Isoflurane, but Not Halothane, Improves Indices of Diastolic Performance in Dogs with Rapid Ventricular, Pacing-induced Cardiomyopathy


Background: The left ventricular (LV) mechanical effects of isoflurane and halothane were examined in dogs with rapid LV pacing-induced cardiomyopathy. These experiments tested the hypothesis that isoflurane and halothane differentially enhance indices of diastolic performance in dogs with moderate LV dysfunction.

Methods: Eight dogs were chronically instrumented for measurement of LV and aortic pressures, subendocardial segment length, and cardiac output. Contractility was quantified by preload recruitable stroke work (M.). Diastolic function was evaluated with a time constant of isovolumic relaxation (γ), segment lengthening velocities and time-velocity integrals during early filling (dL/dt and TTI-E) and atrial systole (dL/dt and TTI-A), and a regional chamber stiffness constant (K). Hemodynamics and LV function were recorded in the conscious state before pacing. The left ventricles of the dogs were then continuously paced at ventricular rates between 220 and 240 beats min⁻¹ for 10 ± 1 days and monitored on a daily basis. After the development of moderate LV dysfunction, pacing was temporarily discontinued, and dogs were studied in sinus rhythm in the conscious state and after 20 min equilibration at 1.1, 1.4, and 1.7 minimum alveolar concentration isoflurane and halothane on separate days.

Results: Chronic rapid pacing increased baseline (sinus rhythm) heart rate, LV end-diastolic pressure, and end-diastolic segment length and decreased mean arterial pressure, LV systolic pressure, and cardiac output. M. decreased and TTI-E increased, consistent with LV systolic and diastolic dysfunction. Reductions in dL/dt and TTI-A occurred, which indicated that LV filling was more dependent on atrial systole. In dogs with cardiomyopathy, isoflurane and halothane increased heart rate and decreased mean arterial pressure, LV systolic pressure, LV end-diastolic pressure, cardiac output, M., and K. Decreases in LV end-diastolic pressure were more pronounced in dogs anesthetized with 1.1 minimum alveolar concentration isoflurane compared with halothane. Halothane-induced decreases in VTI-E and VTI-A and the ratio of early to total LV filling were observed with isoflurane. In contrast, halothane caused dose-related reductions in VTI-E, VTI-A, and VTI-A, and did not improve the ratios of these variables.

Conclusions: Isoflurane, but not halothane, improved several indices of diastolic performance in dogs with pacing-induced LV dysfunction, despite producing simultaneous negative inotropic effects. These findings can be attributed to favorable reductions in LV preload and not to direct lusitropic effects. Improvement of filling dynamics may partially offset the decrement in LV systolic function by isoflurane in the setting of LV dysfunction. (Key words: Anesthetics, volatile: isoflurane; Isoflurane; Heart: diastolic; Diastolic function; Isovolumic relaxation; Ventricular filling; Ventricular compliance; Heart: cardiomyopathy; Failure; Myocardial contractility; Myocardial performance; Preload recruitable stroke work; Rapid pacing.)

VOLATILE anesthetics, including isoflurane and halothane, depress myocardial contractility and produce abnormalities in indices of left ventricular diastolic function in the normal heart. These negative inotropic and lusitropic effects contribute substantially to the circulatory depression observed with these agents. Remarkably, the left ventricular mechanical consequences of volatile anesthetics have not been comprehensively described in either experimental models of heart failure or patients with left ventricular dysfunction. Early in vitro studies demonstrated that volatile
anesthetics cause relatively greater decreases in contractility in failing versus normal isolated myocardium, suggesting that patients with underlying contractile dysfunction may be more sensitive to the myocardial depressant properties of volatile anesthetics. However, further studies in experimental animals or patients have not been performed to support or refute this hypothesis. The actions of volatile anesthetics on diastolic mechanical behavior of the failing heart also remain unanswered, despite the recognition that left ventricular diastolic function is critically important to overall cardiac performance.

Volatile anesthetics may affect left ventricular function by producing favorable alterations in loading conditions and diastolic performance in the presence of left ventricular dysfunction. The current investigation examined the hemodynamic and mechanical actions of isoflurane and halothane in conscious, unsedated dogs after the development of moderate left ventricular dysfunction produced by chronic rapid ventricular pacing. These experiments tested the hypothesis that isoflurane and halothane cause differential and selective improvements in left ventricular filling dynamics in the presence of moderate left ventricular dysfunction. The experimental model used in this investigation has been shown to cause time-dependent biventricular chamber dilation, increases in left and right ventricular filling pressures, abnormalities in intracellular calcium (Ca²⁺) homeostasis, and striking abnormalities in systolic and diastolic function similar to those found in patients with dilated congestive cardiomyopathy. Pacing-induced cardiomyopathy is also characterized by ultrastructural, histologic, and biochemical abnormalities that are similar but not identical to those observed in human dilated cardiomyopathy. Pac ing-induced cardiomyopathy is relatively easy to produce in dogs and provides a satisfactory model in which to study the cardiovascular effects of volatile anesthetics in the setting of left ventricular dysfunction.

