Effects of Halothane on Left Ventricular Function and Distribution of Regional Blood Flow in Dogs and Primates

By Stephen F. Vatner and N. Ty Smith

ABSTRACT

Left ventricular and regional vascular effects of halothane were assessed in dogs and primates in which coronary, mesenteric, renal, and iliac blood flows, arterial blood pressure, left ventricular diameter and pressure, dD/dt (i.e., the velocity of myocardial fiber shortening), and dP/dt were continuously measured in the control resting state, while the conscious animals were breathing O\textsubscript{2}, and during halothane-O\textsubscript{2} anesthesia maintained at 1% or at 2% for 90 minutes (separate experimental days). Halothane caused a concentration-dependent depression of myocardial contractility: \((dP/dt)/P\) fell 68 ± 5% during 2% halothane anesthesia and left ventricular end-diastolic diameter rose. Halothane also caused a redistribution of regional blood flows. At a concentration of 1% halothane, the most intense vasodilatation occurred in the renal bed (renal resistance fell 46 ± 5%), but mesenteric resistance rose (42 ± 15%). With 1% halothane regional vascular resistances tended to rise with time, but with 2% halothane regional blood flows rose with time. A direct vasodilating action of halothane was observed following direct intra-arterial injection of the drug. Probably this action was responsible for the renal and iliac vasodilatations and for the opposition to the metabolically induced vasoconstriction in the coronary bed. Thus, the administration of the most commonly employed potent inhalation anesthetic, halothane, substantially alters myocardial contractility and regional blood flows and resistances. These effects are, in many instances, a function of the concentration of the anesthetic and the duration of its administration.

KEY WORDS

<table>
<thead>
<tr>
<th>iliac flow</th>
<th>anesthesia</th>
<th>renal flow</th>
<th>baboon</th>
<th>mesenteric flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>myocardial contractility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Halothane is one of the most commonly employed general anesthetics in clinical practice, yet the extent to which it alters myocardial contractile state, ventricular function, and regional distribution of blood flow and vascular resistance is still controversial. This controversy has resulted in part because the response to halothane appears to depend on the drug's concentration (1-4), the duration of its administration (1-5), and the precision and extent to which ventilation is controlled (3, 4). Moreover, many earlier studies of the drug's effects have been conducted in isolated muscle (4, 6-9) or in previously anesthetized preparations (10-16) in which the control state has been altered by the general anesthetic's effects on the cardiovascular system. General anesthesia alters the normal responses of the myocardium and the regional circulations to a variety of physiological interventions and pharmacologic agents (17-22) and thus might affect the normal reactions to another pharmacologic agent, halothane. Prior studies using conscious animals and man as controls have been limited by the inability to measure regional flows directly and continuously (4, 23-27). Furthermore, in these studies the interpretation of control values has been complicated by the failure to give 100% oxygen (O\textsubscript{2}) during the control periods (4, 23-27) (even though O\textsubscript{2} was administered with halothane), or by the addition of a preanesthetic or nitrous oxide (4, 24-27). Nitrous oxide, although a weak anesthetic agent, can have a profound effect on the pharmacologic pattern of other agents (4, 28).

The present investigation was designed to circumvent these difficulties. Cardiovascular effects of halothane were studied in healthy, conscious dogs and primates instrumented for direct, continuous measurements of left ventricular diameter, dD/dt (i.e., the velocity of myocardial fiber shor-
Statham P23Db manometer. Blood flow was measured and was confirmed by calibration when the animal was described in detail previously (29, 30). The flowmeter with an ultrasonic Doppler flowmeter, which has been calibrated against aorta. In three dogs, using 2% lidocaine anesthesia, a polyethylene 90 catheters were implanted in the mesenteric and renal arteries, and pressure catheters were inserted in the aorta. In two additional dogs, these latter dogs had heparin-filled Tygon catheters implanted in their aorta. In two mongrel dogs (24-35 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv). A thoracotomy in the fifth left intercostal space, several instruments were implanted. Miniature Konigsberg P2 pressure gauges were inserted snugly against the left ventricular wall through a stab wound in the apex (five dogs). Ultrasonic diameter transducers were implanted on opposing endocardial surfaces of the left ventricle (five dogs). Doppler ultrasonic flow transducers were placed around the left circumflex coronary artery (four dogs), stimulator electrodes were sutured to the left ventricle (three dogs), and heparin-filled Tygon catheters were chronically implanted in the thoracic aorta (five dogs). Using sodium pentobarbital anesthesia (30 mg/kg, iv) and a midline laparotomy, Doppler ultrasonic (six dogs, one baboon [Papio anubis], and one chimpanzee [Anthropopithecus troglodytes]) or Statham SP2200 electromagnetic (one dog) flow probes were placed around the mesenteric, renal, and iliac arteries. Two dogs had both Doppler and electromagnetic flow transducers placed on their left renal artery. All seven of these latter dogs had heparin-filled Tygon catheters implanted in their aorta. In two additional dogs, polyethylene 90 catheters were implanted in the mesenteric and renal arteries along with flow probes on these arteries, and pressure catheters were inserted in the aorta. In three dogs, using 2% lidocaine anesthesia, a catheter was passed retrograde from a branch of the femoral artery to the left iliac artery in the region of the previously implanted flow probes.

