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Desflurane and Isoflurane Exert Modest Beneficial Actions on Left Ventricular Diastolic Function during Myocardial Ischemia in Dogs

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Background: **Volatile anesthetics exert cardioprotective effects during myocardial ischemia. This investigation examined the regional systolic and diastolic mechanical responses to brief left anterior descending coronary artery (LAD) occlusion in the central ischemic zone and in remote normal myocardium in the conscious state and during desflurane and isoflurane anesthesia.**

Methods: **Eighteen experiments were performed in nine dogs chronically instrumented for measurement of aortic and left ventricular pressure, cardiac output, LAD coronary blood flow velocity, and LAD and left circumflex coronary artery subendocardial segment length. Regional myocardial contractility was evaluated with the slope of the preload recruitable stroke work relationship determined from a series of left ventricular pressure-segment length diagrams in the LAD and left circumflex coronary artery zones. Diastolic function was assessed with a time constant of isovolumic relaxation (τ), maximum segment lengthening velocity in LAD and left circumflex coronary artery regions, and regional chamber stiffness constants derived using monoexponential and three-element exponential curve fitting in each zone. On separate experimental days, hemodynamics and indices of regional functional were obtained in the conscious state and during 1.1 and 1.6 minimum alveolar concentration end-tidal desflurane or isoflurane before and during LAD occlusion.**

Results: **In conscious dogs, LAD occlusion abolished regional stroke work, increased chamber stiffness (monoexponential: 0.39 ± 0.04 during control to 1.34 ± 0.39 mm^{-1} during LAD occlusion), and decreased the rate of early ventricular filling in the ischemic zone. These changes were accompanied by increased contractility (slope: 103 ± 8 during control to 112 ± 7 mmHg during LAD occlusion), rapid filling rate (maximum segment lengthening velocity: 46 ± 5 during control to 55 ± 7 $mm \cdot s^{-1}$ during LAD occlusion), and chamber stiffness (monoexponential: 0.43 ± 0.05 during control to 1.14 ± 0.25 mm^{-1} during LAD occlusion) in the normal region. Increases in τ were also observed in the conscious state during the period of myocardial ischemia. Desflurane and isoflurane increased τ and decreased the slope and maximum segment lengthening velocity in a dose-related manner. Monoexponential and three-element exponential curve fitting were unchanged by the volatile anesthetics in the absence of ischemia. Myocardial contractility and rapid filling rate were enhanced in the nonischemic region during LAD occlusion in the presence of desflurane and isoflurane. In contrast to the findings in the conscious state, ischemia-induced increases in τ and chamber stiffness in the ischemic and normal zones were attenuated during anesthesia induced by desflurane and isoflurane.**

Conclusions: **The results indicate that increases in contractility of remote myocardium during brief regional ischemia were preserved in the presence of desflurane and isoflurane anesthesia. In addition, desflurane and isoflurane blunted ischemia-induced increases in τ and regional chamber stiffness in both the ischemic and nonischemic zones. These results demonstrate that the volatile anesthetics may exert important beneficial actions on left ventricular mechanics in the presence of severe abnormalities in systolic and diastolic function during ischemia. (Key words: Anesthetics, volatile: desflurane; isoflurane. Heart, diastole: chamber stiffness; diastolic left ventricular function; isovolumic relaxation; ventricular compliance. Heart, myocardial performance: left ventricular function; myocardial contractility; preload recruitable stroke work.)**

ABRUPT occlusion of a coronary artery causes nearly immediate alterations in regional systolic and diastolic function in the ischemic zone. Systolic segment lengthening, postsystolic shortening, and loss of effective segmental stroke work occur concomitantly with diastolic creep (increases in unstressed segment length), declines in early diastolic filling, and increased

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regional chamber stiffness.[1–10] These mechanical effects are accompanied by increases in total segment shortening, myocardial contractility and rapid ventricular filling rate and decreases in diastolic distensibility in the surrounding nonischemic myocardium.[5,10–16] Alterations in global isovolumic relaxation, left ventricular filling, and chamber compliance may also occur in response to acute interruption of coronary blood flow depending on the extent, intensity, and duration of the ischemic stimulus.[13,17,18]

The actions of volatile anesthetics on the mechanical consequences of acute myocardial ischemia have been inadequately studied. Several previous investigations from this[19] and other laboratories[20–30] have demonstrated that volatile anesthetics exert cardioprotective effects during myocardial ischemia and reperfusion. A variety of mechanisms have been postulated to account for the antiischemic actions of potent inhalational agents including improvement of myocardial oxygen supply-demand relationships caused by negative inotropic and lusitropic effects and favorable alterations in ventricular loading conditions, reduction of intracellular Ca^{2+} overload *via* declines in myocardial Ca^{2+} availability and reserve resulting from partial inhibition of Ca^{2+} channel activity,[31] and attenuation of the detrimental effects of oxygen-derived free radicals.[32] This investigation tested the hypothesis that desflurane and isoflurane do not exacerbate the functional responses to brief (2 min) occlusion of the left anterior descending coronary artery in the central ischemic zone and further, that these volatile anesthetics do not adversely alter systolic and diastolic mechanical compensation for this process in the remote nonischemic zone in chronically instrumented dogs.

Materials and Methods

All experimental procedures and protocols used 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* (DHEW [DHHS] publication no. [NIH] 85-23, revised 1985).

Surgical Implantation of Instruments

The methods used to surgically implant instruments for systemic and coronary hemodynamic monitoring have been described in detail elsewhere.[33–35] Under general anesthesia and aseptic conditions, a thoracotomy was performed in the left fifth intercostal space. Heparin-filled catheters were placed in the descending thoracic aorta for measurement of aortic blood pressure and the right atrium for fluid or drug administration. An ultrasonic flow probe (Transonics, Ithaca, NY) was positioned around the ascending thoracic aorta for measurement of relative cardiac output (minus coronary blood flow).[36] Two pairs of miniature ultrasonic segment length transducers (5 MHz) for measurement of changes in regional contractile function (percent segment shortening) were implanted within the left ventricular subendocardium in the perfusion territories of the left anterior descending (LAD) and the left circumflex coronary arteries (LCCA). A high-fidelity, miniature micromanometer (Model P7, Konigsberg Instruments, Pasadena, CA) was inserted in the left ventricular apex for measurement of continuous left ventricular pressure, the maximum rate of increase and decrease of left ventricular pressure ($+dP/dt_{max}$ and $-dP/dt_{min}$, respectively), and the rate of increase of left ventricular pressure at 50 mmHg ($+dP/dt_{50}$). A heparin-filled catheter was inserted in the left atrial appendage. The left ventricular micromanometer was cross-calibrated *in vivo* against pressures measured *via* arterial and left atrial catheters (Model P50 pressure transducer, Gould, Oxnard, CA).

A single-port, 16-gauge heparin-filled catheter was placed in the apex of the left thoracic cavity between the lung and the chest wall through the thoracotomy incision for subsequent measurement of continuous intrathoracic pressure. A 1.5–2-cm segment of the proximal LAD was isolated and a precalibrated Doppler ultrasonic flow transducer was placed around this vessel for measurement of diastolic coronary blood flow velocity. A miniature hydraulic vascular occluder (In Vivo Metric, Healdsburg, CA) was secured around the LAD distal to the flow transducer for subsequent production of acute coronary artery occlusion.[13] A hydraulic vascular occluder was also placed around the inferior vena cava for abrupt alteration of left ventricular preload. All instrumentation was 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 evacuated by a chest tube. Each dog was fitted with a jacket (Alice King Chatham, Los Angeles, CA) to prevent damage to the instruments and catheters, which were housed in an aluminum box within the jacket pocket.

After surgery, each dog was treated with analgesics as needed (Innovar-Vet [fentanyl and droperidol]; Pitman-Moore, Mundelein, IL). Antibiotic prophylaxis consisted of intramuscular cephalothin (40 $mg \cdot kg^{-1}$) and gentamicin (4.5 $mg \cdot kg^{-1}$). Dogs were allowed to recover for a minimum of 7 days before experimentation. Segment length signals in the LAD and LCCA regions and LAD coronary blood flow velocity were driven and monitored by ultrasonic amplifiers (Crystal Biotech, Hopkinton, MA). End-systolic segment length (ESL) was determined at 10 ms before maximum negative left ventricular dP/dt and end-diastolic segment length (EDL) was determined 10 ms before dP/dt first exceeded 140 $mmHg \cdot s^{-1}$ (immediately before the onset of left ventricular isovolumic contraction).[37] The lengths were normalized according to the method described by Theroux *et al.*[2] Percent segment shortening (% SS) was calculated using the formula: % SS = (EDL − ESL) · 100 · EDL^{-1}. Percent segment shortening during isovolumic contraction (% ISS) and left ventricular ejection (% ESS) in the nonischemic region were calculated using the equations: % ISS = (EDL − EIL) · 100 · EDL^{-1} and % ESS = (EIL − ESL) · 100 · EDL^{-1}, where EIL = end-isovolumic contraction segment length determined at the time when left ventricular pressure exceeded aortic pressure during early systole.[11,14] Systolic lengthening (% SL) and postsystolic shortening (% PSS) in the ischemic zone were calculated using the equations: % SL = (L_{max} − EDL) · 100 · EDL^{-1}, where L_{max} = maximum segment length, and % PSS = (L_{min} − end-systolic segment length) · 100; end-systolic segment $length^{-1}$, where L_{min} = minimum segment length, respectively.[38] An estimate of myocardial oxygen consumption, the pressure work index, was determined using the formula of Rooke and Feigl.[39] Relative diastolic coronary vascular resistance was calculated as the ratio of diastolic arterial pressure to diastolic coronary blood flow velocity. All hemodynamic data were continuously monitored on a polygraph (model 7758A; Hewlett-Packard, San Francisco, CA) and digitized *via* a computer interfaced with an analog to digital converter.

