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Renal Responses to Desflurane and Isoflurane in Patients with Renal Insufficiency

Rainer J. Litz, M.D., Matthias Hübler, M.D.,* Wolfram Lorenz, M.D.,† Volker K. Meier, M.D.,† D. Michael Albrecht, M.D.‡*

Background: **The most consistent risk factor for postoperative renal failure is poor preoperative renal function. Desflurane is not contraindicated in patients with renal disease, but the data regarding its effects on renal function in these patients are sparse.**

Methods: **Only patients with preexisting renal disease were recruited into the study. In 51 adults undergoing elective surgery, general anesthesia was maintained using randomly desflurane or isoflurane according to a standardized protocol. Creatinine, creatinine clearance, and blood urea nitrogen were measured pre- and postoperatively.**

Results: **The administered amounts of the inhaled anesthetic agents were 1.8 ± 2.1 minimum alveolar concentration hours (mean ± SD) of isoflurane (24 patients) and 2.2 ± 1.8 minimum alveolar concentration hours of desflurane (27 patients), respectively. No deterioration in renal parameters was noted when comparing the pre- and postoperative values between the groups and within the groups over time.**

Conclusion: **General anesthesia with desflurane or isoflurane did not aggravate renal impairment in patients with preexisting renal insufficiency.**

A DETERIORATION of preexisting renal dysfunction in the perioperative period is a serious complication of surgery because it is associated with a high mortality rate.[1] Many risk factors for postoperative renal failure have been identified. Antibiotics, surgical stress, intraoperative renal blood flow, and site of surgery are some of the implicated factors. The most consistent risk factor for postoperative renal failure is poor preoperative renal function.[2] Hence, it is important to avoid potentially nephrotoxic substances when performing anesthesia in these high-risk patients. So far, only one study has been conducted in patients with preexisting renal disease to evaluate the renal effects of desflurane.[3] In this study, the number of patients was small (10 patients per group), and only creatinine and blood urea nitrogen (BUN) parameters were used to monitor renal function. Therefore, our aim was to conduct a prospective study in a larger number of renal-compromised patients and to include a more sensitive renal parameter, creatinine clearance, to further evaluate the renal effects of desflurane in these patients.

Methods

The investigation was conducted as an open, randomized phase IV study and approved by the university ethics committee. After obtaining written informed consent, 51 adults undergoing elective surgery with general anesthesia were recruited into the study. Inclusion criteria were an elevated plasma creatinine concentration (normal ranges, < 97 μM for men and < 80 μM for women), and a decreased creatinine clearance (normal ranges, 84–174 ml/min for men and 66–156 ml/min for women) as signs of chronic renal insufficiency. Patients were excluded if one of the following criteria was fulfilled: anemia (defined as hematocrit < 0.25), concomitant impaired liver function, electrocardiographic signs of coronary artery disease, or exposure to anesthesia in the past 7 days.

Patients were premedicated with 7.5 mg midazolam orally 45 min before being taken to the operating room. Allocation to the groups was carried out using a randomization table. The results of the individual allocation were kept in a sealed envelope, which was opened immediately before induction of general anesthesia. Anesthesia and tracheal intubation were established with 3–5 mg/kg sodium thiopental, 2 μg/kg fentanyl, 1.25–2.5 mg droperidol, and 0.1 mg/kg vecuronium. Thereafter, desflurane and isoflurane were given in oxygen (O_2) and nitrous oxide (N_2O; 60%) at a total fresh gas flow (FGF) of 1 l/min. The lungs were ventilated using intermittent positive pressure ventilation. The ventilation pattern was adjusted to maintain end-tidal partial pressure of carbon dioxide (P_{ETCO_2}) between 35 and 40 mmHg. Intraoperative monitoring of the following parameters was performed: electrocardiogram; pulse oximetry; systolic (SAP), diastolic, and mean arterial blood pressures; P_{ETCO_2}; inspiratory and expiratory partial pressures of O_2; and inspiratory and expiratory concentrations of N_2O, desflurane, and isoflurane. The parameters were recorded every 2 min after intubation until surgical incision, every minute during the first 5 min after the surgical incision, and every 5 min thereafter until extubation. The minimum alveolar anesthetic concentration (MAC) hour exposure was calculated from the percent anesthetic concentration and the duration of exposure. MAC values were corrected for age using the equation $MAC_{corrected} = a \cdot 10^{b} \cdot x$, where x is the difference from age 40 yr, b is -0.00269, and a is the MAC at age 40 yr (6.6% for desflurane and 1.17% for isoflurane, respectively).[4] Clinical criteria were used to estimate depth of anesthesia. Signs of inadequate anesthesia were defined as heart rate more than 100 beats/min, SAP more than

* Staff Anesthesiologist, † Resident, ‡ Professor and Chair.

