Effects of Halothane on Left Ventricular Relaxation and Early Diastolic Coronary Blood Flow in the Dog


The effects of graded concentrations of halothane on left ventricular relaxation and phasic coronary blood flow (CBF) were studied in six open-chest, anesthetized dogs. Global and regional left ventricular function were measured. Besides the expected dose-dependent depression of contractility, regional shortening, and cardiac output, halothane caused significant increases in the time constant of relaxation ($T_{max}$), and decreased and delayed the nadir of peak negative left ventricular dP/dt. Dose-dependent reductions of CBF were noted. Percentage CBF during isovolumic relaxation was significantly reduced and showed a strong inverse correlation with $T_{max}$. Halothane appears to interfere with the inactivation process of the heart; this in turn may impede the early rise in CBF during isovolumic relaxation. (Key words: Anesthetics, volatile: halothane. Heart, blood flow: diastolic. Heart, left ventricle: relaxation.)

ALTHOUGH the effects of potent volatile anesthetic agents on systolic ventricular function have been extensively studied,1–8 little attention has been paid to their effects on diastolic ventricular function, especially left ventricular relaxation. Numerous studies have emphasized relaxation abnormalities in hypertrophic cardiomyopathies and in ischemic heart disease,4–8 and in the ischemic and hypertrophic heart, relaxation of the ventricle may be impaired long before contraction abnormalities appear.9 Thus, it has become increasingly evident that diastolic behavior significantly influences cardiac performance. Relaxation is defined as the process by which the heart returns to a precontractile configuration, and there are several major determinants of relaxation including inactivation and loading. In intact hearts, the four major loading parameters of relaxation include deformation during contraction, alterations of impedance late in ejection, the LaPlace relationship, and filling of the coronary reservoir.10 Filling of the coronary arteries starts during isovolumic relaxation and acts as an intramural compressive force on the relaxing cardiac muscle fibers.10 However, previous studies did not include measurement of phasic coronary blood flow (CBF). This study was designed to examine the effect of halothane on left ventricular (LV) relaxation and to explore the relationship between this effect and CBF.

The hypotheses to be tested were that: 1) halothane increases the time constant of isovolumic relaxation and 2) prolongation of the duration of isovolumic relaxation is associated with a disproportionate decrease in CBF during that part of the cardiac cycle.

Methods

Experiments were conducted in six mongrel dogs weighing between 15 and 20 kg. The dogs were premedicated with morphine sulphate 1.5 mg/kg, and anesthesia was induced with thiopental 15 mg/kg. Following tracheal intubation, the lungs were mechanically ventilated (tidal volume 40 ml/kg, rate 12 breaths/min), and anesthesia was maintained with 1.0–1.5% halothane in a mixture of oxygen (33%) in nitrogen with sufficient carbon dioxide to maintain normocarbia. Muscle relaxants were not used. The heart was exposed via a left lateral thoracotomy through the fifth intercostal space and suspended in a pericardial cradle. After removal of the fat pad at the root of the aorta, an electromagnetic flow transducer (SEM 230®, SE Laboratories, Feltham, United Kingdom) was placed around the vessel. The left anterior descending coronary artery was dissected free distal to the second major diagonal branch, and a 3.0 Dacron thread was placed loosely around the artery so that occluded zero flow could be determined. An electromagnetic flow transducer (SEM 230, SE Laboratories) of appropriate diameter was placed around the vessel proximal to the occluder. The low pass filter of the electromagnetic flowmeter was set at 10 Hz.

Left ventricular and aortic pressures were measured with fluid-filled catheters (8F, 2.76 mm outside diameter, Portex Ltd, Hythe, Kent, United Kingdom) attached to Druck strain-gauge pressure transducers (Druck Ltd, Groby, Leicester, United Kingdom). The LV pressure signal was fed to an analog differentiator to derive positive and negative LV dP/dtmax. The amplitude–frequency response of the catheter–transducer system was evaluated before and after completion of the study and found to be flat (±5%) to 36 Hz, with a resonant frequency at 150 Hz, the phase angle being linear with frequency. These characteristics allow faithful reproduction of LV pressure and its first derivative.11 Two pairs of piezoelectric crystals were implanted at subendocardial level approximately 10

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mm apart in the minor axis of the heart for assessment of regional myocardial function by sonomicrometry. One pair of crystals was located in an area supplied by the left anterior descending coronary artery (LAD) and another in an area supplied by the left circumflex coronary artery (LC), as seen in figure 1. Throughout the study, sodium chloride (0.9%) was administered intravenously at a rate of 4 ml·kg⁻¹·min⁻¹.