Experimental Protocol

Dogs (N = 9; weight = 25.7 ± 0. 3 kg; mean ± SEM) were randomly assigned to receive desflurane or isoflurane on separate experimental days. Each dog was fasted overnight, and fluid deficits were replaced before experimentation with 500 ml normal saline, which was continued at 3 $ml \cdot kg^{-1} \cdot h^{-1}$ for the duration of each experiment. After the instrumentation was calibrated, baseline systemic and coronary hemodynamics were recorded in the conscious state. Left ventricular pressure, intrathoracic pressure, and LAD and LCCA segment length waveforms were recorded continuously on the digital oscilloscope for later off-line analysis of diastolic function. Regional myocardial contractility was evaluated using two series of left ventricular pressure-segment length diagrams in the LAD and LCCA zones generated by abrupt constriction of the inferior vena cava, resulting in a reduction of left ventricular systolic pressure by approximately 30 mmHg over 10–15 cardiac cycles (fig. 1).[40,41] Left ventricular pressure-segment length diagrams were rejected if heart rate increased more than 10% above baseline levels during the occlusion. In this case, pressure-length diagrams were repeated after steady-state hemodynamics had been reestablished. Respiratory variation in left ventricular pressure in the conscious state was later reduced off-line by electronically subtracting the continuous intrathoracic pressure waveform from the left ventricular pressure waveform as previously described.[41] The resultant left ventricular transmural pressure-segment length diagrams were used to assess contractile state in conscious dogs in two regions of the heart. The inferior vena caval occlusion was released immediately after recording pressure-length diagrams. During desflurane and isoflurane anesthesia, hemodynamic waveforms and left ventricular pressure-segment length diagrams were recorded in the LAD and LCCA regions at end expiration.

After obtaining data under control conditions, the LAD was acutely occluded using the chronically implanted miniature hydraulic vascular occluder. The left ventricular pressure-segment length diagram in the ischemic region rapidly developed characteristic loss of effective stroke work, dyskinetic systolic lengthening, postsystolic shortening, and diastolic creep (fig. 2). Systemic and coronary hemodynamics and pressure-length waveforms and diagrams were recorded after 2 min of LAD occlusion in the conscious state. Myocardial contractility in the LAD region was not evaluated during acute LAD occlusion because no stroke work was performed by this segment during ischemia. After data had been recorded, the LAD zone was reperfused by releasing the hydraulic occluder. Rapid recovery of regional systolic and diastolic function to preocclusion values occurred in all experiments.

All dogs underwent inhalation induction with desflurane or isoflurane in oxygen followed by tracheal

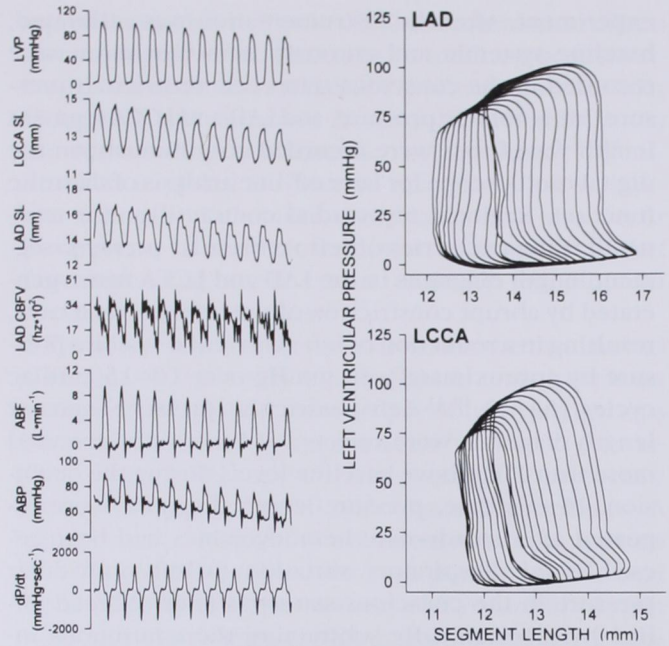

Fig. 1. Continuous left ventricular pressure, left circumflex coronary artery segment length (LCCA SL), left anterior descending coronary artery segment length (LAD SL), left anterior descending coronary blood flow velocity (LAD CBFV), aortic blood flow (ABF), aortic blood pressure (ABP), and the rate of change of left ventricular pressure (dP/dt) wave forms (left) and corresponding LAD and LCCA left ventricular pressure-segment length diagrams (right top and bottom, respectively) resulting from abrupt occlusion of the inferior vena cava in a typical experiment under control conditions (LAD patent).

intubation. Anesthesia was maintained with 1.1 and 1.6 minimum alveolar concentration (MAC) end-tidal desflurane or isoflurane in a random manner in a nitrogen (79%) and oxygen (21%) mixture. End-tidal anesthetic concentrations of desflurane and isoflurane were measured at the tip of the endotracheal tube by an infrared anesthetic analyzer (Datex Capnomac, Helsinki, Finland) calibrated for detection of desflurane. The infrared analyzer was calibrated with known standards before and during experimentation. The canine MAC values for desflurane and isoflurane used in this investigation were 7.2[42] and 1.28%, respectively. Each MAC level was maintained for 30 min. Systemic and coronary hemodynamics were then recorded and left ventricular pressure-segment length wave forms and diagrams were acquired in the manner described earlier before and during LAD occlusion. 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 2 days before subsequent experimentation. A total of 18 experiments in two separate groups (desflurane and isoflurane) were performed in which the same 9 dogs were studied.

Calculation of Indices of Systolic and Diastolic Left Ventricular Function

The slope (M_w) of the regional preload recruitable stroke work relationship was used to determine myocardial contractility in the LAD and the LCCA regions as previously described.[40,41] Briefly, in the conscious state and during anesthetic interventions, left ventricular pressure-segment length diagrams were obtained in the LAD and LCCA regions by transient constriction of the inferior vena cava. The area of each diagram, corresponding to segmental stroke work, was calculated by electronic integration and was plotted against the corresponding EDL for each loop. Linear regression analysis was used to describe the preload recruitable stroke work relationship slope (M_w) and length intercept (L_w): stroke work = $M_w \cdot (EDL - L_w)$. During acute LAD occlusion, no effective regional stroke work was performed in this region (fig. 2) and the preload recruitable stroke work relationship was not calculated. The time constant of isovolumic relaxation (τ) was described assuming a non-zero asymptote of ventricular pressure decay using the method of Raff and Glantz.[43] Left ventricular negative dP/dt was plotted against ventricular pressure in 2-ms intervals between peak negative dP/dt and 5 mmHg above end-diastolic pressure to yield τ as the negative inverse of the slope.[43] Maximum segment lengthening velocity during rapid ventricular filling (dL/dt_{max}) was determined by differentiation of the continuous segment length waveform.[44] Regional chamber stiffness constants were derived in each region by a simple monoexponential equation (K_p) and a three-element exponential relation (K_s) using left ventricular pressure-segment length data between minimum ventricular pressure and the beginning of atrial systole: $P = D \cdot e^{(Kp \cdot L)}$ and $P = A \cdot e^{(Ks \cdot L)} + C$, respectively, where P = left ventricular pressure, K_p and K_s = regional diastolic chamber stiffness constants, L = segment length, and A, C, and D are curve fitting constants. Best-fit iterations were used to determine K_s *via* the Marquardt-Levenberg algorithm with commer-

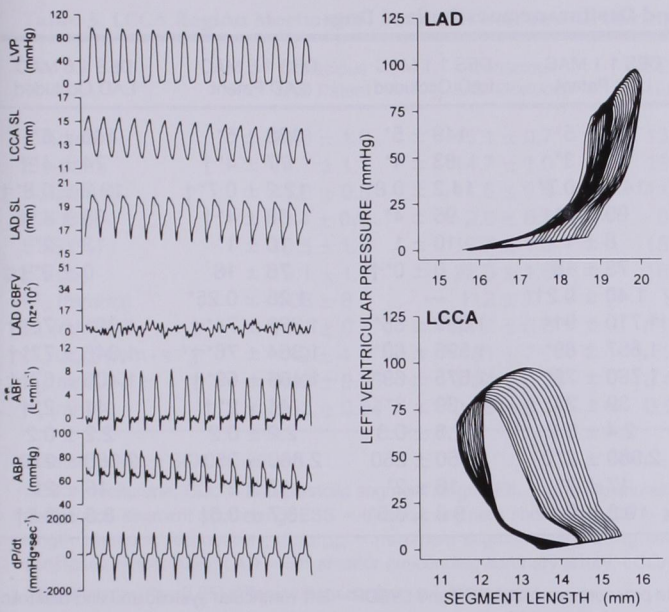

Fig. 2. Continuous left ventricular pressure, left circumflex coronary artery segment length (LCCA SL), left anterior descending coronary artery segment length (LAD SL), left anterior descending coronary blood flow velocity (LAD CBFV), aortic blood flow (ABF), aortic blood pressure (ABP), and the rate of change of left ventricular pressure (dP/dt) wave forms (left) and corresponding LAD and LCCA left ventricular pressure-segment length diagrams (right top and bottom, respectively) resulting from abrupt occlusion of the inferior vena cava in a typical experiment during LAD occlusion. Aneurysmal systolic lengthening, postsystolic shortening, loss of effective stroke work, and diastolic creep occurs in the LAD left ventricular pressure-segment length diagram in response to ischemia in this region. Corresponding isovolumic contraction shortening and early diastolic lengthening in the LCCA left ventricular pressure-segment length diagram also occurs as the contraction and relaxation of nonischemic zone myocardium compensates for the adjacent dyskinetic ischemic region.

cially available software (SigmaPlot version 2.0, Jandel, San Rafael, CA).

