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Influence of Isoflurane on Left Atrial Function in Dogs with Pacing-Induced Cardiomyopathy: Evaluation with Pressure-Volume Relationships

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Abstract

Objective

The actions of volatile anesthetics on left ventricular (LV) function in normal and failing hearts have been previously evaluated, but the effects of these agents on left atrial (LA) function in the presence of LV dysfunction are unknown. The hypothesis was tested that isoflurane alters LA mechanics evaluated with pressure-volume relations.

Design

Prospective.

Setting

Laboratory.

Participants

Barbiturate-anesthetized dogs (n = 8) were instrumented for measurement of aortic, LA, and LV pressures (micromanometers), and LA volume (epicardial orthogonal sonomicrometers) after 3 weeks of rapid ventricular pacing (220 beats/min).

Interventions

LA myocardial contractility (E_{es}) was assessed with end-systolic pressure-volume relations. LA stroke work and reservoir function were assessed by A and V loop area, respectively, from the steady-state pressure-volume diagram. LA-LV coupling was determined by the ratio of E_{es} to LV elastance (E_{LV}). Dogs received 0.6, 0.9, and 1.2 minimum alveolar concentration isoflurane in a random manner, and LA function was determined after a 20-minute equilibration at each dose.

Measurements and main results

Isoflurane significantly ($p < 0.05$) decreased heart rate, mean arterial pressure, LV end-systolic pressure, and LV $+dP/dt_{max}$. Isoflurane produced dose-related reductions in E_{es} and E_{es}/E_{LV}. Declines in LA stroke work, emptying fraction, reservoir volume, V loop area, and the active LA contribution to LV filling also occurred.

Conclusions

The results indicate that isoflurane depresses LA myocardial contractility, impairs LA-LV coupling, and reduces active LA contribution to LV filling in dogs with pacing-induced cardiomyopathy. The impact of isoflurane on LA function in the presence of LV dysfunction has profound effects on cardiac performance.

Keywords

Myocardial contractility, end-systolic pressure-volume relationship, reservoir function, left atrial-left ventricular coupling, left atrial afterload

THE LEFT ATRIUM (LA) is an active contractile chamber, a reservoir for pulmonary venous blood flow when the mitral valve is closed, and a conduit that passively transfers its contents to the left ventricle (LV) when the mitral valve is open.1 These actions facilitate the transition between almost continuous pulmonary venous blood flow and the phasic filling pattern of the LV.2 The effects of volatile anesthetics on LA mechanical function have been recently described in the normal heart.3 Desflurane, isoflurane, and sevoflurane produce direct negative inotropic and lusitropic effects in LA myocardium in vivo3 and in vitro,4, 5 but these agents also preserve reservoir and conduit function in the intact LA at end-tidal concentrations less than 1.0 minimum alveolar concentration (MAC).3 It is significant that this preservation of LA storage capacity and transfer ability contributes to the relative maintenance of LV stroke volume6 observed during administration of these agents by compensating for decreases in LV filling associated with a reduced contribution of LA contraction. The actions of volatile agents on LA performance in the presence of LV dysfunction are unknown. Thus, the effects of isoflurane on LA function were examined using invasively derived pressure-volume relations in dogs with rapid ventricular pacing-induced cardiomyopathy. This experimental model produces time-dependent increases in biventricular chamber size,7, 8 elevations in cardiac filling pressures,9, 10 LV systolic and diastolic function,11, 12 and compensatory LA dilatation.10, 13 Pacing-induced cardiomyopathy is reproducibly produced in dogs and provides a useful model in which to examine the effects of isoflurane on LA function in the presence of LV dysfunction. The present investigation tested the hypothesis that isoflurane adversely alters the mechanical properties of the LA and impairs LA-LV coupling in dogs with pacing-induced cardiomyopathy and, further, that these effects are more pronounced in cardiomyopathic as compared with healthy dogs. LA pressure-volume relations were used to quantify the extent of impairment of LA performance and identify potential mechanisms for its decline.

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, Milwaukee, WI. All conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society and the *Guide for the Care and Use of Laboratory Animals* of the National Institutes of Health (Revised, 1996).

