Renal Function and Hemodynamics during Prolonged Isoflurane-induced Hypotension in Humans

Martin R. Lessard, M.D.,* Claude A. Trépanier, M.D., F.R.C.P.C.+)

The effect of isoflurane-induced hypotension on glomerular function and renal blood flow was investigated in 20 human subjects. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured by inulin and paraaminohippurate (PAH) clearance, respectively. Anesthesia was maintained with fentanyl, nitrous oxide, oxygen, and isoflurane. Hypotension was induced for 236.9 ± 15.1 min by increasing the isoflurane inspired concentration to maintain a mean arterial pressure of 59.8 ± 0.4 mmHg. GFR and ERPF decreased with the induction of anesthesia but not significantly more during hypotension. Postoperatively, ERPF returned to preoperative values, whereas GFR was higher than preoperative values. Renal vascular resistance increased during anesthesia but decreased when hypotension was induced, allowing the maintenance of renal blood flow. We conclude that renal compensatory mechanisms are preserved during isoflurane-induced hypotension and that renal function and hemodynamics quickly return to normal when normotension is resumed. (Key words: Anesthetic techniques: hypotensive. Anesthetics, volatile: isoflurane. Kidney: blood flow; diuresis; filtration, glomerular; function.)

DELIBERATE HYPOTENSION is a widely used technique that has been proven efficacious in decreasing operative blood loss and transfusions in many surgical procedures.1-4 Isoflurane is an effective hypotensive agent, decreasing peripheral resistance while maintaining cardiac output.5 Although cerebral and cardiac effects of isoflurane-induced hypotension have been studied extensively,5-8 data on its renal effects during hypotension are lacking. Reduced urinary output has been observed,4 but the effects on renal blood flow and glomerular function have not been studied. This study was designed to evaluate renal hemodynamics and glomerular function during prolonged isoflurane-induced hypotension in humans.

Materials and Methods

Twenty patients gave written informed consent to enter this protocol, which had been approved by the Hospital Ethics Committee. None of these patients was taking any medication, and all were free of any cardiovascular, cerebrovascular, or renal disease. They were undergoing an elective orthognathic procedure (LeFort I maxillary osteotomy with a mandibular osteotomy).

ANESTHETIC PROTOCOL

Patients received sublingual lorazepam 2 mg as preanesthetic medication. Monitoring included electrocardiogram, urinary output, temperature, and a radial artery catheter for continuous blood pressure monitoring and blood sampling. Anesthesia was induced with fentanyl 5 μg/kg and thiopental 5-7 mg/kg. Atracurium 0.5 mg/kg was given to facilitate nasotracheal intubation. Ventilation via a Bain circuit was controlled with an Ohio V5A ventilator. Both minute ventilation and fresh gas flow were adjusted to maintain normocapnia (arterial carbon dioxide tension [PaCO₂] 35-40 mmHg). Anesthesia was maintained with 60% nitrous oxide in oxygen, incremental doses of fentanyl to a maximum of 20 μg/kg, and isoflurane. When the surgical procedure started, the inspired concentration of isoflurane was increased to maintain a mean arterial pressure (MAP) of 55-65 mmHg.

The fluid regimen was strictly controlled. An intravenous (iv) infusion of lactated Ringer's solution (LR) was started at 2 ml·kg⁻¹·h⁻¹ 2 h preoperatively. When surgery began, the infusion was increased to 6 ml·kg⁻¹·h⁻¹ to meet intraoperative fluid requirements. Blood losses were evaluated by weighing the surgical sponges and by measuring the blood and irrigation fluid in the suction containers. They were replaced with 3 ml LR for each milliliter of blood lost. At the end of the procedure, the preoperative regimen was resumed.

