Anesthesiology
74:1103–1114, 1991

Alteration of Left Ventricular Diastolic Function by Desflurane, Isoflurane, and Halothane in the Chronically Instrumented Dog with Autonomic Nervous System Blockade

Paul S. Pagel, M.D., John P. Kampine, M.D., Ph.D.,† William T. Schmeling, M.D., Ph.D.,‡ David C. Warltier, M.D., Ph.D.§*

The effects of the new volatile anesthetic desflurane on three indices of left ventricular diastolic function were examined and compared to those produced by equianesthetic concentrations of isoflurane and halothane. Diastolic function has been shown to significantly influence systolic performance, but the effects of volatile anesthetics on diastolic function have not been extensively examined. Since autonomic nervous system function may significantly influence hemodynamic actions of anesthetics *in vivo*, experiments were performed in the presence of pharmacologic blockade of the autonomic nervous system. Three groups comprising a total of 23 experiments were performed using 11 dogs instrumented for measurement of aortic and left ventricular pressure, rate of increase of left ventricular pressure (dP/dt), subendocardial segment length, and cardiac output. Systemic hemodynamics were recorded in the conscious state and after 30 min equilibration at 1.0 and 1.5 MAC desflurane, isoflurane, or halothane. Ventricular relaxation was described using invasively derived time constants of isovolumetric relaxation with zero (T_0) or nonzero (T_n) assumptions of asymptotic decay. Chamber and myocardial stiffness, the viscoelastic properties of the ventricle, were described using exponential relationships relating ventricular pressure to segment length and end-diastolic pressure to Lagrangian strain, respectively. Desflurane produced a significant ($P < 0.05$) and dose-dependent increase in isovolumetric relaxation as a evaluated by both time constants (T_0, 22.2 ± 2.0 during control to 33.9 ± 3.5 ms at 1.5 MAC; T_n, 33.1 ± 1.6 during control to 45.1 ± 4.3 ms at 1.5 MAC). Similar degrees of prolongation of isovolumetric relaxation were produced by isoflurane (T_n, 35.6 ± 1.5 during control to 47.1 ± 2.9 ms at 1.5 MAC) and halothane (T_n, 31.7 ± 2.2 during control to 42.3 ± 3.9 ms at 1.5 MAC). Halothane also caused an increase in regional passive chamber stiffness (K_p, 0.46 ± 0.07 during control to 0.88 ± 0.17 mm^{-1} at 1.5 MAC) indicating a decrease in ventricular compliance. No changes in chamber stiffness were observed with desflurane or isoflurane. In addition, no significant changes in myocardial stress–strain relationships as evaluated by nonlinear elastic coefficients, α (gain) and β (myocardial stiffness), were observed with any anesthetic. Although the effects of volatile anesthetics on systolic function could not be entirely excluded from the analysis, the results indicated that desflurane, isoflurane, and halothane produce equivalent degrees of prolongation of isovolumetric relaxation. Halothane also caused a decrease in compliance during passive filling as evaluated by chamber stiffness, but no change in compliance was observed at end diastole as assessed by stress–strain relationships. In contrast, desflurane and isoflurane did not affect ventricular compliance as evaluated by either variable in the chronically instrumented dog with autonomic nervous system blockade. (Key words: Anesthetics, volatile: halothane; isoflurane; desflurane (I-653). Heart: diastole; diastolic left ventricular function; ventricular compliance; myocardial function; isovolumetric relaxation.)

DIASTOLE IS A COMPLEX SEQUENCE of interrelated dynamic processes that remains incompletely understood despite extensive study. No currently available single index of diastolic function completely describes this period of the cardiac cycle. Accurate analysis of diastolic events remains important because several pathologic conditions and pharmacologic agents are known to influence various phases of systolic and diastolic function independently.[1–4] Abnormalities in diastolic function are usually a direct consequence of systolic dysfunction; however, in some patients with ischemic heart disease, hypertrophic or infiltrative cardiomyopathy, or hypertensive heart disease, clinical evidence of congestive heart failure may be manifested because of abnormalities in diastolic function in the absence of or preceding significant impairment of systolic function.[1,2,5,6] Hence, although the absolute prognostic value of abnormal indices of diastolic function remains unknown, it has been clearly established that diastolic performance profoundly influences cardiac function.[7]

Diastole is usually divided into four phases (fig. 1): isovolumetric relaxation, rapid ventricular filling, diastasis (slow ventricular filling), and atrial systole (active filling). Indices of diastolic function have been used to describe active (ventricular relaxation) or passive (viscoelastic properties: chamber and myocardial stiffness) components. Isovolumetric relaxation is an active, energy-dependent process resulting from the dissociation of actin–myosin linkages by reuptake of cytoplasmic calcium into the sarcoplasmic reticulum.[1,7,8] Relaxation is usually described either by invasively derived indices of isovolu-

* Fellow in Anesthesiology.
† Professor and Chairman of Anesthesiology.
‡ Associate Professor of Anesthesiology and Pharmacology.
§ Professor of Anesthesiology, Pharmacology, and Medicine (Division of Cardiology); Vice Chairman for Research, Department of Anesthesiology.

Received from the Departments of Anesthesiology, Pharmacology, and Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin and the Zablocki Veterans Administration Medical Center, Milwaukee, Wisconsin. Accepted for publication February 15, 1991. Supported by United States Public Health Service grants HL 36144 and HL 32911, Anesthesiology Research Training Grant GM 08377, and Veterans Administration Medical Research Funds.

Address reprint requests to Dr. Warltier: Medical College of Wisconsin, MFRC, Room A1000, 8701 West Watertown Plank Road, Milwaukee, Wisconsin 53226.

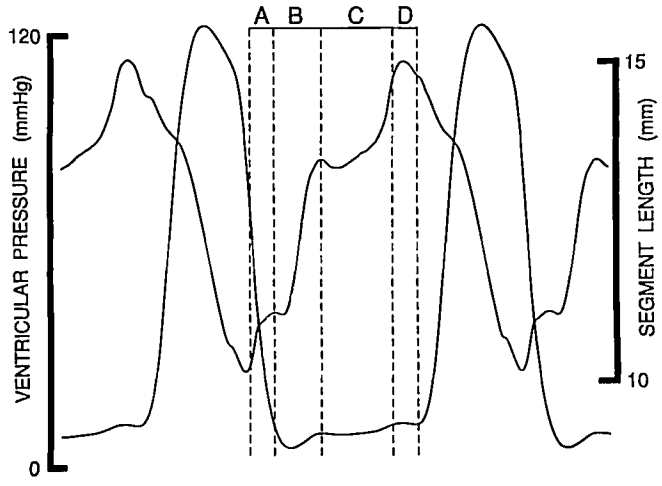

FIG. 1. Phases of left ventricular diastole. *A*, Isovolumetric relaxation; *B*, rapid ventricular filling; *C*, diastasis (slow ventricular filling); *D*, atrial systole.

