Left Ventricular Function in Conscious Man and during Halothane Anesthesia

H. Sonntag, M.D.,* U. Donath, M.D.,† W. Hillebrand, M.D.,† R. G. Merin, M.D.,‡ J. Radke, M.D.†

The effect of halothane on left ventricular (LV) function in healthy, nonmedicated patients before operation was studied. Using local anesthesia, with the aid of fluoroscopy, catheters were placed in the left ventricle, thoracic aorta and pulmonary artery. Thermodilution cardiac output derivatives and left ventricular pressure indices were measured awake and during anesthesia with halothane, 0.9 and 1.8 per cent (end-tidal). Ventilation was controlled to maintain PaCO2 and pH at the awake values. Dose-dependent decreases in cardiac index (3.96 → 3.48 → 2.86 l/min/m²), stroke volume index (50.1 → 44.6 → 38.5 ml/m²), LV dP/dtmax [1.440 → 1.200 → 1.000 mm Hg/sec], dP/dtmax/IP (20.7 → 17.0 → 15.0 sec⁻¹), cardiac work (11.76 → 5.13 → 5.52 × 10² mm Hg/ml/min/kg), and mean aortic pressure (MAP) (94 → 80 → 69 mm Hg), without change in heart rate or systemic vascular resistance (SVR). Preload (LVEDP) and afterload (MAP and SVR) changes could not account for the demonstrated depression in ventricular function. Thus, in man, as in the dog, halothane has a direct depressant effect on LV function. (Key words: Anesthetics, volatile, halothane; Heart, cardiac output; Heart, contractility; Heart, myocardial function; Heart, vascular pressures.)

To quantitate ventricular function in the intact animal, not only must an adequate technique for measurement be used, but the factors known to influence function must be considered.¹ Heart rate, preload and afterload exert important effects on all presently used methods of estimating ventricular function both in vitro and in the intact animal. Although these factors may be accurately controlled in the isolated cardiac muscle preparation, it is usually difficult to accomplish this in the intact animal, particularly when that animal is man. However, when all pertinent modalities are measured, knowledge of the directional changes documented in lower animals makes possible interpretations of results observed in man.²

Although there have been some reasonably satisfactory studies of the effects of halothane on left ventricular performance in animals,³⁴ only one study in which left ventricular pressures were measured in man has been reported.⁵ Filner and Karliner measured pulmonary-artery-occluded pressures in a group of volunteers. However, by design, their subjects were premedicated, anesthesia was induced with thiopental, and succinylcholine was given to facilitate tracheal intubation. We now report the first direct study of the effects of two concentrations of halothane on left ventricular performance in healthy man, with documentation of the major modifying factors as outlined above.

Methods

Nine healthy patients scheduled for saphenous vein ligation or repair of severed peripheral nerves were studied. None showed evidence of cardiac disease. Ages of the patients ranged from 27 to 64 years (mean 36). Average body weight was 73.8 kg (60–90). All patients consented to participate in the investigation after being thoroughly informed about its experimental nature.§

All patients had fasted for more than 8 hours. In order to exclude possible effects of other drugs, no premedication was given. Intravenous fluids were given only to equalize blood losses. A Swan-Ganz catheter was inserted through the right brachial vein and placed in the pulmonary artery. A catheter with a micro-tip manometer was introduced through the left femoral artery and placed in the left ventricle. A 7F Goodale-Lubin catheter (USCI- Inc.) was inserted through the left brachial artery into the thoracic aorta.

