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Changes in Plasma Creatinine Concentration after Cardiac Anesthesia with Isoflurane, Propofol, or Sevoflurane

A Randomized Clinical Trial

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Background: **Renal impairment often follows cardiac surgery. The authors investigated whether sevoflurane produces greater increases in plasma creatinine concentration than isoflurane or propofol after elective coronary artery surgery.**

Methods: **As part of maintenance anesthesia, including during cardiopulmonary bypass, patients were randomly allocated to receive one of three agents: isoflurane (n = 118), sevoflurane (n = 118), or propofol (n = 118). Fresh gas flows were 3 l/min. The preoperative plasma creatinine concentration was subtracted from the highest creatinine concentration in the first 3 postoperative days. A median maximum increase greater than 44 μM (0.5 mg/dl) was regarded as clinically important. Data were analyzed on an intention-to-treat basis. Subgroup analyses were performed on per-protocol patients and those with preoperative renal impairment (creatinine concentration > 130 μM [1.47 mg/dl] or urea > 7.7 mM [blood urea nitrogen, 21.6 mg/dl]).**

Results: **The differences between the groups were small, clinically unimportant, and not statistically significant for the primary analysis and subgroups. The proportions of patients with creatinine increases greater than 44 μM were 15% in the isoflurane group, 17% in the sevoflurane group, and 11% in the propofol group ($P = 0.45$). The median increases were 8 μM in the isoflurane group, 4 μM in the sevoflurane group, and 6 μM in the propofol group. The differences between the three median maximum increases were 1–4 μM ($P > 0.45$). In the subgroup with preoperative renal impairment, the median increases were 10 μM in the isoflurane group, 15 μM in the sevoflurane group, and 5 μM in the propofol group ($P = 0.72$).**

Conclusions: **Sevoflurane did not produce greater increases in creatinine than isoflurane or propofol after elective coronary artery surgery.**

DEBATE still surrounds the effect of sevoflurane on perioperative renal function.[1,2] This issue has not been examined in patients undergoing cardiac surgery who are often at risk of postoperative renal impairment.[3] We recently undertook a study of the time to extubation after cardiac anesthesia with isoflurane, sevoflurane, or propofol (D.A.S., S.P., G.L., and P.L.M., unpublished results, March 2000). In the current study, we investigated whether sevoflurane produces greater increases in plasma creatinine concentration than isoflurane or propofol after elective coronary artery surgery.

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Methods and Materials

The current study was undertaken at the Austin and Repatriation Medical Centre, a tertiary referral hospital affiliated with the University of Melbourne. The Austin and Repatriation Medical Centre Human Research Ethics Committee (Heidelberg, Victoria, Australia) approved the study. Eligible patients were scheduled for elective coronary artery surgery. Exclusion criteria were emergency surgery, valve surgery, obesity (body mass index > 35 kg/m^2), preoperative renal dialysis, and lung disease treated with oral corticosteroids. The last two groups were excluded because they may have required prolonged postoperative ventilation, which would affect the primary end point of time to extubation.

After giving written consent, patients were randomly allocated to receive a standardized, balanced anesthetic approach with one of three maintenance agents: isoflurane (Abbott Australasia, Kurnell, NSW, Australia), sevoflurane (Abbott Australasia), or propofol (Diprifusor target controlled infusion, AstraZeneca, Abbottsford, Victoria, Australia). Our pharmacy staff used a table of random numbers to allocate patients. Pharmacy issued numbered envelopes before the study. The envelopes were kept in the office of the trial coordinator. After randomly allocating the patient on the night before surgery, the trial coordinator told the anesthesiologist for the case which drug the patient would receive. After surgery, intensive care specialists cared for the patients in the cardiac surgery recovery unit. Intensive care unit staff and patients were blinded to the drug allocation.

Anesthetic Approach

Usual cardiac medications were continued until the time of operation. Premedication included intramuscular papavaretum (0.3 mg/kg) and scopolamine (0.006 mg/kg)

and oral diazepam (0.15 mg/kg). Facemask oxygen was given at 6 l/min. These were given together 1–2 h before arrival in the operating room.

