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Desflurane, Sevoflurane, and Isoflurane Impair Canine Left Ventricular–Arterial Coupling and Mechanical Efficiency

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Background: **The effects of desflurane, sevoflurane, and isoflurane on left ventricular–arterial coupling and mechanical efficiency were examined and compared in acutely instrumented dogs.**

Methods: **Twenty-four open-chest, barbiturate-anesthetized dogs were instrumented for measurement of aortic and left ventricular (LV) pressure (micromanometer-tipped catheter), dP/dt_{max}, and LV volume (conductance catheter). Myocardial contractility was assessed with the end-systolic pressure–volume relation (E_{es}) and preload recruitable stroke work (M_{sw}) generated from a series of LV pressure–volume diagrams. Left ventricular–arterial coupling and mechanical efficiency were determined by the ratio of E_{es} to effective arterial elastance (E_a; the ratio of end-systolic arterial pressure to stroke volume) and the ratio of stroke work (SW) to pressure–volume area (PVA), respectively.**

Results: **Desflurane, sevoflurane, and isoflurane reduced heart rate, mean arterial pressure, and left ventricular systolic pressure. All three anesthetics caused similar decreases in myocardial contractility and left ventricular afterload, as indicated by reductions in E_{es}, M_{sw}, and dP/dt_{max} and E_a, respectively. Despite causing simultaneous declines in E_{es} and E_a, desflurane decreased E_{es}/E_a (1.02 ± 0.16 during control to 0.62 ± 0.14 at 1.2 minimum alveolar concentration) and SW/PVA (0.51 ± 0.04 during control to 0.43 ± 0.05 at 1.2 minimum alveolar concentration). Similar results were observed with sevoflurane and isoflurane.**

Conclusions: **The present findings indicate that volatile anesthetics preserve optimum left ventricular–arterial coupling and efficiency at low anesthetic concentrations (<0.9 minimum alveolar concentration); however, mechanical matching of energy transfer from the left ventricle to the arterial circulation degenerates at higher end-tidal concentrations. These detrimental alterations in left ventricular–arterial coupling produced by desflurane, sevoflurane, and isoflurane contribute to reductions in overall cardiac performance observed with these agents *in vivo*. (Key words: Anesthetics, volatile: desflurane, sevoflurane, isoflurane; Heart: myocardial contractility; mechanical efficiency; end-systolic pressure–volume relation; ventricular–arterial coupling; pressure–volume area.)**

OPTIMUM transfer of energy from the left ventricle to the arterial circulation requires appropriate matching of these mechanical systems. Left ventricular–arterial coupling can be described in the time-dependent pressure–volume plane using a series elastic chamber model of the cardiovascular system.[1] The elastances of the contracting left ventricle (E_{es}) and the arterial vasculature (E_a) are determined from left ventricular end-systolic pressure–volume and end-systolic arterial pressure–stroke volume relations, respectively.[1–3] The ratio of E_{es} to E_a defines coupling between the left ventricle and the arterial circulation[1,2] and provides a useful technique for assessment of the actions of pharmacologic agents, including volatile anesthetics, on overall cardiovascular performance *in vivo*.[4,5] Analysis of the pressure–volume relation also creates a framework for the study of left ventricular mechanical efficiency defined by the ratio of stroke work (SW) to pressure–volume area (PVA).[5]

The influence of volatile anesthetics on left ventricular–arterial coupling and mechanical efficiency have not been studied completely. Desflurane, sevoflurane, and isoflurane were shown to reduce myocardial contractility concomitant with decreases in systemic vascular resistance in experimental animals[6–12] and humans.[13–15] These observations suggest that left ventricular–arterial coupling may be maintained during anesthesia because reductions in left ventricular afterload may balance declines in contractile state. This investigation compared the actions of desflurane, sevo-

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flurane, and isoflurane on left ventricular–arterial coupling and mechanical efficiency and tested the hypothesis that these volatile anesthetics do not adversely affect the mechanical relation between the left ventricle and the arterial circulation in open-chest, barbiturate-anesthetized dogs.

Materials and Methods

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

Implantation of Instruments

Mongrel dogs (n = 24) of either sex weighing between 25 and 30 kg were fasted overnight and anesthetized with 25 $mg \cdot kg^{-1}$ sodium pentobarbital and 200 $mg \cdot kg^{-1}$ sodium barbital. Fluid deficits were replaced before experimentation with 500 ml 0.9% saline, which was continued at 3 $ml \cdot kg^{-1} \cdot h^{-1}$ for the duration of each experiment. After tracheal intubation, the dogs lungs were ventilated *via* positive pressure with a mixture (1 $l \cdot min^{-1}$) of oxygen (90%) and air (10%). Respiratory rate and tidal volume were adjusted to maintain acid–base status (pH = 7.35–7.40) and carbon dioxide partial pressure (PCO_2 = 30–35 mmHg) within physiologic limits. The right femoral vein was cannulated for fluid administration. A 7F, dual micromanometer-tipped catheter (Millar Instruments, Houston, TX) was inserted through the left carotid artery and positioned across the aortic valve, with the distal transducer in the left ventricle and the proximal transducer in the ascending thoracic aorta for measurement of continuous left ventricular and arterial pressures, respectively. The peak rate of increase of left ventricular pressure (dP/dt_{max}) was determined by electronic differentiation of the left ventricular pressure waveform. A thoracotomy was performed in the left fifth intercostal space, and the lung was gently retracted. The pericardium was incised, and the heart was temporarily elevated from the thoracic cavity to allow access to the left ventricular apex. A 7F, eight-electrode conductance catheter with a fluid-filled lumen (Webster Labs, Baldwin Park, CA) was inserted into the left ventricular cavity through a small incision in the apex. Using a fluid-filled pressure transducer system, the conductance catheter was positioned so that the distal tip was located in the ascending thoracic aorta just distal to the aortic valve. The conductance catheter was secured firmly with a purse string suture. A hydraulic vascular occluder was positioned around the inferior vena cava for abrupt alteration of left ventricular preload. Lastly, a fluid-filled catheter was placed in the left atrial appendage for administration of hypertonic saline (20%; 5 ml), used to determine parallel conductance volume (V_p). The experimental preparation was allowed to stabilize for at least 30 min after instrumentation was completed.

