

Renal Responses to Low-flow Desflurane, Sevoflurane, and Propofol in Patients

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Background: **The contributing factors that result in significant, postoperative proteinuria and glucosuria after low-flow isoflurane and sevoflurane anesthesia are unknown. The present study compared renal responses after anesthesia with desflurane (negligible metabolism), sevoflurane, or intravenous propofol.**

Methods: **Informed consent was obtained from 52 patients with American Society of Anesthesiologists physical status I–III (aged 36–81 yr). Patients with diabetes or renal insufficiency were excluded. Desflurane (n = 20) or sevoflurane (n = 22), without nitrous oxide, was given at 1 l/min fresh gas flow for elective surgical procedures lasting more than 2 h; 10 patients received propofol without nitrous oxide as the primary anesthetic. Blood and urine chemistries were obtained before surgery. Blood and 24-h urine collections were obtained for 3 days after surgery and were analyzed for liver and renal indices.**

Results: **Length of surgery averaged ~ 300 min (range, 136–750 min), minimum alveolar concentration–hour averaged 4.3 (range, 1.2–11.0), and infusion rates of propofol were 99–168 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Plasma creatinine concentration did not change, plasma blood urea nitrogen decreased significantly, and significant increases in urine glucose, protein, and albumin occurred similarly in all groups. Mean (± SD) postoperative urine glucose values for day 1 after desflurane, sevoflurane, and propofol were 1.4 ± 3.0, 1.1 ± 2.1, and 1.9 ± 2.6 g/d (normal, < 0.5 g/d). The average daily protein/creatinine ratios for postoperative days 2–3 after desflurane, sevoflurane, and propofol were 240 ± 187, 272 ± 234, and 344 ± 243 (normal, < 150 mg/g). Regardless of anesthetic, there were significantly greater urine protein concentrations after surgical procedures in central versus peripheral regions.**

Conclusions: **Alterations in postoperative renal function were common and unrelated to the choice of anesthetic. These findings implicate nonanesthetic factors in producing changes in biochemical indices of renal excretory function. (Key words: Compound A; low-flow anesthesia; nephrotoxicity; renal function.)**

THERE has been a renewed interest in the renal effects of anesthetics in humans. The interest has grown, in part, because high concentrations of a degradation product of sevoflurane, called compound A [CH_2F-O-$C(=CF_2)(CF_3)$], have caused renal injury in a rat model, evidenced by significant proteinuria and glucosuria and biopsy-proven necrosis of renal tubules.[1–3] Compound A is formed during exposure of sevoflurane to standard carbon dioxide absorbents and formation is enhanced by increased temperature of the carbon dioxide absorbent associated with a low fresh gas flow (FGF) delivery system.

In earlier studies in our laboratory, significant proteinuria and glucosuria could not be demonstrated in 24-h urine collections of young volunteers after 4–8 h of approximately 3% sevoflurane (1.25 minimum alveolar concentration [MAC]) delivered in a FGF of 1 or 2 l/min.[4,5] In contrast, surgical patients receiving sevoflurane in a FGF of 1 l/min have demonstrated significant postoperative proteinuria and glucosuria and increases in experimental enzyme markers of renal injury.[6,7] However, in the same study, patients randomized to receive isoflurane (which does not result in compound A formation) also had significant increases in urinary protein and glucose and enzyme markers of injury. This raises the possibility that ether-based anesthetics have a common effect of causing renal dysfunction/injury or that other factors such as surgery or surgical stress might be involved in this process. The present study explored this issue by comparing desflurane, which is extremely stable (minimally metabolized and minimally degraded by hydrated carbon dioxide absorbers), with sevoflurane, which is both metabolized (~ 5%) and degraded by carbon dioxide absorbers. In addition, we evaluated renal function in patients receiving propofol as their primary anesthetic without any volatile anesthetic adjunct. We selected a wide variety of surgical cases of varying lengths in an attempt to gain insight into other potential factors that might be associated with proteinuria and glucosuria after anesthesia and surgery.

