Simultaneous Evaluation of Left Ventricular End-systolic Pressure-volume Ratio and Time Constant of Isovolumic Pressure Decline in Dogs Exposed to Equivalent MAC Halothane and Isoflurane

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The effects of 1.5, 2.0, and 2.5 MAC halothane (N = 8) and isoflurane (N = 6) upon systolic performance and isovolumetric relaxation were evaluated in open chest dogs. Left ventricular internal volume was determined using piezoelectric crystals. Left ventricular end-systolic pressure-volume points were determined for a series of normal sinus beats during transient venous caval occlusions. The slope of the line formed by those points is a load-independent isotropic index (Ees). Left ventricular pressure points during isovolumic relaxation were plotted for computing the time constant of isovolumic pressure decline (T). Both drugs dose-dependently decreased mean arterial blood pressure with no change in heart rate, end-diastolic pressure, or end-diastolic volume. Increasing halothane concentration decreased the time constant of isovolumic pressure decline (T) and the maximum rate of rise of left ventricular pressure (dP/dtMAX). The Ees, maximum rate of rise of left ventricular pressure (dP/dtMAX), and systolic ejection fraction (SEF). Total systemic resistance was unchanged by halothane. Increasing isoflurane concentration decreased Ees and dP/dtMAX. The Ees was significantly larger (P < 0.05) with 2.5 MAC isoflurane than 2.5 MAC halothane. The SEF was unchanged by increasing isoflurane. Total systemic vascular resistance was decreased by increasing isoflurane. Isovolumic relaxation was prolonged and became more load-dependent with increasing halothane concentration. Isoflurane did not alter T, but the load-dependency of T was increased by 2.5 MAC isoflurane. There were no differences in T or its load-dependency between drug groups. These results indicate that both anesthetics evoke load-independent negative inotropic effects. Systolic ejection fraction is maintained during isoflurane anesthesia by decreased systemic vascular resistance and less pronounced negative inotropic effects than equivalent MAC halothane. Increasing halothane concentration prolongs left ventricular relaxation rate and alters its load-dependency. The effects of isoflurane upon LV relaxation rate and its load-dependency are not as pronounced as those of halothane. (Key words: Anesthetics, volatile; halothane; isoflurane. Heart: end-systolic pressure-volume relationship; inotropic state; isovolumic relaxation.)

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The myocardial depressant effects of inhalation anesthetics have been described using systolic performance indices which are influenced by hemodynamic loading factors, as well as intrinsic inotropic state. Indices derived from intraventricular pressure determinations made during isovolumic systole vary directly with intrinsic myocardial contractile strength, but are also directly influenced by altered preload.1,2 The maximum rate of rise of left ventricular pressure (dP/dtMAX) and the maximum unloaded contractile element velocity (VMAX) are examples of isovolumic systolic indices. Ejection phase systolic indices are derived from measurements of ventricular wall motion. These indices vary directly with inotropic state, but are inversely related to afterload.1,2 Systolic ejection fraction (SEF) and the velocity of circumferential fiber shortening (Vd) are examples of ejection phase indices. Inhalation anesthetics may alter inotropic state, preload, and/or afterload through central or peripherally mediated direct or reflex mechanisms. Descriptions of inhalation anesthetic-induced alterations in inotropic state using any of these indices may lack specificity unless loading variables are carefully monitored or artificially controlled.

A load-independent,4–7 end-systolic index of ventricular systolic function can be calculated from pressure-volume data. Left ventricular (LV) pressure-volume loops can be generated in real time when LV pressure and volume are simultaneously displayed on two respective axes. Alterations in LV loading characteristics evoked experimentally by aortic or venous caval occlusion create a series of LV pressure-volume loops which describe the functional characteristics of the LV. In particular, the pattern of changing position of the end-systolic pressure-volume points associated with the series of loops is related to LV intrinsic inotropic state. The relationship between end-systolic pressure (ESP) and end-systolic volume (ESV) for a given cardiac cycle is described algebraically as:

\[ ESP = Ees(ESV-Vd) \]  

