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Direct Negative Inotropic and Lusitropic Effects of Sevoflurane

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Background: **Volatile anesthetics depress left ventricular mechanical performance during multiple phases of the cardiac cycle. The effects of sevoflurane on systolic and diastolic function have yet to be fully evaluated. This investigation characterized the systemic and coronary hemodynamic, inotropic, and lusitropic actions of sevoflurane in chronically instrumented dogs in the presence and absence of autonomic nervous system (ANS) reflexes.**

Methods: **Because ANS activity may influence the actions of volatile anesthetics *in vivo,* experiments were conducted in both ANS-intact and ANS-blocked animals. Eighteen experiments were performed in nine dogs chronically instrumented for measurement of aortic and left ventricular pressure, rate of change of left ventricular pressure, subendocardial segment length, diastolic coronary blood flow velocity, and cardiac output. The preload recruitable stroke work slope was used to assess myocardial contractility. Diastolic function was evaluated by a time constant of isovolumic relaxation, maximum segment lengthening velocity during rapid ventricular filling, and a regional chamber stiffness constant. Dogs were assigned to receive sevoflurane with or without pharmacologic blockade of the ANS in a random fashion. On separate experimental days, systemic and coronary hemodynamics and left ventricular pressure–segment length diagrams and waveforms were recorded in the conscious state and during sevoflurane anesthesia (1.0, 1.25, 1.5, and 1.75 MAC).**

Results: **In dogs with intact ANS reflexes, sevoflurane caused significant ($P < 0.05$) increases in heart rate and dose-related decreases in mean arterial pressure, left ventricular systolic pressure, cardiac output, and diastolic coronary vascular resistance. Sevoflurane also decreased myocardial contractility (preload recruitable stroke work slope 96 ± 4 in the conscious state to 42 ± 3 mmHg at 1.75 MAC). Sevoflurane prolonged isovolumic relaxation (time constant of isovolumic relaxation 35 ± 1 in the conscious state to 51 ± 3 ms at 1.75 MAC) and decreased rapid ventricular filling (maximum segment lengthening velocity 40.2 ± 6.0 in the conscious state to 21.8 ± 3.8 mm · s^{-1} at 1.75 MAC) without affecting regional chamber stiffness. Sevoflurane caused similar alterations in functional indices of left ventricular systolic and diastolic performance in autonomically blocked dogs.**

Conclusions: **Sevoflurane caused direct negative inotropic and lusitropic effects in chronically instrumented dogs with and without ANS blockade. (Key words: Anesthetics, volatile: sevoflurane. Heart, diastole: diastolic left ventricular function; isovolumic relaxation; ventricular compliance. Heart, myocardial performance: left ventricular function; myocardial contractility; preload recruitable stroke work.)**

INTEREST in sevoflurane has been rekindled in recent years because this volatile anesthetic possesses several advantageous biophysical properties, including low tissue-gas solubility coefficients and lack of pungency, which make it attractive for clinical use. The systemic and coronary hemodynamic effects of sevoflurane have been incompletely studied. Sevoflurane has been reported to produce a cardiovascular profile which is similar to that produced by isoflurane.[1–6] Sevoflurane may depress intrinsic myocardial contractility to a similar degree as isoflurane in chronically instrumented dogs[7] and may also result in less direct myocardial depression than enflurane in humans.[8] These observations must be qualified, however, because sevoflurane-induced changes in systemic hemodynamics may have directly influenced the indices of contractile state used in these studies. Recognition that left ventricular function during diastole also contributes significantly to overall cardiac performance[9] provides the rationale for the examination of the effects of sevoflurane on indices of diastolic function which have not been previously characterized.

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This investigation was undertaken to systematically examine the actions of sevoflurane on systemic and coronary hemodynamics and left ventricular systolic and diastolic function in chronically instrumented dogs. Myocardial contractility was evaluated with the preload recruitable stroke work relation slope (M_w), a relatively heart rate- and load-independent and easily quantified index of contractile state *in vivo*.[10-12] The preload recruitable stroke work relation was obtained from a series of left ventricular pressure–segment length loops generated by abrupt reduction of venous return. Diastolic function was assessed using several indices: a time constant of isovolumic relaxation (τ); the maximum segment lengthening velocity (dL/dt_{max}) during rapid ventricular filling; and a regional chamber stiffness constant (K_p). Experiments were performed with both intact and pharmacologically blocked autonomic nervous system (ANS) reflexes to determine the relative role of the ANS in the cardiovascular effects of sevoflurane.

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 of the Care and Use of Animals of the American Physiologic Society and were performed in accordance with the Guide for the Care and Use of Laboratory Animals (Department of Health, Education, and Welfare—Department of Health and Human Services publication (NIH) 85-23, revised 1985).

General Preparation

The surgical implantation of instruments has been documented in detail.[10,11] During general anesthesia using sterile techniques, conditioned mongrel dogs (n = 9; weight 25.8 ± 0.8 kg, mean ± SEM) underwent a left thoracotomy for placement of instruments for measurement of aortic and left ventricular pressure, rate of change of left ventricular pressure (dP/dt), subendocardial segment length, intrathoracic pressure, diastolic coronary blood flow velocity, and cardiac output. A hydraulic vascular occluder was positioned around the inferior vena cava for control of left ventricular preload. All instrumentation was firmly secured, tunneled between the scapulae, and exteriorized *via* several small incisions. The pericardium was left open, the chest wall closed in layers, and the pneumothorax subsequently evacuated by a chest tube.

