.7
Cross-clamp time (min)	105.9±32.8	98.1±29.4	102.6±22.7	80.0±46.7	89.1±45.3	95.1±32.4
Anesthesia time (min)	315.6±72.0	289.3±69.2	301.9±85.6	300.7±108.1	186.3±96.0	363.3±85.9
MAC · h	2.6±0.6	4.8±1.2	2.5±0.7	5.0±1.8	3.1±1.6	3.0±0.7
Blood loss (g)	951.3±553.9	782.2±346.6	848.5±639.4	711.7±407.9	908.5±732.4	899.7±284.5
Cause of renal dysfunction	—	—	—	—	DM, HT, HL, ASO	DM, HT, HL, renal scrolosis

Values are expressed in mean±SD.

BSA = body surface area; LVEF = preoperative left ventricular ejection fraction measured with radionuclide gated blood pool scintigraphy; CI = cardiac index; CCr = creatinine clearance; MAC · h = MAC · hours; DM = diabetes mellitus; HT = hypertension; HL = hyperlipidemia; ASO = arteriosclerosis obliterans. Values are expressed in mean (standard deviation.

§ Significantly different from group 1; ‖ Significantly different from group 2; ‡ Significantly different from group 4.

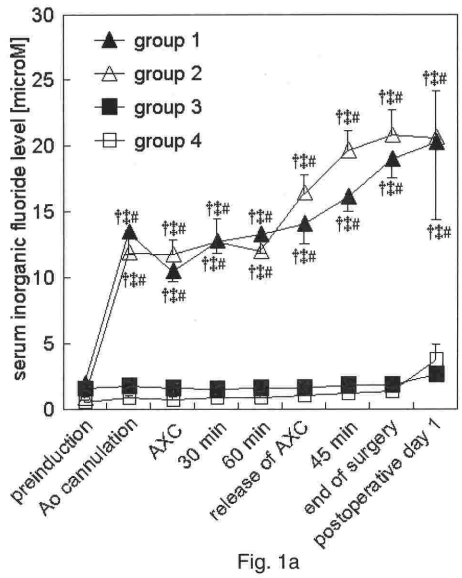

Fig. 1a

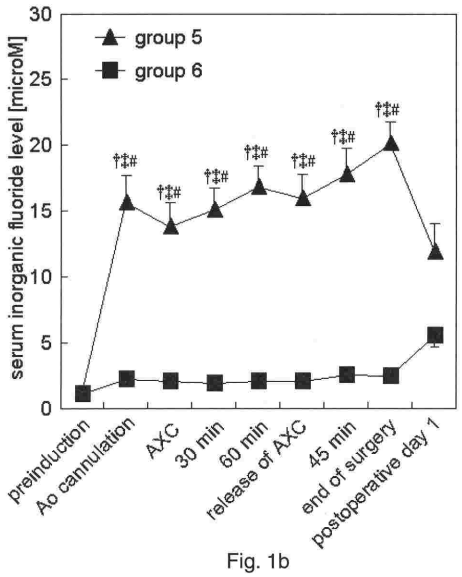

Fig. 1b

Fig. 1a and 1b Serum fluoride levels at each measuring point.

Changes in serum inorganic fluoride levels in the patients with preoperative normal renal function (1a) and impaired renal function (1b) after sevoflurane and isoflurane anesthesia are shown. All values after anesthesia were not different between sevoflurane 0.5 and 1.0MAC. Values for sevoflurane other than at preanesthesia were significantly higher than those of isoflurane 0.5 and 1.0 MAC anesthesia groups. There was no significant increase in fluoride level in isoflurane 0.5 and 1.0 MAC.

Ao = aorta; AXC = aortic cross clamp; 30 min = 30 minutes after aortic cross clamp; 60 min = 60 minutes after aortic cross clamp; 45 min = 45 minutes after release of aortic cross clamp; POD1 = the first postoperative day.

Vertical bars indicate standard deviation. Significant difference is indicated with: § $p < 0.05$ compared with group 1; ‖ $p < 0.05$ compared with group 2; † $p < 0.05$ compared with group 3; ‡ $p < 0.05$ compared with group 4; # $p < 0.05$ compared with group 6.

serum fluoride levels were slightly less than the levels at the aortic cannulation in spite of the continuous administration of sevoflurane through the oxygenator. Serum fluoride levels reached a maximum on the first postoperative day and at the end of surgery in groups 1 and 2, respectively. In contrast, there was no significant increase of serum inorganic fluoride level in the isoflurane groups. The mean peak values of serum fluoride were 21.2, 20.8, 2.7 and 3.8 μM in groups 1-4, respectively. The individual peak values of fluoride were 48.4, 32.6, 4.2 and 7.4 μM in groups 1-4, respectively. The areas under the curve of SF^- of groups 1-4 were 67.5±1.6, 70.7±1.6, 7.8±3.5 and 5.2±3.6 μM · hour, respectively.

(2) Serum inorganic fluoride levels in the impaired renal function groups (Fig. 1b)

In the renal dysfunction groups, serum fluoride levels showed the same trend as in the normal renal function groups and peaked at the end of surgery. The mean peak values of serum fluoride were 19.1 and 2.6 μM in groups 5 and 6, anesthetized with 0.5 MAC of sevoflurane and isoflurane, respectively. Compared to group 6, serum fluoride levels were significantly higher in group 5 at any measuring points. The individual peak values of serum fluoride were 23.7 and 7.9 μM in groups 5 and 6. The areas under the curve of SF^- of groups 5 and 6 were 93.1±0.8 and 12.5±2.0 μM · hour, respectively.

