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Low-flow Sevoflurane Compared with Low-flow Isoflurane Anesthesia in Patients with Stable Renal Insufficiency

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Background: **Sevoflurane is degraded to compound A (CpA) by carbon dioxide absorbents containing strong base. CpA is nephrotoxic in rats. Patient exposure to CpA is increased with low fresh gas flow rates, use of Baralyme®, and high sevoflurane concentrations. CpA formation during low-flow and closed circuit sevoflurane anesthesia had no significant renal effects in surgical patients with normal renal function. Preexisting renal insufficiency is a risk factor for postoperative renal dysfunction. Although preexisting renal insufficiency is not affected by high-flow sevoflurane, the effect of low-flow sevoflurane in patients with renal insufficiency is unknown.**

Methods: **After obtaining institutional review board approval, 116 patients with a stable preoperative serum creatinine concentration 1.5 mg/dl or greater were assessable. Patients were randomized to receive either sevoflurane (n = 59, 0.8–2.5 vol%) or isoflurane (n = 57, 0.5–1.4 vol%) at a fresh gas flow rate of 1 l/min or less. Use of opioids was restricted to a minimum, and Baralyme® was used to increase CpA exposure. Inspiratory and expiratory CpA concentrations were measured during anesthesia. Renal function (serum creatinine and blood urea nitrogen, urine protein and glucose, creatinine clearance) was measured preoperatively and 24 and 72 h after induction.**

Results: **Demographic patient data did not differ between groups. Patients received 3.1 ± 2.4 minimum alveolar concentration–hours sevoflurane or 3.8 ± 2.6 minimum alveolar concentration–hours isoflurane (mean ± SD). Durations of low flow were 201.3 ± 98.0 and 213.6 ± 83.4 min, respectively. Maximum inspiratory CpA with sevoflurane was 18.9 ± 7.6 ppm (mean ± SD), resulting in an average total CpA exposure of 44.0 ± 30.6 ppm/h. There were no statistically significant changes from baseline to 24- and 72-h values for serum creatinine or blood urea nitrogen, creatinine clearance, urine protein, and glucose, nor were there significant differences between both anesthetics.**

Conclusion: **There were no statistically significant differences in measured parameters of renal function after low-flow sevoflurane anesthesia compared with isoflurane. These results suggest that low-flow sevoflurane anesthesia is as safe as low-flow isoflurane and does not alter kidney function in patients with preexisting renal disease.**

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SEVOFLURANE, fluoromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether, was first approved for human use in Japan in 1990. To date, this potent volatile anesthetic is widely used worldwide. However, concerns about its use still exist because of degradation to fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether (compound A [CpA]) by carbon dioxide absorbers of standard anesthesia rebreathing systems. CpA has been shown to be nephrotoxic in rats.[1–3]

Clinical studies in surgical patients with normal renal function have shown no adverse effects of CpA formation during sevoflurane anesthesia at various fresh gas flow rates.[4–10] Corresponding results were obtained in patients with chronically impaired renal function at a relatively high fresh gas flow rate of 4 l/min.[11] Increasing economic pressure necessitates reduction of fresh gas flow rates into the anesthesia rebreathing circuits to the lowest tolerable level for all kinds of surgical interventions and all patients. Fresh gas flow reduction increases CpA concentrations within the circuit and hence CpA exposure.[12] Preexisting renal insufficiency is a risk factor for postoperative renal dysfunction. CpA exposure might impose an additional risk on patients with renal insufficiency who are already at risk for postoperative renal dysfunction. Insufficient data in this patient population have been published so far.

This study was designed to investigate the safety of low-flow sevoflurane anesthesia in patients with a stable renal insufficiency. Comparisons were made against isoflurane, which is accepted to confer no risk of nephrotoxicity. As patient exposure to CpA is higher with lower fresh gas flow rates,[12] use of Baralyme® (Allied Healthcare Products, Inc., St. Louis, MO) instead of soda lime,[2] and high sevoflurane concentrations, we deliberately included those factors in the protocol to increase CpA exposure.