Statistical Analysis

Statistical analysis of data within and between groups in the conscious state, during anesthetic interventions, and during brief LAD occlusion was performed with multiple analysis of variance repeated measures followed by application of Student's *t* test with Bonferroni's correction for multiplicity.[45] Changes within and between groups were considered statistically significant when the *P* value was <0.05. All data are expressed as mean ± SEM.

Results

Brief, 2-min occlusion of the LAD caused significant ($P < 0.05$) increases in heart rate, rate-pressure product, pressure-work index, and left ventricular end-diastolic pressure in conscious dogs (table 1). No change in mean arterial pressure, left ventricular systolic pressure, cardiac output, and systemic vascular resistance occurred. End-systolic and end-diastolic segment length increased and percent segment shortening was abolished in the ischemic zone during brief LAD occlusion (table 2). Systolic lengthening and postsystolic shortening also increased in response to brief ischemia (systolic lengthening and postsystolic shortening = 0.1 ± 0.1 and 0.2 ± 0.2 during control to 4.8 ± 0.6 and 11.9 ± 0.7% during LAD occlusion, respectively). Significant increases in end-diastolic segment length and the length intercept of the preload recruitable stroke work relationship (L_w; 12.1 ± 0.8 during control to 13.6 ± 0.7 mm during LAD occlusion; table 3) in the nonischemic region were also observed during LAD occlusion, suggesting that preload was enhanced in the LCCA segment. Brief LAD occlusion increased total percent segment shortening and percent segment shortening during isovolumic contraction in the LCCA perfusion territory, however, percent segment shortening during left ventricular ejection was unchanged, implying that the regional contribution to left ventricular ejection by the nonischemic zone was unaffected by coronary occlusion and that a fraction of augmented total segment shortening was wasted on expansion of the adjacent ischemic zone during isovolumic contraction. The slope of the preload recruitable stroke work relationship in the nonischemic region increased in response to LAD occlusion (M_w; 103 ± 8 during control to 112 ± 7 mmHg during LAD occlusion; table 3), indicating enhanced contractility in the LCCA zone. No changes in left ventricular $+dP/dt_{max}$ and $+dP/dt_{50}$ were observed during coronary artery occlusion, suggesting that global myocardial contractility was unaffected by the brief LAD occlusion (table 1). However, these isovolumic indices of myocardial contractility are relatively insensitive to regional changes in contractile function.

Alterations in diastolic function also occurred during LAD occlusion. An increase in the time constant of isovolumic relaxation was observed during coronary artery occlusion (τ; 35 ± 1 during control to 38 ± 1 ms during LAD occlusion), consistent with modest prolongation of this phase of diastole (table 1). No change in $-dP/$

Table 1. Hemodynamic Effects of LAD Occlusion in Conscious and Desflurane-anesthetized Dogs

	N	Conscious LAD Patent	Conscious LAD Occluded	DES 1.1 MAC LAD Patent	DES 1.1 MAC LAD Occluded	DES 1.6 MAC LAD Patent	DES 1.6 MAC LAD Occluded
HR (beats/min)	9	82 ± 4	118 ± 6*	144 ± 5*	149 ± 5*	138 ± 5*	140 ± 5*
MBP (mmHg)	9	99 ± 3	96 ± 3	86 ± 3*	83 ± 4*	77 ± 4*†	74 ± 4*†
RPP (mmHg · bpm · 10^3)	9	9.7 ± 0.5	13.4 ± 1.0*	14.3 ± 0.7*	14.2 ± 0.8*	12.2 ± 0.7*†	12.2 ± 0.8*†
LVSP (mmHg)	9	120 ± 3	113 ± 2	99 ± 3*	95 ± 4*	88 ± 4*†	86 ± 4*†
LVEDP (mmHg)	9	8 ± 1	11 ± 1*	8 ± 1	10 ± 1	10 ± 1*	13 ± 2*
DCBFV (Hz · 10^2)	8	59 ± 11	0 ± 0*	73 ± 18	0 ± 0*†	76 ± 18	0 ± 0*†‡
DCVR (mmHg · Hz^{-1} · 10^{-2})	8	1.77 ± 0.22	—	1.40 ± 0.21	—	1.26 ± 0.25*	—
$+dP/dt_{max}$ (mmHg · s^{-1})	9	2,226 ± 139	2,188 ± 143	1,710 ± 91*	1,699 ± 85*	1,392 ± 74*†	1,391 ± 78*†
$+dP/dt_{50}$ (mmHg · s^{-1})	9	2,004 ± 118	1,916 ± 121	1,657 ± 89*	1,595 ± 80*	1,364 ± 76*†	1,346 ± 77*†
$-dP/dt_{min}$ (mmHg · s^{-1})	9	−2,440 ± 65	−2,209 ± 92	−1,780 ± 79*	−1,675 ± 69*	−1,466 ± 69*†	−1,406 ± 67*†
τ (ms)	9	35 ± 1	38 ± 1*	39 ± 2*	39 ± 2*	44 ± 2*†	44 ± 2*†
CO (L · min^{-1})	8	2.5 ± 0.1	2.4 ± 0.1	2.4 ± 0.2	2.3 ± 0.3	2.2 ± 0.2	2.2 ± 0.2
SVR (dynes · s · cm^{-5})	8	3,240 ± 210	3,120 ± 180	2,980 ± 270	2,950 ± 260	2,860 ± 250	2,860 ± 270
SV (ml)	8	31 ± 2	22 ± 1*	17 ± 2*	16 ± 2*	17 ± 2*	16 ± 2*
PWI (ml · min^{-1} · 100 g^{-1})	8	8.6 ± 0.2	9.9 ± 0.4*	10.0 ± 0.4*	9.8 ± 0.5*	8.7 ± 0.5†	8.5 ± 0.5†

Data are mean ± SEM.

DES = desflurane; HR = heart rate; MBP = mean aortic blood pressure; RPP = rate pressure product; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; DCBFV = LAD diastolic coronary blood flow velocity; DCVR = calculated LAD diastolic coronary vascular resistance; τ = time constant of isovolumic relaxation; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; PWI = pressure work index; LAD = left anterior descending coronary artery.

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

† Significantly ($P < 0.05$) different from DES 1.1 MAC LAD patent.

‡ Significantly ($P < 0.05$) different from DES 1.6 MAC LAD patent.

Table 2. LAD Region Mechanical Function before and during LAD Occlusion in Conscious and Desflurane-anesthetized Dogs

	Conscious LAD Patent	Conscious LAD Occluded	DES 1.1 MAC LAD Patent	DES 1.1 MAC LAD Occluded	DES 1.6 MAC LAD Patent	DES 1.6 MAC LAD Occluded
EDL (mm)	16.5 ± 0.8	17.4 ± 0.9*	15.4 ± 0.8*	16.8 ± 0.9*†	16.2 ± 0.8	17.4 ± 0.9†‡
ESL (mm)	12.8 ± 0.7	17.6 ± 1.0*	13.2 ± 0.8	17.7 ± 1.0*†	14.4 ± 0.9*	18.1 ± 1*†‡
L_{max} (mm)	16.5 ± 0.8	18.1 ± 1.0*	15.4 ± 0.8*	18.0 ± 1.0*†	16.2 ± 0.8	18.2 ± 1.0*†‡
L_{min} (mm)	12.7 ± 0.2	15.5 ± 0.9*	13.0 ± 0.8	15.3 ± 0.7*†	14.3 ± 0.8*	16.0 ± 0.8*†‡
SS (%)	22.4 ± 1.8	−1.3 ± 0.8*	14.6 ± 2.1*	−5.0 ± 1.3*†	11.0 ± 2.0*†	−3.7 ± 0.9*†‡
SL (%)	0.1 ± 0.1	4.8 ± 0.6*	0.3 ± 0.2	5.7 ± 0.7*†	0.2 ± 0.1	4.9 ± 7*†‡
PSS (%)	0.2 ± 0.2	11.9 ± 0.7*	0.4 ± 0.3	13.2 ± 1.1*†	0.4 ± 0.3	11.0 ± 0.9*†‡
M_w (mmHg)	94 ± 6	—	68 ± 5*	—	52 ± 4*†	—
L_w (mm)	12.1 ± 0.8	—	12.8 ± 0.6	—	13.6 ± 0.7*	—
dL/dt_{max} (mm · s^{-1})	52 ± 8	36 ± 6*	40 ± 5*	28 ± 4*†	36 ± 5*	22 ± 3*†‡
K_p (mm^{-1})	0.39 ± 0.04	1.34 ± 0.39*	0.35 ± 0.04	0.57 ± 0.12	0.39 ± 0.06	0.77 ± 0.14‡
K_s (mm^{-1})	0.50 ± 0.03	0.77 ± 0.07*	0.41 ± 0.04	0.60 ± 0.12†	0.44 ± 0.05	0.60 ± 0.09

Data are mean ± SEM; n = 9.

DES = desflurane; EDL = end-diastolic segment length; ESL = end-systolic segment length; L_{max} and L_{min} = maximum and minimum segment length, respectively; SS = segment shortening; SL = systolic lengthening; PSS = post systolic shortening; M_w and L_w = LAD preload recruitable stroke work slope and length intercept, respectively; dL/dt_{max} = maximum segment lengthening velocity; K_p and K_s = monoexponential and three-element regional chamber stiffness constants, respectively; LAD = left anterior descending coronary artery.

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

† Significantly ($P < 0.05$) different from DES 1.1 MAC LAD patent.

‡ Significantly ($P < 0.05$) different from DES 1.6 MAC LAD patent.