(3) Urinary inorganic fluoride levels (Fig. 2a and 2b)

Urinary inorganic fluoride levels in groups 1, 2 and 5 showed two peaks, at the aortic cross clamp and the first postoperative day. In groups 3, 4 and 6, urinary inorganic fluoride levels peaked on the first postoperative day. Urinary inorganic fluoride levels were lower at the 30 min and 60 min after initiation of CPB, release of aortic cross clamp and 45 min after aortic

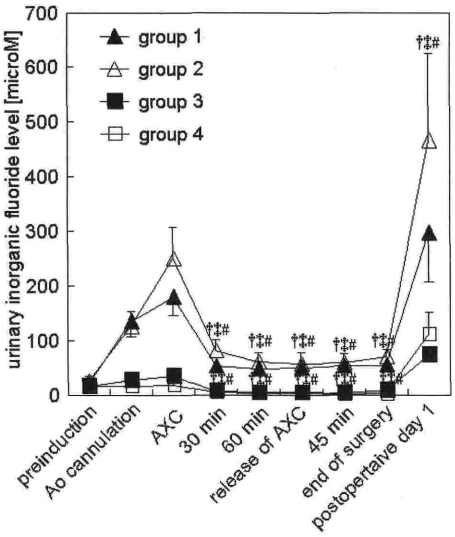

Fig. 2a

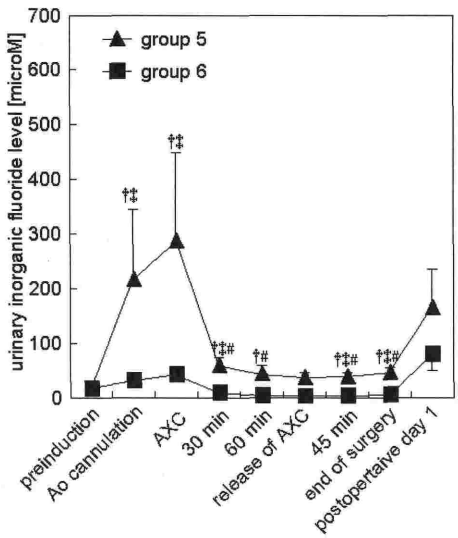

Fig. 2b

Fig. 2a and 2b Urinary inorganic fluoride levels at each measuring point.

Changes in urinary inorganic fluoride levels in the patients with preoperative normal renal function (2a) and impaired renal function (2b) after sevoflurane and isoflurane anesthesia are shown.

Ao = aorta; AXC = aortic cross clamp; 30 min = 30 minutes after aortic cross clamp; 60 min = 60 minutes after aortic cross clamp; 45 min = 45 minutes after release of aortic cross clamp; POD1 = the first postoperative day.

Vertical bars indicate standard deviation. Significant difference is indicated with: § $p < 0.05$ compared with group 1; ‖ $p < 0.05$ compared with group 2; † $p < 0.05$ compared with group 3; ‡ $p < 0.05$ compared with group 4; #$p < 0.05$ compared with group 6.

cross clamp (nearly equals to separation from CPB) than those at the aortic cannulation, aortic cross clamp, end of surgery and the first postoperative day in all groups. In the normal renal function groups, the individual peak values of urinary inorganic fluoride excretion were 776.8, 976.8, 122.1 and 222.1 μM, and the mean peak values were 308.0, 465.7, 70.1 and 111.4 μM in groups 1-4, respectively. In the preexisting renal dysfunction groups, the individual peak values of urinary inorganic fluoride excretion were 374.2 and 161.6 μM and the mean peak values were 176.7 and 84.7 μM in groups 5 and 6, respectively. The areas under the curve of urinary inorganic fluoride levels of groups 1-6 were 356.4 ± 0.6, 360.6 ± 0.5, 61.1 ± 1.3, 36.4 ± 1.6, 580.6 ± 0.2 and 77.2 ± 0.8 μM · hour, respectively.

(4) Urinary inorganic fluoride excretion rate (Fig. 3a and 3b)

Urinary inorganic fluoride excretion rates were almost constant in all groups but group 2. In group 2, urinary inorganic fluoride excretion rate peaked at the aortic cross clamp and at the end of surgery instead of on the first postoperative day. Urinary inorganic fluoride excretion rate was almost constant during CPB period in all groups.

(5) MAC-hours and serum inorganic fluoride levels (Fig. 4a and 4b)

The total amount of sevoflurane were 2.6 ± 0.6, 4.8 ± 1.2 and 3.1 ± 1.6 MAC-hours in group 1, 2 and 5 and isoflurane were 2.5 ± 0.7, 5.0 ± 1.8 and 3.0 ± 0.7 MAC-hours in group 3, 4 and 6, respectively. MAC-hours and serum inorganic fluoride levels before CPB are shown in Fig. 4a and 4b. The groups 1, 4, 5 and 6 showed significant regression lines. Although MAC-hours and changes of serum fluoride levels during CPB and after separation from CPB are also calculated, there was no significant correlation between MAC-hours and the changes of serum inorganic fluoride levels except in group 2 during CPB. Accordingly, we showed serum inorganic fluoride levels only

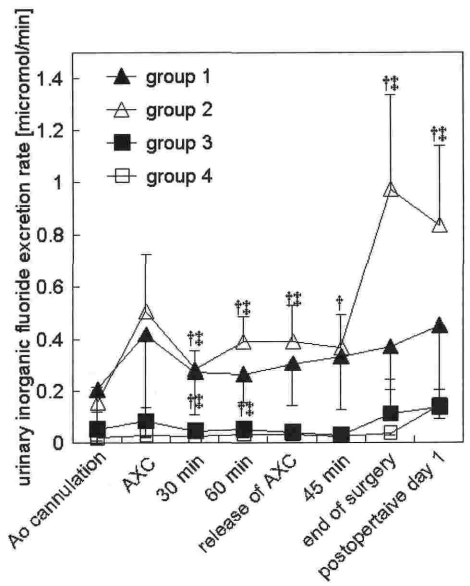

Fig. 3a

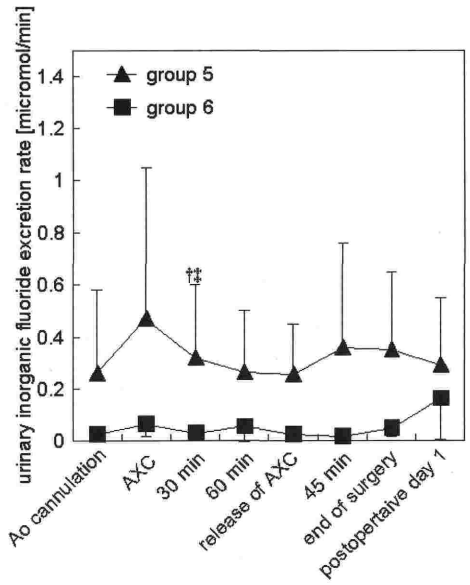

Fig. 3b

Fig. 3a and 3b Urinary inorganic fluoride excretion rates at each measuring point.