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Materials and Methods

After obtaining approval from the Human Studies Subcommittee, Zablocki VA Medical Center, Milwaukee, Wisconsin, nondiabetic patients older than 21 yr, with American Society of Anesthesiologists physical status I–III, were recruited at the VA Medical Center. Candidates were scheduled to undergo an elective procedure, lasting at least 2 h, and were free of renal and hepatic disease (creatinine concentration < 1.5 mg/dl and nor-

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Table 1. Patient Demographics

Anesthetic	n	Age (yr)	Height (cm)	Weight (kg)	Female/Male	ASA Physical Status I/II/III (n)
Desflurane	20	59 (38–81)	175 ± 8	79 ± 17 (47–112)	1/19	3/7/10
Sevoflurane	22	61 (39–79)	176 ± 9	88 ± 17 (68–132)	2/22	0/13/9
Propofol	10	62 (36–79)	178 ± 6	92 ± 26 (66–145)	0/10	0/7/3

Mean ± SD (range).

ASA = American Society of Anesthesiologists.

mal plasma bilirubin, aspartate transaminase [AST], and alanine transaminase concentrations). Patients were excluded if the surgical procedure was genitourinary, cardiac, or aortic in nature or if they had been exposed to general anesthesia in the past 2 weeks.

Patients were given 1–2 mg midazolam as a premedication and were randomized in a block design to receive desflurane, sevoflurane, or propofol. Anesthesia and tracheal intubation were established with sodium thiopental (or propofol), fentanyl (50–100 μg), and vecuronium. Desflurane and sevoflurane were initially given in oxygen (50%) and air at a total FGF of 5 l/min that was decreased to 1 l/min after 5 min. No nitrous oxide was allowed. End-tidal desflurane concentration was maintained between 3% and 8% and sevoflurane between 0.8% and 2.5% end-tidal concentration (equivalent MAC level of 0.5–1.5). Propofol was given in doses that ranged from 100 to 168 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Fresh barium hydroxide was used to fill the carbon dioxide–absorbent canister before each case. Additional fentanyl was permitted during the case if hemodynamic control was not achieved within several minutes by adjusting the primary anesthetic. Nonsteroidal anti-inflammatory drugs were not allowed, but morphine sulfate was titrated at the end of the case as needed.

Blood and urine chemistries were obtained before surgery, and blood and 24-h urine collections continued for 3 days after surgery. Blood was analyzed for liver function– enzymes (AST, alanine transaminase, lactate dehydrogenase), electrolytes, blood urea nitrogen, and creatinine. Urine samples underwent quantitative analysis of creatinine, glucose, albumin, and protein. All samples were analyzed by the VA Medical Center certified laboratory and laboratory personnel, who were blinded to the anesthetic randomization.

Ratios were calculated for urine protein and albumin relative to creatinine, to account for or overcome any imprecision of 24-h urine sampling. Data for each group were averaged, and the SD of the mean was calculated. Repeated-measures analysis of variance was applied to variables measured over time for comparisons between groups. Statistical significance was chosen to be P values less than 0.05. Regression and correlation analyses were applied to relate urine markers to the length of surgery, total or average MAC-h, and intraoperative mean arterial pressure.

The data for all anesthetics were divided into surgeries that were central in origin (abdominal, thoracic, and total hip replacements) and surgeries that were peripheral (*e.g.*, peripheral vascular, knee replacements) and were subjected to correlation analyses to seek relations to urinary markers.

Results

Fifty-two consenting patients (20 desflurane, 22 sevoflurane, 10 propofol) were included in this study (mean age, 60 yr; mean height, 175 cm; mean weight, 83 kg); there were no demographic differences between groups (table 1). In addition, there were no differences between groups for average preoperative heart rate or blood pressure. The average length of surgery and total or average MAC-h also did not differ between groups.