Table 3. LCCA Region Mechanical Function before and during LAD Occlusion in Conscious and Desflurane-anesthetized Dogs

	Conscious LAD Patent	Conscious LAD Occluded	DES 1.1 MAC LAD Patent	DES 1.1 MAC LAD Occluded	DES 1.6 MAC LAD Patent	DES 1.6 MAC LAD Occluded
EDL (mm)	14.6 ± 1.0	15.1 ± 0.7*	13.5 ± 0.8*	14.3 ± 0.9†	14.1 ± 0.9	14.6 ± 0.9†‡
EIL (mm)	14.7 ± 1.1	14.7 ± 1.0	13.3 ± 0.8*	13.7 ± 0.8*	14.0 ± 0.9*	14.1 ± 0.9†
ESL (mm)	11.8 ± 0.8	11.6 ± 0.6	11.2 ± 0.5	11.3 ± 0.5	12.0 ± 0.6	12.0 ± 0.5
ISS (%)	−0.4 ± 0.9	2.6 ± 0.5*	0.6 ± 0.3	3.7 ± 0.6*†	1.0 ± 0.5	3.2 ± 0.6*†‡
ESS (%)	19.5 ± 1.2	19.7 ± 1.5	15.5 ± 2.1*	16.3 ± 2.1*	13.5 ± 1.9*	13.7 ± 1.8*†
SS (%)	19.1 ± 1.1	22.3 ± 1.5*	16.1 ± 2.3*	20.0 ± 2.5*†	14.4 ± 2.0*†	16.9 ± 1.9*†
M_w (mmHg)	103 ± 8	112 ± 7*	85 ± 7*	94 ± 8*	64 ± 4*†	80 ± 6*‡
L_w (mm)	11.1 ± 0.7	11.7 ± 0.8	11.1 ± 0.7	11.8 ± 0.7*†	11.5 ± 0.6	12.3 ± 0.7*†‡
dL/dt_{max} ($mm \cdot s^{-1}$)	42 ± 4	51 ± 7*	31 ± 3*	42 ± 6†	25 ± 3*	32 ± 5*‡
K_p (mm^{-1})	0.43 ± 0.05	1.14 ± 0.25*	0.46 ± 0.06	0.72 ± 0.19	0.54 ± 0.10	0.83 ± 0.26
K_s (mm^{-1})	0.51 ± 0.04	0.86 ± 0.16*	0.52 ± 0.05	0.63 ± 0.06	0.49 ± 0.06	0.58 ± 0.03

Data are mean ± SEM; n = 9.

DES = desflurane; EDL = end-diastolic segment length; EIL = end-isovolumic contraction segment length; ESL = end-systolic segment length; ISS = isovolumic contraction segment shortening; ESS = ejection segment shortening; SS = segment shortening; M_w and L_w = LCCA preload recruitable stroke work slope and length intercept, respectively; dL/dt_{max} = maximum segment lengthening velocity; K_p and K_s = monoexponential and three-element regional chamber stiffness constants, respectively; LAD = left anterior descending coronary artery; LCCA = left circumflex coronary artery.

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

† Significantly ($P < 0.05$) different from DES 1.1 MAC LAD patent.

‡ Significantly ($P < 0.05$) different from DES 1.6 MAC LAD patent.

dt_{min} was observed, however. The rate of rapid ventricular filling was decreased in the ischemic zone (LAD dL/dt_{max}; 52 ± 8 during control to 36 ± 6 $mm \cdot s^{-1}$ during LAD occlusion; table 2) and enhanced in remote normal myocardium (LCCA dL/dt_{max}; 42 ± 4 during control to 51 ± 7 $mm \cdot s^{-1}$ during LAD occlusion; table 3). Significant increases in regional chamber diastolic stiffness constants (K_p and K_s) were observed in both the ischemic and the nonischemic zones during coronary artery occlusion (LAD and LCCA K_p: 0.39 ± 0.04 and 0.43 ± 0.05 during control to 1.34 ± 0.39 and 1.14 ± 0.25 mm^{-1} during LAD occlusion, respectively; tables 2 and 3), consistent with declines in segmental compliance.

The effects of desflurane and isoflurane on systemic and coronary hemodynamics are summarized in tables 1 and 4, respectively. The end-tidal anesthetic concentrations in the current investigation were 7.89 ± 0.10 and 11.50 ± 0.12% for desflurane and 1.41 ± 0.02 and 2.03 ± 0.03% for isoflurane. Desflurane caused significant increases in heart rate, rate-pressure product, pressure-work index, and left ventricular end-diastolic pressure and dose-related decreases in mean arterial pressure, left ventricular systolic pressure, and percent segment shortening in the LAD and LCCA regions before coronary artery occlusion. Decreases in stroke volume also occurred, but cardiac output and systemic vascular resistance were unchanged by desflurane. Diastolic coronary blood flow velocity remained constant and diastolic coronary vascular resistance was reduced at 1.6 MAC desflurane. Dose-dependent decreases in M_w in the both the LAD and LCCA perfusion territories, $+dP/dt_{max}$, and $+dP/dt_{50}$ occurred in desflurane-anesthetized dogs, and consistent with the known negative inotropic effects of this agent. Desflurane also produced dose-related negative lusitropic effects as indicated by increases in τ and decreases in dL/dt_{max} in the LAD and LCCA zones before LAD occlusion. Desflurane caused no changes in K_p or K_s.

Isoflurane caused systemic and coronary hemodynamics effects that were similar to those produced by desflurane (table 4). Isoflurane increased heart rate and decreased mean arterial pressure, left ventricular systolic pressure, diastolic coronary vascular resistance and percent segment shortening in the LAD and LCCA regions. Isoflurane-induced reductions in mean arterial pressure and left ventricular systolic pressure were significantly greater than those observed with desflurane at 1.6 MAC, however. In contrast to the findings with desflurane, isoflurane decreased pressure-work index at 1.6 MAC. Unlike desflurane, isoflurane decreased cardiac output and systemic vascular resistance. Isoflurane depressed myocardial contractility (M_w in the LAD and LCCA regions, $+dP/dt_{max}$ and $+dP/dt_{50}$), prolonged isovolumic relaxation (increased τ and decreased the magnitude of $-dP/dt_{min}$), and attenuated the early ven-

Table 4. Hemodynamic Effects of LAD Occlusion in Conscious and Isoflurane-anesthetized Dogs

	N	Conscious LAD Patent	Conscious LAD Occluded	ISO 1.1 MAC LAD Patent	ISO 1.1 MAC LAD Occluded	ISO 1.6 MAC LAD Patent	ISO 1.6 MAC LAD Occluded
HR (beats/min)	9	79 ± 5	120 ± 6*	127 ± 4*§	132 ± 4*§	123 ± 4*§	127 ± 4*§
MBP (mmHg)	9	94 ± 3	95 ± 3	76 ± 5*	73 ± 5*	65 ± 4*†§	63 ± 3*†§
RPP (mmHg · bpm · 10^3)	9	9.1 ± 0.7	13.4 ± 0.9*	11.2 ± 8*§	11.1 ± 0.8*§	9.6 ± 0.6†§	9.5 ± 0.5†§
LVSP (mmHg)	9	116 ± 2	115 ± 3	89 ± 4*	85 ± 4*	79 ± 4*†§	76 ± 3*†§
LVEDP (mmHg)	9	8 ± 0	12 ± 1*	7 ± 1	10 ± 1*	8 ± 1	11 ± 1
DCBFV (Hz · 10^2)	8	61 ± 14	0 ± 0*	69 ± 16	0 ± 0*†	66 ± 15	0 ± 0*†‡
DCVR (mmHg · Hz^{-1} · 10^{-2})	8	1.66 ± 0.23	—	1.26 ± 0.19	—	1.15 ± 0.22*	—
$+dP/dt_{max}$ (mmHg · s^{-1})	9	2,349 ± 177	2,237 ± 173	1,558 ± 124*	1,436 ± 110*	1,193 ± 105*†	1,187 ± 100*†
$+dP/dt_{50}$ (mmHg · s^{-1})	9	2,035 ± 129	1,917 ± 128	1,512 ± 114*	1,379 ± 94*	1,150 ± 112*†	1,150 ± 100*†
$-dP/dt_{min}$ (mmHg · s^{-1})	9	−2,192 ± 109	−2,169 ± 110	−1,555 ± 102*	−1,417 ± 91*	−1,275 ± 112*†	−1,223 ± 94*†
τ (ms)	9	36 ± 1	40 ± 1*	42 ± 3*	45 ± 3*	46 ± 3*†	46 ± 3*†
CO (L · min^{-1})	8	2.6 ± 0.1	2.4 ± 0.2	2.3 ± 0.1	2.2 ± 0.1*	2.0 ± 0.1*†	1.9 ± 0.1*†
SVR (dyne · s · cm^{-5})	8	2,990 ± 130	3,180 ± 180	2,690 ± 260	2,650 ± 190*	2,610 ± 160*	2,640 ± 140*
SV (ml)	8	33 ± 2	21 ± 2*	18 ± 1*	16 ± 1*	16 ± 1*	15 ± 1*
PWI (ml · min^{-1} · 100 g^{-1})	8	8.8 ± 0.4	10.1 ± 0.6*	8.4 ± 0.5§	8.1 ± 0.6§	7.1 ± 0.4*‡§	7.0 ± 0.4*‡§

Data are mean ± SEM.

ISO = isoflurane; HR = heart rate; MBP = mean aortic blood pressure; RPP = rate pressure product; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; DCBFV = LAD diastolic coronary blood flow velocity; DCVR = calculated LAD diastolic coronary vascular resistance; τ = time constant of isovolumic relaxation; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; PWI = pressure work index; LAD = left anterior descending coronary artery.

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

† Significantly ($P < 0.05$) different from ISO 1.1 MAC LAD patent.

‡ Significantly ($P < 0.05$) different from ISO 1.6 MAC LAD patent.