Urinary inorganic fluoride excretion rates in the patients with preoperative normal renal function (3a) and impaired renal function (3b) after sevoflurane and isoflurane anesthesia are shown. Urinary inorganic fluoride excretion rates are calculated by urinary inorganic fluoride levels over urine excretion rates. Urine excretion rates are calculated by urinary volumes excreted during the measuring points and the previous ones over the duration between the measuring points and the previous ones.

Vertical bars indicate standard deviation. Significant difference is indicated with: § $p < 0.05$ compared with group 1; ‖ $p < 0.05$ compared with group 2; † $p < 0.05$ compared with group 3; ‡ $p < 0.05$ compared with group 4; #$p < 0.05$ compared with group 6.

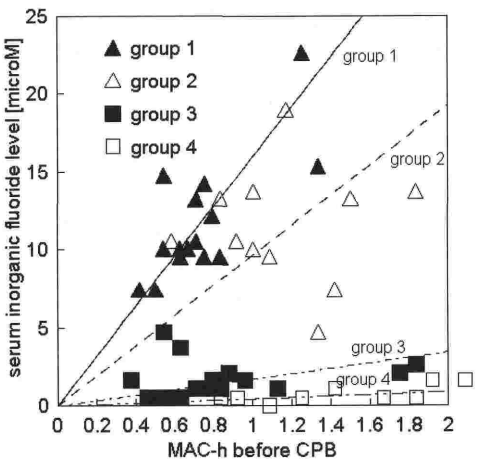

Fig. 4a

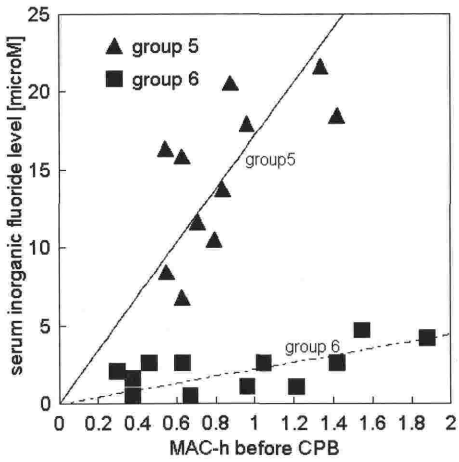

Fig. 4b

Fig. 4a and 4b Serum inorganic fluoride levels and MAC-h before CPB.

This graph shows the relationship between serum inorganic fluoride levels and minimum alveolar concentration-hours (MAC-h) in the patients with preoperative normal renal function (4a) and impaired renal function (4b) before initiation of CPB under sevoflurane and isoflurane anesthesia. Solid and dotted lines show regression lines of each group. Test of regression line showed significance in groups 1, 4, 5 and 6 ($p < 0.05$) and they are shown in solid lines. Others are shown in dotted lines. In each equation of regression line, x means MAC-h, f(x) gives serum inorganic fluoride level and r is correlation coefficient.

group 1: $f(x) = 15.9x$, $r = 0.66$; group 2: $f(x) = 9.6x$, $r = 0.14$; group 3: $f(x) = 1.72x$, $r = 0.14$; group 4: $f(x) = 0.5x$, $r = 0.57$; group 5: $f(x) = 17.2x$, $r = 0.62$; group 6: $f(x) = 2.2x$, $r = 0.62$.

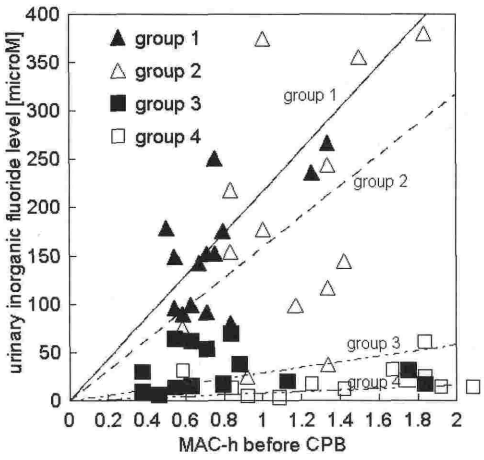

Fig. 5a

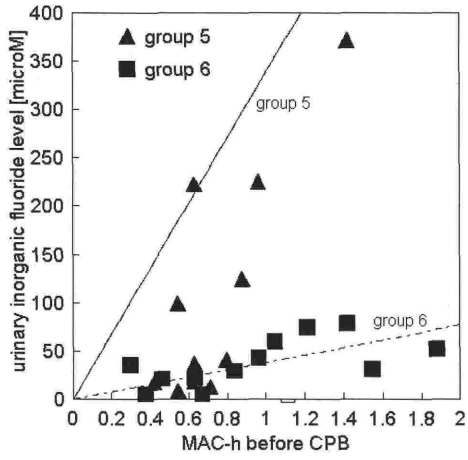

Fig. 5b

Fig. 5a and 5b Urinary inorganic fluoride levels and MAC-h before CPB.