Table 2. Surgical Characteristics

Anesthetic	Length of Procedure (min)	Total MAC-h or Dose	Intraoperative				
			Mean BP (mmHg)	Fentanyl (μg)	EBL (ml)	Crystalloids (ml)	Colloids (ml)
Desflurane	295 (150–750)	4.2 (1.2–10.2)	79 (67–93)	325 (100–800)	653 (50–2,500)	4,415 (2,100–9,800)	265 (0–2,700)
Sevoflurane	323 (180–660)	4.4 (1.6–11.1)	82 (63–98)	300 (50–600)	607 (150–2,400)	4,768 (2,100–13,000)	192 (0–2,200)
Propofol	258 (136–425)	130 (99–168 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	87 (50–105)	315 (100–500)	550 (100–1,500)	3,140 (1,200–7,000)	53 (0–300)

Mean (range).

MAC = minimum alveolar concentration; BP = blood pressure; EBL = estimated blood loss.

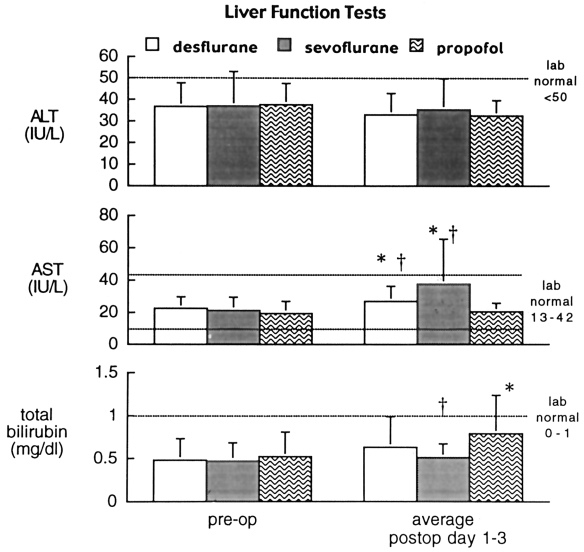

Fig. 1. Liver function tests (mean ± SD) performed preoperatively and the average of tests performed on postoperative days 1–3 for desflurane, sevoflurane, and propofol anesthesia. There were significantly larger increases from preoperative plasma aspartate transaminase (AST) values in the volatile anesthetic groups, and these increases were significantly different from the postoperative value for the propofol group. Total bilirubin was significantly increased from preoperative values in the propofol group, and this increase was significantly greater than that observed in the sevoflurane group. *$P < 0.05$, significantly different from preoperative value; †$P < 0.05$, significantly different from propofol group. ALT = alanine transaminase.

(table 2). Intraoperatively, there were no differences in average mean arterial pressure, heart rate, total use of crystalloid and colloid, and estimated blood loss (table 2). In the perioperative period, the use of antibiotics did not differ between groups. Cefazolin was the most commonly used antibiotic (~ two thirds of all cases). Other antibiotics used, in descending order of frequency, included cefoxitin, metronidazole, vancomycin, cefuroxime, and ciprofloxacin.

There were no differences in preoperative laboratory values determined from urine and blood samples between groups. Within each anesthetic group, there were no differences in liver function test results between postoperative days 1, 2, and 3; therefore, values from these days were averaged (fig. 1). Plasma alanine transaminase, lactate dehydrogenase, and alkaline phosphatase concentrations did not change in any anesthetic group in the postoperative period. There were significantly larger increases in plasma AST concentrations in the volatile anesthetic groups compared with the propofol group. However, the increases in AST between patients receiving sevoflurane and those receiving desflurane were not statistically different. A total of five patients had plasma AST levels that exceeded the laboratory upper limit of normal (n = 1 desflurane, n = 4 sevoflurane; not significant by chi-square analysis). Postoperative total bilirubin levels were significantly increased in the patients receiving propofol compared with those receiving sevoflurane (fig. 1). (See Web Enhancement for more data.)