Materials and Methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care and Use Committee of the Medical College of Wisconsin. All procedures conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society and were performed in accordance with the Guide for the Care and Use of Laboratory Animals (DHEW [DHHS] publication NIH no. 85–23, revised 1985).

Surgical Preparation

The surgical implantation of instruments has been described in detail previously. Briefly, in the presence of general anesthesia and using aseptic techniques, a left thoracotomy was performed in conditioned mongrel dogs for placement of instruments for measurement of aortic, left atrial, and intrathoracic pressures (heparin-filled catheters), subendocardial segment length (ultrasonic crystals), and relative cardiac output (ascending thoracic aortic ultrasonic flow transducer). A high fidelity, miniature micromanometer was positioned in the left ventricle for measurement of continuous left ventricular pressure and the peak rate of increase of left ventricular pressure (dP/dt max). A hydraulic vascular occluder was placed around the inferior vena cava for abrupt alteration of left ventricular preload. Stainless steel pacing electrodes were sutured to the epicardial surface of the left ventricular free wall. All instrumentation was firmly secured, tunneled between the scapulae, and exteriorized via several small incisions. The pericardium was left widely open, the chest wall closed in layers, and the pneumothorax evacuated by a chest tube. Each dog was fitted with a jacket to prevent damage to the instruments and catheters, which were housed in an aluminum box in a jacket pocket. The pacing electrodes were attached to a programmable pacemaker (designed by our laboratory) that also was housed in a jacket pocket. All dogs received systemic analgesia (fentanyl) as needed after surgery. Dogs were allowed to recover a minimum of 7 days before experimentation, during which time all were treated with intramuscular antibiotics (40 mg·kg⁻¹ cefazolin and 4.5 mg·kg⁻¹ gentamicin) and trained to stand quietly in a sling during hemodynamic monitoring. Segment length signals were monitored by ultrasonic amplifiers. End-systolic (ESL) and end-diastolic segment length (EDL) were measured at 10 ms before left ventricular peak negative dP/dt and immediately before the onset of left ventricular isovolumetric contraction, respectively. Percent segment shortening (%SS) was determined using the equation: %SS = (EDL − ESL)·100·EDL⁻¹. The pressure work index, an estimate of myocardial oxygen consumption, was calculated using a previously validated formula. Hemodynamic data were recorded continuously on a polygraph and simultaneously digitized and
recorded on a computer for subsequent analysis of left ventricular pressure-segment length waveforms and diagrams.

**Experimental Protocol**

Each dog was fasted overnight, and fluid deficits were replaced before experimentation with 500 ml 0.9% saline, which was continued at 3 ml·kg⁻¹·h⁻¹ for the duration of each experiment. Continuous left ventricular pressure, intrathoracic pressure, and segment length waveforms were recorded digitally for subsequent analysis of diastolic function. Left ventricular pressure-segment length diagrams, used to assess contractile state, were obtained by abruptly decreasing left ventricular preload via inflation of the inferior vena cava balloon cuff occluder, resulting in an approximately 30-mmHg decline in left ventricular systolic pressure throughout 10–15 cardiac cycles. Respiratory variation in left ventricular pressure was later reduced offline by digital subtraction of the continuous intrathoracic pressure waveform from the left ventricular pressure waveform. Vena caval occlusion was released immediately after waveforms were recorded. Sets of left ventricular pressure-segment length diagrams generated during inferior vena cava occlusion were rejected if the heart rate increased more than 10% above precollection values. In this case, generation of left ventricular pressure-segment length diagrams was repeated after steady-state hemodynamics had been reestablished.

Dogs (n = 8; weight = 27.3 ± 1.4 kg, mean ± SEM) were assigned to receive isoflurane or halothane on separate experimental days after the development of moderate left ventricular dysfunction produced by chronic rapid ventricular pacing. Baseline systemic hemodynamics and left ventricular pressure-segment length waveforms and diagrams were recorded in the conscious state before the initiation of pacing (fig. 1). After control experiments had been completed, the left ventricles of the dogs were paced continuously at ventricular rates between 220 and 240 beats·min⁻¹, with pulse amplitudes between 3 and 5 mA and pulse widths between 0.2 and 0.5 ms, which remained constant for the duration of the experimental protocol.