These graphs show the relationship between urinary inorganic fluoride excretion rate and minimum alveolar concentration-hours (MAC-h) in the patients with preoperative normal renal function (5a) and impaired renal function (5b) before initiation of CPB under sevoflurane and isoflurane anesthesia. Solid and dotted lines show regression lines of each group. The test of regression line slopes showed significance in groups 5 and 6 ($p < 0.05$) and they are shown in solid lines. Others are shown in dotted lines. In each equation of regression line, x means MAC-h, f(x) gives urinary inorganic fluoride excretion and r is correlation coefficient.

group 1: $f(x) = 216x$, $r = 0.38$; group 2: $f(x) = 159x$, $r = 0.44$; group 3: $f(x) = 29.1x$, $r = 0.04$; group 4: $f(x) = 8.23x$, $r = 0.09$; group 5: $f(x) = 337x$, $r = 0.58$; group 6: $f(x) = 38.7x$, $r = 0.64$.

before CPB. Regression lines of sevoflurane anesthesia groups were significantly different from those of isoflurane anesthesia groups irrespective the preoperative renal function during any three periods. In normal renal function groups, regression lines of 0.5 MAC of sevoflurane were significantly different from those of 1.0 MAC, respectively.

(6) MAC-hours and urinary inorganic fluoride levels (Fig. 5a, 5b, 6a and 6b)

MAC-hours and urinary inorganic fluoride levels before CPB are shown in Fig. 5a and 5b. MAC-hours and changes of urinary inorganic fluoride levels during CPB are shown in Fig. 6a and 6b. There was a significant correlation between MAC-hours and urinary inorganic fluoride levels in groups 5 and 6 before CPB and groups 2, 3 and 6 during CPB. We can not yield significant regression lines from MAC-hours and changes of urinary inorganic fluoride levels after separation from CPB. Accordingly we show urinary inorganic fluoride levels before CPB and changes of urinary inorganic fluoride levels during CPB.

(7) Laboratory examination (Table 2a and 2b)

Preoperative values of urinary NAG/creatinine ratio, Uβ_2MG/creatinine ratio and Fcβ_2MG were not significantly different among all groups except group 5. In group 5, the preoperative value of Sβ_2MG was significantly higher than those of groups 1, 2 and 3. NAG/creatinine ratio and Uβ_2MG/creatinine were transitory increased at the arrival in the ICU and decreased on the first postoperative day without any significant difference among the groups except in group 6. In group 1, Uβ_2MG/creatinine on the first operative day was significantly different from the preoperative value. In group 6, Uβ_2 MG/creatinine ratio on the first postoperative day was significantly higher than that of group 4. Fcβ_2MG was not significantly different among all groups. Fcβ_2MG significantly increased at the arrival in the ICU and returned to preoperative value on the first postoperative day except in groups 1, 5, and 6.

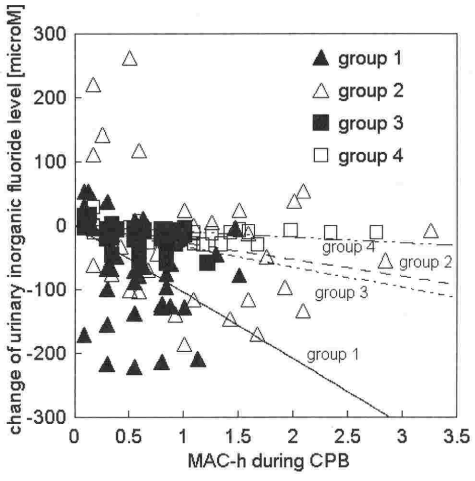

Fig. 6a

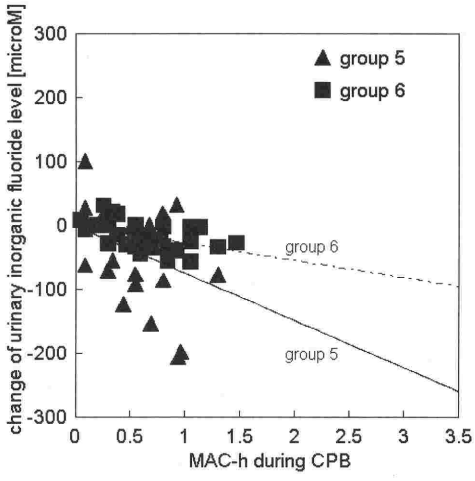

Fig. 6b

Fig. 6a and 6b Changes of urinary inorganic fluoride levels and MAC-h during CPB.

This graph shows the relationship between changes of urinary inorganic fluoride levels and minimum alveolar concentration-hours (MAC-h) in the patients with preoperative normal renal function (6a) and impaired renal function (6b) during CPB under sevoflurane and isoflurane anesthesia. In these graphs, Y-axis is the changes between urinary inorganic fluoride levels during CPB and urinary inorganic fluoride levels at the aortic cross clamp. Solid and dotted lines show regression lines of each group. Test of regression line showed significance in groups 2, 3 and 6 ($p < 0.05$) and they are shown in solid lines. And the lines were significantly different between sevoflurane and isoflurane groups in the patients with normal and impaired renal function. In each equation of regression line, x means MAC-h, f(x) gives the changes of urinary inorganic fluoride level and r is correlation coefficient.

group 1: $f(x) = -104x$, $r = 0.24$; group 2: $f(x) = -26.2x$, $r = 0.89$; group 3: $f(x) = -32.1x$, $r = 0.45$; group 4: $f(x) = -8.7x$, $r = 0.34$; group 5: $f(x) = -74x$, $r = 0.37$; group 6: $f(x) = -26.9x$, $r = 0.50$.

(8) Outcome study (Table 3)

No patients required dialysis to treat renal failure. Patients' requirement of furosemide to keep urination was not different among all groups. Supplemental opioid dosage for sedation and pain control in the ICU and postoperative maximum value of creatinine phosphokinase (CPK) were not different among all groups. In group 5, the intubation period in the ICU was significantly longer than groups 3 and 4. In group 2, the days of the ICU stay were significantly longer than group 4. It is not possible to conclude sevoflurane anesthesia has no effect to shorten the intubation period and the days of the ICU stay because we did not apply the early extubation and fast track policy in this study.

Discussion

There is no difference in pre- and postoperative BUN, Cr, Ccr, in all groups with preoperative normal renal function and with preexisting impaired renal function, respectively. NAG/creatinine ratio, Uβ_2MG/creatinine ratio and Fcβ_2 MG also showed no significant difference among all groups. Combined with the fact that no patients required postoperative hemodialysis or hemofiltration, sevoflurane up to 0.5 MAC could be used as a safe anesthetic even if their preoperative renal function is already impaired.