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Address reprint requests to Dr. Hübler: Department of Anesthesiology and Intensive Care Medicine, Carl Gustav Carus University Hospital, Fetscherstr. 74, 01307 Dresden, Germany. Address electronic mail to: matthias.huebler@mailbox.tu-dresden.de. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

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150 mmHg or increase in SAP of more than 30% compared with the preinduction value, movements, lacrimation, sweating, and salivation. If one of these criteria was fulfilled, the inspiratory concentration of the inhaled anesthetic agent was increased. Anesthesia was supplemented with 2 μg/kg fentanyl if no effect was noted after 5 min. Boluses of vecuronium, 0.015–0.03 mg/kg, were administered when muscle relaxation was judged as inadequate. At the end of surgery, the absence of a clinical relevant neuromuscular blockade was confirmed using a stimulator (train-of-four). The vaporizers were then closed, and FGF was increased to 6 l/min O_2 without N_2O. The ventilator settings remained unchanged until spontaneous ventilation returned. The times until removal of the endotracheal tube, eye opening, following simple commands, recall of name, and recall of birth date were noted.

Blood and urine chemistries were obtained on the day before surgery and the next day after the surgical intervention. The university-certified laboratory analyzed all samples. The laboratory staff was unaware of the result of the randomization, thus minimizing the possibility of a bias. The creatinine clearance was measured by collecting the patients' urine for 24 h. At the end of the collection period, the urine volume was measured, and urine and blood samples were sent to the laboratory for determination of urine and plasma creatinine concentration. Creatinine clearance was then calculated using the equation: creatinine clearance = ($[\text{creatinine}_{\text{urine}}] \cdot \text{volume}_{\text{urine}}$)/$[\text{creatinine}_{\text{plasma}}]$, where $\text{volume}_{\text{urine}}$ was used in ml/min.

Statistics

The values are reported as mean ± SD. We used the unpaired *t* test to compare normally distributed parameters between the two groups and the paired *t* test to compare changes over time. For uncorrelated data that were not normally distributed, we used the nonparametric Mann–Whitney U test. The chi-square test was used to compare discrete variables between the two groups. *Post hoc* Anderson–Hauck test of equivalence was used to further analyze the renal parameters.[5] This test assesses the necessary difference in expected values, which would lead to rejection of equivalence between compared values. It uses group size, measured mean values, and SD as input parameters. This approach, in contrast to the design–power approach, provides a way of quantifying (with *P* values) what was actually determined from the study instead of saying what the study may or may not have accomplished with some degree of certainty (power). For example, a possible outcome of the equivalence testing approach is the conclusion at the 5% level that two means do not differ by more than some specified amount.[6] Throughout this study, $P < 0.05$ is

Table 1. Demographic Data

	Isoflurane	Desflurane	*P* Value
n	24	27	
Age (yr)	57 ± 15	59 ± 13	0.7
BMI (kg/m²)	26.1 ± 3.3	25.4 ± 2.9	0.4
Gender (M/F)	19/5	20/7	0.7
ASA physical status (II/III)	12/12	10/17	0.3
Duration of surgery (min)	109 ± 101	150 ± 128	0.2
MAC hours	1.8 ± 2.1	2.2 ± 1.8	0.2
MAC at end of surgery	0.5 ± 0.2	0.45 ± 0.12	0.2
Intraoperative fluids (ml · kg^{-1} · h^{-1})	24 ± 14	28 ± 24	0.5
Types of surgery			
Urologic	11	15	
Abdominal	5	7	
Traumatologic	3	2	
Gynecologic	2	2	
Others	3	1	

Values are mean ± SD.

BMI = body mass index; ASA = American Society of Anesthesiologists; MAC = minimum alveolar anesthetic concentration.