Materials and Methods

The study was designed as a multicenter (4 investigators; numbers of patients enrolled: P.F.C., n = 61;

Table 1. Criteria for Clinically Significant Increases in Serum Creatinine[14] and Blood Urea Nitrogen

Laboratory Variable	Baseline Value	Criterion
Serum creatinine	≤ 1.9 mg/dl	≥ 0.5 mg/dl increase
	2.0–4.9 mg/dl	≥ 1.0 mg/dl increase
	≥ 5.0 mg/dl	≥ 1.5 mg/dl increase
Blood urea nitrogen	Normal or below lower limit of normal	≥ 1.25 × upper limit of normal
	High	≥ 1.25 × baseline

E.D.K., n = 54; B.M.W., n = 9; T.J.E., n = 8; see Web Enhancement; additional details and images documenting the findings reported here are available in the Web Enhancement), multinational, open-label, randomized, comparative trial. All participating sites received approval from their institutional review boards. Criteria for enrolling a patient were a written informed consent, age older than 18 yr, stable renal insufficiency (qualifying serum creatinine concentration ≥ 1.5 mg/dl measured by standard laboratory procedures at the local laboratory at each site), elective surgery, anticipated anesthesia of more than 2 h, and an American Society of Anesthesiologists physical status of II–IV. Exclusion criteria were a previous unusual response to a halogenated anesthetic, an experimental drug within 28 days before surgery, a history of hemodialysis, and, most importantly, a renal impairment that was transient or expected to improve as a result of the scheduled surgical intervention. Further exclusion criteria were emergency surgery, contrast media before or after surgery, or vascular surgery that could compromise renal blood flow.

Within each site, patients were randomized immediately before anesthesia to sevoflurane and isoflurane in a 1:1 ratio. During maintenance of anesthesia, sevoflurane and isoflurane were administered at a fresh gas flow rate of 1 l/min or less. Oxygen was administered to maintain an inspired oxygen concentration of 30–40%. Nitrous oxide was not given. Fresh Baralyme® with new respiratory tubing and connections were used for each patient. Gas samples for CpA determinations were obtained from the inspiratory and expiratory limbs of the anesthesia circuit within the same respiratory cycle in intervals of 30 min at three sites (P.F.C., E.D.K., T.J.E.). CpA was determined by gas chromatography.[13]

Anesthesia was induced according to the standard procedure at each investigative site. Fentanyl (1–2 μg/kg) could be given during induction and was subsequently minimally administered. Muscle relaxants were administered as needed to facilitate intubation. During maintenance of anesthesia, the end-tidal anesthetic concentrations were adjusted as appropriate for the conduct of anesthesia within 0.8–2.5 vol% for sevoflurane and 0.5–1.4 vol% for isoflurane. Blood pressure and heart rate were maintained within 20% of baseline values.

Patient data were included into analysis if the patient had satisfied all criteria for enrollment (including verification of elevated serum creatinine by the central laboratory), had a duration of low-flow anesthesia 2 h or greater, and maintained a minimum end-tidal study anesthetic concentration at the predefined limits. Blood samples were taken preoperatively, at the end of anesthesia, and at 2, 24, and 72 h after anesthesia. Urine samples were performed preoperatively and 24 and 72 h after anesthesia. Blood and urine samples were evaluated by a central laboratory by standard procedures (UCT International, New York, for US sites, and UCT International, London, GB for European sites).

Statistical Analysis

Data are given as mean values ± SD. Fisher exact test was used to compare incidence of a significant increase from baseline in serum creatinine concentrations between the two treatment groups. The criteria by Hou *et al.*[14] were used to define clinically significant increases in serum creatinine. The criteria for a significant increase in creatinine or blood urea nitrogen (BUN) are provided in table 1. Serum creatinine, BUN, quantitative urine protein, and quantitative urine glucose were analyzed using analysis of variance techniques to evaluate changes from baseline between the 2 groups. The minimum alveolar concentration (MAC)-hours of anesthetic gases for each patient were computed using the area under the curve (AUC) for the MAC (where MAC is the end-tidal concentration divided the MAC multiple, 2.10 vol% for sevoflurane and 1.5 vol% for isoflurane) multiplied by the duration (in hours) of the anesthetic administration. For further analysis, MAC values were adjusted for patient age. All analyses were performed with SAS System procedures GLM and FREQ (SAS Institute, Cary, NC). $P \leq 0.05$ was considered statistically significant. The sample size was calculated using statistical data from an earlier study in a comparable patient population.[11] A minimum of 110 assessable patients were considered sufficient to detect a 20% difference in serum creatinine using an α level of 0.05 (two-sided) with a power greater than 0.08.

