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Effects of Isoflurane on Regional Coronary Blood Flow and Myocardial Tissue Pressure in Chronically Instrumented Dogs

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Background: **The effects of isoflurane on distribution of transmural blood flow and transmural intramyocardial tissue pressure (IMP) were studied in chronically instrumented dogs, to address following aims: (1) to evaluate the direct effects of isoflurane on transmural blood flow distribution in the absence of compounding effects of baseline anesthetics, acute surgery, and indirect effects caused by changes in systemic blood pressures and heart rate—factors that were not well controlled in the past studies; (2) to examine the relation between transmural myocardial perfusion pressure and concurrent changes in transmural blood flow distribution during isoflurane anesthesia; and (3) to evaluate the effects of isoflurane on transmural myocardial oxygen supply–demand relation.**

Methods: **Dogs were allowed to recover at least 1 week after surgery for instrumentation. Blood flow of the left anterior descending coronary artery and subendocardial and subepicardial blood flows, regional IMPs, regional segmental dimension, heart rate, aortic pressure and left ventricular pressure were measured while dogs were awake and during 1.3% isoflurane anesthesia, with and without correction of heart rate and aortic pressure. Concurrently regional myocardial perfusion pressure, regional myocardial stroke work, and systolic pressure time index were calculated, based on direct measurements of IMP in subendocardium and subepicardium.**

Results: **Without correction of aortic pressure, neither left anterior descending coronary artery flow nor transmural blood flow distribution was altered with isoflurane. When aortic pressure and heart rate were corrected to the awake values, left anterior descending coronary artery flow increased (37 ± 2%) and the increase was preferentially distributed to subendocardium, resulting in a shift in transmural blood flow. The subendocardial/subepicardial blood flow ratio increased from 1.2 ± 0.3 to 1.4 ± 0.4 (p, 0.05). The transmural blood flow changes were closely related to changes in regional myocardial perfusion pressure ratio between subendocardium and subepicardium ($r = 0.76$, $P < 0.001$). Concurrent with marked increases in blood flow (55 ± 4% increase), regional myocardial stroke work and systolic pressure time index of subendocardium were decreased more than 50% with isoflurane, resulting in a favorable subendocardial oxygen supply–demand balance.**

Conclusions: **Isoflurane is a coronary vasodilator and redistributes blood flow in favor of subendocardium and depresses subendocardial work when heart rate and aortic pressure are controlled. These changes in regional myocardial blood flow, regional myocardial stroke work, and systolic pressure time index appear to be a result of changes in regional IMP. (Key words: Anesthetics, volatile: isoflurane. Heart: blood flow; intramyocardial tissue pressure; regional myocardial stroke work; transmural blood flow.)**

THE effects of anesthetics on transmural blood flow distribution are of clinical interest because subendocardial ischemia is one of the most common forms of myocardial injury during the perioperative period in patients with or without coronary artery disease.[1–4] Isoflurane, with its known effects of systemic vasodilation, impairment of coronary autoregulation and myocardial depression, is thought to alter intramyocardial blood flow distribution.[5–11] Transmural blood flow redistribution of the left ventricle (LV) depends mainly on dynamic factors (in addition to anatomically fixed structural differences) such as systemic hemodynamics (heart rate [HR] and aortic pressure [AP]), regional vasomotor tone (metabolic and autoregulation) and intramyocardial extravascular compressive pressure.[1,4,12,13] Intramyocardial tissue pressure (IMP) represents the regional compressive pressure external to the intramyocardial vessels and influences local resistance to blood flow.[4,13–20] Although the relative roles of each factor are largely unknown and they are closely interrelated under normal physiologic conditions, regional IMP is thought to play a major role in the regulation of regional myocardial blood flow (RMBF) distribution when metabolic and autoregulation are abolished by coronary vasodilators and systemic hemodynamics are held steady.[4,15,16,18]

Regional IMP is the pressure generated within specific regions of the myocardium and represents the average

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myocardial stress, which is mainly determined by local myocardial contractile force and passively transmitted force from the intraventricular cavity pressure[4,21-23] IMP, therefore, determines not only the regional myocardial perfusion pressure (RMPP) (pressure difference between coronary arterial pressure and regional IMP) and thereby blood flow distribution, but also is an excellent index of regional myocardial oxygen demand.[24,25] With recent improvements in technology for IMP measurements, it is now well established that IMP is different transmurally, and between regions of the LV.[1,4,13,24] The differences are further exaggerated in pathologic conditions, particularly in ischemic myocardium.[24] IMP is dynamic, depending on concurrent regional myocardial contractility and left ventricular pressure (LVP).[1,4,13-25]

Isoflurane, with known vasodilatory and myocardial depressive actions, is expected to alter vascular tone of intramyocardial resistance vessels and IMP and thereby the normal transmural blood flow distribution.[5-8] Although several studies have examined changes in transmural blood flow distribution with isoflurane anesthesia, the results are not in agreement.[9-11,26] The results may be inconsistent because systemic hemodynamics, such as HR and AP, were not controlled or because the studies were performed in models requiring acute surgery and baseline anesthetics other than isoflurane.[9-10,26] Further, none of these studies examined the relations of transmural blood flow changes with the concurrent changes in major regulating factors of RMBF distribution such as RMPP and regional myocardial work.

In the current study, we examined the effects of isoflurane on the LV coronary circulation, total and transmural blood flow distribution, and their relation with RMPP, systolic pressure time index (SPTI) and regional myocardial stroke work (RMSW) calculated using direct measurements of IMP and segmental myocardial fiber length in chronically instrumented dogs in which HR and AP were controlled at awake values. RMPP, RMSW, and SPTI of subendocardium and subepicardium were then related to concomitant changes in subendocardial and subepicardial blood flow measured using a color encoded microsphere technique.

Materials and Methods

Animal Care

The subjects of this study were mongrel dogs weighing 30 kg or more of either sex. The dogs were screened, conditioned, and trained for 1 week before surgical preparation to stand quietly in a sling. Appropriate care under the supervision of a licensed veterinarian was provided to maintain good general condition throughout the study period. All procedures and protocols of this investigation were approved by the animal care and use committee of the Georgetown University Medical Center, Washington, D.C., and conformed to the guiding principles of the American Physiological Society.