Hemodynamic variables and segment length signals were recorded on a Mingograf 81 eight-channel recorder (Elena Schoander, Stockholm, Sweden) and a seven-channel magnetic tape recorder (Store 7 DS, Racal Recorders Ltd., Southampton, United Kingdom). A 1-h period of stabilization was allowed after surgical preparation of the animal was complete.

**Determination of T_{relax}**

Weiss et al.¹² showed that the time course of LV pressure fall under isovolumic conditions is exponential and can be characterized by a time constant (T), or T_{relax}. To derive T_{relax}, high-fidelity recordings of LV pressure were analyzed at 4-9s intervals from the time of cessation of aortic flow to the time (before mitral valve opening) when LV pressure reached a value of 10 mmHg greater than the LV end-diastolic pressure (LVEDP) of the previous beat (fig. 2). The end of isovolumic relaxation is defined by the crossover point of left atrial and LV pressures.¹³ If this point is not determined experimentally, an arbitrary value 10 mmHg above LVEDP has been used.¹⁴ As Yellin et al.¹⁴ have shown that the pressure decline is monoeponential down to approximately 15 mmHg, we have used an end-point 10 mmHg above LVEDP.

Whereas some studies have used peak negative dP/dt as the beginning of the isovolumic period in calculating T_{relax}⁵,¹⁵,¹⁶ others have estimated T_{relax} from various times before¹²,¹⁷ and after¹⁸ peak negative LV dP/dt. Because in this study aortic flow was measured, the beginning of isovolumic relaxation could be accurately determined at the cessation of flow in the aorta. T_{relax} was derived by regression analysis of the logarithms of instantaneous values of pressure against time. The goodness of fit is evidenced by r² values ≥0.99 for all the curves used in this study. This value is similar to that reported by Kumada et al.⁵.

**Determination of Phasic Coronary Blood Flow**

The phasic CBF signal for each cardiac cycle was analyzed and volume flow for each period (systole, diastole,

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and isovolumic relaxation) determined by planimetry (fig. 5). The isovolumic phase was measured from the time of cessation of aortic flow to the time when LV pressure was 10 mmHg above the LVEDP of the previous beat; this coincides with the period during which T_{relax} is calculated. Total diastolic period was measured from the time of cessation of aortic flow to the upslope of the LV dP/dt signal. Systolic flow was measured during the time from the upslope of LV dP/dt until cessation of aortic flow.

End-diastolic length (EDL) was measured at the beginning of the upslope of LV dP/dt. End-systolic length (ESL) was measured at the time aortic blood flow returned to zero. Percent systolic shortening was calculated as the difference between EDL and ESL divided by EDL, and expressed as percent. The time of LV dP/dt_{max} (−) was measured as the interval between the return of aortic flow to zero (end-systole) and the nadir of LV dP/dt.

**Protocol**

The halothane challenges were carried out by increasing the inspired halothane concentration in steps of 0.5% from 0.7% to 2.2%. This corresponds to alveolar concentrations of 0.4%, 0.85%, 1.30%, and 1.75% as determined by refractometry in four of the studies. Recordings were obtained after 15 min at each concentration of halothane. The concentration of halothane was then returned to 0.7%, and additional recordings obtained after 30 min. Only end-expiratory beats were analyzed to standardize the data and eliminate the influence of artificial ventilation.

**Statistical Evaluation**

The dose–response data were analyzed using two-way analysis of variance followed by Duncan’s multiple range test. P values less than 0.05 were considered statistically significant. Student’s paired t tests were used to compare the first and second stages at 0.7% halothane and the effect of decreasing the halothane concentration from
2.2% to 0.7%. All values are expressed as mean ± SEM. Where appropriate, data were subjected to linear regression analysis using the least squares method.

