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Recovery of Contractile Function of Stunned Myocardium in Chronically Instrumented Dogs is Enhanced by Halothane or Isoflurane

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Following brief periods (5–15 min) of total coronary artery occlusion and subsequent reperfusion, despite an absence of tissue necrosis, a decrement in contractile function of the postischemic myocardium may nevertheless be present for prolonged periods. This has been termed "stunned" myocardium to differentiate the condition from ischemia or infarction. Because the influence of volatile anesthetics on the recovery of postischemic, reperfused myocardium has yet to be studied, the purpose of this investigation was to compare the effects of halothane and isoflurane on systemic and regional hemodynamics following a brief coronary artery occlusion and reperfusion. Nine groups comprising 79 experiments were completed in 42 chronically instrumented dogs. In awake, unsedated dogs a 15-min coronary artery occlusion resulted in paradoxical systolic lengthening in the ischemic zone. Following reperfusion active systolic shortening slowly returned toward control levels but remained approximately 50% depressed from control at 5 h. In contrast, dogs anesthetized with halothane or isoflurane (2% inspired concentration) demonstrated complete recovery of function 3–5 h following reperfusion. Because the anesthetics directly depressed contractile function, additional experiments were conducted in which a 15-minute coronary artery occlusion was produced during volatile anesthesia; however, each animal was allowed to emerge from the anesthetized state at the onset of reperfusion. Similar results were obtained in these experiments, demonstrating total recovery of contractile function within 3–5 h following reperfusion. Thus, despite comparable degrees of contractile dysfunction during coronary artery occlusion in awake and anesthetized dogs, the present results demonstrate that halothane and isoflurane produce marked improvement in the recovery of segment function following a transient ischemic episode. Therefore, volatile anesthetics may attenuate postischemic left ventricular dysfunction occurring intraoperatively and enhance recovery of regional wall motion abnormalities during reperfusion. (Key words: Anesthetics, volatile: halothane; isoflurane. Heart, coronary circulation: ischemia; occlusion. Heart, stunned myocardium: postischemic, reperfusion contractile deficit.)

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RESTORATION of blood flow to ischemic myocardium following brief periods of coronary artery occlusion is not necessarily accompanied by an immediate return of contractile function to normal. Experimental studies have shown that return of function may be greatly delayed despite an absence of tissue necrosis and the postischemic myocardium may act as if "stunned."[1] Such phenomena may have important clinical counterparts. For example, a sustained spasm of a large epicardial coronary artery spontaneously resolving after 5–15 min of occlusion or repeated ischemic episodes of brief duration in unstable angina may both result in temporary regional contractile dysfunction. Postischemic abnormalities of contraction may also be present following myocardial reperfusion accomplished by a variety of techniques, such as thrombolytic therapy, angioplasty, or coronary artery bypass graft surgery. After therapeutic interventions to restore perfusion sustained contractile deficits may be present in myocardium requiring inotropic support for hours to days until adequate recovery occurs. Recently, prolonged left ventricular dysfunction has been described in patients with coronary artery disease after perioperative ischemic events.[2]

The mechanism of stunned myocardium is currently unknown, but a number of experimental investigations have been completed describing the time course of recovery of postischemic, reperfused myocardium following various periods of coronary artery occlusion. In addition, a number of pharmacologic interventions have been shown to enhance the recovery of stunned myocardium.[3–7] Nicorandil, a new nicotinamide–nitrate antianginal agent, has been shown to improve functional recovery of postischemic, reperfused myocardium in conscious[4] and pentobarbital-anesthetized dogs.[3] Similarly in pentobarbital-anesthetized dogs, administration of esmolol[5] or superoxide dismutase and catalase[6] enhanced recovery of stunned myocardium. A recent investigation comparing the time course of recovery of contractile function following various periods of occlusion in conscious, chronically instrumented *versus* acute, pentobarbital-anesthetized open chest dogs showed no differences in recovery of function in anesthetized *versus* conscious animals.[7] The present study was specifically designed to ascertain the influence of halothane and isoflurane on the functional

recovery of systolic shortening. The goals of this investigation were to characterize the time course of recovery of contractile function in the postischemic zone following a brief period of coronary artery occlusion in dogs anesthetized with halothane or isoflurane. Chronically instrumented dogs were utilized so that a direct comparison could be made to the conscious state.

Methods

General Preparation

Conditioned mongrel dogs of either sex weighing between 22 and 29 kg were fasted overnight and anesthetized with sodium thiamylal (10 mg/kg, iv). After tracheal intubation anesthesia was maintained with halothane (1.0–1.5%) in 100% oxygen *via* positive pressure ventilation. The left lateral chest wall was shaved, scrubbed, disinfected, and draped. Under sterile conditions a thoracotomy was performed in the L-5 intercostal space. The heart was supported in a pericardial cradle and heparin-filled catheters were inserted into the thoracic aorta and right atrial appendage for measurement of arterial pressure and fluid or drug administration, respectively. A 1.5–2.0 cm section of the proximal left anterior descending coronary artery (distal to the first diagonal branch) was carefully isolated and a precalibrated Doppler ultrasonic flow transducer (20 MHz) was positioned around the vessel for measurement of phasic and mean coronary blood flow velocity. A hydraulic vascular occluder (In Vivo Metric), utilized to produce total coronary artery occlusion (inflation) and reperfusion (deflation), was positioned immediately distal to the ultrasonic flow transducer.

Pairs of miniature ultrasonic segment length transducers (5 MHz) for measurement of changes in regional myocardial segment function (systolic shortening; % SS) were implanted within the subendocardium (10–15 mm apart and 7–9 mm deep) in a circumferential plane in the region of the left ventricular free wall perfused by the left anterior descending coronary artery. Surgical placement of the segment length gauges was facilitated by brief coronary artery occlusion to define the central cyanotic region. A Konigsberg high-fidelity miniature micromanometer (P7) was inserted in the left ventricle through an incision in the apex and tightly secured in position for subsequent recording of left ventricular pressure. The maximum rate of rise of left ventricular pressure (peak positive dP/dt), an index of global left ventricular contractility, was obtained by electronic differentiation of the ventricular pressure waveform. A triangular wave signal with known slope was used to calibrate the differentiator. A catheter was also positioned in the left atrial appendage. The left ventricular micromanometer was cross-calibrated *in vivo* against pressures measured *via* the arterial and left atrial fluid-filled catheters (Statham P50 transducer). All catheters and leads were secured, tunneled between the scapulae, and exteriorized *via* a small incision. The chest wall was closed in layers and pneumothorax evacuated by a chest tube. Each dog was fitted with a jacket to prevent damage to the instruments and catheters that were housed in an aluminum box within the jacket pocket.

After surgery each dog was treated with chloramphenicol (1.5 g bid, po) and allowed to recover for 7–10 days. During this time each dog was trained to stand quietly in a sling during monitoring of hemodynamics. Segment length and coronary blood flow velocity signals were monitored *via* ultrasonic amplifiers (Hartley, Houston, Texas). As in previous studies from this and other laboratories[3–8] using left ventricular dP/dt, end-systolic segment length (ESL) was determined at maximum negative dP/dt and end-diastolic segment length (EDL) was determined at the onset of left ventricular isovolumetric contraction. The lengths were normalized according to the method of Theroux *et al.*[8] Percent segment shortening (% SS) was calculated by use of the equation:

$$\% \text{ SS} = \frac{\text{EDL} - \text{ESL}}{\text{EDL}} \times 100$$

During each experiment hemodynamic data were recorded continuously on a Hewlett-Packard polygraph and digitized with a microcomputer interfaced with an ISAAC analog-to-digital converter (91A) as previously described.[9] The average values of eight consecutive cardiac cycles were utilized. Because conscious dogs have a prominent sinus arrhythmia, data were collected in all experiments during periods of expiration at a stable hemodynamic state. Arterial blood samples were obtained at various intervals for measurement of blood gases (ABL 2) and anesthetic concentrations *via* a modification of a gas chromatographic technique as described by Lowe.[10] Standard concentrations of halothane and isoflurane were made up in millimolar units.

Experimental Protocol

Nine groups comprising of 79 experiments were performed during which global and regional hemodynamics were continuously recorded. All animals were fasted overnight, and prior to experimentation fluid deficits were corrected with 0.9% normal saline. Fluid maintenance was continued at 3 $ml \cdot kg^{-1} \cdot h^{1}$ for the duration of each experiment. Schematized experimental protocols are depicted in figure 1.

