Autoregulation of Renal Blood Flow during Ether, Halothane and Methoxyflurane Anesthesia in Dogs

Hisako Sasaki, Yasuhiko Hashimoto and Kenichi Iwatsuki

Department of Anesthesiology, Tohoku University School of Medicine, Sendai

Sasaki, H., Hashimoto, Y. and Iwatsuki, K. Autoregulation of Renal Blood Flow during Ether, Halothane and Methoxyflurane Anesthesia in Dogs. Tohoku J. exp. Med., 1977, 121 (2), 165-172 — The effects of ether, halothane and methoxyflurane (0.5-1.5 MAC) on renal blood flow and its autoregulation were studied in 24 dogs. The left renal artery was perfused with the animals' own blood by a constant pressure perfusion system. The perfusion pressure ranged from 60 to 200 mmHg. Renal blood flow at the perfusion pressure of 100 mmHg was changed neither by ether nor by halothane, while it was decreased dose-dependently by methoxyflurane. At equipotent anesthetic concentrations the autoregulation of renal blood flow was only slightly impaired by ether, but significantly by halothane and methoxyflurane. Adenosine (100 μg/min) or calcium chloride (10 mg/min) which was infused directly into the renal artery resulted in a restoration of autoregulation impaired by MAC-1 of each anesthetic when perfusion pressure was raised stepwise from 100 to 200 mmHg, but no restoration was observed at low perfusion pressure below 100 mmHg. The results indicate that methoxyflurane exerts a direct constrictive effect on the renal vasculature. Adenosine and calcium may play a significant role on the response of the renal vasculature to raised perfusion pressure. ——— ether; halothane; methoxyflurane; renal blood flow; autoregulation

It has been reported that general anesthetic agents cause a reduction in renal plasma flow and glomerular filtration rate (Burnett et al. 1949; Habif et al. 1951; Blackmore et al. 1966; Deutsch et al. 1966; Leighton and Bruce 1975). Recently, Leighton et al. (1973) have suggested that methoxyflurane impairs the autoregulation of renal blood flow. These experiments, however, have been done under various circumstances and the systemic effects of general anesthetic agents have not been excluded. Therefore, the present study was designed to detect the direct effects of ether, halothane and methoxyflurane on the renal vasculature and on the autoregulation of renal blood flow with a constant perfusion technique in dogs. In addition, the effects of adenosine and calcium on the autoregulation were also studied in the presence of these anesthetic agents.

Received for publication, September 29, 1976.
Presented at the Annual Meeting of the Japan Society of Anesthesiology, May 28, 1976, Tokyo.
Supported by Grant in Aid for Development of Scientific Research, #0770655.
Address reprint requests to: Dr. Yasuhiko Hashimoto, Department of Anesthesiology, Tohoku University School of Medicine, Sendai 980, Japan.
MATERIALS AND METHODS

Twenty-four healthy mongrel dogs of both sexes, weighing 9–13 kg, were anesthetized with intravenous urethane (800 mg/kg) and chloralose (60 mg/kg). Following oral endotracheal intubation, respiration was controlled using a volume-limited respirator (Aika R-50, Ichikawa Shiseido Co.) with pure oxygen. Via a flank incision, the left renal artery was carefully exposed retroperitoneally, and a polyethylene catheter (3 mm OD) was quickly inserted into a cut-end 1 or 2 cm towards the kidney. Heparinized blood of the animal, led from the right femoral artery using a peristaltic pump (Mera CR-3, Senko Ikakogyo Co.), was left flow into the left renal artery through a cannulation flow probe (MF-probe, Nihon Kohden Co.) of an electromagnetic flowmeter (MF-5, Nihon Kohden Co.). A Starling pneumatic resistance was set parallel to this circuit and excess blood was shunted to the right femoral vein to attain constant perfusion pressure. A desired level of perfusion pressure was attained by changing the pressure of the pneumatic resistance. Another polyethylene catheter (3 mm OD) was inserted in the ascending aorta through the left carotid artery for measuring mean systemic blood pressure and taking blood samples (Fig. 1). Renal perfusion pressure and mean systemic blood pressure were measured with electric manometers (RP-5, Nihon Kohden Co.). These parameters, together with renal blood flow, were recorded with a multichannel direct-writing oscillograph (WI-180, Nihon Kohden Co.). At least 30 min elapsed before systemic blood pressure and renal blood flow at a perfusion pressure of 100 mmHg reached a stable level. All experiments were performed during the stable period.