Results

Hemodynamic Data

Heart rate and LVEDP remained unchanged, whereas systolic pressure, LV dP/dt max, aortic blood acceleration, and cardiac output decreased significantly with increasing halothane concentrations (table 1). Halothane caused dose-dependent reductions in LV dP/dt max (−) and increases in T relax. The nadir of LV dP/dt occurred significantly later at the highest halothane concentration. A dose-dependent increase in end-diastolic length was seen in both LAD and LC segments, although this became significant only with the highest concentration of halothane. Percent systolic shortening decreased significantly in both...
TABLE 1. Effects of Graded Increases in Halothane Concentration on the Circulation in 6 Dogs

<table>
<thead>
<tr>
<th>Variable</th>
<th>0.7</th>
<th>1.2</th>
<th>1.7</th>
<th>2.2</th>
<th>0.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspired halothane (%)</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>113 ± 11</td>
<td>108 ± 9</td>
<td>108 ± 8</td>
<td>113 ± 6</td>
<td>114 ± 12</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>98 ± 5</td>
<td>85 ± 3*</td>
<td>75 ± 2*</td>
<td>58 ± 0.5</td>
<td>42.2 ± 0.7†</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>5.0 ± 0.5</td>
<td>4.8 ± 0.5</td>
<td>5.0 ± 0.4</td>
<td>5.8 ± 0.5</td>
<td>67.0 ± 7.7†</td>
</tr>
<tr>
<td>CPP (mmHg)</td>
<td>65.8 ± 4.5</td>
<td>54.8 ± 2.9*</td>
<td>47.8 ± 2.7*</td>
<td>36.0 ± 1.2*</td>
<td>42.2 ± 0.7†</td>
</tr>
<tr>
<td>LV dp/dtmax (+) (mmHg/s)</td>
<td>1,675 ± 110</td>
<td>1,333 ± 71*</td>
<td>942 ± 52*</td>
<td>683 ± 60*</td>
<td>1,720 ± 137†</td>
</tr>
<tr>
<td>Aortic blood acceleration (ml/sec)</td>
<td>4,802 ± 729</td>
<td>3,964 ± 604*</td>
<td>2,839 ± 524*</td>
<td>2,275 ± 320*</td>
<td>4,019 ± 311†</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>1.84 ± 0.3</td>
<td>1.53 ± 0.2*</td>
<td>1.30 ± 0.2*</td>
<td>1.05 ± 0.1*</td>
<td>1.56 ± 0.14†</td>
</tr>
<tr>
<td>LV dp/dtmax (-) (mmHg/s)</td>
<td>1,575 ± 114</td>
<td>1,408 ± 111</td>
<td>1,125 ± 77*</td>
<td>855 ± 62*</td>
<td>1,680 ± 146*</td>
</tr>
<tr>
<td>Tmax (ms)</td>
<td>29.0 ± 1.5</td>
<td>51.1 ± 2.1*</td>
<td>34.8 ± 2.0*</td>
<td>42.5 ± 1.9*</td>
<td>29.7 ± 1.5†</td>
</tr>
<tr>
<td>Time of LV dp/dtmax (-) (ms)</td>
<td>9.3 ± 0.8</td>
<td>9.7 ± 0.8</td>
<td>12.7 ± 1.7</td>
<td>20.0 ± 3.0*</td>
<td>8.8 ± 1.4†</td>
</tr>
<tr>
<td>LAD segment EDL (mm)</td>
<td>12.07 ± 0.40</td>
<td>11.87 ± 0.36*</td>
<td>12.18 ± 0.38*</td>
<td>12.27 ± 0.40*</td>
<td>11.96 ± 0.31</td>
</tr>
<tr>
<td>% Shortening</td>
<td>19.6 ± 2.2</td>
<td>17.4 ± 2.0</td>
<td>14.1 ± 1.7*</td>
<td>10.3 ± 1.8*</td>
<td>19.2 ± 1.0†</td>
</tr>
<tr>
<td>LC segment EDL (mm)</td>
<td>12.15 ± 1.10</td>
<td>12.17 ± 1.11</td>
<td>12.37 ± 1.15*</td>
<td>12.50 ± 1.14*</td>
<td>11.46 ± 1.10</td>
</tr>
<tr>
<td>% Shortening</td>
<td>14.9 ± 2.5</td>
<td>13.1 ± 2.0</td>
<td>11.8 ± 1.6*</td>
<td>10.2 ± 1.4*</td>
<td>14.1 ± 2.8†</td>
</tr>
</tbody>
</table>

Values are given as mean ± SEM.  
* Significantly different from 0.7% halothane (P < 0.05).  
† Significantly different from 2.2% halothane (P < 0.05).  

segments as the halothane concentration increased. When the halothane concentration was returned to 0.7%, all hemodynamic variables returned to their control level, with the exception of aortic blood acceleration, which remained significantly depressed.