Mongrel dogs (n = 8) weighing 30 ± 1 kg (mean ± SEM) were fasted overnight and anesthetized with intravenous propofol (8 mg/kg). Anesthesia was maintained with isoflurane (1%–2%, end-tidal concentration) in oxygen after endotracheal intubation. Under sterile conditions, a bipolar pacing electrode was positioned on the endocardial surface of the right ventricular apex through the right external jugular vein. The lead was connected to a single-chamber pacemaker that was inserted into a pocket in the neck, and the incision was closed. All dogs received buprenorphine (0.3 mg/kg intramuscularly [IM]) for postoperative analgesia as required. Cephalothin (40 mg/kg IM) and gentamicin (4.5 mg/kg IM) were used for antibiotic prophylaxis. Dogs were allowed to recover for 2 days before right ventricular pacing was initiated at 220 beats/min. Pacing was continued for 3 weeks with daily electrocardiographic monitoring to verify the functional integrity of the pacemaker.

The surgical preparation used in the current investigation has been previously described in detail.3, 14 On the day of experimentation, each dog was anesthetized with sodium barbital (200 mg/kg) and sodium pentobarbital (25 mg/kg). Fluid deficits were replaced before experimentation with 500 mL of 0.9% saline, which was continued at 3 mL/kg/h for the duration of each experiment. After endotracheal intubation, the lungs of each dog were ventilated using positive pressure with oxygen. Arterial blood carbon dioxide tensions and acid-base status were maintained within a physiologic range by adjustment of tidal volume and respiratory rate. Temperature was maintained with a heating blanket. Rapid ventricular pacing was discontinued after intubation, and experiments were conducted after normal sinus rhythm had been restored. A 7F, dual micromanometer-tipped catheter was inserted into the aorta and LV through the left carotid artery for measurement of arterial and LV pressures and the maximal rate of increase of LV pressure ($+dP/dt_{max}$). The femoral artery and vein were cannulated for the withdrawal of arterial blood samples and fluid administration, respectively. A thoracotomy was performed in the left fifth intercostal space. A 7F micromanometer-tipped catheter was inserted into the LA through the left upper pulmonary vein for continuous measurement of LA pressure. Two pairs of ultrasonic segment length transducers (5 MHz) were sewn to the anterior and posterior walls (long axis) and medial and lateral walls (short axis) of the LA.3, 14, 15 A hydraulic vascular occluder was placed around the inferior vena cava for abrupt alteration of preload. Hemodynamics were continuously monitored on a polygraph and digitized using a computer interfaced with an analog-to-digital converter.

LA pressure-volume diagrams used to assess LA function were recorded during steady-state hemodynamic conditions at end-expiration after instrumentation had been completed. Left atrial volume (V_{LA}) was determined from the long- and short-axis dimensions using the equation: $V_{LA} = (\pi/6) \cdot (LAX) \cdot (SAX)^2$, where LAX is long axis (anterior-posterior dimension) and SAX is short axis (medial-lateral dimension).3, 15 LA end-diastolic and end-systolic volumes (V_{ed} and V_{es}, respectively) were defined as occurring 10 ms before the peak of the LA pressure "a" wave and at maximum LA elastance during contraction,16 respectively. LA stroke volume and emptying fraction were calculated using standard equations.3, 14 Total LA reservoir volume was determined as the difference between maximal LA volume and V_{es}. LA A and V diagram areas were measured using planimetry.3 A series of differentially-loaded LA pressure-volume diagrams (Fig 1) were obtained at end-expiration. This was accomplished by reducing LA preload by abruptly constricting the inferior vena cava using the hydraulic vascular occluder, resulting in an approximately 10-mmHg decline in mean LA pressure over 10 to 15 cardiac cycles. LA myocardial contractility was evaluated using time-varying elastance.3, 16 This method has been shown to be a relatively heart rate- and load-independent index of LA contractile state in vivo.16 Using linear regression analysis, the LA end-systolic pressure (P_{es}) and V_{es} of each LA pressure-volume diagram were fit to the equation: $P_{es} = E_{es} \cdot (V_{es} - V_0)$, where E_{es} = LA elastance and V_0 = the volume intercept of the relation. Effective LV elastance (E_{LV}) was determined as the ratio of P_{es} to LA stroke volume, and LA-LV coupling was calculated as the ratio of E_{es} to E_{LV}.17