Renal perfusion pressure was changed stepwise from 100 to 200 mmHg, then from 100 to 60 , and renal blood flow was measured to determine autoregulation. After control measurements, ether, halothane and methoxyflurane were delivered into inspired oxygen through the vaporizers, each anesthetic being administered to 8 dogs. The measurements were repeated at least 15 min after stabilization of renal blood flow at the arterial concentrations equivalent to half of minimum alveolar concentration (MAC-0.5), MAC-1.0 and MAC-1.5 in dogs (Eger et al. 1965) of each anesthetic. The arterial concentrations of each anesthetic were determined by a gas chromatography (Model 063, Hitachi Co.) before and after each measurement.
Then, arterial anesthetic concentrations were maintained at those equivalent to MAC -1.0. When a new steady state was attained, 100 μg/min of adenosine or 10 mg/min of calcium chloride was infused into the renal artery using a constant infusion pump (Model 975, Harvard Apparatus Co.), and the effects of each drug on the autoregulation affected by the anesthetics were observed. Arterial pH, P_\text{CO}_2, and base-excess were maintained within normal ranges. Lactated Ringer's solution was continuously dripped into the left external jugular vein throughout the experiments.

The data obtained were expressed as mean values with standard error. Statistical analyses were performed by Student's t-test for paired and unpaired data and p<0.05 was assumed to be statistically significant.

**Results**

**Systemic blood pressure and renal blood flow**

Mean values for mean systemic blood pressure, renal blood flow at the control perfusion pressure of 100 mmHg and arterial concentrations of the anesthetics are summarized in Table 1. There were no significant differences in the control values of each parameter between the groups. Mean systemic blood pressure was significantly elevated by ether at MAC-0.5 and -1.0 (p<0.01). On the other hand, it was decreased dose-dependently by halothane. There were significant differences at MAC-0.5 (p<0.01), MAC-1.0 and MAC-1.5 (p<0.001) of halothane and MAC-1.5 (p<0.01) of methoxyflurane as compared with the control values. Ether and halothane did not cause any significant change in renal blood flow at the perfusion pressure of 100 mmHg. In contrast to these anesthetics, methoxyflurane caused a dose-dependent decrease in renal blood flow. The average reductions in renal blood flow were 10, 18 and 25% at MAC-0.5, -1.0 and -1.5, respectively, and paired analysis revealed statistically significant differences (p<0.01; p<0.001; and p<0.001) as compared with the control.

**Autoregulation of renal blood flow**

Fig. 2 illustrates the pressure-flow relations before and after administration of each anesthetic. Renal blood flow was maintained almost constant within the pressure range between 80 and 180 mmHg without the anesthetics, indicating the autoregulation. However, during the administration of ether, the autoregulation was slightly impaired, but without a statistical significance. On the contrary, the administration of either halothane or methoxyflurane caused a marked dose-dependent impairment in the autoregulation. The pressure-flow curves were shifted to the left and upward by halothane and methoxyflurane when the perfusion pressure was above 100 mmHg, and the curves were shifted to the right and downward when the pressure was below 100 mmHg. The downward shift of the curves was more pronounced in methoxyflurane than in halothane.

**Effect of adenosine and calcium on autoregulation**

After completion of the above study, arterial concentrations of the anesthetics were maintained at those equivalent to MAC-1.0. When a new steady state was
Mean values are shown. *† Significant difference from the corresponding control.

Fig. 2. Effects of ether, halothane and methoxyflurane on the pressure-flow curves (autoregulation). Ordinate: % change in renal blood flow. Abscissa: renal perfusion pressure (mmHg). The values are the average in each group; vertical lines with cross bar represent means with 1 s.e. for 8 dogs.

attained, 100 µg/min of adenosine or 10 mg/min of calcium chloride which was infused directly into the renal artery restored the impaired autoregulation of renal blood flow at high perfusion pressure (>100 mmHg), while no restoration was observed at low perfusion pressure (<100 mmHg) (Fig. 3).

DISCUSSION

The present study showed that methoxyflurane caused a significant dose-dependent reduction in renal blood flow at the perfusion pressure of 100 mmHg (Table 1). The result indicates that methoxyflurane has a direct constrictive
pressure of 100 mmHg before and during the administration of ether, halothane

<table>
<thead>
<tr>
<th></th>
<th>Halothane (n=8)</th>
<th>Methoxyflurane (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAC</td>
<td>Control</td>
</tr>
<tr>
<td>0.5</td>
<td>17±2</td>
<td>18±2</td>
</tr>
<tr>
<td>1.0</td>
<td>25±3</td>
<td>111±11</td>
</tr>
<tr>
<td>1.5</td>
<td>29±3</td>
<td>94±13</td>
</tr>
</tbody>
</table>

* p<0.01 and † p<0.001.