Methods and Instruments

Subendocardial and Subepicardial Intramyocardial Tissue Pressure. These were measured using a microtip needle pressure transducer (Millar, Houston, TX); a stainless steel hypodermic needle which incorporates two miniature pressure transducers (1 × 2 × 1.5 mm), one 2 mm from the tip (subendocardial sensor) and the other 8 mm from the tip (subepicardial sensor). The superior characteristics of this technique for IMP measurements have been described previously.[25,27,28] In brief, this technique has the following advantages: (1) ability to localize pressure measurements at various depths within the myocardial wall, (2) induction of minimum trauma and distortion of the myocardium, (3) high frequency response and insignificant time delay, and (4) easy insertion and extreme stability of the sensor at the site of measurements. In our studies, there was a baseline drift of less than 4 mmHg during the study period of about 1 week. The transducers were tested after recovery from the dog when the experiments were finished. The drift was then corrected for data analysis. We modified the needle for long-term implantation; the distal end of the needle shaft was bent at a right angle 10 mm from the tip, so that the bent portion of the needle could be transfixed with sutures on the epicardial surface.

Despite these advantages of the micromanometer technique, certain precautions should be exercised to minimize the possibility of creating artifacts; forces on the sensor that result from bending moments as the layers of myocardium shear past each other during contraction and relaxation could affect the apparent value of measured IMP. However, with our probe in the anterior free wall, the effects of bending moments were minimal because the shearing strain in canine LV occurs only at sites near the apical region.[29] In addition, the IMP signal is artificially high if the probe is inserted at very shallow angles (less than 10° to the epicardial surface). For this reason, the insertion angle in our

study was within 45–90°, as recommended.[27] With this precaution, rotation of the probe along its longitudinal axis does not affect measured IMP.[27,28]

Regional Segmental Dimension. This was measured using a pair of ultrasonic dimension transducers (Technology Research, Springfield, VA). This technique is now widely used to calculate RMSW.

Regional Myocardial Stroke Work. The LVP–left ventricular volume loop has been shown to represent left ventricular stroke work (LVSW). Subsequently, the LVP–regional segmental length loop was introduced as an index of RMSW.[30] This is an extension of the concept of LVSW, assuming that regional myocardial stress is uniform across regions and is mainly determined by LVP. With recent improvements in the technique for IMP measurements to estimate regional wall stress, it is now certain that IMP is not uniform across the myocardium and is not totally determined by LVP alone, indicating the problem of using LVP to calculate RMSW.[22,24,25] Marked differences between myocardial work calculated based on LVP and IMP have been observed.[25] IMP represents regional average stress which is determined by local contractile force and passively transmitted force from LVP and is therefore considered to be an excellent index of regional myocardial oxygen consumption.[22,24,25,31] Therefore, we calculated subendocardial stroke work (ENDO-RMSW) and subepicardial stroke work (EPI-RMSW) based on subendocardial IMP (ENDO-IMP) and subepicardial IMP (EPI-IMP), respectively. The RMSW was calculated as the integral of changes in length (dl) and IMP for a cardiac cycle (RMSW = IMP × dl). Figure 1 shows a simultaneous illustration of RMSW based on subendocardial IMP, subepicardial IMP and LVP. This figure clearly demonstrates potential errors in estimation of EPI-RMSW or ENDO-RMSW by calculation based on LVP instead of IMPs; RMSW based on LVP grossly overestimates EPI-RMSW and underestimates ENDO-RMSW.

For similar reasons, regional myocardial SPTI, an index of regional myocardial oxygen demand, was also calculated based on subendocardial IMP (ENDO-SPTI) and subepicardial IMP (EPI-SPTI) as described previously.[25,32] The formula for ENDO-SPTI and EPI-SPTI is as follows:

$$\text{SPTI} = \int_{be}^{bs} \text{IMP}\ (t)\ dt$$

where bs = beginning of systole and es = end of systole.

Regional Myocardial Perfusion Pressure. Our calculation of RMPP adapts the principle of the "vascular waterfall" or Starling resistor[19,22,33]; RMBF is driven by pressure gradients determined by inflow pressure (AP) and back pressure in each part of myocardium (appropriate IMPs) external to perfused intramyocardial vessels. Thus, subendocardial perfusion pressure (ENDO-RMPP) and subepicardial perfusion pressure (EPI-RMPP) were calculated based on pressure differences between AP or coronary arterial pressure and respective IMPs rather than left ventricular cavitary pressure. We quantified RMPP by averaging the pressure differences between AP and IMP throughout a cardiac cycle (fig. 2). As shown in this figure, subendocardial IMP is higher than AP or left ventricular cavitary pressure during systole, and therefore, ENDO-RMPP is available only during diastole. In contrast, epicardial IMP is substantially lower than AP during systole, resulting in EPI-RMPP available during systole as well as diastole. RMPP during diastole is higher in subendocardium than in subepicardium as a result of higher diastolic IMP in epicardium than endocardium. The computation formula is as follows:

$$\text{RMPP} = 1/n \sum_{b}^{b+1} [\text{APn} - \text{IMPn}], \text{ for AP} > \text{IMP}$$

where n = number of sample points (12,000 points/min) and b = heart beat number. The ENDO-RMPP/EPI-RMPP ratio was used to compare the ratio of RMBF (ENDO-RMBF/EPI-RMBF). Using AP instead of actual coronary pressure in calculation of RMPP may introduce error because AP is not identical to coronary pressure. In normal conditions, however, both diastolic and systolic pressure differences between aorta and epicardial arterioles (diameter 300 ± 31 μm) are less than 1%.[12] Thus, error in perfusion pressure based on AP is expected to be small. Further, when we use the ratio ENDO-RMPP/EPI-RMPP based on AP, the error will be further minimized because the error was introduced for both ENDO-RMPP and EPI-RMPP.

First Derivative of Left Ventricular Pressure. The first derivative of LVP (dP/dt) was computed as a five-point polyorthogonal transformation of the digital pressure waveform.

Regional Myocardial Blood Flow. The method we employed has been described previously.[34] In brief, polystyrene–divinylbenzene microspheres (15 ± 0.2 μm in diameter; Triton, San Diego, CA) suspended in saline with 0.2% Tween 80 were used to measure RMBF. Approximately 6×10^6 colored spheres were given as a bolus injection (10 s) into the left atrium