All dogs received systemic analgesics (Innovar-Vet [fentanyl-droperidol], Pitman-Moore, Mundelein, IL) as needed after surgery. Dogs were allowed to recover a minimum of 7 days before experimentation during which time all were treated with antibiotics (cephalothin 40 mg/kg and gentamicin 4.5 mg/kg) and trained to stand quietly in an animal sling for hemodynamic monitoring. Coronary blood flow velocity and segment length signals were monitored by ultrasonic amplifiers (Crystal Biotech, Hopkinton, MA). End-systolic segment length was determined at maximum negative left ventricular dP/dt and end-diastolic segment length was determined just before the onset of left ventricular isovolumic contraction. The lengths were normalized according to the method described by Theroux *et al.*[13] Percent segment shortening was calculated as $(EDL - ESL) \times 100 \times EDL^{-1}$, where ESL = end-systolic segment length and EDL = end-diastolic segment length. Relative diastolic coronary vascular resistance was calculated as the quotient of diastolic arterial pressure and diastolic coronary blood flow velocity. Pressure work index, an estimate of myocardial oxygen consumption, was determined using the formula of Rooke and Feigl.[14] The hemodynamic data were continuously recorded on a polygraph (7758A, Hewlett-Packard, San Francisco, CA) and digitized by a computer interfaced with an analog to digital converter. Ventricular pressure and segment length data were also transmitted to a digital storage oscilloscope (4094, Nicolet, Madison, WI) for recording of left ventricular pressure–segment length waveforms and diagrams.

Experimental Protocol

Dogs were randomly assigned to receive sevoflurane with or without ANS blockade on separate experimental days. Each dog was fasted overnight, and fluid deficits were replaced before experimentation with crystalloid (500 ml 0.9% saline) which was continued at 3 $ml \cdot kg^{-1} \cdot h^{-1}$ for the duration of each experiment. Dogs undergoing pharmacological blockade of the ANS received intravenous propranolol (2 $mg \cdot kg^{-1}$), atropine methylnitrate (3 $mg \cdot kg^{-1}$), and hexamethonium (20 $mg \cdot kg^{-1}$). Adequacy of autonomic blockade was established by lack of reflex change in heart rate during an abrupt decline of venous return by inflation of the

inferior vena caval hydraulic occluder before, during and after each experiment.

Left ventricular pressure, intrathoracic pressure, and segment length waveforms were recorded continuously on the digital oscilloscope for later off-line analysis of diastolic function. Left ventricular pressure–segment length diagrams used to assess contractile state were generated by abruptly decreasing left ventricular preload. This was accomplished by constricting the inferior vena cava, resulting in decrease of approximately 30 mmHg in left ventricular systolic pressure over 10–20 cardiac cycles. Respiratory variation in ventricular pressure in the conscious state were later reduced off-line by electronically subtracting the continuous intrathoracic pressure waveform from the left ventricular pressure waveform *via* the digital oscilloscope, as detailed previously.[11] During anesthesia, waveforms were recorded at end expiration. Inferior vena caval occlusion was released immediately after recording of the waveforms. Alteration of preload did not cause a change in heart rate in any experiment.

Hemodynamic data were recorded, and left ventricular pressure–segment length waveforms and loops were obtained in two groups of experiments in dogs with and without ANS blockade. After obtaining data in the conscious state, all dogs underwent inhalation induction with sevoflurane in oxygen followed by intubation of the trachea. Anesthesia was maintained at 1.0, 1.25, 1.5, and 1.75 MAC end-tidal sevoflurane in a nitrogen (79%) and oxygen (21%) mixture. End-tidal anesthetic concentrations of sevoflurane were measured at the tip of the endotracheal tube by an infrared anesthetic analyzer (Datex Capnomac, Helsinki, Finland) calibrated for detection of sevoflurane. The canine MAC value for sevoflurane used in this investigation was 2.36%.[15] Each MAC level was maintained for 30 min, after which hemodynamics were again recorded and left ventricular pressure–segment length waveforms and diagrams acquired in the manner detailed above. Arterial blood gases were maintained at conscious levels by adjusting respiratory rate and nitrogen and oxygen concentrations during each experiment.

The anesthetic was discontinued and emergence allowed to occur after each experiment was completed. Dogs recovered for at least 3 days before undergoing subsequent experimentation. Eighteen experiments in two groups (sevoflurane with and without ANS blockade) were performed in which the same nine dogs were studied.

Calculation of Indices of Systolic and Diastolic Left Ventricular Function

M_w was used to determine myocardial contractility as previously described.[10–12] In the conscious state and at each MAC multiple of sevoflurane, a series of left ventricular pressure–segment length diagrams were obtained by transient constriction of the inferior vena cava. The area of each diagram, which corresponds to segmental stroke work, was plotted against the corresponding end-diastolic segment length for each loop. Linear regression analysis was used to determine M_w and preload recruitable stroke work–length intercept: $S_w = M_w \times (EDL - L_w)$, where EDL = end-diastolic segment length and L_w = stroke work–length intercept. τ was determined assuming a nonzero asymptote of left ventricular pressure decay according to the method of Raff and Glantz.[16] The dL/dt_{max} during rapid ventricular filling was determined by differentiation of the continuous segment length waveform, as previously detailed.[11] K_p was derived from ventricular pressure–segment length data between minimum ventricular pressure and the beginning of atrial systole using a monoexponential relation assuming a simple elastic model.[17]

Statistical Analysis

Statistical analysis of the data within and between groups in the conscious state with and without ANS blockade and during all anesthetic interventions was performed by multiple analysis of variance with repeated measures, followed by use of Bonferroni's modification of Student's *t* test.[18] Changes were statistically significant when the *P* value was < 0.05. The relations between stroke work and end-diastolic segment length (calculation of M_w and preload recruitable stroke work–length intercept) and between $-dP/dt$ and ventricular pressure (calculation of τ) were determined by use of linear regression analysis. Least-squares regression analysis was used to evaluate the exponential relation between ventricular pressure and segment length (calculation of K_p). All data are expressed as mean ± SEM.