The first group of experiments (n = 9) was performed on dogs in the awake, unsedated state to characterize the time course of recovery of contractile function following brief coronary occlusion in the absence of anesthetic. Hemodynamics were continuously recorded each day for 2.5

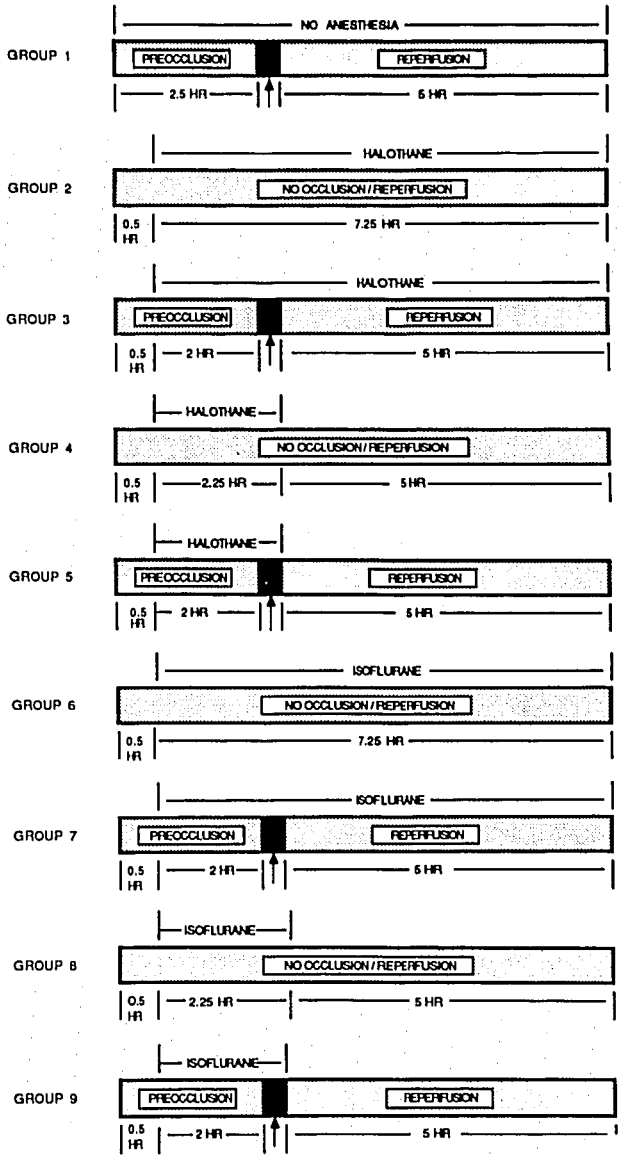

FIG. 1. Schematic representation of various protocols utilized in the nine experimental groups. Group 1 consisted of dogs undergoing coronary artery occlusion and reperfusion without anesthesia. Groups 2 and 3 consisted of dogs anesthetized with halothane without (group 2) or with (group 3) coronary artery occlusion and reperfusion. Groups 4 and 5 consisted of dogs in which halothane anesthesia was maintained for 2.25 h and the animals allowed to emerge from anesthesia without (group 4) or with (group 5) coronary artery occlusion and reperfusion. Groups 6 and 7 consisted of dogs anesthetized with isoflurane without (group 6) or with (group 7) coronary artery occlusion and reperfusion. Groups 8 and 9 consisted of dogs in which isoflurane anesthesia was maintained for 2.25 h and the animals allowed to emerge from anesthesia without (group 8) or with (group 9) coronary artery occlusion and reperfusion. Black bars and arrows in certain groups indicate a 15-min period of coronary artery occlusion.

h under resting conditions. The left anterior descending coronary artery was then totally occluded by inflation of the ballon cuff occluder for a period of 15 min. After this 15-min coronary occlusion reperfusion was accomplished by slow deflation of the occluder over 2 min. Slow reperfusion, monitored by continuous recording of coronary blood flow velocity, was utilized rather than abrupt reflow to prevent excessive ventricular ectopy. In addition, all dogs received lidocaine (1 mg/kg iv) 10 min prior to coronary artery occlusion. Lidocaine (1 mg/kg iv) was also administered immediately prior to reperfusion. Regional segment function and other hemodynamic parameters were recorded before, 15 min following the onset of coronary artery occlusion, and at various intervals during reperfusion for 5 h. No analgesics were utilized during coronary artery occlusion as dogs never exhibited any signs of noxious stimuli with this procedure.

The second group of experiments (n = 10) was performed to determine the effect of sustained halothane anesthesia without coronary artery occlusion and/or reperfusion on regional contractile function over a 7.25-h period. Following a 30-min period of monitoring systemic and coronary hemodynamics in awake, unsedated dogs, anesthesia was induced by mask with halothane (5%) in nitrous oxide and oxygen at high flow rates (7 and 3 l/min, respectively). After tracheal intubation anesthesia was maintained with halothane (2.0% inspired) in 100% oxygen (2 l/min) for a total of 7.25 hours *via* a ventilator (Monaghan 300 D/M; 9–12 breaths/min; tidal volume of 15 ml/kg). Arterial blood gases were obtained at selected intervals and ventilation adjusted to approximate conscious control levels. These experiments served to document the stability of systemic and coronary hemodynamics during halothane anesthesia over an experimental period equivalent to that utilized in those experiments with coronary artery occlusion and reperfusion. The third group of experiments (n = 9) was conducted in an identical fashion to group 1; however, each experiment was completed during halothane anesthesia. Following a 30-min period of monitoring hemodynamics in the conscious state, halothane anesthesia was induced by mask as in group 2. Anesthesia was maintained with halothane (2.0% inspired) in 100% oxygen (2 l/min) for a period of 2 h to ensure a stable hemodynamic state. At the conclusion of 2 h a 15-min coronary artery occlusion followed by reperfusion was accomplished in an identical fashion to group 1. Lidocaine was administered in all dogs subjected to coronary artery occlusion as in the protocol described for group 1. The recovery of contractile function in the postischemic, reperfused region was followed for 5 h. The results of these experiments served to ascertain the degree and time course of recovery of regional contractile function after an ischemic event and subsequent reperfusion during halothane anesthesia.

Because the volatile anesthetics directly depress contractility, the fourth and fifth experimental series were designed to determine the recovery of contractile function

TABLE 1. Summarized Hemodynamic Data in Conscious Dogs before and after a 15-Min Coronary Artery Occlusion (Group 1)

			Reperfusion (h)						
	Preocclusion	Occlusion	0.25	0.50	1	2	3	4	5
HR (beats/min)	87 ± 2	118 ± 7*	88 ± 6	89 ± 5	87 ± 4	90 ± 4	89 ± 3	85 ± 4	89 ± 8
MAP (mmHg)	96 ± 5	97 ± 3	98 ± 4	99 ± 3	100 ± 3	102 ± 3	101 ± 3	96 ± 3	104 ± 4
LVSP (mmHg)	119 ± 6	114 ± 4	120 ± 5	118 ± 4	122 ± 5	125 ± 3	121 ± 3	121 ± 4	128 ± 4
LVEDP (mmHg)	7 ± 1	10 ± 1*	8 ± 1	8 ± 1	8 ± 1	8 ± 1	6 ± 1	8 ± 1	8 ± 1
+dP/dt (mmHg/s)	2,770 ± 200	2,500 ± 160	2,350 ± 170	2,420 ± 170	2,500 ± 180	2,530 ± 190	2,530 ± 190	2,530 ± 180	2,680 ± 170
MCBFV (Hz × 10^2)	33 ± 6	0*	28 ± 6	31 ± 7	30 ± 6	31 ± 6	32 ± 6	30 ± 5	32 ± 6
EDL (mm)	10.0 ± 0.1	10.8 ± 0.2*	10.8 ± 0.2*	10.7 ± 0.1*	10.7 ± 0.1*	10.7 ± 0.1*	10.7 ± 0.1*	10.7 ± 0.1*	10.7 ± 0.1*
ESL (mm)	8.2 ± 0.2	11.2 ± 0.2*	10.3 ± 0.3*	10.1 ± 0.3*	9.9 ± 0.3*	9.9 ± 0.3*	9.8 ± 0.3*	9.7 ± 0.3*	9.6 ± 0.2*
SS (%)	18.5 ± 2.4	−3.4 ± 1.3*	4.9 ± 2.0*	6.1 ± 2.0*	7.6 ± 2.0*	7.8 ± 2.1*	8.5 ± 2.2*	9.4 ± 2.1*	10.1 ± 1.8*

Values are given as mean ± SEM (n = 9).

HR = heart rate; MAP = mean arterial pressure; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; MCBFV = mean coronary blood flow velocity; EDL = end-diastolic segment length; ESL = end-systolic segment length; SS = segment shortening [(EDL − ESL)/EDL × 100].

* Significantly ($P < 0.05$) different from preocclusion.

in the postanesthetic state following coronary artery occlusion during halothane anesthesia. In the fourth group (n = 9) following 30 min of hemodynamic monitoring of awake dogs, anesthesia was induced *via* mask with halothane as described above. Anesthesia was maintained with halothane (2.0% inspired) in 100% oxygen (2 l/min) for a period of 2.25 hours. At the end of this period each dog was allowed to emerge from anesthesia, and global and regional contractile function were monitored for 5 h. During emergence all animals were allowed to breathe room air. These experiments served to determine the influence of emergence from anesthesia (without coronary artery occlusion and reperfusion) on systemic and coronary hemodynamics. In a parallel fashion an additional group (group 5; n = 8) was studied to determine the time course of recovery of contractile function during emergence from halothane anesthesia following coronary artery occlusion. As in group 4 after 30 min of hemodynamic monitoring in the conscious state, halothane anesthesia was induced *via* mask and maintained for 2.25 h. After 2 h of halothane anesthesia a 15-min coronary artery occlusion was performed, and each animal was allowed to emerge from anesthesia concomitant with coronary artery reperfusion.

The experimental groups 6, 7, 8, and 9 were completed in an identical fashion to groups 2, 3, 4, and 5, respectively; however, isoflurane (2.0% inspired) in 100% oxygen (2 l/min) was utilized. Concentrations of volatile anesthetics were chosen to produce varying hemodynamic effects as found in preliminary studies. Thus, no effort was made to control hemodynamics such as heart rate. These experiments were performed to compare the influence of halothane *versus* isoflurane anesthesia (despite markedly different hemodynamic effects) on the functional recovery of postischemic, reperfused myocardium. Thus, the influence of sustained isoflurane anesthesia without and with coronary artery occlusion and reperfusion was studied in groups 6 (n = 10) and 7 (n = 9), respectively. Similarly, the influence of isoflurane anesthesia and subsequent emergence from anesthesia in dogs without and with coronary artery occlusion and reperfusion were studied in groups 8 (n = 8) and 9 (n = 7), respectively. A total of 79 experiments were conducted in which 42 chronically instrumented dogs were randomly assigned to various groups, with the exception that each dog received only one coronary artery occlusion and reperfusion.

