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Importance of Myocardial Loading Conditions in Determining the Effects of Enflurane on Left Ventricular Function in the Intact and Isolated Canine Heart

M. Zimpfer, M.D., H. Gilly, Ph.D.,† P. Krösl, Ph.D.,‡ G. Schlag, M.D.,§ K. Steinbereithner, M.D.¶*

The effects of enflurane (2% and 4% inspired) on left ventricular (LV) function were examined in chronically instrumented dogs, both intact and after isolation of their hearts and lungs from the systemic circulation. Enflurane in the intact dogs increased heart rate (32 ± 5% with 2% and 41 ± 4% with 4%) and elicited striking, dose-dependent decreases in LV stroke shortening (−30 ± 3% and −41 ± 4%), the maximum velocity of LV fiber shortening, dD/dt, (−23 ± 2% and −40 ± 2%), LV systolic pressure (−25 ± 3% and −33 ± 2%), the maximum rise of LV-pressure, dP/dt (−33 ± 5% and −55 ± 3%), and mean aortic pressure (−27 ± 2% and −37 ± 1%). However, the LV diastolic performance was impaired little, *i.e.*, even with the higher concentration the LV end-diastolic pressure rose only moderately (32 ± 4%), while the LV end-diastolic dimensions failed to change significantly; both LV end-diastolic pressure and LV end-diastolic diameter were decreased with the low concentration. Enflurane, after beta-adrenergic blockade alone or after combined beta-adrenergic and cholinergic blockades, or with spontaneous ventilation instead of controlled ventilation, had similar effects. By contrast, in the hearts that were isolated from the systemic circulation and the complex neurohumoral environment, enflurane increased both LV end-diastolic pressure (116 ± 32% and 492 ± 58%) and LV end-diastolic diameter (13 ± 3% and 28 ± 7%). In intact dogs with aortic pressure artificially increased to conscious control levels, enflurane likewise caused a distinct depression of the LV diastolic performance. Thus, LV systolic unloading appears to be mandatory in order to prevent acute myocardial failure from higher doses of enflurane. The observed changes in LV function with enflurane are largely independent of cardiac rate, adrenergic and cholinergic influences, and the hemodynamic consequences of intermittent positive-pressure ventilation. (Key words: Anesthetics, volatile: enflurane. Heart: contractility; myocardial function.)

* Anesthetist, Clinic of Anesthesia and General Intensive Care, University of Vienna, and Research Associate, Ludwig Boltzmann-Institute of Experimental Anesthesiology and Research in Intensive Care.

† Research Associate, Ludwig Boltzmann-Institute of Experimental Anesthesiology and Research in Intensive Care.

‡ Research Associate, Ludwig Boltzmann-Institute of Experimental Traumatology.

§ Professor, Ludwig Boltzmann-Institute of Experimental Traumatology.

¶ Professor, Clinic of Anesthesia and General Intensive Care, University of Vienna, and Ludwig Boltzmann-Institute of Experimental Anesthesiology and Research in Intensive Care.

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Address reprint requests to Dr. Zimpfer: Clinic of Anesthesia and General Intensive Care, University of Vienna, 23 Spitalgasse, 1090 Vienna, Austria.

WHILE ENFLURANE has not been found to induce significant cardiac depression in volunteers or in patients,[1–6] it is now well-recognized, based on studies in both isolated cardiac muscle[7,8] and intact experimental animals,[9] that this compound, like all other volatile anesthetics, induces a direct, dose-dependent, negative inotropic effect. Although several investigators have pointed out that the simultaneous changes in myocardial loading conditions could modify the direct effects of enflurane on the myocardium,[5,6,10] the secondary effects of peripheral vasodilation on left ventricular (LV) dynamics have not been quantitated to our knowledge. In particular, it remains uncertain whether the complex interplay between the cardiac and extracardiac effects results in acute LV dilation and ultimately myocardial failure. It also remains inconclusive whether and to what extent the simultaneous changes in heart rate, neurohumoral counterregulation, as well as the institution of mechanical ventilation contribute to the observed changes in LV function.

The goal of the present study was 1) to investigate the effects of enflurane on LV function during controlled ventilation in intact dogs, and 2) to undertake a comprehensive evaluation of the relative importance of peripheral vasodilation, tachycardia, reflex buffering, and the hemodynamic consequences of intermittent positive-pressure ventilation in interacting with the direct effects of enflurane on myocardial contractility. As it is conceivable that supplemental anesthetic drugs could alter several aspects of the cardiocirculatory system[9,11–13] and thereby complicate the interpretation of the effects of enflurane, the present study was performed in chronically instrumented dogs after recovery from operation. In order to eliminate any scatter as a result of experimental sampling from different groups of the same population, the study was designed for paired comparisons, *i.e.*, the effects of enflurane on LV dynamics were studied in the same hearts: first in the intact animals using a variety of experimental protocols, and then in a modified Starling preparation after isolation of the hearts and lungs from the systemic circulation.

Methods

Ten mongrel dogs weighing between 17 and 34 kg were anesthetized with pentobarbital (30 mg/kg, iv) and