Table 2. Renal Parameters

	Isoflurane	Desflurane	*P* Value (*t* test)	Equivalence
Plasma blood urea nitrogen (mM)				
Preoperative	10.9 ± 8.0	10.5 ± 4.6	0.8	2.9
Postoperative	9.8 ± 7.0	9.5 ± 4.9	0.9	2.5
P value (*t* test)	0.6	0.5		
Equivalence	3.0	2.1		
Plasma creatinine (μM)				
Preoperative	177 ± 77	201 ± 94	0.2	66
Postoperative	168 ± 80	193 ± 95	0.3	67
P value (*t* test)	0.9	0.7		
Equivalence	29	18		
Creatinine clearance (ml/min)				
Preoperative	53.4 ± 23.5	41.8 ± 18.4	0.057	21.6
Postoperative	54.7 ± 22.9	43.8 ± 19.7	0.08	21.1
P value (*t* test)	0.9	0.7		
Equivalence	5.8	5.4		

Values are mean ± SD. Equivalence = necessary difference in expected values, which would lead to rejection of equivalence between compared values (Anderson–Hauck test of equivalence, $P < 0.05$). To convert plasma creatinine from μM (SI unit) to mg/dl (conventional unit), divide μM by 88.4.

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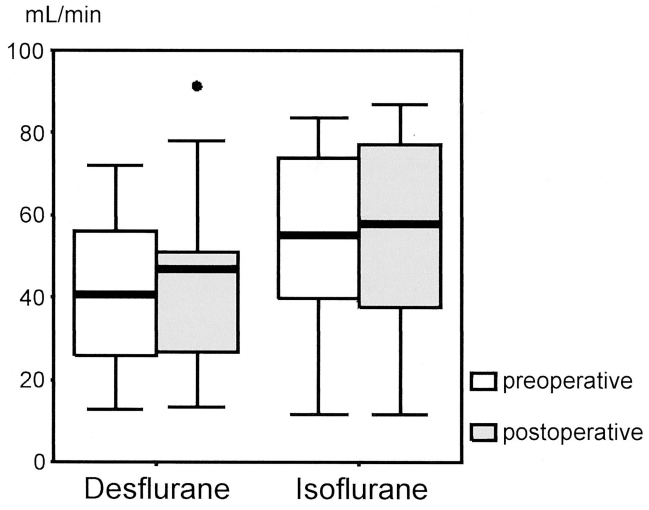

Fig. 1. Preoperative and postoperative creatinine clearance values in ml/min. Medians (thick line), 25th to 75th percentiles (box boundaries), and 10th to 90th percentiles (whiskers) are shown. The outlier beyond the 90th percentile is shown as an individual data point.

considered statistically significant. All analyses were performed using SPSS version 10.0.7 (Chicago, IL) and SAS version 8 (Cary, NC).

Results

The demographic data of the 51 included patients are shown in table 1. No statistically significant differences were noted. The types of surgical interventions were evenly distributed among the groups. Emergence was significantly faster in the desflurane than in the isoflurane group ($P < 0.005$ for all parameters of recovery, data not shown).

The pre- and postoperative values of the renal parameters are shown in table 2 and in figure 1 (creatinine clearance). Plasma creatinine and BUN values were comparable. The difference in creatinine clearances was suggestively significant between the two groups at both measurements. No significant changes were noted when the pre- and postoperative values of each group were compared. Table 2 also includes the results of the Anderson–Hauck test of equivalence. Shown are the necessary differences in expected values, which would have led to rejection of the null hypothesis that the two compared values are equivalent (at the 5% level).

Discussion

The important result of our study is that desflurane did not lead to a deterioration of creatinine clearance in patients with preexisting renal impairment. Most studies investigating effects of desflurane on renal function have been conducted in patients without renal disease.[7–9] Consistently, they found no deterioration of renal function; hence, desflurane is not contraindicated in patients with renal dysfunction. Until today, only one prospective study investigating renal effects of desflurane was performed in patients with preexisting renal disease.[3] In this study, the number of patients was small (10 patients per group), but it confirmed the results from studies performed in healthy patients. The authors used only creatinine and BUN parameters to monitor renal function. The number of patients in our study was much larger, and in addition, creatinine clearance was added as a parameter because it is more sensitive to detect small changes in renal function. Nevertheless, we were unable to find negative effects of desflurane. One drawback of