STATISTICAL ANALYSIS

Statistical analysis of data during control and following coronary occlusion and reperfusion with or without the presence of anesthesia were performed by means of analysis of variance (ANOVA) followed by Dunnett's modification of the *t* test or ANOVA with repeated measures followed by Fisher's least significant difference (LSD). Because equipotent (similar MAC) concentrations of halothane and isoflurane were not utilized, statistical comparisons between anesthetics were not made. Changes between groups or within a group from control were considered significant when the probability (*P*) value was less than 0.05. All data are expressed as mean ± SEM.

Results

TIME COURSE OF RECOVERY OF REGIONAL SEGMENT FUNCTION IN CONSCIOUS DOGS

Systemic and coronary hemodynamics and regional segment function data before, at the end of 15 min of left anterior descending coronary artery occlusion, and

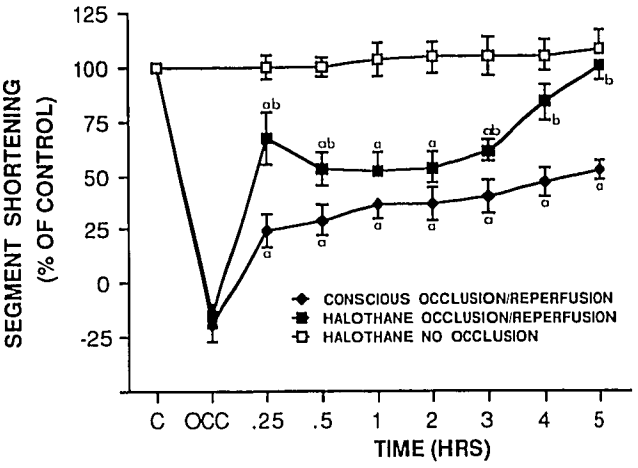

FIG. 2. Segment shortening data (expressed as percent of control; mean ± SEM) during coronary artery occlusion (OCC) and at various times following reperfusion in conscious dogs (group 1) and in dogs anesthetized with halothane (group 3). Comparisons are made at various time points to those animals anesthetized with halothane but not undergoing coronary artery occlusion and reperfusion (group 2). [a]Significant ($P < 0.05$) difference, group 2 (anesthetized without occlusion) *versus* 1 (conscious occlusion) or 3 (occlusion during anesthesia). [b]Significant ($P < 0.05$) difference, group 1 (conscious occlusion) *versus* 3 (occlusion during anesthesia). Note that the control state (C) indicates either the awake, unsedated state (group 1) or following a stable hemodynamic state after 2 h of halothane anesthesia (groups 2 and 3).

during 5 h of reperfusion are summarized in table 1. There were few changes from control in global hemodynamics during coronary artery occlusion or following reperfusion. Heart rate and left ventricular end diastolic pressure were significantly ($P < 0.05$) increased during coronary artery occlusion but returned to control within 15 min following reperfusion and remained stable throughout the duration of the experiment. Concomitant with the increase in heart rate during coronary artery occlusion was a significant increase in the heart rate–systolic pressure product (10.1 ± 0.7 to 13.4 ± 1.5 beats/min · mm Hg × 10^3). Left ventricular systolic and mean arterial pressures and peak positive left ventricular dP/dt were unchanged throughout the experiment.

During coronary artery occlusion regional systolic shortening was replaced by paradoxical systolic lengthening, indicating aneurysmal bulging in the left anterior descending region (fig. 2). The marked decrease of segment shortening during coronary occlusion was associated with large increases in EDL (10.0 ± 0.1 to 10.8 ± 0.2 mm) and ESL (8.2 ± 0.2 to 11.2 ± 0.2 mm). During reperfusion segment shortening slowly improved toward control levels but was still significantly ($P < 0.05$) reduced (52 ± 4% of control) after 5 h of reperfusion.

Effect of Halothane Anesthesia on the Time Course of Recovery of Regional Contractile Function in Chronically Instrumented Dogs

In all dogs following 2 h of halothane (blood halothane concentration 1.71 ± 0.06 mM) anesthesia (n = 36 from groups 2, 3, 4, and 5), there were significant decreases from control in mean aortic pressure (97 ± 2 to 68 ± 2 mmHg), left ventricular systolic pressure (117 ± 2 to 81 ± 2 mmHg), peak positive dP/dt (2600 ± 120 to 990 ± 50 mmHg/s), mean coronary blood flow velocity (32 ± 2 to 23 ± 2 Hz × 10^2) and the heart rate–systolic pressure product (9.6 ± 0.3 to 7.2 ± 0.3 beats/min · mmHg × 10^2). No changes were observed in heart rate (82 ± 2 to 89 ± 3 beats/min), arterial blood *p*H (7.40 ± 0.01 to 7.40 ± 0.01), or arterial P_{CO_2} (33.4 ± 0.5 to 30.4 ± 0.8 mmHg). Because all animals were ventilated with 100% oxygen, there was an increase in arterial P_{O_2} (89 ± 2 to 530 ± 14 mmHg). Concomitant with the decrease in peak positive dP/dt produced by halothane, ESL was significantly increased (8.4 ± 0.1 to 9.0 ± 0.2 mm) and percent

TABLE 2. Summarized Hemodynamic Data in Halothane-anesthetized Dogs (No Occlusion/Reperfusion) (Group 2)

		Halothane Anesthesia (h)					
	Conscious	2†	3‡	4‡	5‡	6‡	7‡
HR (beats/min)	79 ± 4	80 ± 3	82 ± 3	79 ± 4	76 ± 4	73 ± 5	73 ± 6
MAP (mmHg)	97 ± 3	64 ± 6*	69 ± 5*	70 ± 6*	68 ± 6*	67 ± 6*	67 ± 7*
LVSP (mmHg)	120 ± 3	84 ± 5*	84 ± 4*	85 ± 4*	81 ± 4*	81 ± 5*	79 ± 5*
LVEDP (mmHg)	9 ± 1	11 ± 1	10 ± 1	10 ± 2	10 ± 1	9 ± 1	10 ± 1
+dP/dt (mmHg/s)	2,700 ± 130	1,080 ± 100*	1,020 ± 90*	1,000 ± 90*	930 ± 90*	900 ± 110*	900 ± 110*
MCBFV (Hz × 10^2)	33 ± 5	22 ± 3*	25 ± 3	22 ± 3*	21 ± 4*	19 ± 3*	19 ± 4*
EDL (mm)	10.1 ± 0.2	9.9 ± 0.2	10.0 ± 0.2	10.0 ± 0.2	9.9 ± 0.2	9.8 ± 0.2	9.8 ± 0.3
ESL (mm)	8.4 ± 0.4	9.0 ± 0.3*	9.0 ± 0.4	9.0 ± 0.4	8.9 ± 0.4	8.9 ± 0.4	8.8 ± 0.4
SS (%)	16.3 ± 2.6	9.6 ± 2.6*	10.0 ± 2.7*	10.4 ± 3.1*	10.5 ± 3.1	10.0 ± 2.5*	10.0 ± 2.3*
Blood halothane (mM)	—	1.59 ± 0.13	1.94 ± 0.17	1.97 ± 0.17	2.13 ± 0.21	2.20 ± 0.24	2.14 ± 0.15

Values are given as mean ± SEM (n = 10).
* Significantly ($P < 0.05$) different from conscious.
† Time of anesthesia corresponds to halothane preocclusion in table 3.
‡ Time of anesthesia corresponds to halothane + reperfusion 1, 2, 3, 4, 5 in Table 3.

segment shortening significantly reduced (18.3 ± 1.1 to 10.0 ± 1.0%). No change in EDL was observed.

Changes in hemodynamics and regional segment function produced by halothane anesthesia over 7 h in dogs without coronary occlusion and reperfusion (group 2) are summarized in table 2 and figure 2. Following 2 h of anesthesia with halothane systemic and regional hemodynamics remained unchanged over the next 5 h. Global and regional hemodynamics in dogs subjected to a 15-min coronary artery occlusion and 5 h of reperfusion during halothane anesthesia (group 3) are summarized in table 3 and figure 2. Similar to observations in conscious dogs, there was an abrupt increase in left ventricular end-diastolic pressure (9 ± 1 to 14 ± 2 mmHg) during coronary artery occlusion. In contrast to conscious dogs, no changes in heart rate occurred. Furthermore, no alteration in mean arterial pressure, left ventricular systolic pressure, peak positive dP/dt, or double product was observed. Similar to those results obtained in conscious dogs, however, there was a marked increase in EDL and ESL, and systolic shortening was replaced by paradoxical lengthening. During reperfusion few changes in systemic hemodynamics were observed; however, there was a progressive decrease in ESL and a corresponding increase in segment shortening over the 5-h reperfusion period. As compared to conscious dogs, during halothane anesthesia there was a greater recovery of percent segment shortening (fig. 2). By 4 and 5 h of reperfusion segment shortening was not different from dogs anesthetized with halothane that were not subjected to coronary artery occlusion or reperfusion (group 2). Whereas contractile function in dogs subjected to ischemia during halothane anesthesia returned to control by the end of the reperfusion period, unanesthetized dogs (group 1) still exhibited a contractile deficit (50% of control) at 5 h following reperfusion.