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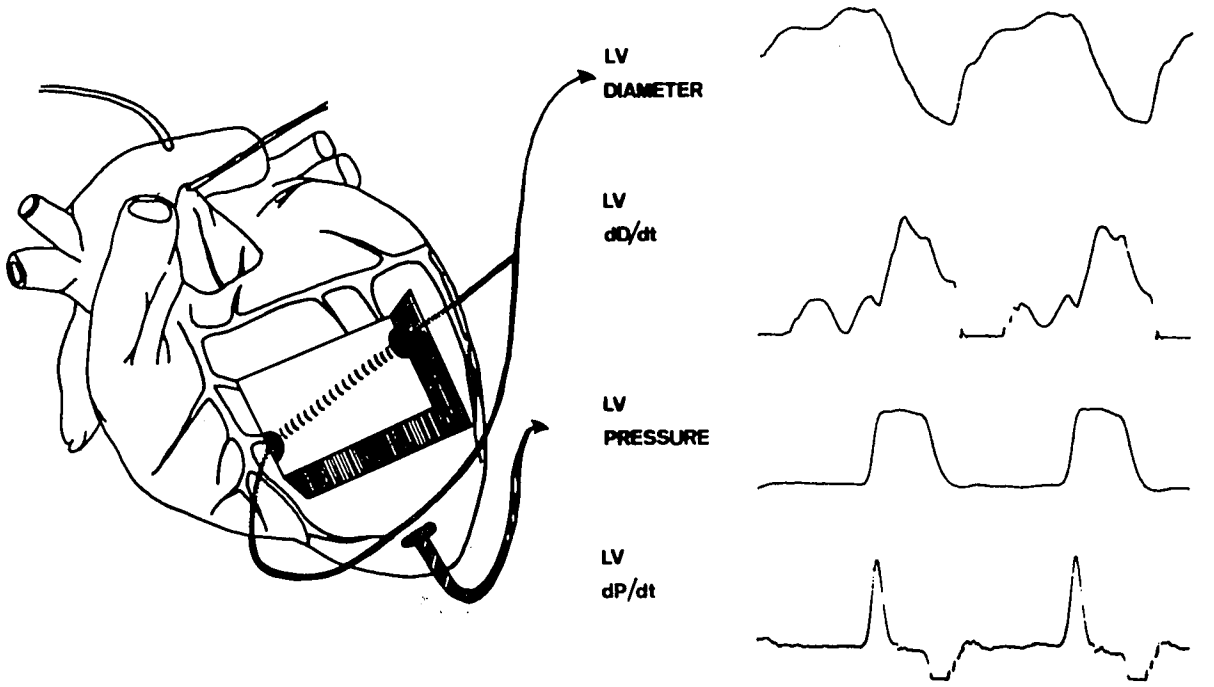

FIG. 1. The instrumentation used is shown schematically in the left-hand panel. A miniature pressure gauge and opposing piezo-electric diameter transducers were inserted into the left ventricle via stab wounds. Catheters were implanted into the left atrium and the aorta. Continuous measurements of LV diameter and its velocity (dD/dt), LV pressure, and the rise of pressure (dP/dt) are shown in the right-hand panel.

underwent a thoracotomy through the left fifth intercostal space. Ultrasonic diameter-transducers were placed on opposing endocardial surfaces through small stab wounds in the anterior and posterior walls of the left ventricle (fig. 1 and table 1). Miniature LV pressure gauges (Konigsberg, California) were inserted into the LV cavity through an apical stab wound, and heparin-filled catheters were implanted in the thoracic aorta and the left atrium. The pericardium was left open and all wires, catheters, and cables were run subcutaneously and exited in the interscapular area. Strict aseptic procedures were observed at all times. The catheters and wires were protected by fitting the dogs in a jacket of stocking gauze.

TABLE 1. Outline of the Experimental Design

Measurements		
1. Aortic pressure	—	Aortic catheter
2. LV-pressure	—	Miniature pressure gauge
3. LV-dimensions	—	Sonic transit time diameter gauge

Protocol

Experiments were conducted:

A. In intact, chronically instrumented dogs on different days and in a randomized sequence (2–9 weeks after surgery):
   1. Conscious control
   2. Enflurane (2% and 4% inspired) and controlled ventilation (O_2, N_2)
      2.1. No other intervention
      2.2. Heart rate held constant (right ventricular or right atrial pacing)
      2.3. Beta-adrenergic blockade (propranolol, 1–1.5 mg/kg, iv)
      2.4. Combined beta-adrenergic (propranolol, 1–1.5 mg/kg, iv) and cholinergic (atropine, 0.15 mg/kg, iv) blockades
      2.5. Aortic balloon inflation
   3. Enflurane (2% inspired) and spontaneous ventilation (O_2, N_2)

B. After isolation of the heart and lungs from the systemic circulation (modified Starling preparation) with either spontaneous or constant heart rate (right ventricular pacing)
   1. Control
   2. Enflurane (2% and 4% inspired), (O_2, N_2).

The experiments were conducted 2 to 9 weeks after surgery; none of the dogs had arrhythmias or systemic infection, and all could exercise normally. While the conscious, unsedated animals reclined quietly, continuous records of LV pressure and LV diameter, the time rate of change of pressure (dP/dt), the time rate of change of diameter, *i.e.*, the velocity of myocardial fiber shortening (dD/dt), mean arterial pressure, and heart rate were obtained. Anesthesia were induced with either a short-acting barbiturate (thiamylal, 4 mg/kg, iv) (n = 21), or by administering enflurane (4% in 50% oxygen and nitrogen) through a canine anesthesia mask (n = 11). After the anesthetic state was sufficiently deep, the trachea was intubated and constant volume intermittent positive-pressure ventilation at a rate of 14 breath per minute with a mixture of oxygen and nitrogen was instituted to produce normocapnia and to keep the arterial oxygen tension approximately 100 mmHg.

Enflurane in concentrations of 2% or 4% was supplied by a vaporizer, calibrated by a gas chromatograph in our laboratory. In four animals the end-tidal concentrations were checked by gas chromatograph also. The order of the dose administration of enflurane was altered. At least 45 min elapsed after each vaporizer setting in order to assure near-complete equilibration of the anesthetic gas.

Experiments were repeated on separate experimental days in a randomized sequence after beta-adrenergic blockade (1–1.5 mg/kg propranolol, iv) (n = 6), after combined beta-adrenergic and cholinergic blockades (0.15 mg/kg atropine, iv) (n = 4), with heart rate held constant [right ventricular pacing (n = 6) or right atrial pacing (n = 2)], and also while the animals were breathing spontaneously (n = 4). In two dogs, balloon-tipped catheters were introduced into the descending aortas via the right femoral arteries and gradually inflated to increase mean aortic pressure to the conscious control level during the administration of enflurane. In the animals with spontaneous respiration, the arterial oxygen tension was maintained by administration of nasal oxygen. However, since we could not achieve anesthesia safely with 4% in this group, we did not attempt studies at the higher concentration. The adequacy of the autonomic blockades was tested with isoproterenol challenge (1 μg/kg, iv) and with acetylcholine challenge (40 μg/kg, iv), respectively.