metric relaxation (peak rate of left ventricular decrease of pressure [−dP/dt] and derived variables or time constants of ventricular relaxation [τ]) or by noninvasive techniques (M-mode and Doppler echocardiography), both of which are variably influenced by systolic function, heart rate, and ventricular loading conditions.[9] Chamber stiffness (change in pressure with respect to volume, dP/dV) is assessed by direct evaluation of diastolic pressure–volume (or pressure–dimension) relationships during passive ventricular filling between minimum ventricular pressure and the onset of atrial systole.[8] Myocardial stiffness denotes resistance to stretching (stress) when cardiac muscle is subjected to a strain at end diastole, providing an indication of late diastolic function, including active filling.[10,11] Passive elements of diastolic function require simultaneous measurement of ventricular pressure and dimension and are directly influenced by loading conditions. Factors extrinsic to the left ventricle, such as right ventricular interaction, myocardial blood flow, and pericardial restraint, also effect diastolic function.[8] Therefore, derivation of meaningful indices of diastolic function requires differentiating between these heterogeneous elements, and interpretation of alterations in diastolic function must be qualified within the limitations of these inherent complexities.[7]

Recent investigations in experimental animals[12–14] and isolated cardiac muscle preparations[15] have suggested that halothane, enflurane, and isoflurane variably affect ventricular relaxation. The effect of volatile anesthetics on ventricular compliance, however, is less well defined. Several early studies[16–18] demonstrated that halothane decreases ventricular compliance, but other investigations[19–22] were unable to support these findings. The effect of isoflurane on myocardial compliance remains to be described. In addition, the actions of the new volatile anesthetic desflurane (I-653) on diastolic function have yet to be characterized. Therefore, the current investigation was undertaken to examine systematically the effects of desflurane, isoflurane, and halothane on left ventricular isovolumetric relaxation, chamber stiffness, and myocardial stress–strain relationships in the chronically instrumented dog. Experiments were performed in the presence of autonomic nervous system blockade because volatile anesthetics have been shown to variably affect underlying autonomic nervous system function[23] and to have indirect effects on systemic hemodynamics mediated through an intact autonomic nervous system.[24] Therefore, the direct actions of desflurane, isoflurane, and halothane on several indices of diastolic function were evaluated independently of autonomic nervous system reflexes.

Materials and Methods

Animal Instrumentation

All experimental procedures and protocols in this investigation were reviewed and approved by the Animal Care Committee of the Medical College of Wisconsin. All conformed to the Guiding Principles in the Care and Use of Animals of the American Physiologic Society and were in accordance with the Guide for the Care and Use of Laboratory Animals.¶

Conditioned mongrel dogs of either sex (N = 11) weighing between 20 and 30 kg were fasted overnight and anesthetized with sodium thiamylal (10 mg/kg). Following tracheal intubation, anesthesia was maintained with halothane (1.5–2.0%) in 100% oxygen using positive-pressure mechanical ventilation (Air Shields VC20-1, Hatboro, PA). A positive end-expiratory pressure of 5 cmH_2O was applied to retard development of atelectasis. Under sterile conditions, a thoracotomy was performed in the left fifth intercostal space. The pericardium was incised, and heparin-filled catheters were placed in the descending thoracic aorta and right atrium for measurement of aortic blood pressure and fluid or drug administration, respectively. An ultrasonic flow probe (Transonics, Ithaca, NY) was positioned around the ascending thoracic aorta for measurement of cardiac output. A pair of miniature ultrasonic segment length transducers (5 MHz) for measurement of changes in regional contractile function (systolic shortening) were implanted in a circumferential plane within the subendocardium (10–15 mm apart and 7–9 mm deep) of the anterior free wall of the left ventricle. A high-fidelity, miniature micromanometer (P7, Konigsberg Instruments, Pasadena, CA) was posi-

¶ Department of Health, Education, and Welfare (Department of Health and Human Services): Publication no. (NIH) 85-23. Revised 1985.

tioned in the left ventricle through an incision in the apex. The peak rate of increase of left ventricular pressure (dP/dt) and the rate of increase of ventricular pressure at 50 mmHg (dP/dt_{50}), indices of global myocardial contractility, were obtained by electronic differentiation of the left ventricular pressure waveform. A heparin-filled catheter was inserted into the left atrial appendage. The left ventricular micromanometer was cross-calibrated *in vivo* against pressures measured *via* the arterial and left atrial catheters (Gould P50 pressure transducer, Oxnard, CA). A hydraulic vascular occluder (In Vivo Metric, Healdsburg, CA) was placed around the thoracic inferior vena cava for sequential alteration of left ventricular preload. All instrumentation was secured, tunneled between the scapulae, and exteriorized *via* several small incisions. The pericardium was left widely open, the chest wall was closed in layers, and the pneumothorax was evacuated by a chest tube. Each dog was fitted with a jacket (Alice King Chatham, Los Angeles, CA) to prevent damage to instruments and catheters, which were housed in a metal box within the jacket pocket.

Each dog was treated with intramuscular analgesics (buprenorphine 0.02 mg/kg) as needed in the immediate postoperative period. Antibiotic prophylaxis consisting of procaine penicillin G (25,000 U/kg) and gentamicin (4.5 mg/kg) was also used. Dogs were allowed to recover for a minimum of 7 days prior to experimentation. During the postoperative period, dogs were trained to stand quietly in a sling during hemodynamic monitoring. Segment length signals were driven and monitored by ultrasonic amplifiers (Crystal Biotech, Boston, MA). End-systolic segment length was determined at maximum negative left ventricular dP/dt,[25] and end-diastolic segment length was determined at the onset of left ventricular isovolumetric contraction. The lengths were normalized according to the method described by Theroux *et al.*[26] Percent segment shortening (%SS) was calculated by use of the equation: %SS = (EDL − ESL) × 100/EDL, where EDL = end-diastolic segment length and ESL = end-systolic segment length. All hemodynamic data were recorded on a polygraph (Hewlett-Packard 7758A, 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 (Nicolet 4094, Madison, WI) for recording of left ventricular pressure–segment length loops.

Mathematical Modeling

Three phases of diastole were studied: isovolumetric relaxation, regional chamber stiffness, and regional myocardial stress–strain relationships. Isovolumetric relaxation (fig. 2A) was described with a monoexponential decay curve using a method developed by Weiss *et al.*[27] The decrease of ventricular pressure between maximum negative dP/dt to 5 mmHg above end-diastolic pressure (physiologically associated with opening of the mitral valve[4]) was plotted against time in 2-ms intervals, and a monoexponential curve fit was described using a least squares regression analysis:

$$P = ae^{-t/T_0} \quad (1)$$

where P = left ventricular pressure, a = ventricular pressure at peak negative dP/dt, and T_0 = the rate of relaxation (fig. 2B).