Dogs were brought to the laboratory on each day after the initiation of pacing, to confirm the functional integrity of the pacemaker and to monitor the development of pacing-induced cardiomyopathy. Pacing was discontinued during and restarted immediately after a brief period of daily hemodynamic monitoring. In conscious, unanesthetized dogs, moderate left ventricular dysfunction was indicated by chamber dilatation (increases in EDL and ESL), an increase in left ventricular end-diastolic pressure (LVEDP) ≤ 20 mmHg), a reduction in left ventricular dp/dt max ≤ 25% of control, and increases in the time constant of isovolumic relaxation (45 ≤ τ ≤ 60 ms) and the regional chamber stiffness constant (0.60 ≤ Ks ≤ 1.00 mmHg). Experiments were conducted when these criteria were met.

Rapid ventricular pacing was discontinued temporarily for the duration of each experiment. Baseline hemodynamics and left ventricular pressure-segment length waveforms and diagrams were recorded 30 min after pacing had been discontinued in conscious dogs. After inhalational induction and tracheal intubation, anesthesia was maintained during positive pressure ventilation at 1.1, 1.4, and 1.7 minimum alveolar concentration (MAC; end-tidal concentrations) isoflurane or halothane in an air–oxygen (25%) mixture. The order of MAC values was assigned randomly. Left ventricular pressure-segment length waveforms and diagrams were obtained after 20-min equilibration at each anesthetic concentration. End-tidal concentrations of volatile anesthetics were measured at the tip of the endotracheal tube by an infrared gas analyzer (Datex Capnomac; Helsinki, Finland) calibrated with known standards before and during experimentation. Arterial
blood gas tensions were maintained at levels obtained in the conscious state by adjustment of air and oxygen concentrations and respiratory rate throughout the experiment. After the completion of each experiment, emergence was allowed to occur, and pacing was reinstated. A total of 16 experiments in 2 separate groups (isoflurane and halothane) were performed in the same 8 chronically instrumented dogs, with moderate left ventricular function induced by rapid ventricular pacing.

**Determination of Indices of Left Ventricular Function**

The slope (M_w) of the regional preload recruitable stroke work relation was used to estimate myocardial contractility. The time constant of isovolumic relaxation (τ) was calculated using the derivative method. Left ventricular filling was quantified using several indices derived from the continuous segment length waveform, as characterized previously. The peak rate of increase of segment length during early ventricular filling (dL/dt_e) and atrial systole (dL/dt_a) and the ratio of these variables (dL/dt_E/A) were determined from examination of the continuous dL/dt waveform. Time-velocity integrals during early ventricular filling (TVI-E) and atrial systole (TVI-A) were calculated by electronic integration, and the ratio of these integrals (TVI-E/A) was determined. The regional chamber stiffness constant (K_w) was derived from left ventricular pressure-segment length data, assuming a simple elastic model as described previously.

**Statistical Analysis**

Statistical analysis of the data within and between groups before and after rapid ventricular pacing and during the administration of isoflurane and halothane was performed by multiple analysis of variance with repeated measures, followed by use of Student’s t test, with Duncan’s adjustment for multiplicity. Changes were considered to be statistically significant when P was less than 0.05. All data are expressed as mean ± SEM.

**Results**

The left ventricles of the dogs were paced for 10 ± 1 days (range, 7–15 days), to meet the criteria for moderate left ventricular dysfunction. Chronic rapid ventricular pacing caused significant (P < 0.05) increases in heart rate, left ventricular end-diastolic pressure, EDL, ESL, (fig. 1) and the length intercept (L_w) of the preload recruitable stroke work relation. Pacing also decreased mean arterial pressure, left ventricular systolic pressure, and stroke volume. Pressure-work index, cardiac output, and systemic vascular resistance were unchanged by pacing. Decreases in M_w, (fig. 2) dP/dt_max, and %SS were observed, consistent with a decline in myocardial contractility. Rapid ventricular
Fig. 3. Histograms that depict the peak rate of segment lengthening during rapid ventricular filling (dL/dt, top panel) and atrial systole (dL/dtA; middle panel) and the ratio of dL/dtE to dL/dtA (bottom panel) in the conscious state before (C; open bar) and after pacing (P) and during 1.1, 1.4, and 1.7 MAC (end-tidal concentration) isoflurane (hatched bars) and halothane (solid bars). *Significantly (P < 0.05) different from P; **Significantly (P < 0.05) different from 1.1 MAC; †Significantly (P < 0.05) different from 1.4 MAC.