Measurement of Left Ventricular Volume

The conductance technique was used to measure left ventricular volume.[16] This method was shown to accurately determine beat-to-beat changes in stroke volume (SV) and end-diastolic volume (EDV) under a variety of experimental conditions *in vivo.*[17–19] The multielectrode catheter was connected to a conductance module designed and constructed in our laboratory that drove a constant current (20 μA at 5 kHz) between the two outermost electrodes and measured the resultant voltage difference between each adjacent remaining electrode. Counterclockwise development of each left ventricular pressure-segmental volume diagram identified electrode-pair signals located within the left ventricle. Measured time-dependent left ventricular volume [V(t)] was determined using the equation:

$$V(t) = G(t) \cdot L^2 \cdot (\alpha \cdot \sigma)^{-1} - V_p$$

where G(t) = the sum of time-dependent conductances from each intraventricular electrode pair, L = the intraelectrode distance (1.0 cm), α = a slope correction factor relating the measured conductance volume to actual left ventricular volume, and σ = the blood conductivity. Parallel conductance (offset) volume (V_p) was determined using the hypertonic saline technique[16,17] and subtracted from measured volume to obtain absolute left ventricular volume during each experimental intervention. No changes in parallel conductance volume were observed during or after administration of volatile anesthetics. Blood conductivity (σ) was determined at each intervention from a 5 ml blood sample using a cuvette that was precalibrated with solutions of known conductivity. No changes in σ were observed during each experiment. Previous investigations have shown that α is approximately equal

to one and remains relatively constant during a variety of physiologic or pharmacologic interventions.[19–21] End-systolic volume (ESV) and EDV were measured at maximum left ventricular elastance[22] and immediately before the onset of left ventricular isovolumic contraction, respectively. Typical hemodynamic waveforms and left ventricular pressure–volume diagrams obtained during abrupt occlusion of the inferior vena cava are depicted in figure 1. Ejection fraction (EF) was determined using the equation: $EF = (EDV - ESV) \cdot EDV^{-1}$. Hemodynamic data were recorded continuously on a polygraph (model 7, Grass Instruments, Quincy, MA) and simultaneously digitized by a computer interfaced with an analog to digital converter for recording and subsequent analysis of left ventricular pressure–volume diagrams.

Experimental Protocol

After instrumentation had been completed, left ventricular pressure–volume diagrams used to assess myocardial contractility were obtained at end-expiration by abruptly decreasing left ventricular preload *via* inflation of the inferior vena caval balloon cuff occluder, resulting in an approximately 25-mmHg decline in left ventricular systolic pressure during 10–15 cardiac cycles (fig. 1). Using linear regression analysis, the end-systolic pressure (P_{es}) and volume (V_{es}) of each left ventricular pressure–volume diagram during the inferior caval occlusion were fit to the equation: $P_{es} = E_{es} \cdot (V_{es} - V_0)$, where E_{es} = left ventricular end-systolic elastance and V_0 = the extrapolated volume intercept of the relation (fig. 2). Myocardial contractility also was evaluated with the preload recruitable stroke work relation derived from the same left ventricular pressure–volume diagrams using linear regression analysis:

$$SW = M_{sw} \cdot (EDV - V_{sw})$$

where SW is stroke work (calculated as the integral of the pressure–volume diagram for each cardiac cycle) and M_{sw} and V_{sw} are the slope and volume intercept of the preload recruitable stroke work relation, respectively (fig. 2).[23] Effective arterial elastance (E_a) was calculated as the ratio of end-systolic arterial pressure and SV under steady-state hemodynamic conditions immediately before inferior vena caval occlusion.[1,2] Left ventricular–arterial coupling was described as the ratio of E_{es} and E_a.[1] The PVA (total mechanical energy) was determined at each intervention as the sum of SW and potential energy, where potential energy = $0.5 \cdot P_{es} \cdot (V_{es} - V_0)$.[24] In this framework, potential energy represents the energy expended by the left ventricle that does not contribute to ejection. The ratio of SW to PVA was used to determine the mechanical efficiency of energy transfer of PVA to externally performed SW.[25]

Dogs were assigned to receive desflurane, sevoflurane, and isoflurane in a random manner in three separate groups of experiments. Baseline systemic hemodynamics and left ventricular pressure–volume diagrams were recorded during control conditions 30 min after the instrumentation was completed. In one group of experiments, 0.6, 0.9, and 1.2 minimum alveolar concentration (MAC) (end-tidal) desflurane was administered. The order of MAC was assigned randomly. Hemodynamics were recorded, and left ventricular pressure–volume diagrams were obtained using the techniques described above after 15 min equilibration at each dose. Desflurane was then discontinued and measurements were repeated after the anesthetic was eliminated. In two other groups of experiments, hemodynamics and left ventricular pressure–volume diagrams were recorded at the time intervals described above in dogs before, during, and after 0.6, 0.9, and 1.2 MAC sevoflurane or isoflurane. The canine 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 by 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 the fluid-filled, conductance, and micromanometer-tipped catheters were confirmed.

