Cardiovascular Effects of Methoxyflurane

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Methoxyflurane is a potent anesthetic agent providing a normal cardiac rhythm, good muscle relaxation and no postoperative hypotension. With increasing depths of anesthesia there is a progressive decrease in arterial pressure. Wasmuth and associates noted during some surgical procedures that the anesthetic concentration had to be increased to a level producing a significant drop in blood pressure in order to achieve sufficient muscle relaxation. There have also been reports that the heart is sensitized to epinephrine during anesthesia with this agent.

The purpose of the present study was to evaluate the effects of methoxyflurane on the cardiovascular system of dogs by monitoring aortic blood pressure, ventricular contractile force, aortic blood flow and heart rate during different levels of anesthesia. These results were also compared with similar experiments in which halothane was used as the primary agent. Changes during induction of anesthesia were monitored in special experiments in which animals were prepared the previous day for recording of heart force, aortic pressure and heart rate.

Methods

Thirty-five mongrel dogs, ranging in weight from 8 to 16 kg., were studied. After induction of anesthesia and a mid-line thoracotomy, aortic pressure was measured through an indwelling polyethylene catheter placed through the femoral artery into the abdominal aorta and analyzed by means of a Statham transducer. Ventricular contractile force was measured with a strain gauge arch sutured to the right ventricle. Total aortic flow (cardiac output minus coronary flow) was measured with a Kiger-Dennard electromagnetic flowmeter. The flowmeter probe was placed around the aorta between its origin and arch. Heart rate was computed electronically, and all parameters were recorded on a Grass oscillograph. Blood pH determinations were also made periodically. In the experiments using previously prepared animals, the same procedures were carried out but were preceded by recordings of the changes occurring during induction of anesthesia. These preparations consisted of induction of anesthesia with thiopental and maintenance on methoxyflurane during the thoracotomy and placement of the arch and aortic catheter. Thoracotomy was performed in the interspace between the fourth and fifth ribs. The number of animals and the anesthetics studied are summarized in table 1.

Inhalation anesthesia was accomplished using a Foregger anesthesia machine equipped with a 'copper kettle' vaporizer. This machine was modified so that high flows could pass through the 'kettle' to vaporize enough methoxyflurane for induction. Later, a double 'copper kettle' machine was obtained with one kettle having a flow capacity of 4 liters/minute. The depth of anesthesia and degree of depression obtained with these two machines were approximately the same for any calculated concentration. Methoxyflurane anesthesia was induced by first passing 1 liter/minute of oxygen through the 'kettle' and gradually increasing the flow to 3 liters/minute. A 3 per cent concentration of halothane was used for induction. A semiclosed technique was used with both of these agents. When anesthesia was induced with thiopental, 20 mg./kg. were given intravenously. Anesthesia was maintained in all animals using a nonrebreathing system. The lungs were artificially ventilated

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changes recorded. Figure 1 illustrates a typical experiment in which heart rate, aortic blood flow, ventricular contractile force and aortic pressure were recorded. As the depth of anesthesia was increased, all parameters were progressively depressed. In a few experiments, if the animal breathed a concentration of 1.00 per cent for long periods of time, arrhythmias developed similar to those shown in the sixth column of figure 1. However, if the agent was withdrawn and oxygen administered the animal readily recovered. In bringing the animals back to control levels, muscle tone returned before the cardiovascular system completely recovered, and readings equal to control values were seldom obtained in the open chest animal. However, values near control were recorded.

Figure 2 summarizes graphically the cardiovascular effects of increasing concentrations of methoxyflurane. Changes in cardiovascular function during maintenance at the various levels of anesthesia were not significantly influenced by the different methods of induction (thiopental or methoxyflurane) or in the type of animal preparation used. Therefore, the results from the 25 animals maintained on methoxyflurane (table 1) were grouped together for simplicity of presentation. The values at a concentration of 0.25 per cent were used as control, and all values at the deeper concentrations were expressed as percentage changes from these. At a concentration of

Fig. 1. Typical experiment in a previously prepared animal showing the effects of increasing concentrations of methoxyflurane on the cardiovascular system. HR—heart rate in beats/minute, ABF—aortic blood flow in cc./minute, VCF—ventricular contractile force in grams, and BP—aortic pressure in mm. Hg. The first column represents the control period in which the animal was awake. After induction the animal was placed on approximately a 0.50 per cent concentration for the thoracotomy and placement of flowmeter probe. The animal was then stabilized at 0.25 per cent for 30–45 minutes, and the same period of stabilization was allowed at all subsequent concentrations.

with a Harvard respirator at a rate of approximately 12 times per minute, with a tidal volume of about 250 ml. depending upon the size of the animal.