Results

A total of 132 patients were enrolled. One patient was discontinued from the study before administration of study drug because he was not treated. Fifteen patients were excluded because of protocol violations (short duration of low flow, low qualifying serum creatinine in central laboratory [while creatinine in site laboratory

Table 2. Demographic Patient Characteristics

Characteristic	Sevoflurane (N = 59)	Isoflurane (N = 57)	Treatment *P* Value
Age (yr)	67.2 (12.7)	68.5 (12.9)	0.860
Gender			1.000
Male	42 (71%)	41 (72%)	
Female	17 (29%)	16 (28%)	
Weight (kg)	77.29 (16.27)	80.27 (18.82)	0.658
Height (cm)	170.19 (10.05)	171.44 (9.78)	0.795
ASA physical status			0.199
II	16 (27%)	19 (33%)	
III	38 (64%)	37 (65%)	
IV	5 (8%)	1 (2%)	

Values are expressed as mean (SD).

ASA = American Society of Anesthesiologists.

was > 1.5 mg/dl], invalid laboratory determinations, lost to follow-up, premature termination of study because of death [P.F.C., n = 1; probable cause: pulmonary embolism], erroneous study medication). The remaining 116 patients were included in the assessable data set; their demographic characteristics are shown in table 2. There were no statistically significant differences in age, height, weight, sex, or American Society of Anesthesiologists physical status. There were also no differences in perioperative variables such as administered drugs, blood loss, and duration of procedures.

There were no statistically significant differences between groups in the average duration of study drug exposure and in duration of the low-flow period (table 3). The total sevoflurane dose tended to be lower than isoflurane dose, mostly because of a slightly shorter duration of surgery (table 3). The average study drug dose was 3.1 ± 2.4 MAC-h for sevoflurane and 3.8 ± 2.6 for isoflurane ($P = 0.136$).

Renal Function Parameters

Serum creatinine and BUN did not change significantly, either within each anesthetic or when compared between groups. BUN values tended to decrease slightly more after isoflurane, but statistical significance was not reached (figs. 1–3). The numbers of patients with clinically significant increases in serum creatinine or BUN at 24 and/or 72 h after anesthesia were comparable (table 4).

No statistically significant differences were observed in mean 24-h urine protein and glucose excretions at 24 and 72 h after anesthesia (table 5).

As expected, the calculated preoperative average creatinine clearance (estimated creatinine clearance = [[140 − age in years] × weight in kilograms]/[72 × serum creatinine concentration in milligrams per deciliter]; multiplied by 0.85 for women)[15] was low and amounted to 36 ml/min in both groups. At 24 h after anesthesia, the measured creatinine clearance after sevoflurane was again 36 ml/min and 37 ml/min after isoflurane. Exactly the same numbers of mean values were obtained at 72 h after anesthesia.

Serum Inorganic Fluoride

Serum inorganic fluoride concentrations increased over time with both anesthetics. However, increases from baseline were far greater with sevoflurane as compared with isoflurane (fig. 4). The maximum mean inorganic fluoride concentration was 36.9 ± 2.2 μM and reached shortly after the end of sevoflurane anesthesia but 6.4 ± 2.4 μM after isoflurane ($P < 0.001$). A total of 17 of 59 patients (29%) who received sevoflurane had a peak serum inorganic fluoride concentration of 50 μM or greater in the study period. Two sevoflurane patients had peak serum inorganic fluoride 50 μM or greater, together with a relatively high CpA concentration greater than 35 ppm. In none of those patients was

Table 3. Duration of Study Drug Exposure and Summary of Study Drug Dose

Data set	Total Duration (min)		Treatment *P* Value
	Sevoflurane (N = 59)	Isoflurane (N = 59)	
Induction to end of anesthesia	217.0 ± 99.0	231.4 ± 84.0	0.156
Low-flow period	201.3 ± 98.0	213.6 ± 83.4	0.206
	Summary of Study Drug Dose		
Dose (MAC/h)	3.1 ± 2.4	3.8 ± 2.6	0.136

Values are expressed as mean ± SD.

MAC = minimum alveolar concentration.