Results

In dogs with intact ANS function, sevoflurane produced a significant ($P < 0.05$) increase in heart rate (table 1). Dose-dependent decreases in mean arterial

Table 1. Systemic and Coronary Hemodynamic Effects of Sevoflurane in Dogs with Intact Autonomic Nervous System Function

	n	Conscious Control	Sevoflurane (MAC)			
			1.0	1.25	1.5	1.75
HR (beats/min)	9	71 ± 3	128 ± 7*	127 ± 6*	118 ± 6*	113 ± 6*†‡
MBP (mmHg)	9	96 ± 4	75 ± 4*	73 ± 3*	67 ± 2*	59 ± 2*†‡
LVSP (mmHg)	9	124 ± 5	89 ± 4*	85 ± 3*	79 ± 2*†	70 ± 2*†‡§
LVEDP (mmHg)	9	9 ± 1	6 ± 1*	6 ± 1*	6 ± 1*	7 ± 1
DCBFV ($Hz \cdot 10^2$)	8	54 ± 7	55 ± 7	54 ± 7	51 ± 8	49 ± 7
DCVR (ru)	8	1.72 ± 0.25	1.44 ± 0.22*	1.41 ± 0.20*	1.40 ± 0.21*	1.23 ± 0.15*
CO ($l \cdot min^{-1}$)	8	2.2 ± 0.2	1.9 ± 0.2	1.8 ± 0.2*	1.7 ± 0.2*	1.5 ± 0.1*†
SVR ($dyne \cdot s \cdot cm^{-5}$)	8	3690 ± 260	3320 ± 210	3450 ± 250	3430 ± 260	3280 ± 250
SV (ml)	8	31 ± 2	14 ± 2*	14 ± 1*	14 ± 1*	13 ± 1*
PWI ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	8	8.3 ± 0.6	8.3 ± 0.6	7.8 ± 0.4	6.9 ± 0.4*†	6.0 ± 0.4*†‡
*p*H (units)	8	7.41 ± 0.01	7.39 ± 0.01	7.40 ± 0.01	7.38 ± 0.01	7.39 ± 0.01
P_{O_2} (mmHg)	8	86 ± 2	106 ± 6*	106 ± ± 5*	110 ± 6*	117 ± 9*
P_{CO_2} (mmHg)	8	32 ± 1	31 ± 1	31 ± 1	33 ± 1	31 ± 1
ET (%)	9	—	2.39 ± 0.03	2.96 ± 0.02†	3.49 ± 0.01†‡	4.11 ± 0.02†‡§

Data are mean ± SEM.

MAC = minimum alveolar concentration; HR = heart rate; MBP = mean aortic blood pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; DCBFV = diastolic coronary blood flow velocity; DCVR = diastolic coronary vascular resistance; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; PWI = pressure work index; ET = end-tidal sevoflurane concentration.

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

† Significantly different ($P < 0.05$) from 1.0 MAC sevoflurane.

‡ Significantly different ($P < 0.05$) from 1.25 MAC sevoflurane.

§ Significantly different ($P < 0.05$) from 1.5 MAC sevoflurane.

pressure, left ventricular systolic pressure, and cardiac output occurred during administration of sevoflurane. No change in systemic vascular resistance was observed. Diastolic coronary vascular resistance was also decreased by sevoflurane. Diastolic coronary blood flow velocity was unchanged during sevoflurane anesthesia. Sevoflurane decreased in the pressure work index (calculated myocardial oxygen consumption) at 1.5 and 1.75 MAC.

Pharmacological blockade of the ANS increased heart rate and decreased mean arterial blood pressure, left ventricular systolic pressure, systemic vascular resistance, and stroke volume (table 2). ANS blockade produced no change in cardiac output, left ventricular end-diastolic pressure, pressure work index, diastolic coronary blood flow velocity, or diastolic coronary vascular resistance. A dose-dependent decrease in heart rate, mean arterial pressure, left ventricular systolic pressure, cardiac output and pressure work index occurred during sevoflurane anesthesia in ANS blocked dogs. No change in diastolic coronary blood flow velocity or systemic vascular resistance occurred during administration of sevoflurane to ANS blocked dogs. A significant decrease in diastolic coronary vascular resistance and an increase in left ventricular end-diastolic pressure were observed at 1.75 MAC.