Analysis of oxygen saturation and hemoglobin concentration (CO-Oximeter 182, Instrumentation Laboratories) and determinations of P02, P CO2, pH, bicarbonate, and base excess (Astrup, Radiometer) were carried out before and after each hemodynamic measurement. Cardiac output was measured fivefold using the thermodilution technique (Model 9510 Cardiac Output Computer, Edwards Laboratories).⁶ Electrocardiogram, phasic and electronically integrated mean

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Table 1. Summary of Results in Conscious Man and during Halothane Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Control (Awake) N = 9</th>
<th>Halothane Anesthesia (End-tidal Vol Per Cent) 0.9 ± 0.1</th>
<th>Halothane Anesthesia (End-tidal Vol Per Cent) 1.8 ± 0.2</th>
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<tr>
<td></td>
<td>SEM</td>
<td>SEM</td>
<td>SEM</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>78</td>
<td>3</td>
<td>76</td>
</tr>
<tr>
<td>Cardiac index (l/min m²)</td>
<td>3.98</td>
<td>0.34</td>
<td>3.48*</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>50.1</td>
<td>4.7</td>
<td>44.6*</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>94</td>
<td>3</td>
<td>80*</td>
</tr>
<tr>
<td>Maximum rate of rise of left ventricular pressure dP/dtmax (mm Hg/sec)</td>
<td>1,440</td>
<td>50</td>
<td>1,200</td>
</tr>
<tr>
<td>dP/dtmax/IP (sec⁻¹)</td>
<td>20.7</td>
<td>1.2</td>
<td>17.7</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>11</td>
<td>0.3</td>
<td>12</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg.min⁻¹.kg⁻¹)</td>
<td>0.97</td>
<td>0.07</td>
<td>0.96</td>
</tr>
<tr>
<td>Heart work (p syst.·HMOV/kg) (mm Hg·m·min⁻¹.kg⁻¹)</td>
<td>11,757</td>
<td>2,708</td>
<td>8,152*</td>
</tr>
<tr>
<td>Hemoglobin (g/100 ml)</td>
<td>14.6</td>
<td>0.5</td>
<td>14.2</td>
</tr>
<tr>
<td>SaO₂ (per cent)</td>
<td>96.5</td>
<td>0.8</td>
<td>96.9</td>
</tr>
<tr>
<td>Pao₂, art. (mm Hg)</td>
<td>93</td>
<td>3</td>
<td>105</td>
</tr>
<tr>
<td>Paco₂, art. (mm Hg)</td>
<td>38</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>pHi</td>
<td>7.40</td>
<td>0.02</td>
<td>7.40</td>
</tr>
<tr>
<td>Base excess (mEq/l)</td>
<td>-2.2</td>
<td>0.2</td>
<td>-1.7</td>
</tr>
</tbody>
</table>

* P < 0.05.

Aortic pressure (Statham P 23 Db), left ventricular pressure (Micro-tip TM PC 350, Millar Instruments), dP/dt, and CO₂ concentration in the expired air (Uras MT, Hartmann and Braun) were recorded simultaneously on a six-channel UV-recorder (C. H. F. Muller/Philips). Left ventricular end-diastolic pressure and mean aortic diastolic pressure were obtained from the recordings. Systemic vascular resistance was calculated as the quotient of mean aortic pressure and cardiac output/kg; heart work as the product of mean systolic aortic pressure and cardiac output/kg.

After a rest period, measurements were made with the patient awake breathing room air. Anesthesia was induced with halothane in increasing concentration by means of a mask. The trachea was intubated during halothane anesthesia without succinylcholine or topical anesthesia. Ventilation was controlled with an Engström respirator to keep end-expired carbon dioxide concentration near awake levels. Halothane was vaporized from a Dräger vaporizer in nitrogen, 70 per cent, and oxygen, 30 per cent. During administration of high concentrations of halothane, oxygen concentration was increased to 50 per cent. End-tidal halothane concentrations were measured by ultraviolet analysis (Narkometer, Hartmann and Braun). Two concentrations of halothane were studied, 0.9 and 1.8 per cent end-tidal. Hemodynamic measurements during anesthesia were made after 15-20 min of stable end-tidal halothane concentration before the start of the surgical procedure.

All data were statistically evaluated. Mean values (ř) and standard errors of the mean (SEM) were calculated. Significant differences were examined at the 5 per cent level by analysis of variance (Kruskal-Wallis).7

Results

Control (awake) data were in the normal range (table 1). Heart rate did not change essentially at any stage of the investigation, while cardiac index decreased from 3.98 to 3.48 and 2.86 l/min·m² (fig. 1). Stroke volume index also decreased, from 50.1 to 44.6 and 38.5 ml/m². There was a significant decrease in aortic pressure (systolic aortic pressure decreased from 123 to 88 mm Hg) (P < 0.01).