CORONARY FLOW

Total coronary blood flow (CBF) decreased in a dose-dependent manner and was only 51% of control at the highest halothane concentration (table 2). Systolic and diastolic CBF as percentages of the total flow remained unchanged, representing between 22% and 27%, and 73% and 79% of total flow, respectively. CBF during the isovolumic period, expressed as a percentage of total diastolic flow, declined significantly as the halothane concentration increased (fig. 4). CBF and its phase-related components returned to control when the halothane concentration was reduced to 0.7%.

Discussion

The negative inotropic effect of halothane is well known and well described in humans and in experimental models.3,19 However, there has been little work assessing the effect of halothane on diastolic LV function. A few studies have examined solely diastolic events in terms of the passive pressure-volume and pressure-diameter relationships at end-diastole. Brower and Merin10 reported a significant decrease in LV compliance following the introduction of a low concentration of halothane (0.6% end-tidal) in the swine. However, increasing the halothane to medium (1.05% end-tidal) and high (1.6% end-tidal) concentrations did not cause additional decreases in compliance. The authors concluded that the effect of the low concentration of halothane was probably due to the deepening of anesthesia rather than an effect of halothane per se. In a study involving total cardiopulmonary bypass, Moores et al.20 observed a significant increase in end-diastolic pressure at a given end-diastolic volume with as little as 0.5% inspired halothane. However, Van Trigt et al.21 found that halothane did not modify ventricular compliance in chronically instrumented dogs. Similarly, recent studies by Greene and Gerson22 concluded that halothane did not affect LV compliance. However, end-diastolic events may be less sensitive to the effects of interventions, such as deepening of halothane.
Fig. 4. Values for total CBF (○), and flow during isovolumic relaxation (●) showing that the reduction of flow during isovolumic relaxation was greater than that of total flow as the concentration of halothane increased. Each point represents the mean (bar SEM) of six experiments.

Anesthesia, than is early LV relaxation. Indeed, during the last decade, the role of ventricular relaxation as a determinant of cardiac function has been emphasized.

In a variety of pathologic conditions ranging from myocardial ischemia and hypertrophic cardiomyopathies to LV failure, abnormalities of ventricular relaxation may occur before systolic function and compliance are substantially disrupted.

In this study, we found that the time constant of LV pressure decline and the time to the nadir of LV dP/dt were prolonged by halothane indicating that isovolumic relaxation was impaired. Because many authors have determined end-systole and beginning of isovolumic relaxation in respect of the nadir of LV dP/dt, using a fixed time interval before or after this point, it is important to stress that halothane delayed the nadir of LV dP/dt in a dose-dependent manner. Determination of end-systole using a fixed time interval before or after the nadir of LV dP/dt may introduce errors when inhalational anesthetics are administered. Many factors are known to affect early relaxation. Previous studies have shown that large variations of heart rate modify $T_{\text{relax}}$, but in this study heart rate remained essentially unchanged and therefore could not have influenced $T_{\text{relax}}$. Preload may also influence LV relaxation. However, in this study LVEDP remained unchanged irrespective of the halothane concentration, and the increases in end-diastolic length were of small magnitude and unlikely to have influenced $T_{\text{relax}}$. Furthermore, recent studies have shown that modest increases in preload do not influence $T_{\text{relax}}$.

Systolic arterial pressure is another determinant of LV isovolumic relaxation, and a linear relationship has been observed between $T_{\text{relax}}$ and systolic arterial pressure. In this study, halothane caused a significant reduction of systolic arterial pressure. This would have caused a decrease and not an increase in $T_{\text{relax}}$. Therefore, the increase in $T_{\text{relax}}$ must be due to the effect of halothane itself and not simply to the effect of halothane on heart rate, preload, or systolic pressure.