In two separate series (groups 4 and 5) dogs were allowed to emerge from anesthesia to avoid the direct depressant effects of halothane on hemodynamics and contractile function. Hemodynamic data before, during, and after halothane anesthesia in dogs not subjected to ischemia (group 4) are summarized in table 4. Following 2 h of halothane dogs (n = 9) were allowed to emerge from anesthesia and were monitored over a period of 5 h. Within the first 30 min of emergence, there was an increase in heart rate and coronary blood flow velocity as compared to the conscious control state. By 1 h, however, hemodynamics were not significantly different from the conscious state. Similarly, no changes in segment shortening from the conscious control were observed over the 5-h emergence period (fig. 3). Similar results (table 5; fig. 3) were obtained in dogs subjected to a 15-min coronary artery occlusion under halothane anesthesia (group 5). In these experiments within the first 60 min of emergence there was also a significant increase in heart rate. In con-

TABLE 3. Summarized Hemodynamic Data in Halothane-anesthetized Dogs before and after a 15-Min Coronary Artery Occlusion (Group 3)

	Conscious Preocclusion	Halothane Preocclusion*	Halothane + Occlusion	Halothane + Reperfusion (h)					
				0.25	0.50	1	2	3	4	5
HR (beats/min)	84 ± 4	94 ± 5	96 ± 6	89 ± 6	90 ± 5	89 ± 4	89 ± 4	87 ± 5	84 ± 5	81 ± 5
MAP (mmHg)	95 ± 4	71 ± 3*	64 ± 5	61 ± 4	63 ± 4	63 ± 3	67 ± 4	66 ± 5	65 ± 5	65 ± 6
LVSP (mmHg)	115 ± 4	82 ± 3*	76 ± 5	75 ± 4	76 ± 5	77 ± 5	81 ± 5	80 ± 5	78 ± 5	79 ± 5
LVEDP (mmHg)	8 ± 1	9 ± 1	14 ± 2‡	12 ± 2	11 ± 2	11 ± 2	10 ± 2	9 ± 1	9 ± 1	9 ± 1
+dP/dt (mmHg/s)	2,570 ± 220	970 ± 60†	820 ± 70	760 ± 60‡	780 ± 60	780 ± 50	820 ± 50	810 ± 50	800 ± 50	790 ± 40
MCBFV (Hz × 10^2)	33 ± 3	24 ± 3†	0‡	23 ± 4	22 ± 4		21 ± 3	21 ± 3	21 ± 3	21 ± 3
EDL (mm)	10.2 ± 0.1	9.6 ± 0.3	10.3 ± 0.3‡	10.1 ± 0.3	10.1 ± 0.3	21 ± 4	10.0 ± 0.4	9.9 ± 0.4	9.9 ± 0.3	9.9 ± 0.4
ESL (mm)	8.4 ± 0.2	8.6 ± 0.2	10.5 ± 0.3‡	9.4 ± 0.2‡	9.6 ± 0.3‡	10.1 ± 0.3		9.3 ± 0.3	9.1 ± 0.3	8.9 ± 0.3
SS (%)	17.7 ± 2.0	10.3 ± 1.5†	−1.4 ± 0.4‡	6.9 ± 1.6‡	5.4 ± 1.1‡	9.5 ± 0.3‡	9.4 ± 0.3‡	6.2 ± 1.0	8.1 ± 0.9	10.0 ± 1.1
Blood halothane (mM)	—	1.70 ± 0.08	—	—	—	5.1 ± 0.8‡ 1.94 ± 0.09	5.2 ± 0.8‡ 2.02 ± 0.07‡	2.13 ± 0.12‡	2.10 ± 0.07‡	2.06 ± 0.12‡

Values are given as mean + SEM (n = 9).
* Two hours postinduction.
† Significantly ($P < 0.05$) different: conscious preocclusion *versus* halothane preocclusion.
‡ Significantly ($P < 0.05$) different: halothane preocclusion *versus* halothane occlusion/reperfusion.

TABLE 4. Summarized Hemodynamic Data during and after Halothane Anesthesia (No Occlusion/Reperfusion) (Group 4)

			Postanesthesia (h)‡						
	Conscious	Halothane†	0.25	0.50	1	2	3	4	5
HR (beats/min)	80 ± 6	90 ± 7	101 ± 12	130 ± 16*	98 ± 9	95 ± 3	93 ± 5	81 ± 6	83 ± 5
MAP (mmHg)	97 ± 7	73 ± 3*	99 ± 7	104 ± 9	104 ± 9	102 ± 6	103 ± 8	101 ± 5	96 ± 8
LVSP (mmHg)	116 ± 6	87 ± 3*	111 ± 4	120 ± 6	117 ± 5	116 ± 5	116 ± 6	115 ± 6	108 ± 6
LVEDP (mmHg)	9 ± 1	9 ± 1	7 ± 1	8 ± 3	9 ± 1	9 ± 2	9 ± 2	8 ± 2	6 ± 2
+dP/dt (mmHg/s)	2,590 ± 270	950 ± 70*	1,730 ± 130	2,920 ± 380	2,910 ± 270	2,650 ± 230	2,540 ± 260	2,540 ± 270	2,510 ± 270
MCBFV (Hz × 10^2)	30 ± 4	24 ± 3	32 ± 4	44 ± 5*	42 ± 4	38 ± 3	32 ± 4	31 ± 3	32 ± 3
EDL (mm)	10.3 ± 0.3	10.1 ± 0.4	10.2 ± 0.4	10.0 ± 0.4	10.2 ± 0.3	10.4 ± 0.3	10.7 ± 0.4	10.8 ± 0.4	10.7 ± 0.4
ESL (mm)	8.3 ± 0.3	9.1 ± 0.5	8.3 ± 0.3	7.9 ± 0.3	8.1 ± 0.2	8.4 ± 0.3	8.5 ± 0.4	8.7 ± 0.4	8.6 ± 0.3
SS (%)	19.4 ± 1.6	10.3 ± 1.7*	18.8 ± 0.8	20.9 ± 1.8	20.9 ± 1.7	19.7 ± 1.1	20.8 ± 1.1	20.1 ± 1.2	20.3 ± 1.2
Blood halothane (mM)	—	1.88 ± 0.16	—	—	0.28 ± 0.08	0.13 ± 0.02	0.90 ± 0.01	0.05 ± 0.02	0.03 ± 0.02

Values are given as mean ± SEM (n = 9).
* Significantly ($P < 0.05$) different from conscious.
† Two hours postinduction.
‡ Times correspond to reperfusion postanesthesia in table 5.

trast to conscious dogs with coronary artery occlusion and reperfusion (group 1), segment shortening in those dogs subjected to ischemia during halothane anesthesia (group 5) returned to control levels by 3 h following reperfusion. Segment shortening was significantly increased as compared to that observed in conscious dogs as early as 30 min following reperfusion.

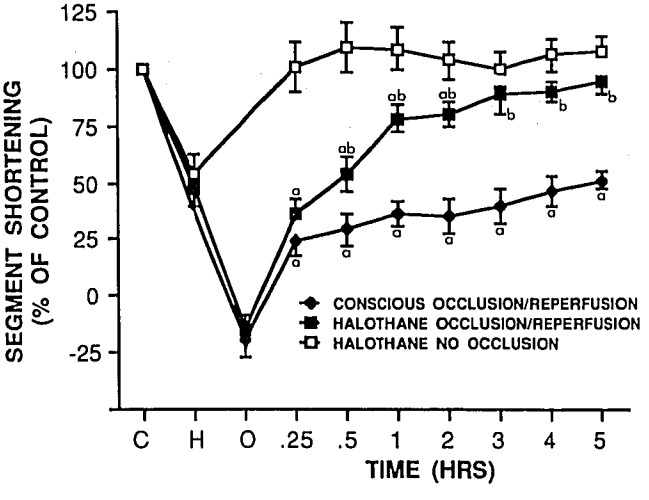

FIG. 3. Segment shortening data (expressed as a percent of control; mean ± SEM) during coronary artery occlusion (O) and at various times following reperfusion in conscious dogs (group 1) and in those animals anesthetized with halothane (H) for 2.25 h (group 5). Comparisons are made at various time points to those animals anesthetized with halothane for 2.25 h and allowed to emerge from anesthesia over a 5-h period but not undergoing coronary artery occlusion and reperfusion (group 4). [a]Significant ($P < 0.05$) difference, group 4 (emergence without prior occlusion) *versus* 1 (conscious occlusion) or 5 (emergence with prior occlusion). [b]Significant ($P < 0.05$) difference, group 1 (conscious occlusion) *versus* 5 (emergence with prior occlusion). Note that the control state (C) indicates the awake, unsedated state of each group.

EFFECT OF ISOFLURANE ANESTHESIA ON THE TIME COURSE OF RECOVERY OF REGIONAL CONTRACTILE FUNCTION

In all dogs following 2 h of isoflurane (blood isoflurane concentration 1.52 ± 0.08 mM) anesthesia (n = 34 from groups 6, 7, 8, and 9), there was a significant decrease in mean aortic pressure (99 ± 2 to 84 ± 2 mmHg), left ventricular systolic pressure (120 ± 2 to 94 ± 2 mmHg), and peak positive left ventricular dP/dt (2,650 ± 100 to 1690 ± 80 mmHg/s). In contrast to halothane-anesthetized dogs, isoflurane produced a significant increase in heart rate (83 ± 3 to 114 ± 3 beats/min) and mean coronary blood flow velocity (29 ± 2 to 39 ± 4 Hz × 10^2). Despite a reduction in systolic blood pressure, no change in the heart rate–systolic pressure product was observed (10.0 ± 0.3 to 10.7 ± 0.4 beats/min · mmHg × 10^2) because of the increase in heart rate produced by isoflurane. No changes occurred in arterial blood *p*H (7.40 ± 0.01 to 7.39 ± 0.01) or arterial P_{CO_2} (33.7 ± 0.5 to 31.4 ± 1.1 mmHg); however, there was an increase in arterial P_{O_2} (87 ± 2 to 500 ± 19 mmHg) during positive pressure ventilation. Isoflurane anesthesia produced a significant reduction in EDL (10.1 ± 0.1 to 9.4 ± 0.1 mm), no change in ESL (8.3 ± 0.1 to 8.3 ± 0.1 mm), and a reduction in percent segment shortening (17.7 ± 0.8 to 12.0 ± 0.8%).

