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Isoflurane and Halothane Do Not Alter the Enhanced Afterload Sensitivity of Left Ventricular Relaxation in Dogs with Pacing-induced Cardiomyopathy

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Background: **The afterload dependence of left ventricular (LV) relaxation is accentuated in the failing heart. The authors tested the hypothesis that isoflurane and halothane alter the afterload sensitivity of LV relaxation in dogs with pacing-induced cardiomyopathy.**

Methods: **Dogs (n = 6) were chronically instrumented for measurement of LV and aortic pressures and subendocardial segment length. Hemodynamics were recorded, and LV relaxation was evaluated with a time constant of isovolumic relaxation (τ) under control conditions and during decreases and increases in LV load produced by abrupt inferior vena caval (IVC) occlusion and phenylephrine (intravenous infusion), respectively, in the conscious state and during isoflurane and halothane anesthesia (1.5 MAC) on separate days before and after the development of pacing-induced cardiomyopathy. The slope (R) of the τ *versus* LV end-systolic pressure (P_{es}) relation was also used to determine the afterload sensitivity of LV relaxation.**

Results: **IVC occlusion and phenylephrine produced similar or less profound changes in P_{es}, regional end-systolic force (an index of LV afterload), and end-systolic segment length in cardiomyopathic compared with healthy dogs. However, IVC occlusion and phenylephrine caused more pronounced alterations in τ in conscious and isoflurane- and halothane-anesthetized dogs after the development of cardiomyopathy. R was also greater in cardiomyopathic compared with healthy dogs (*e.g.*, 0.32 ± 0.03 before pacing to 1.00 ± 0.13 ms/mmHg in conscious dogs). No differences in the load dependence of LV relaxation were observed between the conscious and anesthetized states before and after production of LV dysfunction.**

Conclusions: **The results indicate that isoflurane and halothane do not alter the afterload dependence of LV relaxation in the normal and cardiomyopathic heart. The lack of effect of the volatile anesthetics is probably related to anesthetic-induced reductions in the resistance to LV ejection concomitant with simultaneous negative inotropic effects. (Key words: Anesthetics, volatile: isoflurane; halothane. Heart: diastole; diastolic function; isovolumic relaxation. Heart: failure; rapid pacing; cardiomyopathy.**

RELAXATION of the left ventricle (LV) is an energy-dependent process that is delayed by increases in afterload during LV ejection.[1] This afterload dependence of LV relaxation was first characterized in isolated cardiac muscle preparations from normal hearts.[2,3] More recent investigations in experimental models of LV dysfunction[4,5] and patients with congestive heart failure[6] have indicated that the afterload dependence of LV relaxation is enhanced in failing myocardium. This observation has important clinical consequences because afterload reduction may not only increase LV systolic performance by decreasing impedance to LV ejection but may also increase the rate of LV relaxation and contribute to improvements in LV diastolic filling and compliance.[7] The mechanisms responsible for the increased afterload dependence of relaxation in heart failure have not been completely elucidated, although favorable alterations in intracellular calcium (Ca^{2+}) regulation during diastole[8-10] and improvements in the LV systolic loading sequence during ejection[5] probably play important roles in this process.

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The effects of volatile anesthetics, including isoflurane and halothane, on the afterload dependence of LV relaxation have not been examined. Previous studies suggest that reductions in myocardial contractility adversely modify the afterload sensitivity of LV relaxation.[4,6] Thus, volatile anesthetics may primarily exacerbate the afterload dependence of LV relaxation because these drugs have been shown to produce direct negative inotropic effects in the healthy and in the cardiomyopathic heart.[11] Conversely, isoflurane and halothane decrease LV end-systolic wall stress and increase total arterial compliance *in vivo*,[12-14] suggesting that decreases in the resistance to LV ejection produced by volatile anesthetics may favorably decrease the afterload sensitivity of LV relaxation. The present investigation tested the hypothesis that isoflurane and halothane alter the afterload dependence of LV relaxation in dogs before and after the development of rapid LV pacing-induced cardiomyopathy. This experimental model is characterized by biventricular chamber dilation with elevated filling pressures,[15,16] abnormalities in intracellular Ca^{2+} regulation,[9,10] and LV systolic[17,18] and diastolic dysfunction.[19,20] These features are similar to those observed in patients with idiopathic dilated cardiomyopathy.[21] Pacing-induced cardiomyopathy can be reproducibly generated in dogs and provides a useful model in which to study the increased afterload sensitivity of LV relaxation that occurs in the presence of LV 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 1996).

Surgical Preparation

The surgical implantation of instruments has been previously described in detail.[22,23] 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), LV pressure (high fidelity, miniature micromanometer), and the peak rate of increase and decreases of LV pressure (dP/dt_{max} and $-dP/dt_{min}$, respectively). A hydraulic vascular occluder was placed around the inferior vena cava (IVC) for abrupt reduction of left ventricular preload. Stainless steel pacing electrodes were sutured to the epicardial surface of the LV 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 was closed in layers, and the pneumothorax was 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 that was also housed in a jacket pocket.[22,23]

All dogs received systemic analgesics (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 (cephalothin, 40 mg/kg, and gentamicin, 4.5 mg/kg) 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 30 ms before LV $-dP/dt_{min}$ and immediately before the onset of LV isovolumic contraction, respectively. Percent segment shortening (%SS) was determined using the equation: $\%SS = (EDL\text{-}ESL) \cdot 100 \cdot EDL^{-1}$. Regional end-systolic force (ESF) was calculated as the product of LV end-systolic pressure and ESL, and it was used as an estimate of segmental LV afterload.[24] Hemodynamic data were continuously recorded on a polygraph and simultaneously digitized and recorded on a computer for subsequent analysis of LV pressure waveforms.