Administration of sevoflurane to dogs with intact ANS function dose-dependently decreased M_w (96 ± 4 during the conscious state to 42 ± 3 mmHg at 1.75 MAC) indicating a decrease in intrinsic inotropic state (table 3). No change in the preload recruitable stroke work–length intercept was observed. A concomitant decrease in left ventricular dP/dt_{max}, $+dP/dt_{50}$, and percent segment shortening occurred consistent with direct myocardial depression. Sevoflurane decreased the magnitude of left ventricular $-dP/dt_{min}$ (−2,359 ± 89 in the conscious state to −1,052 ± 70 $mmHg \cdot s^{-1}$ at 1.75 MAC) and increased τ (35 ± 1 in the conscious state to 51 ± 3 ms at 1.75 MAC) in a dose-related manner consistent with delays in isovolumic relaxation. Sevoflurane also dose-dependently decreased dL/dt_{max} (40.2 ± 6.0 in the conscious state to 21.8 ± 3.8 $mm \cdot s^{-1}$ at 1.75 MAC) indicating impairment of early ventricular filling. K_p was unchanged by sevoflurane indicating that

Table 2. Systemic and Coronary Hemodynamic Effects of Sevoflurane in Dogs with Autonomic Nervous System Blockade

	n	Conscious Control	ANS Blockade	Sevoflurane (MAC)			
				1.0	1.25	1.5	1.75
HR (beats/min)	9	72 ± 3*	114 ± 5	97 ± 4*	94 ± 4*	89 ± 4*	87 ± 4*†
MBP (mmHg)	9	93 ± 3*	75 ± 3	62 ± 3*	59 ± 3*	55 ± 3*†	49 ± 3*†‡
LVSP (mmHg)	9	119 ± 3*	91 ± 2	77 ± 2*	74 ± 2*	70 ± 3*†	64 ± 2*†‡§
LVEDP (mmHg)	9	8 ± 1	7 ± 1	8 ± 1	9 ± 1	9 ± 1	10 ± 1*
DCBFV ($Hz \cdot 10^3$)	8	64 ± 5	57 ± 4	53 ± 5	51 ± 5	50 ± 5	50 ± 5
DCVR (ru)	8	1.31 ± 0.11	1.18 ± 0.05	1.11 ± 0.12	1.08 ± 0.10	1.06 ± 0.12	0.96 ± 0.11*
CO ($l \cdot min^{-1}$)	8	2.5 ± 0.2	2.7 ± 0.2	1.8 ± 0.2*	1.7 ± 0.1*	1.6 ± 0.1*	1.6 ± 0.1*
SVR ($dyne \cdot s \cdot cm^{-5}$)	8	3,010 ± 180*	2,230 ± 130	2,970 ± 310	2,780 ± 220	2,730 ± 230	2,540 ± 180
SV (ml)	8	35 ± 2*	24 ± 1	18 ± 2*	19 ± 2*	18 ± 1*	18 ± 2*
PWI ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	8	8.6 ± 0.5	8.7 ± 0.5	6.0 ± 0.3*	5.7 ± 0.3*	5.2 ± 0.3*	4.7 ± 0.3*†‡
*p*H (units)	8	—	7.38 ± 0.01	7.40 ± 0.01	7.41 ± 0.01	7.41 ± 0.02	7.40 ± 0.02
P_{O_2} (mmHg)	8	—	90 ± 4	95 ± 4	98 ± 4	102 ± 3*	103 ± 2*
P_{CO_2} (mmHg)	8	—	32 ± 1	31 ± 1	30 ± 1	30 ± 1	31 ± 1
ET (%)	9	—	—	2.37 ± 0.02	2.96 ± 0.02†	3.50 ± 0.02†‡	4.10 ± 0.02†‡§

Data are mean ± SEM.

ANS = autonomic nervous system; MAC = minimum alveolar concentration; HR = heart rate; MBP = mean aortic blood pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; DCBFV = diastolic coronary blood flow velocity; DCVR = diastolic coronary vascular resistance; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; PWI = pressure work index; ET = end-tidal sevoflurane concentration.

* Significantly different ($P < 0.05$) from ANS blockade.

† Significantly different ($P < 0.05$) from 1.0 MAC sevoflurane.

‡ Significantly different ($P < 0.05$) from 1.25 MAC sevoflurane.

§ Significantly different ($P < 0.05$) from 1.5 MAC sevoflurane.

Table 3. Effects of Sevoflurane on Indices of Left Ventricular Systolic and Diastolic Function in Dogs with Intact Autonomic Nervous System Function

	n	Conscious Control	Sevoflurane (MAC) 1.0	1.25	1.5	1.75
M_w (mmHg)	8	96 ± 4	72 ± 4*	69 ± 5*	55 ± 4*†‡	42 ± 3*†‡§
L_w (mm)	8	13.4 ± 2.2	13.9 ± 2.3	14.0 ± 2.3	14.1 ± 2.3	14.1 ± 2.3
$+dP/dt_{max}$ (mmHg/s)	9	2,469 ± 115	1,565 ± 63*	1,444 ± 43*	1,265 ± 44*	1,070 ± 64*†‡§
$+dP/dt_{50}$ (mmHg/s)	9	2,182 ± 90	1,542 ± 57*	1,435 ± 41*	1,256 ± 43*†	1,036 ± 67*†‡§
$-dP/dt_{min}$ (mmHg/s)	9	−2,359 ± 89	−1,622 ± 69*	−1,495 ± 57*	−1,281 ± 52*†‡	−1,052 ± 70*†‡§
EDL (mm)	9	15.4 ± 2.8	13.9 ± 2.4*	14.0 ± 2.4*	14.1 ± 2.5*	14.3 ± 2.5*
ESL (mm)	9	12.6 ± 2.3	12.0 ± 2.1*	12.3 ± 2.1	12.5 ± 2.2†	12.7 ± 2.2†
SS (%)	9	18.4 ± 1.1	13.2 ± 1.4*	11.7 ± 1.4*	11.0 ± 1.3*	10.9 ± 1.2*†
dL/dt_{max} (mm/s)	9	40.2 ± 6.0	29.1 ± 6.1*	26.3 ± 5.6*	24.0 ± 4.8*†	21.8 ± 3.8*†‡
τ (ms)	9	35 ± 1	38 ± 1	41 ± 2*	46 ± 2*†‡	51 ± 3*†‡
K_p (mm^{-1})	9	0.47 ± 0.05	0.41 ± 0.04	0.42 ± 0.04	0.41 ± 0.04	0.38 ± 0.03

Data are mean ± SEM.