The stability of the changes in hemodynamics and regional segment function produced by isoflurane anesthesia over 7 h in dogs not subjected to coronary artery occlusion and reperfusion (group 6) are summarized in table 6. Following 2 h of anesthesia with isoflurane no further alterations in systemic or regional hemodynamics (fig. 4) occurred over the next 5 h. The changes in global and regional hemodynamics in dogs subjected to a 15-min left anterior descending coronary artery occlusion and re-

perfusion during anesthesia with isoflurane are summarized in table 7 and figure 4. During coronary occlusion there was a decrease in peak positive left ventricular dP/dt but only a small (insignificant) increase in left ventricular end-diastolic pressure. No changes in heart rate were observed. Similar to results obtained in awake, unsedated dogs, there was an abrupt increase in EDL and ESL, and systolic shortening was replaced by paradoxical systolic lengthening. During reperfusion there was a progressive decrease in ESL and EDL as well as a corresponding increase in segment shortening over 5 h of reperfusion. As compared to conscious dogs, there was a significantly greater increase in percent segment shortening (fig. 4) during reperfusion in dogs anesthetized with isoflurane. By 4 and 5 h following reperfusion, segment shortening was not different from those dogs anesthetized with isoflurane not subjected to ischemic insult (group 6). Furthermore, by 2 h following the onset of reperfusion segment function in dogs anesthetized with isoflurane was significantly improved as compared to conscious animals.

In additional experiments (groups 8 and 9) the effects of isoflurane anesthesia was studied in dogs allowed to emerge from anesthesia to avoid any direct depressant effect of isoflurane. Hemodynamic data before, during, and after isoflurane anesthesia in dogs not subjected to ischemia (group 8) are summarized in table 8. Following 2 h of isoflurane anesthesia, dogs were allowed to emerge from anesthesia and studied over a period of 5 h. Within the first 15–30 min following emergence there was a significant increase in heart rate, mean arterial pressure, and peak positive dP/dt as compared to the conscious control state. After 1 h, however, hemodynamics were not significantly different from the conscious state. Similarly, no differences in segment shortening from the conscious control were observed over the 5-h emergence period. Similar results (table 9; fig. 5) were obtained in dogs receiving a 15-min coronary artery occlusion during isoflurane anesthesia (group 9). In these experiments during the first 30 min of emergence there was also a significant increase in heart rate. In contrast to conscious dogs with coronary artery occlusion and reperfusion (group 1), segment shortening in dogs subjected to ischemia during isoflurane anesthesia (group 9) returned to control levels by 2 h following reperfusion. Segment shortening was significantly increased as compared to experiments in conscious dogs 30 min following the onset of reperfusion (fig. 5).

TABLE 5. Summarized Hemodynamic Data in Halothane-anesthetized (Conscious Reperfusion) Dogs before and after a 15-Min Coronary Artery Occlusion (Group 5)

	Conscious Preocclusion	Halothane Preocclusion*	Halothane + Occlusion	Reperfusion (h)					
				0.25	0.50	1	2	3	4	5
HR (beats/min)	84 ± 5	95 ± 4	96 ± 5	85 ± 5	105 ± 9	112 ± 10‡	89 ± 5	89 ± 5	94 ± 8	85 ± 5
MAP (mmHg)	98 ± 4	67 ± 4†	60 ± 5	92 ± 4	96 ± 4	101 ± 3	108 ± 5	100 ± 3	102 ± 2	97 ± 4
LVSP (mmHg)	117 ± 4	79 ± 3†	68 ± 4	107 ± 4	107 ± 5	120 ± 3	126 ± 6	118 ± 3	122 ± 4	115 ± 4
LVEDP (mmHg)	9 ± 1	10 ± 1	14 ± 1	12 ± 2	9 ± 1	9 ± 1	8 ± 1	9 ± 1	10 ± 1	7 ± 1
+dP/dt (mmHg/s)	2,430 ± 360	940 ± 160†	760 ± 130	1,240 ± 170‡	1,750 ± 230	2,530 ± 260	2,650 ± 400	2,570 ± 340	2,500 ± 330	2,460 ± 340
MCBFV (Hz × 10^2)	32 ± 4	21 ± 4†	0§	24 ± 4	29 ± 4	34 ± 4	33 ± 5	30 ± 4	32 ± 4	31 ± 5
EDL (mm)	10.2 ± 0.2	10.3 ± 0.3	11.1 ± 0.3§	10.9 ± 0.3	10.6 ± 0.5	10.6 ± 0.3	10.8 ± 0.3	10.9 ± 0.3	10.7 ± 0.4	10.9 ± 0.4
ESL (mm)	8.2 ± 0.3	9.3 ± 0.3†	11.4 ± 0.4§	10.1 ± 0.4‡	9.4 ± 0.4‡	8.9 ± 0.2	9.1 ± 0.3‡	9.0 ± 0.3	8.8 ± 0.4	9.0 ± 0.4
SS (%)	19.7 ± 2.3	9.9 ± 2.1†	−2.2 ± 1.2§	7.4 ± 2.1‡	11.0 ± 2.8‡	15.1 ± 1.9	15.3 ± 1.6	17.1 ± 2.0	17.5 ± 2.0	18.0 ± 1.7
Blood halothane (mM)	—	1.78 ± 0.15	—	—	—	0.33 ± 0.07	0.17 ± 0.02	0.13 ± 0.01	0.11 ± 0.01	0.09 ± 0.01

Values are given as mean ± SEM (n = 8).
* Two hours postinduction.
† Significantly ($P < 0.05$) different: conscious preocclusion *versus* halothane preocclusion.
‡ Significantly ($P < 0.05$) different: conscious preocclusion *versus* reperfusion.
§ Significantly ($P < 0.05$) different: halothane preocclusion *versus* halothane occlusion.

Discussion

Various experimental models of acute, total, or partial coronary artery occlusion in several species have been utilized to investigate the actions of anesthetics in myocardial ischemia and/or infarction. Most recently, the ef-

TABLE 6. Summarized Hemodynamic Data in Isoflurane-anesthetized Dogs (No Occlusion/Reperfusion) (Group 6)

	Conscious	Isoflurane Anesthesia (h)					
		2†	3‡	4‡	5‡	6‡	7‡
HR (beats/min)	85 ± 4	108 ± 4*	106 ± 6*	100 ± 5	101 ± 5	99 ± 6	100 ± 6
MAP (mmHg)	103 ± 2	90 ± 4*	88 ± 3*	88 ± 4*	87 ± 3*	88 ± 3*	89 ± 3*
LVSP (mmHg)	122 ± 3	97 ± 5*	96 ± 4*	97 ± 4*	97 ± 4*	97 ± 4*	97 ± 4*
LVEDP (mmHg)	9 ± 1	10 ± 1	9 ± 1	9 ± 1	9 ± 1	9 ± 1	9 ± 2
+dP/dt (mmHg/s)	2,760 ± 200	1,620 ± 140*	1,530 ± 110*	1,530 ± 120*	1,520 ± 100*	1,526 ± 90*	1,570 ± 100*
MCBFV (Hz × 10^2)	29 ± 3	33 ± 5	35 ± 5	34 ± 6	35 ± 6	34 ± 7	35 ± 6
EDL (mm)	10.1 ± 0.1	9.7 ± 0.1	9.6 ± 0.1*	9.6 ± 0.1*	9.5 ± 0.2*	9.7 ± 0.2	9.6 ± 0.2*
ESL (mm)	8.2 ± 0.2	8.3 ± 0.2	8.3 ± 0.2	8.3 ± 0.2	8.2 ± 0.2	8.3 ± 0.2	8.2 ± 0.2
SS (%)	19.0 ± 1.7	14.5 ± 1.4*	13.8 ± 1.4*	13.9 ± 1.4*	13.6 ± 1.3*	14.2 ± 1.3*	14.7 ± 1.2*
Blood isoflurane (mM)	—	1.51 ± 0.18	1.59 ± 0.20	1.59 ± 0.18	1.70 ± 0.22	1.86 ± 0.30	1.73 ± 0.23

Values are given as mean ± SEM (n = 10).
* Significantly ($P < 0.05$) different from conscious.
† Time of anesthesia corresponds to isoflurane preocclusion in table 7.
‡ Time of anesthesia corresponds to isoflurane + reperfusion 1, 2, 3, 4, 5 h in table 7.

fects of anesthetics on myocardial function and perfusion have been studied in the presence of a critical coronary artery stenosis in which reactive hyperemia was abolished but flow remained near resting levels.[11,12] Each of these models has dealt with the influence of anesthetics specifically during ischemia. To date, no comprehensive investigation has been completed delineating the influence of volatile anesthetics on the recovery of contractile function following a brief period of coronary occlusion (stunned myocardium).

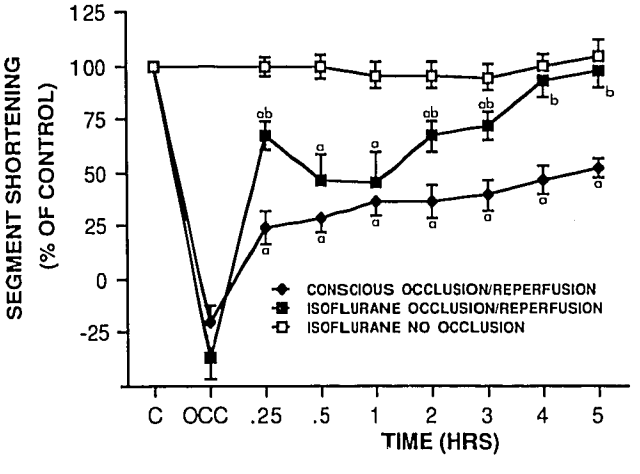

FIG. 4. Segment shortening data (expressed as a percent of control; mean ± SEM) during coronary artery occlusion (OCC) and at various times following reperfusion in conscious dogs (group 1) and in those dogs anesthetized with isoflurane (group 7). Comparisons are made at various time points to those animals of anesthetized with isoflurane but not undergoing coronary artery occlusion and reperfusion (group 6). [a]Significant ($P < 0.05$) difference, group 6 (anesthetized without occlusion) *versus* 1 (conscious occlusion) or 7 (occlusion during anesthesia). [b]Significant ($P < 0.05$) difference, group 1 (conscious occlusion) *versus* 7 (occlusion during anesthesia). Note that the control state (C) indicates either the awake, unsedated state (group 1) or following a stable hemodynamic state after 2 h of isoflurane anesthesia (groups 6 and 7).