Because the method of Weiss *et al.*[27] assumes that ventricular pressure declines to a zero asymptote, the isovolumetric relaxation time constant (T_n) was also calculated assuming a nonzero asymptote using the method of

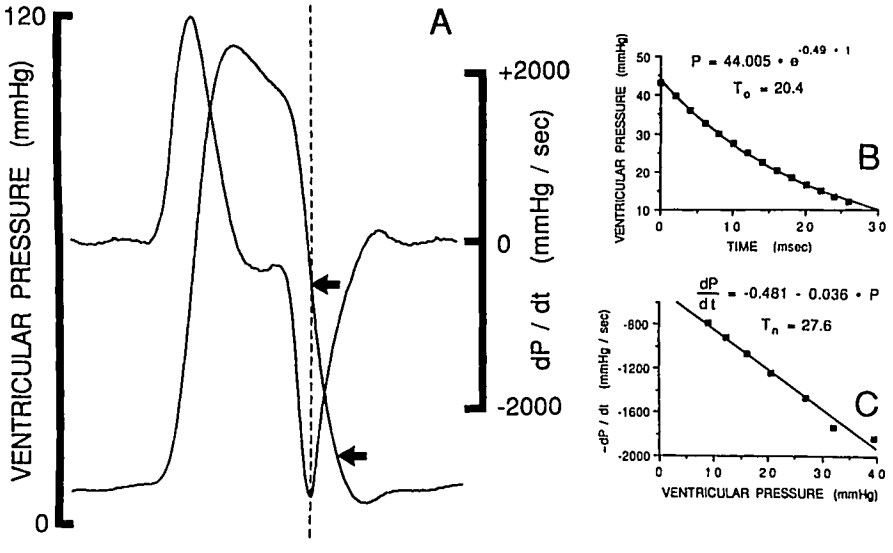

FIG. 2. Methods used to obtain time constants of isovolumetric relaxation (tau; [T_0 and T_n]) from dP/dt and left ventricular pressure waveforms (*A*). The decrease of left ventricular pressure between maximum negative dP/dt and 5 mmHg above end-diastolic pressure are identified by arrows. Left ventricular pressure between these points was plotted against time (*B*) and a least-squares regression analysis was used to describe a monoexponential curve fit: $P = ae^{-t/T_0}$. Negative dP/dt was also plotted against ventricular pressure (*C*), and a linear regression analysis was used to describe the time constant of isovolumetric relaxation assuming a nonzero asymptote: $dP/dt = \frac{c}{T_n} - \frac{P}{T_n}$ (see text).

Thompson *et al.*[28] Ventricular pressure *versus* time data were fitted to a three-constant exponential equation:

$$P = ae^{-t/T_n} + c \quad (2)$$

where c = the true asymptote to which pressure declines and T_n = the rate of relaxation assuming a nonzero asymptote. Following the method described by Raff and Glantz,[29] differentiation of this equation yields:

$$dP/dt = \frac{-a}{T_n} \cdot e^{-t/T_n} \quad (3)$$

and substitution of equation 2 into equation 3 results in:

$$dP/dt = \frac{c}{T_n} - \frac{P}{T_n} \quad (4)$$

Hence, a plot of dP/dt against ventricular pressure between peak negative dP/dt and 5 mmHg above end-diastolic pressure (fig. 2C) yields the nonzero asymptotic isovolumetric time constant (T_n) as the negative inverse of the slope. Therefore, the time constant of isovolumetric relaxation was calculated using both zero (T_0) and nonzero (T_n) asymptotic assumptions. Isovolumetric relaxation was also evaluated using the peak rate of decrease of ventricular pressure (−dP/dt) and the rate of decrease of ventricular pressure at 25 mmHg ($-dP/dt_{25}$), indirect indices of relaxation obtained directly by electronic differentiation of the left ventricular pressure waveform.

Regional chamber stiffness, an indicator of regional compliance during passive ventricular filling, was derived from ventricular pressure–segment length data. Beginning at minimum pressure, ventricular pressure was plotted against corresponding segment length at 2-ms intervals until the onset of atrial systole (incorporating both rapid ventricular filling and diastasis) had been reached, as described by Kurnik *et al.*[4] (fig. 3A). Analogous to the technique of Greene and Gerson,[21] a least-squares regression analysis was used to describe a monoexponential relationship between pressure and segment length (fig. 3B):

$$P = De^{K_p \cdot L} \quad (5)$$

where P = left ventricular pressure, L = corresponding segment length, D = a derived constant, and K_p = the regional chamber stiffness constant.

Left ventricular filling was also evaluated at end diastole using myocardial stress–strain relationships initially described by Mirsky and Parmley[10] and later modified for regional study by Van Trigt *et al.*[22] Sequential changes in end-diastolic pressure and end-diastolic segment length were obtained from left ventricular pressure–segment length loops generated by decreases in preload. Ventricular pressure and segment length waveforms were recorded on the digital oscilloscope in the conscious, autonomically blocked state. The inferior vena cava was then

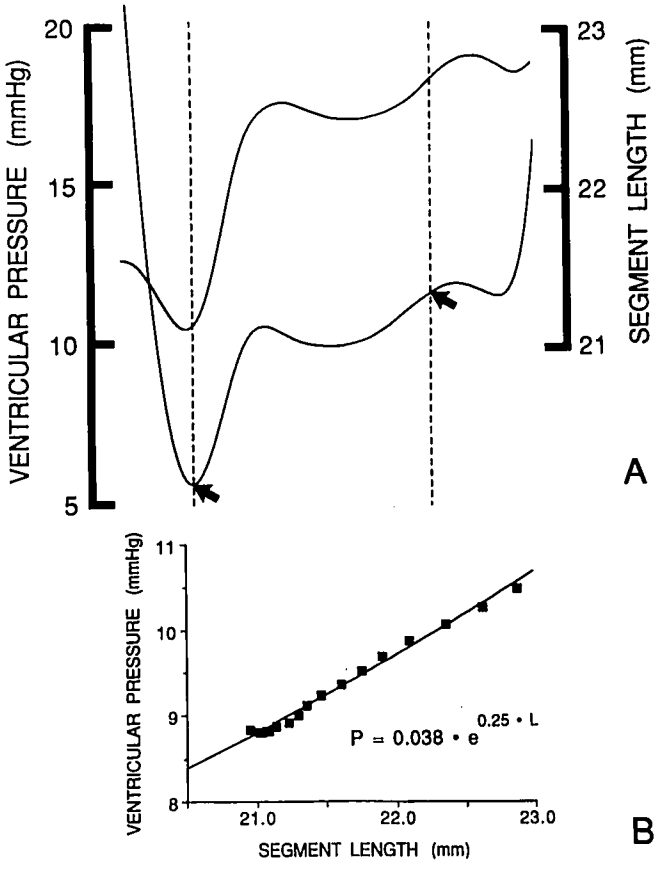

FIG. 3. Method used to calculate chamber stiffness (K_p) from ventricular pressure and segment length waveforms (*A*). Ventricular pressure (lower curve) was plotted against corresponding segment length (upper curve) between minimum ventricular pressure and the onset of atrial systole (dashed lines and arrows, *A*). A monoexponential relationship between ventricular pressure and segment length (*B*) was described by a least squares regression analysis: $P = De^{K_p \cdot L}$ (see text).

carefully constricted to reduce left ventricular systolic pressure in 5–10-mmHg decrements. No changes in heart rate were observed in response to partial occlusion of the inferior vena cava, and this partial constriction was alleviated after each reduction of left ventricular systolic pressure. End-expiratory pressure–length loops consisting of six to eight cardiac cycles were obtained at several decremental levels of ventricular pressure.