After completion of these experiments, six of the ten dogs were premedicated with morphine sulfate (0.5 mg/kg) and anesthetized with thiamylal (4 mg/kg, iv) and piritramide (3 mg/kg, iv). Anesthesia was maintained by giving additional doses of piritramide (0.3 mg/kg, iv) as required. After intubation of the trachea, muscle relaxation (pancuronium, 2–4 mg/h, iv) and artificial ventilation with a mixture of 70% nitrous oxide and 30% oxygen, a sternotomy was performed and the hearts and lungs were isolated from the systemic circulation using a modified Starling preparation similar to that described previously by Abel.[14] A glass cannula was introduced into the left subclavian artery and attached to a reservoir which permitted the control of afterload at a desired level (fig. 2). The blood was returned to the heart after passage through a heat exchanger and a reservoir to control preload via a catheter which was inserted into the anterior aspect of the right ventricle and retained by a purse-string suture. The reservoir and the pump system were filled with the animals own blood. The reservoir was opened gradually before the aorta was tied completely to prevent LV damage from pressure afterload. The right brachiocephalic artery, the left carotid artery, the azygos vein, and the inferior and superior vena cavae also were tied.

After the brachiocephalic artery was tied at its origin and the aorta was tied just distally to the subclavian artery, all flow to the head and the remainder of the body ceased and the animal was presumed dead. That no other collateral flow occurred was demonstrated by the constant reservoir volume. The veins were ligated to prevent any possible backflow and blood loss from the isolated circuit. The vagi and stellate ganglia were not disturbed and presumably lost their activity soon after isolation. Although the onset time of this lost activity was not documented, no evidence of a change in neural activity, heart rate, or myocardial performance was seen during the control period. Similarly, no additional adrenal secretions could now enter the system. Accordingly, no further narcotic analgesics were given during the control period and the nitrous oxide was replaced by nitrogen. Enflurane (2% and 4%) was ad-

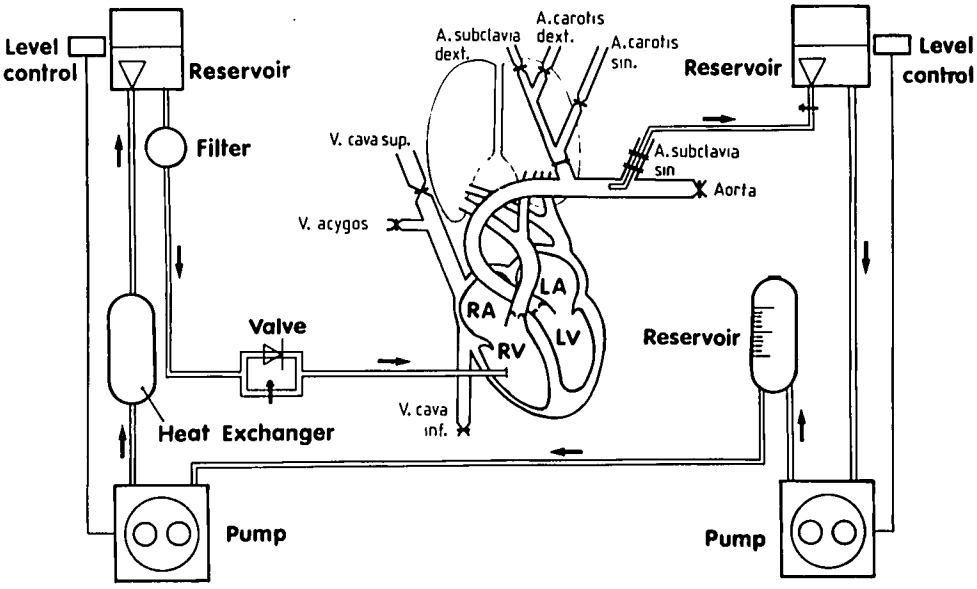

FIG. 2. Diagram of the heart-lung preparation used in these experiments.

TABLE 2. Effects of Enflurane with Ventilation Controlled in Intact, Chronically Instrumented Dogs (n = 8)

	Conscious	Enflurane 2%	Enflurane 4%
Heart rate (beats/min)	83.9 ± 2.5	110.6 ± 5.9†	118.6 ± 6.2†
Mean aortic pressure (mmHg)	92.0 ± 3.1	67.3 ± 1.3†	58.3 ± 2.1†
LV systolic pressure (mmHg)	117.3 ± 3.0	88.0 ± 2.5†	78.3 ± 2.5†
LV end-diastolic pressure (mmHg)	9.1 ± 0.3	6.5 ± 0.4†	12.0 ± 0.5†
LV end-diastolic diameter (mm)	39.3 ± 1.5	36.6 ± 1.4†	38.3 ± 1.3
LV end-systolic diameter (mm)	32.7 ± 1.3	32.0 ± 1.3*	34.4 ± 1.2†
LV stroke shortening (mm)	6.6 ± 1.1	4.6 ± 0.9†	3.9 ± 0.8†
LV dP/dt_{max} (mmHg/s)	2,771 ± 110	1,857 ± 179†	1,243 ± 119†
LV dD/dt_{max} (mm/s)	66.6 ± 2.0	51.2 ± 1.0†	40.0 ± 1.3†

Significantly different from control: * $P < 0.05$; † $P < 0.01$.

ministered the same way as described for the intact animals.

Two additional heart-lung preparations were performed using enflurane–nitrous-oxide–oxygen anesthesia without premedication. After completion of the surgical preparation, enflurane and nitrous oxide were discontinued and replaced by nitrogen. After a 60-min stabilization period, the absence of enflurane in the perfusate was checked by gas chromatography and enflurane (2% and 4%) was then added again to the inspired gas mixture.

In all experiments a sonic, transit time, diameter gauge was used to measure LV diameter.[15,16] The device measures the transit time of sound waves emitted from one piezo-electric crystal to another sutured to the opposing sites of the left ventricle. Since the sonic signal is known to travel through the left ventricle at approximately the speed of sound in water (1.5×10^6 mm/s), the transit time of the signal at any instant indicates the instantaneous distance between the crystals and thus the diameter of the left ventricle. A voltage proportional to transit time is recorded and calibrated in terms of crystal separation. The transit time was calibrated by substituting signals of known time duration from a pulse generator which was referenced to a quartz crystal controlled oscillator frequency. During experiments the received ultrasonic signal was monitored continuously on an oscilloscope. By this method, inaccuracies in instrument triggering, which are readily apparent, can be detected. If the instrument failed to track the separation of the transducer crystals reliably, due to inadequate signal-noise ratio or inadequate opposition of the transducers, the animal was not used for experimentation. The LV pressure gauges were calibrated repeatedly *in vivo* against the left atrial and aortic pressures with calibrated Statham® strain gauge manometers. Heart rate was derived using a cardiotachometer triggered by the LV pressure pulse. A triangular wave signal with known slope was substituted for LV pressure and LV diameter to calibrate the dP/dt and the dD/dt tracings.

