Anesthesiology
59:402–411, 1983

The Effect of Halothane Anesthesia on Myocardial Necrosis, Hemodynamic Performance, and Regional Myocardial Blood Flow in Dogs Following Coronary Artery Occlusion

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The effect of halothane anesthesia on myocardial necrosis resulting from coronary artery ligation was examined in 28 anesthetized mongrel dogs. In 18 dogs, the left anterior descending coronary artery (LAD) was ligated immediately proximal to the first apical diagonal branch, and 1 h later the dogs were assigned randomly either to receive halothane, 0.5–1.0% inspired in room air for 12 h (n = 10) or to awaken without further intervention (control, n = 8). Infarct size was measured by staining the myocardium with triphenyl tetrazolium chloride 24 h after LAD ligation. Infarct size in halothane-treated dogs was 17.8 ± 2.0% of the left ventricle, compared with 27.3 ± 3.3% in control dogs ($P < 0.05$). Myocardial salvage was present transmurally but was greatest in epicardial regions. In 10 additional dogs, hemodynamic variables (heart rate, arterial pressure, left ventricular end-diastolic pressure, peak left ventricular dP/dt, tension-time index, and rate–pressure product) were measured or calculated, and radionuclide-labeled microspheres were injected for measurement of cardiac output and regional myocardial blood flow (RMBF). Thirty minutes after LAD ligation and after initial hemodynamic measurements and microsphere injection, these dogs were assigned randomly to receive either halothane, 1.0%, inspired in room air (n = 5) or no intervention (control, n = 5). After 15 min of halothane inhalation (45 min after LAD ligation in control dogs), measurements were repeated. Halothane inhalation reduced heart rate, arterial pressure, and indexes of left ventricular contractile and pump performance. During halothane treatment, RMBF declined in normal myocardium but not in ischemic regions, while neither normal nor ischemic zone RMBF changed in control dogs. Systemic vascular resistance was unchanged in either group. Thus, halothane was associated with a 35% smaller myocardial infarct, transmural myocardial salvage, reduced heart rate, reduced left ventricular contractile and pump performance, reduced RMBF to nonischemic regions, and unchanged RMBF in the ischemic myocardium. (Key words: Anesthetics, volatile: halothane. Heart: blood flow, myocardial; coronary occlusion; infarction; ischemia.)

THE EXTENT OF MYOCARDIAL NECROSIS resulting either from experimental coronary artery occlusion or clinically from acute myocardial infarction (MI) can be manipulated by a variety of pharmacologic and physiologic interventions.[1] Furthermore, myocardial infarct size relates to subsequent hemodynamic impairment and to morbidity and mortality.[2,3] The relationship between prior MI or known ischemic heart disease and perioperative MI among patients undergoing anesthesia and surgery for a variety of diseases is well established[4–7]; a recurrent MI under these circumstances has a high mortality rate.[4,5] Therefore, the effect of anesthetic drugs on myocardial injury produced by acute ischemia is important. This study was designed to determine the effect of clinically useful concentrations of halothane on myocardial infarct size measured 24 h after coronary occlusion and on hemodynamic performance and regional myocardial blood flow (RMBF) in a canine model of MI produced by a standardized coronary artery ligation.

Materials and Methods

Mongrel dogs of either sex were anesthetized with intravenous thiamylal, 15 mg/kg, and succinylcholine, 1 mg/kg; intubated orotracheally; and mechanically ventilated with room air (tidal volume, 15 ml/kg, and ventilatory rate, 8 breaths/min). The internal jugular vein and carotid artery were cannulated with 16-ga catheters

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Received from the Cardiac Anesthesia Group, Department of Anesthesia, Massachusetts General Hospital, Boston, Massachusetts. Accepted for publication April 28, 1983. Supported in part by training grant #T32-HL7049-03 (R. E. Rude, M.D.) Presented in part at the annual meeting of the Society of Critical Care Medicine, April 1979.

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0003-3022/83/1100/0402 $01.30

for venous access and for measurement of aortic pressure. Standard ECG lead II was monitored continuously. The heart was exposed through a left thoracotomy and suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was dissected free immediately proximal to the first major apical diagonal branch and a suture ligature placed loosely around it. The LAD then was occluded transiently (10–15 s) at that point. Only those dogs developing cyanosis of the cardiac apex during this transient occlusion were studied further. Thus, 28 dogs (mean weight, 21 kg) were included in this study and arbitrarily were assigned to one of two experimental protocols: 18 dogs were included in the infarct size protocol (Group A) and 10 in the hemodynamic and RMBF protocol (Group B). In both groups, 2 min before permanent coronary occlusion, each dog received an intravenous dose of lidocaine, 1 mg/kg. Also, if technical difficulty prolonged the surgical preparation, smaller incremental doses of thiamylal (5 mg/kg) were used to provide additional anesthesia.