In the canine experiments arterial blood pressure was measured using the previously implanted heparin-filled Tygon catheter and a Statham P23Db strain-gauge manometer, but in the primate experiments arterial blood pressure was measured with the miniature pressure gauges, which were calibrated in vivo against a Statham P23Db manometer. Blood flow was measured with an ultrasonic Doppler flowmeter, which has been described in detail previously (29, 30). The flowmeter has a reliable zero reference; in these experiments electrical-zero blood flow was determined repeatedly and was confirmed by calibration when the animal was killed. The relationship between velocity, as measured by the Doppler flowmeter, and volume flow is linear as long as the cross-sectional area of the blood vessel within the transducer remains constant. This linear relationship between velocity and volume flow has been demonstrated previously and confirmed by timed collections of blood flow (30). At autopsy, it was observed that the vessels were firmly attached to the flow transducers through a fibrous scar which minimized the changes in the cross-sectional area of the vessel within the transducers. In three dogs an electromagnetic flowmeter was used to measure renal blood flow. In these experiments, which involved peripheral flow measurements, zero flow was determined by inflating a previously implanted hydraulic occlusion cuff.

Left ventricular pressure was measured with the implanted miniature pressure gauges which were calibrated against a Statham P23Db strain-gauge manometer. An improved ultrasonic transit-time dimension gauge was used to measure left ventricular diameter (31); it measures the transit time of acoustic impulses traveling at the sonic velocity of approximately 1.5 X 10^5 mm/sec between 5- or 3-MHz piezoelectric crystals sutured to the left ventricular endocardium at opposing sites. The dimension gauge was calibrated by substituting signals of known time duration from a calibrated pulse generator. A voltage proportional to transit time was recorded and calibrated in terms of crystal separation. In this manner, a measure of the internal diameter of the left ventricle was continuously recorded. At a constant temperature the drift of the instrument was less than 0.15 mm/hour, and its frequency response was flat to 60 Hz.

The experiments were conducted 2-6 weeks postoperatively when the animals had recovered from surgery and were again vigorous and healthy. While the unsedated conscious dogs were resting quietly, control records of left ventricular pressure (P), left ventricular diameter (D), the rate of change of diameter (dD/dt), left ventricular pressure, dP/dt, arterial blood pressure, and heart rate were obtained with the dogs breathing room air and then with them breathing 100% O2 through a mask. In the dogs in which coronary flow was measured, cardiac frequency was raised using a Medtronic Instruments electronic stimulator to a rate of 130 beats/min for 1 minute at rest and again at various points during anesthesia. In the primates the control recordings were made before and after a dissociative agent, phencyclidine hydrochloride (1 mg/kg, im) was administered to tranquilize the animal. Halothane (2-5%) was then administered to induce anesthesia in all animals. After the anesthetic state was sufficiently deep, the animals were intubated and ventilated mechanically with a Harvard Apparatus respirator; the level of halothane in O2 was adjusted to achieve an end-tidal concentration of 1% or 2%. End-tidal halothane was measured with a Beckman LB-2 infrared analyzer. The readout was digital to three places, and the response time was 80 msec. The instrument was calibrated before each experiment by injecting liquid

\footnote{Construction details available from the authors.}

\footnote{Circuit diagrams available from the authors.}
halothane into a volumetric flask with a Hamilton microliter syringe. Concentrations used were 0.5, 1.0, 2.0, and 3.0%. The calibration was linear. After the desired end-tidal concentration had been achieved, the animal was maintained on this halothane-O₂ mixture for 90 minutes. At this point the concentration was rapidly altered to achieve the alternate desired end-tidal concentration and held for 20 minutes until a steady state was reached. This sequence was repeated the next week reversing the order of end-tidal concentrations. Arterial blood gas measurements using a Radiometer blood gas system (PHM 72, PH 4933, BM 5-3) indicated that arterial oxygen tension (P O₂) ranged from 541 to 586 mm Hg. Ventilation was adjusted to 3.5-3.8% CO₂ (26.6-28.9 mm Hg). By doing so, arterial pH and carbon dioxide tension (P CO₂) could be maintained at values close to control.