Experimental Protocol

All dogs (n = 6; weight = 26.7 ± 0.3 kg; mean ± SEM) were fasted overnight. Fluid deficits were replaced before experimentation with 0.9% saline (500 ml) and continued at 3 $ml \cdot kg^{-1} \cdot h^{-1}$ for the duration of each experiment. Baseline systemic hemodynamics and LV pressure waveforms were recorded in the conscious state before alterations in LV loading conditions were produced. Respiratory variation in LV pressure in conscious dogs was later reduced off-line by digital subtraction of the continuous intrathoracic pressure waveform from the LV pressure waveform. The time constant of LV isovolumic relaxation (τ) was calculated

using the derivative method.[25] A three-constant exponential equation was used as the basis for the calculation of τ assuming a nonzero asymptote of LV pressure decay: $P = ae^{-t/\tau} + c$, where P = LV pressure, t = time (ms), c = the asymptote of LV pressure decline, and a + c = LV pressure at peak negative dP/dt. It can be easily shown that $dP/dt = (c - P)/\tau$. LV negative dP/dt was plotted against LV pressure between peak negative dP/dt and 5 mmHg above LV end-diastolic pressure to yield τ as the negative inverse of the slope. Load reduction was accomplished by abruptly inflating the IVC balloon cuff occluder, resulting in 20–30 mmHg decline in LV end-systolic pressure over 8–15 cardiac cycles. Hemodynamics and waveforms were continuously recorded, and τ was calculated immediately before, during, at the peak reduction in LV end-systolic pressure, and after the IVC occlusion. The load dependence of relaxation during a reduction in afterload was determined using the method of Eichhorn *et al.*[6] Briefly, τ was calculated for each cardiac cycle during the IVC occlusion and plotted against the corresponding LV end-systolic pressure (P_{es}; fig. 1). A linear regression analysis was used to describe the relation between these variables with the equation: $\tau = R \cdot P_{es} + \tau_o$, where R = the $\tau - P_{es}$ slope and τ_o = the value of τ when P_{es} = zero mmHg. Increases in afterload were then produced with a phenylephrine infusion (dose range, 20–60 mg/min, intravenously), resulting in a 30-mmHg increase in P_{es}. After hemodynamics and LV pressure waveforms had been recorded and after τ had been determined at the peak increase of LV end-systolic pressure, the phenylephrine infusion was discontinued, and hemodynamics were allowed to return to baseline levels.

Dogs were assigned to receive isoflurane or halothane on separate experimental days. After inhalational induction and tracheal intubation, anesthesia was maintained during positive pressure ventilation at 1.5 MAC (end-tidal concentration) isoflurane or halothane in an air-oxygen (25%) mixture. End-tidal concentrations of volatile anesthetics at the tip of the endotracheal tube were measured by an infrared gas analyzer that was 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. Hemodynamics and LV pressure waveforms were recorded after 30-min equilibration in the anesthetized state. Decreases and increases in load were then produced by abrupt IVC occlusion and phenylephrine infusion, respectively, and hemodynamics were obtained as described previously.

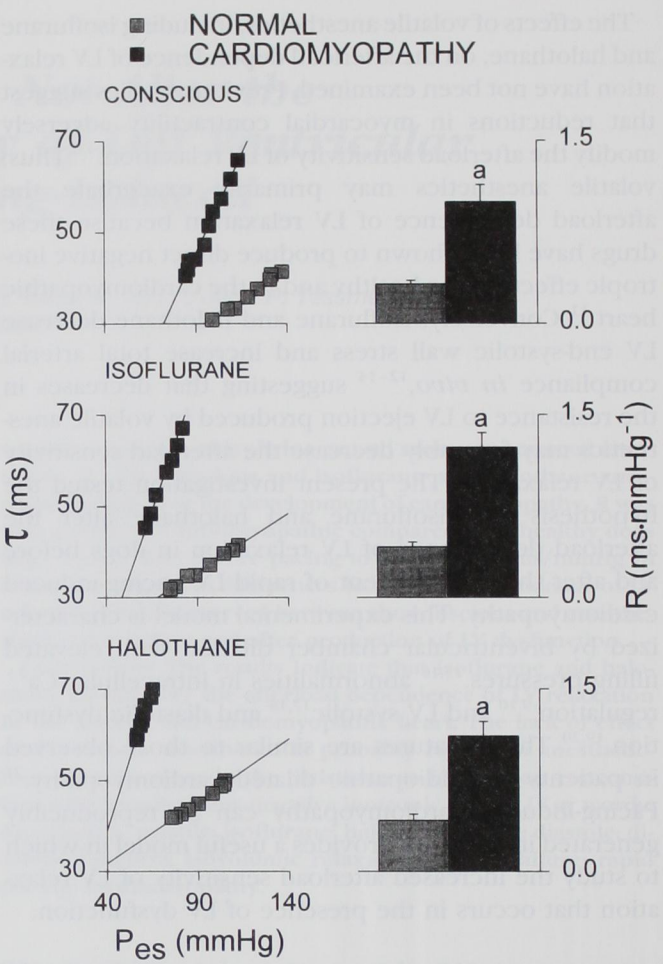

Fig. 1. Linear relationship between the time constant of isovolumic relaxation (τ) and left ventricular end-systolic pressure (P_{es}) during inferior vena caval occlusion (*left panels*) in a typical dog before (*grey squares*) and after (*solid squares*) the development of pacing-induced cardiomyopathy in the conscious state (*top panel*, $\tau = 0.29 \times P_{es} + 2.2$; $r^2 = 0.99$ before compared with $\tau = 0.86 \times P_{es} - 37.0$; $r^2 = 0.98$ after pacing) and during isoflurane (*middle panel*, $\tau = 0.26 \times P_{es} + 12.6$; $r^2 = 0.98$ before compared with $\tau = 1.14 \times P_{es} - 25.7$; $r^2 = 0.99$ after pacing) and halothane (*bottom panel*, $\tau = 0.27 \times P_{es} + 20.9$; $r^2 = 0.98$ before compared with $\tau = 1.25 \times P_{es} - 11.3$; $r^2 = 0.99$ after pacing) anesthesia. The histograms on the right illustrate the slope (R) the τ *versus* P_{es} relationship in the conscious state (*top right panel*) and during isoflurane (*middle right panel*) and halothane (*bottom right panel*) anesthesia before (*hatched bars*) and after pacing (*solid bars*). [a]Significantly different from normal myocardium.

