Anesthesiology 2001; 95:689–98

Desflurane, Sevoflurane, and Isoflurane Affect Left Atrial Active and Passive Mechanical Properties and Impair Left Atrial–Left Ventricular Coupling In Vivo

Analysis Using Pressure–Volume Relations

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Background: **The effects of volatile anesthetics on left atrial function *in vivo* have not been described. The authors tested the hypothesis that desflurane, sevoflurane, and isoflurane alter left atrial mechanics evaluated with invasively derived pressure–volume relations.**

Methods: **Barbiturate-anesthetized dogs (n = 24) were instrumented for measurement of aortic, left atrial, and left ventricular pressures (micromanometers) and left atrial volume (orthogonal sonomicrometers). Left atrial contractility and chamber stiffness were assessed with end-systolic and end-reservoir pressure–volume relations, respectively, obtained from differentially loaded diagrams. Relaxation was determined from the slope of left atrial pressure decline after contraction. Stroke work and reservoir function were assessed by A and V loop areas, respectively. Left atrial–left ventricular coupling was determined by the ratio of left atrial contractility and left ventricular elastance. Dogs received 0.6, 0.9, and 1.2 minimum alveolar concentration desflurane, sevoflurane, or isoflurane in a random manner, and left atrial function was determined after 20-min equilibration at each dose.**

Results: **Desflurane, sevoflurane, and isoflurane decreased heart rate, mean arterial pressure, and maximal rate of increase of left ventricular pressure and increased left atrial end-diastolic, end-systolic, and maximum volumes. All three anesthetics caused dose-related reductions in left atrial contractility, relaxation, chamber stiffness, and stroke work. Administration of 0.6 and 0.9 minimum alveolar concentration desflurane, sevoflurane, and isoflurane increased V loop area. All three anesthetics decreased the ratio of stroke work to total left atrial pressure–volume diagram area, increased the ratio of conduit to reservoir volume, and reduced left atrial contractility–left ventricular elastance to equivalent degrees.**

Conclusions: **The results indicate that desflurane, sevoflurane, and isoflurane depress left atrial contractility, delay relaxation, reduce chamber stiffness, preserve reservoir and conduit function, and impair left atrial–left ventricular coupling *in vivo*.**

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Received from the Departments of Anesthesiology, Medicine, and Pharmacology and Toxicology, the Medical College of Wisconsin, and the Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin; and Arrhythmia Management Research, Medtronic, Inc., Minneapolis, Minnesota. Submitted for publication December 27, 2000. Accepted for publication March 9, 2001. Supported in part by a postdoctoral fellowship from the Northland Affiliate of the American Heart Association, Minneapolis, Minnesota (to Dr. Gare), and by grants No. HL-03690 and HL-63705 (to Dr. Kersten), HL-54820 and GM-08377 (to Dr. Warltier), and AA-12331 (to Dr. Pagel) from the United States Public Health Service, National Institutes of Health, Bethesda, Maryland.

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THE effects of volatile anesthetics on left ventricular (LV) systolic and diastolic function are well known,[1] but the influence of these agents on left atrial (LA) mechanics in the intact heart have not been described. The LA serves three major roles that contribute substantially to overall cardiac performance. The LA is a contractile chamber that actively empties immediately before the onset of LV systole and establishes final LV end-diastolic volume. The LA is also a reservoir that stores pulmonary venous return during LV contraction and relaxation after the closure and before the opening of the mitral valve. Lastly, the LA is a conduit that empties its contents into the LV down a pressure gradient after the mitral valve opens and continues to passively transfer pulmonary venous blood flow during LV diastasis. Volatile anesthetics produce direct negative inotropic actions in LA myocardium *in vitro*,[2,3] but the effect of these agents on LA contractile function *in vivo* have not been quantified or compared to the degree of myocardial depression they produce in the intact LV. Whether volatile anesthetics impact LA relaxation, influence LA chamber stiffness, affect LA reservoir and conduit function, or alter the mechanical coupling between the LA and LV is also unknown. Thus, we examined and compared the effects of desflurane, sevoflurane, and isoflurane on LA function using invasively derived pressure–volume relations in barbiturate-anesthetized dogs. We tested the hypothesis that these volatile agents alter active and passive LA function and impair LA-LV coupling *in vivo*.

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, Milwaukee, Wisconsin. 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).

Implantation of Instruments

Mongrel dogs (n = 24) of either sex weighing between 25 and 30 kg were fasted overnight and anesthetized with sodium barbital (200 mg/kg) and sodium pentobar-

bital (25 mg/kg). 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. 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 physiological range by adjustment of tidal volume and respiratory rate. Temperature was maintained with a heating blanket. A 7-French, dual micromanometer-tipped catheter (Millar Instruments, Houston, TX) 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 time constant of LV isovolumic relaxation (τ) was calculated from the LV pressure and dP/dt wave forms using the derivative method.[4] The femoral artery and vein were cannulated for the withdrawal of arterial blood samples and fluid or drug administration, respectively. A thoracotomy was performed in the left fifth intercostal space. A 7-French micromanometer catheter was inserted into the LA through the appendage for measurement of continuous 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.[5] The posterior crystal was located between the lower left and right pulmonary veins at the junction of the LA, and the anterior crystal was placed on the LA anterior surface to maximize the ultrasonic signal. The medial crystal was positioned adjacent to the pulmonary artery on the medial LA surface, and the lateral crystal located on the lateral LA border.[5] Hemodynamics were continuously monitored on a polygraph and digitized using a computer interfaced with an analog-to-digital converter. We previously demonstrated the temporal hemodynamic stability of this acutely instrumented canine model.[6]

Experimental Protocol

After instrumentation had been completed, LA pressure–volume diagrams used to assess LA function were recorded at end expiration under steady state hemodynamic conditions. LA volume was estimated from the long and short axis dimensions assuming prolate ellipsoid geometry:

$$LAV = (\pi/6) \cdot (SAX)^2 \cdot (LAX), \quad (1)$$

where SAX is short axis or medial–lateral dimension and LAX is long axis or anterior–posterior dimension.[5] LA volume calculated with this technique has been shown to closely correlate with true LA volume determined using water displacement–atrial cast studies.[7] LA end-diastolic and end-systolic volumes (V_{ed} and V_{es}, respectively) were defined at 10 ms before the peak of the LA