All patients received intravenous induction with fentanyl (10 μg/kg), diazepam (0.1 mg/kg), and pancuronium (0.15 mg/kg). More fentanyl (5 μg/kg) was given 2 min before sternotomy. Morphine (0.2 mg/kg) was given during rewarming on cardiopulmonary bypass. At the end of surgery, patients received neuromuscular reversal with neostigmine (2.5 mg) and atropine (1.2 mg).

After induction, patients received a fresh gas flow of 3 l/min with either oxygen or oxygen and air (Ulco anesthetic machine, Ulco Medical, Sydney, NSW, Australia). For the first 12 months of the study, the circle circuits used barium hydroxide as the carbon dioxide absorbent. For the second 12 months, soda lime was used. The change was made for all operating rooms for cost reasons. Absorbents were changed when exhausted rather than before each case. Cardiopulmonary bypass circuits had vaporizers fitted to the fresh gas input. For the entire case, including during cardiopulmonary bypass, patients received one of three maintenance agents: isoflurane (end-tidal concentration, 0.5–2%), sevoflurane (end-tidal concentration, 1–4%), or propofol (target concentration, 1–8 μg/ml). Volatile agents were measured with side-stream gas analysis (M1026A, Hewlett Packard, Boeblingen, Germany). The drugs could be briefly stopped if the anesthesiologist felt this was important. All anesthesia drugs were stopped before transfer to the intensive care unit.

Hypotension (systolic blood pressure $<$ 90 mmHg) was treated with filling to a pulmonary capillary wedge pressure of more than 12 mmHg and bolus doses of 0.5 mg metaraminol. Hypertension (systolic blood pressure $>$ 150 mmHg) was treated with ensuring adequate depth of anesthesia and nitroglycerin infusion. Bradycardia before cardiopulmonary bypass ($<$ 45 beats/min) was treated with atropine, ephedrine bolus doses, or both. Tachycardia before cardiopulmonary bypass ($>$ 90 beats/min) was treated with 20-mg esmolol doses. Cardiopulmonary bypass management involved blood flow of $2.4\ l \cdot min^{-1} \cdot m^{-2}$ and a mean arterial pressure 60–80 mmHg.

For hypotension, bolus doses of 0.5 mg metaraminol were used. For hypertension, isoflurane, sevoflurane, or propofol doses were increased. If hypertension persisted, nitroprusside was started. Anesthetists, perfusionists, surgeons, and intensivists were free to use furosemide, mannitol, dopamine, and hemofiltration.

Plasma creatinine and urea concentrations were measured on the day before surgery and at least once per day for the first 3 postoperative days. Blood was taken using a vacuum technique with lithium heparin tubes (Vacuette, Greiner Labortechnik, Kremsmunster, Austria). These samples were sent to the hospital core laboratory in the Division of Laboratory Medicine. Plasma creatinine and urea concentrations were measured as part of a multicomponent analysis (Hitachi 747, Roche Diagnostics, Sydney, NSW, Australia). The conversion factor for plasma creatinine concentration from micromolars to milligram per deciliter is 0.0113. The conversion factor for plasma urea from millimolars to milligrams per deciliter blood urea nitrogen (BUN) is 2.8. Plasma creatinine was measured by the Jaffe method.[4] The reference range for creatinine was 30–110 μM (0.34–1.24 mg/dl). Plasma urea was measured by a urease kinetic method.[4] The reference range for urea was 2.2–7.7 mM (BUN, 6.2–21.6 mg/dl). Samples were analyzed by scientific staff from the Division of Laboratory Medicine.

An interim safety audit was performed after 150 patients, the results of which were reported at the annual meeting of the Australian and New Zealand College of Anaesthetists in May 1999. We would have stopped if one group had been statistically different from the others.

Statistical Analysis

Data were collected from patient charts and the hospital computer system. Data were stored on a computer spreadsheet (Excel, Microsoft, Seattle, WA). All statistical calculations were performed with Minitab 13 software (Minitab, State College, PA).