GLOMERULAR FILTRATION RATE AND RENAL BLOOD FLOW MEASUREMENTS

Glolomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured by inulin and paraaminohippurate (PAH) clearance techniques, respectively. Two hours preoperatively, iv boluses of inulin 50 mg/kg and PAH 8 mg/kg were administered. Simultaneously, an infusion of inulin and PAH was started to maintain a plasma concentration of 250 μg/ml for inulin and 20 μg/
ml for PAH. This infusion rate was calculated using the following equation for each patient:

\[
\text{inulin (mg/min)} = 0.25 \text{ mg/ml} \times \text{CC}
\]

\[
\text{PAH (mg/min)} = 0.02 \text{ mg/ml} \times \frac{\text{CC} \times 5}{0.79 \times \text{plasma creatinine (mM)}}
\]

where CC is creatinine clearance estimated with the following equation\(^9\):

\[
\text{CC (ml/min)} = \frac{(140 \text{ age [yr]}) \times \text{weight (kg)}}{0.79 \times \text{plasma creatinine (mM)}}
\]

These infusions were maintained throughout the study period. The clearance protocol is illustrated in figure 1. At least 90 min was allowed for equilibration of plasma concentration before beginning measurements. Before they left the ward, patients were asked to urinate, and the preoperative collection period was then started. When the patient arrived in the operating room, the radial artery was cannulated, and blood samples were obtained for inulin and PAH serum concentration and hematocrit (Ht) determination. As soon as the patient was anesthetized, a three-way Foley catheter was inserted. The bladder was immediately emptied and rinsed with 250 ml normal saline.

The preoperative collection period then ended and the anesthesia collection period started. Here also, blood was sampled in the middle of the period, and the bladder was emptied and rinsed at the end of it. During this 30-min period, the patient was kept normotensive and had no surgical stimulation. After the anesthesia collection period was completed, surgery was allowed to begin, and MAP was decreased to the hypotensive level. Ninety minutes after the induction of hypotension, the hypotension collection period began, according to the same methodology as described above. Hypotension was maintained up to mucosal suturing, after which MAP was returned to normal. A final postoperative collection began 60 min after arrival in the recovery room.

Blood samples were immediately centrifuged, and the separated serum was frozen. Urinary output, including the rinsing solution, was measured for each collection period, and a sample was immediately frozen. All these serum and urine samples were later assayed for inulin and PAH concentrations using colorimetric techniques.\(^{10,11}\)

The coefficients of variation were 3.03% for inulin and 2.19% for PAH, both for duplicate samples run on the same day with the same technique. Clearances were calculated with the following equation:

\[
\text{clearance} = \frac{U \times V}{S \times t}
\]

where U and S are the urinary and serum concentrations, respectively, of inulin or PAH; V is the volume of urine plus the rinsing solution; and t is the duration of the collection period. Inulin clearance was then corrected for 1.73 m\(^2\) of body surface area. Effective renal blood flow (ERBF), renal vascular resistance (RVR), and filtration fractions (FF) were calculated with the following equations:

\[
\text{ERBF} = \frac{\text{ERPF}}{1 - \text{Ht}}
\]

\[
\text{RVR} = \frac{\text{MAP}}{\text{ERBF} \times 10^{-3} \times 80}
\]

\[
\text{FF} = \frac{\text{inulin clearance}}{\text{ERPF}}
\]

**Statistical Analysis**

Data are presented as means ± standard error of the mean (SEM). Statistical analysis was done with Fischer's exact test, paired and unpaired Student's t tests, and an analysis of variance (ANOVA) model for repeated measures when appropriate. The level of significance was set at P < 0.05. However, when multiple comparisons were done the Bonferroni correction was applied.

**Results**

Two of the 20 patients included in the study subsequently had to be rejected because of technical problems during assay for serum inulin and PAH concentration. Data from only the 18 remaining patients (5 men and 13
TABLE 1. Patient Characteristics and Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Oliguretic Subgroup</th>
<th>Nonoliguric Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>22.4 ± 1.6</td>
<td>22.2 ± 1.4</td>
<td>22.7 ± 2.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.1 ± 2.9</td>
<td>65.3 ± 3.9</td>
<td>58.8 ± 2.3</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.68 ± 0.04</td>
<td>1.73 ± 0.06</td>
<td>1.64 ± 0.04</td>
</tr>
<tr>
<td>Duration of hypotension (min)</td>
<td>236.8 ± 15.1</td>
<td>230.6 ± 23.1</td>
<td>243.3 ± 20.6</td>
</tr>
<tr>
<td>Dose of isoflurane (MAC-h)</td>
<td>6.77 ± 0.52</td>
<td>7.07 ± 0.79</td>
<td>6.47 ± 0.71</td>
</tr>
</tbody>
</table>

All data are mean ± SEM. No statistical difference between the oliguric and nonoliguric subgroups. BSA = body surface area.