In the dogs with arterial catheters implanted in a renal, mesenteric, or iliac artery, halothane was dissolved in 1.0 ml of the animal’s own blood and administered intra-arterially during the conscious state. These injections were repeated after beta-receptor blockade was tested with histamine (1-2 mg/kg, iv), cholinergic blockade with atropine (0.1-0.3 mg/kg, iv), local alpha-receptor blockade with phentolamine (0.5-1.0 mg/kg, ia), and histaminergic blockade with tripelemamine (1-2 mg/kg, iv), individually or in combination. Beta-receptor blockade was tested with isoproterenol (0.1 μg, ia), cholinergic blockade was tested with acetylcholine (10 μg, ia), alpha-receptor blockade was tested with norepinephrine (1 μg, ia), and histaminergic blockade was tested with histamine (1 μg, ia).

Data were recorded on a multichannel tape recorder and played back on a direct-writing oscillograph at a paper speed of 100 mm/sec. A cardiometer, triggered by the signal from the pressure pulse, provided instantaneous, continuous records of heart rate. Electronic resistance-capacitance filters with a 2-second time constant were used to derive mean arterial blood pressure and mean regional blood flow. Mean regional vascular resistances were calculated as the quotients of mean arterial blood pressure and the appropriate regional blood flow. Late diastolic coronary resistance was calculated as the quotient of late diastolic arterial blood pressure and late diastolic coronary blood flow. Continuous records of dP/dt and dD/dt were derived from the left ventricular pressure and diameter signals, using Philbrick operational amplifiers connected as differentiators having frequency responses of 60 and 30 Hz, respectively. A triangular wave signal with known slope was substituted for pressure and diameter signals for the direct calibration of the dP/dt and dD/dt channels.

The effects of halothane on myocardial force-velocity relationships were assessed by determining the velocity of shortening and the intraventricular pressure at an identical ventricular diameter (isolength point) with a technique described in detail previously (18, 21, 32). All isolength points were obtained during the first one-third of ejection. In addition, the effects on peak dP/dt and the quotient of dP/dt and developed pressure (left ventricular isovolumic pressure minus end-diastolic pressure), i.e., (dP/dt)/P, were examined. The same level of pressure which occurred during isometric contraction, before and after each intervention, was used for this calculation, and dP/dt and intraventricular pressure were determined at that level of pressure. This technique for evaluating the myocardial contractile state has also been described in detail previously (18, 21, 33).

Results

Measurements recorded during halothane-O₂ anesthesia were compared with values recorded while the animal was breathing O₂ in the conscious state (Tables 1 and 2). The first point chosen for measurements during anesthesia represented the maximal decline in arterial blood pressure, which occurred 5-15 minutes after the desired end-tidal concentration had been reached and was designated the early response. The next point, 20 minutes after the desired end-tidal concentration had been established, was designated the steady-state response, since it is known that halothane has equilibrated in the central nervous system at this point (4, 35, 36). A midpoint was chosen which occurred 45 minutes after the early response. The late response occurred 90 minutes after the early response; the difference between these two points represents the effect of time.

EFFECTS OF OXYGEN IN CONSCIOUS DOGS AT REST

Heart rate fell from 78 ± 5 (SE) to 72 ± 4 beats/min (P < 0.05). The changes in arterial and left ventricular pressures and left ventricular diameter and velocity were not significant, but dP/dt and (dP/dt)/P fell from 3,310 ± 40 to 2,970 ± 150 mm Hg/sec and from 43 ± 4 to 38 ± 3 sec⁻¹, respectively (P < 0.05). Late diastolic coronary resistance rose from 1.68 ± 0.09 to 1.92 ± 0.10 mm Hg/ml min⁻¹ (P < 0.05), but the changes in mesenteric, renal, and iliac flows and resistances were not significant.

EFFECTS OF 1% AND 2% HALOTHANE

Arterial Pressure.—With 1% halothane, mean arterial blood pressure fell from 102 ± 4 to 62 ± 4 mm Hg and rose (P < 0.01) with time to 86 ± 7 mm Hg (Fig. 1). When concentration was changed to 2% after the late response, pressure fell (P < 0.01) to 61 ± 6 mm Hg. With 2% halothane, mean arterial blood pressure fell more (P < 0.05) from 100 ± 4 to 48 ± 3 mm Hg, then rose significantly with time to 62 ± 4 mm Hg, and rose further to 90 ± 5 mm Hg when concentration was changed to 1%. Thus, 2% halothane produced significantly greater (P < 0.05) arterial blood pressure...
TABLE 1