MAC = minimum alveolar concentration; M_w and L_w = preload recruitable stroke work slope and length intercept, respectively; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; τ = time constant of isovolumic relaxation; K_p = regional chamber stiffness.

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

† Significantly different ($P < 0.05$) from 1.0 MAC sevoflurane.

‡ Significantly different ($P < 0.05$) from 1.25 MAC sevoflurane.

§ Significantly different ($P < 0.05$) from 1.5 MAC sevoflurane.

this volatile anesthetic does not alter regional ventricular compliance.

ANS blockade decreased M_w, $+dP/dt_{max}$, $+dP/dt_{50}$, percent segment shortening, and the magnitude of $-dP/dt_{min}$ (table 4). No changes in other indices of diastolic function (τ, dL/dt_{max}, and K_p) occurred with ANS blockade. Administration of sevoflurane to dogs with ANS blockade dose-dependently decreased M_w (76 ± 6 in the conscious state to 34 ± 4 mmHg at 1.75 MAC), $+dP/dt_{max}$, $+dP/dt_{50}$, and percent segment shortening indicating direct myocardial depression. Sevoflurane significantly, and in dose-related manner, increased τ (38 ± 1 in the conscious state after ANS blockade to 56 ± 3 ms at 1.75 MAC) consistent with delays in isovolumic relaxation. This observation was supported by a concomitant decrease in the magnitude of $-dP/dt_{min}$, which was proportionally greater than the decrease in left ventricular systolic pressure. Sevoflurane also decreased dL/dt_{max} (45.3 ± 6.8 in the conscious state to 22.2 ± 4.7 $mm \cdot s^{-1}$ at 1.75 MAC) suggesting that sevoflurane may impair early diastolic filling during ANS blockade. No changes in K_p were observed.

Alterations in indices of left ventricular systolic and diastolic function induced by sevoflurane are depicted in figure 1. Sevoflurane caused a dose-dependent decrease in myocardial contractility in both ANS-intact and ANS-blocked dogs without significant differences between groups (M_w 100% in the conscious state before anesthesia to 40 ± 4 and 45 ± 3% of control at 1.75 MAC in ANS-intact and ANS-blocked dogs, respectively). In addition, no significant differences in the negative lusitropic effects of sevoflurane were observed between autonomically intact or blocked dogs during isovolumic relaxation (τ 100% in the conscious state before anesthesia to 150 ± 11 or 148 ± 10% of control at 1.75 MAC in ANS-intact and ANS-blocked dogs, respectively) and rapid ventricular filling (dL/dt_{max} 100% in the conscious state before anesthesia to 53 ± 4 or 47 ± 3% of control at 1.75 MAC in ANS-intact and ANS-blocked dogs, respectively).

Discussion

The systemic and coronary hemodynamic effects of sevoflurane have been described in animals under a variety of experimental conditions. Manohar and Parks[1] demonstrated that sevoflurane caused dose-dependent decreases in cardiac output, stroke volume, mean aortic blood pressure, left ventricular work, and coronary blood flow without change in heart rate or systemic vascular resistance in chronically instrumented pigs.

Table 4. Effects of Sevoflurane on Indices of Left Ventricular Systolic and Diastolic Function in Dogs with Autonomic Nervous System Blockade

	n	Conscious Control	ANS Blockade	Sevoflurane (MAC) 1.0	1.25	1.5	1.75
M_w (mmHg)	8	102 ± 4*	76 ± 6	58 ± 5*	50 ± 4*†	45 ± 4*†	34 ± 4*†‡§
L_w (mm)	8	13.4 ± 2.3	13.4 ± 2.3	13.6 ± 2.3	13.4 ± 2.2	13.5 ± 2.3	13.2 ± 2.3
$+dP/dt_{max}$ (mmHg/s)	9	2,576 ± 108*	1,819 ± 101	1,365 ± 116*	1,226 ± 94*	1,084 ± 83*†‡	912 ± 68*†‡
$+dP/dt_{50}$ (mmHg/s)	9	2,295 ± 94*	1,781 ± 98	1,347 ± 117*	1,214 ± 95*	1058 ± 86*†‡	852 ± 87*†‡§
$-dP/dt_{min}$ (mmHg/s)	9	−2,257 ± 56*	−1,674 ± 66	−1,250 ± 72*	−1,143 ± 72*	−1,017 ± 76*†‡	859 ± 75*†‡§
EDL (mm)	9	16.5 ± 2.8*	16.0 ± 2.6	15.2 ± 2.4*	15.4 ± 2.5*	15.5 ± 2.5	
ESL (mm)	9	13.4 ± 2.2	13.4 ± 2.2	13.0 ± 2.0	13.1 ± 2.1	13.3 ± 2.1	13.5 ± 2.2
SS (%)	9	18.7 ± 1.1*	16.6 ± 1.2	14.5 ± 1.6*	14.0 ± 1.1*	13.5 ± 1.0*	12.7 ± 1.2*†
dL/dt_{max} (mm/s)	9	43.0 ± 6.0	45.3 ± 6.8	28.7 ± 6.1*	26.4 ± 6.0*	23.8 ± 4.8*†	22.2 ± 4.7*†‡
τ (ms)	9	36 ± 1	38 ± 1	44 ± 2*	48 ± 2*	51 ± 3*†	56 ± 3*†‡
K_p (mm^{-1})	9	0.48 ± 0.06	0.45 ± 0.07	0.41 ± 0.05	0.40 ± 0.04	0.41 ± 0.04	0.42 ± 0.04

Data are mean ± SEM.