Using the digital oscilloscope, the end-diastolic pressure and corresponding end-diastolic segment length of each loop were identified (fig. 4A). These values were digitally amplified and converted to the appropriate pressure (mmHg) and length (millimeter) units by use of linear formulas generated from calibration data. Each segment length was normalized using the Lagrangian strain definition:

$$\epsilon = \frac{L_i - L_0}{L_0} \quad (6)$$

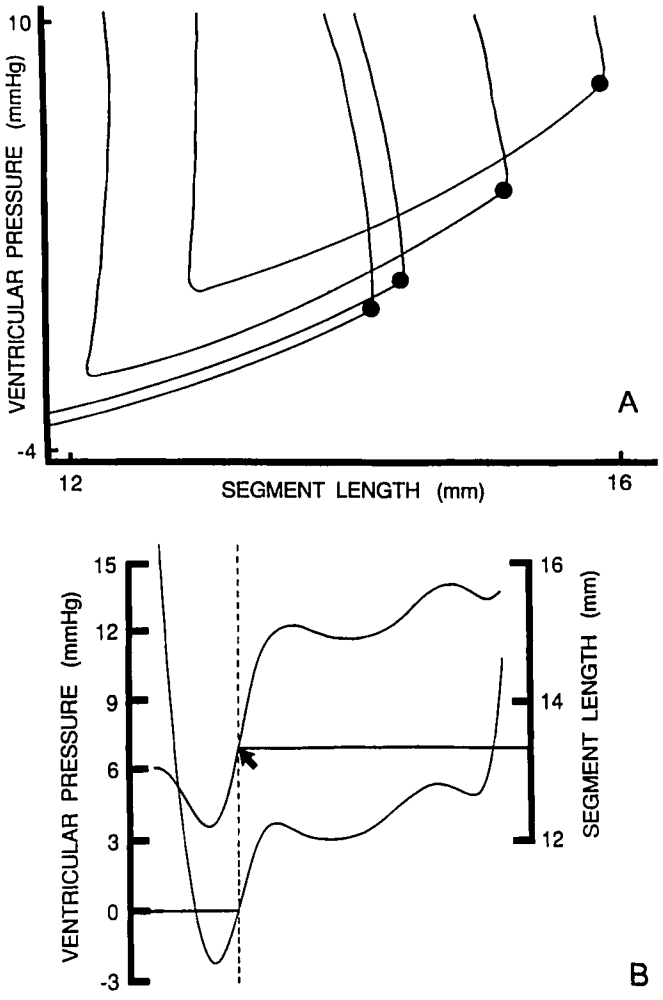

FIG. 4. Schematic illustrations demonstrating the generation of left ventricular end-diastolic pressures and corresponding end diastolic segment lengths necessary to calculate the myocardial stress strain relationship and the method used to estimate L_0, the segment length at 0 mmHg ventricular pressure. Pressure–length loops were obtained by progressive decreases in ventricular pressure produced by partial occlusion of the inferior vena cava. The end-diastolic pressure and end-diastolic length for each loop (large dots) were identified (*A*). End-diastolic length was normalized using the Lagrangian strain definition, and end-diastolic pressure was then plotted against corresponding strain (see text). Unstressed segment length (L_0) was defined during the final partial interior vena caval occlusion as the segment length corresponding to 0 mmHg ventricular pressure (arrow, *B*). The scale of these illustrations has been greatly expanded for clarity.

where ϵ = Lagrangian strain, L_i = end-diastolic segment length for each pressure–length loop, and L_0 = segment length at 0 mmHg ventricular pressure obtained during the final partial vena caval occlusion estimated using a method described by Glower *et al.*[30] (fig. 4B). Regional myocardial stress–strain relationships were obtained by plotting end-diastolic pressure against the corresponding end-diastolic Lagrangian strain for each ventricular pressure–segment length loop, using the equation:

$$P = \alpha(e^{\beta \cdot \epsilon} - 1) \quad (7)$$

where P = end-diastolic pressure; ϵ = Lagrangian strain, and α = gain and β = myocardial stiffness.

Experimental Protocol

Dogs were assigned to receive desflurane, isoflurane, or halothane in a random order on separate days. All dogs were fasted overnight, and fluid deficits were replaced before experimentation with crystalloid (500 ml lactated Ringer's). Maintenance fluid (lactated Ringer's solution) was administered as needed during each experiment in order to maintain relatively constant left ventricular end-diastolic pressure. After instrumentation was calibrated and baseline hemodynamic data were recorded, the autonomic nervous system was pharmacologically blocked with intravenous propranolol (2 mg/kg), atropine methylnitrate (3 mg/kg), and hexamethonium (20 mg/kg). Blockade of the autonomic nervous system was instituted to prevent reflex changes in systemic hemodynamics during anesthetic interventions and during alteration of left ventricular preload in the conscious and anesthetized state and to eliminate potential differential effects of the various anesthetics on autonomic nervous system tone. Adequacy of autonomic blockade was demonstrated by lack of reflex change in heart rate following abrupt decrease in venous return *via* inflation of the inferior vena caval hydraulic occluder. A previous investigation[31] from this laboratory showed that the doses of propranolol, atropine methylnitrate, and hexamethonium used were adequate to block hemodynamic responses to intravenous acetylcholine and isoproterenol for an experiment of longer duration.

Diastolic function using the techniques described above was assessed in the dogs in the conscious state after completion of autonomic nervous system blockade. Dogs were then anesthetized by mask with desflurane, isoflurane, or halothane. Following tracheal intubation, anesthesia was maintained at 1.0 or 1.5 end-tidal concentration (in a random order) in a nitrogen (79%) and oxygen (21%) mixture. End-tidal anesthetic concentrations of desflurane were measured at the tip of the endotracheal tube using an infrared anesthetic gas analyzer (Datex Capnomac, Helsinki, Finland) calibrated by the manufacturer for the detection of desflurane. End-tidal concentrations of halothane and isoflurane were assessed using a mass spectrometer (Marquette Advantage 2000, St. Louis, MO). Both the gas analyzer and the mass spectrometer were calibrated using known standards prior to and during experimentation. Desflurane was delivered using a modified Ohio DM5000 (Omeda, Madison, WI) anesthesia machine incorporating a temperature-controlled vaporizer designed to provide uniform, predictable rates of desflurane

vapor administration. Canine MAC values for desflurane,[32] isoflurane, and halothane used in this study were 7.2, 1.28, and 0.86%, respectively. After 30 min of anesthetic equilibration at a given end tidal concentration, hemodynamics were again recorded and diastolic function was assessed using the methods described above. The anesthetic concentration was then changed, and measurements were repeated after similar equilibration. Arterial blood gases were maintained at conscious levels by adjustment of the nitrogen and oxygen concentrations throughout the experiment. At the completion of all experiments, anesthesia was discontinued and emergence allowed. Prior to subsequent anesthetic intervention, each dog was allowed to recover for 3 days. Thus, a total of 23 experiments in three separate groups (desflurane, isoflurane, or halothane) were completed in which a total of 11 dogs were used.