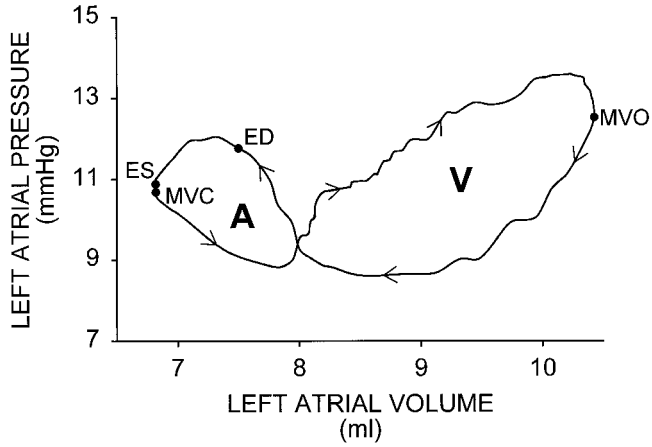

Fig. 1. Steady state left atrial (LA) pressure–volume diagram for a single cardiac cycle observed in a typical experiment. The arrows indicate the time-dependent direction of movement around the diagram. The A portion of the diagram (left loop) incorporates active LA contraction and temporally proceeds in a counterclockwise fashion. The V portion of the diagram (right loop) represents passive LA reservoir function and proceeds in a clockwise manner over time. LA end-diastole and end-systole (ED and ES, respectively) and mitral valve closure and opening (MVC and MVO, respectively) are also depicted on the LA pressure–volume diagram. Left ventricular isovolumic contraction, ejection, and the majority of isovolumic relaxation occur during the time between MVC and MVO illustrated on the LA pressure–volume diagram.

pressure "a" wave and at maximum LA elastance,[8] respectively (fig. 1). LA stroke volume was calculated as the difference between V_{ed} and V_{es}. LA emptying fraction was determined using the equation:

$$EF = (V_{ed} - V_{es}) \cdot 100 \cdot V_{ed}^{-1}. \quad (2)$$

Total LA reservoir and conduit volumes were calculated as the differences between maximal LA volume (V_{max}) and V_{es} and between V_{max} and V_{ed}, respectively.[9] LA A and V diagram areas corresponding to LA stroke work[10,11] and reservoir function,[12] respectively, were determined by planimetry (fig. 1). LA relaxation (R_{LA}) was quantified using the equation[13:]

$$R_{LA} = (P_{max} - P_{min}) \cdot (P_{max})^{-1} \cdot (t_{min} - t_{max})^{-1}, \quad (3)$$

where P_{max} and P_{min} indicate maximum and minimum LA pressure associated with LA contraction and relaxation, respectively, and t_{max} and t_{min} indicate time at P_{max} and P_{min}, respectively.

After steady state LA pressure–volume diagrams had been recorded, a series of differentially loaded LA pressure–volume diagrams used to evaluate LA myocardial contractility and LA-LV coupling were obtained at end expiration by increasing LV and LA afterload with an intravenous bolus dose of phenylephrine (200 μg). This intervention produces an increase in LA pressure between 5 and 10 mmHg with a corresponding increase in LA volume over 10–20 cardiac cycles (fig. 2).[14] LA myo-

