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Effects of sevoflurane anesthesia on plasma inorganic fluoride concentrations during and after cardiac surgery

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Abstract
Purpose. Sevoflurane metabolism results in the production of inorganic fluoride, which is known to be nephrotoxic. Since marked changes in body temperature and hemodynamics in cardiac surgery affect sevoflurane metabolism, plasma inorganic fluoride concentrations may differ in this situation compared with other types of surgery. We therefore measured plasma inorganic fluoride concentrations during and after sevoflurane anesthesia in patients undergoing cardiac surgery.
Methods. Sixteen patients undergoing coronary artery bypass grafting or valve replacement were premedicated with 5–10 mg midazolam and 0.5 mg scopolamine injected intramuscularly. Anesthesia was induced with 5–10 mg midazolam, 0.5–1 mg fentanyl, and 0.12–0.15 mg·kg^{-1} vecuronium. Following tracheal intubation, anesthesia was maintained with oxygen, sevoflurane, and fentanyl. At the onset of cardiopulmonary bypass (CPB), sevoflurane was discontinued, and additional fentanyl, midazolam, and pancuronium were administered. Plasma inorganic fluoride concentrations were measured before anesthesia, immediately before and after CPB, and at 0, 2, 6, 12, 24, and 48 h after anesthesia.
Results. The individual maximum plasma inorganic fluoride concentration was 19.2 ± 7.2 μmol·l^{-1} (mean ± SD; range, 9.2–36.7). The mean plasma inorganic fluoride concentrations increased during anesthesia, but the rate of increase decreased after the initiation of CPB. Concentrations peaked at 2 h after anesthesia and decreased thereafter. The concentrations in three cases continued to increase 2 h after anesthesia.
Conclusion. The plasma inorganic fluoride concentrations observed in patients undergoing cardiac surgery were below nephrotoxic levels. However, the decrease in mean fluoride concentration after anesthesia was slower than that in the previous study in general surgical patients.

Key words: Sevoflurane, Biotransformation, Inorganic fluoride, Cardiac surgery

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Introduction

Sevoflurane has a low blood–gas partition coefficient [1], has a minimal arrhythmic response to epinephrine [2], and does not cause tachycardia [3]. These characteristics suggest that sevoflurane may be useful as an inhalational anesthetic agent during cardiac surgery, because the depth of anesthesia can be adjusted rapidly, providing rapid emergence from anesthesia; exogenous epinephrine safely administ; and causes less tachycardia, which may injure the ischemic heart. However, sevoflurane metabolism results in the production of fluoride [4], which is a nephrotoxin [5–8]. Several studies on plasma inorganic fluoride concentrations during sevoflurane anesthesia have reported no impairment of renal function [9–11]; however, there have been no comparable studies on the use of sevoflurane in cardiac surgery. During cardiac surgery, hypothermia is employed during cardiopulmonary bypass (CPB), there is a subsequent rapid increase in body temperature, and marked changes in hemodynamics lead to changes in hepatic blood flow. These factors may significantly affect the metabolism of anesthetic agents in patients undergoing cardiac surgery, which may in turn affect plasma fluoride concentrations. In this study, we employed sevoflurane anesthesia in patients undergoing cardiac surgery, measured plasma inorganic fluoride concentrations during and after anesthesia, and evaluated changes in renal function based on pre- and post-anesthesia clinical laboratory values.

Materials and methods

This study was approved by the Institutional Committee on Human Research, and informed consent was obtained from all patients.

The subjects were 16 patients of ASA physical status class 2 or 3 undergoing coronary artery bypass grafting

(CABG) ($n = 9$), aortic valve replacement (AVR) ($n = 5$), or mitral valve replacement (MVR) ($n = 2$). Patients with hepatic or renal dysfunction according to history, laboratory findings, or physical examination were excluded from the study.

