Hemodynamic Consequences of the Combination of Isoflurane Anesthesia (1 MAC) and Beta-adrenergic Blockade in the Dog

Daniel M. Philbin, M.D.,* and Edward Lowenstein, M.D.†

The hemodynamic response to the combination of isoflurane (1 MAC) and propranolol (0.5 mg/kg) was studied in 12 intact ventilated dogs following basal anesthesia with chloralose–urethane. When propranolol was administered during isoflurane anesthesia, stroke volume was maintained with a higher pulmonary capillary wedge pressure (2.2 ± 0.7 mm Hg to 6.3 ± 1.4 mm Hg), while systemic vascular resistance remained unchanged. When isoflurane was administered to the previously beta-adrenergically blocked dog, there were declines in systemic pressure and cardiac output (P < 0.01) and in pulmonary arterial pressure and stroke volume (P < 0.05), without change in systemic vascular resistance. When isoflurane was subsequently discontinued, these changes were reversed, and in addition, systemic vascular resistance increased (P < 0.05). These data indicate that isoflurane has pharmacologic properties compatible with a peripheral beta-adrenergic stimulating action. (Key words: Anesthetics, volatile, isoflurane; Heart, isoflurane, propranolol and; Sympathetic nervous system, sympatholytic agents, propranolol.)

PREVIOUS REPORTS have suggested that some of the hemodynamic effects of isoflurane anesthesia result from a beta-adrenergic stimulating action.1 This hypothesis is based primarily upon the observation that administration of isoflurane in healthy human volun-

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Methods

Twelve healthy mongrel dogs, weighing 18.5 to 21.3 kg, received basal chloralose–urethane anesthesia. The trachea of each was intubated with a wide-bore cuffed endotracheal tube. Ventilation was controlled using 100 per cent oxygen and utilizing a nonbreathing system. Polyethylene catheters were placed in the right femoral artery and right atrium for constant monitoring of pressures and for intermittent blood–gas analysis. A balloon-tipped flow-directed Swan-Ganz catheter4 was introduced into the pulmonary artery for monitoring of pulmonary arterial pressure (PA) and pulmonary capillary wedge pressure (PCW), the latter was a reflection of left atrial pressure.

End-tidal isoflurane concentrations were measured by means of a Beckman LB-2 infrared gas analyzer calibrated for isoflurane. Cardiac output was determined by indicator dye-dilution technique, using cardiogreen dye and a Gilford densitometer with sampling from an indwelling catheter in
the abdominal aorta. Duplicate determinations were performed.

Systemic and pulmonary vascular resistance and stroke volume were calculated according to the following formulas:

\[
SVR = \frac{SA_m - CVP_m}{CO} \quad (1)
\]

\[
PVR = \frac{PA_m - PCW_m}{CO} \quad (2)
\]

\[
SV = \frac{CO}{hr} \quad (3)
\]

### Table 1. Protocol

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Basal anesthesia</td>
<td>F. Basal anesthesia</td>
</tr>
<tr>
<td>B. Propranolol</td>
<td>G. Add isoflurane</td>
</tr>
<tr>
<td>C. Add isoflurane to propranolol</td>
<td>H. Add propranolol to isoflurane</td>
</tr>
<tr>
<td>D. Discontinue isoflurane</td>
<td>I. Discontinue isoflurane</td>
</tr>
<tr>
<td>E. Add isoflurane</td>
<td>J. Add isoflurane</td>
</tr>
</tbody>
</table>