The data were recorded continuously on a direct writing oscillograph and collected on a multichannel magnetic tape recorder. Results are expressed as means ± SEM. Significant differences of the various baseline states were determined using the paired *t* test.[17] The effects of enflurane were compared with the conscious control, and changes from control in the different states were compared by analysis of variance and the method of least significant differences.[17] Comparison of relative changes in the intact animals and the isolated heart-lung preparations were made using the group *t* test.[17] *P* values of less than 0.05 were accepted as significant.

Results

Because neither the mode of how anesthesia was induced nor the sequence of dose administration had any significant effect, all data are pooled. While the arterial blood oxygen tension increased with the administration of anesthesia, the arterial blood *p*H and P_{CO_2} values were not significantly different in any of the states studied. Baseline values for the different states in the intact, conscious dogs are shown in tables 2 and 3.

TABLE 3. Baseline Values in the Intact, Conscious Dogs

	Paced (n = 6)	Beta Block (n = 6)	Beta and Cholinergic Block (n = 4)	Spontaneous Respiration, Conscious and Anesthetized (n = 4)
Heart rate (beats/min)	135.8 ± 4.6	77.0 ± 2.6	126.3 ± 9.4	86.5 ± 3.3
Mean aortic pressure (mmHg)	101.7 ± 2.4	87.0 ± 2.3	103.3 ± 3.7	94.5 ± 3.6
LV systolic pressure (mmHg)	123.3 ± 3.1	113.3 ± 3.1	127.8 ± 3.4	118.3 ± 3.3
LV end-diastolic pressure (mmHg)	5.2 ± 0.6	10.1 ± 0.3	9.3 ± 0.3	9.0 ± 0.4
LV end-diastolic diameter (mm)	36.4 ± 1.4	40.1 ± 1.4	35.0 ± 1.6	39.4 ± 2.6
LV end-systolic diameter (mm)	30.9 ± 1.5	33.2 ± 1.6	28.2 ± 2.3	31.1 ± 2.6
LV stroke shortening (mm)	5.5 ± 0.9	6.9 ± 1.1	6.8 ± 1.2	8.3 ± 1.0
LV dP/dt_{max} (mmHg/s)	2,693 ± 97	2,636 ± 112	2,600 ± 248	2,838 ± 175
LV dD/dt_{max} (mm/s)	73.4 ± 2.3	59.1 ± 3.5	65.6 ± 7.4	68.0 ± 3.3

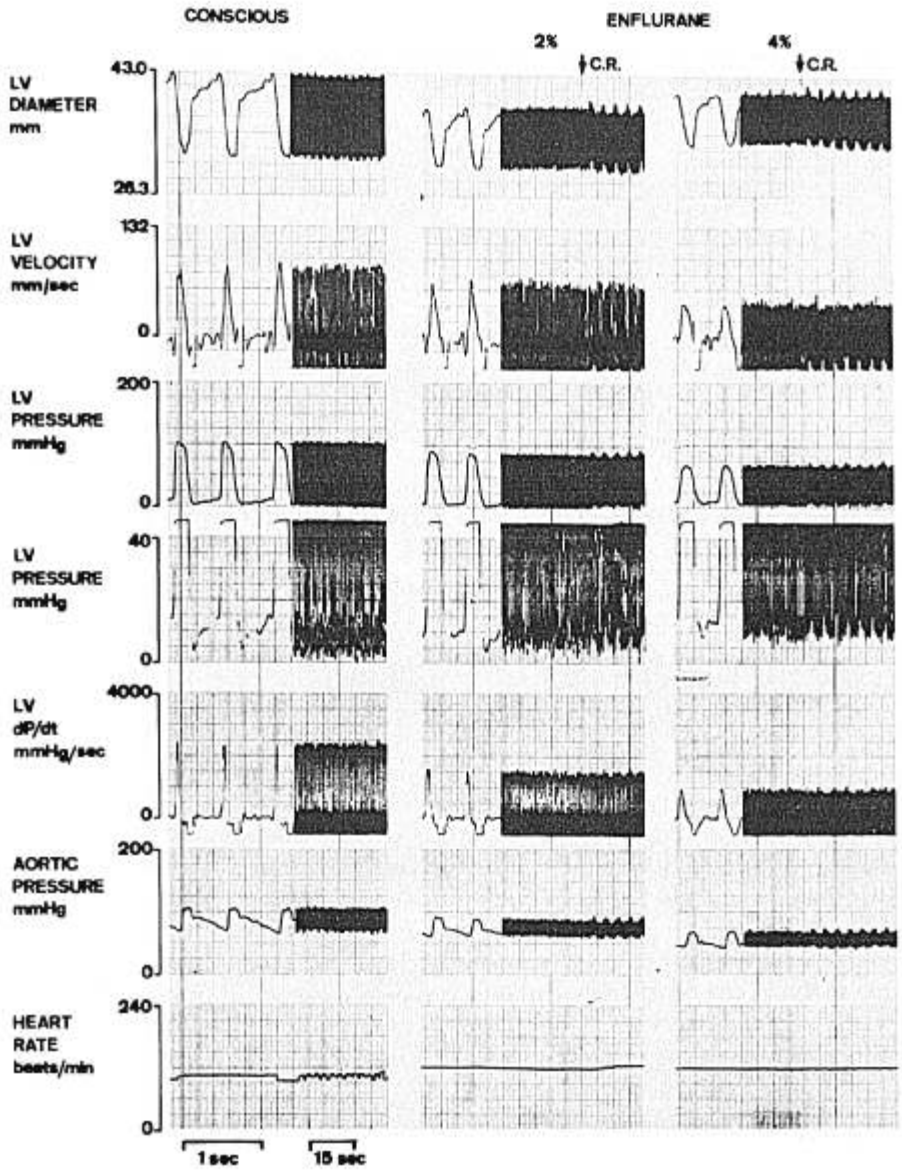

FIG. 3. Typical response to increasing doses of enflurane in an intact, chronically instrumented dog without premedication. Phasic records of LV diameter and its velocity (dD/dt), pressure, end-diastolic pressure, the maximum rise of pressure (dP/dt), aortic pressure, and heart rate are shown. LV end-diastolic diameter did not increase with either of the two concentrations studied. In order to illustrate the absence of significant contributions of intermittent positive-pressure ventilation to the observed changes in LV dynamics, the animal was briefly disconnected from the respirator at each of the two concentrations studied. Arrows (C.R.) indicate the reinstitution of controlled respiration.