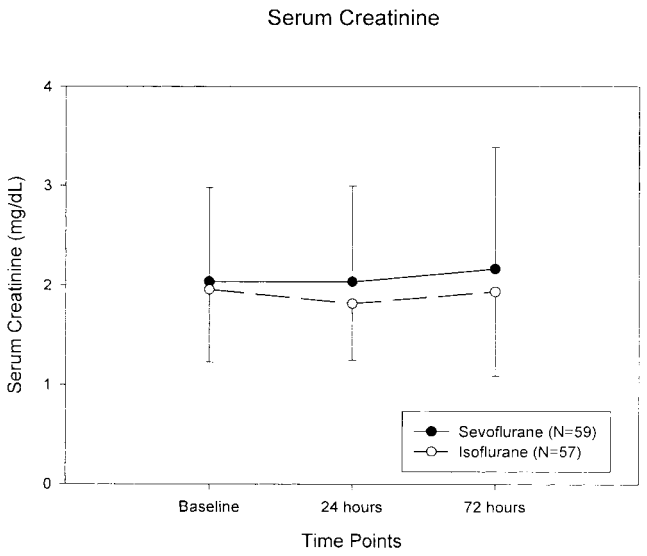

Fig. 1. Serum creatinine values. There was no statistically significant difference between groups.

serum creatinine, BUN, or creatinine clearance increased clinically significantly at 24 or 72 h after anesthesia.

Compound A

The total duration of sevoflurane exposure for 56 patients in which CpA measurements were obtained is given in table 6, and the CpA values are shown in figure 5. The average CpA concentration over time was 13.4 ± 5.8 ppm, the maximum mean CpA concentration being 18.9 ± 7.6 ppm. The calculated average CpA exposure (AUC) was 44.0 ± 30.6 ppm-hr (table 7). A total of 4 sevoflurane-treated patients had CpA exposures (AUC) greater than 100 ppm-hr during the study. In none of those patients was serum creatinine or BUN

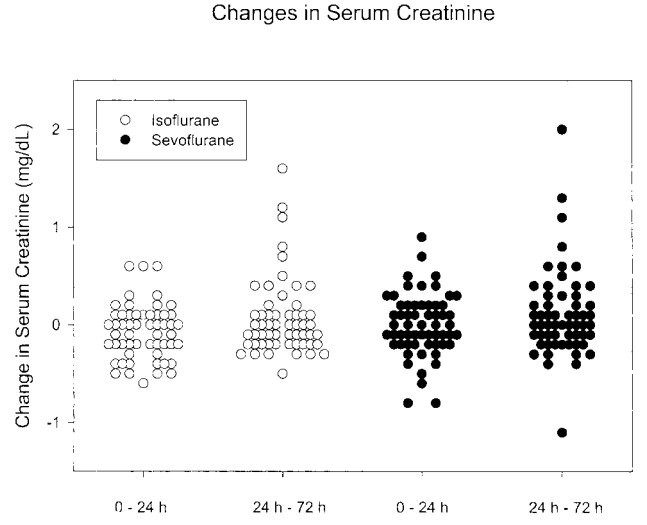

Fig. 2. Changes in serum creatinine. The values show the difference between serum creatinine from 24 h to preanesthesia and 72 h to 24 h. There was no statistically significant difference between groups.

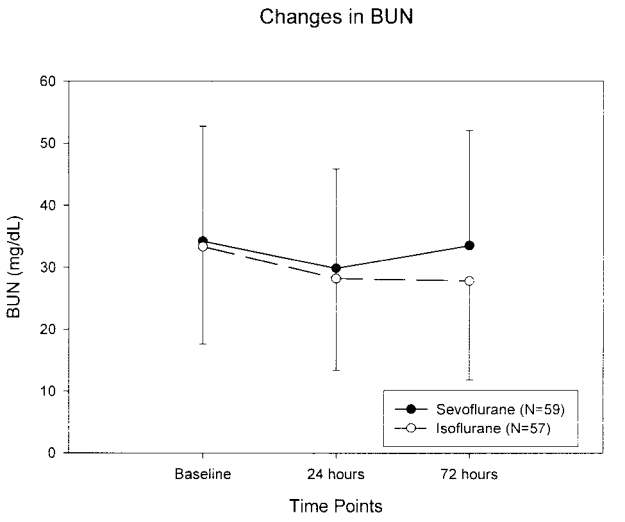

Fig. 3. Blood urea nitrogen samples. There was no statistical significant difference between groups.

increased clinically significantly at 24 or 72 h after anesthesia.