The maximum rate of rise in left ventricular pressure during isometric contraction (dP/dtmax) was significantly diminished, from 1,440 to 1,200 and 1,000 mm Hg/sec. The quotient dP/dtmax/IP also decreased, from 20.7 to 17.7 and 15.0/sec. Left ventricular end-diastolic pressure (LVEDP) increased significantly, from 11 to 12 and 14 mm Hg. Systemic vascular resistance (SVR) remained essentially unchanged. Heart work was significantly decreased, from 11,757 to 8,152 and 5,524 mm Hg·ml/min·kg.

Among the other variables measured, only Pao₂ increased, as a result of the higher inspired oxygen concentration during administration of high concentrations of halothane.

Discussion

Halothane produced dose-dependent depression of the "muscle" (dP/dt) function and "pump" (CI and
SVI) function of the heart in this study. Heart rate did not change. The increase in left ventricular end-diastolic pressure (a preload estimate) should have increased both "pump" and "muscle" function through the Frank-Starling mechanism. Since this did not happen, obviously preload could not have been responsible for the decrease in ventricular function in this study. Afterload effects are complex. The estimate of "muscle" function used in this study, $\frac{dP}{dt_{\text{max}}}$, may be directly proportional to afterload changes, although other investigators report little influence, especially when left ventricular end-diastolic pressure does not change in the same direction. In addition, the relationship between $\frac{dP}{dt}$ and developed pressure in the left ventricle, $\frac{dP}{dt_{\text{max}}}/P$, was also markedly decreased by halothane. This modification of $\frac{dP}{dt}$ is less influenced by both preload and afterload. Calculated systemic vascular resistance was unchanged by halothane, so afterload influence on "pump" function should not have been a factor.

Halothane has been shown to produce similar effects on $\frac{dP}{dt_{\text{max}}}$ when compared with awake values in the dog. However, increased heart rate compensated for the effect at low anesthetic concentrations, so that "pump" function was not depressed. The only reported study of the effect of halothane on left ventricular $\frac{dP}{dt}$ in man was relatively uncontrolled. Halothane dosage was semiquantitatively, as were effects on respiration. The patients were heavily premedicated, and not enough time was allowed for equilibration of the anesthetic. Nevertheless, the changes were similar to those reported in this study. The well-controlled experiments of Eger et al. demonstrated a qualitatively similar decrease in "pump" function with increasing concentrations of halothane, but there was no reasonable measure of left ventricular preload. Quantitatively, their changes were greater, with more depression of aortic pressure and cardiac output, although the end-tidal halothane concentrations were not identical to those used in this study. Eger et al. used the IJ wave of the ballistocardiogram to estimate left ventricular function. This noninvasive technique has been shown to correlate with left ventricular $\frac{dP}{dt}$ in man. As with the "pump" indices, the ballistocardiogram in the study of Eger et al. indicated considerably more depression than did the left ventricular pressure indices in our investigation. There were also several design differences between the two studies. Eger et al. used oxygen as the carrier gas for halothane, while nitrogen, 70 per cent, and oxygen, 30 per cent, were used for halothane, 0.9 per cent, and nitrogen, 50 per cent, and oxygen, 50 per cent, for halothane, 1.8 per cent, in this study. However, there is some evidence that oxygen increases the cardio depressant effect of halothane. Eger's subjects were volunteers, not patients, and were trained to accept intermittent positive-pressure breathing during the awake measurements. Again, however, this maneuver would be expected to decrease the cardio depressant effects, not increase them. The demonstrated effect of
Fig. 2. Schematic presentation of the factors derived from hemodynamic variables that affect oxygen consumption. In the lower half are shown factors that have little influence above, factors with greater influence. The dotted lines show the effects of various hemodynamic values on E2 and E3 (modified from Kettler8 with permission of the author). Changes in the hemodynamic values in response to halothane are indicated by the arrows.