Results

Aortic pressure, contractile force and heart rate were recorded before and during induction with methoxyflurane in the 9 animals prepared 24 hours prior to the experiment. The values obtained at light levels of anesthesia were compared to control values. There was a mean decrease in mean aortic pressure of 27.6 per cent ± S.E. 5.2 and a mean decrease in ventricular contractile force of 19.8 per cent ± 4.6. Both changes were statistically significant (P < .05). Heart rate was not appreciably altered in most cases. The animals were then subjected to a mid-line thoracotomy and a flowmeter probe placed around the aorta. They were then progressively depressed by increasing the concentration of the anesthetic in the inspired air, and the cardiovascular

Fig. 2. This graph summarizes the cardiovascular effects of increasing concentrations of methoxyflurane in the inspired air. There are 20 animals represented at each of the first two concentrations and 5, at 1.00 per cent.
0.50 per cent all three parameters were significantly depressed from the values at 0.25 per cent ($P < .01$). The depression of all parameters at 0.75 per cent was also significantly greater than at 0.50 per cent; while at 1.00 per cent, the depression was not significantly greater than at 0.75 per cent. However, owing to severe depression only 5 animals breathed this concentration as compared to 20 at the first two concentrations. There was a tendency at all concentrations for the aortic flow and pressure to be somewhat more depressed than contractile force, although this was not statistically significant.

In 6 experiments a strain gauge arch was sutured to the left ventricle, and comparisons were made between left ventricular contractile force and stroke work during methoxyflurane anesthesia. These results are plotted graphically in figure 3. Again, the values at a concentration of 0.25 per cent served as the control. At a concentration of 0.50 per cent, stroke work was depressed significantly more than contractile force ($P < .05$). At 0.75 per cent, the difference was not statistically significant ($P > .1$).

The effects of methoxyflurane on the sympathetic nervous system was not studied directly. A few animals, however, were subjected to periods of apnea and the responses recorded manifested the usual sympathetic effects. Figure 4 shows a tracing from a typical experiment. This animal was deeply anesthetized using a concentration of 1.00 per cent of methoxyflurane. The respirator was turned off at the first arrow indicating apnea. The animal was allowed to remain apneic until the heart began to fail, which in this experiment was 4.5 minutes later. The respirator was then turned on and the animal again respired with a 1.00 per cent concentration of methoxyflurane. The rebound responses to ventilation were high in all instances. It can be inferred that the sympathetics were not blocked substantially. Although this rebound effect can be obtained to some degree with denervated adrenal glands, the intensity of the response suggested that the sympathetic nervous system was highly active during apnea. The rebound is generally interpreted as a restoration of myocardial and vascular reactivity in the presence of high blood levels of endogenous catechol amines.

To obtain a comparison between methoxyflurane and an agent with some similar characteristics, 10 animals anesthetized with halothane were studied. Five of these animals were previously prepared as described earlier for recording blood pressure, myocardial contractile force and heart rate during induction of anesthesia. The results were similar to those with methoxyflurane. These animals and 5 others, in which anesthesia was induced with thiopental (table 1), were then respired with increasing concentrations of the agent while aortic pressure, contractile force, aortic flow and stroke work were recorded. The 5

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**Table 1. Schedule of Experiments**

<table>
<thead>
<tr>
<th>No. of Animals</th>
<th>Induction Agent</th>
<th>Maintenance Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiments without recordings during induction</td>
<td>methoxyflurane</td>
<td>methoxyflurane</td>
</tr>
<tr>
<td>10</td>
<td>methoxyflurane</td>
<td>methoxyflurane</td>
</tr>
<tr>
<td>6</td>
<td>thiopental</td>
<td>methoxyflurane</td>
</tr>
<tr>
<td>5</td>
<td>thiopental</td>
<td>halothane</td>
</tr>
<tr>
<td>Experiments with recordings during induction (preparation on previous day with strain gauge arch and aortic catheter)</td>
<td>methoxyflurane</td>
<td>methoxyflurane</td>
</tr>
<tr>
<td>9</td>
<td>methoxyflurane</td>
<td>methoxyflurane</td>
</tr>
<tr>
<td>5</td>
<td>halothane</td>
<td>halothane</td>
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</tbody>
</table>
animals in which anesthesia was induced with thiopental were not used for induction studies and were prepared by the techniques previously described. These values were then compared to those obtained with methoxyflurane. Since methoxyflurane is more potent than halothane, the inspired concentrations of the agents could not be used as a base for comparison. Therefore, we decided to use mean aortic pressure as the standard base. The percentage depression of each parameter was plotted against the corresponding mean aortic pressure measured at each concentration with both agents. The percentage changes in the parameters at each concentration were derived from the values obtained at the lightest level of anesthesia that could be attained with the two agents. Figure 5 shows a scatter diagram in which the percentage depression of contractile force is plotted against the mean aortic pressure for methoxyflurane and halothane. The data in this and the diagrams of figures 6 and 7 regressed linearly as tested by the method of “least squares.” On comparing the regression lines in figure 5 by “covariance,” the slopes and the height of the two
Fig. 6. Comparison of the regression lines formed by plotting the percentage depression of aortic flow against the corresponding arterial pressure during anesthesia with methoxyflurane (Penthrane) and halothane (Fluothane).