Discussion

The results of this investigation show that sevoflurane can be used as safely as isoflurane for low-flow (≥ 1 l/min) anesthesia in patients with chronically impaired renal function. This is concluded from both stable measures of renal function throughout the postoperative course, as well as absence of differences between both anesthetics. No patient suffered a permanent deterioration of preexisting renal insufficiency, and none required postoperative hemodialysis or hemofiltration. Furthermore, there was no relation between CpA exposure and a worsening of the applied markers of renal function, suggesting that this degradation product had no effect. Hence, our results further supplement an ample number of investigations about renal safety of sevoflurane, indicating that its byproduct, CpA, did not add to renal dysfunction in these patients with preexisting disease.[4,6,7,9,10,16,17]

The CpA concentrations in an anesthesia rebreathing circuit, and hence CpA exposure of a patient—among some other factors—largely depend on fresh gas flow into the system. This relation is reciprocal, with the CpA concentration in the anesthesia circuit being much

Table 4. Proportions of Patients with Postanesthesia Serum Creatinine and Blood Urea Nitrogen Increases Considered Clinically Significant

	Number of Patients (%)		*P* Value
Data Set Variable	Sevoflurane (N = 59)	Isoflurane (N = 57)	
Creatinine (mg/dl)	7/59 (12%)	8/56 (14%)	0.785
Blood urea nitrogen	12/58 (21%)	6/55 (11%)	0.201

Table 5. Quantitative 24-h Urine Protein and Glucose

	Sevoflurane		Isoflurane		*P* Value
Evaluation Time Point	N	Mean (SD)	N	Mean (SD)	
Urine protein 24-h (mg/24 h)					
24 hours postanesthesia	59	974 (1,825)	55	1,076 (1,545)	0.354
72 hours postanesthesia	56	1,012 (1,825)	55	1,473 (2,137)	0.127
Urine glucose 24-h (mg/24 h)					
24 hours postanesthesia	59	1,623 (4,457)	56	1,254 (2,126)	0.481
72 hours postanesthesia	57	1,792 (7,238)	54	612 (1,058)	0.146

higher in sevoflurane anesthesia at a flow rate of 1 l/min than in high-flow anesthesia with flow rates of 3 or 6 l/min.[12] Therefore, and if CpA at clinically relevant concentrations were a nephrotoxin in humans, patients receiving low-flow anesthesia would be at an increased risk for renal injury.

To date, many studies have shown no renal effects of low-flow sevoflurane in surgical patients. However, most of these studies were performed in relatively healthy patients and did not involve patients with a preexisting renal insufficiency.[10,18,18–23] Patients with preexisting renal disease are at an increased risk for further postoperative deterioration of function, and CpA nephrotoxicity might add to this risk. Therefore, it appeared necessary to study those patients specifically.

Only few studies were performed to assess the safety of sevoflurane in patients with preexisting renal disease.[11,24,25] Conzen *et al.*[11] randomized 41 patients to receive general anesthesia with sevoflurane or enflurane. As in this study, the inclusion criterion was a stable elevation of serum creatinine or to greater than 1.5 mg/dl. Creatinine and BUN were used as markers of postoperative renal function, and there these parameters remained remarkably stable during the observation period of up to 1 week. McGrath *et al.*[25] randomized 26 patients with preoperative creatinine values between 1.5 and 3.0 mg/dl to receive sevoflurane or isoflurane. Again, there were no differences during postoperative recovery with respect to renal function. However, these studies did not specifically look at the effects of low flow, but were rather designed to rule out toxic effects of inorganic fluoride, a hepatic degradation product of sevoflurane. The anesthetics were given at fresh gas flow rates of 4 l/min[11] and 5 l/min,[25] respectively. CpA concentrations were not measured in these studies, but it appears clear that at such high fresh gas flow rates, exposure to CpA was relatively minor.