EFFECTS OF ENFLURANE IN INTACT DOGS

Spontaneous Rhythm with Either Controlled or Spontaneous Respiration

Enflurane with ventilation held constant increased heart rate and led to progressive, dose-dependent decreases in LV stroke shortening, the maximum velocity of fiber shortening (dD/dt_{max}), LV systolic pressure, the maximum rise of LV systolic pressure (dP/dt_{max}), and mean arterial pressure (figure 3 and table 2). However, even with the high concentration no increase in LV end-diastolic dimensions was noted. In fact, LV end-diastolic diameter was decreased with the low concentration. However, while the LV end-systolic diameter decreased slightly with 2% it was significantly increased above control with 4%. Correspondingly, the decrease in LV stroke shortening was caused by a reduction in end-diastolic dimensions with 2% and the increase in end-systolic dimensions with 4%. LV end-diastolic pressure decreased with 2% and increased above control with 4% albeit to a much lesser degree than in the experiments in the intact animals with aortic balloon inflation and in the isolated heart-lung preparations.

Similar decreases in LV end-diastolic pressure and in LV end-diastolic dimensions with enflurane (2%) were observed while the animals were breathing spontaneously (table 4). Moreover, with apnea after briefly disconnecting an animal from the respirator, no significant changes in LV dynamics were observed with either of the two concentrations studied. Control values in

TABLE 4. Effects of Enflurane on the LV Pressure-dimension Relation in the Intact Dogs

	n	Conscious	Enflurane 2%	Enflurane 4%
LV end-diastolic pressure (mmHg)				
Spontaneous rhythm, no block	8	9.1 ± 0.3	6.5 ± 0.4‡	12.0 ± 0.5‡
Right ventricular pacing	6	5.2 ± 0.6*	3.2 ± 0.8‡	6.1 ± 0.5†
Beta block	6	10.1 ± 0.3*	6.6 ± 0.7‡	8.7 ± 1.1
Beta and cholinergic block	4	9.3 ± 0.3	8.0 ± 0.4†	10.5 ± 0.6
Spontaneous respiration, conscious and anesthetized	4	9.0 ± 0.4	6.6 ± 0.5‡	
LV end-diastolic diameter (mm)				
Spontaneous rhythm, no block	8	39.3 ± 1.5	36.6 ± 1.4‡	38.3 ± 1.3
Right ventricular pacing	6	36.4 ± 1.4*	34.5 ± 1.4‡	36.3 ± 1.5
Beta block	6	40.1 ± 1.4*	35.9 ± 0.7‡	38.7 ± 1.0
Beta and cholinergic block	4	35.0 ± 1.6	33.7 ± 1.6‡	34.7 ± 1.8
Spontaneous respiration, conscious and anesthetized	4	39.4 ± 2.6	36.9 ± 2.5‡	

Significantly different from conscious, spontaneous rhythm, no block: * $P < 0.01$.

Significantly different from the respective conscious control: † $P < 0.05$; ‡ $P < 0.01$.

these experiments were not significantly different from the ones obtained in the same animals in whom anesthesia was administered with ventilation controlled.

Heart Rate Held Constant

Heart rate was held constant by temporary right atrial or right ventricular pacing in the control period and again under steady-state conditions during inhalation of enflurane. Either mode of pacing increased mean arterial pressure and reduced LV end-diastolic pressure, LV end-diastolic diameter, and LV stroke shortening. However, the changes of LV diastolic performance (table 4) and of the other hemodynamic responses to anesthesia with enflurane were not altered significantly by either right atrial or right ventricular pacing.

Autonomic Blockades

Beta-adrenergic blockade with propranolol increased both LV end-diastolic pressure and LV end-diastolic diameter while it reduced LV dP/dt_{max}, LV dD/dt_{max}, and heart rate. Again, enflurane produced LV end-diastolic pressure-diameter relations similar to those described above, *i.e.*, both LV end-diastolic pressure and LV end-diastolic diameter failed to change significantly with 4% while they were decreased by 2%.

Combined beta-adrenergic and cholinergic blockades increased heart rate and mean arterial pressure while LV dP/dt_{max} was reduced. However, the changes in LV end-diastolic pressure and LV end-diastolic diameter with increasing concentrations of enflurane did not differ from the pattern observed in the animals with spontaneous rhythm and without the addition of autonomic blocking agents (table 4).

The presence of the autonomic blocking agents did not significantly affect responses of the other measured hemodynamic variables to enflurane, with the exception of heart rate which increased less after combined beta-adrenergic and cholinergic blockades.

Aortic Balloon Inflation

A steep end-diastolic pressure-diameter relation was detected by inflating an aortic balloon to increase mean arterial pressure to the conscious control level (fig. 4). LV filling pressure rose markedly (by an average of 90% with 2% and by 230% with 4% enflurane) for only small increments in LV dimensions from the conscious control. Thus, provided mean aortic pressure as a rough indicator of LV afterload is held constant in intact dogs, enflurane causes striking impairment of the LV diastolic performance.

Effects of Enflurane in Isolated Heart-lung Preparations with Either Spontaneous Rhythm or with Heart Rate Held Constant

Isolation of the heart and lungs from the systemic circulation with deprivation of the neurohumoral control increased heart rate and mean arterial pressure but decreased LV end-diastolic pressure, LV end-diastolic diameter, and LV stroke shortening (table 5). Enflurane under these conditions led to striking, dose-dependent increases in both LV end-diastolic pressure and LV end-diastolic diameter (figs. 5 and 6). However, while the LV end-diastolic pressure increased to much higher levels (average = 40.0 ± 2.3 mmHg) than it did in the control experiments in the same animals intact, the LV end-diastolic diameter at 4% enflurane in the heart-lung preparations was almost exactly the same as in the control intact.