(1)

When ESP is plotted against ESV for a series of variably loaded cardiac cycles, the ESP-ESV points fall on a straight line having slope Ees, and volume axis intercept Vd. The value of Ees varies directly with intrinsic LV
inotropic state (fig. 1), and is independent of loading conditions.3-7 The validity and specificity of Ees as a load-independent inotropic index has been substantiated in isolated canine left ventricles,8 conscious dogs,9 sedated dogs,10 and humans.10 Describing inotropic state using a load-independent index mathematically isolates the LV from hemodynamic loading factors which may influence the values of load-dependent indices. The load-independency of Ees make it a useful tool for describing the inotropic influences of inhalation anesthetics in experimental animal preparations.

Ventricular diastolic mechanics influence overall cardiac function.11 Ventricular relaxation is a function of two interacting control mechanisms: 1) inactivation, i.e., decay of the biochemical events involved in force generation, and 2) loading factors.12 Inhalation anesthetics may alter diastolic relaxation by altering the ionic and molecular events modulating inactivation-dependent relaxation, or by altering loading conditions. Maximum negative dP/dt (−dP/dt\text{MAX}) has been used as an index of ventricular relaxation. Peak aortic pressure and the timing of aortic valve closure effect the magnitude of −dP/dt\text{MAX}.13 Another criticism of −dP/dt\text{MAX} is that this index describes relaxation at one time point, rather than over the entire period of isovolumic relaxation. Isovolumic LV pressure decline following aortic valve closure is described by the function:

\[ P = e^{AT+B} \text{ or } \ln P = AT + B \quad (2) \]

where e is the base of the natural logarithm, P is LV pressure at time t, A is the slope of an ln P versus t plot, and B is the pressure intercept at time zero.14 The time constant of LV isovolumic pressure decline (T) is the time required for LV pressure to decay from any given pressure following aortic valve closure to 1/e of that pressure. From equation 2, T is the negative inverse slope (−1/A) of the ln P versus t relationship. The value of T decreases when relaxation is enhanced, and increases when relaxation is prolonged (fig. 2). The influence of extramyocardial factors upon T have been investigated with particular emphasis placed upon hemodynamic variables,15-17 transmural pressure,16,17 and the temporal relationships between imposed load and relaxation.18-20 The influence of inhalation anesthetics upon T has not been previously reported.

The objectives of the present study were to: 1) evaluate the systolic effects of three equivalent MAC multiples of halothane and isoflurane using Ees, dP/dt\text{MAX}, and SEF as indices of systolic myocardial performance, and 2) evaluate the diastolic effects of equivalent MAC multiples of halothane and isoflurane using T to describe ventricular relaxation. This information was used to further characterize the effects of halothane and isoflurane on ventricular function in the open chest dog.

**Materials and Methods**

**ANIMAL PREPARATION**

Anesthesia was induced in 14 mongrel dogs of either sex with thiamylal-Na (6-8 mg/kg, iv) and, following

\[ \ln P = AT + B \]

\[ T = \frac{1}{A} \]

\[ \text{Enhanced relaxation} \]

\[ \text{Reduced relaxation} \]

\[ \text{Time} \]
tracheal intubation, maintained with either halothane (HAL, \( n = 8 \)) or isoflurane (ISO, \( n = 6 \)) in oxygen. The dogs were placed in right lateral recumbency and surrounded by warm water heating blankets in order to maintain body temperature at 37° C. Arterial eucapnia (\( \text{PaCO}_2 = 35-45 \text{ mmHg} \)) was maintained by controlled ventilation, and each dog received lactated Ringer's solution (5-10 ml·kg\(^{-1}\)·h\(^{-1}\), iv) throughout the experimental period. Bilateral surgical vagotomy was performed through a midcervical incision. High fidelity micromanometer pressure catheters (Millar Instruments) were electronically zeroed at 37° C and placed in the LV and aorta (Ao) through the carotid arteries. A flow-directed, thermistor-tipped catheter (Edwards Laboratories) was positioned in the main pulmonary artery through a jugular vein. A balloon-tipped aortic occlusion catheter was placed in the descending aorta through a femoral artery. Catheter position was confirmed by observation of characteristic pressure wave forms.