Statistical Analysis

Statistical analysis of the data within and between groups before and during the administration of desflurane, sevoflurane, and isoflurane was performed by multiple analysis of variance with repeated measures, followed by use of Student's *t* test, with Bonferroni's adjustment for multiplicity. Changes were considered statistically significant when the probability (P) value was < 0.05. All data are expressed as mean ± SEM.

Results

Twenty-four dogs were used to provide 21 complete experiments. Three dogs were excluded from analysis because of instrument failure. Desflurane caused sig-

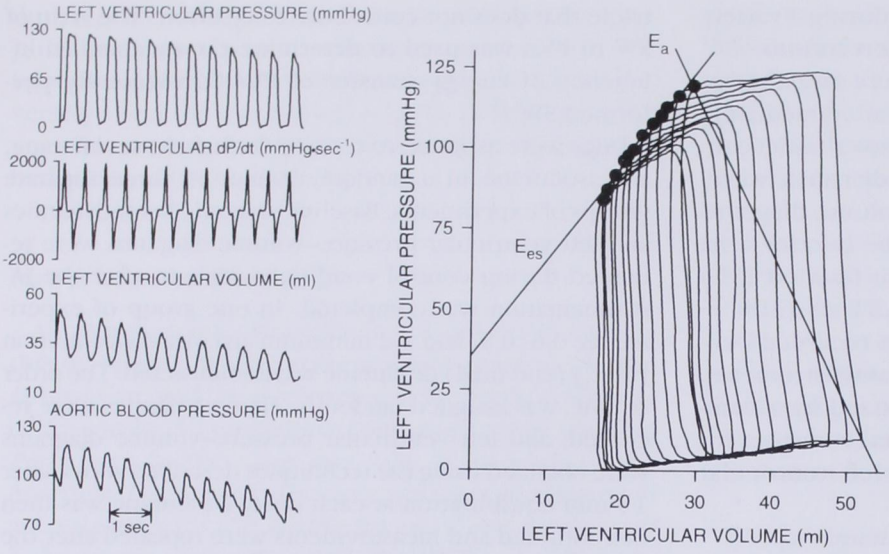

Fig. 1. Continuous left ventricular pressure, left ventricular dP/dt, left ventricular volume, and arterial blood pressure waveforms (left panel) and left ventricular pressure–volume diagrams (right panel) during inferior vena caval occlusion observed in a typical experiment. The left ventricular maximal elastances (solid dots) for each pressure–volume diagram were used to generate the slope (E_{es}) of the end-systolic pressure–volume relation. Effective arterial elastance (E_a) was determined by the ratio of left ventricular end-systolic pressure and stroke volume during steady-state hemodynamic conditions (see text). In the pressure–volume plane, E_a represents the magnitude of the slope connecting end-systole to end-diastole (right panel).

nificant ($P < 0.05$) decreases in heart rate, mean arterial pressure, and left ventricular systolic pressure (table 1). Left ventricular end-diastolic pressure, EDV, and ESV were unchanged by desflurane. A decrease in SV occurred at 1.2 MAC. Dose-related reductions in the slopes of the end-systolic pressure–volume (E_{es}; 3.3 ± 0.5 during control to 1.2 ± 0.2 mmHg · ml^{-1} at 1.2 MAC) and the preload recruitable SW relation (M_{sw}; 57 ± 6 during control to 30 ± 4 mmHg at 1.2 MAC) were produced by desflurane, indicating that a direct depression of myocardial contractility occurred. The volume intercepts (V_0 and V_{sw}, respectively) of these relations remained unchanged. Concomitant reductions in dP/dt_{max} and EF were observed. Desflurane also produced dose-related decreases in E_a (3.3 ± 0.3 during control to 2.1 ± 0.2 mmHg · ml^{-1} at 1.2 MAC). Despite simultaneous declines in E_{es} and E_a, the ratio of these variables (E_{es}/E_a) decreased at the highest concentration of desflurane (1.02 ± 0.16 during control to 0.62 ± 0.14 at 1.2 MAC, fig. 3), indicating that this volatile anesthetic caused an alteration in mechanical coupling of the left ventricle to the arterial circulation. In addition, desflurane also decreased SW/PVA (0.51 ± 0.04 during control to 0.43 ± 0.05 at 1.2 MAC; fig. 3), consistent with a decline in the conversion of total left ventricular energy to external SW. Discontinuation of desflurane caused hemodynamics, contractility (E_{es} and M_{sw}), and afterload (E_a) to return to baseline values.

Sevoflurane and isoflurane caused hemodynamic and mechanical effects very similar to those produced by desflurane (tables 2 and 3, respectively). Sevoflurane and isoflurane decreased heart rate, mean arterial pressure, and left ventricular systolic pressures. No changes in left ventricular end-diastolic pressure, EDV, and ESV were observed. In contrast to the findings with desflurane and isoflurane, SV remained unchanged during sevoflurane anesthesia. Sevoflurane and isoflurane caused dose-related depression of contractile state (E_{es} and M_{sw}) and reductions in E_a (tables 2 and 3). Depression of myocardial contractility and decreases in E_a observed in dogs receiving sevoflurane and isoflurane were similar to those produced by desflurane. Sevoflurane (fig. 4) and isoflurane (fig. 5) caused declines in E_{es}/E_a (*e.g.*, 1.07 ± 0.20 during control to 0.59 ± 0.13 at 1.2 MAC sevoflurane; fig. 4) and SW/PVA (*e.g.*, 0.54 ± 0.06 during control to 0.42 ± 0.05 at 1.2 MAC sevoflurane; fig. 4), indicating that these volatile anesthetics impair normal left ventricular–arterial coupling and mechanical efficiency. Sevoflurane- and isoflurane-induced alterations in coupling and efficiency variables were similar in magnitude to those observed during desflurane anesthesia. Hemodynamics and left ventricular mechanical properties returned to control values after sevoflurane and isoflurane was discontinued.