§ Significantly ($P < 0.05$) different from corresponding desflurane value (table 1).

tricular filling rate. Isoflurane caused no changes in K_p or K_s in the LAD and LCCA zones.

In the presence of desflurane and isoflurane, LAD occlusion caused increases in left ventricular end-diastolic pressure, end-systolic and end-diastolic segment lengths in the ischemic region (tables 2 and 5), and LCCA end-diastolic segment length (tables 3 and 6). The degree of ischemia resulting from a 2-min occlusion of the LAD was functionally similar in conscious and anesthetized dogs as quantified by the degree of changes in percent segment shortening, systolic lengthening, and postsystolic shortening. Significant increases in total percent segment shortening and percent segment shortening during isovolumic contraction were observed in the LCCA perfusion territory concomitant with negative segment shortening (aneurysmal bulging) in the ischemic zone (tables 3 and 6). However, percent segment shortening during left ventricular ejection in the nonischemic region remained unchanged by coronary occlusion in the presence of desflurane and isoflurane, findings that were similar to those observed in the conscious state. No changes in heart rate, mean arterial pressure, left ventricular systolic pressure, cardiac output, systemic vascular resistance, and stroke volume were observed during coronary artery occlusion in anesthetized dogs (tables 1 and 4). In contrast to findings in conscious dogs, brief LAD occlusion during anesthesia did not alter the rate-pressure product or the pressure-work index. Increases in LCCA M_w (*e.g.*, 64 ± 4 before coronary occlusion compared to 80 ± 6 mmHg during occlusion at 1.6 MAC desflurane) were also observed with brief ischemia in the presence of anesthesia, indicating that regional myocardial contractility was enhanced in the nonischemic zone. Relative increases in LCCA M_w in response to regional ischemia were similar in anesthetized *versus* conscious dogs (fig. 3). No change in $+dP/dt_{max}$ and $+dP/dt_{50}$ was observed with LAD occlusion, however, suggesting that global myocardial contractility was unaffected. In contrast to the findings in the conscious state, no change in τ was observed during LAD occlusion in dogs anesthetized with desflurane or isoflurane (fig. 3). The early ventricular filling rate decreased in the LAD zone (36 ± 5 before LAD occlusion compared to 22 ± 3 mm · s^{-1} during LAD occlusion at 1.6 MAC desflurane) and in-

Table 5. LAD Region Mechanical Function before and during LAD Occlusion in Conscious and Isoflurane-anesthetized Dogs

	Conscious LAD Patent	Conscious LAD Occluded	ISO 1.1 MAC LAD Patent	ISO 1.1 MAC LAD Occluded	ISO 1.6 MAC LAD Patent	ISO 1.6 MAC LAD Occluded
EDL (mm)	17.1 ± 0.8	18.0 ± 0.8*	15.6 ± 0.7*	17.1 ± 0.8*†	16.2 ± 0.8*	17.5 ± 0.8*†‡
ESL (mm)	13.0 ± 0.6	18.2 ± 0.9*	12.9 ± 0.6	17.8 ± 0.9*†	14.1 ± 0.7	18.1 ± 0.8*†‡
L_{max} (mm)	17.1 ± 0.8	18.7 ± 0.8*	15.6 ± 0.7*	18.2 ± 0.8*†	16.2 ± 0.7*	18.6 ± 0.8*†‡
L_{min} (mm)	12.9 ± 0.6	15.6 ± 0.9*	12.8 ± 0.6	15.6 ± 0.6*†	13.9 ± 0.6	16.1 ± 0.8*†
SS (%)	24.4 ± 1.8	−1.4 ± 0.8*	17.3 ± 2.0*	−3.8 ± 1.1*†	12.7 ± 2.3*†	−3.8 ± 1.1*†‡
SL (%)	0.1 ± 0.1	4.8 ± 1.1*	0.1 ± 0.1	6.3 ± 0.9*†	0.2 ± 0.2	5.2 ± 0.7*†‡
PSS (%)	0.2 ± 0.1	11.4 ± 1.2*	0.2 ± 0.2	11.8 ± 1.1*†	0.2 ± 0.1	11.3 ± 0.4*†‡
M_w (mmHg)	88 ± 6	—	60 ± 7*	—	43 ± 5*†	—
L_w (mm)	11.7 ± 0.7	—	12.3 ± 0.6	—	13.2 ± 0.8*	—
dL/dt_{max} ($mm \cdot s^{-1}$)	56 ± 7	33 ± 6*	40 ± 5*	26 ± 4*†	35 ± 5*	23 ± 4*†‡
K_o (mm^{-1})	0.39 ± 0.06	0.96 ± 0.11*	0.30 ± 0.03	0.50 ± 0.06†	0.33 ± 0.03	0.54 ± 0.06‡
K_s (mm^{-1})	0.54 ± 0.02	0.69 ± 0.04*	0.47 ± 0.03	0.53 ± 0.05	0.45 ± 0.04	0.54 ± 0.04

Data are mean ± SEM; n = 9.

ISO = isoflurane; EDL = end-diastolic segment length; ESL = end-systolic segment length; L_{max} and L_{min} = maximum and minimum segment length, respectively; SS = segment shortening; SL = systolic lengthening: PSS = post systolic shortening; M_w, and L_w = LAD preload recruitable stroke work slope and length intercept, respectively; dL/dt_{max} = maximum segment lengthening velocity; K_p and K_s = monoexponential and three-element regional chamber stiffness constants, respectively; LAD = left anterior descending coronary artery.

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

† Significantly ($P < 0.05$) different from ISO 1.1 MAC LAD patent.

‡ Significantly ($P < 0.05$) different from ISO 1.6 MAC LAD patent.

creased in the LCCA zone (25 ± 3 before LAD occlusion compared to 32 ± 5 $mm \cdot s^{-1}$ during LAD occlusion at 1.6 MAC desflurane) in response to regional ischemia, findings similar to those observed in the conscious state (fig. 4). However, increases in K_p (fig. 5) and K_s in the normal and ischemic zones produced by brief LAD occlusion were attenuated in desflurane- and isoflurane-anesthetized dogs compared to con-

Table 6. LCCA Region Mechanical Function before and during LAD Occlusion in Conscious and Isoflurane-anesthetized Dogs

	Conscious LAD Patent	Conscious LAD Occluded	ISO 1.1 MAC LAD Patent	ISO 1.1 MAC LAD Occluded	ISO 1.6 MAC LAD Patent	ISO 1.6 MAC LAD Occluded
EDL (mm)	14.6 ± 1.0	15.5 ± 1.0*	13.4 ± 0.8*	14.2 ± 0.9†	13.8 ± 0.9*	14.5 ± 0.9‡
EIL (mm)	14.7 ± 1.0	14.9 ± 1.0	13.3 ± 0.8*	13.5 ± 0.8*	13.6 ± 0.9*	13.9 ± 0.8*
ESL (mm)	11.4 ± 0.7	11.8 ± 0.7	11.1 ± 0.5	11.2 ± 0.5	11.7 ± 0.6	11.9 ± 0.6*
ISS (%)	−0.4 ± 1.0	3.6 ± 0.8*	0.8 ± 0.8	4.6 ± 0.9*†	0.7 ± 0.7	4.2 ± 0.7*†‡
ESS (%)	21.5 ± 1.9	19.5 ± 1.8	15.5 ± 1.7*	15.0 ± 1.5*	13.0 ± 2.0*†	13.5 ± 1.9*
SS (%)	21.1 ± 2.2	23.0 ± 2.0	16.4 ± 2.1*	19.7 ± 2.0†	13.8 ± 2.2*	17.7 ± 2.2‡
M_w (mmHg)	99 ± 9	113 ± 10*	67 ± 5*	80 ± 8*†	54 ± 8*†	66 ± 7*†‡
L_w (mm)	10.6 ± 0.8	11.7 ± 1.0*	10.5 ± 0.6	11.7 ± 0.8†	11.3 ± 0.8	12.0 ± 0.8‡
dL/dt_{max} ($mm \cdot s^{-1}$)	46 ± 5	55 ± 7*	32 ± 3*	38 ± 4	26 ± 2*†	33 ± 4*†
K_p (mm^{-1})	0.38 ± 0.02	0.74 ± 0.08*	0.39 ± 0.05	0.55 ± 0.11*†	0.45 ± 0.06	0.52 ± 0.08*
K_s (mm^{-1})	0.51 ± 0.05	0.76 ± 0.15*	0.51 ± 0.04	0.55 ± 0.04	0.54 ± 0.06	0.58 ± 0.05

Data are mean ± SEM; n = 9.

ISO = isoflurane; EDL = end-diastolic segment length; EIL = end-isovolumic contraction segment length; ESL = end-systolic segment length; ISS = isovolumic contraction segment shortening; ESS = ejection segment shortening; SS = segment shortening; M_w and L_w = LCCA preload recruitable stroke work slope and length intercept, respectively; dL/dt_{max} = maximum segment lengthening velocity; K_p and K_s = monoexponential and three-element regional chamber stiffness constants, respectively; LAD = left anterior descending coronary artery; LCCA = left circumflex coronary artery.

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

† Significantly ($P < 0.05$) different from ISO 1.1 MAC LAD patent.

‡ Significantly ($P < 0.05$) different from ISO 1.6 MAC LAD patent.