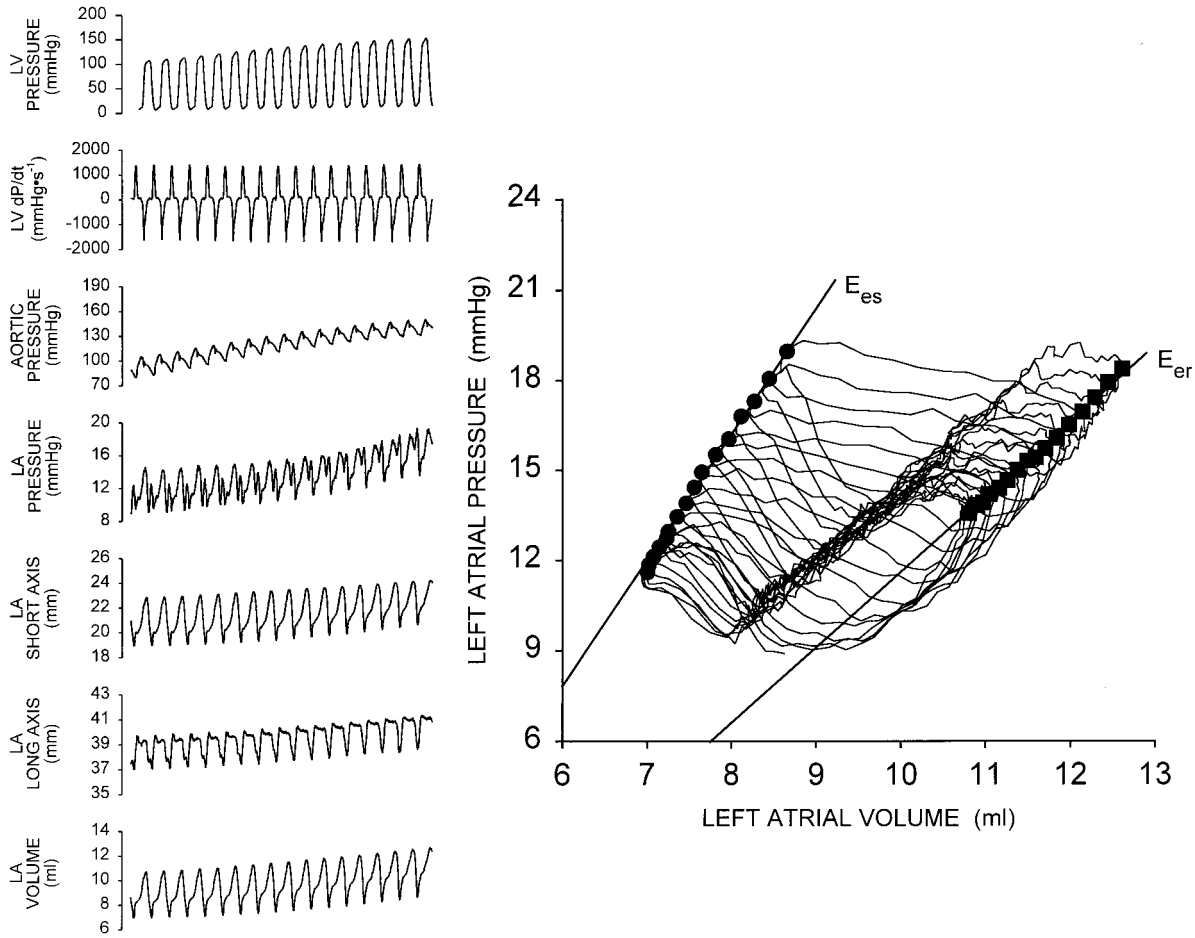

Fig. 2. Continuous left ventricular (LV) pressure, LV dP/dt, aortic pressure, left atrial (LA) pressure, LA short and long axis dimensions, and LA volume wave forms (*left*) and corresponding LA pressure–volume diagrams (*right*) resulting from intravenous administration of phenylephrine (200 μg) observed in a typical experiment. The LA maximum elastance (solid dots) and end-reservoir pressure and volume (solid squares) for each pressure–volume diagram were used to obtain the slopes (E_{es} and E_{er}) and extrapolated volume intercepts of the LA end-systolic and end-reservoir pressure–volume relations to quantify myocardial contractility and dynamic chamber stiffness, respectively.

cardial contractility was evaluated *in vivo* using a time-varying elastance model.[8,14] Using linear regression analysis, the LA end-systolic pressure (P_{es}) and V_{es} of each LA pressure–volume diagram during phenylephrine-induced increases in LA pressure were fit to the following equation:

$$P_{es} = E_{es} \cdot (V_{es} - V_{0s}), \quad (4)$$

where E_{es} is LA elastance and V_{0s} is the extrapolated volume intercept of the relation. LA dynamic elastic stiffness at the end of the reservoir phase (E_{er}) was also calculated from this series of pressure–volume diagrams. The V_{max} and its corresponding pressure (P_{Vmax}) of each LA pressure–volume diagram were fit to the equation using linear regression analysis:

$$P_{Vmax} = E_{er} \cdot (V_{max} - V_{0r}), \quad (5)$$

where V_{0r} is the extrapolated volume intercept of the relation.[15] Effective LV elastance (E_{LV}) was determined as the ratio of P_{es} to LA stroke volume,[15] and LA-LV coupling was described as the ratio of E_{es} to E_{LV} using a series elastic chamber model adapted from LV–arterial coupling.[16]

Dogs were assigned to receive desflurane, sevoflurane, and isoflurane in a random manner in three separate groups of experiments. Baseline systemic hemodynamics and LA pressure–volume diagrams were recorded during control conditions 30 min after instrumentation was completed. In one group of experiments, 0.6, 0.9, and 1.2 minimum alveolar concentration (MAC; end-tidal concentration) desflurane was administered. The order of MAC was assigned randomly. Hemodynamics were recorded, and LA pressure–volume diagrams were obtained using the techniques described above after 20 min equilibration at each dose. In two other groups of experiments, hemodynamics and LA pressure–volume diagrams were recorded at the time intervals described above in dogs before and during administration of 0.6, 0.9, and 1.2 MAC sevoflurane or isoflurane. The canine

Table 1. Hemodynamic Effects of Desflurane

		Desflurane (MAC)		
	Baseline	0.6	0.9	1.2
HR (min^{-1})	133 ± 4	113 ± 5*	111 ± 5*	113 ± 5*
MAP (mmHg)	105 ± 5	88 ± 5*	76 ± 5*†	67 ± 5*†
RPP ($min^{-1} \cdot mmHg \cdot 10^{-3}$)	15.4 ± 0.9	11.3 ± 0.7*	9.6 ± 0.8*†	8.5 ± 0.9*†
LV P_{es} (mmHg)	114 ± 5	97 ± 5*	83 ± 5*†	72 ± 6*†‡
LV P_{ed} (mmHg)	7.6 ± 1.0	9.6 ± 1.5	9.8 ± 1.8	9.8 ± 1.7
LV $+dP/dt_{max}$ (mmHg/s)	1,699 ± 136	1,171 ± 80*	1,000 ± 80*	851 ± 82*†
τ (ms)	37 ± 2	47 ± 4*	53 ± 7*	57 ± 7*
LA P_{es} (mmHg)	8.6 ± 1.3	8.9 ± 1.7	9.5 ± 1.0	8.8 ± 0.8
LA P_{ed} (mmHg)	11.7 ± 1.4	11.6 ± 1.6	12.2 ± 1.7	10.6 ± 1.1
LA P_{mean} (mmHg)	8.3 ± 1.1	9.9 ± 1.5	10.6 ± 1.6	9.7 ± 0.8
LA V_{es} (ml)	6.4 ± 0.4	9.7 ± 0.6*	10.7 ± 0.7*	10.8 ± 0.7*
LA V_{ed} (ml)	8.2 ± 0.5	10.8 ± 0.8*	11.7 ± 0.8*	11.7 ± 0.8*
LA V_{max} (ml)	9.3 ± 0.7	12.7 ± 1.0*	13.3 ± 1.0*	12.9 ± 0.9*
LA V_{0s} (ml)	4.4 ± 0.7	5.5 ± 0.6	6.0 ± 0.5*	6.1 ± 0.8*
LA V_{0r} (ml)	7.3 ± 0.7	7.1 ± 1.2	7.2 ± 1.4	7.5 ± 0.7
PV diagrams (n)	11 ± 2	10 ± 2	11 ± 1	10 ± 2
LA SV (ml)	1.8 ± 0.2	1.1 ± 0.2*	1.0 ± 0.2*	0.9 ± 0.2*
LA RV (ml)	2.9 ± 0.4	3.0 ± 0.5	2.7 ± 0.4	2.1 ± 0.4*
LA EF (%)	22 ± 2	10 ± 1*	9 ± 1*	8 ± 1*
A area (mmHg · ml)	4.5 ± 0.7	3.3 ± 0.7	2.4 ± 0.5*	1.4 ± 0.3*†
V area (mmHg · ml)	0.8 ± 0.1	2.3 ± 0.2*	2.1 ± 0.3*	1.4 ± 0.1†‡
[ET] (%)	—	4.5 ± 0.1	6.4 ± 0.0	8.7 ± 0.1

Data are mean ± SEM; n = 8.