ANS = autonomic nervous system; MAC = minimum alveolar concentration; M_w and L_w = preload recruitable stroke work slope and length intercept, respectively; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; τ = time constant of isovolumic relaxation; K_p = regional chamber stiffness.

* Significantly different ($P < 0.05$) from ANS blockade.

† Significantly different ($P < 0.05$) from 1.0 MAC sevoflurane.

‡ Significantly different ($P < 0.05$) from 1.25 MAC sevoflurane.

§ Significantly different ($P < 0.05$) from 1.5 MAC sevoflurane.

Lerman *et al.*[2] found that sevoflurane (1.5 MAC) decreased heart rate and systolic arterial pressure without changing cardiac index in acutely instrumented, newborn swine. In contrast, Crawford *et al.*[3,4] showed that sevoflurane caused little change in systemic hemodynamics with the exception of declines in mean arterial pressure at 1.5 MAC in spontaneously breathing rats. Increased carbon dioxide tension probably resulted in sympathetic nervous system stimulation[19,20] which obscured the direct cardiovascular depressant effects of sevoflurane in these studies.[3,4] Conzen *et al.*[5] observed dose-dependent decreases in heart rate, cardiac output, rate-pressure product, systemic vascular resistance as well as declines in coronary blood flow and coronary vascular resistance in rats anesthetized with hypotensive concentrations of sevoflurane. Lethal concentrations of sevoflurane decreased heart rate, mean arterial pressure, and cardiac output without altering systemic vascular resistance in swine, in contrast to isoflurane which decreased systemic vascular resistance without changing heart rate.[6] Bernard *et al.*[7] reported that sevoflurane and isoflurane produced nearly identical changes in systemic and coronary hemodynamics in chronically instrumented dogs. The findings of Bernard *et al.*[7] demonstrated that sevoflurane and isoflurane caused similar increases in heart rate and coronary blood flow, and decreases in systemic and coronary vascular resistance.

In the current investigation, sevoflurane produced increases in heart rate which were not dose-related in dogs with intact ANS function. This sevoflurane-induced tachycardia probably resulted from baroreflex activation of the sympathetic nervous system because direct negative chronotropic effects were observed with sevoflurane during pharmacological blockade of the ANS. Similar decreases in heart rate, consistent with depression of phase-4 sinoatrial node depolarization, have been described for isoflurane, enflurane, and halothane *in vitro*[21] and have also been observed with volatile anesthetics, including desflurane, during ANS blockade *in vivo*.[17] Sevoflurane caused dose-related decreases in mean arterial pressure, left ventricular systolic pressure and cardiac output without changes in calculated systemic vascular resistance supporting the observations of Manohar and Parks[1] and Cork *et al.*[6] in swine. Alterations in these variables were qualitatively similar to those produced by desflurane, halothane, and enflurane, but not isoflurane, in previous investigations in dogs from this[22] and other laboratories.[23–26]