Left Ventricular Dynamic Effects of Halothane

<table>
<thead>
<tr>
<th></th>
<th>Halothane</th>
<th>Conscious O2 control</th>
<th>Early response (Δ Control)</th>
<th>Steady-state response (Δ Control)</th>
<th>Midpoint response (Δ Control)</th>
<th>Late response (Δ Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>76 ± 5</td>
<td>25 ± 9†</td>
<td>18 ± 7†</td>
<td>12 ± 5</td>
<td>8 ± 5†</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>68 ± 4</td>
<td>34 ± 6†</td>
<td>53 ± 11†</td>
<td>49 ± 7†</td>
<td>49 ± 7†</td>
<td></td>
</tr>
<tr>
<td>Left ventricular pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>118 ± 6</td>
<td>−30 ± 4†</td>
<td>−29 ± 4†</td>
<td>−23 ± 4†</td>
<td>−21 ± 4†</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>117 ± 4</td>
<td>−52 ± 5†</td>
<td>−50 ± 4†</td>
<td>−46 ± 4†</td>
<td>−43 ± 4†</td>
<td></td>
</tr>
<tr>
<td>Iso</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>115 ± 7</td>
<td>−30 ± 4†</td>
<td>−30 ± 4†</td>
<td>−23 ± 4†</td>
<td>−20 ± 4†</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>114 ± 4</td>
<td>−52 ± 5†</td>
<td>−49 ± 4†</td>
<td>−46 ± 4†</td>
<td>−42 ± 4†</td>
<td></td>
</tr>
<tr>
<td>EDP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>8 ± 1</td>
<td>−2 ± 1</td>
<td>−2 ± 1</td>
<td>0 ± 1</td>
<td>1 ± 1†</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>8 ± 1</td>
<td>−2 ± 1</td>
<td>−2 ± 1</td>
<td>0 ± 1</td>
<td>1 ± 1†</td>
<td></td>
</tr>
<tr>
<td>Left ventricular diameter (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>33.4 ± 2.7</td>
<td>−2.5 ± 0.3†</td>
<td>−2.5 ± 0.3†</td>
<td>−1.1 ± 0.2†</td>
<td>−0.8 ± 0.2†</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>32.9 ± 2.4</td>
<td>−1.2 ± 0.9</td>
<td>−0.9 ± 0.9</td>
<td>0.8 ± 0.8</td>
<td>1.7 ± 0.5†</td>
<td></td>
</tr>
<tr>
<td>End-systolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>27.0 ± 2.7</td>
<td>−1.5 ± 0.3†</td>
<td>−1.5 ± 0.3†</td>
<td>−0.6 ± 0.3</td>
<td>−0.3 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>26.3 ± 2.4</td>
<td>2.1 ± 0.6†</td>
<td>2.6 ± 0.8††</td>
<td>3.2 ± 0.9†</td>
<td>5.4 ± 0.9††</td>
<td></td>
</tr>
<tr>
<td>Peak dP/dt (mm Hg/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>2970 ± 150</td>
<td>−1200 ± 200†</td>
<td>−1180 ± 200†</td>
<td>−110 ± 170†</td>
<td>−1010 ± 190†</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>2960 ± 100</td>
<td>−1990 ± 100†</td>
<td>−1990 ± 100†</td>
<td>−1900 ± 120†</td>
<td>−1890 ± 120†</td>
<td></td>
</tr>
<tr>
<td>(dP/dt)/P (sec⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>38 ± 4</td>
<td>−15 ± 4†</td>
<td>−15 ± 4†</td>
<td>−14 ± 4†</td>
<td>−14 ± 4†</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>38 ± 3</td>
<td>−26 ± 4†</td>
<td>−26 ± 4†</td>
<td>−25 ± 4†</td>
<td>−25 ± 4†</td>
<td></td>
</tr>
<tr>
<td>Iso</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>67 ± 5</td>
<td>−15 ± 3†</td>
<td>−14 ± 3†</td>
<td>−14 ± 3†</td>
<td>−13 ± 3†</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>64 ± 4</td>
<td>−38 ± 4†</td>
<td>−38 ± 3†</td>
<td>−37 ± 4†</td>
<td>−37 ± 4†</td>
<td></td>
</tr>
</tbody>
</table>

All values are means ± SE; Iso = isoletharg and EDP = end-diastolic pressure; Δ = change from.

*Change significant from conscious O2, P < 0.05.
†Late response significantly different from early response, P < 0.01.
‡Change significant from conscious O2, P < 0.01.
§Response at 2% significantly different from response at 1%, P < 0.05.
¶Late response significantly different from early response, P < 0.05.
‖Response at 2% significantly different from response at 1%, P < 0.01.

Heart Rate.—With 1% halothane, heart rate increased from 76 ± 5 to 101 ± 10 beats/min during the early period and then fell (P < 0.05) to 84 ± 6 beats/min during the later period (Fig. 1). When concentration was changed to 2% at this point, heart rate rose (P < 0.05) to 122 ± 9 beats/min. With 2% halothane, heart rate rose from 68 ± 4 to 102 ± 7 beats/min, increased (P < 0.01) with time to 117 ± 6 beats/min (Fig. 1), and fell (P < 0.05) to 90 ± 6 beats/min when concentration was changed to 1%. The midpoint and later heart rate increases were significantly greater (P < 0.01) than those that occurred with 1% halothane. Thus, 2% halothane tended to cause greater increases in heart rate, most likely due to the lower arterial blood pressure and the greater reflex drive.