Tennant and Wiggers[13] first described systolic bulging of myocardium in an area distal to an acute coronary artery occlusion. Since this initial observation, many investigators have demonstrated that acute coronary artery obstruction results in a contractile deficit within the ischemic zone characterized by a prompt dyskinesis, which ultimately develops into holosystolic expansion within minutes.[8] With sustained coronary artery occlusion (>20 min) myocardium may become irreversibly damaged, depending on the balance between oxygen supply (coronary collaterals) and oxygen demand. Following reperfusion of irreversibly damaged tissue, little or no recovery of contractile function would be expected to occur. In contrast, it was assumed that following shorter periods of ischemia (<20 min) not resulting in tissue necrosis, regional contractile function is restored coincident with reperfusion of the affected myocardial segment. Recent experimental investigations do not support this assumption. With brief periods of total coronary artery occlusion followed by reperfusion, while no tissue necrosis occurs, a decrement in function, depression of biochemical processes, and change in ultrastructure of the postischemic myocardial segment may be present for prolonged periods.[14,15] Furthermore, despite the initial return of antegrade coronary blood flow to control levels, perfusion heterogeneity (especially to subendocardium) may exist in the postischemic region.[16] Other investigations, however, have not shown a prolonged reduction of subendocardial blood flow despite a decrement in regional segment function.[17] Ultimately, the contractile function of stunned myocardium recovers over a period of time varying from hours to days.

The basis for this slow recovery of regional segment function is unknown. Certain studies have demonstrated that myocardial high-energy phosphates are reduced from control for prolonged periods after reperfusion.[18] In contrast, Allison and Holsinger[19] have documented complete

TABLE 7. Summarized Hemodynamic Data in Isoflurane-anesthetized Dogs before and after a 15-Min Coronary Artery Occlusion (Group 7)

	Conscious Preocclusion	Isoflurane Preocclusion	Isoflurane + Occlusion	Isoflurane + Reperfusion (h)						
				0.25	0.50	1	2	3	4	5
HR (beats/min)	84 ± 5	115 ± 6†	115 ± 6	102 ± 6	105 ± 5	102 ± 5	97 ± 5	95 ± 5‡	92 ± 6‡	95 ± 4‡
MAP (mmHg)	95 ± 3	81 ± 3†	79 ± 3	78 ± 3	78 ± 2	75 ± 2	72 ± 4	75 ± 4	81 ± 5	77 ± 6
LVSP (mmHg)	118 ± 3	92 ± 3†	85 ± 3	84 ± 3	85 ± 3	84 ± 3	81 ± 4‡	83 ± 5	89 ± 5	85 ± 5
LVEDP (mmHg)	8 ± 1	8 ± 1	10 ± 1	11 ± 1	10 ± 1	9 ± 1	8 ± 1	8 ± 1	7 ± 1	7 ± 1
+dP/dt (mmHg/s)	2,620 ± 130	1,840 ± 180†	1,330 ± 110‡	1,310 ± 80‡	1,370 ± 80	1,250 ± 90‡	1,280 ± 90‡	1,300 ± 100‡	1,460 ± 140	1,370 ± 140
MCBFV (Hz × 10^2)	27 ± 2	44 ± 9†	0‡	36 ± 7	31 ± 4	33 ± 3	32 ± 3	32 ± 4	31 ± 3	33 ± 4
EDL (mm)	9.9 ± 0.1	9.1 ± 0.2†	10.3 ± 0.3‡	9.9 ± 0.2‡	9.8 ± 0.2‡	9.7 ± 0.2	9.6 ± 0.2	9.6 ± 0.2	9.6 ± 0.2	9.4 ± 0.2
ESL (mm)	8.1 ± 0.1	7.9 ± 0.1	10.7 ± 0.3‡	9.1 ± 0.2‡	9.2 ± 0.2‡	9.1 ± 0.2‡	8.8 ± 0.2‡	8.7 ± 0.1	8.4 ± 0.1	8.2 ± 0.1
SS (%)	17.7 ± 1.5	12.4 ± 1.7†	−3.5 ± 0.8‡	8.1 ± 1.2‡	6.2 ± 1.8‡	6.2 ± 2.1‡	8.3 ± 1.3‡	9.0 ± 1.4	11.2 ± 1.5	12.1 ± 2.1
Blood isoflurane (mM)	—	1.58 ± 0.18	—	—	—	1.71 ± 0.24	1.75 ± 0.24	1.85 ± 0.23	1.72 ± 0.18	1.76 ± 0.19

Values are given as mean ± SEM (n = 9).
* Two hours postinduction.
† Significantly ($P < 0.05$) different: conscious preocclusion *versus* isoflurane preocclusion.
‡ Significantly ($P < 0.05$) different: isoflurane preocclusion *versus* isoflurane occlusion/reperfusion.

TABLE 8. Summarized Hemodynamic Data during and after Isoflurane Anesthesia (No Occlusion/Reperfusion) (Group 8)

	Conscious	Isoflurane*	Postanesthesia (h)†						
			0.25	0.50	1	2	3	4	5
HR (beats/min)	84 ± 5	111 ± 7‡	153 ± 7‡	138 ± 13‡	92 ± 6	88 ± 6	85 ± 7	78 ± 5	83 ± 6
MAP (mmHg)	100 ± 4	83 ± 6‡	120 ± 7‡	111 ± 6	112 ± 5	107 ± 3	99 ± 4	101 ± 3	103 ± 3
LVSP (mmHg)	119 ± 4	95 ± 3‡	138 ± 6‡	128 ± 4	128 ± 4	126 ± 4	120 ± 3	120 ± 4	122 ± 5
LVEDP (mmHg)	10 ± 1	10 ± 1	11 ± 1	9 ± 1	12 ± 1	10 ± 1	8 ± 1	8 ± 1	8 ± 1
+dP/dt (mmHg/s)	2,760 ± 280	1,610 ± 130‡	3,720 ± 300‡	3,490 ± 260	2,960 ± 250	2,840 ± 220	2,620 ± 280	2,620 ± 270	2,650 ± 300
MCBFV (Hz × 10^2)	32 ± 5	37 ± 4	41 ± 7	41 ± 7	39 ± 7	38 ± 5	35 ± 5	36 ± 5	36 ± 5
EDL (mm)	10.1 ± 0.2	9.5 ± 0.2‡	9.7 ± 0.4	10.0 ± 0.2	10.4 ± 0.2	10.4 ± 0.2	10.4 ± 0.2	10.4 ± 0.2	10.4 ± 0.2
ESL (mm)	8.2 ± 0.2	8.3 ± 0.3	7.7 ± 0.3	7.9 ± 0.3	8.3 ± 0.3	8.6 ± 0.3	8.6 ± 0.3	8.5 ± 0.2	8.5 ± 0.2
SS (%)	18.8 ± 2.1	12.2 ± 1.7‡	20.5 ± 2.2	21.0 ± 1.7	19.8 ± 1.4	17.5 ± 1.7	17.8 ± 2.3	18.4 ± 1.9	18.3 ± 2.1
Blood isoflurane (mM)	—	1.50 ± 0.20	—	—	0.11 ± 0.01	0.07 ± 0.01	0.05 ± 0.02	0.04 ± 0.01	0.03 ± 0.01

Values are given as mean ± SEM (n = 8).
* Two hours postinduction.
† Times correspond to reperfusion postanesthesia in table 9.
‡ Significantly ($P < 0.05$) different from conscious.

TABLE 9. Summarized Hemodynamic Data in Isoflurane-anesthetized (Conscious Reperfusion) Dogs before and after a 15-Min Coronary Artery Occlusion (Group 9)

