Effects of Sevoflurane and Isoflurane on Cardiac and Coronary Dynamics in Chronically Instrumented Dogs

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To assess the hemodynamic properties of the new inhalational anesthetic sevoflurane, 22 dogs were chronically instrumented for measurement of heart rate, aortic, left ventricular and left atrial pressures, cardiac output, and coronary blood flow. Dogs were randomly assigned to two groups, receiving either 1.2 and 2 MAC of sevoflurane (n = 11) or isoflurane (n = 11). At 1.2 and 2 MAC, sevoflurane produced an increase in heart rate (+60 ± 12% and +54 ± 9%, respectively), dose-dependent aortic hypotension (−22 ± 4% and −32 ± 4%, respectively), systemic vasodilatation (−22 ± 5% and −19 ± 5%, respectively), dose-dependent decrease in stroke volume (−31 ± 6% and −48 ± 4%, respectively), and left ventricular dp/dt (−40 ± 4% and −61 ± 10%, respectively). Cardiac output decreased only at 2 MAC (−17 ± 6%). Finally, coronary blood flow increased at 1.2 MAC of sevoflurane (+29 ± 8%). Except for heart rate, sevoflurane and isoflurane produced similar effects. At 1.2 MAC, sevoflurane produced a greater increase in heart rate than isoflurane (+60 ± 12% vs. +33 ± 9%). The authors conclude that, except for heart rate, the effects of sevoflurane on cardiac function and coronary blood flow are almost identical to those induced by isoflurane in the chronically instrumented dog. (Key words: Anesthetics, volatile: sevoflurane; isoflurane. Heart: blood flow; cardiac output; contractility; myocardial function.)

SEVOFLURANE is a nonirritating, pleasant-smelling, volatile anesthetic agent that provides rapid induction and awakening consistent with its low blood solubility (blood gas λ 0.6).1,2 The drug has recently been approved for clinical use in Japan.† † Manohar and Parks3 reported that sevoflurane induces a dose-dependent decrease in cardiac output, mean arterial blood pressure (MAP), and coronary blood flow without changes in heart rate in chronically instrumented pigs. However, baseline heart rate was elevated (> 120 beats per min) in these animals.

Among inhalational anesthetics, isoflurane has been demonstrated to have the least myocardial depressant properties.4 This "sparing" effect is mostly due to its systemic vasodilatory properties.4 In addition, isoflurane is the newest and most widely used inhaled anesthetic in the United States. Thus, isoflurane seems the appropriate reference against which to compare the properties of a new inhalation anesthetic.

This study was designed to assess the effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs.

Materials and Methods

The study was approved by the Baylor Animal Protocol Committee. As previously described,6 22 dogs (weight 16–28 kg) were surgically instrumented through a left thoracotomy during endotracheal halothane anesthesia with: 1) a pulsed Doppler flow probe (Baylor College of Medicine, Houston, Texas) around the circumflex coronary artery (2- or 3-mm diameter); 2) a miniature high-fidelity transducer (Konigsberg Inc., Pasadena, California) in the left ventricle; 3) Tygon catheters (Tygon, Norton Inc., Akron, Ohio) in the abdominal aorta and left atrium; 4) an electromagnetic flow probe (Micron Inc., Los Angeles, California) around the pulmonary artery. Before chest closure, 0.5% bupivacaine was infiltrated around the intercostal nerves for postoperative analgesia. After chest closure, the pneumothorax was evacuated and the chest drain removed before the dogs awakened. The instrumentation and catheters were exteriorized into a specially designed pouch that was sewn to the posterior cervical region and protected by a specially designed animal jacket. The animals were nursed carefully through the first 24 h with iv fluids and systemic analgesics (meperidine) as necessary. Dogs were carefully trained to lie quietly and were studied at least 10 days after surgery, when hemocrit was > 30%, and only if body temperature, appetite, and general appearance were normal.