A left thoracotomy was performed at the fifth intercostal space. Pneumatic occlusion cuffs were secured around the cranial and caudal venae cavae. Three pairs of piezoelectric crystals (Scheufler and Assoc.) were implanted for determination of LV base-apex major axis epicardial diameter, LV anterior-posterior minor axis epicardial diameter, and LV equatorial wall thickness. Total anesthesia time for animal preparation, catheter placement, and thoracic implants was 90-120 min.

**DATA ACQUISITION**

End-expired anesthetic gas concentrations were monitored using a quartz crystal detector (Engstrom). Each animal was allowed to equilibrate for at least 20 min with end-expired anesthetic gas concentrations corresponding to 1.5, 2.0, and 2.5 MAC HAL or ISO\(^{21} \) (1.3%, 1.7%, and 2.2% HAL; 2.2%, 3%, and 3.8% ISO, respectively). The following physiologic variables were monitored or calculated at each anesthetic concentration: heart rate (HR) and lead II electrocardiogram (ECG), thermodilution cardiac output (CO), mean aortic pressure (AoP), systemic vascular resistance (SVR = AoP/CO), LV end-diastolic pressure (EDP), LV peak-systolic pressure (PSP), LV internal volume \( V_I = \pi/6 (b^2h^2) (a-1.1h) \) where \( a \) is LV major axis epicardial dimension, \( b \) is LV minor axis epicardial dimension, and \( h \) is LV equatorial wall thickness\(^{22} \) at end-diastole and end-systole (EDV and ESV, respectively), LV end-systolic circumferential wall stress \( \text{CWS} = (\text{PSP} \times b/2)/2h \), LV systolic ejection fraction \( \text{SEF} = (\text{EDV} - \text{ESV})/\text{EDV} \), \( \text{dP}/\text{dt}_{\text{MAX}} \), and \( -\text{dP}/\text{dt}_{\text{MAX}} \). The ECG, LV and Ao pressures, \( \text{dP}/\text{dt}, a, b, \) and \( h \) were displayed and recorded using an Electronics for Medicine VR12 monitor (Honeywell). Analog pressure and LV dimension traces were hand-digitized (Digi Pad\(^{\circ} \), GTCO Corp, Rockville, MD) prior to calculation of derived variables.

The \( E_{ES} \) was determined using linear regression of the PSP and ESV points of ten consecutive beats at sequentially decreasing preload during a transient (15 s) venae caval occlusion (VCO). The time constant of isovolumic pressure decline was determined using linear regression of the natural logarithm of LV pressure \( \text{versus} \) time during isovolumic diastole. In the present study, the LV pressure at the time of \( -\text{dP}/\text{dt}_{\text{MAX}} \) was designated \( P_0 \). The LV pressure at \( P_0 \) and the LV pressures at \( (P_0 + 10) \) ms and \( (P_0 + 20) \) ms were then used to derive \( T \). An index of the load dependency of \( T \) was derived at each MAC level. This index (K) is the slope of the line formed by plotting PSP \( \text{versus} \ T \) for a normally loaded heart, followed by those values determined for three consecutive beats at sequentially increasing afterload during a transient aortic occlusion.\(^{18} \)

**EXPERIMENTAL PROTOCOL**

Surgical preparation of each dog was performed at approximately 1.5 MAC using the inhalation agent to be studied. Arterial \( \text{pH} \) and blood gases were determined and any existing respiratory or metabolic abnormalities were corrected. Interventions and measurements were repeated at 1.5, 2.0, and 2.5 MAC in random order in each dog. Five injections of 0° C 5% dextrose were performed during a ventilatory pause for determination of thermodilution cardiac output. Three of these values were averaged after exclusion of the high and low values for the set of five. At least two VCO and aortic occlusions were performed for determinations of \( E_{ES} \) and K, respectively. The \( T \) values were computed for five beats prior to any vascular occlusions. Only beats occurring in normal sinus rhythm were accepted for analysis. The LV mean pressure and AoP were allowed to stabilize to their preocclusion values between interventions.