	Conscious Preocclusion	Isoflurane Preocclusion*	Isoflurane + Occlusion	Reperfusion (h)					
				0.25	0.50	1	2	3	4	5
HR (beats/min)	78 ± 6	110 ± 5†	110 ± 5	122 ± 13‡	135 ± 9‡	109 ± 8	89 ± 6	91 ± 8	86 ± 5	80 ± 6
MAP (mmHg)	97 ± 5	81 ± 4†	76 ± 5	109 ± 5	108 ± 7	103 ± 5	102 ± 4	96 ± 5	101 ± 4	98 ± 4
LVSP (mmHg)	121 ± 7	91 ± 5†	91 ± 5	118 ± 8	123 ± 9	126 ± 8	119 ± 7	123 ± 10	119 ± 8	119 ± 6
LVEDP (mmHg)	10 ± 1	8 ± 1	12 ± 2§	13 ± 2	11 ± 3	11 ± 2	10 ± 1	11 ± 1	9 ± 1	9 ± 1
+dP/dt (mmHg/s)	2,450 ± 160	1,660 ± 220†	1,350 ± 150	2,260 ± 240	2,950 ± 50	2,830 ± 290	2,530 ± 210	2,680 ± 250	2,520 ± 220	2,520 ± 220
MCBFV (Hz × 10^2)	33 ± 8	38 ± 9	0§	47 ± 13	49 ± 10	42 ± 8	37 ± 7	36 ± 7	38 ± 8	38 ± 8
EDL (mm)	10.2 ± 0.1	9.4 ± 0.1†	10.4 ± 0.2§	10.3 ± 0.2	10.4 ± 0.2	10.5 ± 0.2	10.7 ± 0.2§	10.5 ± 0.2	10.7 ± 0.2‡	10.7 ± 0.2‡
ESL (mm)	8.6 ± 0.1	8.5 ± 0.2	10.7 ± 0.2§	9.5 ± 0.2‡	9.1 ± 0.2	9.1 ± 0.2	9.1 ± 0.2	9.0 ± 0.1	9.2 ± 0.1‡	9.2 ± 0.2
SS (%)	15.9 ± 1.1	8.9 ± 1.3†	−3.2 ± 0.8§	8.1 ± 1.6‡	13.1 ± 1.5	13.4 ± 1.3	14.1 ± 1.1	14.6 ± 1.3	14.2 ± 1.1	14.3 ± 1.0
Blood isoflurane (mM)	—	1.51 ± 0.16	—	—	—	0.14 ± 0.02	0.10 ± 0.02	0.09 ± 0.02	0.06 ± 0.01	0.02 ± 0.01

Values are given as mean ± SEM (n = 7).
* Two hours postinduction.
† Significantly ($P < 0.05$) different: conscious preocclusion *versus* isoflurane preocclusion.
‡ Significantly ($P < 0.05$) different: conscious preocclusion *versus* reperfusion.
§ Significantly ($P < 0.05$) different: isoflurane preocclusion *versus* isoflurane occlusion.

restoration of adenine nucleotides and other tissue metabolites after 5–15 min of reperfusion following a 20-min coronary occlusion. Other studies have also indicated that postischemic contractile dysfunction may not be related to inadequate postischemic ATP levels.[20,21] There is increasing evidence that postischemic dysfunction in the stunned myocardium may be partially due to the production of oxygen-derived free radicals.[22–24] Results from this laboratory have shown that postischemic contractile function may be enhanced by superoxide dismutase and catalase administered prior to a brief coronary artery occlusion.[22] Still other factors, such as changes in calcium homeostasis,[25] disruption of cardiac sympathetic neural responsiveness,[26] neutrophil activation–migration,[23] or myocardial cell swelling and edema[27] may also be responsible for the prolonged deficit in regional contractile function. Although many hypotheses have been advocated, no single factor has yet been identified to be the mechanism of stunned myocardium.

In the present experiments the effects of the volatile anesthetics on the recovery of function during reperfusion following a brief period of ischemia were determined in chronically instrumented dogs following halothane or isoflurane without basal sedation. Thus, the results were compared directly with data generated in the awake, unsedated state to avoid nonspecific effects of a basal anesthetic, inducing agent such as thiopental and/or surgical stimulus. Halothane and isoflurane were studied because these agents may have varying effects on the ischemic or postischemic region. For example, whereas halothane may be beneficial for ischemic myocardium,[28–32] isoflurane may exacerbate ischemia.[33–35] In addition, rather than simply utilizing equipotent (MAC) concentrations of anesthetics, concentrations were selected that provided markedly different hemodynamic effects.

The results demonstrate that the recovery of segment function of postischemic, reperfused myocardium is markedly enhanced during anesthesia with either halothane or isoflurane. Experiments were conducted during which coronary artery occlusion and reperfusion were carried out during general anesthesia or during which only occlusion occurred during anesthesia and the dogs allowed to emerge from anesthesia simultaneous with reperfusion. In the latter experiments the recovery of function during reperfusion was thus studied in the awake, unsedated state in the absence of anesthetic-induced depression of myocardial contractility. In either case by 3–5 h following initiation of reflow, recovery of function was near normal. This is in contrast to conscious dogs in which recovery was approximately 50% that of the preocclusion state at 5 h following the onset of reperfusion.

The two types of experiments conducted were completed for multiple reasons. Both halothane and isoflurane directly depressed regional contractile function prior to

coronary artery occlusion. Therefore, total recovery of function would be considerably less in the presence *versus* absence of anesthetic. An additional test of the ability of these agents to enhance recovery of function following an ischemic insult was made in dogs allowed to emerge from anesthesia. Thus, a direct comparison was made to the preanesthetic, conscious state. The present results in either type of experiment have indicated that halothane and isoflurane are equally as efficacious in hastening the return of function within the previously ischemic zone.

The mechanism by which the volatile anesthetics increase functional recovery of postischemic myocardium is presently unknown; however, such actions might be divided into events produced by the anesthetics in the occlusion period and/or within the immediate reperfusion period. The volatile anesthetics may reduce the severity of ischemia during coronary artery occlusion by decreasing myocardial oxygen demand. Thus, myocardial tissue trauma may have been less and recovery of function faster and more complete following halothane or isoflurane. The two anesthetics selected for study had varying effects on hemodynamics. Halothane significantly reduced the heart rate–systolic pressure product, an indirect index of myocardial oxygen demand. However, isoflurane did not change the double product but was equally as effective as halothane in enhancing recovery. Also, equivalent degrees of paradoxical aneurysmal bulging in systole occurred in all experiments during coronary occlusion, indicating the presence of severe ischemia in the area of placement of ultrasonic crystals.[36] Thus, the cardioprotective effect of anesthetics occurred without preventing the loss of systolic wall function that occurs during ischemia. In more peripheral regions to the central ischemic zone, however, a reduction in oxygen requirements during anesthesia may have reversed systolic lengthening to shortening. In the present study only central ischemic zone function was studied. Halothane was found to prevent the increase in heart rate during coronary occlusion observed in conscious dogs. Likewise no increase in heart rate occurred during coronary occlusion in dogs anesthetized with isoflurane; however, in these experiments heart rate in the presence of isoflurane alone was equally as high as in conscious dogs during coronary artery occlusion. Thus, although improvement in oxygen supply–demand balance may provide a mechanism whereby halothane or isoflurane act to reduce the intensity of an ischemic event, the varying hemodynamic actions of the anesthetics in this study would not support such a hypothesis. Other potential mechanisms whereby anesthetic agents might enhance the recovery of function may include an action to limit an influx of calcium during early reperfusion and/or stabilization of myocardial cell membranes preventing deleterious ionic fluxes or accumulation of tissue water.

An additional consideration is that during emergence

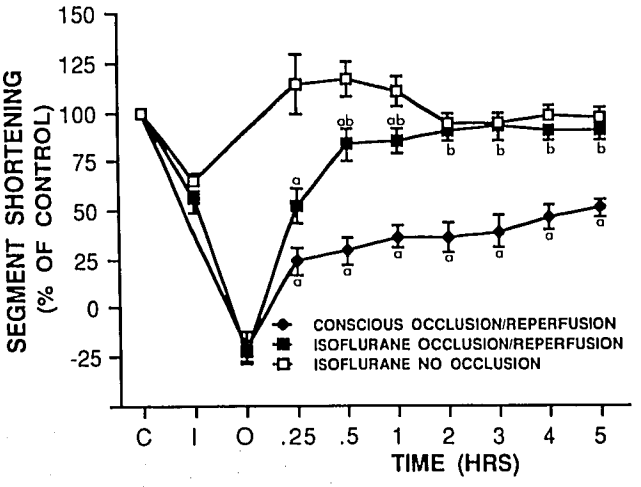

FIG. 5. Segment shortening data (expressed as a percent of control; mean ± SEM) during coronary artery occlusion (O) and at various times following reperfusion in conscious dogs (group 1) and in those animals anesthetized with isoflurane (I) for 2.25 h (group 9). Comparisons are made at various time points to those animals anesthetized with isoflurane for 2.25 h and allowed to emerge from anesthesia over a 5-h period but not undergoing coronary artery occlusion and reperfusion (group 8). [a]Significant ($P < 0.05$) difference, group 8 (emergence without prior occlusion) *versus* 1 (conscious occlusion) or 9 (emergence with prior occlusion). [b]Significant ($P < 0.05$) difference, group 1 (conscious occlusion) *versus* 9 (emergence with prior occlusion). Note that the control state (C) indicates the awake, unsedated state of each group.

from anesthesia an increase in sympathetic tone was observed as reflected by increases in heart rate, peak positive dP/dt, and/or arterial pressure. In awake, unsedated dogs various inotropes (including catecholamines) have been shown to be as equally effective in stunned as in normal myocardium.[37] Thus, contractile reserve of postischemic, reperfused myocardium may be similar to that of normal myocardium. An increase in sympathetic outflow during emergence in the present study may have increased the contractility of postischemic myocardium early after reperfusion. However, reflex changes in hemodynamics secondary to sympathetic activation were not present by 1–2 h following reperfusion and, therefore, are unlikely to be an explanation for the enhancement of recovery of contractile function later after reperfusion.

Results of Freedman *et al.*[38] have demonstrated that enflurane enhances postischemic functional recovery of isolated rat hearts. These workers found that control and enflurane-treated, isolated rat hearts developed contracture at identical times and had equivalent high-energy phosphate stores during a period of global ischemia. However, during reperfusion hearts treated with enflurane demonstrated greater recovery of ventricular function coincident with higher ATP and creatine phosphate levels. These authors suggested that this might be due to a protection of mitochondrial function by enflurane dur-

ing reperfusion. Similar to enflurane, halothane and isoflurane in the present investigation may have prevented the deleterious increase in cytoplasmic and mitochondrial calcium content occurring during reperfusion injury[39] *via* blockade of calcium influx through voltage-dependent slow channels[40–42] or stimulation of calcium uptake into sarcoplasmic reticulum.[43,44] With less mitochondrial dysfunction in the presence of these volatile anesthetics, ATP and creatine phosphate levels may be preserved to a greater extent.