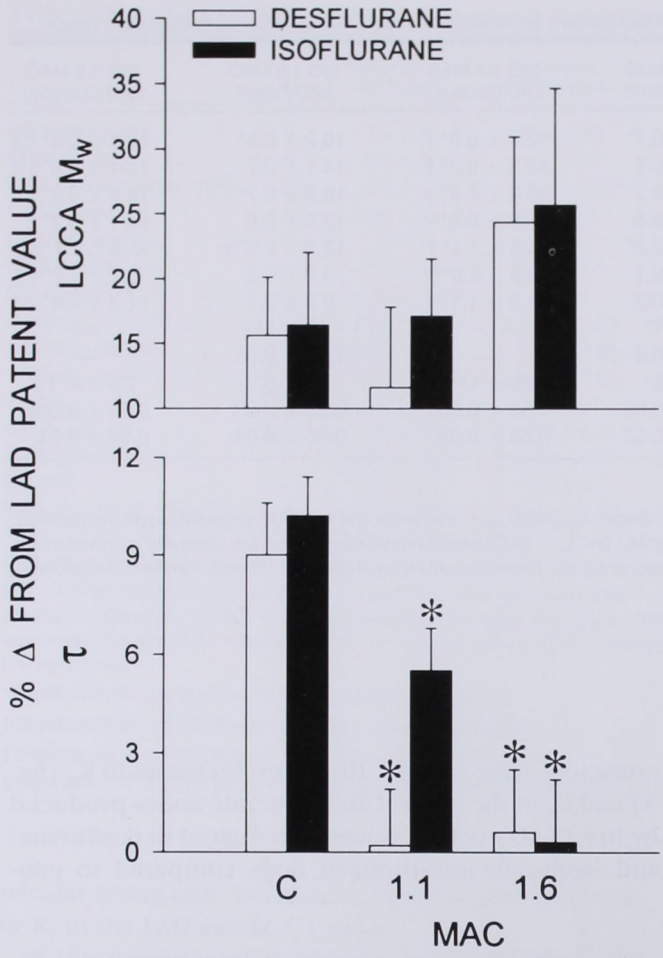

Fig. 3. Histograms illustrating the percent change (Δ) from the left anterior descending coronary artery (LAD) patent value in the slope of the left circumflex coronary artery (LCCA) preload recruitable stroke work relationship (M_w) and the time constant of isovolumic relaxation (τ) in conscious (C) and desflurane- and isoflurane-anesthetized dogs. *Significantly ($P < 0.05$) different from control.

scious control subjects. No differences in alterations of left ventricular systolic and diastolic function by ischemia were observed between the desflurane and isoflurane groups.

Discussion

Regional myocardial ischemia resulting from sudden coronary artery occlusion produces a series of characteristic systolic and diastolic mechanical effects in both the central ischemic zone and remote normal myocardium. Loss of effective stroke work, dyskinetic systolic lengthening, and postsystolic shortening occur within 60 s after the interruption of coronary flow.[1–3] This contractile dysfunction is accompanied by diastolic creep (increased unstressed segment length),[4–5] decreases in regional diastolic distensibility,[4–10] and attenuated early diastolic filling rates in the ischemic zone.[10] Rapid remodeling of nonischemic myocardium occurs as a compensatory response to the mechanical burden imposed by the ischemic area.[12] Increases in total segment shortening are observed in the normal zone that are directly proportional to the size of the ischemic region.[13] However, no change occurs in ejection segment shortening in the normal zone because a portion of the total shortening is expended in stretching the ischemic zone during isovolumic contraction.[11,14] Myocardial contractility may also increase in the non-

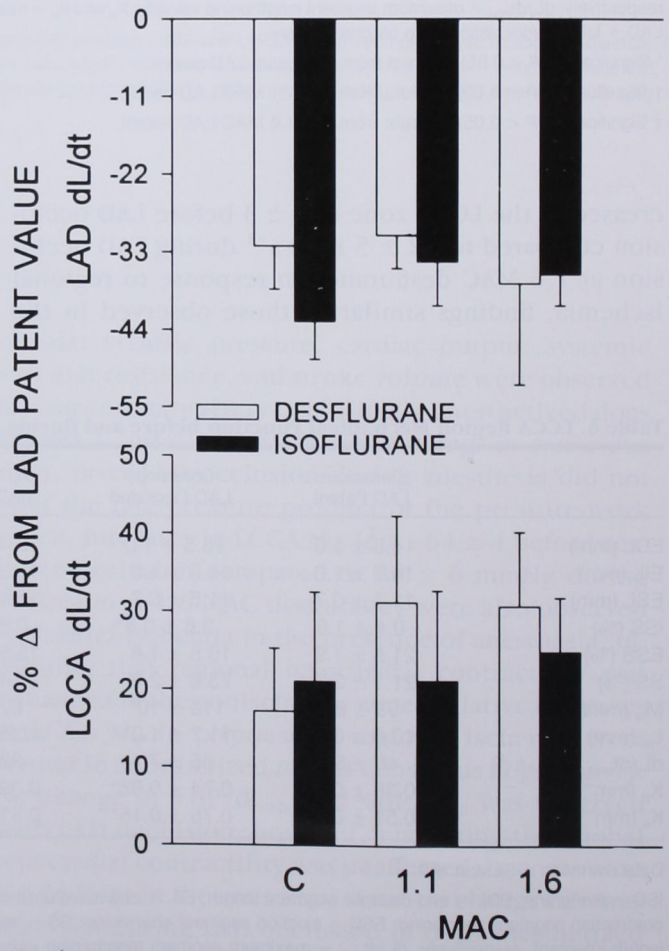

Fig. 4. Histograms illustrating the percent change (Δ) from the left anterior descending coronary artery (LAD) patent value in LAD and left circumflex coronary artery (LCCA) maximum lengthening velocity in conscious (C) and desflurane- and isoflurane-anesthetized dogs.

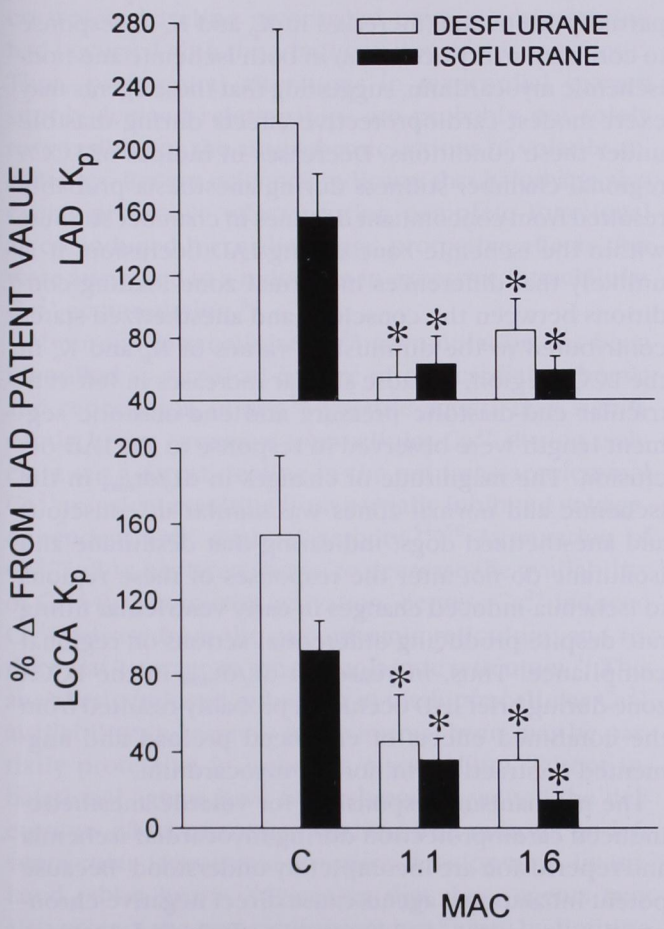

Fig. 5. Histograms illustrating the percent change (Δ) from the left anterior descending coronary artery (LAD) patent value in LAD and left circumflex coronary artery (LCCA) regional chamber stiffness (K_p) in conscious (C) and desflurane- and isoflurane-anesthetized dogs. *Significantly ($P < 0.05$) different from control.

ischemic region, presumably *via* a Frank-Starling mechanism.[15,16] An increase in myocardial stiffness in normal myocardium also occurs in response to regional ischemia.[5] The etiology of this decrease in compliance at a site remote from the ischemic locus remains unclear; however, this phenomenon may occur as a result of physiologic adaptation to altered global ventricular shape resulting from regional ischemia[5] or tethering of the nonischemic myocardium to the adjacent ischemic zone. Enhanced early peak filling rates have also been observed in normal myocardium during regional ischemia, effects that have been proposed to result from the combined actions of declines in segmental compliance and increases in preload and contractility.[10,46] Global left ventricular function may also be affected depending on the severity and duration of the ischemic stimulus and the quantity of affected myocardium.[13,17] Transient but significant increases in τ and decreases in $+dP/dt_{max}$ and the magnitude of $-dP/dt_{min}$ occur within seconds after the onset of proximal coronary occlusion. These effects are probably related to marked regional contractile dyssynchrony produced by the acutely ischemic zone.[18] These alterations in global systolic and diastolic function partially resolve within 60 s after the onset of regional ischemia consistent with rapid, compensatory remodeling of nonischemic myocardium.[18]

A substantial body of experimental evidence supports the contention that volatile anesthetics exert beneficial effects during myocardial ischemia and reperfusion injury. Halothane has been shown to attenuate ST segment changes caused by brief coronary artery occlusion.[20,21] Decreased lactate production by isolated canine hearts with a severe LAD stenosis has been observed during enflurane anesthesia when perfusion pressure was artificially controlled.[22] Halothane-induced reductions in regional contractile function were well tolerated and did not precipitate frank systolic dysfunction during a severe LAD constriction in open-chest, acutely instrumented dogs.[23] Halothane also reduced myocardial infarct size after LAD occlusion in dogs.[24] Potent inhalational anesthetics have been shown to enhance recovery of systolic function of stunned myocardium in the isolated heart[25–28] and when these agents were administered before and during,[47] but not after,[48,49] brief periods of myocardial ischemia *in vivo,* effects that were accompanied by preservation of high energy phosphate levels.[29] In addition, halothane preserved contractile function and ultrastructural integrity in isolated rat hearts during reperfusion after normothermic cardioplegic arrest.[30] Because volatile anesthetics appear to produce protective effects during acute myocardial ischemia and reperfusion, the current investigation was designed to examine the hypothesis that desflurane and isoflurane do not adversely alter the systolic and diastolic mechanical responses to regional myocardial ischemia in the central ischemic and remote nonischemic zones.