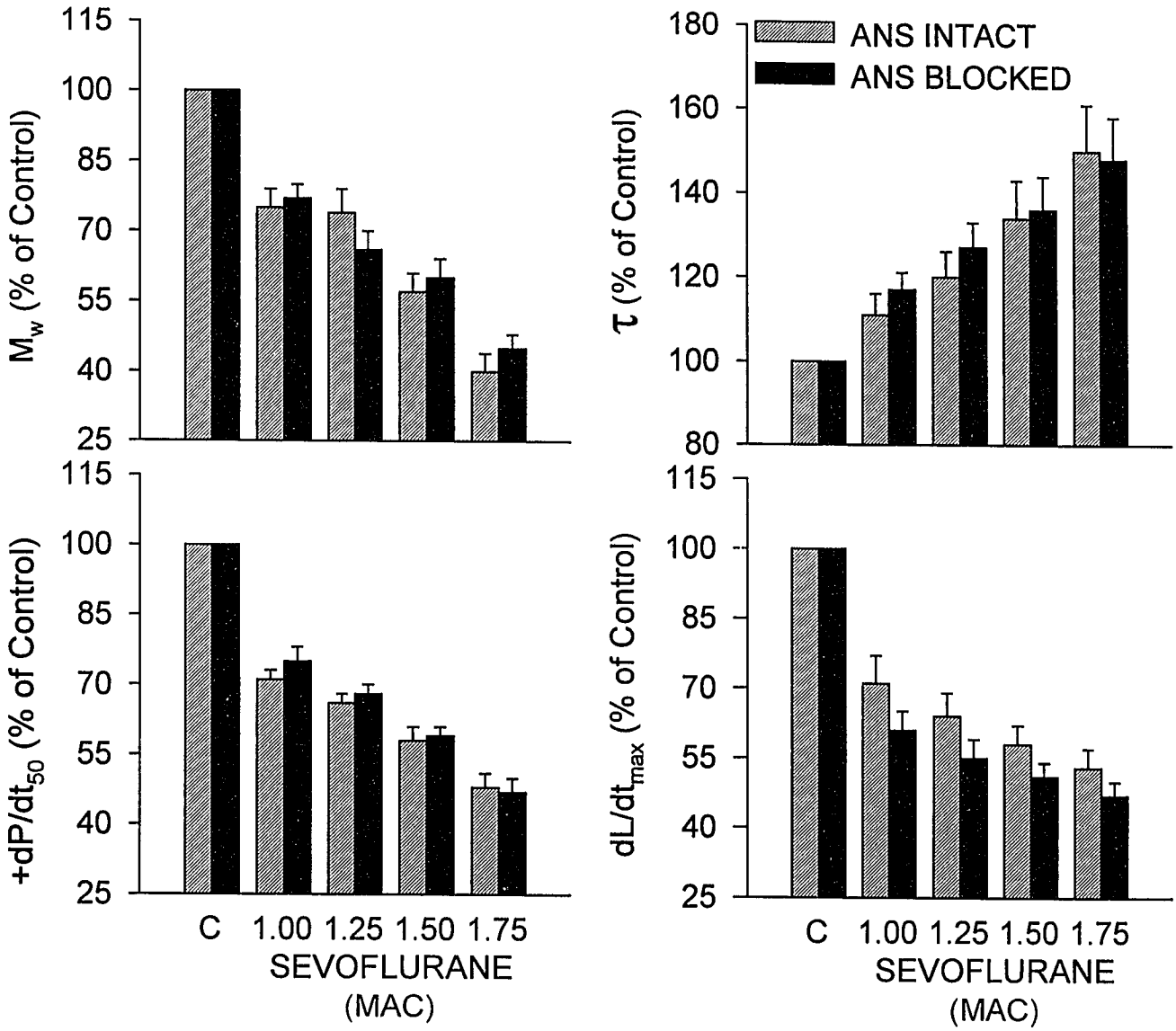

Fig. 1. Comparison of the effects of sevoflurane on indices of left ventricular systolic and diastolic function in the absence and presence of autonomic nervous system (ANS) blockade (ANS-intact and ANS-blocked, respectively). Data are presented as percentage of control before anesthesia (C). All data during sevoflurane in both ANS-intact and ANS-blocked groups are significantly ($P < 0.05$) different from (C). At equivalent MAC, no differences between dogs with and without ANS function were observed. M_w = preload recruitable stroke work slope; τ = time constant of isovolumic relaxation; dL/dt_{max} = maximum segment lengthening velocity during rapid ventricular filling.

In contrast to the current findings, Bernard *et al.*[7] demonstrated that sevoflurane decreased systemic vascular resistance similar to that caused by isoflurane in chronically instrumented dogs. The reasons for this difference between the current investigation and the study of Bernard *et al.*[7] are unclear, although differences in the location of chronically implanted flow probes (descending thoracic aorta *vs.* pulmonary artery) used to measure cardiac output or the position of the dog during anesthesia (suspended in a retraining sling *vs.* lying in lateral position) may have been contributing factors. Kikura and Ikeda[8] observed a sevoflurane–nitrous ox-

ide–induced decrease in left ventricular end-systolic wall stress (a quantitative measure of afterload) in humans, suggesting that sevoflurane decreases impedance to left ventricular outflow *via* a decreased peripheral vascular resistance. Cardiac output was not measured and systemic vascular resistance was not calculated in that study,[8] however.

Sevoflurane decreased diastolic coronary vascular resistance without altering diastolic coronary blood flow velocity in dogs with and without ANS activity. These observations support the findings of Conzen *et al.*[5] in pigs and partially support the results of Bernard *et al.*[7] in dogs. A dose-related decrease in calculated myocardial oxygen consumption was observed with sevoflurane in both the autonomically intact and blocked states in the current investigation. Because coronary blood flow is coupled to myocardial oxygen consumption, maintenance of diastolic coronary blood flow velocity with a concomitant decrease in diastolic coronary vascular resistance combined with a decreased myocardial oxygen consumption suggest that sevoflurane may produce direct coronary vasodilatory actions. This conclusion requires qualification, however, because myocardial oxygen extraction or coronary sinus oxygen tension were not directly measured in the current investigation.

Two previous investigations have examined the effects of sevoflurane on myocardial contractility *in vivo*.[7,8] Bernard *et al.*[7] demonstrated that sevoflurane and isoflurane nearly identically decreased myocardial contractility as evaluated by left ventricular peak positive dP/dt, an isovolumic index of contractile state which is heart rate and preload dependent.[27] Nevertheless, these observations strongly implied that sevoflurane and isoflurane affect intrinsic inotropic state to similar degrees because these volatile anesthetics caused similar changes in heart rate and ventricular loading conditions.[7] Kikura and Ikeda[8] compared the effects of sevoflurane–nitrous oxide and enflurane–nitrous oxide on myocardial contractility in ASA physical status 1 or 2 patients before elective surgery. Transthoracic (conscious state) and transesophageal echocardiography (during anesthesia) were used to derive the relation between left ventricular end-systolic wall stress and heart rate–corrected velocity of circumferential fiber shortening. This relation has been shown to be a relatively preload independent index of contractility which incorporates changes in afterload into its calculation[28] and has been used clinically to assess acute changes in contractility in patients with hypertensive[29] and dilated cardiomyopathies.[30] Although different patient groups were studied in the conscious and anesthetized states, the results of Kikura and Ikeda[8] suggested that myocardial depression was less pronounced in patients anesthetized with sevoflurane–nitrous oxide when compared with those anesthetized with enflurane–nitrous oxide. Quantification of these changes in contractile function was difficult, however, because the linearity of the relation between left ventricular end-systolic wall stress and velocity of circumferential fiber shortening degenerated at higher anesthetic concentrations. Observed changes in more conventional echocardiographically derived measures of contractile function, including velocity of circumferential fiber shortening alone, fractional shortening, and ejection fraction, also supported the hypothesis that sevoflurane produces less myocardial depression than enflurane in humans.[8]