Discussion

The current results indicate that desflurane, sevoflurane, and isoflurane produce similar reductions in myocardial contractility, as evaluated by E_{es} and M_{sw} derived from left ventricular pressure–volume diagrams generated using the conductance catheter technique to invasively measure continuous left ventricular

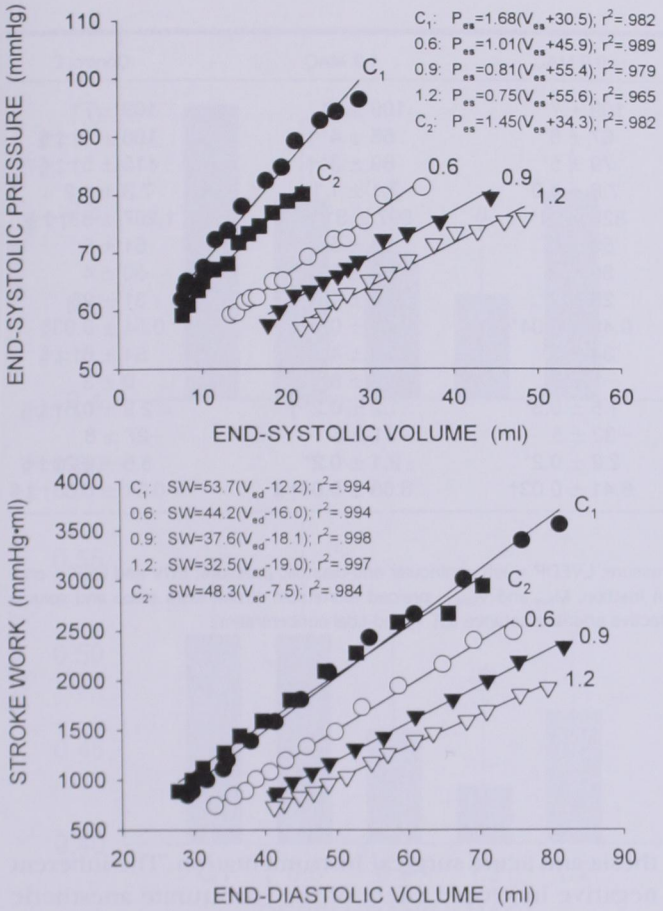

Fig. 2. End-systolic pressure–volume (top panel) and stroke work–end-diastolic volume relations (bottom panel) before (control 1; C_1), during 0.6, 0.9, and 1.2 minimum alveolar concentration, and after isoflurane (control 2; C_2) in a typical experiment. P_{es} and V_{es} = end-systolic pressure and volume, respectively; SW = stroke work; V_{ed} = end-diastolic volume.

volume. The current findings confirm and extend the results of previous investigations from our laboratory[7,8,26] in which regional preload recruitable SW derived using sonomicrometry was used as a relatively heart rate- and load-independent index of contractile state in chronically instrumented dogs. The negative inotropic effects of volatile anesthetics were accompanied by reductions in E_a, confirming the findings of several previous investigations that indicate that desflurane, sevoflurane, and isoflurane decrease resistance to left ventricular outflow.[9–14,27] These observations suggest that mechanical matching between the left ventricle and the arterial vasculature may be preserved during anesthesia because reductions in left ventricular afterload may balance declines in contractile state. This hypothesis was tested using a series elastic chamber model of left ventricular–arterial coupling quantified with the ratio of left ventricular end-systolic elastance (E_{es}) to effective arterial elastance (E_a).[1,2] Left ventricular SW has been shown to be maximized when E_{es} equals E_a in both isolated and intact hearts.[2–4]

The current investigation is the first to examine the effects of volatile anesthetics on left ventricular–arterial coupling and mechanical efficiency derived from a series of differentially loaded left ventricular pressure–volume diagrams *in vivo*. The results indicate that desflurane, sevoflurane, and isoflurane maintain nearly optimum left ventricular–arterial coupling and mechanical efficiency at low concentrations (<0.9 MAC), however, these vasodilating negative inotropes adversely affect mechanical matching between the left ventricle and arterial circulation and reduce the transfer of total left ventricular energy to external SW at higher anesthetic concentrations.

Decreases in E_{es} observed with desflurane, sevoflurane, and isoflurane occurred in a dose-dependent manner in the presence of the basal barbiturate anesthetic. In contrast, relatively large decreases in E_a were observed at the 0.6 MAC concentration of the volatile anesthetics that were not further reduced at the 0.9 and 1.2 MAC doses. These findings suggest that a decrease in peripheral sympathetic nervous system tone may have accompanied the low dose of the volatile agents with little further effect and higher doses.