### Table 2. Group I, Hemodynamic Effects of Isoflurane and Propranolol

<table>
<thead>
<tr>
<th></th>
<th>A Control</th>
<th>B Propranolol</th>
<th>C Propranolol - Isoflurane</th>
<th>D Propranolol</th>
<th>E Propranolol - Isoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>130 ± 30</td>
<td>170 ± 34</td>
<td>123 ± 21</td>
<td>153 ± 30</td>
<td>117 ± 18</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>163 ± 11</td>
<td>139 ± 5</td>
<td>128 ± 10</td>
<td>133 ± 6</td>
<td>129 ± 8</td>
</tr>
<tr>
<td>Pulmonary arterial pressure (mm Hg)</td>
<td>13.4 ± 1.7</td>
<td>16.2 ± 1.4</td>
<td>13.0 ± 1.5</td>
<td>15.1 ± 1.6</td>
<td>13.3 ± 1.8</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>4.8 ± 0.7</td>
<td>7.4 ± 1.3</td>
<td>6.7 ± 1.8</td>
<td>6.3 ± 1.2</td>
<td>7.4 ± 1.2</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>2.4 ± 0.8</td>
<td>2.9 ± 0.7</td>
<td>3.8 ± 1</td>
<td>3.1 ± 0.8</td>
<td>3.0 ± 0.7</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>4.21 ± 0.9</td>
<td>3.03 ± 0.4</td>
<td>2.04 ± 0.3</td>
<td>2.76 ± 0.5</td>
<td>1.91 ± 0.2</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>26 ± 4</td>
<td>22 ± 3</td>
<td>16 ± 2</td>
<td>21 ± 4</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>Peripheral vascular resistance (dynes-sec/cm²)</td>
<td>182 ± 33</td>
<td>245 ± 28</td>
<td>256 ± 32</td>
<td>365 ± 88</td>
<td>279 ± 22</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes-sec/cm²)</td>
<td>3.940 ± 1.160</td>
<td>5.024 ± 1.503</td>
<td>5.027 ± 1.614</td>
<td>5.437 ± 1.703</td>
<td>5.632 ± 1.782</td>
</tr>
</tbody>
</table>

* Mean ± SE.
SV = stroke volume (ml/beat)
HR = heart rate (beats/min)
CO = cardiac output (l/min)

Protocol

Following induction of basal anesthesia and placement of monitoring cannulas, control measurements were performed and blood samples obtained. The dogs were then divided into two groups of six animals each (table 1). In Group I propranolol (0.5 mg/kg) was administered intravenously to establish beta blockade and all measurements repeated. Isoflurane was administered until a steady state of 1 MAC (1.46 ± 0.25 per cent)7 was established and the measurements then performed again, after which isoflurane was discontinued, a reinforcing dose of propranolol (0.25 mg/kg) administered, and the measurements performed for the fourth time. Isoflurane was then reintroduced at 1 MAC for the final (fifth) series of measurements.

In Group II, 1 MAC isoflurane was established prior to the development of beta blockade and measurements performed. Propranolol (0.5 mg/kg) was then administered and measurements repeated. Isoflurane was discontinued, measurements repeated, the beta blockade reinforced, and isoflurane reintroduced at the same concentration for the final (fifth) series of measurements. At intervals throughout the study, the presence or absence of beta blockade was confirmed by the hemodynamic response to intermittent injections of isoproterenol (2 μg injected as a bolus).

This experimental design thus yielded data from five interventions: 1) isoflurane added to basal anesthesia (n = 6); 2) propranolol added to basal anesthesia (n = 6); 3) propranolol added to isoflurane anesthesia (n = 6); 4) isoflurane anesthesia after pro-