Patients received their regular cardiac medications until they were called to the operating room. Premedication was 5–10 mg midazolam and 0.5 mg scopolamine injected intramuscularly 30 min before induction of anesthesia. Anesthesia was induced with 5–10 mg midazolam, 0.5–1 mg fentanyl, and 0.12–0.15 $mg \cdot kg^{-1}$ vecuronium. Following tracheal intubation, anesthesia was maintained with oxygen, sevoflurane, fentanyl, and pancuronium. Systolic blood pressure and heart rate were maintained within 20% of the preoperative value by adjusting the sevoflurane concentration. Hypertensive responses that were not controlled with the maximum concentration of sevoflurane were treated with a bolus of 50–100 μg fentanyl. Hypotension was treated with a bolus of 50–100 μg phenylephrine. Tachycardia that was not controlled with sevoflurane was treated with a bolus of 50–100 μg fentanyl. Bradycardia associated with hypotension was treated with 4–8 mg ephedrine. Nitroglycerin was administered continuously at 0.5–1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during anesthesia. At the onset of CPB, sevoflurane was discontinued, and additional fentanyl, midazolam, and pancuronium were administered. After CPB, low-dose (0.5%–1%) sevoflurane was administered. Hypertension was treated with a bolus of 50–100 μg fentanyl and an increase in sevoflurane concentration. Dopamine was infused to maintain more than 2.3 $l \cdot min^{-1} \cdot m^{-2}$ of cardiac index (CI). If the CI was greater than 2.3 $l \cdot min^{-1} \cdot m^{-2}$ but the mean blood pressure was less than 65 mmHg, 50–100 $\mu g \cdot min^{-1}$ of phenylephrine was infused.

During anesthesia, end-tidal CO_2 concentrations and inspired and end-tidal sevoflurane concentrations were monitored by mass spectrometry (Medical Gas Analyzer 1100, Perkin Elmer, Pomona, CA, USA). The mass spectrometer was calibrated against a known concentration of sevoflurane that was verified by calibration with a gas chromatograph (model GC-9A, Shimadzu, Kyoto, Japan). Mean blood pressure (MBP), heart rate (HR), and central venous pressure (CVP) were monitored during the study period. A thermodilution catheter (Swan-Ganz CCO, Baxter, Irvine, CA, USA) was inserted to monitor CI after the induction of anesthesia.

The radial artery was cannulated to permit blood samples to be obtained for plasma inorganic fluoride analysis during and after anesthesia. Plasma inorganic fluoride analysis was performed before anesthesia, immediately before and after CPB, and 0, 2, 6, 12, 24, and 48 h after anesthesia using an ion-selective electrode (Orion Research, Cambridge, MA, USA) calibrated against a standard solution of sodium fluoride.

Clinical laboratory studies for blood urea nitrogen (BUN) and serum creatinine were performed before anesthesia and on days 1, 2, and 4 after anesthesia.

Hemodynamic and clinical laboratory values were compared using repeated-measures analysis of variance (ANOVA) and Student's t-test. A P value less than 0.05 was considered statistically significant. All values were calculated as means ± SD.

Results

The study patients were 6 women and 10 men with a mean age of 60 ± 11 years (range, 32–73), a mean height of 157 ± 7 cm (range, 145–170), and a mean body weight of 53 ± 10 kg (range, 36–69). The duration of anesthesia was 6.94 ± 1.06 h (range, 5.17–8.67), the duration of CPB was 2.17 ± 0.54 h (range, 1.00–2.83), and sevoflurane %hour (inhaled sevoflurane concentration · duration of anesthesia) was 6.25 ± 2.20 (range, 3.33–10.80). The lowest core temperature of the CPB was 30.1 ± 1.2 °C (range, 28.4–31.9).

Hemodynamic parameters during the study period are shown in Fig. 1. HR increased after CPB and decreased gradually thereafter. MBP decreased after the induction of anesthesia and tended to increase after CPB. CVP increased after CPB, stabilized until 24 h after anesthesia, and decreased 48 h after anesthesia. CI increased gradually after CPB (Fig. 1). There were no significant hemodynamic differences between the types of surgery.

The individual maximum plasma inorganic fluoride concentration was 19.2 ± 7.2 $\mu mol \cdot l^{-1}$ (range, 9.2–36.7), with peak levels reached at the end of anesthesia in 3 patients, 2 h after anesthesia in 10 patients, 6 h after anesthesia in 1 patient, 12 h after anesthesia in 1 patient, and 24 h after anesthesia in 1 patient. No correlation was found between %hour of sevoflurane and individual maximum plasma fluoride concentration (Fig. 2).