Pacing also produced diastolic dysfunction, as indicated by increases in \( r \) (fig. 2) and alterations of left ventricular filling (figs. 3 and 4). Decreases in dL/dtE and TVI-E and increases in dL/dtA and TVI-A were produced by chronic pacing, which indicated that the rate and extent of total left ventricular filling depends, to a greater extent, on atrial systole in dogs with pacing-induced cardiomyopathy. These changes in the pattern of left ventricular filling were accomplished by reductions in dL/dtE/A and TVI-E/A. Rapid ventricular pacing also caused an increase in \( K_1 \), concomitant with the increase in left ventricular end-diastolic pressure.

Ioflurane increased heart rate and decreased mean arterial pressure, left ventricular systolic and end-diastolic pressures, EDL, cardiac output, and stroke volume in dogs with moderate left ventricular dysfunction (table 1). Ioflurane-induced reductions in left ventricular end-diastolic pressure were not dose-related, and were most pronounced at the 1.1 MAC dose. Systemic vascular resistance declined in MAP at 1.7 MAC, fig. 3, which indicated that myocardial flexibility occurred. In the conscious state, 1.1 MAC increase in \( r \) (57%) was concomitant with mean diastolic pressure normalizations in i oflurane. Declines in dL/dtE/A, which indicated that ventricular filling patterns varied (fig. 3). In the conscious state, the reduction in filling during atrial systole was reflected in the proportion of TVI-E to TVI-A (fig. 4). During atrial systole, isoflurane anesthesia resulted in an increase of 0.3 mmHg after pacing (P) by isoflurane (fig. 4).

Table 1. Hemodynamic data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Value</th>
<th>1.1 MAC</th>
<th>1.4 MAC</th>
<th>1.7 MAC</th>
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<tr>
<td>HR (beats·min⁻¹)</td>
<td>bpm</td>
<td>7.8±1</td>
<td>8.1±1</td>
<td>8.3±1</td>
<td>8.6±1</td>
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<td>MAP (mmHg)</td>
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<td>68.4±1</td>
<td>67.3±1</td>
<td>66.1±1</td>
<td>64.9±1</td>
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<td>LVSP (mmHg)</td>
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<td>100.3±2</td>
<td>99.4±2</td>
<td>98.5±2</td>
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<td>LVEDP (mmHg)</td>
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<td>18.4±1</td>
<td>17.6±1</td>
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<td>16.0±1</td>
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<td>dP/dt max (mmHg·s⁻¹)</td>
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<td>1.3±0.1</td>
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<td>SV (l/min)</td>
<td>l/min</td>
<td>3.1±0.1</td>
<td>2.9±0.1</td>
<td>2.7±0.1</td>
<td>2.6±0.1</td>
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<td>EEL (mm)</td>
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<td>3.5±0.1</td>
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<td>3.2±0.1</td>
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<td>ESR (mm)</td>
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<td>0.8±0.1</td>
<td>0.7±0.1</td>
<td>0.6±0.1</td>
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<td>TVI-E (mm)</td>
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<td>TVI-A (mm)</td>
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<td>20.1±0.3</td>
<td>19.8±0.3</td>
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<tr>
<td>dL/dtA</td>
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<td>3.4±0.1</td>
<td>3.3±0.1</td>
<td>3.2±0.1</td>
<td>3.1±0.1</td>
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</table>

Data are mean ± SEM.

HR = heart rate; MAP = mean arterial pressure; dP/dt max = maximum negative dP/dt; SV = stroke volume; EEL = end-systolic elastance; ESR = end-systolic radii; TVI-E = time–velocity integral of early filling; TVI-A = time–velocity integral of atrial filling.

*Significantly (P < 0.05) different from P; †Significantly (P < 0.05) different from 1.1 MAC.

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VOLATILE ANESTHETICS AND LV DYSFUNCTION

Table 1. Hemodynamic Effects of Isoflurane in Dogs with Moderate Left Ventricular Dysfunction