Fig. 3. Changes in autoregulation during a direct renal arterial infusion of 100 μg/min of adenosine or 10 mg/min of calcium chloride at MAC 1.0 of ether, halothane and methoxyflurane. Ordinate: renal blood flow (ml/min). Abscissa: renal perfusion pressure (mmHg). The values are the average in each group; vertical lines with cross bar represent means with 1 S.E.

effect on the renal vasculature. On the other hand, ether and halothane caused no apparent changes in renal blood flow, indicating that the absence of a direct vasoconstrictive effect by these anesthetics. Burnett et al. (1949) reported that the third phase of ether anesthesia decreased renal blood flow and glomerular filtration rate averaging 39% and 21%, respectively. Habif et al. (1951) reported a 52% reduction in renal blood flow and a 45% decrease in the glomerular filtration rate during ether anesthesia. Blackmore et al. (1966) reported that 2% halothane anesthesia for 1 hr caused a decrease in renal plasma flow by 16% and in glomerular filtration rate by 20%. A similar result was reported by other investigators.
(Deutsch et al. 1966). However, these decreases might be largely due to the changes in systemic circulation by ether or by halothane, since in our experiments these anesthetics within the range of 0.5–1.5 MAC showed little direct effect on renal blood flow.

Leighton et al. (1973) suggested that methoxyflurane impairs the autoregulation of renal blood flow. Recently Leighton and Bruce (1975) reported that a reduction in total renal blood flow during methoxyflurane anesthesia was accompanied by a proportionally larger decrease in outer cortical flow than in inner cortical and juxtamedullary flow and they suggested that these renal hemodynamic responses might be attributable to methoxyflurane-induced nephropathy. In our experiments a significant dose-dependent reduction in renal blood flow was shown in methoxyflurane and its direct vasoconstrictive effect on the renal vasculature was clearly demonstrated.

In the present study, a marked impairment of autoregulation of renal blood flow was observed during halothane and methoxyflurane anesthesia. Adenosine or calcium chloride which was infused directly to the renal artery restored the autoregulation impaired by these anesthetics when perfusion pressure was raised (Figs. 2 and 3). The automatic adjustment of smooth muscle tone in the renal artery to a change in the perfusion pressure within a range of 80 and 180 mmHg has been considered to be one of the processes involved in the autoregulation. Since Gordon et al. (1966) observed a release of an adenosine compound in the blood stream of the ischemic kidney, much interest has been focussed on its possible physiological role in the renal circulation. Thurau (1964) postulated that adenosine monophosphate (AMP) played an important role in the autoregulation, and his report was supported by the results in the bioassay studies of renal venous blood by Scott et al. (1965). The major fate of AMP in the kidney is its degradation to adenosine by 5'-nucleotidase (Weiseman et al. 1969). Adenosine has been reported to constrict the renal vasculature specifically, while it is a potent vasodilator in other organs (Hashimoto and Kumakura 1965) and potentiates the renal vasoconstrictive effect of norepinephrine (Hashimoto and Kokubun 1971). Furthermore, recently it has been reported that calcium antagonists abolish the autoregulation of renal blood flow (Ono et al. 1974). In view of these reports, it may strongly suggest that adenosine contributes to the autoregulation of renal blood flow by mediating calcium movements. The present study suggests that ether slightly, but halothane and methoxyflurane significantly, inhibits calcium movements through their direct effects on the renal vascular smooth muscle.

Here it is interesting to note that the impaired autoregulation was not restored either by calcium or by adenosine at low perfusion pressure. Systemic hypotension is not rare during anesthesia, and the first victim of it is a decrease in renal blood flow. Miller et al. (1966) demonstrated that once a decrease in renal blood flow occurred with halothane, vasopressors only constricted the renal vascular beds furthermore in spite of an increase in systemic blood pressure. Leighton et al. (1976) reported that furosemide did not increase total renal plasma flow when a
reduction in renal blood flow was induced by methoxyflurane.

In conclusion, the present study shows that methoxyflurane exerts a direct vasoconstrictive effect on the renal vasculature and both halothane and methoxyflurane significantly impair the autoregulation of renal blood flow. The impairment of autoregulation was restored by adenosine or calcium chloride at high perfusion pressure. However, no restoration was observed at low perfusion pressure. Care should be taken to avoid hypotension during halothane and methoxyflurane anesthesia, since the patients may not be protected by the renal autoregulatory mechanism.

Acknowledgment

We acknowledge the excellent technical assistance of Mr. Shoichi Obara.

References

J. Physiol., 208, 813–824.