The mean plasma inorganic fluoride concentration increased rapidly until the initiation of CPB and increased gradually thereafter until 2 h after anesthesia (Fig. 3). The concentration peaked 2 h after anesthesia, reaching a maximum of 17.4 ± 5.6 $\mu mol \cdot l^{-1}$, and then decreased to 66% of its peak value (11.5 ± 6.5 $\mu mol \cdot l^{-1}$) 24 h after anesthesia and to 44% (7.6 ± 4.9 $\mu mol \cdot l^{-1}$) 48 h after anesthesia.

The individual plasma inorganic fluoride concentration decreased after the end of anesthesia in 3 patients, or 2 h after anesthesia in 10 patients (data not shown). The concentration in one AVR patient decreased 6 h after anesthesia (Fig. 4) and 12 h after anesthesia in another AVR patient. In another CABG patient, the

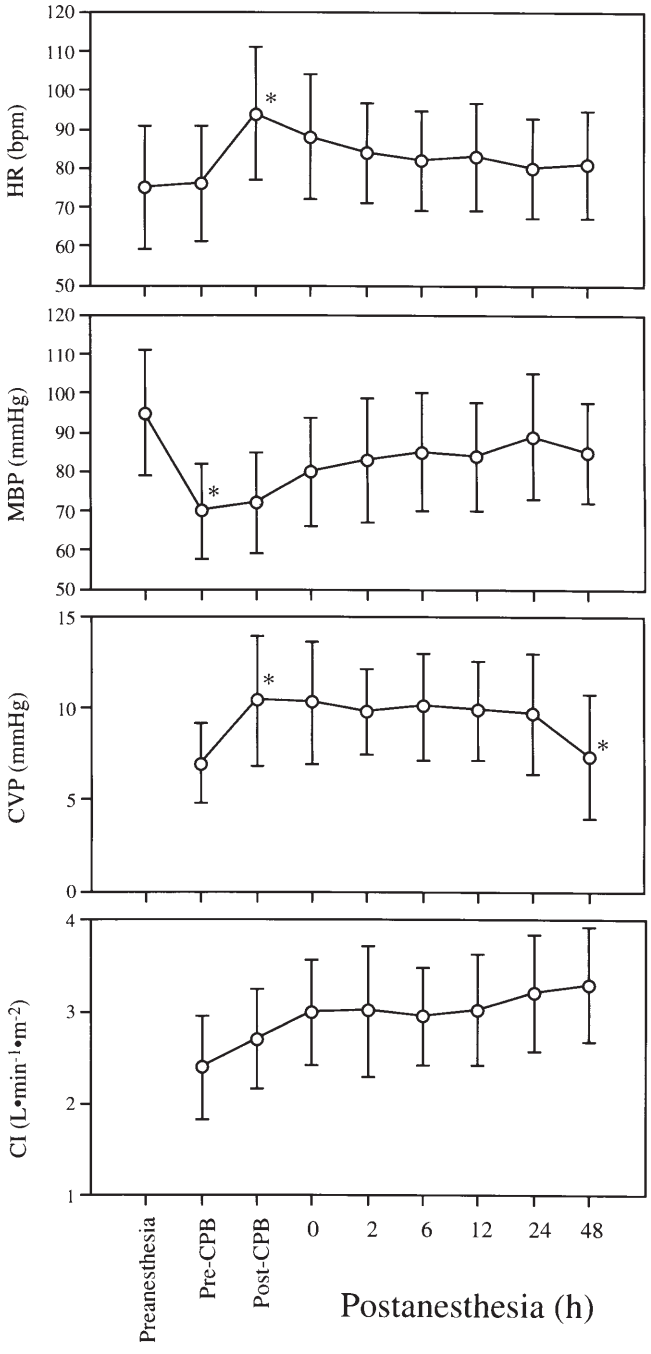

Fig. 1. Heart rate (*HR*), mean blood pressure (*MBP*), central venous pressure (*CVP*), and cardiac index (*CI*) at specific times. $*P < 0.05$ vs prior value. Values are shown as means ± SD ($n = 16$). *CPB*, Cardiopulmonary bypass

concentration decreased after the end of anesthesia but increased 6 h after anesthesia and peaked 24 h after anesthesia, and then decreased (Fig. 4).