The duration of anesthesia to lessen the cardio-depressant effect of halothane again would work in the opposite direction, as these studies were short-term. Thus, the only explanation we are left with for the lesser effects of similar halothane concentrations is the different subject population, that is, German patients versus American volunteers. In addition, although it is not stated in the report, the volunteers in the study of Eger et al. were all male (N. T. Smith, personal communication), whereas four of the nine patients in this study were female.

The work of Filiner and Karliner showed even more depression of "pump" function than that seen by Eger et al. They hypothesized that prior drug administration (diazepam, thiopental, succinylcholine) might have left residual effects. Until the present work, theirs was the only controlled study where left heart filling pressures were examined. Pulmonary-artery wedge or occluded pressure approximates left ventricular end-diastolic pressure during most circumstances, unless there is mitral-valve disease or a marked pulmonary vascular derangement. They chose to examine left ventricular function by measuring systolic time intervals. Reitan and Smith have shown that systolic time intervals correlate well with aortic blood flow acceleration in the dog.16 Although the latter has often been described as a "load-independent" measure of left ventricular performance, in fact, the documentation is incomplete. As Filiner and Karliner pointed out, there is considerable evidence that systolic time intervals are sensitive to both preload and afterload. In view of this, it is particularly surprising that halothane, 1.47 per cent end-tidal, produced no change in systolic time intervals compared with 1.05 per cent, as aortic pressure and cardiac index were significantly changed. It seems unlikely that the small but significant increase in pulmonary-artery-occluded pressure could be responsible for this effect. Rather, the sensitivity of the measure of systolic time intervals must be suspect, as the authors suggested.

Although halothane produced vasodilation in some organs in previous studies,18,16 the sum of earlier findings together with the results of this study strongly...
indicates that the predominant cardiovascular effect of halothane is a dose-dependent depression of ventricular function. We would agree with the conclusion of Pryse-Roberts et al. based on their experiments in dogs. In man as well, "the halothane depressed ventricle is characterized by a failure to empty rather than a failure to fill."11

Bretschneider et al. have produced a "complex hemodynamic parameter" with which left ventricular oxygen consumption can be calculated from hemodynamic measurements.17 Correlation with measured ventricular oxygen consumption was good in dogs (r = 0.85).16 Table 2 shows the additive parts of the formula. In normal cardiac working conditions the basal myocardial O2 consumption (E0) is of little importance (only 10 per cent) for myocardial oxygen demand, as are the electrophysiologic processes at the cell membrane (E1, only 8 per cent) and the inactivation of the contractile system (E2, only 1 per cent). Therefore, the discussion may be restricted to the parts E2 and E3. The energy demand of the systolic wall tension (E2) and the tension development during isometric contraction (E3) together account for 75–80 per cent of total myocardial energy demand.

In the upper part of figure 2 the influences of some hemodynamic modalities on E2 and E3 can be seen. Systolic wall tension can be calculated from the end-systolic and the maximal systolic pressure. dP/dtmax is determined by the inotropic state of the myocardium. Left ventricular end-diastolic pressure reflects "preload," and the aortic pressure is used for "afterload." Heart rate influences dP/dtmax by the mechanism of "frequency inotropism."18 During halothane anesthesia, E0, E1, and E2 either do not change at all or change at most only slightly. End-systolic volume and the systolic wall tension were not determined under the experimental conditions used. They can only be estimated by the marked decrease of systolic pressure. In our investigation all other factors were diminished by halothane, except left ventricular end-diastolic pressure, which increased. The overall effect would be a marked decrease in myocardial oxygen consumption, as has been documented to occur in dogs.4,18 It only remains now to confirm this calculation in man.

In summary, halothane produced dose-dependent depression of left ventricular function in healthy patients. The effects are remarkably similar to those previously seen in chronically instrumented dogs except for the lack of increase in heart rate.4,14 Calculated myocardial oxygen consumption appeared to change in the same fashion as well, although actual measurement is necessary to prove this.

References

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