After control experiments had been completed, the LV of each dog was continuously paced at rates between 220 and 240 beats/min as previously described.[22,23] Dogs were brought to the laboratory on

Table 1. Hemodynamic Effects of Altered Loading Conditions in Conscious and Isoflurane-anesthetized Dogs with Normal Left Ventricular Function

	Conscious			Isoflurane (1.5 MAC)		
	Control	IVC Occlusion	Phenylephrine	ISO Alone	IVC Occlusion	Phenylephrine
HR (beats · min^{-1})	86 ± 3	111 ± 3*	91 ± 7	129 ± 8*	131 ± 7	84 ± 12†
MAP (mmHg)	109 ± 4	81 ± 4*	140 ± 3*	82 ± 7*	58 ± 5†‡	112 ± 5†‡
P_{es} (mmHg)	133 ± 3	90 ± 3*	167 ± 2*	96 ± 4*	63 ± 6†‡	127 ± 4†‡
P_{ed} (mmHg)	8 ± 1	−2 ± 2	16 ± 2*	7 ± 1	0 ± 2†	5 ± 1†
$+dP/dt_{max}$ (mmHg · s^{-1})	2,430 ± 185	1,938 ± 107*	2,642 ± 275	1,544 ± 162*	1,209 ± 146†‡	1,887 ± 172†‡
$-dP/dt_{min}$ (mmHg · s^{-1})	−2,351 ± 138	−2,100 ± 62	−2,741 ± 230*	−1,592 ± 158*	−1,259 ± 177†‡	−1,814 ± 94‡
τ (ms)	37 ± 2	29 ± 2*	49 ± 5*	40 ± 2	36 ± 2	52 ± 3†
EDL (mm)	23.1 ± 1.3	18.9 ± 1.3*	25.1 ± 1.2*	20.8 ± 1.4*	18.3 ± 1.4†	23.6 ± 1.2†
ESL (mm)	16.9 ± 1.2	14.9 ± 1.3*	19.0 ± 1.3*	16.9 ± 1.4	15.9 ± 1.6	18.4 ± 1.3†
SS (%)	27.0 ± 1.5	21.6 ± 2.9*	24.7 ± 2.4	18.8 ± 2.0*	13.5 ± 3.2†‡	23.1 ± 2.1†
ESF (mmHg · mm)	2,246 ± 141	1,325 ± 98*	3,163 ± 236*	1,625 ± 166*	993 ± 123†‡	2,350 ± 217†‡

Data are mean ± SEM; n = 6.

IVC = inferior vena cava; ISO = isoflurane; HR = heart rate; MAP = mean aortic blood pressure; P_{es} and P_{ed} = left ventricular end-systolic and end-diastolic pressure, respectively; $+dP/dt_{max}$ and $-dP/dt_{min}$ = maximum rate of increase and decrease of left ventricular pressure, respectively; τ = time constant of isovolumic relaxation; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; ESF = regional end-systolic force.

* Significantly ($P < 0.05$) different from control.

† Significantly ($P < 0.05$) different from ISO alone.

‡ Significantly ($P < 0.05$) different from corresponding conscious value.

each day after the initiation of pacing to monitor the development of pacing-induced cardiomyopathy. Pacing was discontinued during and restarted immediately after this brief period of daily hemodynamic monitoring and was temporarily discontinued for the duration of each experiment. Systemic hemodynamics and LV pressure waveforms were recorded under steady-state conditions 30 min after pacing had been discontinued in conscious dogs (sinus rhythm), after 30 min equilibration at 1.5 MAC isoflurane or halothane, and during a decrease and increase in LV afterload in the conscious and anesthetized states as described previously. After the completion of each experiment, emergence was allowed to occur, and pacing was reinstituted. Thus, 24 experiments in four separate groups (isoflurane and halothane before and after the development of pacing-induced cardiomyopathy) were performed in the same six chronically instrumented dogs.

Statistical Analysis

Statistical analysis of the data within and between groups before and after rapid LV pacing, during the conscious state or the isoflurane- and halothane-anesthetized states, and during alterations in LV loading conditions was performed by analysis of variance (ANOVA) with repeated measures, followed by use of Student's *t* test with Duncan's adjustment for multiplicity. Linear regression analysis was used to describe the relation between τ and P_{es} during IVC occlusion. Changes were considered to be statistically significant when the *P* value was <0.05. All data are expressed as mean ± SEM.

Results

Occlusion of the IVC caused significant increases in heart rate and decreases in mean arterial pressure and LV end-systolic and end-diastolic pressures (P_{es} and P_{ed}, respectively) in conscious dogs before pacing (tables 1 and 2). Concomitant decreases in EDL, ESL, and ESF were observed. Reductions in dP/dt_{max}, %SS, and τ also occurred. Administration of phenylephrine produced hemodynamic effects in conscious dogs that were nearly opposite to those caused by IVC occlusion. Increases in mean arterial pressure, P_{es}, P_{ed}, EDL, ESL, and ESF were accompanied by increases in τ and the magnitude of $-dP/dt_{min}$.