The urine volumes were 2117 ± 671 ml during anesthesia, 3264 ± 873 ml between 0 and 24 h, and 2009 ± 456 ml between 24 and 48 h after anesthesia.

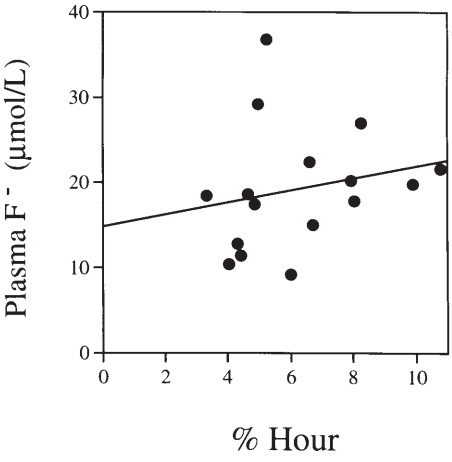

Fig. 2. Correlation between maximum plasma F^- concentration and % hours in each patient ($r^2 = 0.046$, $P = 0.432$)

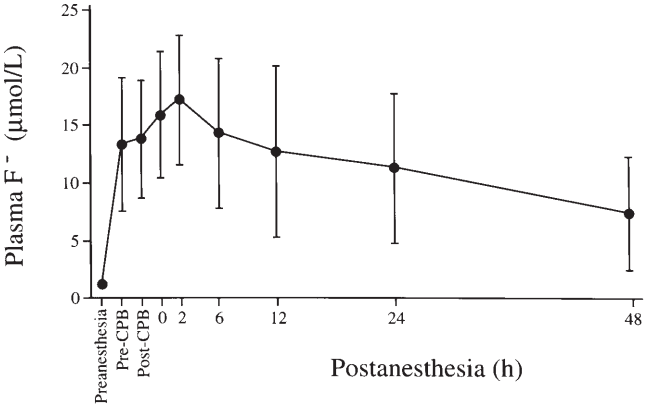

Fig. 3. Mean plasma fluoride concentrations during and after sevoflurane anesthesia. Values are shown as means ± SD ($n = 16$). *CPB*, Cardiopulmonary bypass

No significant differences were seen in blood urea nitrogen (BUN) and serum creatinine values between blood samples obtained before and after anesthesia (Table 1).

Discussion

In this study, we measured plasma inorganic fluoride concentrations over time in patients undergoing cardiac surgery under sevoflurane anesthesia. Our results revealed significant differences in plasma inorganic fluoride concentrations between patients undergoing cardiac surgery and patients undergoing other surgical procedures or volunteers [9–11].

One of the differences noted was that the rate of increase in fluoride concentration decreased during

anesthesia, and this decrease was observed after the initiation of CPB. This difference is thought to be due to the use of hypothermia during CPB and the decrease in hepatic circulation after weaning from CPB, which inhibited the metabolism of sevoflurane. Thus, plasma fluoride concentrations increased gradually after the initiation of CPB. In addition, a positive correlation was seen between sevoflurane %hour (inhaled sevoflurane concentration · duration of anesthesia) and fluoride concentration [9,10]. In this study, the sevoflurane concentration was kept low to maintain blood pressure after weaning from CPB, which would also contribute to a gradual increase in fluoride concentration.

The other difference observed was the slow decrease in mean fluoride concentration after anesthesia, compared with that seen after general surgery and in volunteers. In patients undergoing general surgery and in volunteers, the plasma fluoride concentration decreased to less than 50% of its peak value 12 to 24 h after anesthesia [9–11], whereas in this study, the concentration was about 66% of its peak value even 24 h after anesthesia. In general, because sevoflurane is eliminated by exhalation immediately after the termination of anesthesia [12], fluoride concentrations decrease rapidly. Furthermore, plasma inorganic fluoride concentrations peaked 0–3 h after anesthesia [9–11]. However, in this study, the concentrations in three patients peaked 6–24 h after anesthesia. After cardiac surgery, peripheral circulatory depression may lead to delayed elimination of sevoflurane from muscle and fatty tissues, and as circulation improves after surgery, sevoflurane is gradually released into the blood and metabolized.