**STATISTICAL ANALYSIS**

Data were analyzed using two-way analysis of variance for repeated measures, and \( t \) tests when appropriate. A \( P \) value < 0.05 was considered significant.

**RESULTS**

**SYSTEMIC HEMODYNAMICS**

There were no significant differences \( (P < 0.05) \) in hemodynamic variables between anesthetic groups (table 1). Heart rate, EDP, and EDV were unchanged.
TABLE 1. Hemodynamic Responses of Dogs Anesthetized with Equivalent MAC Halothane or Isoflurane

<table>
<thead>
<tr>
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<th>Halothane MAC</th>
<th>Isoflurane MAC</th>
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<tr>
<td></td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>121 ± 3</td>
<td>120 ± 2</td>
</tr>
<tr>
<td>CO (ml·kg⁻¹·min⁻¹)</td>
<td>83.3 ± 5.5</td>
<td>67.9 ± 4.9†</td>
</tr>
<tr>
<td>AoP (mmHg)</td>
<td>98 ± 8</td>
<td>78 ± 6†</td>
</tr>
<tr>
<td>SVR (dyn·s·cm⁻⁵)</td>
<td>4919 ± 357</td>
<td>4834 ± 317</td>
</tr>
<tr>
<td>EDP (mmHg)</td>
<td>1.0 ± 1</td>
<td>2.0 ± 1</td>
</tr>
<tr>
<td>EDV (cm³)</td>
<td>65 ± 10</td>
<td>62 ± 11</td>
</tr>
<tr>
<td>CWS (dyne·cm⁻¹)</td>
<td>218 ± 19</td>
<td>182 ± 15</td>
</tr>
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</table>

HR = heart rate; CO = thermodilution cardiac output + body weight (kg); AoP = mean aortic pressure; SVR = systemic vascular resistance; EDP = left ventricular end-diastolic pressure; EDV = left ventricular end-diastolic volume; CWS = left ventricular end-systolic circumferential wall stress. Values are mean ± SEM; HAL n = 8, ISO n = 6.

* Significantly different within group, 2.5 vs. 1.5 MAC (P < 0.05).
† Significantly different within group, 2.0 vs. 1.5 MAC (P < 0.05).
‡ Significantly different within group, 2.5 vs. 2.0 MAC (P < 0.05).

by either anesthetic. Halothane significantly decreased (P < 0.05) CO at 2.0 and 2.5 MAC compared to 1.5 MAC. Isoflurane significantly decreased (P < 0.05) CO only at 2.5 MAC compared to 1.5 MAC. Aortic pressure was significantly reduced (P < 0.05) with increasing concentrations of either anesthetic. Systemic vascular resistance was unchanged by increasing MAC HAL, but was significantly decreased (P < 0.05) at 2.5 MAC ISO compared to 1.5 MAC. Both agents significantly decreased (P < 0.05) CWS at 2.5 MAC compared to 1.5 MAC.

**Systolic Function**

Heart rate was unchanged during VCO. The E<sub>ES</sub> tended to decrease with increasing HAL concentration, and was significantly decreased (P < 0.05) at 2.5 MAC HAL compared to 1.5 MAC HAL (table 2). The E<sub>ES</sub> was significantly decreased (P < 0.05) at both 2.0 and 2.5 MAC ISO compared to 1.5 MAC ISO, whereas that for 2.0 and 2.5 MAC ISO were not significantly different (P < 0.05) from each other. The E<sub>ES</sub> was significantly less (P < 0.05) at 2.5 MAC HAL than 2.5 MAC ISO. The dP/dt<sub>MAX</sub> was significantly decreased (P < 0.05) by both 2.0 and 2.5 MAC HAL compared to 1.5 MAC HAL. The depression of dP/dt<sub>MAX</sub> by increasing MAC ISO became significant (P < 0.05) at 2.5 MAC. The SEF was significantly decreased (P < 0.05) by 2.5 MAC HAL compared to 1.5 MAC HAL. The SEF did not change within the ISO group.