Left Ventricular Pressure.—Peak and isoletharg left ventricular pressures changed in similar fashion to mean arterial blood pressure at both concentrations. With 1% halothane, left ventricular end-diastolic pressure fell (P < 0.01) from 8 ± 1 to 5 ± 1 mm Hg, rose (P < 0.05) with time to 7 ± 1 mm Hg, and then rose further to 8 ± 1 mm Hg (P < 0.01) when concentration was changed to 2%. Left ventricular end-diastolic pressure at 2% halothane fell from 8 ± 1 to 6 ± 1 mm Hg, rose (P < 0.01) with time above control to 9 ± 1 mm Hg, and then fell to 7 ± 1 mm Hg when concentration was changed to 1% halothane.

Diameter.—With 1% halothane, left ventricular...
end-diastolic diameter fell from 33.4 ± 2.7 to 30.9 ± 2.6 mm (Fig. 1), gradually rose (P < 0.05) with time to 32.6 ± 2.6 mm, and increased (P < 0.05) to 33.9 ± 2.3 mm when concentration was changed to 2%. Left ventricular end-systolic diameter fell (P < 0.05) from 27.0 ± 2.7 to 25.5 ± 2.7 mm, rose slightly but not significantly with time, and then increased (P < 0.05) from 26.7 ± 2.8 to 30.2 ± 2.6 mm when concentration was changed to 2%. With 2% halothane, left ventricular end-diastolic diameter fell from 32.9 ± 2.4 to 31.7 ± 1.7 mm, rose with time (P < 0.01) above control to 34.6 ± 2.0 mm (Fig. 2), and fell slightly to 33.0 ± 1.8 mm when concentration was changed to 1%. Only the late response was significantly different from that with 1% halothane. Left ventricular end-systolic diameter rose from 26.3 ± 2.4 to 28.4 ± 2.2 mm, increased (P < 0.05) slightly to 31.1 ± 2.3 mm with time, and fell (P < 0.01) to 27.5 ± 1.8 mm with the concentration change to 1%. Increases in end-systolic diameter were all greater (P < 0.01) at 2% than they were at 1% halothane.

**Contractility.**—With 1% halothane, peak dP/dt fell (P < 0.01) from 2,970 ± 150 to 1,770 ± 150 mm Hg/sec (Fig. 1), rose slightly with time, and then fell (P < 0.01) to 930 ± 100 mm Hg/sec when concentration was changed to 2%. The changes in (dP/dt)/P and peak and isolength velocity followed a similar pattern (Table 1). With 2% halothane, the myocardial depressant effects were greater (P < 0.05) than they were with 1% halothane (Fig. 1). Peak dP/dt fell from 2,960 ± 100 to 970 ± 130 mm Hg/sec, rose slightly (P < 0.05) to 1,070 ± 165 mm Hg/sec with time, and then increased (P < 0.01) further to 1,750 ± 170 mm Hg/sec when concentration was changed to 1%. The responses for (dP/dt)/P and peak and isolength velocity were similar (Table 1).

** Coronary Bed.**—Since significant reverse flow during systole may have occurred during halothane-induced hypotension, late diastolic coronary flow and resistance were used to assess the coronary dynamic effects of halothane. With 1% halothane, late diastolic flow fell from 41 ± 3 to 29 ± 3 ml/min (P < 0.05) and rose slightly (NS) with time. Late diastolic resistance decreased slightly (NS) from a control of 1.91 ± 0.12 mm Hg/
ml min⁻¹ and rose slightly with time (Fig. 1). With 2% halothane, late diastolic coronary flow fell from 40 ± 3 to 26 ± 3 ml/min. Late diastolic coronary resistance fell from 1.93 ± 0.10 to 1.82 ± 0.16 mm Hg/ml min⁻¹ with 2% halothane (Fig. 1). With heart rate constant, coronary resistance rose slightly (NS) with 2% halothane. These changes at 2% were not significantly different from those at 1%. Thus, halothane's tendency to dilate the coronary bed was offset by a reduction in myocardial metabolic demand, which tends to constrict the coronary bed.

**Mesenteric Bed.**—With 1% halothane, flow fell (P < 0.01) from 289 ± 21 to 128 ± 21 ml/min (Fig. 3), rose slightly but not significantly with time, and fell slightly but not significantly with change in concentration. Calculated resistance rose (P < 0.05) from a control value of 0.37 ± 0.03 to 0.52 ± 0.07 mm Hg/ml min⁻¹, rose further (P < 0.05) to 0.66 ± 0.06 mm Hg/ml min⁻¹ with time (Fig. 1), and fell (P < 0.05) when concentration was changed to 2%. With 2% halothane, flow fell by an amount similar to that observed with 1% halothane, and, likewise, the changes with time and concentration were not significant. However, the mesenteric resistance response was significantly different at 2% (Fig. 1); resistance failed to rise during the early responses and did not change significantly with time. However, when concentration was changed to 1%, mesenteric resistance rose slightly (P < 0.05) (Fig. 3). Thus, halothane produced similar reductions in mesenteric flow at both concentrations, but with 2% halothane resistance was not elevated since arterial blood pressure had
Measurements of phasic left ventricular (LV) diameter, velocity, and pressure and of diastolic pressure, dP/dt, and heart rate during conscious O2 control (left) and during 2% halothane (right). Note that left ventricular diameter increased substantially during halothane anesthesia from the early to the late response.