One of our serious concerns to anesthetize CABG surgery patients is to avoid awareness and recall. Because no one enrolled in this study complained of intraoperative awareness at postoperative interview, all our anesthetic methods, sevoflurane and isoflurane 0.5 and 1.0 MAC combined with fentanyl 20 $\mu g \cdot kg^{-1}$ could provide a sufficient depth of anesthesia. And our previous electroencephalographic study with spectral edge frequency 90% (pEEG monitor, Dräger, Lue-

Table 2a. Laboratory Examinations of Renal Tubular Function

group	1	2	3	4	5	6
BUN ($mg \cdot dL^{-1}$)						
Preoperative	16.8±4.2	14.4±4.1	15.3±4.2	14.0±6.8	23.9±12.2‖†‡	24.9±11.1‡
At arrival in ICU	17.0±3.0	14.8±3.8	14.5±3.3	15.0±7.0	18.9±6.1	24.1±10.1§‖†‡
Postoperative day 1	16.6±4.3	15.4±4.3	14.7±3.0	15.1±6.7	20.6±7.0	27.3±13.5§‖†‡
Postoperative day 3	20.5±6.7	21.0±3.9∫∬♯	21.3±7.5∫∬♯	19.8±8.4∫∬♯	26.8±8.3	31.7±6.2§‖†‡
Serum creatinine	($mg \cdot dL^{-1}$)					
Preoperative	1.0±0.2	0.9±0.2	0.9±0.1	0.8±0.4	1.2±0.5†‡	1.6±0.9§‖†‡
At arrival in ICU	1.1±0.2	1.0±0.3	0.8±0.1	1.1±1.1	1.5±0.8	1.7±1.1†
Postoperative day 1	1.3±0.3∫∬	1.2±0.2∫	1.1±0.2∫∬	1.1±0.5	1.6±0.7‡	2.1±1.3§‖†‡
Postoperative day 3	1.1±0.2♯	1.0±0.2	0.9±0.1♯	0.9±0.4	1.5±0.9‖†	1.9±1.0§†‡
Creatinine clearance	($mL \cdot min^{-1}$)					
Preoperative	70.1±9.4	84.1±16.1‡	70.9±8.8	63.7±26.4	43.6±12.0§‖†‡	40.3±14.5§‖†‡
At arrival in ICU	63.8±141.2∫	21.4±8.8∫	18.8±6.6∫	24.8±25.7∫	24.4±21.0	12.1±8.3
Postoperative day 1	105.6±76.1∬	109.5±81.2∬	112.2±56.5∫∬	101.6±63.0∫∬	91.2±72.3	61.2±55.4∬

Values are expressed in mean±SD.

§ Significantly different from group 1; ‖ Significantly different from group 2; † Significantly different from group 3; ‡ Significantly different from group 4; ∫ Significantly different from preoperative value in the same group; ∬ Significantly different from 'at arrival in ICU' value in the same group; ♯ Significantly different from 'postoperative day 1' value in the same group.

Table 2b. Laboratory Examinations of Renal Tubular Function

group	1	2	3	4	5	6
NAG index ($U \cdot g^{-1}$)						
Preoperative	5.9±2.4	3.7±2.1	5.9±6.2	7.1±7.9	6.5±3.3	8 .4±5.0
At arrival in ICU	41.4±59.4∫	53.0±49.9∫	65.7±68.9∫	30.9±28.9∫	46.8±28.1∫	50.7±27.2∫
Postoperative day 1	10.6±4.3∬	7.6±4.2∬	7.9±3.2∬	5.3±4.0	12.1±6.4∬	18.9±12.9‡∬
Serum β_2 microglobuline ($ng \cdot L^{1}$)						
Preoperative	1.6±0.3	1.4±0.5	1.6±0.4	1.3±0.5	3.4±4.3§‖‡	2.6±1.4
At arrival in ICU	1.4±0.3	1.4±0.5	1.1±0.4∫	0.8±0.5∫	2.1±2.1‖†	2.1±0.4
Postoperative day 1	1.5±0.4	1.4±0.6	1.0±0.4∫	0.8±0.4∫	5.9±10.7	2.2±0.7
Urine β_2 microglobuline index ($\mu g \cdot g^{-1}$)						
Preoperative	1.0±0.7	1.7±2.9	17.0±56.5	6.9±15.8	1.8±1.9	3.3±7.0
At arrival in ICU	70.1±85.4∫	196.7±172.5∫	256.5±150.3∫	81.5±100.9∫	156.2±132.2∫	328.1±413.3∫
Postoperative day 1	60.9±94.7∫	63.6±120.5∬	25.8±37.3∬	11.2±13.3	125.4±143.6	271.9±313.1§‖†‡¶
Fractional clearance of β_2 microglobuline ($\times 10^3$)						
Preoperative	0.7±0.5	1.5±3.3	5.9±18.7	3.0±6.0	1.1±1.3	2.0±4.4
At arrival in ICU	54.0±66.5∫	160.6±123.9∫	181.6±99.5∫	58.2±62.0∫	153.9±180.2∫	182.6±178.4∫
Postoperative day 1	44.1±74.7	46.8±75.4∬	22.7±29.8∬	10.6±10.4∬	107.7±138.4	94.7±171.4

Values are expressed in mean±SD.

§ Significantly different from group 1; ‖ Significantly different from group 2; † Significantly different from group 3; ‡ Significantly different from group 4; ¶ Significantly different from group 5; ∫ Significantly different from preoperative value in the same group; ∬ Significantly different from 'at arrival in ICU' value in the same group.