Postoperative plasma creatinine concentration was not changed, but blood urea nitrogen significantly decreased in all anesthetic groups (fig. 2). Twenty-four-hour urine excretions of glucose, albumin, and protein were significantly increased from baseline, with no differences between groups (fig. 3). The number of patients with elevated urine glucose values at baseline and at postsurgery days 1, 2, and 3, respectively, are as follows: des-

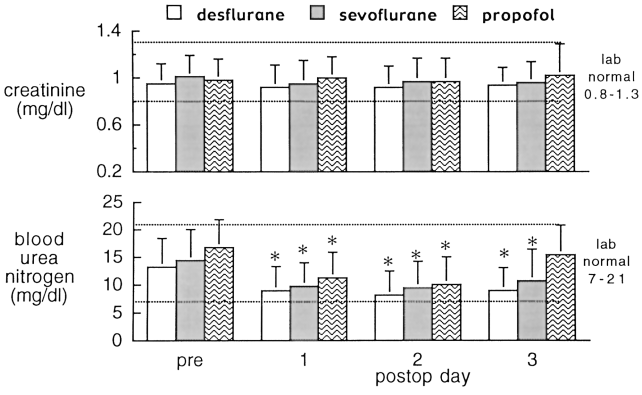

Fig. 2. Plasma values (mean ± SD) of creatinine and blood urea nitrogen before and for 3 days after surgery with desflurane, sevoflurane, or propofol anesthesia. There were no significant changes in creatinine on any day in any group. Plasma blood urea nitrogen decreased (but not below normal values) in all groups on postoperative days 1 and 2 and remained decreased on day 3 for the two volatile anesthesia groups, but returned to preoperative values in the propofol group. *$P < 0.05$, significantly different from preoperative value.

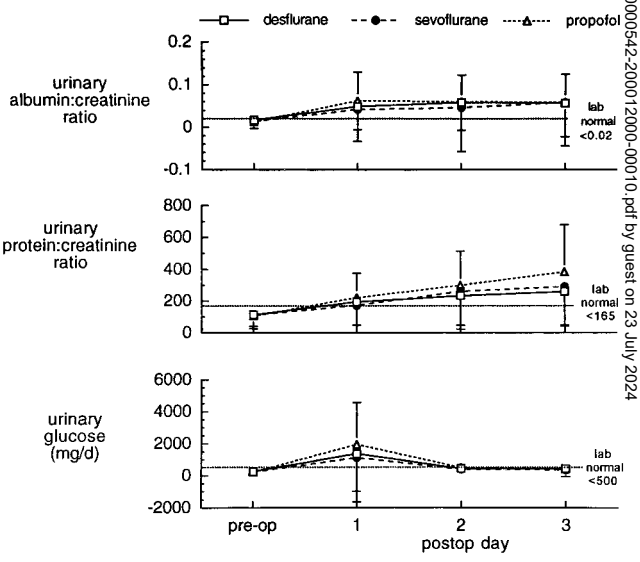

Fig. 3. Urine parameters (mean ± SD) before and for 3 days after surgery with desflurane, sevoflurane, or propofol anesthesia. Albumin and protein were significantly increased above preoperative levels for the 3 days postoperatively, but the increases were not different between anesthetics. Glucose was significantly increased above preoperative (and normal) levels on day 1 after surgery. *$P < 0.05$, significantly different from preoperative value on all postoperative days; †$P < 0.05$, significantly different from preoperative value on postoperative day 1.

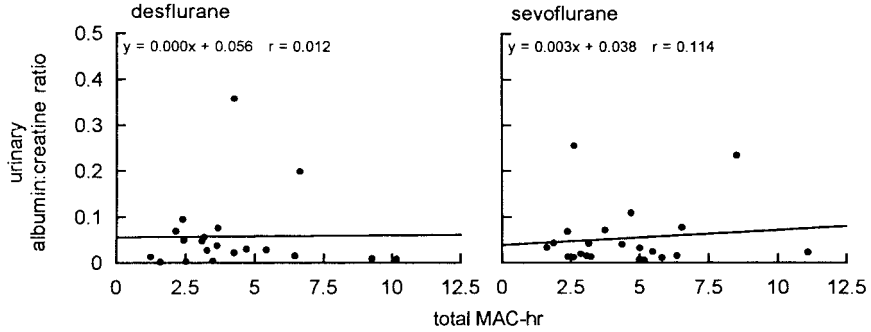

Fig. 4. There was no relation between postoperative albumin:creatinine responses and minimum alveolar concentration times hours of anesthesia (MAC-h) exposure to either sevoflurane (*left*) or desflurane (*right*). For this analysis, we used the average albumin:creatinine excretion from postoperative days 2 and 3, which represents the period of greatest response.