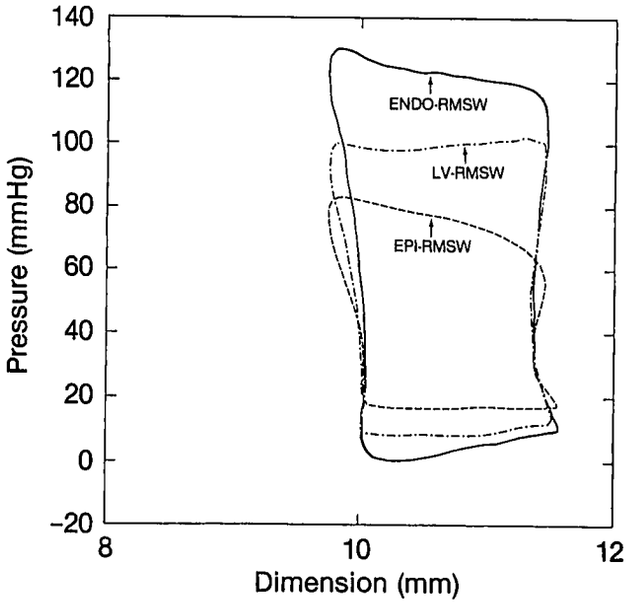

Fig. 1. Regional myocardial stroke work (RMSW) based on intramyocardial tissue pressure (subendocardial and subepicardial) and left ventricular pressure for a complete cardiac cycle. ENDO-RMSW = RMSW based on subendocardial intramyocardial tissue pressure; EPI-RMSW = RMSW based on subepicardial intramyocardial tissue pressure; LV-RMSW = RMSW based on left ventricular pressure.

via an atrial catheter. Before injection, the microsphere suspension was vortexed (Vortex Genie 2, Fisher Scientific, Pittsburgh, PA) for 10 s and 10 ml of warm saline were used to flush the catheter after the injection. Ten seconds before microsphere injection, collection of reference arterial blood was started and continuously withdrawn from the aorta *via* the internal mammary catheter at a rate of 6 ml/min for 100 s. At the conclusion of the study, the dog was killed using a pentobarbital overdose, and the anterior wall of the LV near the site of the IMP needle was harvested. The tissue samples (five 2-g cubic samples of whole myocardial tissue) were then subdivided into subendocardium and subepicardium of approximately equal thickness. The tissue and blood samples were digested using KOH and Tween 80 solution in a water bath. The digested samples were vacuum-filtered with a polycarbon membrane filter (8-μm pores and 25-mm diameter) (Fisher Scientific) fitted to a filtering flask. The membrane filter was placed into an Eppendorf tube containing a solvent (N,N-dimethyl formamide) and vortexed, followed by centrifugation (model 235C, Fisher Scientific). The dye solution was pipetted into a cuvette and photometric absorption analysis was then accomplished using a spectrophotometer (diode array model 8452A, Hewlett-Packard, Palo Alto, CA). The absorbances of the samples were used for RMBF calculation using the following formula:

$$\text{RMBF} = (\text{ABS-t}) \times (\text{BF-ref}) + \sum (\text{ABS-ref})$$

where ABS-t = absorbance of tissue sample; BF = reference blood flow; and ABS-ref is absorbance of reference blood sample.

Intrapleural Pressure. Because we compared the conditions of spontaneous breathing (awake) with that of positive pressure ventilation (under isoflurane anesthesia) in a closed chest dog model, all the pressures measured (including IMPs) were corrected for intrathoracic pressure by subtracting concurrent intrapleural pressure.

Surgical Preparation and Instrumentation

After induction of anesthesia with sodium thiopental (25 mg/kg), the trachea of each dog was intubated and the lungs were mechanically ventilated. Anesthesia was then maintained with isoflurane (1.2–2%) and under sterile conditions, a thoracotomy was performed through the left fifth intercostal space.

Instrumentation was established as follows. A fluid-filled polyvinyl chloride catheter was inserted through the left internal mammary artery into the aortic arch. A catheter-tipped micromanometer was passed through this catheter into the aortic arch for the measurement of AP during the studies. Also, this was used for with-

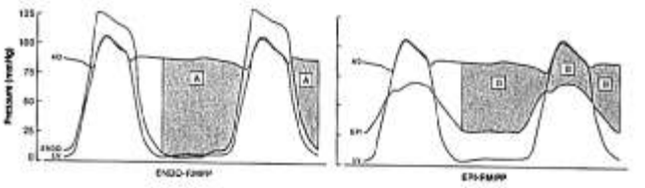

Fig. 2. Regional myocardial perfusion pressure (RMPP) based on (*A*) subendocardial intramyocardial tissue pressure (ENDO-RMPP) and (*B*) subepicardial intramyocardial tissue pressure (EPI-RMPP). Shaded area in (*A*) = the area between the aortic pressure (AO) curve and the subendocardial intramyocardial tissue pressure curve (ENDO); this area is a measure of RMPP (for the subendocardium) based on regional intramyocardial tissue pressure. The left ventricular (LV) pressure curve is also illustrated for purposes of comparison. Shaded area in (*B*) = the area between the aortic pressure (AO) curve and the subepicardial intramyocardial tissue pressure curve (EPI) and is a measure of RMPP (for the subepicardium) based on regional IMP. Again, the LV pressure curve is also illustrated.

drawing blood for RMBF measurements using color encoded microspheres.[34]

A silicon rubber catheter was implanted into the left atrium to be used for microsphere injection for RMBF measurements, as well as for passing a micromanometer into the LV cavity for LVP measurements during subsequent studies.

An appropriately sized Doppler ultrasonic flow probe was placed around the left anterior descending coronary artery (LAD) just proximal to the first major diagonal branch for continuous blood flow measurements, and another flow probe was placed around the main pulmonary artery for cardiac output (CO) measurements.

A pair of ultrasonic dimension transducers was implanted 10–12 mm apart in the midportion of myocardium of the anterior wall. This was used to calculate RMSW in conjunction with IMP and LVP as described earlier.

A precalibrated microtip needle pressure transducer for IMP measurements was inserted into the anterior wall of the LV in the vicinity of the dimension transducers. Proper location of transducers in the subendocardium and subepicardium was confirmed by postmortem examination.

Bipolar pacing wires were sewn into the left atrial appendage.

A silicon rubber catheter ending in a compliant silicone elastomere bag was inserted into the left pleural space, so that during studies, a micromanometer could be introduced to measure intrathoracic pleural pressure.

The electrical wires and catheters were exteriorized dorsal to the thoracotomy incision. The pericardium and the chest was closed in layers. The dog was fitted with a jacket to prevent damage to the instruments and catheters. Chest tubes were removed when drainage became insignificant. Intermittent doses of duramorphine (0.3 mg/kg) through an indwelling epidural catheter provided excellent post operative analgesia without respiratory depression. Cephalexin (35 mg/kg bid) and aspirin (325 mg/day) were administered throughout the study period. The internal mammary and left atrial catheters were flushed periodically with heparin to maintain patency.

Protocol and Data Acquisition

Twenty dogs were successfully instrumented and survived surgical preparation. Two died from surgical complications within 1 day; 2 died of unknown causes; and 3 were excluded from the study because of instrument failure. Thus, 13 dogs were allowed full recovery of at least 1 week and subjected to experiments.