Table 3. Outcome of Each group

group	1	2	3	4	5	6
First response to verbal stimuli (min)	168.8±191.1	91.8±45.2	115.9±62.5	89.9±29.0	156.3±140.1	194.9±150.7
Intubation (min)	883.4±528.3	793.8±337.9	601.1±370.5	630.4±337.3	1213.7±809.4†‡	899.3±221.3
Furosemide during CPB(mg)	3.5±4.6	7.9±12.2	2.9±7.0	8.6±6.4	14.1±16.1	10.0±8.2
furosemide in ICU(mg)	9.8±13.6	13.9±25.1	6.7±8.6	13.3±20.3	16.9±23.3	17.1±23.7
Additional morphinein ICU (mg)	3.2±4.2	3.8±4.7	4.3±7.5	2.1±3.4	5.7±5.4	2.2±4.6
Maximum CPK(IU(L-1)	938±727	1046±1103	1019±669	819±510	770±601	1043±682
ICU stay (days)	4.8±0.8	5.1±1.4‡	4.8±0.9	3.6±1.6	5.1±1.1	4.4±1.8

Values are mean±standard deviation.

maximum CPK = the highest value of creatinine phosphokinase by the seventh postoperative day.

† Significantly different from group 3; ‡ Significantly different from group 4.

beck, Germany) revealed sevoflurane 0.5 MAC with fentanyl 20 μg·kg-1 provides adequate anesthesia depth.

Ccr is an accurate mean of quantifying the degree of renal function.[16,17] In general, patients whose Ccr less than 50 mL · min^{-1} needs special attention perioperatively to keep their renal function.[18] In the outcome studies, CABG surgery patients with mean Ccr less than 30 mL·min^{-1} or serum creatinine more than 2.2 mg·dL^{-1} was reported to be predictive of mortality.[13~15] Tsukamoto et al. compared the effect of sevoflurane on renal tubular function with that of isoflurane in patients with Ccr between 10 and 55 mL · min^{-1} in non-cardiac surgery.[11] In our patients, 25% tile of Ccr was 52.5 mL · min^{-1}. Accordingly we divided our patients receiving cardiac surgery into two groups, normal and impaired renal function, by the preoperative Ccr of 55 mL · min^{-1}. Because sevoflurane releases inorganic fluoride what could be one of the contributing factors to damage the renal tubules, it is necessary to evaluate the renal tubular function. In this study, renal tubular injury can be quantified in combination with SF^-, UF^-, Ccr, NAG/creatinine ratio, Uβ_2MG/creatinine ratio and Fcβ_2MG.

Because the previous studies demonstrates that the elimination half life of SF^- is 21.6 hours and NAG/creatinine ratio, Sβ_2MG, Uβ_2MG/creatinine ratio, Fcβ_2MG and Ccr decline from the peak values on the first postoperative day.[12,19,20] We measured serum and urinary inorganic fluoride levels, NAG/creatinine ratio, Uβ_2 MG/creatinine ratio, Fcβ_2MG and Ccr till the first postoperative day then the evaluation of renal function was continued with BUN and Cr till the third postoperative day.

Changes of serum fluoride after anesthetic administration are dependent on the duration of anesthesia, the lipid solubility of the anesthetic, and metabolism of the anesthetic.[21] Duration of anesthesia was not significantly different among our groups. Our data demonstrated that serum fluoride levels gradually increased in both sevoflurane and isoflurane anesthesia groups during CPB (Fig. 1a and 1b), urinary inorganic fluoride level was lower during CPB than before and after CPB (Fig. 2a and 2b) and urinary inorganic fluoride excretion rate was steady during CPB (Fig. 3a and 3b). Many factors such as hypotension, hypothermia, redistribution of blood flow, hemodilution, lung isolation and the usage of membrane oxygenator during CPB may play some roles in these changes of serum and urinary inorganic fluoride. Hypotension, hypothermia and redistribution of hepatic blood flow decrease the metabolic function of the liver and decrease fluoride production in liver cells. Hemodilution can lower serum fluoride level and sevoflurane concentration around renal tubules. In normothirmic or mild hypothermic CPB, the glomerular filtration rate (GFR) does not change.[22] Relatively fixed low GFR might cause steady urinary inorganic fluoride excretion rate and low urinary inorganic fluoride level during CPB (Fig. 3a and 3b). Higher GFR at post-CPB

period allows high urinary inorganic fluoride excretion rate in group 2 at the end of surgery (Fig. 3a). Because serum and urinary inorganic fluoride levels do not increase during CPB, this high urinary inorganic fluoride excretion rate in group 2 does not mean inorganic fluoride accumulation during CPB. The relation between MAC-hours and serum fluoride changes indicates that groups 1 and 5 and groups 3 and 6 show similar regression curves before CPB, respectively (Fig. 4a and 4b). This means that renal function is not a major factor for determination of serum fluoride levels at sevoflurane and isoflurane 0.5 MAC. The gradient of regression curves for groups 1 and 3 are almost double of those for groups 2 and 4 (Fig. 4a). This means that serum fluoride levels before CPB is determined not MAC-hours but the duration of administration. This also suggests kidneys can manage sevoflurane and isoflurane 1.0 MAC anesthesia. Serum fluoride level during CPB is almost stable in any groups. Urinary inorganic fluoride before CPB seems also the duration dependent. Urinary inorganic fluoride levels during and after CPB are stable. Mannitol and furosemide are common diuretics to administer during CPB and can increase Ccr and decrease Cr. In our institute, mannitol 25 g is an additional component of CPB priming solutions to expect diuresis and renal protection. During the surgical course, furosemide was administered to keep the urine outflow greater than 0.5 $mL \cdot kg^{-1} \cdot h^{-1}$. Furosemide dosage was not different among the groups (Table 3).

In patients anesthetized with methoxyflurane, there was a correlation between serum fluoride concentrations and severity of renal dysfunction. No effect was reported at peak fluoride < 40 μM, subclinical toxicity was accompanied by peak fluoride of 50-80 μM; mild toxicity was observed at 90-120 μM; and overt nephrotoxicity occurred at 80-175 μM.[23] In this study, all values of serum fluoride levels were less than 50 μM. And our laboratory data showed enzymuria and urinary inorganic fluoride excretion were not related to serum fluoride levels. These suggest sevoflurane and isoflurane both 0.5 and 1.0 MAC in patients with normal renal function and sevoflurane and isoflurane 0.5 MAC in patients with impaired renal function do not damage renal tubular cells according to methoxyflurane studies.