<table>
<thead>
<tr>
<th></th>
<th>F Control</th>
<th>G Isoflurane</th>
<th>H Isoflurane + Propranolol</th>
<th>I Propranolol</th>
<th>J Propranolol + Isoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>125 ± 5</td>
<td>92 ± 10</td>
<td>78 ± 8</td>
<td>127 ± 5</td>
<td>96 ± 10</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>131 ± 11</td>
<td>134 ± 11</td>
<td>111 ± 5</td>
<td>114 ± 8</td>
<td>113 ± 6</td>
</tr>
<tr>
<td>Pulmonary arterial pressure (mm Hg)</td>
<td>12.0 ± 1.6</td>
<td>11.4 ± 1.5</td>
<td>12.8 ± 1.3</td>
<td>12.8 ± 1.7</td>
<td>13.2 ± 1.6</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>4.3 ± 1.3</td>
<td>3.2 ± 0.7</td>
<td>6.3 ± 1.4</td>
<td>5.8 ± 1.5</td>
<td>6.2 ± 1.5</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>3.3 ± 0.7</td>
<td>3.6 ± 0.8</td>
<td>5.3 ± 0.7</td>
<td>4.0 ± 0.8</td>
<td>4.3 ± 0.5</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>2.82 ± 0.2</td>
<td>2.32 ± 0.2</td>
<td>1.92 ± 0.2</td>
<td>2.35 ± 0.2</td>
<td>1.77 ± 0.1</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>22 ± 1</td>
<td>18 ± 2</td>
<td>17 ± 2</td>
<td>21 ± 1</td>
<td>16 ± 1</td>
</tr>
<tr>
<td>Peripheral vascular resistance (dynes-sec/cm²)</td>
<td>225 ± 35</td>
<td>282 ± 35</td>
<td>266 ± 28</td>
<td>232 ± 17</td>
<td>312 ± 15</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes-sec/cm²)</td>
<td>3,504 ± 202</td>
<td>3,014 ± 152</td>
<td>3,239 ± 482</td>
<td>4,307 ± 344</td>
<td>4,218 ± 486</td>
</tr>
</tbody>
</table>

* Mean ± SE.
of these five groups. This method of analysis was employed to compensate for any change that might have occurred due to deterioration of the experimental preparation or differences in the control states of the animals studied.

**Results**

Tables 2 and 3 present the hemodynamic data for the two groups. Changes in cardiac output, heart rate, and systemic vascular resistance for the two groups are summarized in Figure 1.

**Isoflurane Added to Basal Anesthesia**

\( n = 6 \) (F to C)

Significant declines occurred in systemic blood pressure and systemic vascular resistance. Pulmonary vascular resistance increased \((P < .05)\), although the absolute value was still within normal limits.

**Propranolol Added to Basal Anesthesia**

\( n = 6 \) (A to B)

Propranolol caused significant increases in pulmonary capillary wedge pressure and systemic vascular resistance. The decline in heart rate did not achieve statistical significance \((t = 1.77, P = 0.1)\), in spite of the high control heart rate, averaging 163 beats/min in Group I.

**Propranolol Added to Isoflurane Anesthesia**

\( n = 6 \) (G to H)

The addition of propranolol during isoflurane anesthesia caused a virtual doubling of pulmonary capillary wedge pressure from 3.2 to 6.3 mm Hg \((P < .01)\) and a decrease in heart rate. No other measurement was significantly changed.

**Isoflurane Anesthesia After Propranolol Pretreatment**

\( n = 18 \)

B to C; D to E; I to J

Isoflurane, 1 MAC, caused significant declines in blood pressure, cardiac output, pulmonary arterial pressure, and stroke volume.
DISCONTINUATION OF ISOFLURANE AFTER ISOFLURANE–PROPRANOLOL

(n = 12) (C TO D; H TO I).

When isoflurane was discontinued, systemic blood pressure, cardiac output, stroke volume, and systemic vascular resistance increased significantly.

No significant change in arterial blood gases or pH was observed. The two control groups were comparable, the only significant difference being in cardiac output (P < 0.05).

The administration of isoproterenol (2 μg, iv) to the control group produced a 30 per cent increase in heart rate (172 ± 20 beats/ min) and a fall in diastolic pressure. This increase in heart rate was also observed in the isoflurane group. No response was obtained in the presence of propranolol.

Discussion

The sympathetic nervous system was divided into alpha and beta components by Ahlgquist. The beta-adrenergic system has since been further subdivided into central (cardiac) beta, receptors and peripheral or beta-receptors. Beta stimulation produces inotropic and chronotropic enhancement; beta stimulation causes peripheral vasodilation as well as bronchodilation and metabolic effects. Alpha-adrenergic stimulation has no cardiac effect, and causes peripheral constriction.

Beta-adrenergic blockade is employed most commonly for one of two indications. The first is treatment of tachyarrhythmias. It has been recommended for this indication during halothane anesthesia by Johnstone. In contrast, beta-adrenergic blockade during anesthesia with an agent relying upon sympathetic stimulation to maintain circulatory stability (e.g., diethyl ether) has been shown to be hazardous, as alpha-adrenergic activity is unopposed. The second, and probably most frequent, use of beta-adrenergic blockade is for treatment of angina pectoris.