Typical response of phasic and mean arterial pressures, mesenteric flow, heart rate, and calculated mean mesenteric resistance to halothane. Note that mesenteric flow was depressed to a similar extent at both 1% and 2%, but mesenteric resistance was elevated much more at 1%.
fallen by a greater amount. The mesenteric bed was the only bed which responded with constriction, and this response only occurred with 1% halothane.

**Renal Bed.**—Renal flow, $169 \pm 11 \text{ ml/min}$, did not change significantly with 1% halothane, with time, or with change in concentration (Fig. 1). Calculated renal resistance fell ($P < 0.01$) from $0.61 \pm 0.05$ to $0.34 \pm 0.04 \text{ mm Hg/ml min}^{-1}$, rose ($P < 0.05$) with time to $0.55 \pm 0.08 \text{ mm Hg/ml min}^{-1}$ (Fig. 1), and fell ($P < 0.05$) to $0.33 \pm 0.05 \text{ mm Hg/ml min}^{-1}$ when concentration was changed to 2%. With 2% halothane, flow fell slightly but not significantly and did not change significantly with time or concentration (Fig. 1). Renal resistance fell with 2% halothane as it did with 1% halothane (Fig. 4); however, unlike the response at 1%, renal resistance failed to increase with time. Thus, there was significantly more ($P < 0.05$) dilation at the midpoint and the last point with 2% halothane. Thus, the renal bed responded with the greatest dilation of all the beds studied.

**Iliac Bed.**—With 1% halothane, iliac flow, $114 \pm 8 \text{ ml/min}$, did not change significantly. Iliac resistance fell ($P < 0.05$) from $0.93 \pm 0.10$ to $0.69 \pm 0.13 \text{ mm Hg/ml min}^{-1}$ (Fig. 1), rose slightly ($P < 0.05$) with time to $0.84 \pm 0.11 \text{ mm Hg/ml min}^{-1}$, and fell slightly when concentration was changed to 2%. With 2% halothane, flow fell ($P < 0.05$) from $119 \pm 6$ to $76 \pm 17 \text{ ml/min}$, rose ($P < 0.05$) with time to $95 \pm 16 \text{ ml/min}$, and rose further ($P < 0.05$) when concentration was changed to 1%. Iliac resistance fell as it did with 1% halothane but failed to rise with time (Fig. 1). The changes in iliac flow and resistance were not significantly different with 1% and 2% halothane (Table 2).

In summary, 1% halothane depressed myocardial contractility and produced a differential effect on regional resistance (Fig. 5). Dilatation occurred to a greater extent in the renal and to a lesser extent in the iliac bed. Little change occurred in the coronary bed, but the mesenteric bed responded with significant constriction. The major circulatory adaptation that occurred with prolonged 1% halothane anesthesia was an increase in resistance in the regional beds, but regional flows showed little change. Since heart rate fell and stroke volume, as estimated from changes in left ventricular diameter, rose slightly, cardiac output appeared to
CARDIOVASCULAR EFFECTS OF HALOTHANE

remain roughly constant with time, corroborating the findings of little change in regional flows with time. Moreover, 2% halothane caused more marked cardiac depression and also produced a differential pattern on regional resistances (Fig. 5). Dilatation was again most intense in the renal bed and least intense in the mesenteric bed. In contrast to the findings with 1% halothane, the major circulatory adaptation to prolonged 2% halothane anesthesia was an increase in flow to the regional beds, but regional resistances changed little with time. The increases in regional flows with time correlated with the increases in cardiac output that appeared to occur since heart rate and stroke volume, as estimated from left ventricular diameter measurements, increased with time.

DIRECT INTRA-ARTERIAL ADMINISTRATION OF HALOTHANE

When halothane, 0.1 ml, was dissolved in 10 ml of blood and administered in a bolus of 1 ml to the mesenteric, renal, or iliac beds, it caused a striking increase (+156%) in flow without affecting pressure. This increase in flow persisted with intraarterial administration of halothane after beta-receptor blockade with propranolol, alpha-receptor blockade with phentolamine, cholinergic blockade with atropine, and histaminergic blockade with tripelennamine (Fig. 6).