Each dog was fasted before experiments. Routine arterial blood gases, electrolytes and hematocrit were measured using a GEM SYSTEM (Mallinckrodt Sensor System, Ann Arbor, MI) the day before experiments and abnormal values (mainly *p*H and potassium) were corrected if necessary. After the connection of electrical wires and catheters, the dog was held standing quietly in a sling for least 10–15 min without agitation. On a few occasions (in 2 of 13 dogs that were included in the statistical analysis) a small dose of diazepam (0.05–0.10 mg/kg) was used for sedation. Blood flows (main pulmonary artery and LAD), segmental dimension of anterior wall and pressures (LVP, AP, intrapleural cavity, ENDO-IMP, and EPI-IMP) were continuously monitored. All signals were filtered by a 50-Hz analog filter and continuously recorded on a polygraph and digitized in real time at an eight-channel sampling rate of 200 Hz by an analog to digital converter (model 1012, ADAC, Woburn, MA). Data were then analyzed using a computer program as described above. While the dog was standing quietly, baseline awake hemodynamic data including HR, blood flows, dimensions, and pressures were obtained. Then the heart was paced with atrial wires at 115 beats/min in 8 dogs and 120 beats/min in the other 5 dogs, and hemodynamic data were obtained.

Anesthesia was induced with isoflurane through a mask, with a small dose of sodium thiopental (1 mg/kg intravenously) to aid inhalation induction. After tracheal intubation with a cuffed endotracheal tube, the lungs were mechanically ventilated with isoflurane in 100% oxygen using an anesthesia machine equipped with a vaporizer and a ventilator. Arterial oxygen saturation, end-tidal carbon dioxide and isoflurane were continuously monitored using a POET agent analyzer equipped with a pulse oximeter (Criticare Systems, Waukesa, WI). End-tidal carbon dioxide was maintained between 30–35 mmHg. When end-tidal isoflurane concentration was equilibrated at 1.3% at least for 20 min and hemodynamics were steady, baseline isoflurane data were obtained. If HR was less than 115 beats/min, the heart was paced at 115 or 120 beats/min to match the rate of awake paced data, and data were obtained again. Finally, the data were recorded after correcting mean AP at values of awake dogs atrially paced by using a phenylephrine infusion. In our preliminary studies (in two dogs, six trials), total LAD flow or RMBF dis-

tribution with the correction of mean aortic pressure (MAP) by phenylephrine infusion was not significantly different than during the correction of MAP with intraaortic balloon inflation. RMBF was measured only during the following points: awake paced, isoflurane paced, and isoflurane paced with phenylephrine. At the conclusion of the study, the dogs were killed using a pentobarbital overdose. Myocardial samples for RMBF measurements were obtained as described above.

Statistical Analysis

Statistical analysis was performed on data obtained from 13 dogs. All data collected repeatedly at different stages of the experiments were analyzed with one-way analysis of variance with repeated measures, and Dunnett's *t* test was used to compare pairwise differences between baseline and experimental time points. For comparison between two IMPs (between subepicardial IMP and corresponding subendocardial IMP) Student's *t* test for paired data was used. Correlation between RMPP and RMBF was tested by simple linear regression analysis for two variables. A P value less than 0.05 was considered statistically significant. All values were expressed as mean ± standard error of the mean.

Results

Global Left Ventricular Hemodynamics

HR, CO, MAP, LVP, and maximum dP/dt (dP/dt_{max}) are summarized in table 1. CO, MAP, and dP/dt_{max} decreased significantly after isoflurane anesthesia regardless of pacing. With phenylephrine infusion during isoflurane anesthesia to correct MAP to baseline awake values, systolic and diastolic APs were also increased to the levels of awake values, but CO and dP/dt_{max} remained depressed with elevated left ventricular end-diastolic pressure ($P < 0.05$ compared with awake paced). LAD flow under isoflurane anesthesia was not significantly different from awake values regardless of pacing. However, with correction of mean AP to awake levels, LAD flow increased significantly ($P < 0.05$ compared with awake paced), indicating that isoflurane had a significant coronary vasodilator effect. Figure 3 shows a representative graphic recording of hemodynamic changes in one dog.

Intramyocardial Tissue Pressure

As summarized in table 2, peak systolic ENDO-IMP was significantly higher than EPI-IMP during the awake period with or without pacing ($P < 0.05$). During isoflurane anesthesia, systolic ENDO-IMP was significantly depressed. Even with correction of systemic pressure to the level of awake values using a phenylephrine infusion, systolic ENDO-IMP was significantly lower than during awake states ($P < 0.05$). Contrary to ENDO-IMP, systolic EPI-IMP showed an insignificant drop during isoflurane, resulting in narrowing of systolic pressure differences between the two regions. When systolic IMP was normalized for corresponding LVP, ENDO-IMP was 1.2 ± 0.1 during awake periods and dropped below unity (0.9 ± 0.1) during periods of pacing with isoflurane and phenylephrine. Such changes were not observed in EPI-IMP normalized for corresponding LVP. Thus, the results indicate isoflurane depressed systolic endocardial IMP selectively more than LVP or epicardial IMPs.

Table 1. Hemodynamics and Left Anterior Descending Coronary Artery (LAD) Blood Flow during Awake and Isoflurane Anesthesia

	LAD Flow (ml/min)	HR (beats/min)	CO (L/min)	AP (mmHg)			LVP (mmHg)		dP/dtMax (mmHg/min)
				S	D	M	S	D	
Awake-B	31 ± 4	95 ± 5	3.2 ± 0.2	137 ± 6	102 ± 6	117 ± 6	138 ± 7	12 ± 1	2,431 ± 142
Awake-P	35 ± 4	116 ± 1*	3.2 ± 0.2	139 ± 6	113 ± 6	123 ± 6	140 ± 6	11 ± 1	2,321 ± 196
Iso-B	27 ± 3†	102 ± 5	2.3 ± 0.3*†	98 ± 5*†	75 ± 5*†	85 ± 5*†	97 ± 5*†	12 ± 2	1,306 ± 111*†
Iso-P	27 ± 3†	117 ± 2*	2.2 ± 0.3*†	92 ± 4*†	72 ± 5*†	83 ± 3*†	92 ± 5*†	11 ± 1	1,213 ± 117*†
Iso-P-N	48 ± 6*†	117 ± 2*	2.3 ± 0.3*†	134 ± 6	115 ± 5	127 ± 6	138 ± 5	15 ± 2†	1,403 ± 96*†

HR = heart rate; CO = cardiac output; AP = aortic pressure; LVP = left ventricular pressure; dP/dtMax = maximum first time derivative of LVP; S = systolic; D = diastolic; M = mean; Awake-B = awake baseline; Awake-P = awake paced at 115–120 beats/min; Iso-B = isoflurane (1.3%) baseline; Iso-P = isoflurane (1.3%) and paced at 115–120 beats/min; Iso-P-N = isoflurane paced and blood pressure corrected. Values are expressed as mean ± SEM.