Similar results were obtained with heart rate held constant in these experiments and also if the surgical

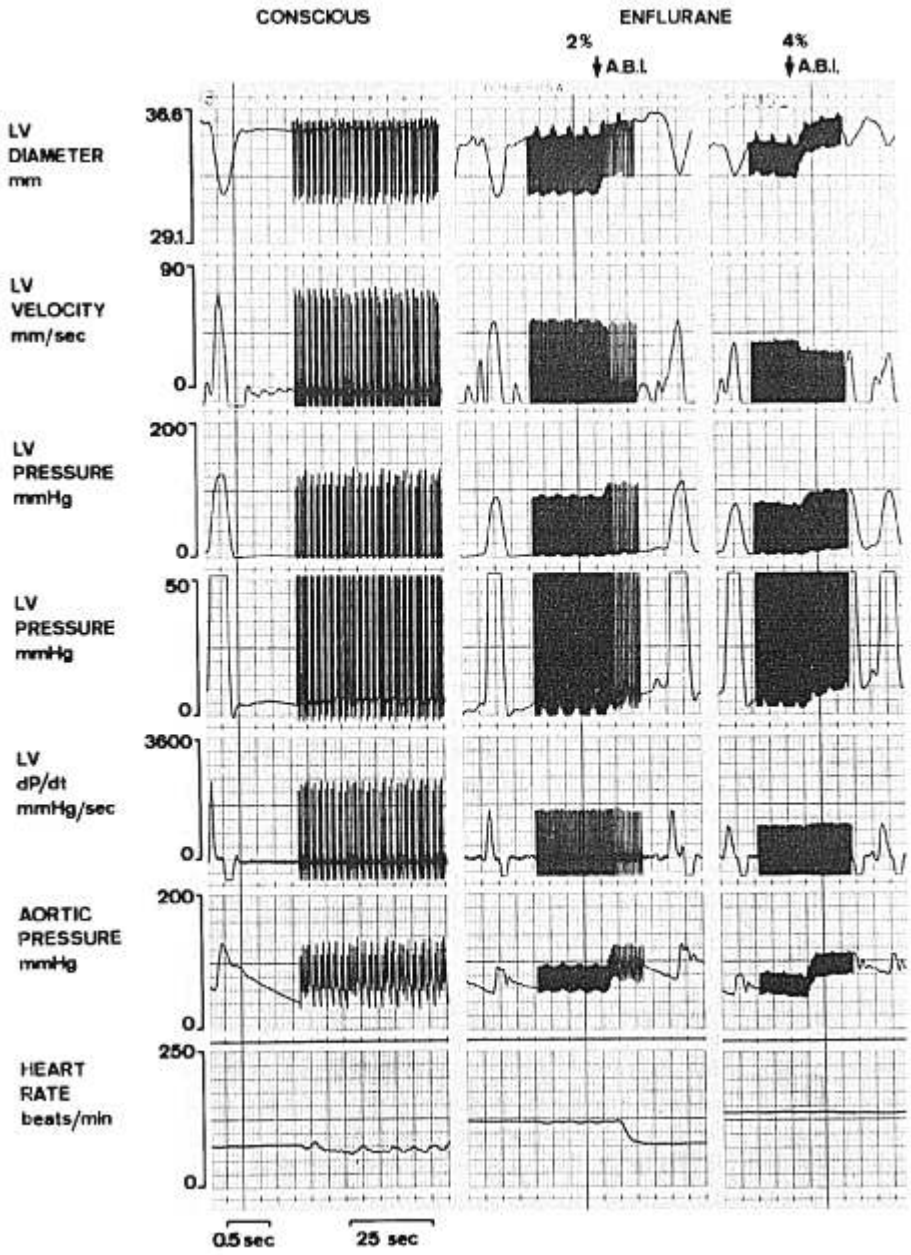

FIG. 4. Recordings of LV diameter, dD/dt, pressure, end-diastolic pressure, dP/dt, and heart rate from an intact, chronically instrumented dog. With outflow pressure increased to control levels by aortic balloon inflation (A.B.I.) both LV end-diastolic pressure and LV end-diastolic diameter were increased by enflurane. Note that although LV end-diastolic pressure increased markedly with A.B.I., the LV end-diastolic diameter rose only slightly from the conscious control. The absence of changes in heart rate during 4% enflurane and A.B.I. points towards a striking depression of the arterial baroreceptor reflex at this concentration.

preparation was performed in enflurane–nitrous-oxide–oxygen anesthesia instead of the morphine–piritramide–nitrous-oxide–oxygen anesthesia. In these latter experiments LV end-diastolic pressure and diameter were increased by an average of 105% and 15% with 2% enflurane, and by 410% and 25% with 4% enflurane.

Discussion

It is well-recognized that measurements of cardiac output alone are of limited value in characterizing the contractile performance of the heart.[18] However, as a result of the inherent difficulties in obtaining precise and reproductible measurements of LV dimensions in the *in vivo* mammalian heart, the vast majority of studies concerned with the hemodynamic effects of volatile anesthetics in both intact experimental animals and humans have been limited to periodic measurements of cardiac output and its derived variables.

The principal finding of this investigation is that, although enflurane impairs LV systolic performance of the normal dog, the LV diastolic performance seems to be well-maintained, *i.e.*, even with the higher concentration there was only a moderate increase in LV end-diastolic pressure with no increase in LV end-diastolic diameter. In fact, with 2% enflurane, even a decrease

TABLE 5. Baseline Values in the Isolated Heart-lung Preparations (n = 6)

Heart rate (beats/min)	107.5 ± 20.5*
Mean aortic pressure (mmHg)	118.8 ± 3.2†
LV systolic pressure (mmHg)	128.8 ± 4.7
LV end-diastolic pressure (mmHg)	6.5 ± 0.7†
LV end-diastolic diameter (mm)	31.6 ± 3.9†
LV end-systolic diameter (mm)	27.7 ± 3.8
LV stroke shortening (mm)	3.9 ± 0.2†
LV dP/dt (mmHg/s)	2,825 ± 463
LV dD/dt_{max} (mm/s)	69.6 ± 27.2

Significantly different from intact, conscious spontaneous rhythm, no block: * $P < 0.05$; † $P < 0.01$.

in LV end-diastolic diameter occurred along with a decrease in LV end-diastolic pressure. This point is of potential benefit for patients with ischemic heart disease as, according to Laplace's law, the average circumferential wall stress is related directly to the internal radius of the left ventricle. The tension within the left ventricular wall has not only been recognized for years to be one of the primary determinants of myocardial oxygen consumption,[19] but also is known to determine the extravascular restrictive force on myocardial blood flow.[20] In this connection, it is of interest that recently, in an investigation in open-chest anesthetized dogs, Lowenstein *et al.*[21] reported that halothane increases LV end-diastolic myocardial fiber length and LV end-diastolic pressure, and causes localized myocardial dysfunction, including paradoxical motion in an area supplied by an acute critically narrowed coronary artery.