* Significantly ($P < 0.05$) different from baseline. † Significantly ($P < 0.05$) different from 0.6 minimum alveolar concentration (MAC) desflurane. ‡ Significantly ($P < 0.05$) different from 0.9 MAC desflurane.

HR = heart rate; MAP = mean arterial pressure; RPP = rate–pressure product; LV = left ventricle; $+dP/dt_{max}$ = maximum rate of increase of left ventricular pressure; τ = time constant of LV isovolumic relaxation; LA = left atrium; P_{es}, P_{ed}, and P_{mean} = end-systolic, end-diastolic, and mean pressures, respectively; V_{es}, V_{ed}, V_{max}, V_{0s}, and V_{0r} = end-systolic, end-diastolic, maximum, E_{es} intercept, and E_{er} intercept volumes, respectively; PV = pressure–volume; SV = stroke volume; RV = reservoir volume; EF = emptying fraction; [ET] = end-tidal concentration.

MAC values for desflurane, sevoflurane, and isoflurane used in this investigation were 7.20, 2.36, and 1.28%, respectively. End-tidal concentrations of volatile anesthetics were measured at the tip of the endotracheal tube using an infrared gas analyzer (Datex Capnomac, Helsinki, Finland) that was calibrated with known standards before and during experimentation. 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

Statistical analysis of data within and between groups before and during the administration of desflurane, sevoflurane, and isoflurane was performed with multiple analysis of variance with repeated measures followed by the Student *t* test (two-sided) with Bonferroni correction for multiplicity. Linear regression analyses were used to determine the slopes (E_{es} and E_{er}) and volume intercepts (V_{0s} and V_{0r}) of the LA end-systolic and end-reservoir pressure–volume relations used to determine LA myocardial contractility and chamber stiffness, respectively. A P value < 0.05 was considered significant. All data are expressed as mean ± SEM.

Results

No differences in systemic hemodynamics or indices of LA function were noted between experimental groups after instrumentation had been completed. Desflurane produced significant ($P < 0.05$) decreases in heart rate, mean arterial and LV systolic pressures, rate–pressure product, and LV $+dP/dt_{max}$ and an increase in τ (table 1). LV end-diastolic pressure and LA end-systolic, end-diastolic, and mean pressures were unchanged. Increases in LA end-diastolic, end-systolic, maximum, and end-systolic intercept volumes (V_{0s}) were observed. Declines in LA stroke volume, emptying fraction, and stroke work (A loop area) also occurred (fig. 3 and table 1). Desflurane produced dose-related reductions in E_{es} (3.6 ± 0.2 during baseline to 2.4 ± 0.2 mmHg/ml during 1.2 MAC; $r^2 \geq 0.98$), R_{LA} (6.0 ± 0.6 during baseline to 3.6 ± 0.3 s^{-1} during 1.2 MAC), and E_{er} (3.1 ± 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, delayed relaxation, and reduced chamber stiffness, respectively (fig. 4). Increases in V loop area were observed during 0.6 and 0.9 MAC desflurane anesthesia, indicative of enhanced reservoir function (fig. 3). Thus, a decrease in the active LA contribution to LV filling occurred during administration of desflurane (83 ± 3% during base-

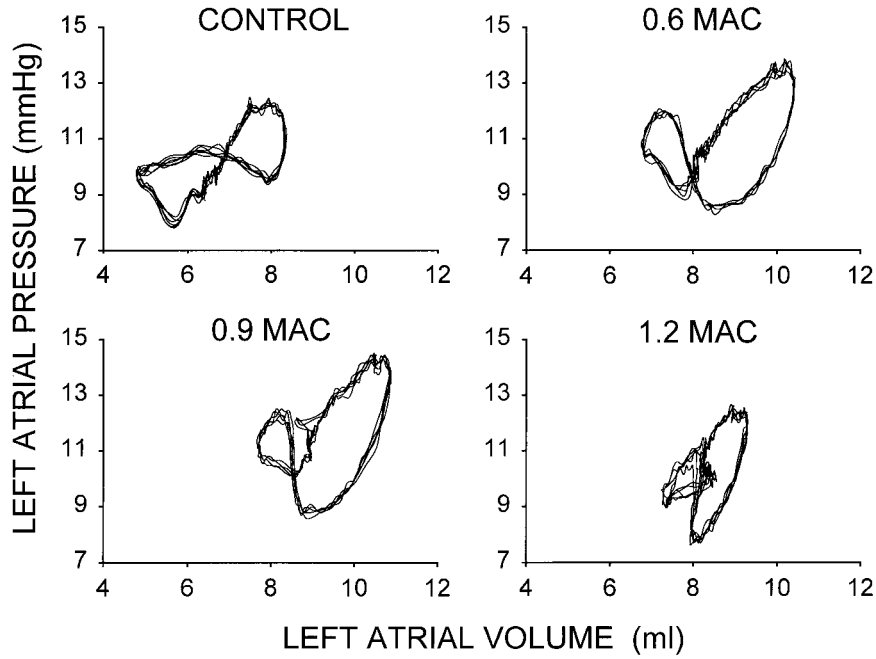

Fig. 3. Steady state left atrial (LA) pressure–volume diagrams obtained during control conditions (*top left*) and during administration 0.6, 0.9, and 1.2 minimum alveolar concentration (MAC) desflurane (*top right and bottom left and right*) in a typical experiment. A decrease in LA stroke work (A loop area) and compensatory increases in LA volume and V loop area occur during administration of 0.6 and 0.9 MAC desflurane anesthesia. However, V loop area decreases at 1.2 MAC, consistent with a subsequent impairment of the passive component of the LA contribution to LV filling.

line to 46 ± 6% during 1.2 MAC; fig. 5). Total LA reservoir volume was unchanged at lower concentrations of desflurane but decreased at 1.2 MAC (table 1). The ratio of conduit to reservoir volume increased (36 ± 4 during baseline to 57 ± 5 during 1.2 MAC; fig. 5) during desflurane anesthesia. A dose-related reduction in E_{es}/E_{LV} (0.85 ± 0.13 during baseline to 0.25 ± 0.04 during 1.2 MAC; fig. 5) was observed during the administration of desflurane, indicating that impairment of LA-LV coupling had occurred.