<table>
<thead>
<tr>
<th>HR (beats·min⁻¹)</th>
<th>MAP (mmHg)</th>
<th>LVSP (mmHg)</th>
<th>LVEPD (mmHg)</th>
<th>dP/dtmax (mmHg·s⁻¹)</th>
<th>CO (L·min⁻¹)</th>
<th>SV (ml)</th>
<th>EDL (mm)</th>
<th>ESL (mm)</th>
<th>SS (%)</th>
<th>Kₚ (mm⁻¹)</th>
<th>PWI (ml·min⁻¹·100 g⁻¹)</th>
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<tr>
<td>75 ± 3*</td>
<td>103 ± 3*</td>
<td>124 ± 5*</td>
<td>8 ± 1*</td>
<td>2,494 ± 170*</td>
<td>2.5 ± 0.3*</td>
<td>34 ± 4*</td>
<td>20.4 ± 2*</td>
<td>15.1 ± 1.4*</td>
<td>25.7 ± 1.7*</td>
<td>0.34 ± 0.07*</td>
<td>8.8 ± 0.4*</td>
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<td>88 ± 7</td>
<td>83 ± 2</td>
<td>102 ± 3</td>
<td>19 ± 1</td>
<td>1,721 ± 138</td>
<td>2.1 ± 0.3</td>
<td>26 ± 4</td>
<td>24.1 ± 1.6</td>
<td>19.5 ± 1.2</td>
<td>18.7 ± 2.3</td>
<td>0.93 ± 0.14</td>
<td>7.4 ± 0.4</td>
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Data are mean ± SEM; n = 8. HR = heart rate; MAP = mean aortic pressure; LVSP and LVEPD = left ventricular systolic and end-diastolic pressure, respectively; dP/dtmax = maximum rate of increase of left ventricular pressure; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; Kp = regional chamber stiffness constant; PWI = pressure–work index.

* Significantly (P < 0.05) different from before pacing.
† Significantly (P < 0.05) different from 1.1 MAC isoflurane.

Vascular resistance was unchanged. Dose-dependent declines in Mₚ (67 ± 4 after pacing to 40 ± 5 mmHg at 1.7 MAC; fig. 2), dP/dtmax, and %SS were observed, which indicated that a reduction in myocardial contractility occurred. Despite this decline in intrinsic inotropic state, 1.1 MAC isoflurane caused a significant decrease in τ (57 ± 4 after pacing to 50 ± 3 ms; fig. 2) concomitant with a reduction in left ventricular end-diastolic pressure, suggesting that pacing-induced abnormalities in isovolumic relaxation were improved. Declines in dL/dtₑ and dL/dtᵢ occurred with isoflurane, which indicated that the peak rate of early and late ventricular filling was attenuated by this volatile anesthetic (fig. 3). In contrast, there was no change in TVI-E at 1.1 MAC isoflurane, which suggested that the extent of filling during this phase of diastole was unaffected in the presence of moderate left ventricular dysfunction (fig. 4). Reductions in the extent of filling during atrial systole (TVI-A) were observed during isoflurane anesthesia that were not dose-related. As a result, an increase in the ratio of TVI-E to TVI-A (3.3 ± 0.3 after pacing to 3.3 ± 0.4 at 1.1 MAC) was produced by isoflurane (fig. 4). Reductions in Kₚ also were observed in isoflurane-anesthetized dogs with pacing-induced cardiomyopathy concomitant with declines in left ventricular end-diastolic pressure.

Halothane caused systemic hemodynamic actions in dogs with moderate left ventricular dysfunction that were somewhat different than those produced by isoflurane (table 2). Dose-related decreases in mean arterial pressure, left ventricular systolic pressure, cardiac output, stroke volume, and pressure–work index occurred in halothane-anesthetized, cardiomyopathic dogs. Systemic vascular resistance was unchanged. Reductions in left ventricular end-diastolic pressure and EDL also were observed in dogs anesthetized with halothane. Isoflurane caused more pronounced decreases in left ventricular end-diastolic pressure than halothane at 1.1 MAC (~10 ± 1 with isoflurane compared with ~6 ± 1 mmHg with halothane). Halothane decreased Mₚ, dP/dtmax, and %SS in a dose-dependent manner, which indicated a direct negative inotropic effect. Halothane produced a relatively greater degree of systolic depression than equi-MAC isoflurane in dogs with moderate left ventricular dysfunction (fig. 2). In contrast to isoflurane, halothane did not reduce τ at 1.1 MAC and caused increases in this variable at higher concentrations. Halothane caused dose-related reductions in dL/dtₑ and dL/dtᵢ, TVI-E, and TVI-A, which indicated that the rate and extent of early and late ventricular filling were reduced by this volatile anesthetic (figs. 3 and 4). The ratio of dL/dtₑ to dL/dtᵢ, and TVI-E to TVI-A remained unchanged during the administration of halothane to dogs with pacing-induced cardiomyopathy, in contrast...
to the findings with isoflurane. Halothane reduced $K_v$ concomitant with decreases in left ventricular end-diastolic pressure. Halothane-induced decreases in $K_v$ were similar to those observed with isoflurane.