The anesthetic management of patients in the presence of beta-adrenergic blockade is controversial. The hazard of discontinuing therapy is that myocardial oxygen demand and supply may again become unbalanced, leading to ischemia or even infarction. However, the danger of profound beta blockade is emphasized by Viljooen, who presented a series of five fatalities in cases in which patients received large doses of propranolol up to the time of coronary-artery surgery; he recommended that beta-blocking agents be discontinued at least two weeks prior to coronary-artery surgery. On the other hand, Prys-Roberts has demonstrated a tenfold decrease in the frequency of ischemic changes of the EKG during induction of anesthesia in hypertensive patients pretreated with prazolol, a cardioselective beta-adrenergic blocker.

It is thus important to know whether an anesthetic agent has a beta-adrenergic action, and if so, how beta-adrenergic blockade is tolerated in the presence of the agent. Furthermore, it is important to know whether there is a difference between anesthesia in the presence of a previously established beta blockade and production of beta blockade during anesthesia. An anesthetic agent that could be employed without hazard in combination with beta blockade would be useful.

The purpose of these experiments was to document the hemodynamic response to the combination of isoflurane and profound beta-adrenergic blockade with propranolol. The proposed beta-adrenergic action of isoflurane is of potential importance in reversing blockade and increasing myocardial oxygen consumption. The choice of propranolol was dictated by the fact that it is the only beta-adrenergic blocking agent available for clinical use in the United States. Propranolol, besides being a beta-adrenergic blocker, has a quinidine-like action that produces myocardial depression. The consequences of the combination of isoflurane anesthesia and a “pure” beta-adrenergic blocking agent might therefore be somewhat different.

The use of basal anesthesia (chloraloseurethane) allowed us to evaluate the response to the addition of isoflurane anesthesia in the presence of an established beta blockade. Since the basal anesthesia was present in both groups, they may be considered to have had comparable starting points. There is the possibility that chloraloseurethane itself may be a beta-adrenergic blocking agent. However, the administration
of 2 \( \mu g \) isoproterenol in the control periods produced an average 30 per cent increase in heart rate. This same response was produced after the addition of isoflurane, but not after propranolol had been administered. Thus, any such effect of the basal anesthetic would not interfere with interpretation of the results. The responses of the basally anesthetized animal to isoflurane are similar in most respects to those reported for normal human volunteers—the only exceptions being in heart rates and stroke volumes. Isoflurane did not increase, but rather decreased, blood pressure and systemic vascular resistance. Propranolol likewise did not produce a decline in heart rate, although others have reported that as much as 2 mg/kg may be necessary to produce this effect in dogs.\textsuperscript{16}

In these experiments, the addition of propranolol during isoflurane administration produced a decline in ventricular performance, as evidenced by the increase in pulmonary capillary wedge pressure in the face of unchanged systemic vascular resistance and stroke volume. The lack of increase in systemic vascular resistance might indicate occupation of the peripheral beta-adrenergic receptors by isoflurane.

The combination of isoflurane and propranolol produced the lowest cardiac outputs and stroke volumes in this study. When isoflurane was added to the beta-adrenergically-blocked dog, blood pressure, cardiac output, and stroke volume decreased, without change in ventricular filling pressure, evidence of a decline in cardiac performance. Thus, we have not been able to demonstrate a cardiac beta effect in these experiments.

However, while the addition of isoflurane to the beta-blocked dog did not decrease systemic vascular resistance, when it was discontinued systemic vascular resistance increased. Conversely, the administration of propranolol first produced an increase in systemic vascular resistance, but not in the presence of isoflurane. The isoflurane would appear to be exerting an inhibitory effect upon constriction of the peripheral resistance bed. These findings suggest, though do not prove, a peripheral beta stimulating action of isoflurane.