Sevoflurane and isoflurane caused systemic hemodynamic effects that were very similar to those produced by desflurane (tables 2 and 3). In contrast to the findings during desflurane anesthesia, sevoflurane and isoflurane increased LV end-diastolic and LA pressures. Like desflurane, these volatile agents increased LA volume and produced dose-related decreases in E_{es} (*e.g.*, 4.2 ± 0.3 during control to 2.6 ± 0.2 mmHg/ml during 1.2 MAC isoflurane), R_{LA} (*e.g.*, 5.2 ± 0.4 during control to 2.9 ± 0.3 s^{-1} during 1.2 MAC sevoflurane), and E_{er} (*e.g.*, 3.2 ± 0.3 during baseline to 2.1 ± 0.2 mmHg/ml during 1.2 MAC isoflurane). Stroke volume, emptying fraction, and stroke work also declined. Increases in V loop area occurred during the administration of 0.6 and 0.9 MAC sevoflurane and isoflurane. A reduction in active LA contribution to LV filling (*e.g.*, 75 ± 6% during control to 34 ± 4% during 1.2 MAC isoflurane) and an increase in conduit volume relative to total reservoir volume (*e.g.*, 32 ± 7% during control to 62 ± 4% during 1.2 MAC isoflurane) were also observed (fig. 5). Sevoflurane and isoflurane also reduced E_{es}/E_{LV} (*e.g.*, 0.99 ± 0.24 during control to 0.19 ± 0.07 during 1.2 MAC isoflurane), consistent with attenuation of LA-LV coupling. No differences in hemodynamics or indices of LA function were observed among anesthetic groups.

Discussion

Paradise *et al.*[17–19] were the first to describe the negative inotropic effects of halothane and methoxyflurane in rat atrial myocardium *in vitro*. Subsequent investigations demonstrated that halothane, isoflurane, sevoflurane, and desflurane also depress the contractile function of atrial myocardium obtained from guinea pigs,[20] rabbits,[21] and humans.[2,3,22] These actions have been attributed to reductions in transsarcolemmal calcium (Ca^{2+}) influx through voltage-dependent Ca^{2+} channels and decreases in Ca^{2+} availability from the sarcoplasmic reticulum,[21] mechanisms that are very similar to those responsible for anesthetic-induced depression of ventricular myocardium.[1] To our knowledge, the current investigation is the first to quantify the negative inotropic effects of volatile agents in the intact LA using invasively derived pressure–volume analysis. The results indicate that desflurane, sevoflurane, and isoflurane reduce LA contractility by approximately 50% at an end-tidal concentration of 1.2 MAC. The magnitude of this negative inotropic effect in LA myocardium was similar to the degree of LV contractile depression produced by these agents as quantified with both end-systolic pressure–volume relations and preload recruitable stroke work in a similar canine model.[6] Desflurane, sevoflurane, and isoflurane also impaired LA and LV relaxation (as evaluated with R_{LA} and τ, respectively) to similar degrees in the current investigation. These data suggest that volatile anesthetics produce equivalent alterations in contractil-

ity and relaxation in LA compared with LV myocardium *in vivo*. The magnitude of decreases in E_{es} and R_{LA} produced by the volatile anesthetics was also similar, suggesting that contraction–relaxation coupling was not affected by desflurane, sevoflurane, or isoflurane anesthesia in the intact LA. The latter results confirm and extend recent findings in isolated human atrial myocardium demonstrating that these anesthetics do not alter contraction–relaxation coupling *in vitro*.[3]

The current results indicate that volatile anesthetics also alter the passive filling and emptying characteristics of the LA. The area of the LA pressure–volume V loop represents the total passive elastic energy stored by the LA during the reservoir phase[13] and is an index of reservoir function.[12] This passive elastic energy is derived from the combined effects of LA relaxation,[13,23] LA chamber stiffness,[5,9,24] the descent of the cardiac base

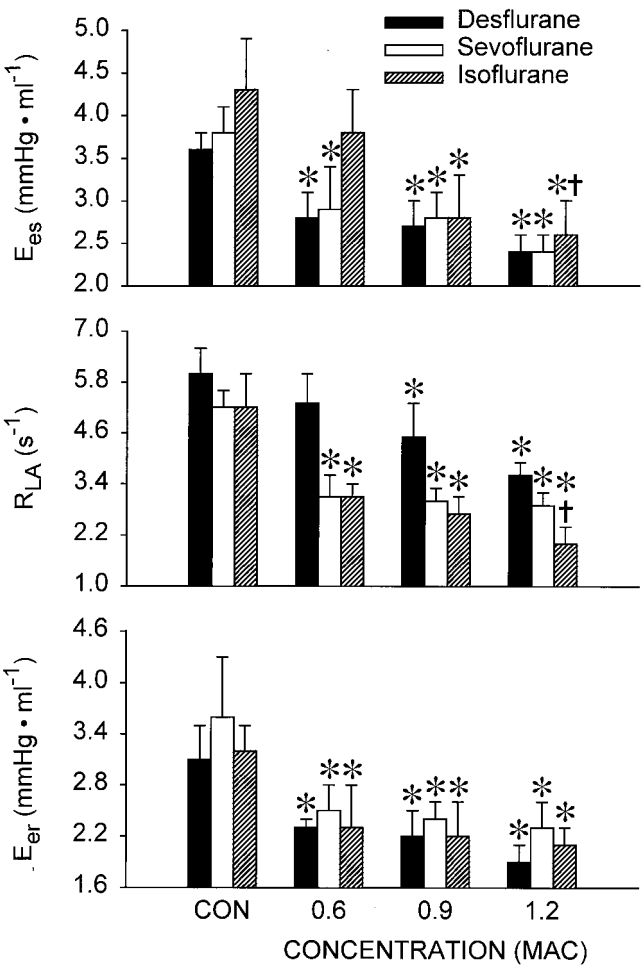

Fig. 4. Histograms depicting the slope (E_{es}; *top*) of the left atrial (LA) end-systolic pressure–volume relation, LA relaxation (R_{LA}; *middle*), and the slope (E_{er}; *bottom*) of the LA end-reservoir pressure–volume relation (dynamic chamber stiffness) during baseline conditions (CON) and during administration of 0.6, 0.9, and 1.2 minimum alveolar concentration (MAC) desflurane (solid bars), sevoflurane (open bars), or isoflurane (hatched bars). *Significantly ($P < 0.05$) different from CON; †Significantly ($P < 0.05$) different from 0.6 MAC.