### Discussion

The effects of volatile anesthetics on left ventricular mechanics in models of myocardial dysfunction have not been studied comprehensively. Isoflurane and enflurane have been shown to cause greater reductions in maximum shortening velocity ($V_{max}$) and the peak rate of force development (+dF/dt) in papillary muscles from failing hearts than in those from normal hearts.2,3 These findings suggested that the combined direct negative inotropic effects of volatile anesthetics and failing myocardium were more pronounced than the actions of the anesthetics alone, and provided indirect evidence that patients with underlying contractile dysfunction may be more sensitive to the myocardial depressant properties of volatile anesthetics. This supposition has not been examined extensively in vivo, however. In experimental models of regional myocardial ischemia20 or infarction,21 declines in contractile function caused by volatile anesthetics were well tolerated, and did not precipitate frank systolic dysfunction. In fact, inhalational agents were shown to exert important beneficial effects on mechanical function during myocardial ischemia and reperfusion injury. Volatile anesthetics reduce experimental myocardial infarct size,22 preserve metabolic and ultrastructural integrity during regional ischemia and reperfusion,23-26 enhance the recovery of stunned myocardium,27 and improve indices of diastolic performance during brief coronary artery occlusion.28 Halothane and isoflurane also were shown to produce beneficial decreases in left ventricular preload and afterload in patients with heart failure and coronary artery disease, respectively.29-32 These improvements in ventricular loading conditions in patients with compromised left ventricular function may serve to partially offset the direct negative inotropic effects of anesthetics and contribute to maintenance of overall cardiac performance by optimizing the operating range of the heart on the Starling curve or by improving left ventricular diastolic function. These hypotheses have not been tested in models, or patients with, heart failure.

The current results indicate that chronic rapid ventricular pacing causes hemodynamic and mechanical

### Table 2. Hemodynamic Effects of Halothane in Dogs with Moderate Left Ventricular Dysfunction

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<thead>
<tr>
<th></th>
<th>After Pacing</th>
<th>Halothane (MAC)</th>
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<tr>
<td></td>
<td>1.1</td>
<td>1.4</td>
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<tr>
<td>HR (beats·min⁻¹)*</td>
<td>87±4</td>
<td>99±4*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>86±3</td>
<td>69±3*</td>
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<tr>
<td>LVSP (mmHg)</td>
<td>100±3</td>
<td>78±3*</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>19±1</td>
<td>13±1§</td>
</tr>
<tr>
<td>dP/dt max (mmHg·s⁻¹)</td>
<td>1,710±125</td>
<td>1,015±65*</td>
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<tr>
<td>CO (l·min⁻¹)</td>
<td>2.3±0.2</td>
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<tr>
<td>SVR (dyne·s·cm⁻⁴)</td>
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<td>3,220±240</td>
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<tr>
<td>SV (ml)</td>
<td>27±2</td>
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<tr>
<td>ELD (mm)</td>
<td>24.5±1.7</td>
<td>23.6±1.8*</td>
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<tr>
<td>ESL (mm)</td>
<td>19.9±1.2</td>
<td>20.0±1.3</td>
</tr>
<tr>
<td>SS (%)</td>
<td>19.8±2.4</td>
<td>14.8±2.3*</td>
</tr>
<tr>
<td>$K_v$ (mmHg·min⁻¹·100 g⁻¹)</td>
<td>0.97±0.12</td>
<td>0.42±0.12*</td>
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<tr>
<td>PWI (ml·min⁻¹·100 g⁻¹)</td>
<td>7.7±0.4</td>
<td>6.3±0.3*</td>
</tr>
</tbody>
</table>

Data are mean ± SEM; $n = 8$.

HR = heart rate; MAP = mean aortic pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; $dP/dt_{max}$ = maximum rate of increase of left ventricular pressure; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume; ELD and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; $K_v$ = regional chamber stiffness constant; PWI = pressure–work index.

*Significantly ($P < 0.05$) different from after pacing.
†Significantly ($P < 0.05$) different from 1.1 MAC halothane.
‡Significantly ($P < 0.05$) different from 1.4 MAC halothane.
§Significantly ($P < 0.05$) different from corresponding isoflurane value (table 1).
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effects in dogs similar to those effects reported by other investigators.\textsuperscript{6-9, 11, 13} Sinus tachycardia, decreases in arterial pressure, and increases in left ventricular dimension and filling pressure were accompanied by decreases in intrinsic inotropic state, prolongation of isovolumic relaxation, attenuation of the rate of early ventricular filling, and decreases in chamber compliance. No changes in cardiac output or systemic vascular resistance were observed in dogs after 10 days of rapid ventricular pacing, confirming the findings of Shannon et al.\textsuperscript{5} Reductions in cardiac output and increases in systemic vascular resistance were reported in the canine pacing-induced cardiomyopathy model after 4–5 weeks of pacing, concomitant with the appearance of clinical signs of congestive heart failure.\textsuperscript{13, 35} However, ascites, peripheral edema, pulmonary congestion, and weight gain were not observed in any dog during pacing in the current investigation. Therefore, the cardiovascular effects of isoflurane and halothane were examined in dogs with moderate left ventricular dysfunction that had not yet decompensated into frank congestive heart failure.