Women) are included in the following results. Patient characteristics, duration of hypotension, and dose of isoflurane are reported in table 1. Mean blood loss was 580.8 ± 61.1 ml; no patient had to be transfused. Mean urinary output was 1.47 ± 0.20 ml/min. Nine patients (50%) presented a period of oliguria (<0.5 ml·kg⁻¹·h⁻¹) during the hypotensive period.

Values of MAP, GFR, ERPF, ERBF, RVR, and FF are given in table 2. GFR, ERPF, and ERBF were significantly reduced with induction of anesthesia, but no further significant decrease was observed when hypotension was induced. Compared with preoperative measures, GFR was higher in the postoperative period, but ERPF or ERBF were comparable to preoperative values. FF increased during anesthesia and hypotension and did not return to preoperative values in the postoperative period. The calculated RVR increased during anesthesia and remained slightly elevated in the postoperative period. However, the RVR were significantly lower during hypotension than during normotensive anesthesia.

Data were subsequently analyzed by dividing patients according to their urinary output, into an oliguric group and a nonoliguric group. These data are reported in tables 1 and 3. These two groups were comparable, and there was no significant difference in the variation of their GFR, ERPF, ERBF, RVR, or FF.

**Discussion**

Renal function can be affected by induced hypotension, because during hypotension MAP is usually decreased to less than the lower limit of renal autoregulation (80–180 mmHg). Glomerular filtration is known to decrease during inhalation anesthesia. However, more complete data on the response of the kidney to isoflurane-induced hypotension are lacking. For the current study of renal blood flow and glomerular function, clearance techniques were chosen because of their safety and low degree of invasiveness. Inulin clearance is the gold standard by which GFR is measured. However, renal blood flow is more difficult to measure. PAH is completely filtered and secreted by the nephron. Its renal extraction ratio is 0.9018 and is not altered by hypotension. A small fraction of blood perfusing the nonexcretory tissues (renal

**TABLE 2. Renal Function and Hemodynamic Data: All Patients**

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Anesthesia</th>
<th>Hypotension</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>88.7 ± 1.5</td>
<td>83.7 ± 2.0</td>
<td>59.8 ± 0.4</td>
<td>108.0 ± 2.6</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>0.38 ± 0.010</td>
<td>0.36 ± 0.011</td>
<td>0.32 ± 0.009</td>
<td>0.34 ± 0.012</td>
</tr>
<tr>
<td>GFR (ml·min⁻¹·m²⁻¹)</td>
<td>113.8 ± 5.7</td>
<td>97.2 ± 6.0</td>
<td>91.4 ± 5.6</td>
<td>144.5 ± 8.9</td>
</tr>
<tr>
<td>ERPF (ml·min⁻¹·m²⁻¹)</td>
<td>495.7 ± 25.0</td>
<td>292.5 ± 20.1</td>
<td>263.6 ± 15.1</td>
<td>501.9 ± 28.8</td>
</tr>
<tr>
<td>ERBF (ml·min⁻¹·m²⁻¹)</td>
<td>810.3 ± 48.1</td>
<td>457.6 ± 32.7</td>
<td>385.2 ± 20.0</td>
<td>769.2 ± 46.4</td>
</tr>
<tr>
<td>RVR</td>
<td>9474.0 ± 540.0</td>
<td>15979.2 ± 1069.8</td>
<td>13112.8 ± 860.7</td>
<td>11928.1 ± 664.5</td>
</tr>
<tr>
<td>FF</td>
<td>0.22 ± 0.007</td>
<td>0.35 ± 0.014</td>
<td>P &lt; 0.001*</td>
<td>P &lt; 0.005†</td>
</tr>
</tbody>
</table>

All data are mean ± SEM. ANOVA for repeated measures followed by paired t test with Bonferroni correction: *Pre versus anes; †Anes versus hypo; ‡Pre versus post.