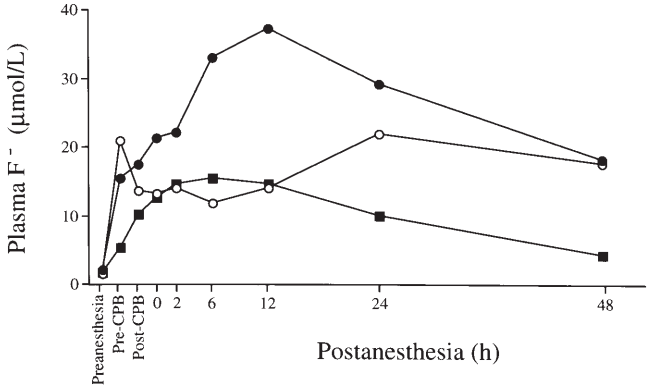

Fig. 4. Plasma fluoride concentrations with late peak in the three patients during and after sevoflurane anesthesia. *Closed circles* and *closed squares*, AVR patients; *open circles*, CABG patients. *CPB*, Cardiopulmonary bypass

The other difference observed was that there was no correlation between the individual maximum plasma fluoride concentration and %hour of sevoflurane. Several factors are thought to affect the metabolism of sevoflurane in patients undergoing cardiac surgery, which may in turn affect plasma fluoride concentrations.

Methoxyflurane nephrotoxicity is caused by plasma fluoride concentrations in excess of 50 μmol·l^{-1} [7]. However, sevoflurane nephrotoxicity was not observed, even when the fluoride concentration exceeded 50 μmol·l^{-1} [10,11]. One reason is that sevoflurane is eliminated faster than methoxyflurane, and therefore the area under the plasma fluoride concentration curve is smaller for sevoflurane than for methoxyflurane [9–11]. The other reason is that the intrarenal metabolism of methoxyflurane may result in impaired urine-concentrating ability whereas the relative lack of intrarenal metabolism of sevoflurane and therefore the lack of intrarenal fluoride provides a greater safety margin for sevoflurane [13,14]. In our patients, the maximum fluoride concentration was 19.2 ± 7.2 μmol·l^{-1} (range, 9.2–36.7), significantly lower than 50 μmol·l^{-1}. However, the decrease in fluoride concentration after anesthesia in our study was slower than that in the previous study. Furthermore, in three cases, the fluoride concentration increased significantly after anesthesia.

A recent report suggests that plasma fluoride concentrations depend not only on the dose of sevoflurane but also on the ASA grade of the patient and the type of surgery [15]. Since our study group consisted of patients undergoing CABG, AVR, and MVR, the plasma fluoride concentration may differ according to the type of cardiac surgery. However, a slow decrease in fluoride concentration after anesthesia can be seen in any type of cardiac surgery, and a late peak in concentration is seen in both CABG and AVR patients. Furthermore, hemodynamic differences are larger between patients

Table 1. Results of clinical laboratory tests

Test	Preanesthesia	Day 1 postanesthesia	Day 2 postanesthesia	Day 4 postanesthesia
BUN (mg·dl^{-1})	13.5 ± 5.3	11.8 ± 5.4	11.9 ± 5.9	12.4 ± 3.3
Creatinine (mg·dl^{-1})	0.72 ± 0.18	0.66 ± 0.18	0.66 ± 0.21	0.60 ± 0.17

BUN, Blood urea nitrogen. Values are shown as means ± SD.

having the same type of surgery than between different types of surgery. Therefore, our observations are due to the general physiological and hemodynamic response in cardiac surgery rather than to the specific type of cardiac surgery.

We concluded that the plasma inorganic fluoride concentrations observed in this study were significantly lower than the threshold for methoxyflurane nephrotoxicity. A slow decrease in mean fluoride concentration after anesthesia was observed, as compared with that seen following general surgery and in volunteers. The increases in fluoride concentration in the three patients undergoing cardiac surgery were observed 6–24 h after sevoflurane anesthesia.

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