In the current investigation, sevoflurane dose-dependently decreased myocardial contractility as evaluated by M_w. The findings indicate that the negative inotropic effects of sevoflurane occur independent of ANS activity because similar declines in M_w were observed during sevoflurane anesthesia with and without ANS blockade. Sevoflurane decreased contractility to approximately 40–45% of control values at 1.75 MAC. This magnitude of contractile depression has been previously reported by this laboratory for isoflurane and desflurane in the presence[31] and absence[32] of ANS tone using an identical experimental preparation. Thus, the current results indicate that sevoflurane probably causes a similar degree of direct myocardial depression as that caused by desflurane and isoflurane. In contrast, halothane has been shown to depress contractile state to less than 30% of baseline levels at 1.75 MAC,[33] suggesting that sevoflurane causes less depression of inotropic state than halothane in dogs.

The effects of sevoflurane on several indices of left ventricular diastolic function were also evaluated in the current investigation. Diastolic mechanics have been shown to play an important role in overall cardiac performance, and diastolic dysfunction has been implicated as an important contributing factor in the pathogenesis of congestive heart failure.[9] Previous investigations from this[11,17,34] and other laboratories[35,36] have demonstrated that volatile anesthetics alter indices of diastolic performance during isovolumic relaxation and early ventricular filling but do not, with the possible exception of halothane,[37,38] appear to alter ven-

tricular chamber compliance.[17,39] Sevoflurane caused a dose-related increase in τ and a decrease in the magnitude of $-dP/dt_{min}$ consistent with delays in the isovolumic relaxation phase of diastole. Sevoflurane also blunted rapid ventricular filling as indicated by decreases in dL/dt_{max} but did not affect regional chamber stiffness. These alterations in indices of early diastolic performance occurred in both ANS-intact and ANS-blocked dogs, indicating that the sevoflurane-induced increases in τ and decreases in dL/dt_{max} were independent of underlying ANS tone.

The dose-related change in τ produced by sevoflurane was qualitatively greater than that reported for equi-MAC concentrations of desflurane, isoflurane, and halothane (*e.g.*, τ 45 ± 3, 47 ± 3, and 42 ± 4 ms, respectively, at 1.5 MAC) in ANS-blocked dogs in a previous investigation in this laboratory using the identical experimental preparation,[17] indirectly suggesting that sevoflurane may produce a relatively greater negative lusitropic effect than other volatile anesthetics. However, sevoflurane-induced alterations in dL/dt_{max} were similar in magnitude to those reported for isoflurane and halothane at 1.25 and 1.5 MAC,[11,34] implying that sevoflurane causes a similar degree of impairment in early ventricular filling when compared with that caused by other volatile anesthetics. A strict statistical comparison between the results of the current and those of previous investigations[11,17,34] was not performed, however.

The effects of sevoflurane on indices of diastolic function must be interpreted within the constraints of the concomitant changes in systemic hemodynamics and contractile state observed during sevoflurane anesthesia. τ has been shown to be dependent on heart rate, ventricular loading conditions, and inotropic state,[40] and changes in these variables may have contributed to the elevation of τ with sevoflurane. Heart rate and afterload effects can probably be excluded as causes for prolonged isovolumic relaxation because a sevoflurane-induced increase in τ was observed in both the ANS-intact and ANS-blocked states, experimental conditions that resulted in directly opposite alterations in heart rate and no change in calculated systemic vascular resistance. In addition, end-systolic segment length remained essentially unchanged during sevoflurane anesthesia in both experimental groups, providing indirect evidence that no changes in cellular myofibrillar length had occurred. Increased affinity of the contractile apparatus for calcium at longer muscle lengths[41] has been described which could account for prolongation of isovolumic relaxation, however, no changes in end-systolic segment length were observed indicating that increases in τ were not myocyte length-related. A sevoflurane-induced delay in isovolumic relaxation because of depression of myocardial contractility cannot be completely excluded from the analysis, however. The rate of rapid ventricular filling (as evaluated with dL/dt_{max}) is directly affected by relaxation rate and is also dependent on the gradient between left atrial and left ventricular pressure during this phase of diastole.[40,42,43] This gradient was not specifically measured in this investigation. No change in K_p was observed with sevoflurane administration in either experimental group, indicating that this volatile anesthetic does not affect this measure of regional compliance.

In summary, the results of the current investigation indicate that sevoflurane causes a baroreflex-mediated increase in heart rate and a dose-related decrease in mean arterial pressure, left ventricular systolic pressure, cardiac output and calculated myocardial oxygen consumption (pressure work index) with relative maintenance of systemic vascular resistance and diastolic coronary blood flow velocity in chronically instrumented dogs with intact ANS reflexes. Sevoflurane also decreased diastolic coronary vascular resistance, suggesting that sevoflurane may possess slight coronary vasodilating properties. Sevoflurane depressed myocardial contractility (as assessed by M_w), prolonged isovolumic relaxation (τ and $-dP/dt_{min}$), and decreased dL/dt_{max} during rapid ventricular filling without affecting K_p in ANS-intact and ANS-blocked dogs, suggesting that the left ventricular systolic and diastolic mechanical consequences of sevoflurane occur independent of ANS activity.

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