A single previous study compared the influence of isoflurane and halothane on left ventricular–arterial coupling using a single-beat method to determine E_{es} and V_0 without altering the loading conditions of the left ventricle in pentobarbital and α-chloralose-anesthetized, acutely instrumented dogs.[28] The authors demonstrated that low concentrations of halothane (1 MAC), but not isoflurane, reduced E_{es}/E_a, consistent with depression of mechanical coupling between the left ventricle and the arterial circulation.[28] However, isoflurane decreased E_{es}/E_a at 2 MAC, suggesting that the vasodilating effects of this volatile agent were unable to compensate adequately for relatively greater declines in contractility. Although single-beat derivation of E_{es} was validated previously,[29] interpretation of the results of Kawasaki *et al.*[28] requires qualification because of several major potential limitations with this method. Single-beat analysis of left ventricular end-systolic pressure–volume relations assumes symmetric left ventricular pressure rise and fall and requires extrapolation of peak isovolumic-developed pressure from

Table 1. Hemodynamic Effects of Desflurane

	Control 1	0.6 MAC	0.9 MAC	1.2 MAC	Control 2
HR (beats · min^{-1})	130 ± 12	106 ± 7*	109 ± 7*	109 ± 6*	109 ± 7*
MAP (mmHg)	97 ± 4	74 ± 7*	67 ± 6*	56 ± 4*†	106 ± 4†‡§
LVSP (mmHg)	108 ± 5	85 ± 6*	79 ± 5*	69 ± 3*†	115 ± 5†‡§
LVEDP (mmHg)	6.1 ± 1.4	6.8 ± 1.1	7.6 ± 1.0	7.1 ± 1.1	7.3 ± 1.2
dP/dt_{max} (mmHg · s^{-1})	1,440 ± 103	944 ± 88*	826 ± 71*	697 ± 31*†	1,267 ± 83†‡§
EDV (ml)	56 ± 4	59 ± 5	59 ± 6	58 ± 5	61 ± 5
ESV (ml)	25 ± 4	29 ± 4	30 ± 5	32 ± 5*	30 ± 4
SV (ml)	30 ± 2	30 ± 2	29 ± 2	26 ± 1*†	31 ± 2§
EF	0.56 ± 0.04	0.52 ± 0.03	0.49 ± 0.04*	0.47 ± 0.04*	0.54 ± 0.03§
M_{SW} (mmHg)	57 ± 6	38 ± 3*	34 ± 3*	30 ± 4*	54 ± 6†‡§
V_{SW} (ml)	−2 ± 6	−6 ± 6	−1 ± 5	2 ± 8	0 ± 3
E_{es} (mmHg · ml^{-1})	3.3 ± 0.5	1.9 ± 0.3*	1.5 ± 0.3*	1.2 ± 0.2*†	2.9 ± 0.5†‡§
V_0 (ml)	−26 ± 5	−27 ± 9	−32 ± 8	−31 ± 6	−27 ± 8
E_a (mmHg · ml^{-1})	3.3 ± 0.3	2.4 ± 0.2*	2.2 ± 0.2*	2.1 ± 0.2*	3.5 ± 0.2†‡§
ET (%)	—	4.47 ± 0.06	6.41 ± 0.03†	8.68 ± 0.04†‡	0.31 ± 0.03†‡§

Data are mean ± SEM; n = 7.

HR = heart rate; MAP = mean arterial pressure; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; EDV and ESV = end-diastolic and end-systolic volume, respectively; SV = stroke volume; EF = ejection fraction; M_{SW} and V_{SW} = preload recruitable stroke work slope and volume intercept, respectively; E_{es} = end-systolic elastance; V_0 = volume intercept; E_a = effective arterial elastance; ET = end-tidal concentration.

* Significantly ($P < 0.05$) different from control 1.

† Significantly ($P < 0.05$) different from 0.6 MAC desflurane.

‡ Significantly ($P < 0.05$) different from 0.9 MAC desflurane.

§ Significantly ($P < 0.05$) different from 1.2 MAC desflurane.

the left ventricular pressure waveform of an ejecting beat.[29,30] The single-beat estimation of E_{es} assumes that V_0 remains constant during inotropic interventions, but V_0 was shown to be altered significantly by changes in ventricular loading conditions or contractile state.[31] In addition, assumptions of complete linearity and total load-independence of the end-systolic pressure–volume relation may represent inappropriate simplifications because previous studies demonstrated that some degree of curvilinearity and afterload dependence is inherent to the relation.[32–34] Lastly, a recent investigation showed that single-beat estimation of E_{es} also may be relatively insensitive to changes in inotropic state when compared with E_{es} derived invasively from left ventricular pressure–volume diagrams.[30] Despite these potential limitations, the current results support the findings of Kawasaki *et al.*[28] and indicate that isoflurane does not adversely affect left ventricular–arterial coupling at anesthetic concentrations < 0.9 MAC.

The current results should be interpreted within the constraints of several possible shortcomings. Our results may differ from those obtained in conscious, chronically instrumented dogs because of the cardiovascular depression associated with barbiturate anesthesia and acute surgical instrumentation. The inherent negative inotropic effect of the barbiturate anesthetic may have contributed to a more profound depression of contractility with desflurane, sevoflurane, and isoflurane in the current study than was previously observed in chronically instrumented dogs.[6–10,35] In addition, lack of a conscious control state may make difficult a comparison of the current results to previous studies that examined the mechanical effects of volatile anesthetics. The possibility of drug interaction between the basal barbiturate anesthetics and volatile agents used in this investigation also cannot be excluded completely from the analysis. Nevertheless, the value of E_{es}/E_a observed under control conditions before and after administration of volatile anesthetics was similar to that observed in conscious dogs.[4] Previous studies demonstrated that E_{es},[33,36] but not M_{sw},[23,37] may be sensitive to acute alterations in left ventricular afterload. Therefore, reductions in E_a during desflurane, sevoflurane, and isoflurane anesthesia may have partially attenuated the decreases in E_{es} produced by these agents. However, decreases in the magnitude of E_{es} and M_{sw} in response to the volatile anesthetics were appropriately matched, indicating that reductions in afterload