RESULTS IN THE BABOON AND CHIMPANZEE

Effects of Phencyclidine Hydrochloride.—In the dissociated state, heart rate increased from 64 to 98 beats/min, mean arterial blood pressure rose from 92 to 112 mm Hg, mesenteric and renal flows changed little, and mesenteric and renal resistance rose by 18% and 21%, respectively.

Effects of 100% O2.—Heart rate decreased to 90 beats/min, and mean arterial blood pressure and renal and mesenteric resistances all fell slightly on administration of 100% O2.

Effects of Halothane.—With 1% halothane, mean arterial blood pressure decreased by a maximum of 50 mm Hg at the early point and rose toward control, reaching a value of 68 mm Hg at the late response. Heart rate changed little. Mesenteric flow decreased by 65% and was 61% below control at the late response, but renal flow did not change significantly at the early response and was 6% below control at the late response. Mesenteric resistance had increased by 49% at the early point and by 56% at the late point; renal resistance had decreased by 45% at the early point and by 56% at the late point. Thus, the response to 1% halothane for arterial blood pressure, mesenteric and renal flows, and mesenteric and renal resistances were essentially the same in the dogs and the primates. The effects on heart rate were different, probably due to the tachycardiac effects of phencyclidine.

Discussion

General anesthesia alters the normal cardiovascular responses to a variety of physiological (17–19) and pharmacologic (20–22) interventions.
These alterations may be in part due to the unknown influences of the general anesthetic agent on the cardiovascular system. The goal of this study was to elucidate the manner in which the cardiovascular system of the normal, healthy, conscious animal is altered by halothane, the most commonly employed potent inhalation agent in clinical anesthesia. It must be mentioned, however, that halothane is often administered to patients in association with another anesthetic or after premedication; under these conditions, the effects of halothane may well be different from those reported in the present study which was conducted in conscious, unpremedicated dogs.

Although most previous studies have indicated that halothane has a negative inotropic effect (4, 6, 7), the extent to which halothane depresses myocardial contractility is difficult to determine from studies in previously anesthetized animals or isolated papillary muscle preparations. In the present study, one of the most striking effects of halothane was its marked depression of myocardial contractility as evidenced by marked reductions in peak dP/dt, (dP/dt)/P, and the force-velocity relationship; these reductions were clearly concentration dependent. An additional indication of halothane's cardiac depressant action was observed with the passage of time. At a constant concentration of halothane, end-diastolic diameter tended to rise; in fact, it increased above preanesthesia control levels with 2% halothane. The elevation of end-diastolic diameter with time with 2% halothane might have been underestimated, since heart rate was significantly elevated, a factor which is known to decrease cardiac size (19).

The reductions in contractility evidenced by the reductions in systolic left ventricular pressure (−45%) and velocity (−64%) at isoleth length and those in (dP/dt)/P (−68%) at constant heart rate suggest a considerable fall in myocardial oxygen consumption (37−39) and a considerable rise in coronary resistance, since coronary vascular resistance is directly dependent on myocardial oxygen requirements (37−39). However, late diastolic coronary resistance did not rise significantly above control values obtained with or without atrial pacing, indicating that halothane probably acts to dilate the coronary bed directly and that this action opposes the tendency toward constriction caused by the reduction in myocardial oxygen demand.

Halothane produced a differential effect on regional vascular resistances (Fig. 5): the most prominent vasodilatation occurred in the kidney, and none occurred in the mesenteric bed. This finding may be in part due to the kidney's well-developed autoregulatory mechanisms (40). However, autoregulatory theory indicates that, following a fall in arterial blood pressure, flow rises towards control after an initial fall. In many of these experiments, renal flow remained above control even during the maximal fall in pressure (Fig. 4).

The response of the renal bed to halothane is still controversial. The prevailing concept is derived from studies utilizing the para-aminohippurate (PAH) method of measuring renal flow; these studies have found a marked reduction in PAH clearance and they have concluded that marked renal vasoconstriction (4, 24, 41, 42) or little change (27) occurs. Other studies utilizing more direct techniques have indicated that renal vasodilatation occurs (4, 14, 23). The present study also indicated that the renal bed was dilated by halothane. Since a similar renal vasodilatation was observed in the primates as well as in the dogs in this investigation and since renal constriction was observed in dogs as well as in man with the PAH method (42), the difference between the results of the present study and those indicating intense renal vasoconstriction (4, 24, 41, 42) is probably not due to species differences. It is more likely that the difference is due to the techniques employed. If halothane and its consequent hypotension alter the renal extraction of PAH or redistribute renal flow away from the peritubular capillary network, then the PAH technique can be a misleading indicator of renal blood flow.