**Diastolic Function**

Heart rate was unchanged during transient aortic occlusions, and PSP rapidly returned to baseline following aortic balloon deflation. Isovolumic relaxation was prolonged (P < 0.05) by 2.5 MAC HAL compared to 1.5 MAC HAL (table 2). Relaxation was significantly more dependent on PSP (increased K, P < 0.05) in dogs exposed to 2.0 and 2.5 MAC HAL compared to 1.5 MAC HAL. Relaxation rate was unchanged by increasing MAC ISO. The load dependency of T was significantly increased (P < 0.05) by 2.5 MAC ISO compared to 1.5 MAC ISO. There were no significant differences (P < 0.05) in T or K between anesthetic groups.

**Table 2.** Systolic and Diastolic Myocardial Performance Indices Derived from Dogs Anesthetized with Equivalent MAC Halothane or Isoflurane

<table>
<thead>
<tr>
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<th>Halothane MAC</th>
<th>Isoflurane MAC</th>
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<tr>
<td></td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>E&lt;sub&gt;ES&lt;/sub&gt; (mmHg/CC)</td>
<td>4.8 ± 0.5</td>
<td>3.5 ± 0.5</td>
</tr>
<tr>
<td>dP/dt&lt;sub&gt;MAX&lt;/sub&gt; (mmHg/s)</td>
<td>1779 ± 138</td>
<td>1320 ± 79†</td>
</tr>
<tr>
<td>SEF (%)</td>
<td>24 ± 2</td>
<td>22 ± 2</td>
</tr>
<tr>
<td>T (ms)</td>
<td>30 ± 2</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>K (mmHg/mmHg)</td>
<td>0.31 ± 0.03</td>
<td>0.59 ± 0.09†</td>
</tr>
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</table>

E<sub>ES</sub> = slope of end-systolic pressure-volume relationship during venae cavae occlusion; dP/dt<sub>MAX</sub> = maximum rate of rise of left ventricular pressure; SEF = systolic ejection fraction; T = time constant of isovolumic pressure decline; K = slope of peak systolic left ventricular pressure – T relationship during aortic occlusion. Values are mean ± SEM; HAL n = 8, ISO n = 6.

* Significantly different within group, 2.5 vs. 1.5 MAC (P < 0.05).
† Significantly different within group, 2.0 vs. 1.5 MAC (P < 0.05).
‡ Significantly different within group, 2.5 vs. 2.0 MAC (P < 0.05).
§ Significantly different between groups at 2.5 MAC (P < 0.05).
Discussion

CRITIQUE OF METHODS

The nature of the experimental preparation and range of anesthetic concentrations used in the present study must be critically evaluated in comparing our results with those of other investigations. An anesthetic-free control state was not evaluated because of the methodology. Our observations, therefore, apply only to the range of concentrations used. The present results describe the effects of HAL and ISO on the open-chest canine cardiovascular system, after bilateral vagotomy. Negative inotropic drug effects may be more pronounced in open-chest than closed-chest dogs. Bilateral vagotomy was included in the experimental protocol to obviate reflex parasympathetic influences modulating contractile performance and heart rate during aortic and caval occlusions. The relative contributions of the sympathetic and parasympathetic nervous systems as modulators of cardiovascular homeostasis differ between conscious dogs and anesthetized dogs. Parasympathetic influences may exert primary control in conscious dogs, but be of less influence in anesthetized dogs having higher sympathetic tone. Sympathetic reflexes were intact in the present study. Altered pleural pressure may change hemodynamics, thereby altering ventricular relaxation. The lack of pericardial restriction is also artificial, although the direct influence of the pericardium on LV diastolic mechanics is minimal in conscious dogs.