Fig. 7. Comparison of the regression lines formed by plotting the percentage depression of stroke work against the corresponding arterial pressure during anesthesia with methoxyflurane (Penthrane) and halothane (Fluothane).
lines were not significantly different \( (P > 0.1) \). In figure 6 a similar comparison was made with the aortic flow plotted against the aortic pressure. Again the slopes of the two lines were similar; however, the difference in the heights was highly significant \( (P < .001) \). This indicated a greater depression of total aortic flow with methoxyflurane for any given depression of blood pressure. Figure 7 compares stroke work changes with these two agents. These results were similar to those obtained with the aortic flow. The slopes of the lines were similar while the heights were significantly different \( (P < .001) \). Again this represents a greater degree of depression with methoxyflurane.

**Discussion**

In a recent study in which comparisons were made between the cardiovascular and respiratory effects of methoxyflurane and halothane, Dobkin and Fedoruk \(^{14}\) reported that, in dogs during spontaneous breathing, mean arterial pressure and cardiac output were depressed slightly more with halothane while respiration was depressed to a greater extent with methoxyflurane. During mechanical respiration they found no difference in the degree of cardiac depression with the two agents. These investigators used only one concentration of the anesthetics in their study.

The present results indicate that ventricular contractile force, aortic pressure and total aortic flow are progressively depressed with increasing inspired concentrations of methoxyflurane. Left ventricular stroke work was also found to be depressed somewhat more than left ventricular contractile force. When compared with halothane, the percentage contractile force depression for any comparable depression of blood pressure with the two agents was not found to be significantly different. However, aortic flow and stroke work were depressed significantly more with methoxyflurane than with halothane. This indicates that the heart may be working less efficiently at a given force of contraction with methoxyflurane resulting in a greater decrease in cardiac output. This difference could be due to a smaller decrease in peripheral resistance with methoxyflurane than is seen with halothane. However, on analyzing peripheral resistance changes with these two agents, no consistent pattern of depression could be found with either agent. There is probably only a limited clinical significance to the greater decrease in stroke work and output with methoxyflurane since the distinction did not become evident except at deep levels of anesthesia.

The mechanism of depression with methoxyflurane appears similar to that of halothane. Severinghaus and Cullen \(^{13}\) concluded that the reduction in cardiac output and arterial pressure during halothane administration was primarily due to cardiac depression and not to ganglionic blockade. Long and Pittinger \(^{15}\) have shown in dogs, as have others \(^{17,18}\) in patients, that ventricular contractile force is significantly depressed during halothane administration. Mahaffey et al. \(^{14}\) have also shown in dogs that the contractile force depression still occurs during sympathetic blockade with the pressure maintained at normal levels by means of methoxamine infusion, indicating that the myocardial depression was not secondary to sympathetic blockade or hypotension. Our results suggest a similar action for methoxyflurane. The sympathetic nervous system does not appear to be blocked as was evidenced by the responses obtained following apnea. Also, in a few experiments, methoxamine was administered to increase the blood pressure, and during this period contractile force remained depressed. This would indicate that the myocardial depression is not secondary to hypotension.

Other investigators \(^{17,2}\) have reported that arrhythmias were not seen during anesthesia with methoxyflurane. In a few instances during deep levels of anesthesia animals did develop arrhythmias in this study. However, since they occurred only when the circulation was markedly depressed, these arrhythmias may have been due to hypoxia.

**Summary**

Changes in aortic blood pressure, ventricular contractile force, total aortic flow, heart rate and stroke work were recorded during positive pressure inhalation of increasing concentrations of methoxyflurane or halothane in 35 open chest dogs. Fourteen of the animals were anesthetized and prepared for recording aortic pressure, ventricular contractile force and heart
rate 24 hours prior to the experiment. Changes in these parameters were studied the following day during induction of anesthesia with methoxyflurane or halothane.

Our results show that the degree of cardiovascular depression occurring during induction and in light levels of anesthesia with methoxyflurane and halothane are similar. In deep levels of anesthesia, the degree of ventricular contractile force depression with methoxyflurane was not significantly different from that obtained with halothane. On the other hand, the percentage depression of total aortic flow and stroke work was significantly greater during deep methoxyflurane anesthesia.

During methoxyflurane anesthesia left ventricular stroke work was depressed to a greater degree than left ventricular contractile force. The sympathetic nervous system was not blocked by methoxyflurane as indicated by the rebound responsiveness to ventilation following apnea.

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References
13. Ibid., Ch. 13, p. 394.