Isoflurane and halothane produced similar but not identical hemodynamic effects (tables 1 and 2, respectively). Isoflurane and halothane increased heart rate and decreased mean arterial pressure and P_{es}. P_{ed} and

Table 2. Hemodynamic Effects of Altered Loading Conditions in Conscious and Halothane-anesthetized Dogs with Normal Left Ventricular Function

	Conscious			Halothane (1.5 MAC)		
	Control	IVC Occlusion	Phenylephrine	HAL Alone	IVC Occlusion	Phenylephrine
HR (beats · min^{-1})	82 ± 4	112 ± 4*	96 ± 10	103 ± 8	110 ± 6	106 ± 4
MAP (mmHg)	101 ± 4	74 ± 2*	129 ± 5*	76 ± 3*	58 ± 2†‡	108 ± 3†‡
P_{es} (mmHg)	123 ± 7	85 ± 3*	160 ± 8*	90 ± 4*	64 ± 1†‡	124 ± 3†‡
P_{ed} (mmHg)	6 ± 2	−4 ± 2*	15 ± 3*	8 ± 1	2 ± 2†‡	18 ± 2†
$+dP/dt_{max}$ (mmHg · s^{-1})	2,398 ± 158	1,887 ± 144*	2,630 ± 280	1,167 ± 83*	985 ± 71‡	1,246 ± 54‡
$-dP/dt_{min}$ (mmHg · s^{-1})	−2,252 ± 161	−1,919 ± 152	−2,779 ± 325*	−1,404 ± 134*	−1,185 ± 103‡	−1,518 ± 76‡
τ (ms)	39 ± 2	29 ± 2*	48 ± 4*	48 ± 4*	39 ± 3†‡	61 ± 4†‡
EDL (mm)	23.3 ± 1.2	19.3 ± 1.2*	24.9 ± 1.4*	22.8 ± 1.5	19.8 ± 1.4†	25.2 ± 1.4†
ESL (mm)	17.2 ± 1.1	14.5 ± 1.1*	18.6 ± 1.0*	18.8 ± 1.0*	17.0 ± 1.1†‡	20.9 ± 1.0†‡
SS (%)	26.4 ± 1.5	24.9 ± 3.9	25.1 ± 1.3	17.0 ± 1.6*	14.0 ± 2.7	17.1 ± 1.4
ESF (mmHg · mm)	2,084 ± 73	1,216 ± 80*	2,934 ± 84*	1,676 ± 38*	1,086 ± 66†‡	2,587 ± 110†‡

Data are mean ± SEM; n = 6.

IVC = inferior vena cava; HAL = halothane; HR = heart rate; MAP = mean aortic blood pressure; P_{es} and P_{ed} = left ventricular end-systolic and end-diastolic pressure, respectively; $+dP/dt_{max}$ and $-dP/dt_{min}$ = maximum rate of increase and decrease of left ventricular pressure, respectively; τ = time constant of isovolumic relaxation; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; ESF = regional end-systolic force.

* Significantly ($P < 0.05$) different from control.

† Significantly ($P < 0.05$) different from HAL alone.

‡ Significantly ($P < 0.05$) different from corresponding conscious value.

EDL decreased in isoflurane- but not in halothane-anesthetized dogs. Conversely, an increase in ESL was observed in the presence of halothane but not isoflurane. Isoflurane and halothane caused similar reductions in ESF. Decreases in dP/dt_{max} and %SS produced by halothane were greater than those observed during isoflurane anesthesia. No change in τ occurred during administration of isoflurane. In contrast, halothane increased τ. Alterations in load caused by IVC occlusion and phenylephrine produced hemodynamic actions during isoflurane and halothane anesthesia that were similar but not identical to those observed in the conscious state. Alterations in mean arterial pressure and P_{es} produced by these interventions were accompanied by simultaneous changes in P_{ed}, EDL, dP/dt_{max}, and %SS. In contrast to the findings in conscious dogs, IVC occlusion did not affect heart rate in the presence of isoflurane and halothane. Phenylephrine decreased heart rate in isoflurane- but not halothane-anesthetized dogs. The slope (R) of the $\tau - P_{es}$ relationship was similar in the conscious and anesthetized states (*e.g.*, 0.32 ± 0.03 during control to 0.41 ± 0.05 ms/mmHg during 1.5 MAC isoflurane, $P > 0.05$; fig. 1). An average of 9 ± 1 cardiac cycles were used to determine R with $r^2 \geq 0.93$ in dogs before pacing. Changes in τ (fig. 2), ESF (fig. 3), and ESL (fig. 4) produced by IVC occlusion and phenylephrine during administration of isoflurane and halothane were also similar to those observed in conscious dogs.

Chronic rapid ventricular pacing produced marked changes in hemodynamics (*e.g.*, table 1 *vs.* table 3) that were similar to those previously described.[22,23] Significant increases in baseline heart rate (underlying sinus rhythm), P_{ed}, EDL, and ESL and decreases in mean arterial pressure and P_{es} were observed after 18 ± 2 days of pacing. No change in ESF occurred. Pacing also caused direct negative inotropic and lusitropic effects as indicated by reductions in dP/dt_{max}, the magnitude of $-dP/dt_{min}$, and %SS and increases in τ (*e.g.*, 37 ± 2 before to 62 ± 7 ms after pacing; table 1 *vs.* table 3). Decreases in mean arterial pressure and P_{es} produced by IVC occlusion in cardiomyopathic dogs (tables 3 and 4) were similar to those observed in healthy dogs. The slope of the $\tau - P_{es}$ relation obtained during IVC occlusion was significantly greater in conscious dogs with cardiomyopathy (R, 0.32 ± 0.03 before pacing to 1.00 ± 0.13 ms/mmHg after pacing; $P < 0.05$; fig 1). An average of 8 ± 1 cardiac cycles were used to determine R with $r^2 \geq 0.92$ in dogs after pacing. Decreases in τ produced by IVC occlusion after pacing were also greater in magnitude than those observed before pacing was initiated (fig. 2). These findings occurred despite the fact that