To determine the direct effects of halothane, the drug was administered intra-arterially to the regional beds through indwelling arterial catheters in conscious dogs. Halothane caused striking increases in flow in the iliac (Fig. 6), renal, and mesenteric beds in the absence of a change in arterial blood pressure, suggesting a direct dilating action. The fact that beta- and alpha-receptor blockade as well as cholinergic and histaminergic blockade failed to prevent the dilatation (Fig. 6) further supports the hypothesis that halothane acts to dilate the peripheral vessels directly. However, it should be pointed out that the concentrations of halothane used in the intra-arterial injection studies were far greater than those attained in the experiments in which halothane was administered by inhalation.

Despite halothane's direct action to dilate peripheral vessels including the mesenteric vessels, the mesenteric bed did not dilate with 2% halothane and actually reacted with significant

Circulation Research, Vol. XXXIV, February 1974
Cardiovascular Effects of Halothane

Vasoconstriction with 1% halothane in the primates and the dogs. There are several possible mechanisms to explain this finding. Halothane releases vasopressin (8, 9) and also tends to activate baroreceptor reflexes because it induces a drop in arterial blood pressure; this drop would in turn elicit reflex vasoconstriction. The results of this study suggest that the mesenteric bed is most sensitive to these effects induced by halothane hypotension and that this bed is less sensitive to its direct vasodilator action. Relevant to this point are the findings that reflex vasoconstriction in response to hypotension induced by a variety of low-output states are most intense in the mesenteric and least intense in the renal bed (43). The fact that mesenteric constriction was less at 2% halothane indicates that the central reflex mechanisms may have been depressed by the anesthetic (17) or that the direct vasodilating action of halothane is greater.

Halothane’s action on the cardiovascular system is a complex synthesis of its direct depressant effects on the heart and peripheral resistance vessels and the multiple cardiovascular regulatory mechanisms which are brought into play by the halothane-induced hypotension, low cardiac output, and central nervous system effects. It is therefore understandable that considerable controversy exists as to halothane’s “cardiovascular effects.” It is apparent from the present study that the left ventricular and regional vascular effects of halothane are not only different depending on concentration but also are quite different at the same concentration over an extended period of time. One explanation for the changes observed with time, in particular the rise in peripheral resistance observed at 1% halothane, may well be reflex circulatory adjustment to the prolonged hypotension and the low cardiac output. This gradual rise in regional resistances with time was not apparent at 2% halothane, again suggesting that reflex control of the circulation was further depressed and virtually ineffective.

The circulatory adjustments that occurred with time in response to halothane appeared to be different at the two concentrations studied. During light anesthesia (1% halothane), the regional resistances rose with time, but no consistent pattern was observed for regional blood flows. With prolonged deep halothane anesthesia (2%), a different pattern emerged; regional blood flows rose with time as did heart rate and stroke volume estimated from changes in left ventricular dimensions. The findings at 2% halothane are consistent with observations in man which indicate that cardiac output rises with duration of halothane administration (1–5). The results of the present study indicate that this rise in cardiac output is shared by the mesenteric, renal, and iliac beds. The results of the present study are also consistent with the hypothesis that the major circulatory adjustment to prolonged light anesthesia in which reflex control is impaired to a lesser extent is an increase in regional vascular resistances, but when reflex control is further depressed, as in deep halothane anesthesia, autoregulation of cardiac output occurs, an effect noted by Granger and Guyton (44) in animals without neural vascular control.

Thus, the results of the present study indicate that halothane exerts a variety of effects on the cardiovascular system. The nature of these effects has important clinical application, since halothane is the most commonly employed potent inhalation anesthetic. Moreover, the results of these experiments are also of physiological importance, since classical experimental design in anesthetized preparations does not generally attribute importance to the administration of the general anesthetic. Halothane causes a marked depression of myocardial contractility, to the extent that the Frank-Starling mechanism is activated and an increase in end-diastolic cardiac size occurs. In addition, halothane produces a differential pattern of change in regional blood flows and resistances: dilatation occurs in the coronary bed and is countered by metabolic vasoconstriction, more pronounced dilatation occurs in the iliac bed, the most intense dilatation occurs in the renal bed, and the mesenteric circulation is least affected by the direct vasodilator action of halothane and actually responds with substantial constriction during light anesthesia. Renal vasodilation and mesenteric vasoconstriction were observed in the primates as well as in the dogs. The difference between the results of the present study and those reported previously can be explained in part by the ability to measure blood flows, pressures, and cardiac dimensions directly and continuously from the conscious state to the halothane-anesthetized state without the complicating influences of prior preanesthetics or general anesthesia. In addition, the present study took into account the effects of time; the passage of time produces substantial changes which have been generally disregarded previously.

Acknowledgment

We acknowledge the technical assistance of T. Manders, D.
P. McKown, and F. Werner and the help in preparation of the manuscript from V. Fowler. The generous supplies of propranolol from the Ayerst Company and phentolamine from the Ciba Company are appreciated. We are also grateful for the encouragement and advice of Drs. A. C. Barger and E. Braunwald.

References


Circulation Research, Vol. XXIV, February 1974