On the day of the experiment, dogs were randomly assigned to two groups, receiving either 2.8% and 4.7% end-tidal concentrations of sevoflurane (n = 11) or 1.6% and 2.6% concentrations of isoflurane (n = 11), i.e., concentrations equal to 1.2 and 2 MAC, respectively.1,6 For each anesthetic, the order of concentrations was also ran-
domized. Animals were anesthetized via a mask; the trachea of each animal was intubated; and using a Harvard ventilator (Harvard Apparatus, South Natick, Massachusetts), the lung of each animal was ventilated with a mixture of oxygen, nitrogen, and the appropriate anesthetic agent. Ventilation and \( \text{Fi}_{2}\) were adjusted to maintain arterial blood gases and \( \text{pH} \) at awake levels (Instrumentation Laboratory, Inc., Lexington, Massachusetts). End-tidal anesthetic (Beckman LB®-2, Beckman, Inc., Schiller Park, Illinois) and CO\(_2\) concentrations (Lifespan 100®, Biochem International, Inc., Waukesha, Wisconsin) were continuously monitored, using infrared absorption techniques. Lactated Ringer's solution (3–5 mg·kg\(^{-1}·\text{h}^{-1}\)) was infused via a foreleg vein. Rectal temperature, measured by a thermocouple probe (Yellow Springs Instruments, Yellow Springs, Ohio), was maintained at awake levels throughout the experiment.

Using a Gould polygraph (Gould Inc., Cleveland, Ohio), hemodynamic variables were continuously recorded at 25 mm/min during the entire experiment, except for the times of data collection (25 mm/s) and for the left ventricular dp/dt calibration (200 mm/s). Measurements (heart rate, aortic blood pressure, cardiac output, left ventricular dp/dt, left atrial pressure, coronary blood flow, and arterial blood gases) were performed prior to anesthesia and during a brief apneic period 15 min after obtaining a constant end-tidal anesthetic concentration.

In addition to the recorded variables, we calculated the systemic and coronary vascular resistances as the ratio between MAP and cardiac output or coronary blood flow; the rate-pressure product as the product of aortic systolic pressure \( \times \) heart rate \( \times 10^{-3} \), and stroke volume as the ratio between cardiac output and heart rate.

For each anesthetic, changes were analyzed using an analysis of variance for repeated measure design. When significant, multiple comparisons within and between groups were performed using Student's \( t \) tests followed by Bonferroni corrections. Alpha was set at a level of 0.05. Data are presented as mean ± SEM.

## Results

Effects of sevoflurane and isoflurane on cardiac function are presented in table 1. Changes in coronary blood flow are illustrated in figure 1.

Sevoflurane and isoflurane administrations were associated with tachycardia, similar systemic vasodilation, a similar dose-dependent decrease in aortic blood pressure, stroke volume, left ventricular dp/dt, and no change in left atrial pressure. In addition, at 2 MAC both sevoflurane and isoflurane produced a significant decrease in cardiac output. There were no significant between-group differences in the hemodynamic values collected prior to and during anesthesia, except that at 1.2 MAC, sevoflurane elicited a significantly higher heart rate than did isoflurane. Finally, an increase in coronary blood flow was recorded with sevoflurane at 1.2 MAC and with isoflurane at 2 MAC. Both anesthetic agents induced a decrease in coronary vascular resistance that was dose-dependent only with isoflurane.