Statistical Analysis

Statistical analysis of data within and between groups during the conscious state with and without autonomic nervous system blockade and during all anesthetic interventions was performed by analysis of variance (ANOVA) with repeated measures followed by application of Bonferroni's modification of the *t* test. Changes within and between groups were considered statistically significant when the probability (*P*) value was < 0.05. Least-squares regression analysis was used to characterize the relationships between isovolumetric pressure decrease and time (calculation of T_0), diastolic pressure and segment length (calculation of K_p), and end-diastolic pressure and Lagrangian strain (calculation of elastic gain, α, and myocardial stiffness, β). The relationship between dP/dt and ventricular pressure used to calculate T_n was described using a linear regression analysis. All data were expressed as mean ± standard error of the mean (SEM).

Results

Autonomic nervous system blockade produced significant ($P < 0.05$) increases in heart rate and decreases in mean arterial pressure, left ventricular systolic pressure, dP/dt, dP/dt_{50}, and systemic vascular resistance (tables 1–3). No changes in left ventricular end-diastolic pressure, cardiac output, stroke volume, or percent segment shortening were observed in any group. No differences in baseline hemodynamics with or without autonomic nervous system blockade were noted between groups. A small increase in arterial oxygen tension (Pa_{O_2}) was observed in all anesthetized animals whose lungs were ventilated using positive pressure. Correlation coefficients obtained for the calculation of the isovolumetric relaxation time constants, T_0 and T_n, were $r \geq 0.995$ and $r \geq 0.99$, respectively, in both conscious and anesthetized dogs. The correlations between ventricular pressure and segment length (calculation of chamber stiffness, K_p) and between end-diastolic pressure and Lagrangian strain (calculation of α and β) were $r \geq 0.98$ and $r \geq 0.96$, respectively.

Administration of desflurane produced a significant decrease in heart rate, mean arterial pressure, left ventricular systolic pressure, and cardiac output (table 1). Global myocardial contractility, as assessed by dP/dt and dP/dt_{50}, decreased in a dose-dependent fashion. Percent segment shortening, an index of regional contractile

TABLE 1. Hemodynamic Effects of Desflurane

	Conscious Control	ANS Blockade	Desflurane (MAC) 1.0	Desflurane (MAC) 1.5
HR (beats per min)	77 ± 5	112 ± 7*	95 ± 6*†	91 ± 6†
MAP (mmHg)	88 ± 3	67 ± 5*	59 ± 3*†	51 ± 3*†
LVSP (mmHg)	117 ± 3	93 ± 5*	85 ± 2*	76 ± 3*†
LVEDP (mmHg)	11 ± 1	11 ± 1	12 ± 2	14 ± 3
dP/dt_{max} (mmHg/s)	2185 ± 140	1766 ± 69*	1319 ± 97*†	964 ± 81*†‡
dP/dt_{50} (mmHg/s)	1902 ± 94	1683 ± 59*	1302 ± 93*†	937 ± 89*†‡
CO (l/min)	2.8 ± 0.3	3.1 ± 0.3	2.4 ± 0.2*	2.1 ± 0.2*†
SV (ml)	36 ± 5	28 ± 2*	26 ± 2†	24 ± 2*
SVR (dyne·s·cm^{-5})	2750 ± 290	1840 ± 200*	2010 ± 140*	2000 ± 190*
SS (%)	21.1 ± 1.5	21.0 ± 1.6	16.9 ± 1.9*†	12.6 ± 2.2*†
*p*H (u)	—	7.38 ± 0.01	7.39 ± 0.02	7.37 ± 0.02
P_{CO_2} (mmHg)	—	32 ± 1	30 ± 2	30 ± 1
P_{O_2} (mmHg)	—	83 ± 2	91 ± 8	100 ± 6†
ET (%)	—	—	7.3 ± 0.03	10.5 ± 0.19†

All data are mean ± SEM (n = 8).

HR = heart rate; MAP = mean arterial pressure; LVSP and LVEDP = left ventricular systolic pressure and end-diastolic pressure, respectively; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; SS = segment shortening; ET = end-tidal anesthetic concentration; ANS = autonomic nervous system.

* Significantly ($P < 0.05$) different from conscious control.
† Significantly ($P < 0.05$) different from ANS blockade.
‡ Significantly ($P < 0.05$) different from 1.0 MAC.

TABLE 2. Hemodynamic Effects of Isoflurane

	Conscious Control	ANS Blockade	Isoflurane	
			1.0 MAC	1.5 MAC
HR (beats per min)	80 ± 5	115 ± 6*	97 ± 4*†	93 ± 4*†
MAP (mmHg)	90 ± 5	76 ± 4*	59 ± 3*†	49 ± 3*†
LVSP (mmHg)	120 ± 4	98 ± 4*	81 ± 4*†	72 ± 3*†‡
LVEDP (mmHg)	10 ± 1	10 ± 1	10 ± 1	11 ± 1
dP/dt_{max} (mmHg/s)	2319 ± 142	1869 ± 97*	1353 ± 106*†	947 ± 81*†‡
dP/dt_{50} (mmHg/s)	1923 ± 73	1685 ± 63*	1309 ± 89*†	889 ± 92*†‡
CO (l/min)	2.7 ± 0.2	2.9 ± 0.3	2.4 ± 0.3	1.9 ± 0.2*†
SV (ml)	34 ± 3	25 ± 2*	24 ± 2*	21 ± 2*†
SVR (dyne·s·cm^{-5})	2820 ± 330	2230 ± 250*	2100 ± 140*	2140 ± 170*
SS (%)	19.4 ± 2.3	21.4 ± 2.0	19.6 ± 1.3	14.2 ± 1.5*†‡
*p*H (u)	—	7.39 ± 0.02	7.37 ± 0.02	7.39 ± 0.01
P_{CO_2} (mmHg)	—	35 ± 1	32 ± 2	30 ± 2
P_{O_2} (mmHg)	—	82 ± 3	92 ± 3†	97 ± 5†
ET (%)	—	—	1.31 ± 0.01	1.95 ± 0.01‡

All data are mean ± SEM (n = 8).
HR = heart rate; MAP = mean arterial pressure; LVSP and LVEDP = left ventricular systolic pressure and end-diastolic pressure, respectively; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; SS = segment shortening; ET = end-tidal anesthetic concentration; ANS = autonomic nervous system.

* Significantly ($P < 0.05$) different from conscious control.
† Significantly ($P < 0.05$) different from ANS blockade.
‡ Significantly ($P < 0.05$) different from 1.0 MAC.

function, also declined. No change in systemic vascular resistance or left ventricular end-diastolic pressure was observed (table 1). Desflurane produced dose-dependent increases in T_0 (fig. 5; 22.2 ± 2.0 during control to 33.9 ± 3.5 ms at 1.5 MAC) and T_n (fig. 6; 33.1 ± 1.6 during control to 45.1 ± 4.3 ms at 1.5 MAC), indicating a prolongation of isovolumetric relaxation. Decreases in peak $-dP/dt$ (−1,636 ± 103 during control to −1,317 ± 94 and −994 ± 94 mmHg/s at 1.0 and 1.5 MAC, respectively) and $-dP/dt_{25}$ (fig. 7; −1,033 ± 106 during control to −848 ± 111 and −695 ± 99 mmHg/s at 1.0 and 1.5 MAC, respectively), indirect indices of isovolumetric relaxation, were also observed. No change in regional chamber stiffness, K_p, occurred following administration of desflurane (table 4). Similarly, no changes in regional myocardial stress strain relationships were observed (table 4).