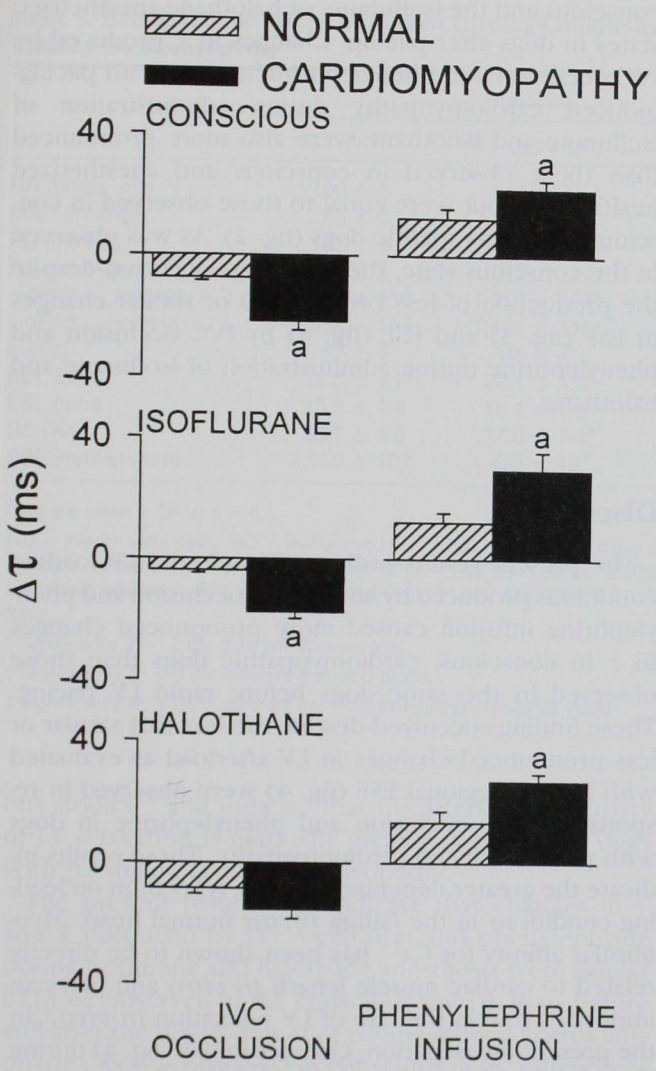

Fig. 2. Histograms illustrating changes (Δ) in the time constant of isovolumic relaxation (τ) during a decrease and increase in left ventricular afterload produced by inferior vena caval (IVC) occlusion (*left*) and phenylephrine infusion (*right*), respectively, in the conscious state (*top panel*) and during isoflurane (*middle panel*) and halothane (*bottom panel*) anesthesia before (*hatched bar;* normal) and after (*solid bar;* cardiomyopathy) the development of pacing-induced cardiomyopathy. [a]Significantly different from normal myocardium.

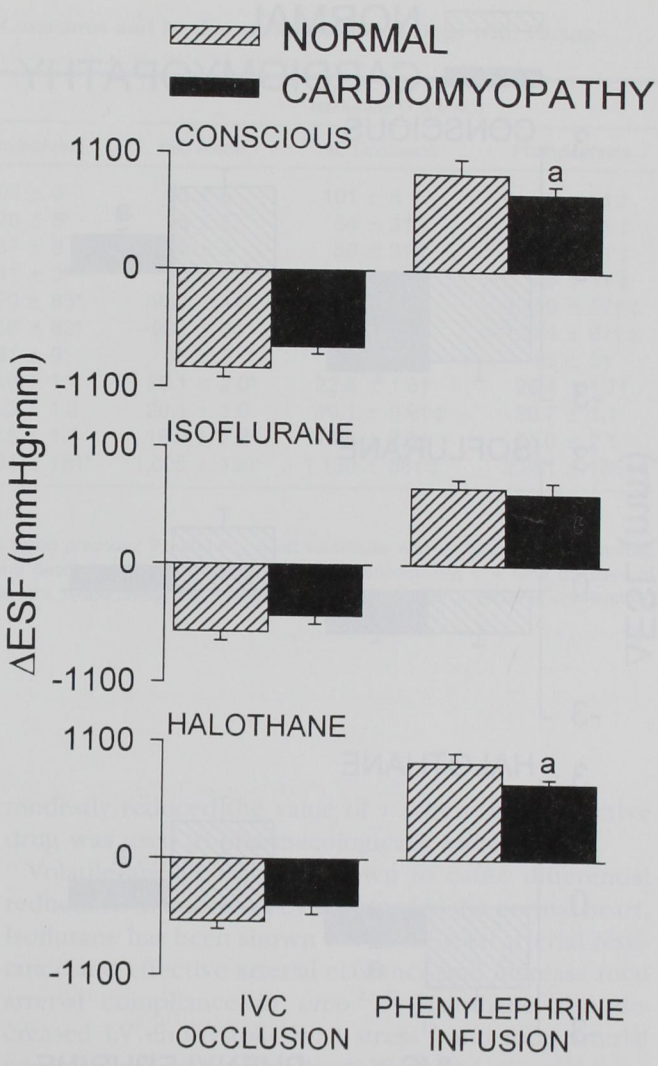

Fig. 3. Histograms illustrating changes (Δ) in regional end-systolic force (ESF) during a decrease and increase in left ventricular afterload produced by inferior vena caval (IVC) occlusion (*left*) and phenylephrine infusion (*right*), respectively, in the conscious state (*top panel*) and during isoflurane (*middle panel*) and halothane (*bottom panel*) anesthesia before (*hatched bar;* normal) and after (*solid bar;* cardiomyopathy) the development of pacing-induced cardiomyopathy. [a]Significantly different from normal myocardium.

IVC occlusion produced similar or less pronounced reductions in ESF (fig. 3) and ESL (fig. 4) in the presence of pacing-induced cardiomyopathy. Analogously, increases in τ during administration of phenylephrine were greater in conscious, cardiomyopathic than in healthy dogs concomitant with similar or less profound increases in ESF and ESL.