The daily medians, median 95% confidence intervals (CIs), and interquartile ranges were calculated for each day, for each group, for both creatinine and urea. The maximum preoperative to postoperative change in creatinine was found by subtracting the preoperative value from the highest available value from the first 3 postoperative days (postoperative minus preoperative). This change could be an increase or a decrease. We proposed that a 44 μM (0.5 mg/dl) median increase in creatinine concentration was clinically important.[5]

Changes in creatinine were analyzed by calculating the median changes and the 95% CIs for the medians. The point estimates of the differences between the medians and 95% CIs were calculated. Three Mann–Whitney U tests were used to compare the three groups to test the null hypotheses, where $P < 0.05$ was significant.

The proportions of patients in each group that had postoperative increases in plasma creatinine greater than 44 μM (0.5 mg/dl) were compared with a chi-square test, and 95% CIs were calculated. The changes in plasma urea concentration were compared with a Kruskal-Wallis test.

The number of patients for this study was chosen after a power analysis for time to extubation. The sample size of three groups of 120 patients, however, allowed an 80% power to detect a 19-μmol (0.21-mg/dl) difference between two groups ($P < 0.05$). Analysis was performed on an intention-to-treat basis. *P* values were not modified for multiple testing.

Table 1. Demographic Data and Renal Impairment Risk Factors

	Isoflurane	Sevoflurane	Propofol
Available data (n)	118	118	118
Age (yr) [median (IQR)]	66 (59–72)	67 (58–74)	65 (55–72)
Female/male	22/96	23/95	20/98
Renal impairment [n (%)]	25 (21)	36 (31)	37 (32)
Bypass time (min) [median (IQR)]	98 (79–117)	92 (70–114)	98 (78–128)
Diabetes [n (%)]	34 (29)	23 (19)	42 (36)

IQR = interquartile range; renal impairment = creatinine > 130 μM (1.47 mg/dl), urea > 7.7 mM (21.6 mg/dl blood urea nitrogen), or both.

We analyzed two subgroups. The first excluded all protocol violations and was a per-protocol analysis. The second included only patients with preoperative renal impairment defined as creatinine greater than 130 μM (1.47 mg/dl), urea greater than 7.7 mM (BUN, 21.6 mg/dl), or both. Kruskal-Wallis tests were used for both analyses.

Results

The creatinine and urea data for individual patients can be found in the Web Enhancement. The conversion factor for plasma creatinine concentration from micromolars to milligrams per deciliter is 0.0113. The conversion factor for plasma urea from millimolars to milligrams per deciliter BUN is 2.8.

The study was conducted from February 1998 to February 2000. Five hundred six patients were eligible, and 360 patients were eventually randomly allocated (table 1). One hundred two patients were eligible but were not screened because of late changes in operation schedules or none of the investigators being available to see the patient. The majority of the patients were men, and a quarter were older than 70 yr. Data from six patients could not be analyzed because they either did not have surgery or they died before any postoperative data were produced. Each of the three groups—isoflurane, sevoflurane, and propofol— had 118 patients with data for analysis. The data were analyzed on an intention-to-treat basis (fig. 1) and then on a per-protocol basis. Thirty-four patients were excluded from the per-protocol analysis, and 10% of the intention-to-treat group.

Examining the data in several ways, we did not find evidence of clinically important or statistically significant differences in renal function between the three groups. The daily summary statistics for creatinine and urea are shown in tables 2 and 3. The three groups are similar on all days. Box plots of the maximum changes in creatinine for the groups (fig. 2) show the similarities between the groups and the lack of symmetry in the data distributions. The median maximum increases in creatinine for all three groups were less than 44 μM (0.5 mg/dl) and were clinically unimportant: isoflurane, a 8-μM increase (95% CI, 4–11); sevoflurane, a 4-μM increase (95% CI, 1–10); and propofol, a 6-μM increase (95% CI, 3–8).