The significant inverse correlation between isovolumic CBF and the time constant of LV pressure decline (fig. 5) suggests a close association between these variables. Halothane may have exerted its primary effect either on relaxation on or CBF, which is one of the extrinsic determinants of LV relaxation. As blood flows from the aorta into the coronary vascular tree, wall thickness increases by as much as 10% in humans and 25% and the difference in wall thickness between the extremes of complete coronary occlusion and reactive hyperemia may be as large as 25% in dogs. Increases in wall thickness due to the rapid filling of the coronary arteries augment the intramyocardial pressure, and this augmentation of the total load facilitates relaxation.

Halothane selectively decreased early CBF. This may be the cause of the delayed isovolumic relaxation. However, most studies of the effects of halothane on the coronary circulation have shown that halothane does not interfere with its overall local regulation and, indeed, in this study halothane did not alter the ratio of systolic or diastolic to total CBF. Therefore, it is unlikely that halothane exerted a direct effect on the coronary vasculature and much more likely that halothane exerted its effect on the inactivation process of cardiac contraction rather than on the extrinsic determinants of relaxation.

Fig. 5. A significant inverse relationship is demonstrated between $T_{\text{relax}}$ and CBF during isovolumic relaxation expressed as a percentage of diastolic flow. Each point represents the mean (bar SEM) of six experiments.

$r = 0.984$
HALOTHANE PROLONGS LEFT VENTRICULAR RELAXATION

The reduction in early CBF may be a consequence rather than the cause of delayed relaxation. In contrast to the results from this study, Housmans and Murat have observed that halothane, enflurane, and isoflurane accelerate the time course of isometric relaxation in isolated ferret papillary heart muscles. This acceleration of relaxation can be interpreted as a reduction in load sensitivity, with relaxation becoming load-insensitive at the higher anesthetic concentrations. The discrepancy between delayed relaxation in the intact dog heart and accelerated relaxation in the ferret papillary heart muscle may relate to species differences, to the marked difference in rate of stimulation, and to the difference between preload and peak developed force (or pressure) between the two models. Housmans and Murat proposed that the decreased load sensitivity may result from a relative insufficiency of calcium-sequestering systems, a reduced affinity of troponin C for calcium, or an altered responsiveness of the myofibrils to calcium.

Inactivation depends upon the active transport of calcium ions away from the troponin to the sarcoplasmic reticulum. The systolic calcium concentration may remain abnormally high (and relaxation abnormally slow or incomplete) when the calcium pump fails, when calcium leaks from the sarcoplasmic reticulum, when the myocytes are unable to extrude the excess calcium, or when the affinity of the troponin for calcium is excessive. Although most investigations of the biochemical basis of halothane’s effect on the heart have been undertaken because of its negative inotropy, it is likely that alterations in calcium ion fluxes within the myoplasm or across the sarcoplasm are responsible for the effect of halothane on LV isovolumic relaxation. Indeed, in voltage-clamp preparations of isolated guinea pig myocytes, Terrar and Victory have shown that halothane decreases both the second inward current across the sarclemma and the tail current that represents the calcium-stimulated current within the myocytes. These reductions in calcium fluxes would be expected to impair both systolic and diastolic function. Whereas previous studies have examined either systolic or late diastolic function, this study has shown that halothane exerts marked effects on both contraction and early relaxation in the intact heart. The effect on early relaxation may be a physiologic correlate of the disruption of sarcoplasmic reticular function.

The implications of the negative “lusitropic” (a term introduced by Smith and Katz to describe diastolic relaxation properties), as well as the negative inotropic effect on the heart are as follows: prolonged relaxation as indicated by reduced isovolumic pressure decline means that tension in the myocardium has not properly dissipated at the time rapid filling begins. The sustained tension may not only adversely affect filling but can also increase oxygen demand. The delayed inactivation appears to prevent the early increase in CBF and may compromise the oxygen balance. This may be of little consequence for the normal myocardium but could lead to significant worsening of regional function in areas of the myocardium with poor blood supply. Because gradual reductions in CBF cause an increase in the time constant of LV pressure decline, a vicious circle could evolve and explain, at least partly, the adverse effect of halothane on the compromised myocardium. Analysis of LV isovolumic relaxation may shed some light on the mechanism of action of potent inhalational anesthetics on the normal and on the compromised myocardium.

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