Isoflurane and halothane decreased mean arterial pressure, P_{es}, P_{ed}, EDL, and ESF in dogs with pacing-induced cardiomyopathy (tables 3 and 4). No changes in heart rate and ESL occurred with the volatile anesthetics. Similar to the findings in dogs before pacing, halothane caused more pronounced decreases in myocardial contractility (dP/dt_{max} and %SS) than isoflurane. Halothane, but not isoflurane, increased τ in cardiomyopathic dogs. Occlusion of the IVC and administration of phenylephrine caused hemodynamic effects in anesthetized dogs

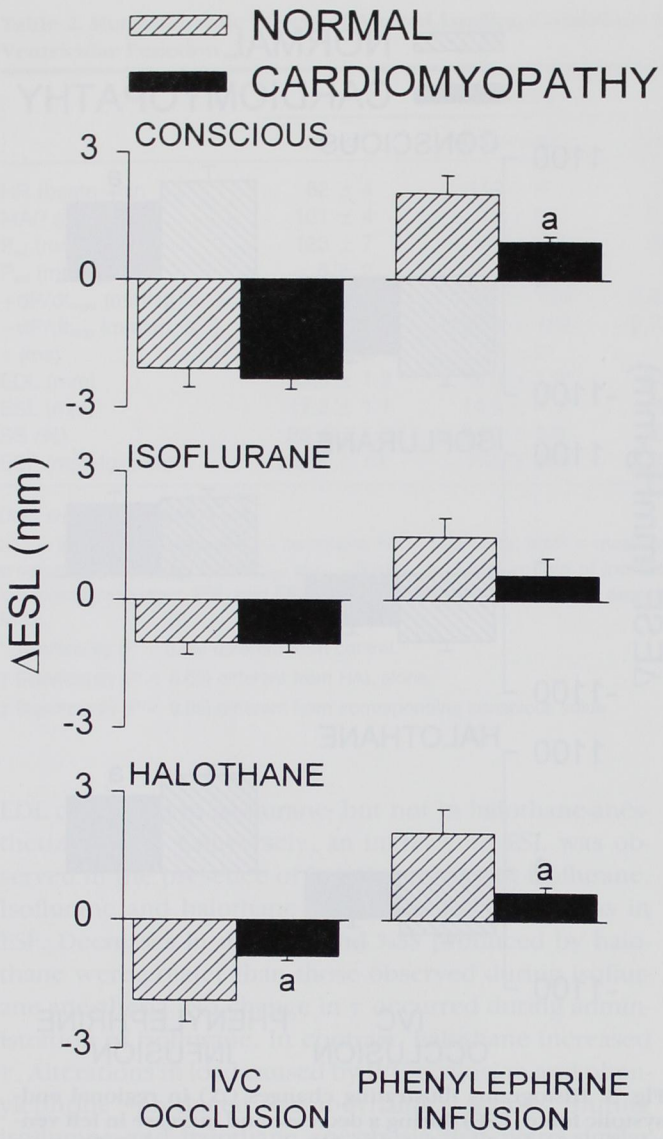

Fig. 4. Histograms illustrating changes (Δ) in end-systolic segment length (ESL) during a decrease and increase in left ventricular afterload produced by inferior vena caval (IVC) occlusion (*left*) and phenylephrine infusion (*right*), respectively, in the conscious state (*top panel*) and during isoflurane (*middle panel*) and halothane (*bottom panel*) anesthesia before (*hatched bar;* normal) and after (*solid bar;* cardiomyopathy) the development of pacing-induced cardiomyopathy. [a]Significantly different from normal myocardium.

after pacing that were similar to those observed before pacing. The slope (R) of the $\tau - P_{es}$ relation was significantly greater in cardiomyopathic compared with healthy dogs during isoflurane and halothane anesthesia (fig. 1), similar to the findings in conscious dogs. However, no differences in R were observed between the conscious and the isoflurane- or halothane-anesthetized states in dogs after pacing. Changes in τ produced by IVC occlusion and phenylephrine in dogs with pacing-induced cardiomyopathy during administration of isoflurane and halothane were also more pronounced than those observed in conscious and anesthetized healthy dogs but were equal to those observed in conscious, cardiomyopathic dogs (fig. 2). As was observed in the conscious state, these findings occurred despite the production of less pronounced or similar changes in ESF (fig. 3) and ESL (fig. 4) by IVC occlusion and phenylephrine during administration of isoflurane and halothane.

Discussion

The present results indicate that altered LV loading conditions produced by abrupt IVC occlusion and phenylephrine infusion caused more pronounced changes in τ in conscious, cardiomyopathic dogs than those observed in the same dogs before rapid LV pacing. These findings occurred despite the fact that similar or less pronounced changes in LV afterload as evaluated with P_{es} and regional ESF (fig. 4) were observed in response to IVC occlusion and phenylephrine in dogs with pacing-induced cardiomyopathy. These results indicate the greater dependence of LV relaxation on loading conditions in the failing *versus* normal heart. Myofibrillar affinity for Ca^{2+} has been shown to be directly related to cardiac muscle length *in vitro* and plays an important role in the rate of LV relaxation *in vivo*.[3] In the present investigation, changes in ESL (fig. 4) during alterations in LV loading conditions were equal or greater in dogs before *versus* after development of cardiac dysfunction. Thus, the differences in the magnitude of changes in τ observed between healthy and cardiomyopathic dogs probably cannot be attributed to differences in LV afterload and end-systolic muscle length between these experimental groups. The slope (R) of the $\tau - P_{es}$ relationship derived from a series of consecutive cardiac cycles during IVC occlusion has been shown to be a linear, relatively afterload-independent index of LV relaxation that incorporates changes in LV end-systolic pressure into its calculation.[4,6] Increases in R have been used previously to quantify enhanced afterload sensitivity in patients with congestive heart failure.[6] In the present study, R was significantly greater in dogs after pacing (fig. 2). These findings taken together confirm and extend the observations of previ-

Table 3. Hemodynamic Effects of Altered Loading Conditions in Conscious and Isoflurane-anesthetized Dogs with Pacing-induced Cardiomyopathy