SYSTOLIC FUNCTION

The primary sites of anesthetic-induced cardiovascular depression have been examined in animal studies using myocardial performance indices of varying specificity for intrinsic inotropic state. Previous findings in closed-chest dogs have inquired that dose-dependent decreases in arterial blood pressure during HAL anaesthesia are the result of the combined negative inotropic effects of HAL, plus the characteristic lack of change in SVR with increasing HAL concentration. The attenuation of α2- but not α1-adrnergic vasoconstriction has been suggested as the mechanism whereby HAL interferes with vascular tone, and may explain why vasopressor activity is maintained during HAL anesthe-sia. Isoflurane contrasts with HAL in that the negative inotropic effects of ISO are partially offset by the characteristic dose-dependent reduction in SVR induced by increasing ISO concentration. The present study examines these putative differences using a load-independent inotropic index. The $E_{ES}$ is insensitive to preload; equation 1 does not contain a term for EDV. Changing afterload is incorporated into the determination of $E_{ES}$, and $E_{ES}$ is insensitive to controlled alterations in afterload impedance in isolated canine LV. Changes in preload or afterload which may have occurred in response to HAL or ISO should not have directly affected $E_{ES}$ determinations in the present study.

Changes in venous return during venae caval occlusion may evoke reflex alterations in inotropic state. Parasympathetic and sympathetic nervous system responses are characterized by their differing time constants. Vagal responses are typically rapid, having time constants of less than a second. Sympathetic responses are more slowly activated, having a time constant of about 8 s. Caval occlusion in conscious dogs evokes a heart rate response which lags behind the pressure change, indicating that the autonomic response to this hemodynamic manipulation is at least partly mediated by the sympathetic nervous system. Vagal reflex control of cardiac function mediated by sinoaortic (high pressure) and cardiopulmonary (low pressure) baroreceptors was obviated by surgical vagotomy in the present study. Reflex alterations in efferent sympathetic activity mediated by LV mechanoreceptors occur in response to changes in LV end-diastolic segment length, and are attenuated in HAL-anesthetized dogs. It is doubtful that sympathetic reflexes contributed to our determinations of $E_{ES}$, because preload was unchanged over the range of HAL and ISO concentrations used in the present study; therefore, cardiopulmonary receptor afferent activity should not have changed between anesthetic concentrations. Preload-dependent alterations in autonomic afferent activity may occur between the unanesthetized state and 1.5 MAC, but this was not evaluated in the present study.

The results of the present study demonstrate the load-independent negative inotropic effects of HAL and ISO, and indicate that HAL is a more potent myocardial depressant than ISO at 2.5 MAC. The experimental and practical value of $E_{ES}$ as a load-independent inotropic index is apparent when comparing simultaneously determined values of $dP/dt_{MAX}$ and SEF.

A drug-induced alteration of $dP/dt_{MAX}$ must be evaluated in terms of any simultaneous change in EDV (preload). The changes in $dP/dt_{MAX}$ reported in the present study reflect changing inotropic state similar to $E_{ES}$ because EDV did not change appreciably within or between anesthetic groups.

Systolic ejection fraction is an afterload-sensitive inotropic index. Systolic wall stress (afterload), derived by the LaPlace relationship, is directly related to intraventricular systolic pressure and radius, and inversely related to wall thickness. Left ventricular fiber shortening and CWS are inversely related, i.e., the derived value of an ejection phase inotropic index will increase as CWS decreases or as contractility increases. Wall stress was
significantly decreased by 2.5 MAC HAL or ISO in the present study, but SEF was significantly reduced only in the HAL group. Systemic vascular resistance was unchanged by increasing HAL concentration, but decreased with increasing ISO. Our observation of decreased SEF despite concurrently decreased CWS in HAL-anesthetized dogs reflects the combined adverse effects of reduced myocardial contractility (reduced EES at 2.5 MAC HAL), and the lack of change in SVR. Although EES values indicate that ISO is also a negative inotrope, SEF did not change within the ISO group. The most plausible explanation for this observation is that both CWS and SVR were significantly reduced by 2.5 MAC ISO. The EES values at 2.5 MAC ISO were significantly greater than 2.5 MAC HAL; therefore, smaller changes in SEF should be anticipated under similar loading conditions.