* $P < 0.05$ *versus* Awake-B value.

† $P < 0.05$ *versus* Awake-P value.

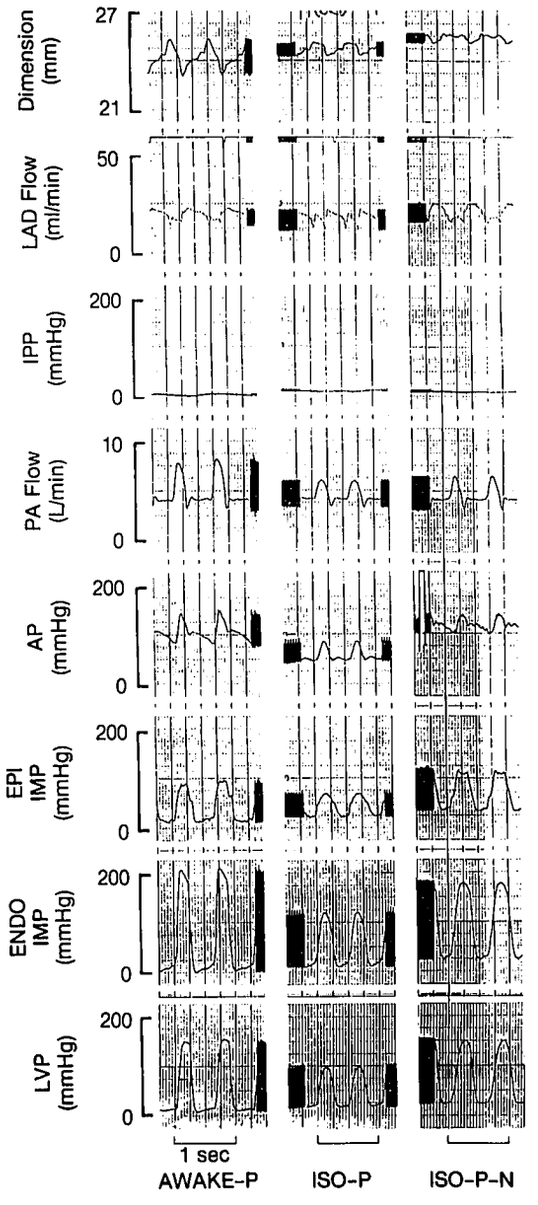

Fig. 3. Actual tracings of pressures, dimensions, and blood flow obtained from a representative dog. Awake-P = awake baseline and paced heart; ISO (1.3%)-P = isoflurane anesthesia (1.3%) and paced; ISO-P-N = isoflurane anesthesia, paced, and aortic pressure corrected to baseline value with phenylephrine; LVP = left ventricular pressure; ENDO-IMP = subendocardial intramyocardial tissue pressure; EPI-IMP = subepicardial intramyocardial tissue pressure; AP = aortic pressure; PA flow = pulmonary arterial blood flow; IPP = intrapleural pressure; LAD flow = left anterior descending coronary arterial blood flow; Dimension = segmental dimension in the anterior wall of the left ventricle.

In contrast to systolic IMP, end-diastolic IMP was higher in the subepicardium than the subendocardium during awake periods ($P < 0.05$), and this trend was maintained throughout the period of isoflurane anesthesia, although end-diastolic pressure rose significantly in both the subendocardium and subepicardium when AP was corrected to awake values.

Regional Myocardial Perfusion Pressure, Regional Myocardial Stroke Work, and Systolic Pressure Time Index

Results are summarized in table 3. During awake periods, RMPP was similar between subendocardium and subepicardium. With isoflurane, RMPP decreased in both regions; when MAP was corrected with phenylephrine, subendocardial RMPP increased to near awake values while subepicardial RMPP remained low, significantly below awake values. As a result, the ratio ENDO-RMPP/EPI-RMPP increased significantly ($P < 0.05$).

RMSW of the subendocardium was significantly higher than the RMSW of subepicardium during awake periods. With isoflurane, RMSW decreased in both subendocardial and subepicardial regions, but to a different degree; RMSW decreased more than 65% in the subendocardium whereas subepicardial RMSW decreased less than 50%. Likewise, SPTI decreased differentially: subendocardial SPTI decreased more than 30%, and subepicardial SPTI decreased less than 10%.

Regional Myocardial Blood Flow and Relation with Regional Myocardial Perfusion Pressure and Systolic Pressure Time Index

As shown in table 3, RMBF was higher in the subendocardium than subepicardium during awake periods, and was virtually unchanged in both regions with isoflurane despite significant decreases in perfusion pressure. RMBF increased significantly upon correction of AP to the level of awake values, preferentially in the subendocardium. As a result, ENDO-RMBF/EPI-RMBF ratio increased, which is the same directional change as the RMPP. Regression analysis (fig. 4) between the ratio of RMPP and RMBF revealed a significant positive relation between these two parameters ($r = 0.69$, $P < 0.001$). When awake values were eliminated from the analysis, the correlation coefficient increased to 0.76. Figure 5 is a scattergram showing the distribution of subendocardial SPTI and corresponding RMBF during awake paced recording and recording with pacing and use of isoflurane and phenylephrine. Points during iso-

Table 2. Changes in Intramyocardial Tissue Pressure (IMP) and Its Ratio to Left Ventricular Pressure (LVP) during Awake Control and Isoflurane Anesthesia

	Systolic (mmHg)				Diastolic (mmHg)			
	Endo	Endo/LVP	Epi	Epi/LVP	Endo	Endo/LVP	Epi	Epi/LVP
Awake-B	152 ± 11	1.2 ± 0.1	92 ± 9*	0.7 ± 0.1	9 ± 2	0.7 ± 0.2	19 ± 3*	2.5 ± 0.9
Awake-P	149 ± 12	1.1 ± 0.1	95 ± 8*	0.7 ± 0.1	7 ± 2	0.8 ± 0.3	18 ± 2*	2.2 ± 0.5
Iso-B	107 ± 7†	1.1 ± 0.1	85 ± 9*	0.9 ± 0.1	10 ± 2	1.1 ± 0.3	20 ± 2*	2.6 ± 0.7
Iso-P	95 ± 7†	1.1 ± 0.1	79 ± 9*	0.9 ± 0.1	9 ± 2	1.3 ± 0.6	20 ± 2*	2.6 ± 0.9
Iso-P-N	121 ± 10†	0.9 ± 0.1	92 ± 11*	0.7 ± 0.1	13 ± 2†	1.0 ± 0.3	29 ± 3*†	2.2 ± 0.5

Endo = endocardial IMP; Epi = epicardial IMP; Endo/LVP = endocardial to left ventricular pressure ratio; Epi/LVP = epicardial to left ventricular pressure ratio; Awake-B = awake baseline; Awake-P = awake and paced at 115–120 beats/min; Iso-B = isoflurane (1.3%) baseline; Iso-P = isoflurane (1.3%) and paced at 115–120 beats/min; Iso-P-N = isoflurane (1.3%), paced at 115–120 beats/min and blood pressure corrected. Values expressed are mean ± SEM.