Since propranolol is said to produce similar adrenergic blockades of peripheral and cardiac beta receptors,\textsuperscript{9} it is somewhat puzzling that cardiac performance is depressed when isoflurane and propranolol are combined. Possibly this is related to the membrane activity of propranolol, or to a combination of membrane depression produced by propranolol with myocardial depression by isoflurane that overcomes any beta stimulation produced by isoflurane.\textsuperscript{11} Alternately, it is possible that the primary beta-adrenergic action, if any, produced by isoflurane is on the resistance bed, and the previously reported changes in heart rate are secondary to the decrease in blood pressure consequent to the reduction of systemic vascular resistance, rather than central beta stimulation.

The present data were obtained employing profound beta-adrenergic blockade and only one concentration of isoflurane. It is possible that less complete beta blockade, as is frequently employed clinically, and other concentrations of isoflurane might demonstrate the presence of a cardiac beta sympathomimetic effect.

References

Respiration

PULMONARY FUNCTION AFTER LUNG RESECTION After pneumonectomy about 30 to 50 per cent of patients adapt well to the decreased breathing surface and the restricted pulmonary circulation. Adaptation is accomplished in two ways: oxygen demands must be decreased, or there must be maximal utilization of ventilation, gas exchange, and pulmonary perfusion. Eight patients, aged 46 to 55 years, who had, preoperatively, no essential change in pulmonary function, were studied. When their status was tested three to four years after pneumonectomy, alveolar ventilation at rest had increased by 43 per cent. On breathing hypoxic mixtures (14, 16, and 14 per cent oxygen), pneumonecomized patients reacted as do acclimatized mountainers at 4,000-5,000-meter altitudes: ventilation increased and \( P_{A}O_{2} \) fell to 28-33 mm Hg. This resulted in slightly elevated alveolar oxygen tensions (\( P_{A}O_{2} \)) of 108-117 mm Hg. At rest, \( P_{A}O_{2} \) was low-normal, but during exercise it decreased significantly in 6 of 8 patients. \( P_{A}O_{2} \) at rest was definitely lower than the relatively high \( P_{A}O_{2} \) would suggest, and could be compared to a \( P_{A}O_{2} \) of healthy patients at an altitude of 3,000 meters. Ventilation rose by 30 to 50 per cent, while perfusion increased by 100 per cent, resulting in a \( V_{A}/Q_{c} \) quotient of 0.4 instead of 0.8. At rest, \( Q_{c} \) (pulmonary capillary blood flow) amounted to 4-5.2 l/min after pneumonectomy, with a capillary blood volume of 30 to 40 ml. This resulted in a “contact time” of about 0.44 to 0.6 seconds.

\[
\text{Contact time} = \frac{\text{capillary blood volume in } l \times 60}{\text{capillary blood flow in } l/min}
\]

During work, \( Q_{c} \) rose more than the \( V_{c} \) (pulmonary capillary blood volume), resulting in a decrease of contact time. Normal controls usually have a contact time of about 0.74 seconds; pneumonectomized patients at rest, 0.44 seconds, and during exercise, 0.36 to 0.30 seconds. This will be significant if \( P_{A}O_{2} \) falls simultaneously (usually by 6-8 mm Hg). At rest, only the changed \( V/Q \) ratio will be responsible for a lowered \( P_{A}O_{2} \); with exercise, a shortened contact time will contribute considerably to a low \( P_{A}O_{2} \). At rest, the pulmonary circulation was usually well adapted after pneumonectomy. During work, however, there was a significant rise in mean pulmonary arterial pressure with increased pulmonary blood flow amounting to about twice the value in controls. Resistance likewise was higher in normal controls. During work, the resistance in the pulmonary vascular bed was significantly reduced both in normal controls and in pneumonectomized patients. This serves to explain the capacity of many a pneumonectomized patient to be able to work. Such conditions can conceivably be predicted preoperatively by occluding one pulmonary artery with a balloon catheter. (Daum, S.: Adaption of the Pulmonary Circulation and Gas Exchange following Pneumonectomy, Pneumonologik 147:187-193, 1972.) ABSTRACTER’S COMMENT: “Contact time,” or exposure time of pulmonary capillary blood to alveolar air, is an interesting concept.