### Table 1. Variations in Cardiac Function Awake and During 1.2 MAC and 2 MAC of Sevoflurane and Isoflurane

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>1.2 MAC</th>
<th>2 MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HR (beats/min)</strong></td>
<td>85 ± 2</td>
<td>135 ± 8*</td>
<td>131 ± 6*</td>
</tr>
<tr>
<td><strong>SAP (mmHg)</strong></td>
<td>11 (11)</td>
<td>108 ± 8*</td>
<td>113 ± 8*</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>11 (11)</td>
<td>104 ± 4*</td>
<td>79 ± 5*</td>
</tr>
<tr>
<td><strong>DAP (mmHg)</strong></td>
<td>11 (11)</td>
<td>106 ± 5*</td>
<td>88 ± 6*</td>
</tr>
<tr>
<td><strong>LAP (mmHg)</strong></td>
<td>11 (11)</td>
<td>75 ± 3*</td>
<td>59 ± 3*</td>
</tr>
<tr>
<td><strong>CO (l/min)</strong></td>
<td>11 (11)</td>
<td>75 ± 3*</td>
<td>60 ± 4*</td>
</tr>
<tr>
<td><strong>SV (ml)</strong></td>
<td>11 (11)</td>
<td>58 ± 3*</td>
<td>47 ± 4*</td>
</tr>
<tr>
<td><strong>LV dp/dt (mmHg/s)</strong></td>
<td>1.3 ± 0.5</td>
<td>2.1 ± 0.7</td>
<td>2.3 ± 0.7</td>
</tr>
<tr>
<td><strong>SVR (mmHg·min(^{-1}·1^{-1}))</strong></td>
<td>19 ± 0.1</td>
<td>21.5 ± 1.5</td>
<td>15.3 ± 1.4*</td>
</tr>
<tr>
<td><strong>LV dp/dt (mmHg/s)</strong></td>
<td>24.4 ± 0.9</td>
<td>18.0 ± 1.6</td>
<td>18.0 ± 1.6</td>
</tr>
<tr>
<td><strong>SVR (mmHg·min(^{-1}·1^{-1}))</strong></td>
<td>3379 ± 196</td>
<td>2043 ± 175*</td>
<td>2043 ± 175*</td>
</tr>
<tr>
<td><strong>SVR (mmHg·min(^{-1}·1^{-1}))</strong></td>
<td>2915 ± 169</td>
<td>1832 ± 145*</td>
<td>1297 ± 103*</td>
</tr>
</tbody>
</table>

Mean ± SEM.

n = number of observations. S = sevoflurane. I = isoflurane. HR = heart rate. SAP = systolic arterial pressure. MAP = mean arterial pressure. DAP = diastolic arterial pressure. LAP = left atrial pressure. CO = cardiac output. SV = stroke volume. LV dp/dt = maximum rate of rise of left ventricular pressure. SVR = systemic vascular resistance.

* \( P < 0.05 \) versus awake; † \( P < 0.05 \) versus 1.2 MAC; ‡ \( P < 0.05 \) versus isoflurane.
SEVOFLURANE AND CARDIAC FUNCTION

Fig. 1. Effects of sevoflurane (A) and isoflurane (C) on coronary blood flow (CoBF) and vascular resistance (VR) and on rate-pressure product (RPP). Mean ± SEM. tP < 0.05 versus awake; tP < 0.05 versus 1.2 MAC.

Discussion

The hemodynamic properties of isoflurane were similar to those we have previously observed in chronically instrumented dogs.7,8 Although at 1.2 MAC isoflurane did not affect cardiac pump function, myocardial depression at 2 MAC was evidenced by decreases in MAP, left ventricular dP/dt, and stroke volume in the absence of a further decrease in the duration of diastolic ventricular filling or change in left atrial pressure. Except for heart rate, no differences were observed between sevoflurane and isoflurane. Like isoflurane, sevoflurane induced the same level of dose-dependent hypotension. Since at 1.2 MAC of sevoflurane cardiac output was unchanged, the decrease in arterial blood pressure was mainly related to systemic vasoconstriction. At 2.0 MAC of sevoflurane, the further decrease in arterial blood pressure was most likely the result of myocardial depression. Whereas, in both groups, no further changes between 1.2 and 2 MAC were recorded in systemic vascular resistance and heart rate, the decrease in left ventricular dP/dt and cardiac output documented the myocardial depression induced by the increase in anesthetic concentration.

It is established that changes in left ventricular dP/dt depend on intrinsic myocardial contractility, pre- and afterload, and heart rate.9 Sevoflurane and isoflurane induced the same dose-dependent decrease in left ventricular dP/dt and afterload and did not affect preload. Because tachycardia was more pronounced at 1.2 MAC of sevoflurane than at an equipotent concentration of isoflurane, for the same degree of intrinsic myocardial depression, the reduction in left ventricular dP/dt should have been less marked during sevoflurane anesthesia. Thus, our findings suggested that sevoflurane is slightly more myocardial depressant than is isoflurane.