The current investigation is the first to comprehensively examine the influence of volatile anesthetics on left ventricular systolic and diastolic function in a canine model of pacing-induced cardiomyopathy. The results confirm and extend the findings of Reiz et al.\textsuperscript{30-32} in patients, and indicate that isoflurane and halothane cause systemic hemodynamic effects and mechanical actions in dogs with moderate left ventricular dysfunction that are different than those in dogs\textsuperscript{34, 35} and humans\textsuperscript{38, 39} with normal left ventricular function. Isoflurane and the lowest dose of halothane increased heart rate in dogs with moderate left ventricular dysfunction. However, this anesthetic-induced tachycardia was attenuated compared with the increases in heart rate observed with isoflurane and halothane in healthy, chronically instrumented dogs.\textsuperscript{37} Similar results were reported in rabbits with doxorubicin-induced cardiomyopathy,\textsuperscript{40} and may reflect increases in central sympathetic nervous system tone and withdrawal of parasympathetic nervous system activity associated with the development of heart failure.\textsuperscript{31} Isoflurane, and to a lesser extent, halothane, caused profound reductions in left ventricular end-diastolic pressure and chamber dimension in dogs with pacing-induced cardiomyopathy. These findings support previously observed declines in pulmonary artery occlusion pressure during isoflurane and halothane anesthesia in patients with coronary artery disease and heart failure.\textsuperscript{30-32} and indicate that venodilation represents a major hemodynamic action of these anesthetics in the presence of moderate left ventricular dysfunction. The results also demonstrate that isoflurane and halothane cause similar dose-related decreases in cardiac output and stroke volume. These findings agree with the previous observations in patients with heart failure\textsuperscript{30} and cardiomyopathic rabbits.\textsuperscript{30} Despite isoflurane- and halothane-induced decreases in left ventricular filling pressures, the relative reductions in cardiac output and stroke volume that occurred in the current investigation were similar to those observed in this laboratory in dogs with normal left ventricular function.\textsuperscript{37} These findings suggest that volatile anesthetics do not adversely reduce cardiac output and stroke volume in the presence of moderate left ventricular dysfunction to a greater extent than that observed in the presence of normal ventricular function.

In contrast to the findings in patients,\textsuperscript{30} however, no changes in calculated systemic vascular resistance were observed during the administration of isoflurane and halothane in dogs with pacing-induced cardiomyopathy because decreases in mean arterial pressure were matched by reductions in cardiac output. These results suggest that isoflurane and halothane do not affect left ventricular afterload in the presence of moderate left ventricular function. This contention requires considerable qualification, however, because systemic vascular resistance has been shown to be an incomplete quantitative index of afterload \textit{in vivo}.\textsuperscript{42} The current findings in cardiomyopathic dogs contrast with the results in healthy dogs\textsuperscript{34, 35} and volunteers\textsuperscript{40} that demonstrate declines in systemic vascular resistance with isoflurane. Increases in peripheral sympathetic nervous system tone associated with left ventricular dysfunction\textsuperscript{11} may have attenuated expected decreases in systemic vascular tone associated during isoflurane anesthesia in the current investigation. This hypothesis remains to be tested, however.

Isoflurane and halothane caused dose-related decreases in myocardial contractility in dogs with moderate left ventricular dysfunction as quantified with $M_0$, a relatively heart rate- and load-independent index of inotropic state \textit{in vivo}. Concomitant reductions in $+\text{dP}/\text{d}t_{max}$ also were observed. Halothane-induced contractile depression was consistently greater than that caused by isoflurane at equi-MAC concentrations, confirming the findings of several previous investigations.\textsuperscript{34, 35, 43} that indicated that isoflurane and halothane cause differential reductions in contractile state in the...
normal canine heart. Halothane also produced relatively greater decreases in cardiac output than isoflurane at 1.4 (−31 ± 5 vs. −18 ± 7%, respectively) and 1.7 MAC (−44 ± 8 vs. −25 ± 8%, respectively). The magnitude of the depression of myocardial contractility produced by isoflurane and halothane in dogs with moderate left ventricular dysfunction was similar to that produced by these volatile anesthetics in healthy dogs. These results indicate that the negative inotropic actions of volatile anesthetics do not synergistically depress myocardial contractility in the presence of moderate left ventricular dysfunction.