Units: MAP, mmHg; hematocrit, vol/vol; GFR, ml·min⁻¹·m²⁻¹; ERPF and ERBF, ml·min⁻¹·m²⁻¹; RVR, dynes·cm⁻⁻¹·s⁻¹.
Table 3. Renal Function and Hemodynamic Data: Oliguric and Nonoliguric Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Anesthesia</th>
<th>Hypotension</th>
<th>Postanesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>Oliguric</td>
<td>89.7 ± 2.0</td>
<td>85.6 ± 3.3</td>
<td>60.1 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>Nonoliguric</td>
<td>87.7 ± 2.2</td>
<td>81.8 ± 2.3</td>
<td>59.4 ± 0.6</td>
</tr>
<tr>
<td>GFR</td>
<td>Oliguric</td>
<td>125.4 ± 7.1</td>
<td>105.6 ± 9.6</td>
<td>98.2 ± 9.0</td>
</tr>
<tr>
<td></td>
<td>Nonoliguric</td>
<td>101.2 ± 7.0</td>
<td>88.8 ± 6.4</td>
<td>84.5 ± 6.3</td>
</tr>
<tr>
<td>ERPF</td>
<td>Oliguric</td>
<td>528.6 ± 36.1</td>
<td>319.1 ± 31.2</td>
<td>287.0 ± 18.9</td>
</tr>
<tr>
<td></td>
<td>Nonoliguric</td>
<td>622.7 ± 32.4</td>
<td>395.9 ± 23.7</td>
<td>240.2 ± 21.7</td>
</tr>
<tr>
<td>ERBF</td>
<td>Oliguric</td>
<td>868.8 ± 75.9</td>
<td>502.5 ± 53.9</td>
<td>422.0 ± 23.1</td>
</tr>
<tr>
<td></td>
<td>Nonoliguric</td>
<td>751.9 ± 56.6</td>
<td>412.3 ± 53.7</td>
<td>348.4 ± 28.8</td>
</tr>
<tr>
<td>RVR</td>
<td>Oliguric</td>
<td>8996.6 ± 756.6</td>
<td>14970.3 ± 1246.2</td>
<td>11652.4 ± 706.7</td>
</tr>
<tr>
<td></td>
<td>Nonoliguric</td>
<td>9101.3 ± 780.9</td>
<td>17088.1 ± 1733.1</td>
<td>14573.2 ± 1454.5</td>
</tr>
<tr>
<td>FF</td>
<td>Oliguric</td>
<td>0.24 ± 0.008</td>
<td>0.34 ± 0.018</td>
<td>0.34 ± 0.021</td>
</tr>
<tr>
<td></td>
<td>Nonoliguric</td>
<td>0.21 ± 0.011</td>
<td>0.32 ± 0.022</td>
<td>0.34 ± 0.019</td>
</tr>
</tbody>
</table>

All data are mean ± SEM.

Units: MAP, mmHg; GFR, ml·min⁻¹·1.73 m²⁻¹; ERPF and ERBF, ml/min; RVR, dynes·cm⁻⁵·s⁻¹. ANOVA for repeated measures: no statistical difference between subgroups.

capsule, pelvis, and perinephric fat) is not cleared of its PAH. Therefore, PAH clearance measures ERPF, which represents about 90% of total renal plasma flow. ERBF can then be calculated from ERPF and Ht.

Clearance measurements have been reported to be inaccurate during low urinary output states because, under these circumstances, even a small amount of urine not recovered from the bladder yields a large error in the calculation of GFR and ERPF. To avoid this problem, some investigators have increased the diuresis with mannitol. We preferred instead to thoroughly rinse the bladder at the end of each collection period in order to collect all the urine, thus decreasing the likelihood of an error in the clearance calculations.

Our clearance protocol differs slightly from standard methods. First, the Foley catheter was inserted at the induction of anesthesia to avoid discomfort to the patient. Therefore, the preanesthesia period included a short period of anesthesia. This is probably negligible, since GFR and ERPF measured this way are in agreement with reported values for normal subjects. Second, because there was no equilibration period before normotensive anesthesia clearance measurements, the validity of these data could be questioned. However, we observed a 40% decrease of ERPF and ERBF with induction of anesthesia, which is comparable to data from other studies. For instance, Mazze et al. found that isoflurane anesthesia alone reduces renal blood flow by 49%. The probable mechanism of this decrease is a redistribution of blood flow away from the kidney because of the combination of decreased systemic vascular resistance (SVR) and increased RVR. Our data suggest that this increase of RVR is caused mostly by an increased tonus of the glomerular efferent arteriole, as indicated by the 50% increase of FF. All measurements of the normotensive ERPF were made before the beginning of the surgical procedure because it is known that surgical stimulus causes a further increase of RVR.