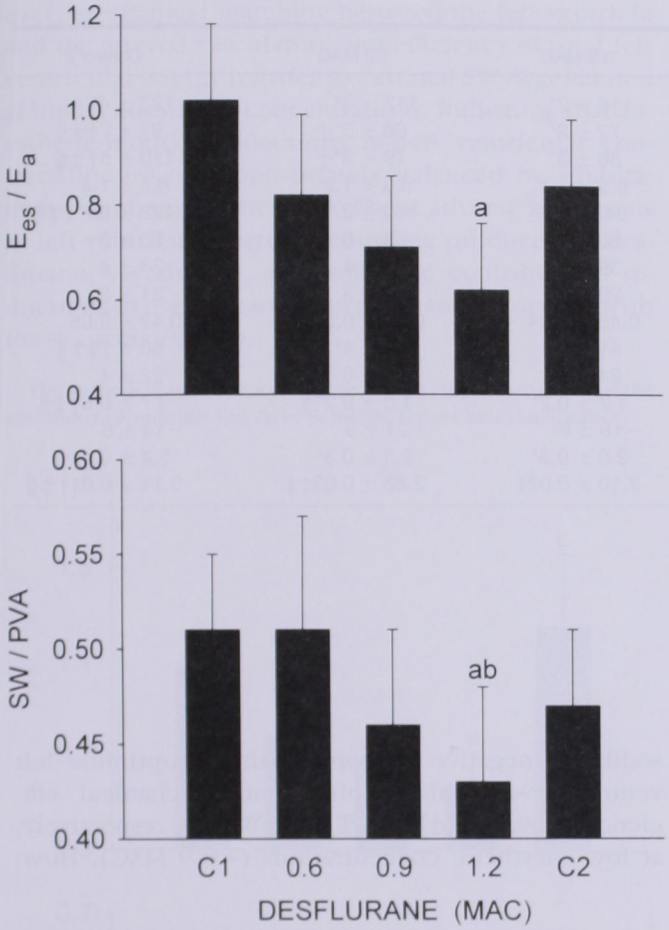

Fig. 3. Histograms depicting left ventricular–arterial coupling (E_{es}/E_a; top panel) and mechanical efficiency (stroke work [SW]/pressure–volume area [PVA]; bottom panel) before (control 1; C_1), during 0.6, 0.9, and 1.2 minimum alveolar concentration, and after desflurane (control 2; C_2). [a]Significantly ($P < 0.05$) different from C1; [b]Significantly ($P < 0.05$) different from 0.6 minimum alveolar concentration desflurane.

probably did not adversely affect evaluation of contractility using E_{es}. The slope of the end-systolic pressure–volume relation also was reported to be curvilinear over a wide range of pressures.[32,34,38] However, over the relatively narrow range of pressures observed in the current investigation, the end-systolic pressure–volume relation was shown to be essentially linear.[38] A previous study[19] demonstrated that E_{es} and V_0 were consistently underestimated with the conductance catheter measurement of left ventricular volume. However, alterations E_{es} in response to interventions that alter contractile state (*e.g.*, autonomic nervous system blockade and dobutamine) were appropriately detected and quantified with the conductance technique, as compared with three-dimensional sonomicrometry.[19] Therefore, it is likely that decreases in myocardial contractility produced by desflurane, sevoflurane, and isoflurane were quantified accurately, with E_{es} calculated from conductance catheter-derived left ventricular volume.

Effective arterial elastance is a composite coupling variable influenced by systemic vascular resistance and total arterial compliance. However, E_a cannot be used to quantify alterations in left ventricular afterload, because this parameter ignores characteristic aortic impedance, an important high frequency component of the arterial vascular behavior. Left ventricular afterload is a complex description of frequency-dependent arterial mechanical properties that be strictly quantified only with aortic input impedance.[27,39] Nevertheless, E_a provides a useful framework for the analysis of left ventricular–arterial coupling relations *in vivo*.[1,2] The calculation of SV required for the determination of E_a using the conductance technique also was validated previously, under a variety of experimental conditions.[16,17] We assumed that the slope correction factor (α) used in the determination of left ventricular volume was equal to 1.[40,41] The value of α may vary, to some degree, between dogs because of differences in left ventricular geometry. However, this potential source of bias was probably eliminated, because dogs were assigned to receive desflurane, sevoflurane, and isoflurane in a random manner. Recent evidence also suggests that α also may vary with the changes in left ventricular volume that occur during the cardiac cycle or as a result of rapid changes in ventricular volume (as may occur during vena caval occlusion).[42–44] Such volume-dependent alterations in α theoretically may contribute to a relative underestimation of SV and EDV.[43] The value of V_p may change during large alterations in left ventricular volume,[19,20] again introducing possible error in the measurement of absolute left ventricular volume during experimental interventions or abrupt alteration of preload. However, potential errors in α and V_p were probably minimized in this investigation because left ventricular arterial coupling and mechanical efficiency were described using ratios (E_{es}/E_a and SW/PVA) of volume-derived variables. Despite these potential limitations, the conductance method used to determine left ventricular volume in the current study has been widely established as a valid technique for the determination of beat-to-beat changes in SV and EDV under a wide variety of experimental conditions *in vivo*.[17–19,45]