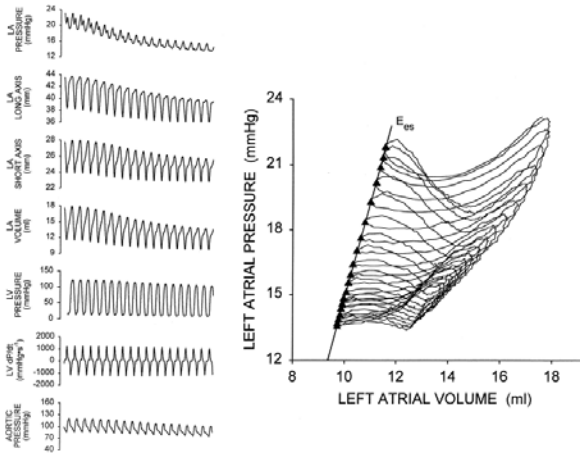

Fig 1. Continuous LA pressure, LA short- and long-axis dimensions, LA volume, LV pressure, LV dP/dt, and aortic blood pressure waveforms (left) and corresponding LA pressure-volume diagrams (right) resulting from inferior vena caval occlusion in a typical experiment. The LA maximal elastance (solid triangles) for each pressure-volume diagram was used to obtain the slope (E_{es}) and extrapolated volume intercept (V_0) of the LA end-systolic pressure-volume relationship to quantify myocardial contractility.

Baseline systemic hemodynamics and LA pressure-volume diagrams were recorded under control conditions 60 minutes after instrumentation was completed. Dogs were assigned to receive 0.6, 0.9, or 1.2 MAC (end-tidal concentration) isoflurane in a random manner. End-tidal concentrations of isoflurane were measured at the tip of the endotracheal tube using an infrared anesthetic analyzer (Datex Capnomac, Helsinki, Finland) that was calibrated with known standards before and during experimentation. The canine MAC value used for isoflurane in the present investigation was 1.28%. Hemodynamics were recorded, and LA pressure-volume diagrams were obtained using the techniques described above after 20 minutes of equilibration at each dose. Additional intravenous fluids (0.9% saline) were infused as required during administration of isoflurane to maintain constant LV preload because isoflurane has been shown to produce venodilation in dogs with dilated cardiomyopathy.7, 8 At the end of each experiment, the heart was electrically fibrillated, and the positions of all catheters, micromanometers, and ultrasonic crystals were confirmed.

Statistical analysis of data before and during the administration of isoflurane was performed using analysis of variance with repeated measures, followed by Student-Newman-Keuls test. Linear regression analysis was used to determine the slope (E_{es}) and volume intercept (V_0) of the LA end-systolic pressure-volume relationship. Changes between interventions were considered statistically significant when the probability (p) value was less than 0.05. All data are expressed as mean ± SEM.

Results

Dogs were paced for 21 ± 1 days before experimentation. The hemodynamic effects of isoflurane are summarized in Table 1. Isoflurane caused significant ($p < 0.05$) decreases in heart rate, mean arterial and LV systolic pressures, rate-pressure product, and LV $+dP/dt_{max}$. Left ventricular end-diastolic pressure and LA mean, end-systolic, and end-diastolic pressures were unchanged. An increase in LV end-systolic volume was also observed during administration of isoflurane, but no changes in LA end-diastolic and maximum volumes occurred. Isoflurane produced dose-related reductions in E_{es} (2.9 ± 0.4 during baseline to 1.9 ± 0.3 mmHg · mL during 1.2 MAC; $r^2 \geq 0.95$), consistent with depression of LA myocardial contractility Fig 2, Fig 3. Decreases in LA stroke volume, stroke work (A loop area), and emptying fraction also occurred. Isoflurane caused a dose-related decrease in E_{es}/E_{LV} (0.64 ± 0.12 during baseline to 0.17 ± 0.05 during 1.2 MAC; Fig 3), indicating impaired mechanical coupling between the LA and LV. Dose-related declines in total reservoir volume occurred during administration of isoflurane. A decrease in V loop area was observed during administration of 0.9 MAC isoflurane. Isoflurane decreased the active LA contribution to LV filling (83 ± 3% during baseline to 60 ± 11% during 1.2 MAC; Fig 3).