**DIASTOLIC FUNCTION**

Hearts which perform abnormally during diastole are likely to do so during systole, and abnormal diastolic performance may precede poor systolic performance. Anesthetics and other drugs may impair systolic function if they impair diastolic function, particularly if an abnormal diastolic condition is acutely exacerbated by the drug.

Diastolic pressure-volume relationships or stress-strain relationships are used to describe changes in LV compliance. The effects of HAL upon LV diastolic compliance have been investigated in open-chest dogs. Greene and Gerson found no difference in LV diastolic compliance at 1 or 2 MAC in halothane-anesthetized dogs given infusions of sodium nitroprusside and phenylephrine which altered pulmonary capillary wedge pressure from 5 to 25 mmHg. Their results substantiate previous studies reporting no effect of HAL upon LV diastolic compliance.

Left ventricular end-diastolic mechanical properties were not altered by HAL or ISO in the present study, but isovolumic relaxation and the load dependency of relaxation were affected by both drugs. Relaxation was significantly prolonged by 2.5 MAC HAL, and the apparent load-dependency of relaxation was significantly increased by increasing MAC HAL. These results contrast with those of the ISO group in which relaxation was unaltered by increasing MAC ISO, and the apparent load dependency of relaxation was significantly increased only by 2.5 MAC ISO. The changes in apparent afterload-dependency of T in the present study may have been due to anesthetic-induced alterations of systolic myocardial loading. Left ventricular relaxation is mainly influenced by the sequence of systolic loading rather than the absolute pressure or load in isolated canine hearts, and changes in loading sequence during afterload interventions (e.g., aortic clamping) are the cause of the apparent afterload dependency of T in open-chest, pentobarbital-anesthetized dogs. Aortic occlusion increases peak systolic pressure because of increasing resistance, but the aortic pressure pattern is also changed due to the alteration in vascular capacitance. Drugs may alter LV relaxation by influencing loading sequence through changes in arterial compliance as well as by direct myocardial effects. The effects of HAL and ISO upon arterial compliance were not investigated in the present study, but differences in LV loading sequence due to potentially differing affects on vascular compliance between HAL and ISO may contribute to differences in apparent afterload-dependency of relaxation.

Aortic occlusion evokes autonomic reflex activity, which may affect relaxation. Reflex responses to aortic occlusion in morpheine-sedated dogs are entirely parasympathetically mediated, based on their short time constant. Reflex effects on relaxation were obviated by surgical vagotomy in the present study.

Coronary arterial flow exerts a mechanical effect on relaxation. Engorgement of a compliant coronary bed increases wall thickness, thereby increasing chamber stiffness, and enhancing relaxation. The mechanical effects of coronary flow may become more significant in diseased hearts. Isoflurane dilates coronary arterioles in intact canine hearts. Isoflurane-evoked coronary arteriolar dilation may have contributed to the differing dependence of LV relaxation on vascular loading between HAL and ISO in the present study. Neither muscle mechanics nor coronary blood flow were specifically investigated as determinants of T in the present study.

Anesthetics may also modulate myocardial relaxation by altering metabolic processes controlling inactivation. Affects on inactivation may be direct, or mediated by alterations in coronary flow. Differential direct effects of HAL and ISO on myocardial calcium dynamics influencing contractile performance have been demonstrated in isolated right ventricular guinea pig papillary muscle. Inactivation-dependent relaxation mechanisms may also be differentially affected by HAL and ISO, but this was not investigated in the present study.

We conclude that the systolic effects of HAL and ISO reflect their individual direct effects on both myocardial contractility and systemic vascular resistance between 1.5 and 2.5 MAC. Their affects on diastolic relaxation may be attributable to differential effects on systolic loading, coronary flow, or myocardial calcium dynamics.

**References**


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