When hypotension was induced with isoflurane, RVR decreased slightly, thus limiting the RBF decrease that would have been expected with the decrease in renal perfusion pressure. A direct vasodilating effect of isoflurane on the glomerular afferent arteriole is a possibility. However, it is more likely that the normal compensatory mechanisms of the kidney account for this hemodynamic pattern. There are two main mechanisms responsible for the preservation of renal perfusion in the presence of a decreased blood pressure. First, the normal kidney autoregulates its blood flow, keeping an almost constant RBF within a MAP range of 80–100 mmHg. The second possible mechanism is the intrarenal secretion of prostaglandins PGE₂ and PGF₂α. Both are potent renal vasodilators. Isoflurane produces hypotension by decreasing the SVR. In these circumstances, the normal renal response is a dilatation of the glomerular afferent arteriole to decrease RVR, allowing the maintenance of a normal ratio between RVR and SVR.

Our data suggest that this response, probably mediated by renal prostaglandins, seems to be preserved during isoflurane-induced hypotension. ERPF and ERBF were only slightly and not significantly decreased despite a marked decrease in perfusion pressure. This, combined with the increased tonus of the efferent arteriole, maintains an adequate glomerular capillary hydrostatic pressure, thus minimizing the decrease of GFR. In fact, even if urinary output decreased during hypotension, GFR was maintained to the normotensive level. FF remained increased during hypotensive anesthesia. The renin–angiotensin system is believed to be responsible for this response. Plasma renin activity has recently been reported.
to be increased during isoflurane-induced hypotension.\textsuperscript{24} This suggests that the renin–angiotensin system might be an important factor in the maintenance of GFR during isoflurane-induced hypotension.

The current study shows that isoflurane-induced hypotension, even of long duration (236.9 ± 15.1 min), does not result in irreversible alterations of glomerular function in young patients without preexisting renal disease. Other investigators have reported similar results with different agents but for much shorter hypotensive periods. Thompson et al. found no difference between pre- and postoperative creatinine clearance when using halothane and nitroprusside as hypotensive agents.\textsuperscript{1} However, the duration of hypotension was less than 90 min. Behnia et al., studying nitroprusside-induced hypotension of 110-min duration, found a decrease in the GFR but no significant difference between pre- and postoperative creatinine clearance, although the latter did not return to preoperative values.\textsuperscript{18} Although we used isoflurane alone to induce hypotension, our anesthetic protocol included fentanyl and nitrous oxide. The effect on renal function could have been different if higher concentrations of isoflurane had been used both to induce hypotension and to maintain anesthesia without any other anesthetic.

The comparison between the oliguric and nonoliguric groups suggests that the oliguria observed during the hypotensive period is not caused by a low renal blood flow, since ERPF is similar in both groups. It also suggests that a decreasing urinary output during induced hypotension does not necessarily indicate a lower renal blood flow or a compromised GFR. This oliguria may be explained by an increased tubular reabsorption and an increased secretion of anti-diuretic hormone (ADH). This hormone is known to be stimulated by surgery,\textsuperscript{25} intermittent positive pressure ventilation,\textsuperscript{26} or hypotension.\textsuperscript{27} The rapid return of a normal diuresis at the end of hypotension combined with the ERBF and GFR values measured in the recovery period strongly suggest that this oliguria is a physiologic rather than pathologic response to induced hypotension. The increase in GFR measured in the recovery period probably may be explained by a persistent increased efferent arteriolar tonus mediated by persistent elevated angiotensin levels, as suggested by the elevated RVR and FF.\textsuperscript{28}

Our iv fluid regimen may also be part of the explanation. These young patients received only crystalloids both for basic fluid requirements and blood loss replacement. Their mean hematocrit decreased from 0.58 to 0.34 (table 1). This hemodilution surely resulted in a decrease of plasma oncotic pressure. Glomerular filtration is driven by the glomerular capillary hydrostatic pressure minus Bowman’s capsule hydrostatic pressure minus plasma oncotie pressure. A decrease in plasma oncotic pressure may explain both the increased FF and GFR measured in the recovery period.

In conclusion, we studied renal function by clearance techniques during prolonged isoflurane-induced hypotension in young healthy patients. Our data suggest that renal compensatory mechanisms are well preserved and minimize the decrease of renal perfusion and GFR. Renal function and blood flow quickly return to normal when normotension is resumed.

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References