Table 1. Hemodynamic Effects of Isoflurane

	Baseline	**Isoflurane (MAC)**		
		0.6	**0.9**	**1.2**
HR (beats)	117 ± 4	111 ± 6	104 ± 7∗	97 ± 7∗, †
MAP (mmHg)	100 ± 4	87 ± 4∗	76 ± 5∗	60 ± 5∗, †, ‡
RPP (mmHg · 10^3/min)	12.8 ± 0.6	10.8 ± 0.8∗	8.9 ± 1.0∗	6.7 ± 0.9∗, †, ‡
LV P_{es}(mmHg)	109 ± 5	98 ± 3	85 ± 3∗, †	67 ± 4∗, †, ‡
LV P_{ed} (mmHg)	18.0 ± 2.8	18.8 ± 2.3	18.0 ± 2.2	17.6 ± 1.8

LV +dP/dt$_{max}$ (mmHg/s)	1324 ± 85	1079 ± 68∗	863 ± 54∗, †	683 ± 42∗, †
LA P$_{es}$ (mmHg)	16.6 ± 2.2	17.4 ± 2.2	17.5 ± 2.2	16.0 ± 1.8
LA P$_{ed}$ (mmHg)	17.7 ± 2.1	17.9 ± 2.3	18.5 ± 2.1	17.4 ± 1.9
LA P$_{mean}$ (mmHg)	17.9 ± 2.1	18.4 ± 2.2	18.7 ± 2.1	17.7 ± 1.8
LA V$_{es}$ (mL)	13.5 ± 2.0	15.1 ± 2.1∗	16.2 ± 2.2∗	16.7 ± 2.2∗, †
LA V$_{ed}$ (mL)	17.0 ± 3.0	16.9 ± 2.8	17.8 ± 3.0	17.9 ± 2.8
LA V$_{max}$ (mL)	19.6 ± 2.8	20.5 ± 2.7	21.0 ± 2.8	20.9 ± 2.8
LA V$_{o}$ (mL)	9.5 ± 1.9	8.3 ± 1.7	9.7 ± 2.0	9.5 ± 2.0
PV Diagrams (n)	12 ± 1	12 ± 1	12 ± 1	12 ± 1
LA SV (mL)	3.6 ± 0.7	1.9 ± 0.5∗	1.8 ± 0.6∗	1.6 ± 0.5∗
LA RV (mL)	6.1 ± 0.8	5.4 ± 0.7	4.9 ± 0.7∗	3.9 ± 0.7∗, †
LA EF(%)	21 ± 2	11 ± 2∗	9 ± 2∗	8 ± 2∗
A Area (mmHg · mL)	7.3 ± 2.1	3.0 ± 0.8∗	2.2 ± 0.5∗	1.8 ± 0.7∗
V Area (mmHg · mL)	1.3 ± 0.3	1.2 ± 0.4	0.9 ± 0.2∗	1.0 ± 0.4

NOTE. Data are mean ± SEM (n = 8).

Abbreviations: HR, heart rate; MAP, mean arterial pressure; RPP, rate-pressure product; LV, left ventricle; LA, left atrium; +dP/dt$_{max}$, maximum rate of increase of left ventricular pressure; P$_{es}$, P$_{ed}$, and P$_{mean}$, end-systolic, end-diastolic, and mean pressures, respectively; V$_{es}$, V$_{ed}$, V$_{max}$, V$_{0}$, end-systolic, end-diastolic, maximum, and E$_{es}$ intercept volumes, respectively; PV, pressure-volume; SV, stroke volume; RV, reservoir volume; EF, emptying fraction; A and V Area, area of the active and passive loops, respectively, of the steady-state LA pressure-volume diagram.