Table 2. Daily Creatinine Data (μM)

	Isoflurane	Sevoflurane	Propofol
Preoperative			
n	118	118	119
Median	96	98	99
95% CI	93–100	95–104	94–101
IQR	87–111	89–114	87–111
Day 1			
n	118	118	117
Median	96	101	97
95% CI	91–101	93–106	95–103
IQR	82–112	85–120	86–118
Day 2			
n	118	118	118
Median	97	101	101
95% CI	92–101	93–109	95–106
IQR	87–120	82–129	83–117
Day 3			
n	111	109	109
Median	93	95	94
95% CI	90–97	88–102	89–99
IQR	84–113	84–124	81–112

Conversion factor for creatinine μM to mg/dl: 0.0113.

CI = confidence interval; IQR = interquartile range.

The differences between the maximum increases in creatinine for the groups were small, clinically unimportant, and not statistically significant. Comparing isoflurane to sevoflurane, the isoflurane increase was greater by a median of 4 μM (95% CI, 3 μM less to 7 μM greater; $P = 0.46$). Comparing isoflurane to propofol, the isoflurane increase was greater by a median of 1 μM (95% CI, 4 μM less to 6 μM greater; $P = 0.71$). Comparing sevoflu-

Table 3. Daily Urea Data (mM)

	Isoflurane	Sevoflurane	Propofol
Preoperative			
n	118	118	119
Median	6.4	6.8	6.8
95% CI	5.9–6.6	6.4–7.4	6.2–7.1
IQR	5.2–7.4	5.5–8.1	5.5–8.1
Day 1			
n	118	118	117
Median	6.5	6.6	6.3
95% CI	6.0–7.0	6.2–7.0	5.8–6.9
IQR	5.4–7.7	5.3–9.0	5.1–7.9
Day 2			
n	118	118	118
Median	7.8	7.6	7.9
95% CI	7.3–8.3	7.0–8.9	7.4–8.8
IQR	6.3–10	5.6–11.0	6.1–10.1
Day 3			
n	111	109	109
Median	7.6	7.4	7.7
95% CI	6.9–8.2	7.1–8.4	6.6–8.7
IQR	6.2–10.6	6.1–11.5	5.9–10.8

Conversion factor for urea mM to mg/dl blood urea nitrogen: 2.8.

CI = confidence interval, IQR = interquartile range.