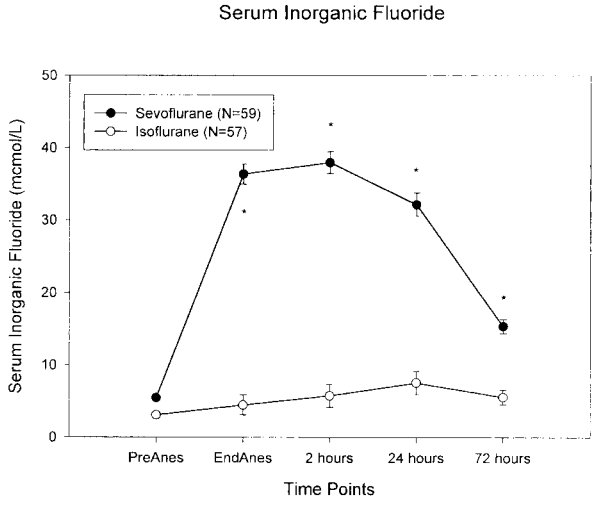

Fig. 4. Serum inorganic fluorides during and after sevoflurane or isoflurane anesthesia. Data are presented as mean ± SD. *Statistical significance between both groups ($P < 0.001$).

One previous study investigated the effects of low-flow anesthesia in patients with preexisting renal disease. Inclusion criteria and protocol were similar to that of the present study. At a fresh gas flow of 1 l/min, no differences serum creatinine, BUN, and creatinine clearance were detected.[26] However, the total number of enrolled patients (N = 17) is far too small to allow conclusions regarding the safety of sevoflurane, and the investigators admit that a larger sample size than that studied is required to resolve the issue of sevoflurane safety in patients with renal insufficiency.

Our present study was deliberately designed to produce as high CpA concentrations as possible during routine clinical low-flow conditions. Fresh Baralyme® was used for each anesthetic, and we tried to achieve high end-expired sevoflurane concentrations, mainly by reducing the amount of opioids allowed for intraoperative use.

During our study conditions, sevoflurane anesthesia was associated with a 44.0 ± 30.6 ppm-hr exposure to CpA and an average peak CpA concentration of 18.9 ± 7.6 ppm. Mean peak CpA concentrations of recent studies involving clinical patients ranged between 20 and 32 ppm.[2,6,9,27] Our peak CpA values are similar to

Table 6. Duration of Sevoflurane Exposure in Patients in Whom Compound A Was Measured

	Total Duration (min)	
Data set	Entire Anesthetic Period	Low-flow Period
All evaluable patients		
N	56	56
Mean ± SD	216.0 ± 97.5	199.6 ± 96.4
Range	125–629	120–624

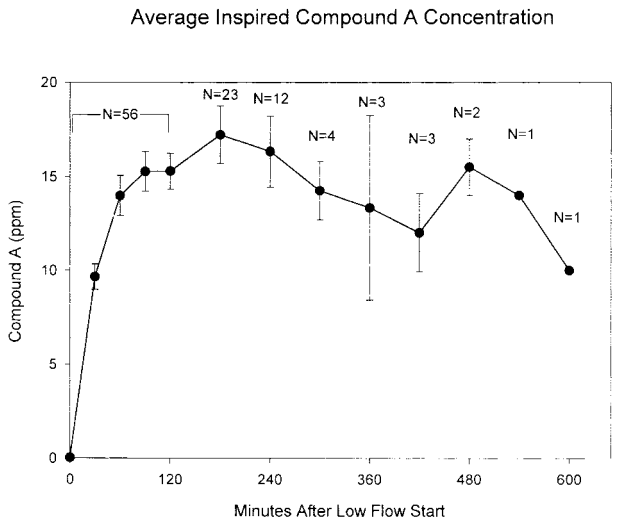

Fig. 5. Average inspired compound A concentration after the start of low-flow period over time. The compound A concentration was measured with a gas chromatography method.

those reported previously. An almost identical maximum CpA concentration was measured in a recent study investigating a comparable patient population.[26] Therefore, we assume that peak concentrations of this range reflect the typical exposure and are representative for patients with impaired renal function.