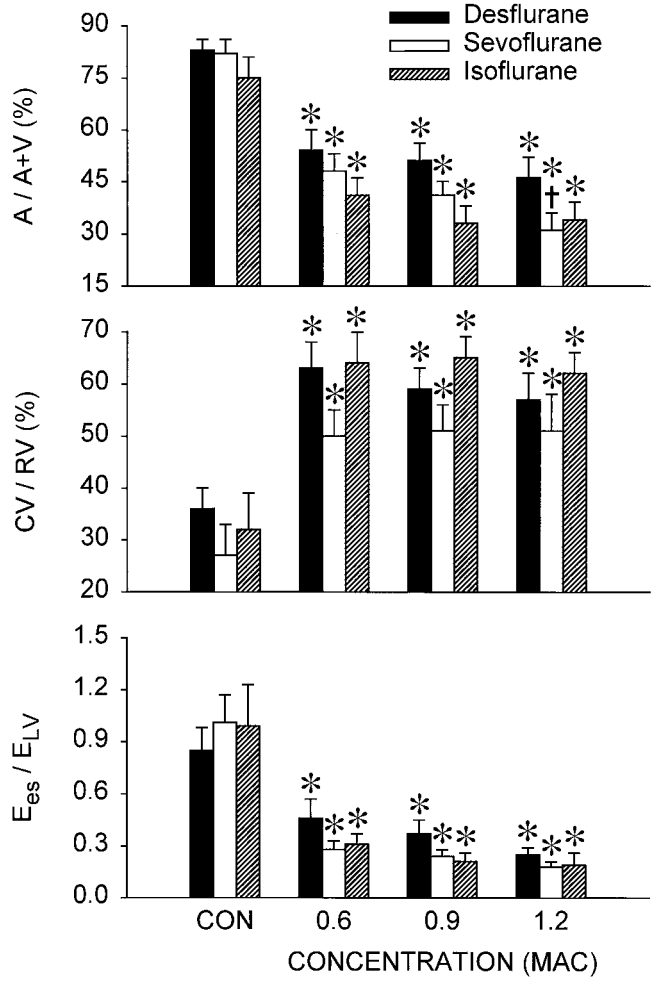

Fig. 5. Histograms depicting the ratio of the left atrial (LA) A loop to total pressure–volume diagram area (A/A + V; *top*), the ratio of LA conduit to total reservoir volume (CV/RV; *middle*), and LA–left ventricular coupling (E_{es}/E_{LV}; *bottom*) during baseline conditions and during administration of 0.6, 0.9, and 1.2 minimum alveolar concentration (MAC) desflurane (solid bars), sevoflurane (open bars), or isoflurane (hatched bars). *Significantly ($P < 0.05$) different from CON; †Significantly ($P < 0.05$) different from 0.6 MAC.

during LV systole,[13,25] and the right ventricular systolic pulse pressure transmitted through the pulmonary circulation.[26] The stored passive energy of the reservoir phase is returned after the mitral valve opens (*e.g.*, during the LA conduit phase) to facilitate LV filling and is an important determinant of LV stroke volume and cardiac output.[13,24] Increases in V loop area were observed during 0.6 and 0.9 MAC desflurane, sevoflurane, and isoflurane anesthesia. Total LA reservoir volume also remained unchanged at both of these anesthetic concentrations of desflurane and isoflurane. These findings suggest the LA reservoir function is maintained or enhanced during the administration of less than 1.0 MAC concentrations of desflurane, sevoflurane, or isoflurane. Such preservation of reservoir function may contribute to the relative maintenance of LV stroke volume at these anesthetic concentrations[6] by compensating for decreases in

Table 2. Hemodynamic Effects of Sevoflurane

		Sevoflurane (MAC)		
	Baseline	0.6	0.9	1.2
HR (min^{-1})	134 ± 4	106 ± 4*	107 ± 4*	111 ± 4*
MAP (mmHg)	98 ± 5	89 ± 5	76 ± 4*†	67 ± 4*†
RPP ($min^{-1} \cdot mmHg \cdot 10^{-3}$)	14.4 ± 0.6	10.5 ± 0.5	8.9 ± 0.4*†	8.1 ± 0.6*†
LV P_{es} (mmHg)	108 ± 5	97 ± 4	82 ± 4*†	72 ± 5*†
LV P_{ed} (mmHg)	9.3 ± 0.6	12.0 ± 1.4*	11.8 ± 1.0*	11.9 ± 1.0*
LV $+dP/dt_{max}$ (mmHg/s)	1,662 ± 102	1,038 ± 52*	886 ± 56*	793 ± 58*†
τ (ms)	40 ± 2	55 ± 6*	63 ± 5*	65 ± 5*
LA P_{es} (mmHg)	8.1 ± 0.6	12.4 ± 1.3*	12.0 ± 1.3*	11.5 ± 0.9*
LA P_{ed} (mmHg)	10.8 ± 0.8	13.7 ± 1.3*	13.1 ± 1.2*	12.7 ± 0.9*
LA P_{mean} (mmHg)	9.6 ± 0.6	12.8 ± 1.1*	12.7 ± 1.3*	12.3 ± 0.9*
LA V_{es} (ml)	8.0 ± 0.8	11.2 ± 0.9*	11.3 ± 0.8*	11.0 ± 0.7*
LA V_{ed} (ml)	10.1 ± 0.6	12.3 ± 1.1*	12.3 ± 1.0*	11.9 ± 0.7*
LA V_{max} (ml)	10.8 ± 0.7	13.5 ± 1.1*	13.3 ± 1.0*	12.8 ± 0.8*
LA V_{0s} (ml)	5.9 ± 0.8	6.3 ± 1.3	6.2 ± 1.1	6.4 ± 0.8
LA V_{0r} (ml)	7.9 ± 1.1	7.7 ± 1.3	7.4 ± 1.2	6.8 ± 1.3
PV diagrams (n)	8 ± 1	10 ± 2	10 ± 1	8 ± 1
LA SV (ml)	2.0 ± 0.2	1.2 ± 0.2*	1.0 ± 0.2*	0.9 ± 0.1*
LA RV (ml)	2.8 ± 0.3	2.3 ± 0.3	2.0 ± 0.3*	1.8 ± 0.3*
LA EF (%)	22 ± 3	9 ± 1*	8 ± 1*	7 ± 1*
A area (mmHg · ml)	3.9 ± 0.6	1.6 ± 0.4*	1.0 ± 0.2*	0.6 ± 0.1*
V area (mmHg · ml)	0.8 ± 0.2	1.7 ± 0.4*	1.5 ± 0.3*	1.4 ± 0.3
[ET] (%)	—	1.4 ± 0.0	2.1 ± 0.0	2.8 ± 0.0

Data are mean ± SEM; n = 8.