* $P < 0.05$ *versus* corresponding Endo-IMP value.

† $P < 0.05$ *versus* Awake-P value.

flurane lie above and to the left of the points of during the awake state, suggesting subendocardial luxury perfusion during isoflurane.

Discussion

The effects of isoflurane on coronary blood flow and intramyocardial blood flow distribution have been the subjects of numerous studies that have reported conflicting data, mainly because of the confounding effects of baseline anesthetics other than isoflurane, acute surgery, and concurrent changes in HR and systemic blood pressure.[6–11,35,36,37] Furthermore, none of the previous studies addressed the relation between intramyocardial blood flow distribution and RMPP or regional myocardial work, two major local factors determining RMBF.[1,4] To address these deficits, we studied the effects of isoflurane on coronary blood flow, distribution of transmural blood flow, and IMPs in chronically instrumented dogs under conditions of controlled HR and MAP in the absence of baseline anesthetics and acute surgery.

The main findings of our study were that (1) isoflurane depresses global myocardial function and dilates coronary vessels; (2) isoflurane induces transmural blood flow redistribution in favor of subendocardium when HR and systemic pressure are controlled; (3) this blood flow redistribution appears to be related to differential changes in transmural IMPs with isoflurane; and (4) isoflurane decreases myocardial work concurrent with the increase in myocardial blood flow, resulting in a favorable oxygen supply–demand balance particularly in the subendocardium.

Our findings regarding the effects of isoflurane on LV global function are consistent with those of previous reports.[9,26,35,36] CO and dP/dt_{max} decreased concurrently with systemic hypotension. LAD blood flow remained unchanged despite decreases in systemic blood pressure, indicating coronary vasodilation. When systemic pressure and HR were corrected to levels of the awake stage, there was a significant increase in LAD flow during isoflurane anesthesia, confirming the coronary vasodilatory action of isoflurane.[9,10] Because most *in vitro* studies on isolated epicardial arterial rings have demonstrated no significant vasodilatory effects of isoflurane, the vasodilation we observed may have been mainly in the intramyocardial resistance vessels, as suggested in previous studies.[37–39] However, isoflurane did not induce significant coronary vasodilation in one study.[40] It is not possible to identify the exact reason for this discrepancy, but it probably results from differences in experimental models. This study was on an acute model, requiring surgical preparation and baseline anesthetics other than "isoflurane, anesthetic to be tested" and systemic pressure was allowed to fall significantly.

Transmural blood flow distribution is normally regulated by multiple factors, including regional differences in capillary anatomy and vascular innervation, and dynamic factors such as local vascular tone, metabolism or work, AP, HR, and myocardial tissue pressure (regional IMP).[1,4,12,13,14] Interpretation of the relative contribution to transmural blood flow redistribution of one particular factor separated from all other factors is extremely difficult because they are closely interrelated. Vasodilation, particularly of the intramyocardial distributory vessels, has been reported to induce intramyocardial blood flow redistribution. This phenomenon was thought to be attributable to the loss

Table 3. Regional Myocardial Perfusion Pressure (RMPP), Stroke Work (RMSW), Blood Flow (RMBF) and Systolic Pressure Time Index (SPTI) during Awake and Isoflurane Anesthesia

	RMPP (mmHg)			RMBF (ml·100 g^{-1}·min^{-1})			RMSW (erg·cm^{-2}·10^3)		SPTI (mmHg·s)	
	Endo	Epi	Endo/Epi	Endo	Epi	Endo/Epi	Endo	Epi	Endo	Epi
Awake-B	74 ± 5	77 ± 6	0.96 ± 0.02	—	—	—	13.2 ± 2	9.2 ± 2*	—	—
Awake-P	73 ± 6	80 ± 7	0.91 ± 0.1	110 ± 12	94 ± 10*	1.2 ± 0.3	11.0 ± 3	8.0 ± 2*	29 ± 3	20 ± 3*
Iso-B	45 ± 4†	44 ± 4†	1.02 ± 0.07	—	—	—	3.9 ± 1†	2.9 ± 1*†	—	—
Iso-P	41 ± 3†	42 ± 4†	0.98 ± 0.02	110 ± 13	83 ± 10*	1.3 ± 0.08	3.3 ± 1†	2.5 ± 1*†	17 ± 2†	17 ± 2
Iso-P-N	69 ± 5	64 ± 6†	1.07 ± 0.01†	171 ± 15†	128 ± 0.04†	1.4 ± 0.04	5.3 ± 2†	4.5 ± 1*	20 ± 2†	19 ± 2

Endo = endocardium; Epi = epicardium; Endo/Epi = endocardial to epicardial ratio; Awake-B = awake baseline; Awake-P = awake and paced at 115–120 beats/min; Iso-B = isoflurane (1.3%) baseline; Iso-P = isoflurane (1.3%) and paced at 115–120 beats/min; Iso-P-N = isoflurane, paced at 115–120 beats/min and blood pressure corrected. Values are expressed as mean ± SEM.

* $P < 0.05$ *versus* corresponding Endo-IMP value.

† $P < 0.05$ *versus* Awake-P value.

of regulation of vascular tone (metabolic and autoregulation).[4,7–11] Empirically, such vasodilation has been utilized to unveil the role of mechanical factors in regulation of transmural blood flow distribution. Under the conditions of steady HR and systemic pressure in the presence of maximum coronary vasodilation, IMP as a remaining variable factor was thought to play a major role in blood flow redistribution, although actual IMPs were not measured.[4,15,16,18]

IMP is the pressure generated in the myocardium and is a direct reflection of average regional myocardial stress.[4,21–23] Although there are significant variations in reported IMP, which largely depend on methodology, there is general agreement that systolic IMP decreases from subendocardium to subepicardium. Systolic subendocardial IMP equals or exceeds LVP in normal myocardium.[4,21–25] We observed a similar systolic IMP gradient. Diastolic IMP has been less frequently measured, mainly because of technical difficulties related to low pressures, and the reported distribution of diastolic IMPs across the LV wall has not been consistent. With the recent availability of ultraminiature pressure transducers, it is now possible to measure the diastolic IMP in the subepicardium and subendocardium with minimum distortion.[24,25,27,28] With this technique, recent studies reported that the gradient of diastolic IMP across the LV wall is the reverse of systolic IMP gradients.[28,41]