Renal function in this study was mainly assessed by serum creatinine and BUN. This was done because both measures are clinically widely used, are inexpensive, and have been successfully applied as predictive measures of renal function.[28,29] In addition, we measured urine output to quantify creatinine clearance and determined urinary excretion of glucose and protein. Thereby we did to not only evaluate function of the renal glomeruli, but also function of the tubular system.[30]

There were no differences in serum creatinine or creatinine clearance between isoflurane- and sevoflurane-treated patients. This is in good agreement with findings of many other investigations.[4–6,9,10] Serum BUN decreased from baseline to 24 and 72 h after anesthesia in both groups. There was tendency for BUN to decrease slightly more after isoflurane as compared with sevoflurane. Albeit we do not have an explanation for this tendency, there is no doubt that a further deterioration of a renal function should be reflected by an increase in BUN rather than a decrease. Even more, the more specific markers of renal function, *i.e.*, creatinine clearance, urinary glucose, and protein, did not differ between the groups.

Seven patients (12%) in the sevoflurane group and eight patients (14%) in the isoflurane group fulfilled the criteria for further deterioration of renal function.[14] There were no statistical difference between groups. Novis *et al.*[31] reviewed 28 studies examining the potential risk factors for perioperative renal failure. Of 30 variables reviewed, preoperative factors such as increased serum creatinine, increased blood urea nitrogen, and preexisting renal insufficiency were repeatedly found to be significant predictors of postoperative renal failure. Other major causes for an acute deterioration of function were a decreased renal perfusion, major surgery, infusion of contrast media, or other nephrotoxic drugs. Two of the seven sevoflurane and three of the eight isoflurane patients in this study who fulfilled the Hou criteria for clinically significant increase of creatinine or BUN, had received nephrotoxic drugs (aminoglycoside or ciclosporin) during the study period. This may well explain the worsened renal function. One sevoflurane patient developed severe congestive heart failure caused by a myocardial infarction 4 h after anesthesia. One isoflurane patient received contrast media 24 h after anesthesia. Thus, in virtually all of these patients, there were factors present that, by themselves, could easily explain the transient deterioration of function.

Sevoflurane is metabolized by hepatic cytochrome P450 to hexafluoroisopropanol and inorganic fluoride. Circulating inorganic fluoride has been said to produce renal damage in patients following methoxyflurane anesthesia. Depending on the dose of methoxyflurane and—associated with it the concentrations of inorganic fluoride—the damages as seen in clinical practice ranged from minor and transient fluid imbalances to overt renal failure requiring dialysis. Peak serum inorganic fluoride concentration greater than 30 μM are regularly observed in patients after sevoflurane.[23,32–34] Peak fluoride concentrations of similar size have been associated with transient renal damage (reduced concentrating ability following intravenous vasopressin) after enflurane anesthesia in healthy volunteers. Interestingly, such findings were not reproduced after sevoflurane, albeit serum fluoride concentrations were above those seen after enflurane.[34]

Table 7. Compound A Concentrations in the Anesthesia Circuit

	Compound A Concentration (All Sevoflurane-evaluable Patients)	
Variable	Inspiratory Gas	Expiratory Gas
Average concentration (ppm)		
N	56	56
Mean ± SD	13.4 ± 5.8	9.8 ± 4.2
Range	0–36	4–29
Maximum concentration (ppm)		
N	56	56
Mean ± SD	18.9 ± 7.6	14.1 ± 5.3
Range	0–45	6–34
AUC (ppm/h)		
N	55	55
Mean ± SD	44.0 ± 30.6	31.0 ± 21.5
Range	0–138	8–99

ppm = parts per million; AUC = area under the curve.

There is ample evidence to date that the circulating inorganic fluoride associated with sevoflurane anesthesia is devoid of problems.[4,32,34–37] This has also been confirmed in patients with preexisting renal disease during high-flow anesthesia.[11,25] The results of this study now extend this statement to low-flow anesthesia. We also did not find a relation between serum inorganic fluoride or with CpA concentrations and the markers of renal function. In 17 sevoflurane-treated patients, serum inorganic fluoride exceeded 50 μM. None of these patients had a clinically significant increase in serum creatinine or BUN, and urinary glucose and protein also were unchanged.

As mentioned previously, the most obvious risk factor for postoperative renal failure in surgical patients is poor preoperative renal function.[31] Our study was exclusively performed in patients with preexisting renal disease, which per definition were at a considerable risk for further postoperative deterioration. From both an absence of clinically significant postoperative deterioration of preexisting renal insufficiency and from stable measures of renal function in the postoperative period, we conclude that low-flow sevoflurane anesthesia is safe in patients with chronically impaired renal function.

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