Table 2. Hemodynamic Effects of Sevoflurane

	Control 1	0.6 MAC	0.9 MAC	1.2 MAC	Control 2
HR (beats · min^{-1})	131 ± 4	115 ± 4*	116 ± 2*	117 ± 3*	123 ± 4*
MAP (mmHg)	104 ± 7	80 ± 4*	72 ± 2*	66 ± 3*†	97 ± 7†‡§
LVSP (mmHg)	120 ± 6	93 ± 5*	86 ± 3*	79 ± 3*†	110 ± 5†‡§
LVEDP (mmHg)	7.3 ± 1.5	6.2 ± 1.4	6.5 ± 1.4	5.8 ± 1.2	6.5 ± 1.4
dP/dt_{max} (mmHg · s^{-1})	1,745 ± 70	1,066 ±48*	943 ± 32*	860 ± 27*†	1,422 ± 65*†‡§
EDV (ml)	61 ± 5	66 ± 5	66 ± 5	64 ± 6	63 ± 3
ESV (ml)	31 ± 4	37 ± 4	36 ± 4	36 ± 4	33 ± 4
SV (ml)	31 ± 3	29 ± 3	29 ± 3	28 ± 3	31 ± 3
EF	0.50 ± 0.03	0.45 ± 0.04	0.45 ± 0.04	0.44 ± 0.04	0.49 ± 0.05
M_{SW} (mmHg)	62 ± 6	45 ± 6*	41 ± 4*	36 ± 4*	60 ± 7†‡§
V_{SW} (ml)	19 ± 5	22 ± 6	24 ± 5	23 ± 6	22 ± 4
E_{es} (mmHg · ml^{-1})	3.5 ± 0.5	2.0 ± 0.4*	1.7 ± 0.2*	1.3 ± 0.2*†	3.7 ± 0.6†‡§
V_0 (ml)	−13 ± 8	−16 ± 7	−18 ± 6	−21 ± 9	−14 ± 6
E_a (mmHg · ml^{-1})	3.5 ± 0.4	2.9 ± 0.3	2.6 ± 0.3*	2.5 ± 0.3*	3.4 ± 0.4‡§
ET (%)	—	1.43 ± 0.02	2.10 ± 0.03†	2.83 ± 0.03†‡	0.14 ± 0.01†‡§

Data are mean ± SEM; n = 7. See table 1 for abbreviations.

* Significantly ($P < 0.05$) different from control 1.

† Significantly ($P < 0.05$) different from 0.6 MAC sevoflurane.

‡ Significantly ($P < 0.05$) different from 0.9 MAC sevoflurane.

§ Significantly ($P < 0.05$) different from 1.2 MAC sevoflurane.

In summary, the current results demonstrate that desflurane, sevoflurane, and isoflurane decrease myocardial contractility and reduce left ventricular afterload in barbiturate-anesthetized, open-chest dogs. These vasodilating negative inotropes maintain optimum left ventricular–arterial coupling and mechanical efficiency, as evaluated by E_{es}/E_a and SW/PVA, respectively, at low anesthetic concentrations (<0.9 MAC). How-

Table 3. Hemodynamic Effects of Isoflurane

	Control 1	0.6 MAC	0.9 MAC	1.2 MAC	Control 2
HR (beats · min^{-1})	124 ± 5	112 ± 3*	111 ± 3*	110 ± 4*	114 ± 5*
MAP (mmHg)	90 ± 4	71 ± 3*	65 ± 2*	61 ± 2*†	82 ± 5†‡§
LVSP (mmHg)	110 ± 3	92 ± 2*	86 ± 3*	82 ± 2*†	101 ± 3‡§
LVEDP (mmHg)	7.5 ± 1.2	5.6 ± 1.2	5.5 ± 1.4	6.4 ± 1.3	6.1 ± 1.2
dP/dt_{max} (mmHg · s^{-1})	1,629 ± 82	1,357 ± 62*	1,191 ± 70*†	1,079 ± 64*†	1,515 ± 62†‡§
EDV (ml)	59 ± 3	56 ± 3	56 ± 2	57 ± 2	55 ± 3
ESV (ml)	28 ± 2	27 ± 2	29 ± 2	31 ± 2	26 ± 2§
SV (ml)	31 ± 3	30 ± 3	28 ± 3*	26 ± 2*	29 ± 3
EF	0.53 ± 0.03	0.52 ± 0.03	0.49 ±0.04	0.46 ± 0.04*†	0.53 ± 0.03§
M_{SW} (mmHg)	59 ± 6	53 ± 5*	44 ± 4*†	38 ± 4*†‡	64 ± 4†‡§
V_{SW} (ml)	15 ± 3	20 ± 3	19 ± 3	18 ± 4	19 ± 3
E_{es} (mmHg · ml^{-1})	3.7 ± 0.6	2.8 ± 0.4*	2.0 ± 0.3*†	1.9 ± 0.3*†	4.1 ± 0.7‡§
V_0 (ml)	−6 ± 6	−3 ± 6	−13 ± 8	−16 ± 7	−3 ± 6§
E_a (mmHg · ml^{-1})	3.0 ± 0.3	2.6 ± 0.3	2.5 ± 0.3*	2.4 ± 0.2†	2.9 ± 0.3‡§
ET (%)	—	0.75 ± 0.01	1.16 ± 0.01†	1.55 ± 0.02†‡	0.09 ± 0.02†‡§

Data are mean ± SEM; n = 7. See table for abbreviations.

* Significantly ($P < 0.05$) different from control 1.