∗Significantly ($p < 0.05$) different from baseline.

†Significantly ($p < 0.05$) different from isoflurane 0.6 MAC.

‡Significantly ($p < 0.05$) different from isoflurane 0.9 MAC.

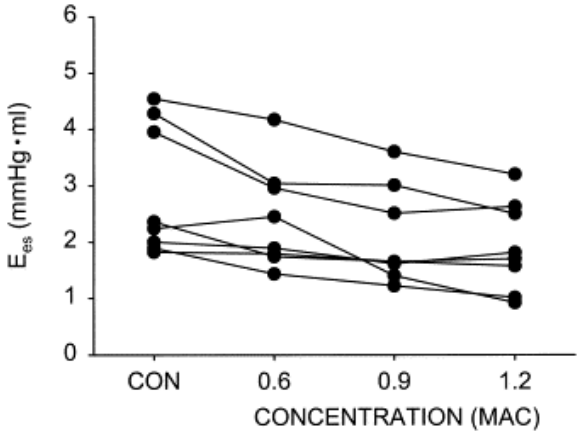

Fig 2. End-systolic pressure-volume slope (E$_{es}$) for each dog under baseline conditions (CON) and during administration of 0.6, 0.9, and 1.2 MAC isoflurane.

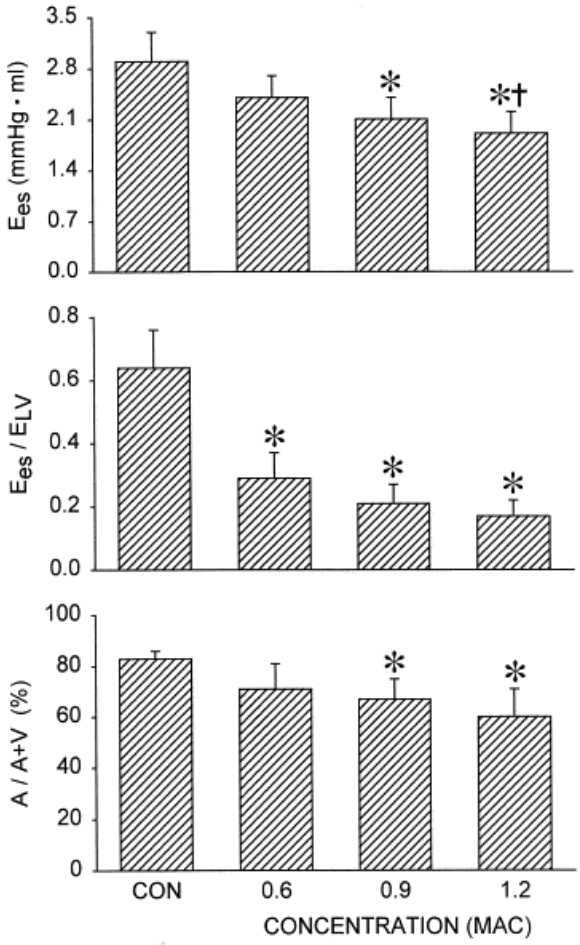

Fig 3. Histograms depicting the slope (E_{es}; top panel) of the LA end-systolic pressure-volume relation, LA-LV coupling (E_{es}/E_{LV}; middle panel), and the ratio of the LA A loop area to total pressure-volume diagram area (A/A+V; bottom panel) under baseline conditions (CON) and during the administration of 0.6, 0.9, and 1.2 MAC isoflurane. ∗Significantly ($p < 0.05$) different from baseline; †significantly ($p < 0.05$) different from 0.6 MAC.