It is important to note that by using more indirect techniques in healthy volunteers, *i.e.*, transthoracic M-mode echocardiography, Rathod *et al.*[5] reported decreased end-diastolic dimensions following induction of anesthesia with enflurane. However, presumably due to the short equilibration period allowed and the low anesthetic concentrations used, the authors failed to detect a decrease in myocardial fiber shortening and concluded that the LV function is well-maintained with enflurane. By contrast, as has been shown previously in intact, chronically instrumented dogs,[9] enflurane in the present study led to a progressive, dose-dependent decrease in myocardial contractility. The most striking differences noted were those for LV fiber shortening, the maximum velocity of LV fiber shortening (dD/dt_{max}), and the maximum rise of LV pressure (dP/dt_{max}). Considering that the end-systolic volume is largely independent of changes in preload and is determined by and varies directly with afterload and inversely with the inotropic state,[22] the increase in end-systolic diameter with the high concentration in the face of arterial hypotension gives further evidence of the striking myocardial depressant action of enflurane.

In order to evaluate the effects of anesthetic agents on cardiac function, it becomes necessary to critically discriminate between changes in both the contractile performance which can be attributed to alterations in myocardial fiber length and those induced by direct effects on the heart, *i.e.*, the intrinsic contractility. Therefore, experiments also were conducted with heart rate held constant because it was suspected that the enflurane-induced tachycardia could partly mask some of its direct, negative inotropic effects due to the Bowditch-

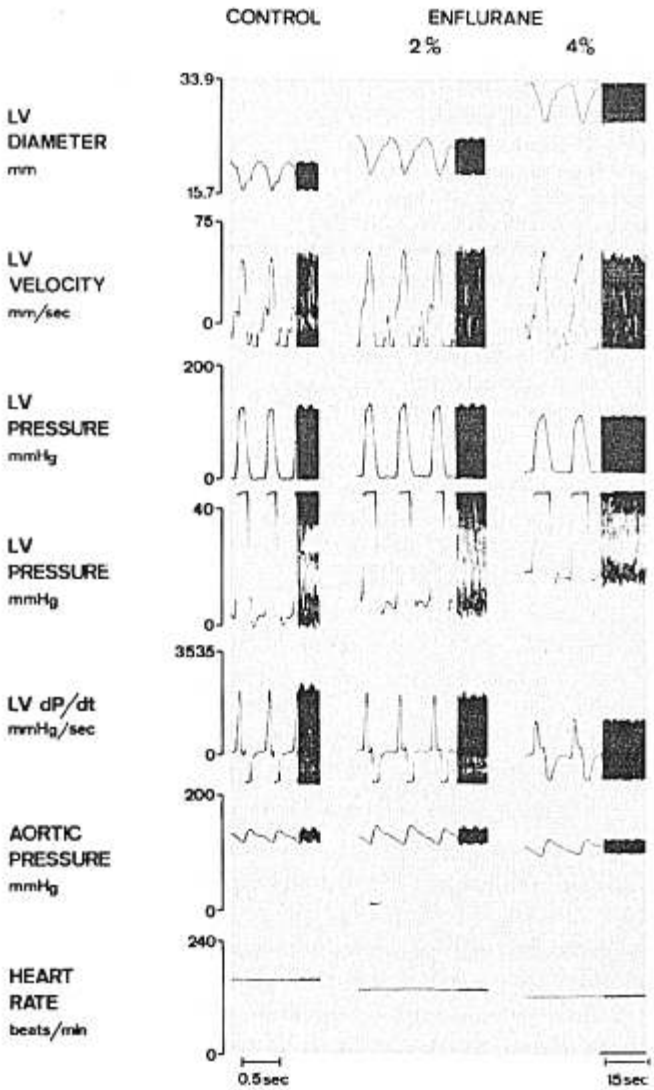

FIG. 5. Effects of enflurane in an isolated heart-lung preparation in which LV diameter, dD/dt, LV pressure, dP/dt, aortic pressure, and heart rate were measured. In contrast to results in intact dogs with LV systolic unloading, LV end-diastolic pressure and LV end-diastolic diameter were increased considerably with both concentrations studied. Note that although the experiment was performed with "constant afterload" it was not possible to maintain LV systolic pressure and mean aortic pressure at control levels during the administration of 4% enflurane.

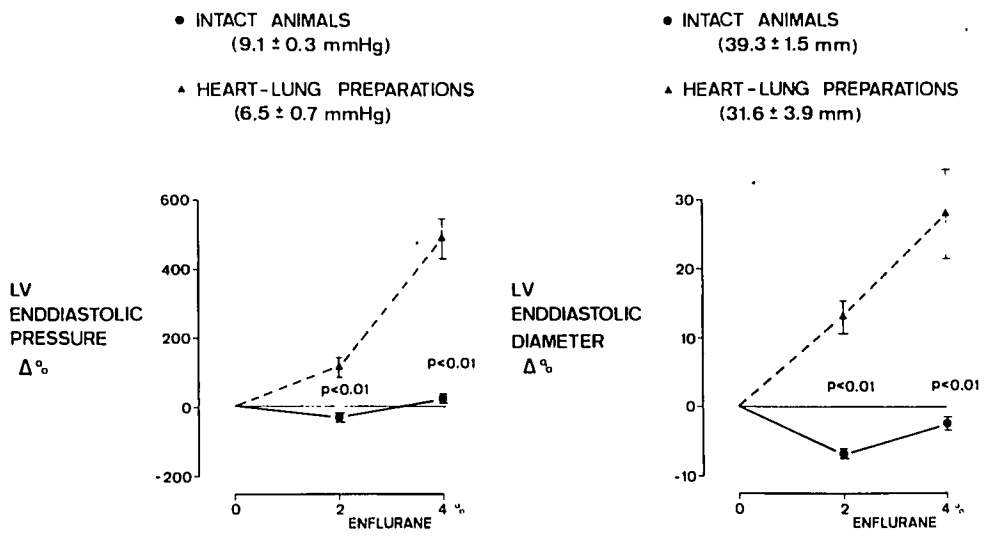

FIG. 6. Comparison of the effects of enflurane on the LV pressure-dimension relation in intact, chronically instrumented dogs (n = 8) and after isolation of the hearts and lungs from the systemic circulation (n = 6). The occurrence of acute LV failure in the isolated heart-lung preparations clearly demonstrates the importance of LV-systolic unloading to preserve myocardial pump performance with increasing concentrations of enflurane.

mechanism. However, enflurane under these conditions elicited similar changes in LV dynamics, *i.e.*, LV internal dimensions failed to increase with either of the concentrations studied while LV end-diastolic pressure increased only slightly with the higher concentration.