flurane = 1, 7, 5, 2; sevoflurane = 1, 7, 3, 3; propofol = 1, 7, 2, 2. The number of patients with elevated urine albumin values at baseline and at postsurgery days 1, 2, and 3, respectively, are as follows: desflurane = 5, 10, 13, 11; sevoflurane = 3, 10, 13, 12; propofol = 2, 8, 6, 7. The number of patients with elevated urine protein values at baseline and at postsurgery days 1, 2, and 3, respectively, are as follows: desflurane = 2, 11, 10, 14; sevoflurane = 5, 9, 12, 15; propofol = 1, 5, 7, 8. (See Web Enhancement for more data.) There was no relation between the total MAC-h exposure to sevoflurane or desflurane and albumin, protein, and glucose excretion in the postoperative period (fig. 4).

There were 19 surgeries in central locations and 7, 10, and 2 patients were randomized to desflurane, sevoflurane, and propofol, respectively. There were 33 surgeries in peripheral locations and 13, 12, and 8 patients were randomized to desflurane, sevoflurane, and propofol, respectively. When the data were divided based on surgical site, significantly increased urinary excretion rates for protein and albumin became apparent in patients undergoing surgery on central locations compared with those undergoing surgery on peripheral sites (fig. 5). There was equal distribution of MAC-h, blood loss, and use of crystalloids and colloids between surgical groups. There was an equal distribution of antibiotic use in central *versus* peripheral surgeries with one exception. Six of 19 patients who underwent central surgeries received metronidazole and cefoxitin combination therapy, whereas no one who underwent peripheral surgeries received this antibiotic combination. These six patients all had major bowel surgery.

Discussion

The present randomized prospective study demonstrates that postoperative albuminuria, proteinuria, and glucosuria are common findings in patients receiving low-flow sevoflurane, desflurane, or intravenous propofol as their primary anesthetic for surgical procedures. Although compound A was only inspired by patients receiving sevoflurane, we were unable to identify any differences in the frequency or extent of abnormal renal markers compared with desflurane (which is minimally metabolized and degraded) or compared with the sedative hypnotic, propofol. This raises several interesting questions. First, what factor or factors are involved in the development of proteinuria and glucosuria after anesthesia and surgery? Second, does transient proteinuria or glucosuria portend important renal injury or impairment?

Relevant to these questions is the ongoing debate of how best to evaluate and interpret postoperative renal function.[8–10] Clearly, the clinical standard has been to monitor changes in blood urea nitrogen and serum creatinine, which are easily measured and have proven to be prognostically important in medicine. In addition, microalbuminuria has been used to follow the progression of renal impairment associated with diabetic nephropathy.[11–13] However, neither proteinuria nor glucosuria has been shown to have a prognostic relevance in terms of renal injury–impairment in nondiabetic patients.[9] To our knowledge there also is no known pathologic injury or prognostic value associated with transient (1–2 days) increases in urinary protein or glucose.