	Conscious			Isoflurane (1.5 MAC)		
	Control	IVC Occlusion	Phenylephrine	ISO Alone	IVC Occlusion	Phenylephrine
HR (beats · min^{-1})	100 ± 6	117 ± 5	108 ± 6	98 ± 6	101 ± 8	72 ± 9†‡
MAP (mmHg)	88 ± 5	72 ± 3*	120 ± 5*	66 ± 5*	54 ± 3†‡	98 ± 4†‡
P_{es} (mmHg)	107 ± 6	81 ± 4*	137 ± 8	79 ± 4*	59 ± 3†‡	110 ± 3†‡
P_{ed} (mmHg)	24 ± 1	2 ± 1*	31 ± 3*	15 ± 1*	7 ± 1†‡	25 ± 1†‡
$+dP/dt_{max}$ (mmHg · s^{-1})	1,518 ± 116	1,259 ± 104*	1,770 ± 85*	939 ± 44*	858 ± 39‡	1,459 ± 57†‡
$-dP/dt_{min}$ (mmHg · s^{-1})	−1,536 ± 114	−1,491 ± 115*	−1,756 ± 62*	−982 ± 64*	−930 ± 44‡	−1,264 ± 67†‡
τ (ms)	62 ± 7	38 ± 4*	81 ± 9*	63 ± 3	46 ± 3†	93 ± 5†
EDL (mm)	26.5 ± 1.7	22.1 ± 1.6*	26.9 ± 1.7	25.1 ± 2.0*	22.6 ± 1.6†	26.4 ± 1.7†
ESL (mm)	20.5 ± 1.4	18.1 ± 1.3*	21.3 ± 1.3	20.1 ± 1.0	19.1 ± 0.9†‡	20.7 ± 1.1
SS (%)	22.7 ± 1.0	17.8 ± 1.4*	20.5 ± 1.4	18.9 ± 2.2*	14.6 ± 2.0†	21.0 ± 2.1
ESF (mmHg · mm)	2,159 ± 107	1,439 ± 48*	2,894 ± 181*	1,605 ± 139*	1,130 ± 88†‡	2,281 ± 135†‡

Data are mean ± SEM; n = 6.

IVC = inferior vena cava; ISO = isoflurane; HR = heart rate; MAP = mean aortic blood pressure; P_{es} and P_{ed} = left ventricular end-systolic and end-diastolic pressure, respectively; $+dP/dt_{max}$ and $-dP/dt_{min}$ = maximum rate of increase and decrease of left ventricular pressure, respectively; τ = time constant of isovolumic relaxation; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; ESF = regional end-systolic force.

* Significantly ($P < 0.05$) different from control.

† Significantly ($P < 0.05$) different from ISO alone.

‡ Significantly ($P < 0.05$) different from corresponding conscious value.

ous studies[5,6] and indicate that the afterload sensitivity of LV relaxation is markedly greater in conscious dogs with pacing-induced cardiomyopathy.

The present results also indicate that changes in τ and R produced by IVC occlusion and phenylephrine during isoflurane and halothane anesthesia were similar to those observed in the conscious state in dogs before and after the development of pacing-induced cardiomyopathy. As was observed in conscious dogs, differences in the changes in τ and R that occurred in anesthetized dogs before and after pacing did not result from differences in indices of LV afterload or end-systolic muscle length between experimental groups. Changes in ESF and ESL resulting from IVC occlusion and phenylephrine were equal or less pronounced in cardiomyopathic compared with healthy dogs during anesthesia. These findings establish that isoflurane and halothane do not alter the afterload dependence of LV relaxation in the normal and cardiomyopathic heart. These results should be qualified, to some degree, because phenylephrine increased $+dP/dt_{max}$ in cardiomyopathic but not in healthy dogs, consistent with a small positive inotropic effect. Although $+dP/dt_{max}$ is known to depend on heart rate, LV loading conditions, and peak developed LV systolic pressure,[26] increases in $+dP/dt_{max}$ caused by phenylephrine in the failing heart may have modestly reduced the value of τ when this vasoactive drug was used to pharmacologically increase P_{es}.

Volatile anesthetics are known to cause differential reductions in indices of LV afterload in the normal heart. Isoflurane has been shown to reduce total arterial resistance and effective arterial elastance and increase total arterial compliance *in vivo*.[13,27] Halothane also decreased LV end-systolic wall stress[12] and total arterial compliance[13] in healthy dogs. We[22] and others[12] have demonstrated that isoflurane and halothane reduce ESF and LV end-systolic wall stress in canine models of LV dysfunction. These actions should contribute to improved LV systolic performance because of reductions in resistance to ejection. However, anesthetics also cause dose-related depression of myocardial contractility in the intact heart by disrupting Ca^{2+} metabolism in the cardiac myocyte.[28] This detrimental decrease in systolic function may have effectively negated any potential benefit accrued by anesthetic-induced reductions in LV afterload in determining the effects of these agents on the afterload dependence of LV relaxation in the present study. Higher concentrations (> 1 MAC) of isoflurane and halothane have been shown to impair the mechanical matching of the LV to the arterial circulation in a series elastic chamber model of LV-arterial coupling *in vivo*.[27,29] Thus, although isoflurane and hal-

Table 4. Hemodynamic Effects of Altered Loading Conditions in Conscious and Halothane-anesthetized Dogs with Pacing-induced Cardiomyopathy

	Conscious			Halothane (1.5 MAC)		
	Control	IVC Occlusion	Phenylephrine	HAL Alone	IVC Occlusion	Phenylephrine
HR (beats · min^{-1})	101 ± 5	122 ± 9*	108 ± 4	96 ± 7	105 ± 6	89 ± 6
MAP (mmHg)	90 ± 4	67 ± 4*	125 ± 4*	61 ± 4*	49 ± 1b†‡	93 ± 4†‡
P_{es} (mmHg)	112 ± 6	75 ± 3*	143 ± 3*	69 ± 5*	51 ± 2†‡	100 ± 4†‡
P_{ed} (mmHg)	24 ± 2	1 ± 1*	38 ± 3*	17 ± 2*	8 ± 2†‡	30 ± 3†‡
$+dP/dt_{max}$ (mmHg · s^{-1})	1,560 ± 75	1,198 ± 50*	1,675 ± 78*	753 ± 55*	656 ± 24‡	968 ± 54†‡
$-dP/dt_{min}$ (mmHg · s^{-1})	−1,549 ± 106	−1,376 ± 81*	−1,699 ± 98*	−881 ± 94*	−716 ± 49‡	−1,137 ± 75†‡
τ (ms)	61 ± 6	40 ± 3*	84 ± 15*	69 ± 4*	53 ± 5†‡	96 ± 6†
EDL (mm)	26.1 ± 1.9	22.3 ± 1.6*	26.1 ± 1.8	25.4 ± 2.0*	23.3 ± 1.8†	26.2 ± 1.9
ESL (mm)	20.5 ± 1.6	18.1 ± 1.2*	21.5 ± 1.7	21.6 ± 1.6*	20.7 ± 1.5†‡	22.2 ± 1.5
SS (%)	21.3 ± 0.8	18.4 ± 2.0	18.1 ± 0.9	14.8 ± 1.2*	10.8 ± 1.5†‡	15.2 ± 1.4‡
ESF (mmHg · mm)	2,293 ± 192	1,349 ± 76*	3,076 ± 240*	1,494 ± 149*	1,056 ± 72†	2,208 ± 168†‡