It has been demonstrated that volatile anesthetics dramatically depress the autonomic control of the cardiovascular system.[12,13] However, it is possible that a reflex, positive inotropic effect mediated through either high or low pressure baroreceptors could attenuate the direct effects of enflurane on myocardial contractility. This is unlikely since experiments after either beta-adrenergic blockade alone or after combined beta-adrenergic and cholinergic blockades failed to significantly alter the changes in LV function with enflurane, except for the lesser increase in heart rate in the latter experiments. However, this difference was due to a great extent to the abnormally high baseline values for heart rate in the presence of atropine. These findings are at variance with those obtained by Horan *et al.*[23] who pointed out that the combination of propranolol and enflurane causes striking cardiovascular dysfunction and arterial hypotension in both acutely and chronically instrumented dogs. Although we are not able to provide a conclusive explanation for this disparity, it might be speculated that in the study of Horan *et al.*, propranolol was given under conditions of enhanced sympathetic tone due to associated environmental or surgical stress. In this connection, two important differences between this investigation and that of Horan *et al.* deserve mention. The first is that, as one common carotid artery was tied, most of the latter experiments were conducted with unilateral carotid baroreceptor unloading. Secondly, the values reported for arterial blood pressure under 1 MAC enflurane were surprisingly high, *i.e.*, they were almost exactly at the same level as the conscious control of the present experiments and those conducted by Merin *et al.*[9]

Concerning extrinsic effects on myocardial contractility, there is also a remote possibility that the institution of intermittent positive-pressure ventilation could impede venous return, lower preload, and thereby mask some of the myocardial depression from enflurane. However, also with spontaneous ventilation, the decrease in fiber shortening with 2% enflurane was associated with a small but significant reduction in LV end-diastolic pressure and in LV end-diastolic diameter. It is important to note that a pronounced respiratory depression during anesthesia could skew the results and cause an underestimation of the mechanical consequences of artificial ventilation since hypercarbia is known to induce reflex cardiovascular stimulation.[24] However, the arterial carbon dioxide concentration failed to change significantly with the concentrations studied in these experiments. The absence of significant changes in LV function after briefly disconnecting the animals from the respirator during 4% enflurane gives further evidence that mechanical ventilation *per se* plays only a moderate role in modulating the direct cardiac effects of enflurane.

The simultaneous changes in LV end-diastolic pressure and LV end-diastolic diameter with enflurane in the intact animals imply that the low dose increases LV compliance (dV/dP), and the high dose decreases LV compliance. However, the relationship between pressure and volume is curvilinear and concave upward towards the X-axis,[25] and no definite conclusions can be drawn from our present data, as we did not examine this problem in a rigorous fashion, *i.e.*, by constructing a family of LV compliance curves.

It has been reported that the cardiac response to increased aortic pressure depends mainly on the level of LV contractility.[26] The critical role played by the impedance to LV ejection in determining myocardial pump performance in the face of a depressed inotropic state became directly apparent by studying the effects of enflurane either in the animals intact with aortic balloon inflation or in the isolated heart-lung preparations. Enflurane under these conditions also caused striking impairment of the LV-diastolic performance as evidenced by the marked, dose-dependent increase in LV end-diastolic pressure in the intact animals, and in both LV end-diastolic pressure and LV end-diastolic diameter in the isolated heart-lung preparations. Regarding these latter differences, it is important to keep in mind that both LV end-diastolic pressure and LV end-diastolic diameter were depressed markedly during the control state in the isolated heart-lung preparations as compared with the control intact. It has been demonstrated previously that at the low initial heart rates with physiologic filling pressures existing in intact, conscious animals[27–30] and humans,[31] end-diastolic cardiac size is near maximal, and the left ventricle is operating near the inflection of the pressure-diameter curve. As a consequence, acute elevations in LV end-diastolic pressure cannot profoundly increase LV end-diastolic volume and, thereby, the strength of myocardial contraction. This concept is supported further by the present study in that 1) LV end-diastolic diameter at 4% enflurane in the isolated heart-lung preparations was almost exactly the same as in the intact control, and 2) that in spite of the depressant action of enflurane on myocardial contractility, it was not possible to increase LV end-diastolic dimensions significantly above control in the intact animals with aortic balloon inflation. It is, however, important to point out that the difference between the control values for LV end-diastolic diameter in the intact, conscious animals *versus* the isolated heart preparations is not only on the basis of heart rate. This is because of the artificially increased LV outflow resistance with the lower flow rates[14] and the depressed LV filling pressure in our isolated heart preparation. In this connection it seems noteworthy that the reduction of LV filling pressure after isolation of the hearts appears to be even more striking when the negative intrapleural pressure in the intact animals is considered. However, in the isolated hearts working on the flat portion of the pressure-diameter curve, the importance of LV systolic unloading to preserve myocardial performance might even have been underestimated, because the pronounced increase in LV end-diastolic dimensions should tend to sustain cardiac performance through the Frank-Starling's law. Furthermore, it was not possible to maintain outflow pressure at the control level with the high concentration and, as a consequence, the stress to the left ventricle in terms of afterload was not exactly the same throughout these experiments.

In order to study possible confounding influences of narcotic analgesics the effects of enflurane were studied again in two isolated heart-lung preparations which were performed without these agents. However, this modification had little effect on the response to enflurane. Thus, provided morphine and piritramide were present after isolation of the hearts and lungs from the systemic circulation, these compounds do not seem to contribute significantly to the action of enflurane in the isolated heart-lung preparations.

In conclusion, in intact, chronically instrumented dogs with controlled ventilation, enflurane elicits a striking, dose-dependent, negative, inotropic effect although with little impairment of the LV diastolic performance. Several conceivable mechanisms, including changes in heart rate, neural reflex buffering, and the mechanical consequences of artificial ventilation, were eliminated as possibly significant influences in determining the observed changes in LV function. LV systolic unloading appears to be mandatory in order to prevent acute heart failure from higher concentrations of enflurane. Finally, the data in this investigation do not support the concept that in the intact, healthy dog the combination of propranolol and enflurane causes much more deterioration in cardiac performance than enflurane alone.

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