Isoflurane produced hemodynamic changes in the presence of autonomic nervous system blockade similar to those caused by desflurane. Decreases in heart rate,

TABLE 3. Hemodynamic Effects of Halothane

	Conscious Control	ANS Blockade	Halothane (MAC)	
			1.0	1.5
HR (beats per min)	82 ± 4	124 ± 7*	103 ± 6*†	98 ± 6*†
MAP (mmHg)	84 ± 4	78 ± 2	61 ± 3*†	56 ± 3*†
LVSP (mmHg)	116 ± 3	102 ± 3*	87 ± 3*†	81 ± 3*†
LVEDP (mmHg)	11 ± 1	10 ± 1	10 ± 2	11 ± 1
dP/dt_{max} (mmHg/s)	2389 ± 98	1880 ± 86*	1265 ± 74*†	896 ± 74*†‡
dP/dt_{50} (mmHg/s)	2031 ± 66	1722 ± 88*	1242 ± 71*†	878 ± 76*†‡
CO (l/min)	3.1 ± 0.3	3.6 ± 0.4	2.7 ± 0.2†	2.2 ± 0.2*†
SV (ml)	40 ± 5	30 ± 4*	27 ± 4*	23 ± 3*
SVR (dyne·s·cm^{-5})	2860 ± 170	1810 ± 180*	1930 ± 220*	2160 ± 250*
SS (%)	16.3 ± 1.3	14.0 ± 1.6	11.9 ± 1.4*	8.3 ± 1.8*†‡
*p*H (u)	—	7.38 ± 0.02	7.38 ± 0.02	7.39 ± 0.02
P_{CO_2} (mmHg)	—	32 ± 1	30 ± 1	30 ± 1
P_{O_2} (mmHg)	—	80 ± 3	101 ± 5†	107 ± 9†
ET (%)	—	—	0.90 ± 0.01	1.33 ± 0.01‡

All data are mean ± SEM (n = 7).
HR = heart rate; MAP = mean arterial pressure; LVSP and LVEDP = left ventricular systolic pressure and end-diastolic pressure, respectively; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; SS = segment shortening; ET = end-tidal anesthetic concentration; ANS = autonomic nervous system.

* Significantly ($P < 0.05$) different from conscious control.
† Significantly ($P < 0.05$) different from ANS blockade.
‡ Significantly ($P < 0.05$) different from 1.0 MAC.

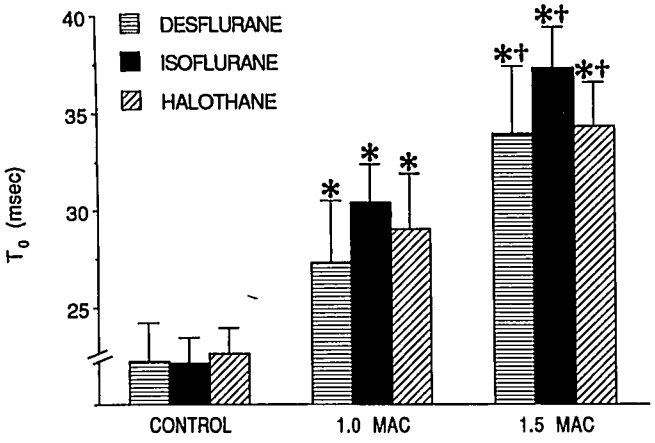

FIG. 5. Effects of desflurane, isoflurane, and halothane on the time constant of isovolumetric relaxation calculated using a zero decay assumption (T_0). *Significantly ($P < 0.05$) different from autonomically blocked, conscious control; †significantly ($P < 0.05$) different from 1.0 MAC.

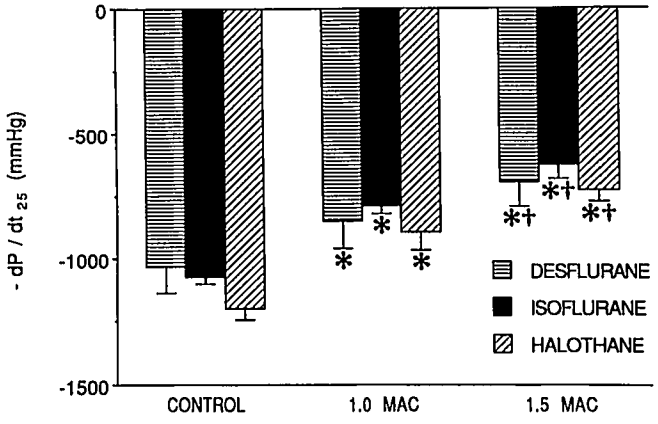

FIG. 7. Effects of desflurane, isoflurane, and halothane on isovolumetric relaxation assessed by the rate of decrease of ventricular pressure at 25 mmHg ($-dP/dt_{25}$). *Significantly ($P < 0.05$) different from autonomically blocked, conscious control; †significantly ($P < 0.05$) different from 1.0 MAC.

mean arterial pressure, left ventricular systolic pressure, cardiac output and myocardial contractility, as assessed by dP/dt, dP/dt_{50}, and percent segment shortening, were observed (table 2). No change in left ventricular end-diastolic pressure or systemic vascular resistance were produced by isoflurane. Like desflurane, isoflurane produced dose-dependent increases in both time constants of isovolumetric relaxation (T_0, 22.1 ± 1.3 during control to 37.3 ± 2.1 ms at 1.5 MAC; T_n, 35.6 ± 1.5 during control to 47.1 ± 2.9 ms at 1.5 MAC) as well as in −dP/dt (−1738 ± 126 during control to −1202 ± 94 and −888 ± 81 mmHg/s at 1.0 and 1.5 MAC, respectively) and $-dP/dt_{25}$ (figs. 5–7). No changes in regional chamber stiffness, K_p, or stress–strain relationships were observed during isoflurane anesthesia (table 4).

Halothane anesthesia caused decreases in heart rate, mean arterial pressure, left ventricular systolic pressure, dP/dt, dP/dt_{50}, percent segment shortening, and cardiac output. No changes in left ventricular end-diastolic pressure or systemic vascular resistance were observed (table 3). Halothane produced significant increases in both time constants (figs. 5 and 6) of isovolumetric relaxation (T_0, 22.6 ± 1.3 during control to 34.3 ± 2.3 ms at 1.5 MAC; T_n, 31.7 ± 2.2 during control to 42.3 ± 3.9 ms at 1.5 MAC). This prolongation of ventricular relaxation was reflected in significant changes in −dP/dt (−1,961 ± 83 during control to −1,430 ± 96 and −1,196 ± 103 mmHg/s at 1.0 and 1.5 MAC, respectively) and in $-dP/dt_{25}$ (fig. 7) as well. Regional chamber stiffness (table 4) was increased by halothane (K_p, 0.46 ± 0.07 during control to 0.88 ± 0.17 mm^{-1} at 1.5 MAC). No changes in myocardial stress–strain relationships (α and β) were observed (table 4).