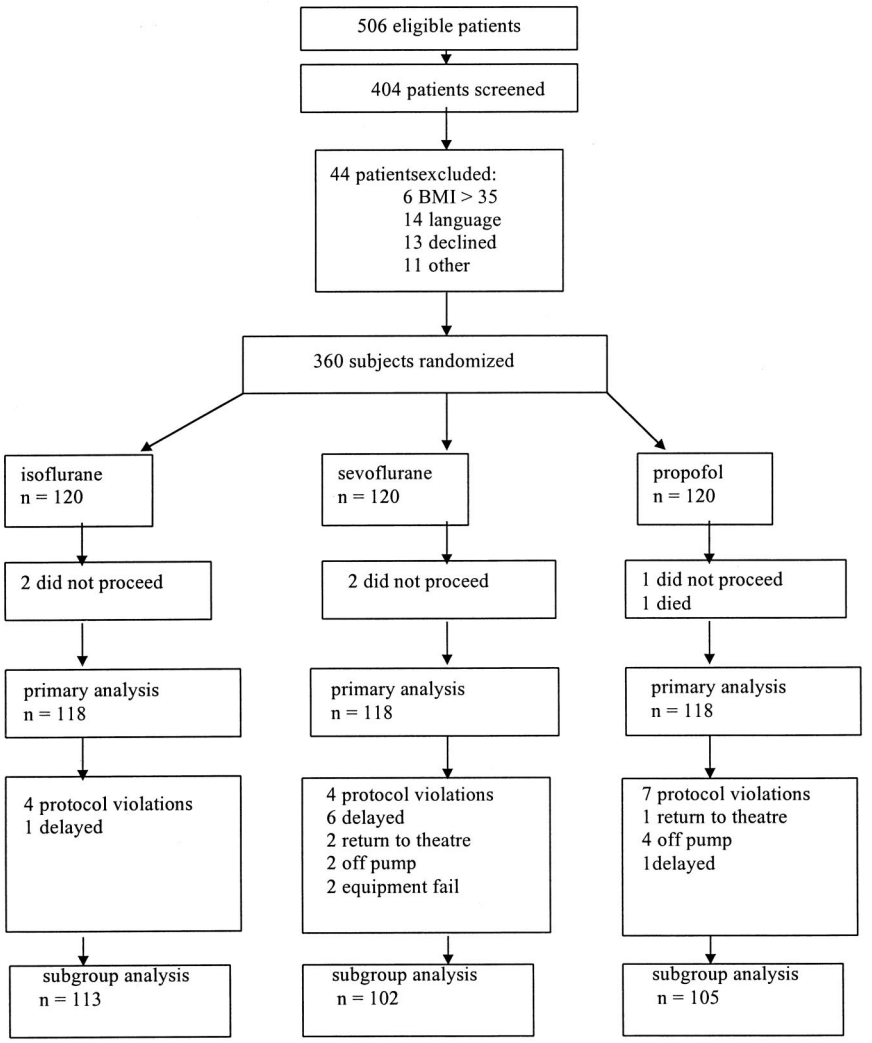

Fig. 1. Flow diagram showing the numbers of patients at each stage of the analysis. BMI = body mass index.

rane to propofol, the sevoflurane increase was less by a median of 1 μM (95% CI, 6 μM less to 4 μM greater; $P = 0.66$).

The proportions of patients in each group with postoperative increases in creatinine greater than 44 μM (0.5 mg/dl) differed slightly (fig. 1): the isoflurane group had 17 of 118 (15%; 95% CI, 9–21%), the sevoflurane group had 20 of 118 (17%; 95% CI, 10–24%), and the propofol group had 13 of 118 (11%; 95% CI, 5–17%). The differences were not statistically significant ($P = 0.45$; chi-square = 1.59; 2 *df*). Death, hemofiltration, and discharge creatinine data for these patients are shown in table 4.

We performed two subgroup analyses. In the per-protocol subgroup analysis, the results were almost identical to those of the intention-to-treat analysis (table 5). Again, the small differences were not statistically significant ($P = 0.97$; H = 0.061; 2 *df*). In the subgroup of patients with a preoperative creatinine greater than 130 μM (1.47 mg/dl) or urea greater than 7.7 mM (BUN, 21.6 mg/dl), data were available for 98 patients (table 6). The groups had small differences that were not statistically significant. The Kruskal-Wallis test comparing the three groups had a P value of 0.72 (H = 0.664; 2 *df*).

The median postoperative maximum increases in urea were similar: isoflurane, 2.2 mM (95% CI, 1.7–2.8); sevoflurane, 1.4 mM (95% CI, 1.0–2.1); and propofol, 1.7 mM (95% CI, 0.7–2.3). The differences were not statistically significant ($P = 0.39$; H = 1.88; 2 *df*).

Two patients died within the first 3 postoperative days. One propofol patient died from sudden, unresponsive hypotension 3 h after arriving in the intensive care unit. One sevoflurane patient died on the first postoperative day from ventricular failure. Four patients needed postoperative hemofiltration within the first 3 days: two from the isoflurane group and two from the sevoflurane group.

Discussion

Main Findings

We conducted a randomized trial of 360 patients undergoing elective coronary artery surgery using anesthesia with isoflurane, sevoflurane, or propofol. We found