Inhalational anesthetics have been found to depress baroreflex function; the extent of depression varies among anesthetics, with both halothane and enflurane being more depressant than isoflurane.11 At 1.2 MAC, and for the same degree of hypotension, tachycardia was more pronounced with sevoflurane than with isoflurane. Consequently, our results suggest that a low concentration of sevoflurane may be less depressant to baroreflex function than is isoflurane. With both anesthetic agents, the increase in concentration resulted in an additional decrease in blood pressure, but did not result in a further and different between-group increase in heart rate. Thus, our data also suggest that at high concentrations the baroreflex function was depressed to a similar degree by both anesthetic agents. This hypothesis needs to be confirmed with specific assessments of baroreflex function.

In this study, 2 MAC isoflurane led to an increase in coronary blood flow, whereas no significant changes were observed at 1.2 MAC. These results agree with data previously obtained in chronically instrumented dogs for the low concentration, but differed for the high concentration.7-9 In fact, no significant changes in coronary blood flow were previously found during administration of isoflurane at 3.3% end-tidal concentration. The reason for this discrepancy may be the different high concentration (2.5 MAC vs. 2 MAC) at which the studies were performed. In the present study, the increased coronary blood flow was associated with a driving pressure higher than that previously recorded during 2.5 MAC of isoflurane.7-9

Sevoflurane, like isoflurane, appeared to be a potent coronary vasodilator if coronary vasodilation is defined as decrease in coronary vascular resistance (the relationship between perfusion pressure and flow in the coronary circulation). However, regulation of coronary circulation is known to be dependent on myocardial oxygen demand. Therefore, a more physiologic definition of coronary vasodilation would include documentation of a disparity between myocardial oxygen supply and demand, namely a decrease in myocardial A-V oxygen difference. Our model did not allow for the measurement of coronary venous oxygen so that we could not determine this aspect of coronary physiology. The heart rate-systolic blood pressure product (rate-pressure product) has been shown to be a reasonable estimate of myocardial oxygen demand. Con-
sequently, the comparison between rate-pressure product and coronary blood flow should allow for better understanding of anesthetic effects on myocardial oxygen balance (fig. 1). Sevoflurane appeared to have beneficial effects on this balance because at 1.2 MAC its administration was associated with an increase in coronary blood flow and no significant changes in rate-pressure product. However, it may be argued that at a high concentration of sevoflurane, coronary blood flow decreased because no additional coronary vasodilation occurred in the presence of a more marked hypotension. On the other hand, an increase in sevoflurane concentration was also associated with myocardial depression, leading not only to a further decrease in cardiac output, arterial pressure, and LV dP/dt, but also a decrease in myocardial oxygen demand (rate-pressure). Thus, the coronary flow response may have been autoregulatory. However, additional studies are needed to determine the effects of sevoflurane on myocardial oxygen consumption and extraction. In addition, since sevoflurane appears to produce a similar coronary vasodilation to isoflurane, the production of “coronary steal” is theoretically possible.

It is unclear as to why our results differ from those of Manohar and Parks. Although the coronary circulation of the pig resembles that of humans in that collateral circulation is not as apparent during chronic ischemia. In fact, there is little documentation that normal coronary physiology is significantly different between dog, pig, and humans. Inasmuch as this is not an ischemic model, there seems little to choose between dog and pig except for the fact that dogs are easier to instrument and train. It is of some interest that the effects on the coronary circulation reported by Manohar and Parks for isoflurane also differ from those reported by other investigators both in dogs and humans.

To conclude, the present study indicated that in chronically instrumented dogs, the effects of sevoflurane on systemic and coronary hemodynamics were almost identical to those induced by isoflurane in equipotent concentrations. The only difference between the two inhalational anesthetic agents was more pronounced tachycardia induced by sevoflurane at low concentration. Two of the major advantages of isoflurane compared with halothane and enflurane have been the lower blood gas λ producing more rapid induction and emergence from anesthesia and less marked depression of cardiac pump function. If studies in humans corroborate our results in chronically instrumented dogs, then sevoflurane would appear to be a superior anesthetic to isoflurane because of the faster induction and emergence coupled with a similar hemodynamic profile.

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References