New consideration has been given to several experi

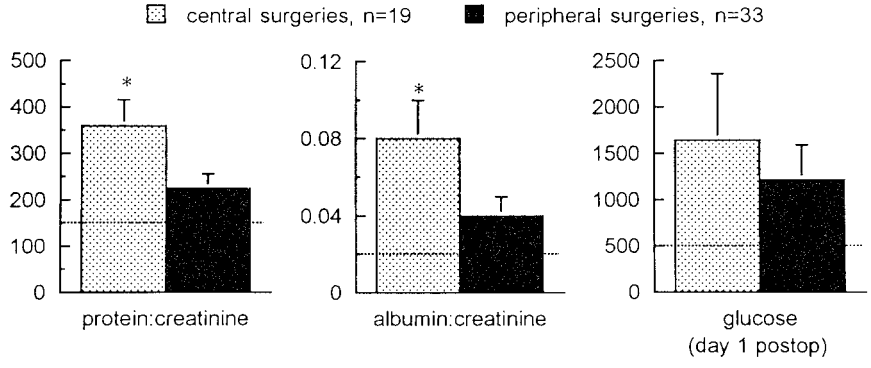

Fig. 5. Urine findings (mean ± SD) when patients were divided based on site of surgery. This analysis combined data from all three anesthetics and then segmented the data into central *versus* peripheral surgical procedures. There were significantly (*$P = 0.05$) greater increases in urinary protein and albumin excretion in patients who underwent surgery in central sites (thoracic, abdominal, and hip replacement). Dashed lines show the normal laboratory value for that variable.

mental enzyme markers (*N*-acetyl-β-D-glucosaminidase and α-glutathione-*S*-transferase) as potentially sensitive indices of renal tubule cell injury in rats exposed to compound A.[2,3,14] However, these indices have not correlated with the extent of proteinuria and glucosuria during isoflurane and sevoflurane anesthesia.[6,7]

In the present study, we identified nearly 50% of patients in each anesthetic group with abnormal increases in urine glucose concentration and more than 50% of patients in each group with abnormal increases in urinary protein and albumin excretion. If these findings do not reflect injury, then how might they be explained? Are they simply functional changes and not "injury"? Small amounts of protein, albumin, and glucose are filtered at the glomerulus, and the majority is reabsorbed in the proximal tubules. There are three common mechanisms to increase urinary excretion of these substances: a direct increase in glomerular capillary wall leak, an increase in glomerular hydrostatic pressure, and decreased tubular resorption. Glomerular hydrostatic pressure can be increased by efferent arteriolar constriction that might occur during states of high sympathetic tone (not unusual in postoperative patients). Kharasch *et al.*[6] suggested that the renal findings in patients after sevoflurane or isoflurane anesthesia are so inconsistent that it is not possible to implicate any one common site of action of anesthesia and surgery on renal function. Interpreting these renal changes is complicated by the fact that the laboratory normal limits for daily protein, albumin, and glucose have been established from healthy individuals not undergoing surgery. Interestingly, other nonsurgical but stressful procedures have been associated with proteinuria.[15–18] For example, in healthy volunteers undergoing strenuous exercise, an average of 150 μg/min of albumin (> 200 g/d) has been identified in urine samples.[17] These transient changes are considered nonpathologic, *i.e.*, a functional change (although renal biopsy specimens have not been obtained to verify lack of injury).

We observed a significant increase in urinary glucose excretion that occurred 1 day after surgery but returned toward normal over the subsequent 2 days. In contrast, there was a gradual and progressive increase in urinary protein and albumin on days 1–3 after surgery. We specifically evaluated the relation between sevoflurane (and desflurane) MAC-h and urinary excretion of albumin, glucose, or protein and found no significant association (fig. 4). This absence of a significant association agrees with a prior analysis in surgical patients receiving sevoflurane in a FGF of 1 l/min.[6] In this previous study, experimental markers of renal cell injury and urinary excretion of protein and glucose in the postoperative period did not correlate with the inspired compound A concentrations, the total compound A exposure (concentration × time) or with the sevoflurane exposure (MAC-h). In this earlier study, isoflurane was used as the comparator anesthetic and, similar to this study that used desflurane as a comparator, glucosuria and proteinuria in the postoperative period were similar in sevoflurane-treated patients. In addition, our study used a second comparator group that received only propofol as their primary anesthetic. In this group, significant proteinuria and glucosuria also were observed. The lack of statistical associations between anesthetic agent or anesthetic exposure and renal outcome points toward nonanesthetic factors, *e.g.*, surgical or postoperative factors, that influence renal function.