Discussion

The current results confirm previous findings from this7, 8 and other laboratories,9, 11, 12 indicating that rapid ventricular pacing of 3 weeks' duration increases LV filling pressures and produces LV systolic dysfunction (eg, reductions in LV +dP/dt_{max}). The results further indicate that this model of pacing-induced cardiomyopathy also produces LA dilatation and elevates LA filling pressures as compared with the findings in healthy dogs.3, 14 Increases in LA stroke work, stroke volume, and reservoir volume were also observed concomitant with augmented LA preload, confirming the previous observations10, 13 in a similar canine model. In contrast to the methods of Hoit et al10, 13 who used 3 to 4 weeks of rapid ventricular pacing at 250 beats/min until signs of heart failure were present (eg, ascites, dyspnea, reduced LA emptying fraction), the authors chronically paced canine hearts at 220 beats/min for 21 ± 1 days. Thus, the actions of isoflurane on LA function were studied in the presence of LV dysfunction but not frank congestive heart failure. LA pressure was also maintained during administration of isoflurane using additional intravenous fluids because previous studies7, 8 reported that this volatile agent produces venodilation in the presence of elevated cardiac filling pressures in dogs with pacing-induced LV dysfunction. This method allowed for evaluation of LA function independent of isoflurane-induced reductions in LA pressure and volume.

The current results suggest that LA contractile dysfunction occurred as a result of 3 weeks of rapid ventricular pacing. A modest decline in E_{es} was observed in the presence of pacing-induced cardiomyopathy as compared with the normal LA (eg, 2.9 ± 0.4 *v* approximately 3.7 ± 0.2 mmHg · mL in a previous study3), although a statistical comparison of the current and previous results was not specifically conducted because different methods were used to generate a series of LA pressure-volume diagrams in these respective studies. These findings are qualitatively similar to those reported by Hoit et al.10 The LA emptying fraction was also similar in cardiomyopathic and normal hearts in the current and previous investigations, respectively (21 ± 2% *v* 22 ± 2%).3 This similarity in LA emptying fraction was observed despite marked increases in LA pressure and volume in dogs as compared to those without cardiomyopathy. Increases in LA pressure and volume would be expected to enhance this ejection phase measure of LA pump performance. These findings also indirectly support the contention that a reduction in intrinsic LA contractility had occurred after rapid ventricular pacing. The current investigation is the first to quantify the negative inotropic effects of a volatile anesthetic in the intact LA during LV dysfunction using invasively derived pressure-volume analysis. The results indicate that isoflurane produces a dose-related depression of LA myocardial contractility in dogs with pacing-induced cardiomyopathy as quantified using E_{es}. The magnitude of this depressant effect was similar to the degree of depression observed with this volatile agent in the normal LA (67 ± 6 *v* 61 ± 8% of control during 1.2 MAC) in a previous investigation3 using an identical barbiturate-anesthetized, acutely instrumented preparation in healthy dogs. These data show that isoflurane does not cause an exaggerated negative inotropic effect in LA myocardium in the presence of LV dysfunction.

The current results also indicate LA-LV coupling is impaired in dogs after 3 weeks of rapid ventricular pacing. A decrease in the ratio of E_{es} to E_{LV} was observed in the presence of LV dysfunction as compared with the healthy dogs (0.64 ± 0.12 in the present *v* 0.99 ± 0.24 in our previous study3). LA afterload is determined primarily by the elastic characteristics of LV myocardium and LV diastolic pressure in the absence of mitral valve pathology.1 A reduction in LV compliance determined using invasively derived pressure-dimension relations concomitant with an increase in LV diastolic pressure has been previously reported in this canine model of pacing-induced cardiomyopathy.8 When combined with declines in LA E_{es}, this increase in LA afterload observed after 3 weeks of pacing contributed to the reduction in E_{es}/E_{LV} in cardiomyopathic dogs. The results also indicate that isoflurane causes dose-related impairment of LA-LV coupling that was similar in cardiomyopathic as compared with healthy dogs3 (34 ± 11 *v* 21 ± 5% of control during 1.2 MAC). These data imply that the presence of reduced LV compliance and increased LV diastolic pressure do not affect alterations in the transfer of LA kinetic energy to the LV produced by isoflurane. Isoflurane has been shown to cause LV diastolic dysfunction by delaying isovolumic relaxation and attenuating early LV filling concomitant with depression of myocardial contractility in the healthy canine heart,18 but this volatile agent modestly improves these indices of LV diastolic performance in dogs with pacing-induced cardiomyopathy.8 Nevertheless, isoflurane does not affect LV compliance independent of alterations in LV preload in healthy and cardiomyopathic dogs.8, 18 Thus, it is likely that isoflurane-induced reductions in E_{es}/E_{LV} observed in the current investigation resulted primarily from depression of LA contractility and not because of alterations in the material properties of the LV caused by the volatile agent.