The current findings indicate that a brief, 2-min LAD occlusion produces dyskinetic early systolic segment lengthening, postsystolic shortening, and loss of effective stroke work in the ischemic zone. The degree of ischemia produced by progressive coronary artery constriction and complete occlusion can be quantified by

the degree of systolic lengthening and postsystolic shortening in the ischemic zone.[38] These variables were similar in the LAD region in the conscious state and in the presence of desflurane or isoflurane anesthesia, suggesting that the relative intensity of the ischemia in this zone was similar in the conscious and anesthetized states. This conclusion requires qualification, however, because regional myocardial metabolism was not specifically measured in the ischemic zone. Left anterior descending coronary artery ischemia increased total segment shortening in the normal zone, however, ejection shortening was unaffected, indicating that a percentage of total LCCA shortening was wasted tethering the adjacent ischemic muscle. These findings are consistent with the studies of Lew *et al.*[11] and Noma *et al.*[14] Desflurane and isoflurane did not alter the percentage of normal zone shortening expended during isovolumic contraction during the 2-min LAD occlusion. Compensatory increases in LCCA myocardial contractility were observed in the conscious state and were preserved during desflurane and isoflurane anesthesia. The results confirm and extend the findings of Lowenstein *et al.*[23] and indicate that like halothane, desflurane and isoflurane do not adversely affect the systolic compensatory responses of normal myocardium to distant ischemia. The increase in myocardial contractility observed in the nonischemic zone during regional ischemia was similar in the presence and absence of anesthetics, suggesting that the Frank-Starling mechanism, the presumed cause of increase in intrinsic inotropic state under these conditions,[15,16] remains fully intact despite the inherent myocardial depressant properties of desflurane and isoflurane.[50]

Brief LAD occlusion caused diastolic creep (as indicated by increases in L_w), reduced the rate of early ventricular filling, and increased regional chamber stiffness in the ischemic zone, confirming the results of several previous investigations.[4–10] These changes in ischemic zone diastolic behavior were accompanied by a modest but significant prolongation of isovolumic relaxation and increased the early ventricular filling rate and regional chamber stiffness in the nonischemic region in conscious dogs, verifying the observations of Kumada *et al.*,[18] Takahashi *et al.*,[10] and Marsch *et al.*[5] Volatile anesthetics have been shown to prolong isovolumic relaxation and blunt early rapid ventricular filling, actions that occur in conjunction with direct negative inotropic effects.[34,35,51,52] Despite these intrinsic negative lusitropic effects, isoflurane and desflurane abolished ischemia-induced increases in τ and partially attenuated increases in K_p and K_s in response to coronary artery occlusion in both ischemic and nonischemic myocardium, suggesting that these agents may exert modest cardioprotective effects during diastole under these conditions. Decreases in indices of LCCA regional chamber stiffness during anesthesia probably resulted from concomitant declines in chamber stiffness within the ischemic zone during LAD occlusion. It is unlikely that differences in normal zone loading conditions between the conscious and anesthetized states contributed to the diminished values of K_p and K_s in the LCCA region, because similar increases in left ventricular end-diastolic pressure and end-diastolic segment length were observed in response to the LAD occlusion. The magnitude of changes in dL/dt_{max} in the ischemic and normal zones was similar in conscious and anesthetized dogs, indicating that desflurane and isoflurane do not alter the responses of these regions to ischemia-induced changes in early ventricular filling rate despite producing differential actions on regional compliance. Thus, increases in dL/dt_{max} in the LCCA zone during brief LAD occlusion probably resulted from the combined effects of enhanced preload and augmented contractility in normal myocardium.

The mechanisms responsible for volatile-anesthetic-induced cardioprotection during myocardial ischemia and reperfusion are incompletely understood. Because potent inhalational agents cause direct negative chronotropic, inotropic, and lusitropic effects and decrease left ventricular afterload to varying degrees, the beneficial effects of these anesthetics may be attributed to a favorable reduction in myocardial oxygen demand required for active contraction with concomitant relative preservation of energy-dependent vital cellular processes *via* decreases in basal metabolic rate. In the current investigation, significant increases in heart rate and calculated indices of myocardial oxygen consumption (rate-pressure product and pressure-work index) occurred during brief LAD occlusion in conscious dogs. In contrast, these variables remained unchanged in response to regional ischemia in desflurane- and isoflurane-anesthetized dogs. The findings suggest that desflurane and isoflurane may provide a degree of protection against ischemic injury by blunting increases in heart rate and myocardial oxygen consumption that occur with acute regional myocardial ischemia in the conscious state. However, rate-pressure product and pressure-work index before LAD occlusion were greater than conscious values in dogs anesthetized with 1.1 MAC desflurane, but not isoflurane, indicating that in-

creases in baseline myocardial oxygen consumption had occurred with the administration of this anesthetic. Thus, preferential alterations in myocardial oxygen supply-demand relationships are probably not solely responsible for the antiischemic actions of volatile anesthetics. Recent evidence indicates that halothane also exerts protective effects during complete functional arrest induced by cardioplegia, protective effects that were attributed to a reduction in excessive intracellular Ca^{2+} accumulation.[30]

Abnormal intracellular Ca^{2+} accumulation has been identified as a critical feature of myocardial ischemia and reperfusion injury.[53] Volatile agents may significantly lower excessive intracellular Ca^{2+} during ischemia *via* a direct decline in the net transsarcolemmal Ca^{2+} transient resulting from partially inhibited voltage-dependent Ca^{2+} channel activity.[54–58] Attenuation of Ca^{2+} influx has been shown to decrease the availability of Ca^{2+} for contractile activation, depress Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum, and reduce Ca^{2+} storage in the sarcoplasmic reticulum.[31] This anesthetic-induced reduction in total intracellular Ca^{2+} availability and reserve in the normal heart may be partially protective in ischemic myocardium. Potent inhalational agents have been shown to reduce the deleterious effect of oxygen-derived free radicals on left ventricular isovolumic pressure development in isolated rabbit hearts, suggesting that these agents may also protect the myocardium against injury by limiting intracellular Ca^{2+} accumulation.[32] Thus, partial attenuation of regional ischemia-induced diastolic dysfunction observed in the current investigation may also result from favorable alterations in intracellular Ca^{2+} homeostasis produced by desflurane and isoflurane through a variety of potential mechanisms.

In summary, the current investigation has demonstrated that transient coronary occlusion modestly prolonged isovolumic relaxation and abolished regional stroke work, increased chamber stiffness, and decreased early ventricular filling rate in the ischemic zone coincident with enhanced regional contractility, increased early filling, and decreased chamber compliance in the remote normal region in the conscious state. Regional ischemia-induced increases in myocardial contractility and early filling rates were preserved in the normal zone during desflurane and isoflurane anesthesia. In contrast to the findings in the conscious state, however, increases in τ and chamber stiffness in the ischemic and normal zones, which occurred in response to brief LAD occlusion, were attenuated in the presence of desflurane and isoflurane. The current results indicate that these volatile anesthetics exert beneficial effects on diastolic mechanical activity in chronically instrumented dogs in the presence of myocardial ischemia.

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References

1. Tennant R, Wiggers CJ: The effect of coronary occlusion on myocardial contraction. Am J Physiol 112:351–361, 1935

2. Theroux P, Franklin D, Ross Jr J, Kemper WS: Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. Circ Res 35:896–908, 1974

3. Theroux P, Ross Jr J, Franklin D, Kemper WS, Sasayama S: Regional myocardial function in the conscious dog during acute coronary occlusion and responses to morphine, propranolol, nitroglycerin, and lidocaine. Circulation 53:302–314, 1976

4. Hess OM, Osakada G, Lavelle JF, Gallagher KP, Kemper WS, Ross Jr J: Diastolic myocardial wall stiffness and ventricular relaxation during partial and complete coronary occlusions in the conscious dog. Circ Res 52:387–400, 1983

5. Marsch SCU, Wanigasekera VA, Ryder WA, Wong LSS, Foex P: Graded myocardial ischemia is associated with a decrease in diastolic distensibility of the remote nonischemic myocardium in the anesthetized dog. J Am Coll Cardiol 22:899–906, 1993

6. Edwards II CH, Rankin JS, McHale PA, Ling D, Anderson RW: Effects of ischemia on left ventricular regional function in the conscious dog. Am J Physiol 240:H413–H420, 1981

7. Paulus WJ, Grossman W, Serizawa T, Bourdillon PD, Pasipoularides A, Mirsky I: Different effects of two types of ischemia on myocardial systolic and diastolic function. Am J Physiol 248:H719–H728, 1985

8. Amano J, Thomas Jr JX, Lavallee M, Mirsky I, Glover D, Manders WT, Randall WC, Vatner SF: Effects of myocardial ischemia on regional function and stiffness in conscious dogs. Am J Physiol 252:H110–H117, 1987

9. Visner MS, Arentzen CE, Parrish DG, Larson EV, O'Connor MJ, Crumbley III AJ, Bache RJ, Anderson RW: Effects of global ischemia on the diastolic properties of the left ventricle in the conscious dog. Circulation 71:610–619, 1985

10. Takahashi T, Levine MJ, Grossman W: Regional diastolic mechanics of ischemic and nonischemic myocardium in the pig heart. J Am Coll Cardiol 17:1203–1212, 1991