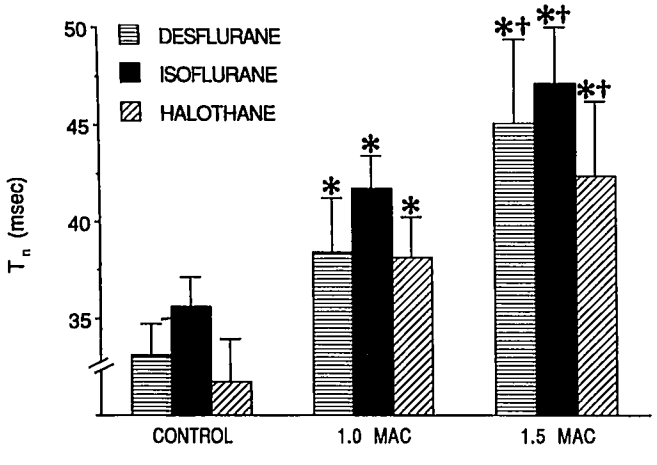

FIG. 6. Effects of desflurane, isoflurane, and halothane on the time constant of isovolumetric relaxation calculated assuming a non-zero asymptote (T_n). *Significantly ($P < 0.05$) different from autonomically blocked, conscious control; †significantly ($P < 0.05$) different from 1.0 MAC.

Discussion

Attempts to quantitatively describe ventricular function during diastole have been stimulated by the recognition that diastolic mechanics significantly influence overall cardiac performance and that diastolic dysfunction may precede or substantially contribute to abnormalities of systolic function in various pathologic states.[1,2,5–8] Currently available indices of diastolic function focus on measurement of a diverse and complex set of separate but interrelated processes that are not directly comparable. Measurement of these indices is complicated because di-

TABLE 4. Effects of Desflurane, and Isoflurane, and Halothane on Indices of Left Ventricular Compliance

	n	ANS Blockade	Desflurane (MAC) 1.0	Desflurane (MAC) 1.5
K_p (mm^{-1})	8	0.57 ± 0.10	0.55 ± 0.08	0.57 ± 0.11
α	8	2.5 ± 0.7	2.6 ± 0.8	3.0 ± 0.9
β	8	5.8 ± 1.3	5.8 ± 1.7	6.1 ± 1.1
			Isoflurane (MAC) 1.0	Isoflurane (MAC) 1.5
K_p (mm^{-1})	8	0.50 ± 0.12	0.73 ± 0.17	0.69 ± 0.17
α	8	2.2 ± 0.7	3.4 ± 0.7	4.1 ± 0.9
β	8	6.0 ± 1.2	5.1 ± 1.0	4.8 ± 0.9
			Halothane (MAC) 1.0	Halothane (MAC) 1.5
K_p (mm^{-1})	7	0.46 ± 0.07	0.83 ± 0.19*	0.88 ± 0.17*
α	7	2.3 ± 0.4	2.6 ± 0.6	3.2 ± 0.9
β	7	5.8 ± 0.8	6.3 ± 0.7	7.2 ± 0.9

All data are mean ± SEM.
K_p = regional chamber stiffness; α = stress–strain elastic gain; β = stress–strain myocardial stiffness; ANS = autonomic nervous system.
* Significantly ($P < 0.05$) different from ANS blockade.

astolic function depends on several determinants: active, energy-dependent forces (ventricular relaxation), passive viscoelastic properties (muscle or chamber stiffness), and extrinsic factors (ventricular interaction, pericardial restraint, and myocardial blood flow), as well as conditions that effect myocardial function in systole (preload, afterload, heart rate, and contractility).[8] The diversity of events occurring during diastole makes it unlikely that a single index of diastolic function can adequately describe this period of the cardiac cycle, and, in fact, the implications of diastolic dysfunction may be different depending on the period of diastole affected.[7] Therefore, assessment of diastolic function is complicated because of the heterogeneity of the event and the multiple factors that influence it.

The effects of volatile anesthetics on left ventricular diastolic function have not been comprehensively examined. Previous investigations have focused primarily on myocardial compliance or isovolumetric relaxation. Goldberg and Phear[16] reported that halothane altered myocardial compliance in rat left ventricular muscle *in vitro*. Rusy *et al.*[17] described alterations in left ventricular end-diastolic volume using high-speed biplane cineradiography following administration of halothane or cyclopropane in dogs. Similarly, Moores *et al.*[18] showed that halothane, but not morphine sulfate or major regional conduction block, altered diastolic compliance as assessed by a depression of stroke volume at equivalent left ventricular end-diastolic pressures following total cardiopulmonary bypass in acutely instrumented swine.

While the aforementioned studies have suggested that halothane decreases ventricular compliance, other investigations have been unable to support this conclusion. Hamilton *et al.*[19] described qualitative alterations in ventricular diastolic pressure–volume relationships after administration of cyclopropane but not halothane in open-chest dogs. These findings were partially supported in an elegant study by Brower and Merin.[20] Using angiography to assess left ventricular volume in swine, these investigators demonstrated a decrease in ventricular compliance following administration of 0.6% halothane. However, no further alterations in left ventricular compliance with increasing concentrations of halothane were observed. The lack of dose-dependent alterations in compliance were attributed to unavoidable changes in end-diastolic pressure, contractile performance, and heart rate, factors that the authors described as "patently impossible" to completely control.[20] Greene and Gerson[21] used an exponential pressure–volume relationship derived from invasively measured end-diastolic pressure and end-diastolic volume obtained noninvasively by echocardiography to describe ventricular compliance in open-chest dogs. No differences in compliance were produced by administration of 1 *versus* 2 MAC halothane. Van Trigt *et al.*[22] adapted a stress–strain model originally formulated by Mirsky and Parmley[10] and described end-diastolic pressure–minor axis strain as an index of diastolic function that included active filling at end diastole. Administration of 1 or 2% halothane resulted in no significant changes in this regional stress–strain relationship, demonstrating

that halothane did not appear to alter end-diastolic myocardial compliance.

In the current investigation, halothane altered regional chamber stiffness, K_p, at 1.0 MAC without further change at 1.5 MAC. Although ventricular loading conditions remained very stable for halothane in the presence of autonomic nervous system blockade, the conclusion that halothane affects passive viscoelastic properties must be qualified because decreases in heart rate and systolic performance may have concomitantly altered diastolic compliance. In addition, no alterations in stress strain gain (α) or myocardial stiffness (β) were observed with halothane, confirming the findings of Van Trigt *et al.*[22] and suggesting that diastolic compliance as assessed by a pressure–strain relationship at end diastole is unaffected by halothane. The effects of isoflurane or of the new volatile anesthetic desflurane on diastolic compliance have not been previously described. No significant changes in chamber stiffness (K_p) or stress–strain relationships were observed in the current investigation with administration of desflurane or isoflurane, although a trend toward increases in regional chamber stiffness may have occurred with isoflurane.