The results further indicate that LA reservoir function is relatively unaffected by 3 weeks of rapid ventricular pacing. Total reservoir volume was greater in cardiomyopathic as compared with healthy dogs (6.1 ± 0.8 *v* 2.9 ± 0.4 mL^3) concomitant with increases in LA pressure and volume. However, LA pressure-volume V loop area remained unchanged, confirming previous findings.10 The area of the V loop is an index of reservoir function that represents the total passive elastic energy stored by the LA during the reservoir phase.19 When combined with the observed increase in LA stroke work (A loop area), the lack of change in V loop area suggests that LV filling is more dependent on the contribution of atrial systole than on the storage capability of the LA in this experimental model of LV dysfunction. Isoflurane reduced reservoir volume and V loop area in the present

investigation, suggesting that this volatile agent adversely affects reservoir function after rapid ventricular pacing. In contrast, reservoir volume was maintained and V loop area increased at isoflurane concentrations less than 1.0 MAC in the previous study.3 The latter data indicate that reservoir function was preserved or even enhanced by the inhalation anesthetic in the normal canine heart. Thus, unlike the findings in healthy dogs, the current results suggest that LA reservoir function may not compensate for isoflurane-induced reductions in the contribution of LA contraction to LV stroke volume during evolving heart failure.

The current results should be interpreted within the constraints of several possible limitations. LA volume was modeled using prolate ellipsoid geometry15, 20 that was previously validated in the normal canine LA.21 Whether this geometric assumption may be applied in the setting of pronounced LA dilatation concomitant with LV dysfunction remains to be tested. However, each dog also served as its own control. Pressure-volume analysis of LA function does not strictly quantify retrograde pulmonary venous blood flow during LA contraction. This retrograde blood flow increases in conjunction with elevations in LA pressure and volume22 and may falsely elevate LA emptying fraction by reducing minimal LA volume as depicted in the LA pressure-volume diagram. However, LA pressure was maintained at a constant value in the current investigation, and it appears unlikely that isoflurane-induced decreases in emptying fraction resulted from differential alterations in retrograde pulmonary venous blood flow. The linearity and relative load-independence of the LA end-systolic pressure-volume relationship used to determine E_{es} have been validated in the isolated16 and intact heart20 but have not been extensively characterized in the dilated LA. Nevertheless, E_{es} was calculated within the physiologic operating range of LA pressure and volume by using inferior vena caval constriction to reduce preload.10 In a previous study in normal dogs,3 an intravenous bolus of phenylephrine was used to increase LA afterload and produce a differentially-loaded series of LA pressure-volume diagrams used for the determination of E_{es}. Although this method of altering LA loading conditions is different from that used in the present investigation (ie, inferior vena caval occlusion), E_{es} calculations were conducted over a similar range of LA pressures (ie, 8 to 20 mmHg) in both the previous3 and present studies. Thus, it appears highly unlikely that differences in the techniques used to generate a series of LA pressure-volume diagrams are responsible for reductions in E_{es} observed in cardiomyopathic as compared with normal dogs. Isoflurane-induced reductions in heart rate and mean arterial pressure may also have contributed to reductions in E_{es}, but the LA end-systolic pressure-volume relation has been shown to reflect alterations in LA myocardial contractility independent of changes in heart rate and loading conditions in the isolated, ejecting canine LA.16

In summary, the current results indicate that isoflurane decreases LA myocardial contractility, impairs LA-LV coupling, and compromises reservoir function in dogs with pacing-induced cardiomyopathy. These data suggest that isoflurane-induced depression of LA function contributes to further reductions in overall cardiac performance via multiple mechanisms during evolving heart failure.

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