In dogs with moderate left ventricular dysfunction, 1.1 MAC isoflurane caused an approximately 12% reduction in τ that occurred with a concomitant decline in left ventricular end-diastolic pressure, despite a simultaneous decrease in myocardial contractility. In contrast, isoflurane was shown to cause dose-related increases in τ in the normal heart, consistent with a direct negative lusitropic effect. The dependence of cardiac muscle relaxation on acute decreases in preload has been suggested previously in vitro, and recently established in vivo. Lower myofibrillar affinity for Ca²⁺ at shorter muscle lengths also has been well documented. Therefore, increases in the rate of left ventricular relaxation produced by isoflurane in dogs with pacing-induced cardiomyopathy probably occurred as a direct result of declines in left ventricular end-diastolic pressure and end-diastolic segment length and not because of a direct positive lusitropic effect. In contrast to the findings with isoflurane, the 1.1 MAC dose of halothane did not alter τ, and higher concentrations of this inhalational agent caused increases in this variable. These results can probably be attributed to more pronounced negative inotropic actions of halothane combined with less pronounced reductions in left ventricular preload. The value of τ also has been shown to be directly proportional to left ventricular afterload and inversely related to heart rate. However, the differential effects of 1.1 MAC isoflurane and halothane on left ventricular pressure decay are probably not related to alterations in these determinants of τ because no changes in calculated systemic vascular resistance occurred and similar increases in heart rate were observed in isoflurane- and halothane-anesthetized, cardiomyopathic dogs.

Isoflurane maintained TVI-E, decreased TVI-A, and increased TVI-E/A, consistent with preservation of the extent of early left ventricular filling, reduction in the contribution of atrial systole, and improvements in the pattern of left ventricular filling, respectively, in dogs with pacing-induced cardiomyopathy. These results occurred in conjunction with reductions in left ventricular end-diastolic pressure, indicating that isoflurane selectively enhances indices of left ventricular filling by causing favorable reductions in preload. This improvement in filling dynamics may serve to partially offset the negative inotropic effects of isoflurane in the setting of moderate left ventricular dysfunction. In contrast, halothane depressed indices of early and late ventricular filling and failed to improve the ratios of these variables, indicating that this volatile anesthetic does not enhance left ventricular filling dynamics. These results probably occurred because halothane caused greater declines in myocardial contractility and less pronounced reductions in left ventricular end-diastolic pressure than equi-MAC concentrations of isoflurane. Decreases in Ks were observed with isoflurane and halothane concomitant with reductions in left ventricular end-diastolic pressure and chamber dimension. Therefore, the venodilating actions of isoflurane, and to a lesser extent, halothane, decreased left ventricular end-diastolic pressure and end-diastolic length along the left ventricular diastolic pressure-length curve (fig. 1). These beneficial alterations in the operating position of the heart imply that the left ventricle operates on a flatter, more compliant region of the diastolic pressure-length relation in isoflurane- and halothane-anesthetized, compared with conscious, dogs with pacing-induced cardiomyopathy. Interpretation of the effects of isoflurane and halothane on left ventricular diastolic function in dogs with pacing-induced cardiomyopathy should also be qualified because the pericardium remained open after surgical implantation of instruments and during the development of left ventricular dysfunction.

In summary, the current results indicate that isoflurane shortens isovolumic relaxation, preserves the rate and extent of early left ventricular filling, enhances the pattern of filling, reduces regional chamber stiffness, and causes beneficial shifts in the operating position of the heart along left ventricular pressure–segment length diagram, despite producing simultaneous negative inotropic effects in chronically instrumented dogs with moderate left ventricular dysfunction induced by rapid pacing. These findings can probably be attributed to favorable reductions in left ventricular preload and not to direct lusitropic effects. In contrast, halothane caused more pronounced reductions in myocardial contractility and cardiac output than isoflurane at higher doses, an

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higher doses, and did not improve indices of relaxation or filling in dogs with moderate left ventricular function. Despite these actions, halothane anesthesia was relatively well-tolerated in dogs with moderate left ventricular dysfunction and did not precipitate frank left ventricular failure. Improvement of filling dynamics by isoflurane occurs in the setting of left ventricular dysfunction, and may contribute to relative maintenance of cardiac output under these conditions, despite simultaneous reductions in myocardial contractility.

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