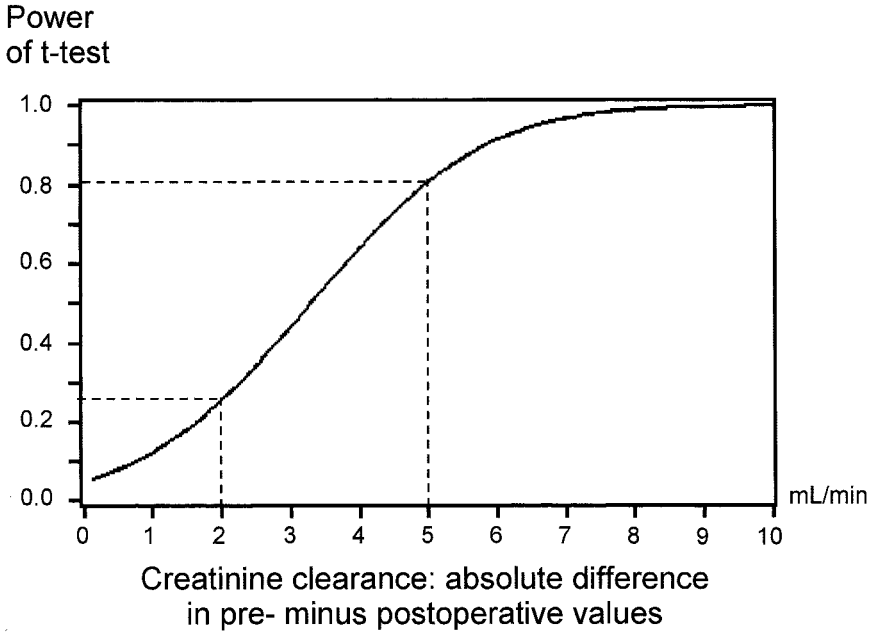

Fig. 2. Cumulative power analysis using the SD of the creatinine clearance (desflurane group) and the group size as input parameters.

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our study was that the protocol included the administration of N_2O and, if necessary, allowed additional boluses of fentanyl. These two substances are commonly used to supplement general anesthesia, but they also decrease the exposure to volatile anesthetic agents, thereby maybe decreasing the power of the study to detect changes and differences in renal parameters.

Many laboratory tests have been proposed to monitor renal function and to identify patients with renal disease. We used an increased plasma creatinine concentration to identify patients with renal disease. Because the value can be falsely high as a result of low intravascular volume, large muscle mass, or physical activity, the renal impairment was confirmed by measuring creatinine clearance. We did not use BUN as an inclusion criterion because of its dependence on nonrenal factors like protein intake. A recent study evaluated renal responses to the anesthetic agents desflurane, sevoflurane, and propofol in patients without preexisting renal disease.[9] The authors found an abnormal increase in urine glucose concentration in nearly 50% of patients, and an abnormal increase in urinary protein and albumin excretion in more than 50% of patients. The interpretation of these results is complicated by the fact that the laboratory normal limits are usually established from healthy persons not undergoing surgery. In addition, an increased perioperative sympathetic tone can increase glomerular hydrostatic pressure by efferent arteriolar constriction, thus causing alterations in renal function. Therefore, the authors concluded that alterations in postoperative renal function were common and unrelated to the choice of anesthetic agent.

Our study may be criticized because the number of patients was not high. Our primary hypothesis was that desflurane would not induce deterioration in creatinine clearance. Based on this assumption, a power analysis could not be performed *a priori*. A nonsignificant result of the *t* test does not allow the rejection of the hypothesis that the values are not significantly different or, in other words, it does not allow the conclusion that the compared values are the same. Therefore, we applied the Anderson–Hauck test to assess the level of equivalence between the found values. In addition, we performed *post hoc* a cumulative power analysis using the SD of the creatinine clearance (desflurane group) and the group size as input parameters (fig. 2). According to this analysis, the power of our study to detect an absolute effect of 2 ml/min was only 25% assuming a type 1 error of 0.05 (two sided). To increase the power of our study to 80%, a sample size of 220 would have been necessary to find statistically significant differences of such small amount. The cumulative power analysis showed also that the power of our study was 80% to detect an absolute difference of 5 ml/min. This represents a generally accepted level of power, but the clinical significance of a change in creatinine clearance of only 5 ml/min is questionable. Therefore, the assumption that desflurane did not deteriorate glomerular filtration rate to a clinically relevant degree seems justified.

In summary, we found no differences in postoperative renal function in patients with renal insufficiency receiving desflurane or isoflurane, nor did we find differences between the two volatile anesthetic agents.

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