11. Lew WYW, Chen ZY, Guth B, Covell JW: Mechanisms of augmented segment shortening in nonischemic areas during acute ischemia of the canine left ventricle. Circ Res 56:351–358, 1985

12. Lew WYW, Ban-Hayashi E: Mechanisms of improving regional and global ventricular function by preload alterations during acute ischemia in the canine left ventricle. Circulation 72:1125–1134, 1985

13. Lew WYW: Influence of ischemic zone size on nonischemic area function in the canine left ventricle. Am J Physiol 252:H990–H997, 1987

14. Noma S, Askenase AD, Weintraub WS, Klein LW, Agarwal JB, Helfant RH: Augmentation of contraction in remote nonischemic zone during acute ischemia. Am J Physiol 255:H301–H310, 1988

15. Sunagawa K, Maughan WL, Sagawa K: Effect of regional ischemia on the left ventricular end-systolic pressure-volume relationship of isolated canine hearts. Circ Res 52:170–178, 1983

16. Little WC, O'Rourke RA: Effect of regional ischemia on the left ventricular end-systolic pressure-volume relation in chronically instrumented dogs. J Am Coll Cardiol 5:297–302, 1985

17. Akaishi M, Schneider RM, Mercier RJ, Naccarella FF, Agarwal JB, Helfant RH, Weintraub WS: Relation between left ventricular global and regional function and extent of myocardial ischemia in the canine heart. J Am Coll Cardiol 6:104–112, 1985

18. Kumada T, Karliner JS, Pouleur H, Gallagher KP, Shirato K, Ross Jr J: Effects of coronary occlusion on early diastolic events in conscious dogs. Am J Physiol 237:H542–H549, 1979

19. Warltier DC, Al-Wathiqui MH, Kampine JP, Schmeling WT: Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. ANESTHESIOLOGY 69:552–565, 1988

20. Bland JHL, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. ANESTHESIOLOGY 45:287–293, 1976

21. Gerson JI, Hickey RF, Bainton CR: Treatment of myocardial ischemia with halothane or nitroprusside-propranolol. Anesth Analg 61:10–14, 1982

22. Van Ackern K, Vetter HO, Bruckner UB, Madler C, Mittman U, Peter K: Effects of enflurane on myocardial ischaemia in the dog. Br J Anaesth 57:497–504, 1985

23. Lowenstein E, Foex P, Francis CM, Davies WL, Yusuf S, Ryder WA: Regional ischemic ventricular dysfunction in myocardium supplied by a narrowed coronary artery with increasing halothane concentration in the dog. ANESTHESIOLOGY 55:349–359, 1981

24. Davis RF, DeBoer LW, Rude RE, Lowenstein E, Maroko PR: The effect of halothane anesthesia on myocardial necrosis, hemodynamic performance, and regional myocardial blood flow in dogs following coronary artery occlusion. ANESTHESIOLOGY 59:402–411, 1983

25. Buljubasic N, Stowe DF, Marijic J, Roerig DL, Kampine JP, Bosnjak ZJ: Halothane reduces release of adenosine, inosine, and lactate with ischemia and reperfusion in isolated hearts. Anesth Analg 76:54–62, 1993

26. Coetzee A, Brits W, Genade S, Lochner A: Halothane does have protective properties in the isolated ischemic rat heart. Anesth Analg 73:711–719, 1991

27. Marijic J, Stowe DF, Turner LA, Kampine JP, Bosnjak ZJ: Differential protective effects of halothane and isoflurane against hypoxic and reoxygenation injury in the isolated guinea pig heart. ANESTHESIOLOGY 73:976–983, 1990

28. Freedman BM, Hamm DP, Everson CT, Wechsler AS, Christian II CM: Enflurane enhances postischemic functional recovery in the isolated rat heart. ANESTHESIOLOGY 62:29–33, 1985

29. Kanaya N, Fujita S: The effects of isoflurane on regional myocardial contractility and metabolism in "stunned" myocardium in acutely instrumented dogs. Anesth Analg 79:447–454, 1994

30. Lochner A, Harper IS, Salie R, Genade S, Coetzee AR: Halothane protects the isolated rat myocardium against excessive total intracellular calcium and structural damage during ischemia and reperfusion. Anesth Analg 79:226–233, 1994

31. Rusy BF, Komai H: Anesthetic depression of myocardial contractility: A review of possible mechanisms. ANESTHESIOLOGY 67:745–766, 1987

32. Tanguay M, Blaise G, Dumont L, Beique G, Hollmann C: Beneficial effects of volatile anesthetics on decrease in coronary flow and myocardial contractility induced by oxygen-derived free radicals in isolated rabbit hearts. J Cardiovasc Pharmacol 18:863–870, 1991

33. Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Comparison of end-systolic pressure-length relations and preload recruitable stroke work as indices of myocardial contractility in the conscious and anesthetized, chronically instrumented dog. ANESTHESIOLOGY 73:278–290, 1990

34. Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Alteration of left ventricular diastolic function by desflurane, isoflurane, and halothane in the chronically instrumented dog with autonomic nervous system blockade. ANESTHESIOLOGY 74:1103–1114, 1991

35. Harkin CP, Pagel PS, Kersten JR, Hettrick DA, Warltier DC: Direct negative inotropic and lusitropic effects of sevoflurane. ANESTHESIOLOGY 81:156–167, 1994

36. Hartman JC, Olszanski DA, Hullinger TG, Brunden MN: In vivo validation of a transit-time ultrasonic volume flow meter. J Pharmacol Toxicol Methods 31:153–160, 1994

37. Wilkison DM, Preuss KC, Warltier DC: A microcomputer-based package for determination of regional and global cardiac function and coronary hemodynamics. J Pharmacol Methods 12:59–67, 1984

38. Safwat A, Leone BJ, Norris RM, Foex P: Pressure-length loop area: Its components analyzed during graded myocardial ischemia. J Am Coll Cardiol 17:790–796, 1991

39. Rooke GA, Feigl EO: Work as a correlate of canine left ventricular oxygen consumption, and the problem of catecholamine oxygen wasting. Circ Res 50:273–286, 1982

40. Glower DD, Spratt JA, Snow ND, Kabas JS, Davis JW, Olsen CO, Tyson GS, Sabiston Jr DC, Rankin JS: Linearity of the Frank-Starling relationship in the intact heart: The concept of preload recruitable stroke work. Circulation 71:994–1009, 1985

41. Pagel PS, Warltier DC: Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. ANESTHESIOLOGY 78:100–108, 1993

42. Doorley BM, Waters SJ, Terrell RC, Robinson JL: MAC of I-653 in beagle dogs and New Zealand white rabbits. ANESTHESIOLOGY 69: 89–91, 1988

43. Raff GL, Glantz SA: Volume loading slows left ventricular isovolumic relaxation rate: Evidence of load-dependent relaxation in the intact dog. Circ Res 48:813–824, 1981

44. Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Reversal of volatile anesthetic-induced depression of myocardial contractility by extracellular calcium also enhances left ventricular diastolic function. ANESTHESIOLOGY 78:141–154, 1993

45. Wallenstein S, Zucker CL, Fleiss JL: Some statistical methods useful in circulation research. Circ Res 47:1–9, 1980

46. Brutsaert DL, Rademakers FE, Sys SU: Triple control of relaxation: Implications in cardiac disease. Circulation 69:190–196, 1984

47. Warltier DC, Gross GJ, Brooks HL, Preuss KC: Improvement of postischemic, contractile function by the calcium channel blocking agent nitrendipine in conscious dogs. J Cardiovasc Pharmacol 12 (Suppl 4):S120–S124, 1988

48. Mattheussen M, Rusy BF, Van Aken H, Flameng W: Recovery of function and adenosine triphosphate metabolism following myocardial ischemia induced in the presence of volatile anesthetics. Anesth Analg 76:69–75, 1993

49. Belo SE, Mazer CD: Effect of halothane and isoflurane on post-ischemic "stunned" myocardium in the dog. ANESTHESIOLOGY 73: 1243–1251, 1990

50. Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Influence of volatile anesthetics on myocardial contractility *in vivo:* Desflurane versus isoflurane. ANESTHESIOLOGY 74:900–907, 1991

51. Humphrey LS, Stinson DC, Humphrey MJ, Finney RS, Zeller PA, Judd MR, Blanck TJJ: Volatile anesthetic effects on left ventricular relaxation in swine. ANESTHESIOLOGY 73:731–738, 1990

52. Ihara T, Shannon RP, Komamura K, Pasipoularides A, Patrick T, Shen YT, Vatner SF: Effects of anaesthesia and recent surgery on diastolic function. Cardiovasc Res 28:325–336, 1994

53. Morgan JP: Abnormal intracellular modulation of calcium as a major cause of cardiac contractile dysfunction. N Engl J Med 325: 625–632, 1991

54. Bosnjak ZJ, Kampine JP: Effects of halothane on transmembrane potentials, Ca^{2+} transients, and papillary muscle tension in the cat. Am J Physiol 251:H374–H381, 1986

55. Bosnjak ZJ, Aggarwal A, Turner LA, Kampine JM, Kampine JP: Differential effects of halothane, enflurane, and isoflurane on Ca^{2+} transients and papillary muscle tension in guinea pigs. ANESTHESIOLOGY 76:123–131, 1992

56. Lynch III C, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. ANESTHESIOLOGY 55:360–368, 1981

57. Lynch III C: Differential depression of myocardial contractility by halothane and isoflurane *in vitro*. ANESTHESIOLOGY 64:620–631, 1986

58. Eskinder H, Rusch NJ, Supan FD, Kampine JP, Bosnjak ZJ: The effects of volatile anesthetics on L- and T-type calcium channel currents in canine cardiac Purkinje cells. ANESTHESIOLOGY 74:919–926, 1991