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

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

§ Significantly ($P < 0.05$) different from 1.2 MAC isoflurane.

ever, mechanical matching between the left ventricle and the arterial vasculature and efficiency of total left ventricular energy transfer to external SW degenerated at higher anesthetic concentrations, indicating that anesthetic-induced reductions in left ventricular contractility are not appropriately balanced by simultaneous declines in afterload. These adverse alterations in left ventricular–arterial coupling produced by desflurane, sevoflurane, and isoflurane contribute to reductions in overall cardiac performance observed with these agents *in vivo*.

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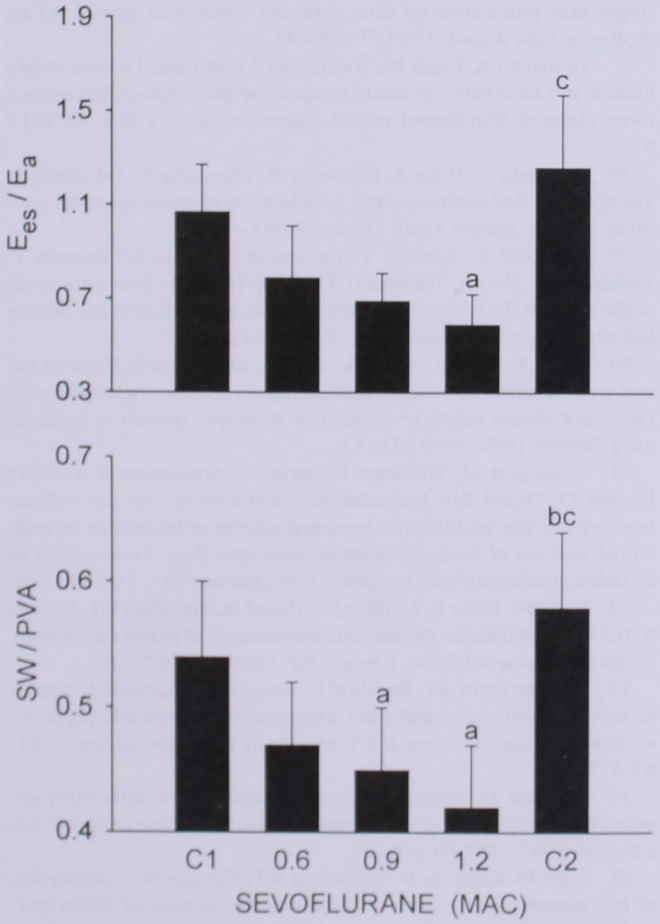

Fig. 4. Histograms depicting left ventricular–arterial coupling (E_{es}/E_a; top panel) and mechanical efficiency (stroke work [SW]/pressure–volume area [PVA]; bottom panel) before (control 1; C_1), during 0.6, 0.9, and 1.2 minimum alveolar concentration, and after sevoflurane (control 2; C_2). [a]Significantly ($P < 0.05$) different from C_1; [b]Significantly ($P < 0.05$) different from 0.9 minimum alveolar concentration sevoflurane; [c]Significantly ($P < 0.05$) different from 1.2 minimum alveolar concentration sevoflurane.

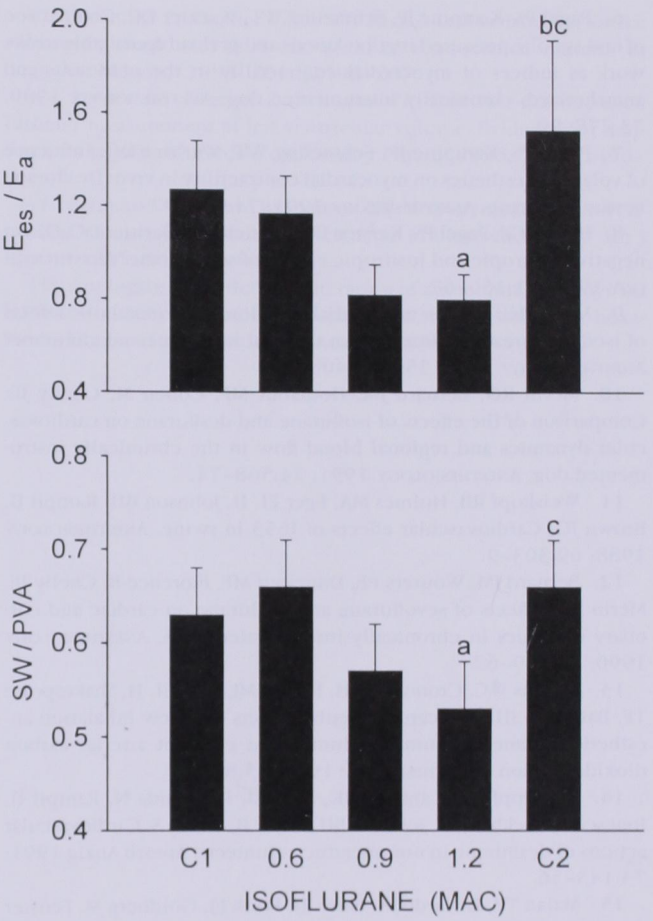

Fig. 5. Histograms depicting left ventricular–arterial coupling (E_{es}/E_a; top panel) and mechanical efficiency (stroke work [SW]/pressure–volume area [PVA]; bottom panel) before (control 1; C_1), during 0.6, 0.9, and 1.2 minimum alveolar concentration, and after isoflurane (control 2; C_2). [a]Significantly ($P < 0.05$) different from C_1; [b]Significantly ($P < 0.05$) different from 0.9 minimum alveolar concentration isoflurane; [c]Significantly ($P < 0.05$) different from 1.2 minimum alveolar concentration isoflurane.

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