* Significantly ($P < 0.05$) different from baseline. † Significantly ($P < 0.05$) different from 0.6 minimum alveolar concentration (MAC) sevoflurane.

HR = heart rate; MAP = mean arterial pressure; RPP = rate–pressure product; LV = left ventricle; $+dP/dt_{max}$ = maximum rate of increase of left ventricular pressure; τ = time constant of LV isovolumic relaxation; LA = left atrium; P_{es}, P_{ed}, and P_{mean} = end-systolic, end-diastolic, and mean pressures, respectively; V_{es}, V_{ed}, V_{max}, V_{0s}, and V_{0r} = end-systolic, end-diastolic, maximum, E_{es} intercept, and E_{er} intercept volumes, respectively; PV = pressure–volume; SV = stroke volume; RV = reservoir volume; EF = emptying fraction; [ET] = end-tidal concentration.

LV filling associated with a diminished contribution of LA systole. Desflurane, sevoflurane, and isoflurane reduced LA chamber stiffness (E_{er}) despite modest increases in LA pressure, indicating that LA compliance is improved by volatile agents. The maintenance or improvement of reservoir function observed at lower anesthetic concentrations is most likely related to these decreases in LA chamber stiffness because the delays in LA relaxation and declines in LV systolic function (as indicated by $+dP/dt_{max}$) that also occurred would be expected to reduce reservoir function.[13] However, V loop area and total reservoir volume decreased at 1.2 MAC, suggesting that LA reservoir function may eventually be compromised by higher anesthetic concentrations, presumably because of further impairment of LA relaxation and LV contractility. The decreases in the ratio of LA stroke work to total pressure–volume diagram area (*e.g.*, A/A+V) and the increases in the ratio of LA conduit to total reservoir volume (fig. 5) produced by desflurane, sevoflurane, and isoflurane also emphasize that the LA contribution to LV filling becomes less active and more passive during the administration of these volatile agents.

Desflurane, sevoflurane, and isoflurane maintained or increased LA end-systolic pressure and produced dose-related reductions in LA stroke volume and stroke work concomitant with decreases in E_{es}. As a result, declines in the ratio of LA to LV elastance (E_{es}/E_{LV}) were observed, consistent with impaired mechanical matching between these elastic chambers. Volatile anesthetics have been shown to produce LV diastolic dysfunction by delaying LV isovolumic relaxation and impairing early LV filling in association with direct negative inotropic effects.[27] In the absence of mitral valve disease, LA afterload is primarily determined by the material properties of LV myocardium. Thus, the impairment of transfer of kinetic energy from the LA to the LV observed in the current investigation most likely resulted from the combination of LA contractile depression and LV systolic and diastolic dysfunction. Volatile anesthetic–induced abnormalities in LA-LV matching in the current study were greater than impairment of LV-arterial coupling evaluated using a similar series elastic chamber model in our previous investigation[6] because these agents produce beneficial alterations in the determinants of LV afterload[28,29] that partially compensate for simultaneous depression of LV myocardial contractility.

The current results should be interpreted within the constraints of several potential limitations. Estimation of LA volume with epicardial orthogonal sonomicrometry assuming a prolate ellipsoid model has been shown to closely correlate with true LA volume using a cast displacement technique.[7] Nevertheless, LA anatomy in the intact heart deviates from this geometric model to some

Table 3. Hemodynamic Effects of Isoflurane

		Isoflurane (MAC)		
	Baseline	0.6	0.9	1.2
HR (min^{-1})	128 ± 5	102 ± 5*	100 ± 6*	103 ± 4*
MAP (mmHg)	107 ± 4	89 ± 4*	76 ± 4*†	67 ± 3*†
RPP ($min^{-1} \cdot mmHg \cdot 10^{-3}$)	15.1 ± 1.1	10.2 ± 0.9*	8.5 ± 0.9*	7.7 ± 0.4*†
LV P_{es} (mmHg)	117 ± 3	98 ± 4*	82 ± 4*†	74 ± 2*†
LV P_{ed} (mmHg)	9.0 ± 1.2	11.1 ± 1.5*	11.1 ± 1.3*	11.8 ± 1.3*
LV $+dP/dt_{max}$ (mmHg/s)	1,668 ± 48	1,230 ± 41*	994 ± 42*†	848 ± 39*†‡
τ (ms)	38 ± 2	49 ± 3*	53 ± 4*	56 ± 4*
LA P_{es} (mmHg)	8.0 ± 0.9	10.5 ± 1.3*	10.0 ± 1.1	11.4 ± 1.7*
LA P_{ed} (mmHg)	10.1 ± 1.2	11.6 ± 1.3	11.1 ± 1.2	12.4 ± 1.7*
LA P_{mean} (mmHg)	8.9 ± 0.9	10.8 ± 1.3	10.5 ± 1.1*	11.1 ± 1.7*
LA V_{es} (ml)	6.3 ± 0.4	9.0 ± 0.7*	9.3 ± 0.6*	8.9 ± 0.6*
LA V_{ed} (ml)	8.0 ± 0.4	9.7 ± 0.7*	10.1 ± 0.6*	9.5 ± 0.6*
LA V_{max} (ml)	8.8 ± 0.5	11.5 ± 0.9*	11.5 ± 0.7*	10.4 ± 0.7*
LA V_{0s} (ml)	3.9 ± 0.7	4.4 ± 0.9	4.8 ± 0.8	5.6 ± 0.7
LA V_{0r} (ml)	5.2 ± 0.8	5.8 ± 0.8	5.5 ± 1.3	5.9 ± 0.5
PV diagrams (n)	12 ± 2	11 ± 2	11 ± 2	9 ± 2
LA SV (ml)	1.7 ± 0.3	0.7 ± 0.1*	0.7 ± 0.1*	0.6 ± 0.1*
LA RV (ml)	2.5 ± 0.3	2.5 ± 0.4	2.2 ± 0.3	1.6 ± 0.3*
LA EF (%)	21 ± 3	8 ± 1*	7 ± 1*	7 ± 1*
A area (mmHg · ml)	4.2 ± 1.1	1.7 ± 0.3*	1.3 ± 0.3*	0.9 ± 0.2*
V area (mmHg · ml)	1.2 ± 0.3	2.9 ± 0.7*	2.3 ± 0.3*	1.6 ± 0.3
[ET] (%)	—	0.8 ± 0.0	1.2 ± 0.0	1.6 ± 0.0