Recently, the question has been raised as to whether the methoxyflurane-like renal syndrome, or so-called inorganic fluoride nephrotoxicity apply to sevoflurane. In spite of high serum inorganic fluoride level during anesthesia, sevoflurane is not nephrotoxic due to the less area under the curve of serum inorganic fluoride level or relative absence of renal biotransformation to inorganic fluoride compared to methoxyflurane. Mazze concluded that clinical inorganic fluoride nephrotoxicity has not been observed with sevoflurane despite high blood fluoride levels in non-cardiac surgery.[24] The present data also showed the less area under the curve in sevoflurane anesthesia than reported for methoxyflurane. Endoplasmic reticulum in the liver cells is the principal site of metabolizing sevoflurane and methoxyflurane.[20,25] Two to 5 % of inhaled sevoflurane and 75 % of inhaled methoxyflurane are metabolized to fluoride.[20] Only renal proximal tubular cells, the target site of fluoride ion, have the similar endoplasmic reticulum with liver cells have and produce more inorganic fluoride than the rest of the kidney produces.[20,25~27] Urinary inorganic fluoride level, NAG/creatinine ratio, U β_2 MG/creatinine ratio and Fcβ_2 MG reflect renal tubular damage. NAG exists in the renal tubular cells and is released into the urine after damage to renal tubules but does not increase due to the disturbance of renal tubular reabsorption alone. β_2 MG is present on the cell surface and appears as a free monomer in all body fluids, including plasma. β_2 MG in plasma is freely filtered through the glomerulus and more than 99 % is reabsorbed in the proximal convoluted tubules. The U β_2 MG/creatinine ratio increases when there is a disturbance in renal tubular reabsorption. NAG/creatinine ratio represents the excretion of NAG, Uβ_2 MG/creatinine ratio and Fcβ_2 MG represent excretion of β_2MG. All of them indicate the renal tubular function.[11,28,29] However, Mazze emphasized that these markers do not always reflect the severity of renal function in clinical situation.[30] They are markedly affected by various factors such as surgery, circadian rhythm, nephrotoxic antibodies, hypertens-

ive episodes, prostatic hypertrophy, nonsteroidal anti-inflamatory drugs, radiocontrast dye and contamination from seminal fluid.[31] The combination of serum and urinary inorganic fluoride levels, NAG/creatinine ratio, Uβ_2 MG/creatinine ratio and Fcβ_2 MG with Ccr and BUN could give us more accurate information on the effect of anesthetics on renal function. In spite of high serum and urinary inorganic fluoride levels on the first postoperative day, NAG/creatinine ratio, Sβ_2 MG, Uβ_2MG/creatinine ratio, Fcβ_2MG and Ccr showed no significant difference between the sevoflurane anesthesia groups (groups 1, 2 and 5) and the isoflurane anesthesia groups (groups 3, 4 and 6). Urinary NAG andβ_2MG do not represent a toxic event specific to sevoflurane and neither clinical nor biochemical renal dysfunction occurred postoperatively.

Sevoflurane-induced nephrotoxicity may also be caused by fluoromethyl-2,2-difluoro-1-trifluoromethyl vinyl ether (Compound A).[24] Compound A is produced with the reaction between sevoflurane and soda lime. Factors predisposing circuits toward greater Compound A concentrations include higher sevoflurane concentrations, use of barium hydroxide lime, higher absorbent temperature and lower fresh gas flow.[32] All these factors could be excluded in our study. Fresh gas flow was 5 L · min^{-1} before and after CPB. It is enough to neglect Compound A concentration. And during CPB, 5 L · min^{-1} fresh gas from the anesthetic machine flowed directly to the gas inlet of the oxygenator and dumped from the outlet.

In this study, the lowest preoperative Ccr was 10 mL · min^{-1} from group 5. His Ccr at the arrival in the ICU and on the first postoperative day was 18.6 mL · min^{-1} and 14.0 mL · min^{-1}, respectively. He did not need hemodialysis and/or hemofiltration postoperatively. His preoperative BUN and Cr were 53.5 mg · dL^{-1} and 3.8 mg · dL^{-1}. They were 34.7-39.2 mg · dL^{-1} and 2.6-3.7 mg · dL^{-1} postoperatively. He did not show any complication after sevoflurane 0.5 MAC anesthesia.

Conclusions

Sevoflurane has potentially useful characteristics for cardiac surgery, such as minimal arrhythmic response to epinephrine and a lesser tendency for tachycardia.[8,27] Fluoride production depends largely on the inhalational concentration of sevoflurane. Although our study was performed in small number of patients and not dose-dependent fashion due to ethical reason, our results indicated that 0.5 MAC sevoflurane does not aggravate the intra- and postoperative renal function in CABG surgery patients with preoperative renal dysfunction and both 0.5 MAC and 1.0 MAC in patients with normal renal function did not aggravate renal function postoperatively. And our results in CABG surgery may simply apply to other cardiac surgery because CABG surgery patients potentially suffering from systemic atherosclerotic change which affects major organs. Patients who receive cardiac surgery other than CABG have relatively lower risk than CABG patients have. These mean that sevoflurane 0.5 MAC can be safely used for cardiac surgery generally in patients with impaired and normal renal function.