Many factors common to anesthesia and surgical procedures have been implicated in the cause of renal dysfunction/injury, but none has been validated in prospective studies. Antibiotics, surgical stress, preexisting renal disease, intraoperative blood pressure, site of surgery, and anesthetics are some of the implicated factors. We sought additional associations by separating the data set based on length of procedure, site of surgery, and intraoperative mean arterial pressure. There were no significant correlations between length of procedure and renal outcome (urinary glucose on day 1 or average protein:creatinine or albumin:creatinine on days 2 and 3) for any of the anesthetics. Similarly, no anesthetic showed an association between mean intraoperative blood pressure and renal markers. We divided the data set into cases involving mainly surgery in central locations (intraabdominal, intrathoracic, and total hip replacements, n = 19) and cases in which surgery was performed on peripheral sites (knees, hands, neck, peripheral vascular, n = 33). Between these two groups, there were no differences in intraoperative mean arterial pressure, length of surgery, or total or average MAC-h of anesthesia. However, there were significant differences in urinary protein and albumin concentrations between central and peripheral surgical categories (fig. 5). A similar but nonsignificant trend for greater glucose excretion in the central surgical procedure group was apparent.

We also evaluated use of antibiotics and found, in general, similar use in all treatment groups. Cefazolin was the most frequent antibiotic, and it has been associated with increases in liver function tests and proteinuria.[19] We also noted a frequent use of metronidazole and cefoxitin in combination for intraabdominal surgeries. Metronidazole has been associated with albuminuria and nephrotoxicity, and cefoxitin has been associated with increased liver function tests and proteinuria.[19] Thus, we cannot rule out antibiotic use as a cause of postoperative hepatic or renal changes.

We noted significant increases in AST test results in patients receiving sevoflurane and desflurane (but not propofol). The majority of these increases remained below the upper limit of normal. These effects have been reported previously with sevoflurane and isoflurane.[6,20–22]

Based on the findings in this study, we conclude that the clinical use of approximately 1 MAC sevoflurane in a

FGF of only 1 l/min for procedures ranging from 3 to 10 h did not have clinically significant adverse effects on renal function. Proteinuria, albuminuria, and glucosuria were similar after operations with desflurane, propofol, or sevoflurane, and there were no associations between intraoperative blood pressure, length of surgery, or anesthetic concentration and abnormal renal findings. These data indicate that nonanesthetic factors are primary determinants of urinary protein and glucose excretion. The greater changes in urinary excretion of protein and glucose after surgery in central *versus* peripheral regions suggest that the glomerular capillary hemodynamic effects from central surgical procedures or surgical stress may be involved in the postoperative changes in renal function. This finding needs to be evaluated in a prospective study with adequate control of confounding variables. The frequent use of antibiotics in the surgical population and their association with renal (and hepatic) effects must also be considered as possible contributors to abnormal laboratory findings.

Limitations

Although rodent models indicate a direct association between compound A exposure and renal cell necrosis, we consciously chose not to measure compound A exposures in the present study. This decision was based on the earlier demonstration of a close correlation ($r = 0.96$) between sevoflurane MAC-h and inspired compound A levels in surgical patients, thus obviating the need for the measurement.[6] Part of this decision also was based on the possibility of imprecision in the measurement of compound A. Obtaining these samples mandates collection in airtight syringes, injection into a glass bottle without contamination, and shipping *via* air to an independent laboratory for analysis within 36 h. Earlier work has identified a time-dependent interaction of compound A with the rubber in the neck of the glass vials (E. Kharasch, oral communication, 1996). Previous studies that have measured compound A from the circuit have produced reasonably consistent results indicating that 1 l/min FGF of approximately 1 MAC sevoflurane through normally hydrated barium hydroxide should result in inspired concentrations of compound A between 15 and 30 ppm.[6,7,23] If we assume, on average, 25 ppm-h in the inspired circuit, then patients in the present study were exposed to between 75 and 275 ppm-h of compound A (mean = 135 ppm-h). Based on MAC-h, the patients with the greatest exposure to compound A did not have the largest change in renal markers (fig. 4).

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