Data are mean ± SEM; n = 8.

* Significantly ($P < 0.05$) different from baseline. † Significantly ($P < 0.05$) different from 0.6 minimum alveolar concentration (MAC) isoflurane. ‡ Significantly ($P < 0.05$) different from 0.9 MAC isoflurane.

HR = heart rate; MAP = mean arterial pressure; RPP = rate–pressure product; LV = left ventricle; $+dP/dt_{max}$ = maximum rate of increase of left ventricular pressure; τ = time constant of LV isovolumic relaxation; LA = left atrium; P_{es}, P_{ed}, and P_{mean} = end-systolic, end-diastolic, and mean pressures, respectively; V_{es}, V_{ed}, V_{max}, V_{0s}, and V_{0r} = end-systolic, end-diastolic, maximum, E_{es} intercept, and E_{er} intercept volumes, respectively; PV = pressure–volume; SV = stroke volume; RV = reservoir volume; EF = emptying fraction; [ET] = end-tidal concentration.

degree, and estimates of absolute LA volume using this technique may not be completely accurate. However, previous studies[5,14] demonstrated that changes in LA volume produced by a variety of perturbations may be precisely determined using this assumption of LA geometry. Each dog also served as its own control in the present investigation. An increase in LA pressure was used to obtain a series of LA pressure–volume diagrams for the determination of E_{es} because of the low operating range of pressure and volume in normal canine LA. Pilot experiments demonstrated that an intravenous bolus of phenylephrine caused more gradual and predictable increases in LA pressure and volume than mechanical aortic constriction. The same dose of phenylephrine was used before and during the administration of desflurane, sevoflurane, or isoflurane to produce increases in LA pressure of similar magnitude during these experimental conditions. Phenylephrine has been shown to exert positive inotropic effects by activating α_1-adrenoceptors and the intracellular second messenger inositol triphosphate,[30,31] but these actions are substantially more pronounced in failing compared with normal myocardium.[30] There is little evidence to suggest that volatile anesthetics differentially modulate the LA contractile response to α_1-adrenoceptor agonists,[20] but this possibility cannot be completely excluded from the analysis. It is also unlikely that residual circulating phenylephrine affected the results because systemic hemodynamics were allowed to return to steady state conditions before subsequent interventions were performed, and desflurane, sevoflurane, and isoflurane caused cardiovascular effects in the current investigation that were nearly identical to those observed in our previous study using the same end-tidal anesthetic concentrations in a very similar canine model.[6]

Desflurane may directly stimulate release of catecholamines from atrial[3] and ventricular[32] myocardium. It is possible that such an effect that could partially attenuate the direct negative inotropic actions of this agent. However, we have previously demonstrated that desflurane produces equivalent degrees of LV myocardial depression in the presence[33] and absence[34] of pharmacologic blockade of the autonomic nervous system in dogs. Analysis of LA function in pressure–volume phase space does not consider retrograde pulmonary venous blood flow that occurs during LA systole. However, this retrograde flow is minimal in the normal LA because of the peristaltic-like configuration of LA contraction and the unique valve-like anatomy of the pulmonary venous-LA junction.[35] The relative linearity and load dependence of LV end-systolic pressure–volume relations are well known,[36] but the extent to which these potential

limitations apply to determinations of LA contractility using this method *in vivo* have not been extensively described.[14] Nevertheless, LA E_{es} was determined in the current investigation within the normal operating range of LA pressure and volume in which the linearity and load independence of the LA end-systolic pressure–volume relation has been established.[8,14] In contrast to the linear relation used to define E_{er} in the current investigation, the use of an exponential equation to describe alterations in LA dynamic chamber stiffness has been advocated by some investigators,[5,9] analogous to methods used to characterize the diastolic elastic properties of the LV.[37] However, linear end-reservoir pressure–volume relations have also been shown to precisely quantify increases in LA stiffness associated with myocardial infarction and dilated cardiomyopathy in humans with correlation coefficients exceeding 0.90 for these relations.[15] Thus, we chose to use a linear LA end-reservoir pressure–volume model to describe anesthetic-induced changes in LA chamber stiffness. This technique produced r^2 values greater than or equal to 0.95 in all experiments. Volatile anesthetic–induced reductions in heart rate may have contributed to declines in E_{es} and R_{LA} or affected other indices of LA function to some degree. However, the decreases in heart rate produced by volatile agents were not dose-related, in contrast to reductions in LA and LV contractility, LA and LV relaxation, LA stroke work, and LA stiffness. Lastly, acute surgical instrumentation during barbiturate anesthesia has been shown to produce substantial baseline LV systolic and diastolic dysfunction,[38] and the current results should be considered within the possible shortcomings of this model.

In summary, the current results indicate that desflurane, sevoflurane, and isoflurane alter the active and passive mechanical properties of the LA evaluated with pressure–volume relations. These volatile agents depressed LA myocardial contractility, delayed relaxation, reduced dynamic chamber stiffness, enhanced reservoir function, and impaired LA-LV coupling *in vivo*. The actions of volatile anesthetics on LA function and its contribution to global cardiac performance are complex. Volatile agents attenuate the active mechanical properties of the LA but preserve or even enhance passive mechanical characteristics, partially offsetting these deleterious effects.

The authors thank John P. Tessmer, B.S., and John G. Krolikowski, B.A. (Research Scientists, Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI), for technical assistance.

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