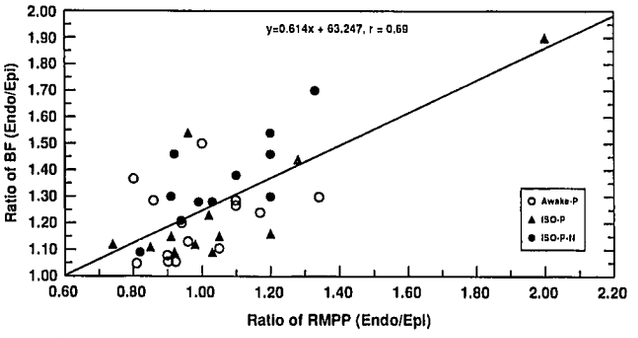

Fig. 4. Simple linear regression analysis between the ratio of subendocardial perfusion pressure to subepicardial perfusion pressure (Endo/Epi) and the subendocardial/subepicardial blood flow ratio (Endo/Epi) for all values, including awake values ($r = 0.69$, $P < 0.001$). ENDO-BF = subendocardial blood flow; EPI-BF = subepicardial blood flow; open circles = awake paced; triangles = isoflurane paced; filled circles = isoflurane paced, with phenylephrine. When awake values were eliminated from the analysis, the correlation coefficient increased (0.76, $P < 0.001$).

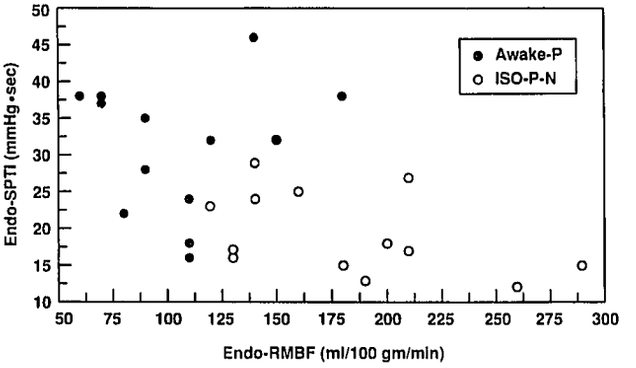

Fig. 5. Scattergram showing distribution of subendocardial systolic pressure time index (ENDO-SPTI) *versus* subendocardial blood flow (ENDO-RMBF) during awake paced (filled circles) and isoflurane paced with phenylephrine (open circles). The points representing awake paced data lie above and left to the points representing isoflurane paced with phenylephrine, indicating luxury perfusion during isoflurane anesthesia.

Our observation of consistently higher subepicardial diastolic pressures than subendocardial pressures throughout the study periods is compatible with these recent reports. The observed systolic IMP distribution across the LV free wall (ENDO-IMP > EPI-IMP), in our study as well as in previous reports, is consistent with the distribution of the radial stress calculated on the basis of Laplace's law, as well as other more sophisticated mathematical calculations based on experimental models.[4,22] However, diastolic IMP gradients based on theoretical calculations predict diastolic IMP will be higher in the subendocardium, which contradicts measured diastolic IMP gradients.[28,41] The values may be discrepant because the mathematical calculations assume that LVP is the source of IMP and the myocardium is considered to be passive and noncontractile.[22,41] Rather, the myocardium is the active contractile tissue and the current views dictate that myocardial contraction is the origin of both IMP and LVP and therefore, IMP largely depends on regional myocardial function. This view has been supported by a series of observations; IMP changes independently from LVP in response to changes in regional myocardial contractility.[4,22,24,31] In one study, the issue whether active tension is developed during diastole was specifically examined; resting diastolic epicardial IMP was higher than diastolic endocardial pressure in beating hearts at various filling pressures. In contrast to beating hearts, the subepicardial diastolic IMP was lower than subendocardial IMP in arrested hearts with potassium chloride at both high and low distending pressures. Based on these observations, the investigators concluded that myocardial tone is actively maintained during diastole particularly in subepicardial layers.[41]

It has been suggested that IMP exerts its effects by altering extravascular compressive pressure, and thus determines regional transmural perfusion pressure (coronary arterial pressure minus IMP).[13-24] Because both coronary arterial pressure and IMP are dynamically changing throughout a cardiac cycle and are not uniform across the LV free wall, it is logical to calculate the average RMPP by integrating pressure differences between regional (subendocardium or subepicardium) IMP and AP (assuming AP approximates coronary arterial pressure) during a whole cardiac cycle.[12] Diastolic pressure time index (an integration of pressure differences between AP and LVP during diastole) has been used to estimate diastolic perfusion pressure.[1,4,42] The idea of RMPP is an extension of diastolic pressure time index to the whole cardiac cycle, replacing LVP with regional IMP. The computation of RMPP and potential error of calculating RMPP using AP instead of coronary arterial pressure are described in the Materials and Methods.

Our findings of subendocardial and subepicardial RMBF in awake dogs are in general agreement with previous studies.[4,7-9] Subendocardial flow was slightly higher than in the subepicardium. RMPP ratio, however, was near unity, indicating perfusion pressure was not the sole determining factor for blood flow distribution in awake dogs.[1,4] Isoflurane increased the ENDO-RMBF/EPI-RMBF ratio when HR and AP were corrected, consistent with concurrent increase in ratio of RMPP. The relation between ratios of ENDO-RMPP/EPI-RMPP and ENDO-RMBF/EPI-RMBF was significantly positive (correlation coefficient of 0.69 with all values included), with improvement when the awake values were excluded (coefficient of 0.76), suggesting that RMPP plays a more prominent role in regulation of transmural blood flow redistribution when coronary arteries were dilated and metabolic regulation is impaired with isoflurane as reported previously.[5,9,10,11] Our findings, however, differ from the results of previous studies performed in chronically instrumented dogs, which failed to observe redistribution of transmural blood flow with isoflurane.[8,24] In one study, where AP and HR were not controlled, AP was lower and HR was higher during isoflurane anesthesia than awake control.[24] It is known that lower blood pressure and tachycardia favors blood flow shift toward the subepicardium.[1,4] In another study, transmural blood flow distribution was not altered by isoflurane in spite of controlled HR and AP.[8] This study, however, was performed in dogs whose major coronary arteries were either occluded or stenosed to create a "steal-prone" anatomy. Thus, it is possible that coronary blood flow to the normal zone may have been increased to cope with compensatory hyperfunction of normal myocardium.[43,44] In this study, systolic shortening and diastolic blood flow velocity of the region supplied by the left circumflex coronary artery rose more than 20% over resting values when the LAD was occluded, and RMBF and the ratio of subendocardial/subepicardial blood flow of the normal region during the control period were substantially higher than values reported in other studies[4,9] and in the current study. This indicates that blood flow to the normal zone was already increased and shifted to the subendocardium. Therefore, isoflurane was not able to dilate coronary arteries supplying normal myocardium any further resulting in no blood