References

1) Aps C, Hutter JA, Williams BT : Anaesthetic management and postoperative care of cardiac surgical patients in a general recovery ward. Anaesthesia 41: 533-537, 1986
2) Cheng DC : Pro: Early extubation after cardiac surgery decreases intensive care unit stay and cost. J Cardiothorac Vasc Anesth 9 : 460-464, 1995
3) Schwender D, Kaiser A, Klasing S, et al : Midlatency auditory evoked potentials and explicit memory in patients undergoing cardiac surgery. Anesthesiology 80 : 493-501, 1994
4) Flezzani P, Croughwell ND, McIntyre RW, et al : Isoflurane decreases the cortisol response to cardiopulmonary bypass. Anesth Analg 65 : 1117-1122, 1986
5) Samuelson PN, Reves JG, Kirklin JK, et al : Comparison of sufentanil and enflurane-nitrous oxide anesthesia for myocardial revascularization. Anesth Analg 65 : 217-226, 1986
6) Walsh ES, Paterson JL, O'Riordan JB, et al : Effect of high-dose fentanyl anesthesia on the metabolic and endocrine response to cardiac surgery. Br J Anaesth 53 : 1155-1156, 1981
7) Bovill JG, Sebel PS, Stanlay TH : Opioid analgesics in anesthesia: with special reference to their use in cardiovascular anesthesia. Anesthesiology 61 : 731-755, 1984
8) Navarro R, Weiskopf RB, Moore MA, et al : Human anesthetized with sevoflurane or isoflurane have similar arrhythmic response to epinephrine. Anesthesiology 80 :

545-549, 1994
9) Biebuyck JF, Eger II EI : New inhaled anesthetics. Anesthesiology 80 : 906-922, 1994
10) Thomson IR : New volatile anaesthetics in cardiovascular anaesthesia: One step forward, two steps back? Can J Anaesth 23 : 883-889, 1996
11) Tsukamoto N, Hirabayashi Y, Shimizu R, et al : The effect of sevoflurane and isoflurane anesthesia on renal tubular function in patients with moderately impaired renal function. Anesth Analg 82 : 909-913, 1996
12) Holper K, Struck E, Sebening F : The diagnosis of acute renal failure (ARF) following cardiac surgery with cardiopulmonary bypass. J Thorac Cardiovasc Surg 27 : 231-237, 1979
11) Tsukamoto N, Hirabayashi Y, Shimizu R, et al : The effect of sevoflurane and isoflurane anesthesia on renal tubular function in patients with moderately impaired renal function. Anesth Analg 82 : 909-913, 1996
13) Higgins TL, Estafanous FG, Loop FD, et al : Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. JAMA 267 : 2344-2348, 1992
14) Magovern JA, Sakert T, Magovern GJ, et al : A model that predicts morbidity and mortality after coronary artery bypass graft surgery. J Am Col Card 28 : 1147-1153, 1996
15) Ferraris VA, Ferraris SP : Risk factors for postoperative morbidity. J Thorac Cardiovasc Surg 111 : 731-741, 1996
16) Hilberman M, Derby GC, Spencer RJ, et al : Sequential pathophysiological changes characterizing the progression from renal dysfunction to acute renal failure following cardiac operation. J Thorac Cardiovasc Surg 79 : 838-844, 1980
17) Wilson RF, Soullier G, Antonenko D : Creatinine clearance in critically ill surgical patients. Arch Surg 114 : 461-467, 1979
18) Kovatsis PG : Specific Considerations with Renal Disease, In:Davidson JK, Eckhardt WF, Perese DA eds, Clinical Anesthesia Procedures of the Massachusetts General Hospital Fourth Edition, Boston, Little, Brown and Company, 1993, pp. 56
19) Goldberg ME, Cantillo J, Larijani GE, et al : Sevoflurane versus isoflurane for maintenance of anesthesia: Are serum inorganic fluoride ion concentrations of concern. Anesth Analg 82 : 1268-1272, 1996
20) Kharasch ED : Biotransformation of sevoflurane. Anesth Analg 81 : S27-S38, 1995
21) Levine MF, Sarner J, Lerman J, et al : Plasma inorganic fluoride concentrations after sevoflurane anesthesia in children. Anesthesiology 84 : 348-353, 1996
22) Lema G, Meneses G, Urzua J, et al : Effects of extracorporeal circulation on renal function in coronary surgery patients. Anesth Analg 81 : 446-451, 1995
23) Mazze RI, Trudell JR, Cousins MJ : Methoxyflurane metabolism and renal dysfunction: Clinical correlation in man. Anesthesiology 35 : 247-252, 1971
24) Mazze RI, Jamison R : Renal effects of sevoflurane. Anesthesiology 83 : 443-445, 1995
25) Kharasch ED, Thummel KE : Identification of cytochrome P450 2E1 as predominant enzyme catalyzing human liver microsomal defluorination of sevoflurane, isoflurane and methoxyflurane. Anesthesiology 79 : 795-807, 1993
26) Kharasch ED, Hankins DC, Thummel KE : Human kidney methoxyflurane and sevoflurane metabolism. Intrarenal fluoride production as a possible mechanism of methoxyflurane nephrotoxicity. Anesthesiology 82 : 689-699, 1995
27) Rooke GA, Ebert T, Muzi M, et al : The hemodynamic and renal effects of sevoflurane and isoflurane in patients with coronary artery disease and chronic hypertension. Anesth Analg 82 : 1159-1165, 1996
28) Frink EJ, Malan TP, Isner RJ, et al : Renal concentrating function with prolonged sevoflurane or enflurane anesthesia in volunteers. Anesthesiology 80 : 1019-1025, 1994
29) Kharasch ED, Fink EJ, Zager R, et al : Assessment of low-flow sevoflurane and isoflurane effects on renal function using sensitive markers of tubular toxicity. Anesthesiology 86 : 1238-1253, 1997
30) Mazze RI, Jamison RL : Low-flow (1 L/min) sevoflurane: Is it safe? Anesthesiology 86 : 1225-1227, 1997
31) Higuchi H, Sumikura H, Sumita S, et al : Renal function in patients with high serum fluoride concentrations after prolonged sevoflurane anesthesia. Anesthesiology 83 : 449-458, 1995
32) Ebert TJ, Messana LD, Uhrich TD, et al : Absence of renal and hepatic toxicity after four hours of 1.25 minimum alveolar anesthetic concentration sevoflurane anesthesia in volunteers. Anesth Analg 86 : 662-667, 1998

(Circ Cont 23 : 293～306, 2002)