Data are mean ± SEM; n = 6.

IVC = inferior vena cava; HAL = halothane; HR = heart rate; MAP = mean aortic blood pressure; P_{es} and P_{ed} = left ventricular end-systolic and end-diastolic pressure, respectively; $+dP/dt_{max}$ and $-dP/dt_{min}$ = maximum rate of increase and decrease of left ventricular pressure, respectively; τ = time constant of isovolumic relaxation; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; ESF = regional end-systolic force.

* Significantly ($P < 0.05$) different from control.

† Significantly ($P < 0.05$) different from HAL alone.

‡ Significantly ($P < 0.05$) different from corresponding conscious value.

othane cause primary reductions in resistance to LV ejection as evaluated with ESF before and after pacing, these drugs probably do not reduce the afterload sensitivity of LV relaxation because of concomitant negative inotropic effects.

Volatile anesthetics have been shown to decrease the rate of LV relaxation in the normal heart concomitant with depression of myocardial contractility.[11] Volatile anesthetics may theoretically produce negative lusitropic effects and adversely alter afterload dependence of LV relaxation because prolongation of the diastolic Ca^{2+} transient may occur as a result of increased Ca^{2+} leak from the sarcoplasmic reticulum.[30] Recent evidence also suggests that alterations in indices of LV relaxation produced by halothane occur as a result of myocardial depression and not because of direct alterations in diastolic relaxation mechanics.[12] Thus, it is unlikely that volatile anesthetics would directly affect the afterload dependence of LV relaxation by adversely altering intracellular diastolic Ca^{2+} homeostasis in normal myocardium. Theoretically, such a process may be possible in failing myocardium because preexisting abnormalities in diastolic Ca^{2+} regulation are characteristic features that contribute to LV diastolic dysfunction in this setting.[8] Although this contention remains to be tested *in vitro*, we have demonstrated here and in a previous study[22] that LV relaxation is not synergistically worsened by volatile anesthetics and, in the case of isoflurane, may actually be improved in the presence of LV dysfunction. These findings probably occurred as a result of favorable reductions in preload (P_{ed} and EDL) and afterload (as determined by ESF) and not because of direct positive lusitropic effects. These data confirm the clinical observations that halothane and isoflurane produce beneficial reductions in LV preload and afterload in patients with compensated heart failure[31,32] and suggest that anesthetic-induced changes in LV loading conditions play a predominant role in determining the relaxation behavior of the cardiomyopathic heart *in vivo*.

The present results should be interpreted within the constraints of several potential limitations. Regional ESF (calculated as the product of P_{es} and ESL) was used as an estimate of global ESF and LV afterload.[24] The magnitude of changes in regional ESF observed during IVC occlusion in healthy and cardiomyopathic dogs in the present study was similar to previous observations[5] in dogs using ESF calculated with LV end-systolic volume. Decreases in regional ESF produced by halothane in healthy and cardiomyopathic dogs were also similar in magnitude to reductions in LV end-systolic wall stress observed in chronically instrumented dogs before (de-

pressed LV function) and after (normal) recovery from acute surgical interventions.[12] Regional ESF also decreased with isoflurane in the presence and absence of pacing-induced cardiomyopathy, confirming that this volatile anesthetic reduces LV afterload in the intact cardiovascular system.[12,13] Thus, although regional ESF appears to accurately reflect alterations in LV afterload produced by IVC occlusion, phenylephrine, and volatile anesthetics before and after pacing, the present findings should be qualified because LV wall thickness was not measured and because LV end-systolic force and wall stress were not calculated as strictly quantitative measures of LV afterload. Alterations in LV $-dP/dt_{min}$ produced by changes in loading conditions did not always parallel changes in τ observed with these interventions. However, LV $-dP/dt_{min}$ may not accurately reflect changes in the rate of LV relaxation because this variable highly depends on peak-developed LV pressure in contrast to time constants of isovolumic relaxation derived using a variety of mathematical models.[33] Although changes in the afterload sensitivity of LV relaxation observed in the present investigation were obtained in dogs with LV dysfunction that had not decompensated into congestive heart failure, our data in conscious dogs confirm previous findings[5] obtained in the presence of heart failure. Nevertheless, the results obtained during isoflurane and halothane anesthesia may have been different if rapid LV pacing had been continued until dogs developed clinical symptoms of heart failure. The results should also be qualified because a dose-response relationship to volatile anesthetics was not examined. Lastly, although the canine pacing-induced cardiomyopathy model used in the present investigation has been shown to be similar in many respects to human idiopathic cardiomyopathy,[21] the present results may have been different in heart failure resulting from pressure-overload hypertrophy or infiltrative disease processes.

In summary, the present results confirm that the afterload sensitivity of LV relaxation evaluated by changes in τ and the slope of the $\tau - P_{es}$ relation is enhanced in conscious dogs with pacing-induced cardiomyopathy. The results also indicate that isoflurane and halothane do not alter the afterload dependence of LV relaxation in the normal and cardiomyopathic heart. These findings probably occurred because volatile anesthetic-induced reductions in the resistance to LV ejection were accompanied by simultaneous negative inotropic effects.

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