flow shifts.[45] Because subendocardial coronary flow reserve is lost at higher perfusion pressure than is subepicardial reserve, and is nearly exhausted at critical coronary stenosis, coronary vasodilators are known to produce "steal" of blood flow from subendocardium to subepicardium.[11,45-47] Such an effect is particularly prominent with drugs with predominant vasodilatory action on intramyocardial small vessels, the proposed site of action of isoflurane.[37] The effects of isoflurane anesthesia on transmural blood flow distribution have been studied in a canine model of fixed coronary stenosis.[11,46] In one study, isoflurane decreased the ENDO-RMBF/EPI-RMBF ratio in the region distal to a fixed coronary artery stenosis but increased it in a normal region.[46] In another study in a similar model, although the ENDO-RMBF/EPI-RMBF ratio was decreased, a true transmural coronary steal (with a decrease in subendocardial blood flow accompanying transmural redistribution) was not observed in the stenotic area.[11] This study suggested that although isoflurane is a vasodilator, it is either not a potent vasodilator, or the negative inotropic effects that accompany its vasodilatory properties modify the redistribution, acting to maintain subendocardial blood flow. Although IMP was not measured in this study, it is likely that the negative inotropic property of isoflurane may have reduced IMP particularly in the subendocardium as was observed in our study, and thus, it acted to maintain endocardial blood flow by decreasing compressive forces on subendocardial arterioles.[48,49] Both studies, however, were performed in acute surgical models with coronary stenosis requiring surgery and baseline anesthetics, and HR or AP was not closely controlled. Therefore, it is difficult to compare to those results with the results of long-term studies in which HR and blood pressure are controlled, as in the current study.[8]

Because IMP is the average stress of a particular region of myocardium, mainly reflecting local myocardial contractile function, IMP is considered an index of regional myocardial oxygen consumption.[4,21-25,31] Previously, IMP was shown to correlate well with myocardial oxygen consumption.[24,31] SPTI based on LVP (area underneath the LVP curve during systole), an index used to represent myocardial demand,[4] was significantly different from concurrent SPTI based on IMP, raising serious doubt whether SPTI based on LVP adequately represents regional myocardial oxygen demand.[25,32] In line with this concept and incorporating the concept of the pressure–length loop based on LVP as an index of RMSW,[30] we calculated SPTI and RMSW using the IMP as described in Materials and Methods. In the current study, RMSW based on IMP decreased significantly both in subendocardium and subepicardium with isoflurane, but this decrease was more prominent in the subendocardium (65% decrease) than in subepicardium (50% decrease). However, this interpretation of differential changes in RMSW has a technical limitation; because we used dimension transducers implanted in the mid portion of the LV wall to calculate both ENDO-RMSW and EPI-RMSW, this is certain to introduce some error compared with actual RMSW based on dimension transducers in the subepicardium and subendocardium. Considerable evidence indicates that myocardial fiber shortening is not uniform across the LV wall; inner circumference shortens more than outer circumference during systole.[50,51] Thus, we may have underestimated ENDO-RMSW and overestimated EPI-RMSW. However, providing the error introduced remained constant for both regions, the errors in estimating percentage changes in RMSW of each region should be small. SPTI showed similar trends to RMSW: SPTI decreased more in subendocardium, mainly because isoflurane depressed systolic IMP more in subendocardial than subepicardial regions. The predominant decreases in indices (RMSW and SPTI) representing subendocardial oxygen demands in the presence of preferential increases in ENDO-RMBF support the idea that isoflurane impairs autoregulation of coronary flow and creates a state of luxury perfusion beyond metabolic needs.[9-11] Although the exact mechanisms for this differential effect on IMPs are not clear, there have been studies reporting that increases in inotropism (by sympathetic stimulation or infusion of inotropes) elevated subendocardial IMP more than LVP, and the reverse was observed with negative inotropes.[22,24,49,52] Halothane depressed endocardial IMP more than LVP or subepicardial IMP in a dose-dependent fashion and improved endocardial viability ratio (diastolic pressure time index/SPTI).[32,53] Thus, the observed differential depression of IMP with isoflurane is likely a nonspecific finding common to any interventions that exert negative inotropic effects.

Significant positive relations between the ratio of RMPP and RMBF during isoflurane anesthesia strongly suggest that changes in transmural IMP distribution resulting from a negative inotropic effect of isoflurane is responsible, at least in part, for the observed changes in transmural blood flow distribution. However, there are other possible explanations for the preferential increases in subendocardial blood flow. Differential cor-

onary vasodilation by isoflurane is one possibility. However, there is no evidence that isoflurane dilates subendocardial vessels more than subepicardial vessels although the proposed site of action of isoflurane is on intramyocardial small vessels.[37] The other possibilities are related to the use of phenylephrine to raise the AP. An effect of "reverse coronary steal" with phenylephrine is possible because it has been demonstrated that vasoconstriction may augment subendocardial blood flow in an ischemic area of myocardium or during coronary hypoperfusion.[54,55] An opposing effect with phenylephrine is also possible because it raised left ventricular end-diastolic pressure. The increase in left ventricular end-diastolic pressure may limit the increase in subendocardial flow.[56] It is difficult to know to what extent these effects played roles in transmural flow redistribution in our study, but it is likely that the effects of one would partially negate those of the other. Furthermore, infusion of phenylephrine directly into a coronary artery which was already dilated with adenosine did not shift the ratio of RMBF.[57] Thus, we postulate that changes in IMPs rather than differential vasodilation or phenylephrine infusion played a significant role in the increase in the ENDO-RMBF/EPI-RMBF ratio. Although the current study was not designed to examine the controversial issue of "isoflurane induced coronary steal," [5,7,8] it is important to study the role of regional IMP in determining blood flow distribution of LV with steal-prone anatomy.

In summary, isoflurane induced coronary vasodilation and increased blood flow preferentially toward the subendocardium when MAP and HR were controlled. The increases in blood flow in subendocardium occurred in the presence of decreases in subendocardial RMSW and SPTI, indicating impairment of local metabolic regulation. Transmural blood flow distribution was correlated positively with the changes in transmural perfusion pressures calculated based on regional IMPs, suggesting that changes in transmural blood flow are influenced by transmural IMP changes under the conditions of coronary vasodilation and impaired metabolic regulation induced by isoflurane anesthesia.

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