The effect of volatile anesthetics on left ventricular relaxation has recently been reported in investigations conducted *in vivo*[12–14] and *in vitro*.[15] A study by Swanson and Muir[12] in acutely instrumented, open-chest dogs demonstrated prolongation of the time constant of isovolumetric relaxation (τ) calculated using the monoexponential technique of Weiss *et al.*[27] by 2.5 MAC halothane. No changes in τ were observed with isoflurane or with halothane at lower concentrations (1.5 and 2.0 MAC), however, suggesting that these anesthetics have little effect on ventricular relaxation. Doyle *et al.*[13] examined the effects of halothane on isovolumetric relaxation and early diastolic coronary blood flow in open-chest dogs. In contrast to the findings of Swanson and Muir,[12] dose-dependent increases in the time constant of isovolumetric relaxation (prolongation of relaxation) were noted with increases in halothane concentration. In addition, the close relation between decreases in isovolumetric coronary blood flow and increases in the time constant of isovolumetric relaxation suggested an intriguing potential mechanism by which coronary perfusion may be altered in the presence of halothane.

Most recently, a study by Humphrey *et al.*[14] examined the effects of halothane, enflurane, and isoflurane on left ventricular relaxation in open-chest swine anesthetized with ketamine, pentobarbital, and pancuronium. In this series of experiments, the isovolumetric constant of relaxation (τ) was calculated using the nonzero asymptotic assumption of Thompson *et al.*[28] This method of calculating τ may be more physiologically appropriate than the monoexponential technique, since ventricular pressure is not artificially constrained to decline to zero, but rather decays to a true asymptote.[28,29] The investigators[14] found that halothane and enflurane produced increases in the time constant consistent with delays in ventricular relaxation that were maintained in the presence of atrial pacing and acute increases in aortic blood pressure. Similar increases in τ were observed with isoflurane[14]; however, these changes were not maintained in the presence of atrial pacing and increases in arterial pressure, suggesting that isoflurane at 1.5 MAC may induce less alteration in ventricular relaxation than does halothane or enflurane. The interpretation of these results, however, must be qualified because of high baseline heart rates, the concomitant use of intravenous anesthetics and neuromuscular blocking agents, and significant increases in left ventricular end-diastolic pressure at high anesthetic concentrations observed in an acute animal preparation.

These three investigations[12–14] indicate that volatile anesthetics appear to delay ventricular relaxation to varying degrees. Conversely, an *in vitro* study by Housmans and Murat[15] using ferret papillary muscle exposed to halothane, isoflurane, or enflurane suggested that a slowing of isotonic lengthening and an abbreviation of the rate of isometric relaxation was produced by volatile anesthetics. Extrapolation of these results to the intact heart implied that ventricular compliance may be decreased and isovolumetric relaxation may be enhanced in the presence of volatile anesthetics. These conclusions[15] appear to directly contradict the findings of the current and previous investigations[12–14] *in vivo* with respect to isovolumetric relaxation, but they also seem to support some previous studies[16–18] that suggest that such anesthetics may decrease ventricular compliance. However, as noted by Humphrey *et al.*,[14] Housmans and Murat[15] studied a period of relaxation (peak force to one half peak force) that may precede the period described by the time constant of isovolumetric relaxation. Although the results between *in vitro* and *in vivo* models may not be directly comparable, several questions remain regarding this marked discrepancy between findings in isolated *versus* intact hearts and warrant further study.

The current investigation represents the first study of the effect of volatile anesthetics on left ventricular relaxation in a chronically instrumented animal model. Isovolumetric relaxation was assessed by using both zero (T_0) and nonzero (T_n) asymptotic assumptions for the calculation of the time constant of relaxation as well as by using indirect indicators of isovolumetric relaxation (peak $-dP/dt$ and $-dP/dt_{25}$). Both T_0 and T_n increased in a dose-dependent fashion in the presence of all three anesthetics, indicating that desflurane, isoflurane, and halothane prolong isovolumetric relaxation to an equal degree. Time constants of isovolumetric relaxation have been shown to be variably affected by changes in heart rate and loading

conditions.[7] A decrease in heart rate was observed with all three anesthetics at 1.0 MAC (reflecting direct depression of phase-4 sinoatrial node repolarization[33]), which may partially explain the observed increases in the relaxation period. However, no significant change in heart rate was observed between 1.0 and 1.5 MAC for any anesthetic, indicating that alterations in isovolumetric relaxation observed between these two doses cannot be attributed solely to changes in heart rate. In addition, loading conditions as assessed by left ventricular end-diastolic pressure and systemic vascular resistance remained stable for all three anesthetics throughout each experiment. The findings for T_0 and T_n were supported by less-negative values of $-dP/dt$ and $-dP/dt_{25}$. The precision with which these indirect indicators of relaxation reflected prolongation of isovolumetric relaxation can probably be attributed to the relative stability of heart rate and loading conditions observed during each experiment.[34]

The results of this investigation confirm the findings of Doyle *et al.*[13] for halothane and partially support those of Humphrey *et al.*[14] for isoflurane and halothane. Dose-dependent increases in all measures of isovolumetric relaxation were observed for both isoflurane and halothane, and no differences between agents could be identified. An uncontrolled variable in this analysis involved the differential effect of halothane and isoflurane on systolic performance. Halothane has been shown in previous investigations from this[25] and other laboratories[24,35] to produce greater decreases in contractile function than isoflurane at equianesthetic concentrations. These differences in contractile performance between halothane and isoflurane may have offset potential differences between these agents during relaxation. Thus, the conclusion that halothane and isoflurane affect isovolumetric relaxation equally must be qualified because differences in contractile performance between these agents may be of critical importance and cannot be completely eliminated. Desflurane has been shown to produce negative inotropic effects very similar to those of isoflurane in the presence of autonomic nervous system blockade.[36] Results of this investigation indicate that desflurane and isoflurane also prolong relaxation to an equal degree within the limitations of the current series of experiments.

The properties of the left ventricle in diastole contribute not only to the rate but also to the extent of ventricular filling. While diastolic function is important, the clinical ramifications of alteration of any individual phase of diastole has yet to be well defined. The results of this investigation indicate that all three volatile anesthetics prolong isovolumetric relaxation to an equal degree in chronically instrumented dogs with autonomic nervous system blockade. Furthermore, desflurane and isoflurane produced no effect on regional chamber stiffness or myocardial stress–strain relationships, indicating that these agents do not alter ventricular compliance. In contrast, halothane produced an increase in chamber stiffness, suggesting that this anesthetic may affect ventricular elastic properties. However, this conclusion must be qualified because no alterations in the pressure–strain relationship at end diastole were noted. Whether the effects of volatile anesthetics on diastolic function are exacerbated in disease processes manifesting abnormal diastolic function requires further evaluation.

The authors extend their appreciation to Doug Hettrick, David Schwabe, and John Tessmer for technical assistance and to Mimi Mick for preparation of the manuscript. The authors are indebted to Dr. Ron Ferrone of Anaquest, Murray Hill, NJ for graciously supplying desflurane.

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