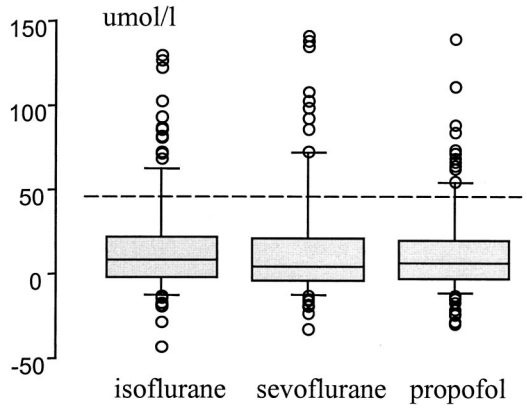

Fig. 2. Box plots of the maximum changes in plasma creatinine concentration after cardiac surgery. Conversion factor for creatinine (micromolars to milligrams per deciliter) is 0.0113. The boxes contain the medians and interquartile ranges. The bars are the 90% limits of the ranges, and the dots are outliers. The dotted line marks a 44-μM (0.5-mg/dl) increase, regarded as clinically important. Four data points are not in the graph: propofol, 249 μM; sevoflurane, 165, 199, and 326 μM. All isoflurane points are in the graph. The plots show the similarities between the groups and the asymmetry within the groups.

that the changes in plasma creatinine concentration from before to after surgery were similar for the three groups. None of the median 95% CIs included clinically important increases. Between the three groups there were similar proportions of patients with clinically important increases in creatinine of more than 44 μM (0.5 mg/dl).

These results suggest that, compared with isoflurane and propofol, sevoflurane did not produce greater increases in creatinine after elective coronary artery surgery. This conclusion is supported by our other findings: that the results are the same if analyzed on an intention-to-treat or per-protocol basis, the groups were similar on each postoperative day, and the subgroups with preoperative renal impairment had similar changes in creatinine.

Along with creatinine, urea is frequently used in routine clinical chemistry. However, plasma urea concentration is less reliable than creatinine as a measure of renal function.[6] This is why our analysis focused on creatinine rather than urea. However, the urea results support the creatinine results, showing no important differences between the three groups.

Table 4. Outcome Data for Those with Creatinine Increases Greater than 44 μM

	Isoflurane	Sevoflurane	Propofol
Patients (n)	17	20	13
Preoperative renal impairment (n)	5	11	7
Died (n)	1	0	0
Hemofiltration (n)	1	2	1
Hemofiltration and died (n)	1	0	0
Discharge creatinine			
Median (μM)	125	117	131
Range (μM)	88–211	91–297	82–233

Conversion factor for creatinine μM to mg/dl: 0.0113.

Preoperative renal impairment = creatinine > 130 μM (1.47 mg/dl), urea > 7.7 mM (21.6 mg/dl blood urea nitrogen), or both.

Table 5. Per-protocol Subgroup Analysis of Creatinine Changes

	Isoflurane	Sevoflurane	Propofol
Patients (n)	113	102	105
Median change (μM)	8	7	6
95% CI (μM)	3–11	2–13	3–10
IQR (μM)	−2 to 21	−3 to 26	−3 to 24

Conversion factor for creatinine μM to mg/dl: 0.0113.

CI = confidence interval; IQR = interquartile range.

Comparison with Other Studies

Two recent studies have compared changes in creatinine after sevoflurane anesthesia and other agents for noncardiac surgery. Both had similar findings to ours. Mazze *et al.*[7] analyzed 22 studies comparing sevoflurane with isoflurane, enflurane, or propofol. With almost 3,500 patients, they found no differences in postoperative changes in creatinine and urea between the anesthetic agents. Groudine *et al.*[2] conducted a randomized trial comparing sevoflurane and isoflurane in 188 patients and found no differences in postoperative creatinine, urea, albuminuria, and glycosuria.

In a volunteer study without surgery, Eger *et al.*[8] found no differences in creatinine and urea after sevoflurane or desflurane anesthesia. They did, however, find increases in protein excretion and urinary loss of renal enzymes in the sevoflurane group and concluded that these changes suggested clinically important effects of sevoflurane on renal tubule function. When Ebert *et al.*[9] duplicated the study by Eger *et al.*, they again found no important changes in creatinine and urea, but they also failed to find important changes in urinary protein, glucose, and enzymes. In a recent clinical study, Higuchi *et al.*[10] used low-flow sevoflurane and found increased urinary enzyme concentrations that were reduced by probenecid. In other clinical studies in patients undergoing noncardiac surgery, Bito *et al.*,[11] Obata *et al.*,[12] and Kharasch *et al.*[13] found no important differences between sevoflurane and isoflurane in creatinine, urea, and the urinary markers.