Postischemic contractile deficits analogous to the experimentally produced stunned state may be found in a variety of clinical conditions. A recent investigation by Coriat *et al.*,[2] in which myocardial perfusion scintigraphy with ^{201}thallium and radionuclide ventriculography were performed preoperatively and postoperatively in patients with coronary artery disease having noncardiac surgery, documented the perioperative occurrence of stunned myocardium. Patients with intraoperative electrocardiographic evidence of myocardial ischemia demonstrated prolonged left ventricular dysfunction. Other studies in patients following coronary artery bypass grafting[45] or thrombolytic therapy[46] also indicate a delay in recovery of function despite early return of coronary artery perfusion. Such prolonged contractile deficits may require inotropic support until recovery ultimately occurs. Although extrapolation of experimental studies to the clinical situation must be made with caution, the results of this study indicate that the time course of recovery of function of previously ischemic myocardium is enhanced by halothane or isoflurane. The results may indicate that transient, ischemic events occurring during anesthesia with halothane or isoflurane are not followed by as severe a contractile deficit as in the absence of anesthesia.

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References

1. Braunwald E, Kloner RA: The stunned myocardium: Prolonged, postischemic ventricular dysfunction. Circulation 66:1146–1149, 1982
2. Coriat P, Fauchet M, Bousseau D, Mundler O, Rous AC, Echter E, Viars P: Left ventricular dysfunction after non-cardiac surgical procedures in patients with ischemic heart disease. Acta Anaesthesiol Scand 29:804–810, 1985
3. Lamping KA, Gross GJ: Improved recovery of myocardial segment function following a short coronary occlusion in dogs by nicorandil, a potential new antianginal agent, and nifedipine. J Cardiovasc Pharmacol 7:158–166, 1985
4. Shimshak TM, Preuss KC, Gross GJ, Brooks HL, Warltier DC: Recovery of contractile function in post-ischemic, reperfused myocardium of conscious dogs: Influence of nicorandil, a new antianginal agent. Cardiovasc Res 20:621–626, 1986
5. Kloner RA, Kirshenbaum J, Lange R, Antman EM, Braunwald E: Experimental and clinical observations on the efficacy of esmolol in myocardial ischemia. Am J Cardiol 56:40F–48F, 1985
6. Gross GJ, Farber NE, Hardman HF, Warltier DC: Beneficial actions of superoxide dismutase and catalase in stunned myocardium of dogs. Am J Physiol 250:H372–H377, 1986
7. Preuss KC, Gross GJ, Brooks HL, Warltier DC: Time course of recovery of "stunned" myocardium following variable periods of ischemia in conscious and anesthetized dogs. Am Heart J 114:696–703, 1987
8. Theroux P, Franklin D, Ross J Jr, 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
9. 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
10. Lowe HJ: Flame ionization detection of volatile organic anesthetics in blood, gases and tissues. ANESTHESIOLOGY 25:808–814, 1964
11. Priebe HJ, Foex P: Isoflurane causes regional myocardial dysfunction in dogs with critical coronary artery stenoses. ANESTHESIOLOGY 66:293–300, 1987
12. Hickey RF, Verrier ED, Baer RW, Vlahakes GJ, Fein G, Hoffman JI: A canine model of acute coronary artery stenosis: effects of deliberate hypotension. ANESTHESIOLOGY 59:226–236, 1983
13. Tennant R, Wiggers CJ: The effect of coronary occlusion on myocardial contraction. Am J Physiol 112:351–361, 1935
14. Jennings RB, Schaper J, Hill ML, Steenbergen C Jr, Reimer KA: Effect of reperfusion late in the phase of reversible ischemic injury. Circ Res 56:262–278, 1985
15. Kloner RA, DeBoer LW, Darsee JR, Ingwall JS, Hale S, Tumas J, Braunwald E: Prolonged abnormalities of myocardium salvaged by reperfusion. Am J Physiol 241:H591–H599, 1981
16. Heyndrickx GR, Baig H, Nellens P, Leusen I, Fishbein MC, Vatner SF: Depression of regional blood flow and wall thickening after brief coronary occlusions. Am J Physiol 234:H653–H659, 1978
17. Matsuzaki M, Gallagher KP, Kemper WS, White F, Ross J Jr: Sustained regional dysfunction produced by prolonged coronary stenosis: Gradual recovery after reperfusion. Circulation 68: 170–182, 1983
18. Ellis SG, Henschke CI, Sandor T, Wynne J, Braunwald E, Kloner RA: Time course of functional and biochemical recovery of myocardium salvaged by reperfusion. J Am Coll Cardiol 1:1047–1055, 1983
19. Allison TB, Holsinger JW Jr: Myocardial metabolism and regional myocardial blood flow in the canine left ventricle following twenty minutes of circumflex artery occlusion and reperfusion. J Mol Cell Cardiol 15:151–161, 1983
20. Pieper GM, Farber NE, Gross GJ: Dazoxiben protects adenine nucleotide loss without improving segment dysfunction in the "stunned" myocardium. J Mol Cell Cardiol 18(suppl 3):56, 1986
21. Greenfield RA, Swain JL: Disruption of myofibrillar energy use: Dual mechanisms that may contribute to postischemic dysfunction in stunned myocardium. Circ Res 60:283–289, 1987
22. Gross GJ, Farber NE, Hardman HF, Warltier DC: Beneficial actions of superoxide dismutase and catalase in stunned myocardium of dogs. Am J Physiol 250:H372–H377, 1986
23. Engler R, Covell JW: Granulocytes cause reperfusion ventricular dysfunction after 15-minute ischemia in the dog. Circ Res 61: 20–28, 1987

24. Bolli R, Zhu WX, Hartley CJ, Michael LH, Repine JE, Hess ML, Kukreja RC, Roberts R: Attenuation of dysfunction in the post-ischemic "stunned" myocardium by dimethylthiourea. Circulation 76:458–468, 1987
25. Krause S, Hess ML: Characterization of cardiac sarcoplasmic reticulum dysfunction during short-term, normothermic, global ischemia. Circ Res 55:176–184, 1984
26. Ciuffo AA, Ouyang P, Becker LC, Levin L, Weisfeldt ML: Reduction of sympathetic inotropic response after ischemia in dogs. J Clin Invest 75:1504–1509, 1985
27. Kloner RA, Ganote CE, Jennings RB: The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 54:1496–1508, 1974
28. MacLeod BA, Augereau P, Walker MJ: Effects of halothane anesthesia compared with fentanyl anesthesia and no anesthesia during coronary ligation in rats. ANESTHESIOLOGY 58:44–52, 1983
29. Jang TL, MacLeod BA, Walker MJ: Effects of halogenated hydrocarbon anesthetics on responses to ligation of a coronary artery in chronically prepared rats. ANESTHESIOLOGY 59:309–315, 1983
30. Smith G, Rogers K, Thorburn J: Halothane improves the balance of oxygen supply to demand in acute experimental myocardial ischemia. Br J Anaesth 52:577–583, 1980
31. 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
32. Moores WY, Weiskopf RB, Dembitsky WP, Utley JR: Comparative effects of halothane and morphine anesthesia on myocardial function and metabolism during cyanosis in swine. Surg Forum 30:221–223, 1979
33. Reiz S, Balfors E, Sorensen MB, Ariola S Jr, Friedman A, Truedsson H: Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. ANESTHESIOLOGY 59:91–97, 1983
34. Reiz S, Ostman M: Regional coronary hemodynamics during isoflurane–nitrous oxide anesthesia in patients with ischemic heart disease. Anesth Analg 64:570–576, 1985
35. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH: Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. ANESTHESIOLOGY 66:280–292, 1987
36. Vatner SF: Correlation between acute reductions in myocardial blood flow and function in conscious dogs. Circ Res 47:201–207, 1980
37. Shimshak T, Brooks H, Gross GJ, Warltier DC: Comparison of effects of dopamine and milrinone on normal and stunned myocardium in conscious dogs. Pharmacologist 27:216, 1985
38. Freedman BM, Hamm DP, Everson CT, Wechsler AS, Christian CM: Enflurane enhances postischemic functional recovery in the isolated rat heart. ANESTHESIOLOGY 62:29–33, 1985
39. Jennings RB, Ganote CE: Mitochondrial structure and function in acute myocardial ischemic injury. Circ Res 38:80–91, 1976
40. Lynch C, Vogel S, Pratila MG, Sperelakis N: Enflurane depression of myocardial slow action potentials. J Pharmacol Exp Ther 222:405–409, 1982
41. Lynch C, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. ANESTHESIOLOGY 55:360–368, 1981
42. Lynch C: Differential depression of myocardial contractility by halothane and isoflurane *in vitro*. ANESTHESIOLOGY 64:620–631, 1986
43. Blanck TJ, Thompson M: Enflurane and isoflurane stimulate calcium transport by cardiac sarcoplasmic reticulum. Anesth Analg 61:142–145, 1982
44. Blanck TJ, Thompson M: Calcium transport by cardiac sarcoplasmic reticulum: Modulation of halothane action by substrate concentration and pH. Anesth Analg 60:390–394, 1981
45. Tyson GS Jr, Olsen CO, Maier GW, Davis JW, Sethi GK, Scott SM, Sabiston DC Jr, Rankin JS: Dimensional characteristics of left ventricular function after coronary artery bypass grafting. Circulation 66:16–25, 1982
46. Stack RS, Phillips HR, Grierson DS, Behar VS, Kong Y, Peter RH, Swain JL, Greenfield JC Jr: Functional improvement of jeopardized myocardium following intracoronary streptokinase infusion in acute myocardial infarction. J Clin Invest 72:84–95, 1983