Table 6. Creatinine Changes in Those with Preoperative Renal Impairment

	Isoflurane	Sevoflurane	Propofol
Patients (n)	25	36	37
Median (μM)	10	15	5
95% CI (μM)	−3 to 32	−4 to 27	−3 to 19
IQR (μM)	−5 to 41	−10 to 53	−5 to 24

Conversion factor for creatinine μM to mg/dl: 0.0113.

Preoperative renal impairment = creatinine > 130 μM (1.47 mg/dl), urea > 7.7 mM (21.6 mg/dl blood urea nitrogen), or both; CI = confidence interval; IQR = interquartile range.

Compared with the previous studies, our study had greater chance of finding increases in postoperative creatinine for several reasons: most patients underwent cardiopulmonary bypass,[14] a quarter were older than 70 yr,[3] a quarter had preoperative renal impairment,[3] and a quarter had diabetes.[3] Like Mazze and Jamison[15] and Groudine *et al.*,[2] we used plasma creatinine concentration as our primary marker for renal function because it has been validated as clinically important,[16] is more reliable than urea as a routine test of renal function,[6] and it does not increase nursing workload as creatinine clearance does.[17] We did not measure urinary enzymes because of the increased nursing workload, the cost, and because the clinical importance of urinary enzymes is unclear.[18]

Study Limitations

Like all studies on renal function, our study was limited by the lack of clear definitions for renal impairment and renal failure.[14,19] Added to this are the various definitions of important postoperative changes in plasma creatinine.[5,20] We used the work of Hou *et al.*[5] to define clinically important increases in creatinine (> 44 μM [0.5 mg/dl]). Like Mazze *et al.*,[7] we extrapolated the values of Hou *et al.* for individuals to group changes. In the absence of other data, the data of Hou *et al.* for individuals gave the best available estimate for group changes. However, we did compare the proportions of individual patients who exceeded a 44-μM increase in creatinine.

Another limitation is the amount of patient exposure to the sevoflurane product compound A. Some believe compound A has important renal effects.[21] In an editorial accompanying the study by Mazze *et al.*,[7] Bedford and Ives[1] argued that many human studies have not exposed subjects to doses of compound A that are toxic and are possible in some clinical settings. The likely compound A exposure was reduced in our study by a fresh gas flow of 3 l/min, the absorbents being changed only when exhausted,[22] and the cardiopulmonary bypass time without carbon dioxide absorbent.

Another limitation, shared with all clinical trials, was protocol violations. We believe the overall rate of 10% violations, although undesirable, was not excessive. We tried to deal with this by using intention-to-treat and per-protocol analyses, with similar results. A related problem, similar to the study by Groudine *et al.*,[2] was that postoperative data were available for all patients on each of the 3 postoperative days. By day 3 we had data on 329 of 354 patients. Most of those with missing data had normal creatinine concentrations postoperatively. We believe that the missing data did not affect the results.

Some commentators suggest one limitation in pharmaceutical research is commercial conflict of interest.[15,23] None of the researchers for this study were paid by drug companies. However, we received equivalent funding from the suppliers of propofol (AstraZeneca) and the suppliers of isoflurane and sevoflurane (Abbott Australasia).

Conclusions and Future Research

Using plasma creatinine concentration as a marker of renal function, we conclude from our large randomized trial that sevoflurane does not worsen renal function more than isoflurane or propofol after elective coronary artery surgery if fresh gas flows of 3 l/min are used.

There are several areas for future study. Important perioperative increases in creatinine concentration for groups of patients need to be defined. Furthermore, important differences between groups need to be defined to allow study of treatment effects. Future studies should examine the effect of doses of compound A that some think may be toxic[1] in patients with increased risk of postoperative deterioration in renal function. The most important group is those with preexisting renal impairment.[19,24]

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