Group A: Infarct Size Protocol

All 18 dogs in this group underwent suture ligation of the LAD at the location previously selected. The chest was closed in layers and the pleural space evacuated. One hour after LAD ligation, generally less than 75–90 min from the time of anesthetic induction, these dogs were assigned randomly to one of two treatment subgroups. Ten dogs received halothane at an inspired concentration of 0.5–1.0% in room air delivered by a previously calibrated Fluotec Mark II vaporizer with 5-l/min, fresh-gas flow and controlled ventilation. The concentration of halothane was adjusted to the minimum inspired concentration that prevented movement and was maintained at that level for the next 12 h. Subsequently, these 10 dogs were allowed to emerge from anesthesia. They were extubated after spontaneous ventilation had resumed satisfactorily and received no further intervention. The eight dogs assigned to the control group emerged from the initial thiamylal anesthetic after chest closure, were extubated after randomization, and, after spontaneous ventilation had resumed satisfactorily, they received no further intervention.

For all 18 dogs, heart rate and arterial pressure were recorded before LAD ligation, 1 h after ligation (immediately before they were assigned to a treatment subgroup), and 2, 3, 4, 6, 12, and 24 h after ligation. The dogs were killed 24 h after LAD ligation with thiamylal followed by sufficient KCl (2 mEq/l) to produce electrocardiographic arrest. The hearts were removed and coded so that all further measurements were obtained

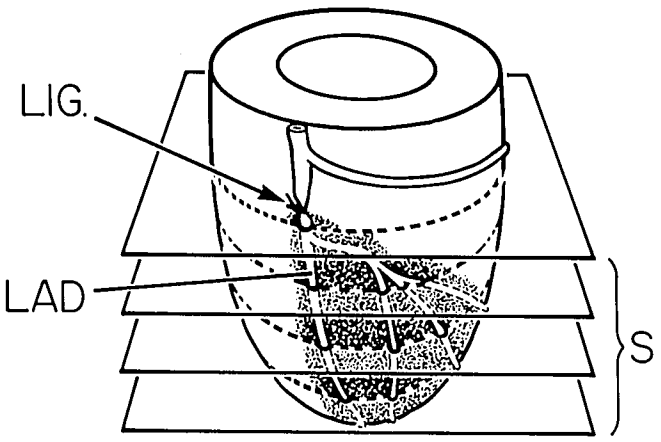

FIG. 1. The figure schematically represents the left ventricle and shows the left anterior descending (LAD) coronary artery, the site of LAD ligation (LIG), the extent of ischemic myocardium (shaded area), and the planes of sectioning (S).

from the hearts without the authors knowing the treatment (halothane or control) subgroup. The distance from the LAD ostium to the site of occlusion was measured by insertion of a calibrated probe. The left ventricle including the interventricular septum was dissected free of right ventricular, atrial, and valvular tissues and sectioned into 1.0- to 1.5-cm thick slices parallel to the atrioventricular groove, beginning at the level of the ligation. This procedure, shown schematically in figure 1, produced four sections of left ventricular myocardium below (distal to) and one section above (proximal to) the LAD ligature. The sections of myocardium then were incubated in triphenyl tetrazolium chloride (TTC) for 30 min at 37°C, followed by immersion in 10% formal saline to demarcate the normal (staining brick red) from the infarcted (staining pale yellow) myocardium.[8]

Transparent tracings were drawn from the upper and lower surface of each tissue section, indicating the boundary between normal and infarcted myocardium. These tracings then were planimetered to determine the relative amount of the left ventricle involved in the infarction. Next, the tissue sections were dissected to physically separate normal from infarcted myocardium, and the size of infarction was determined directly from the weight of the infarcted myocardium, expressed both as the weight of the infarct and as a percentage of the total left ventricular weight.

After planimetric measurement, the transparencies were examined further. The geometry of the infarction was assessed by marking each tracing at the midpoint of the infarction for epicardial, midmyocardial, and endocardial levels. At each level for each tracing, the total circumference and the portion of the circumference oc-

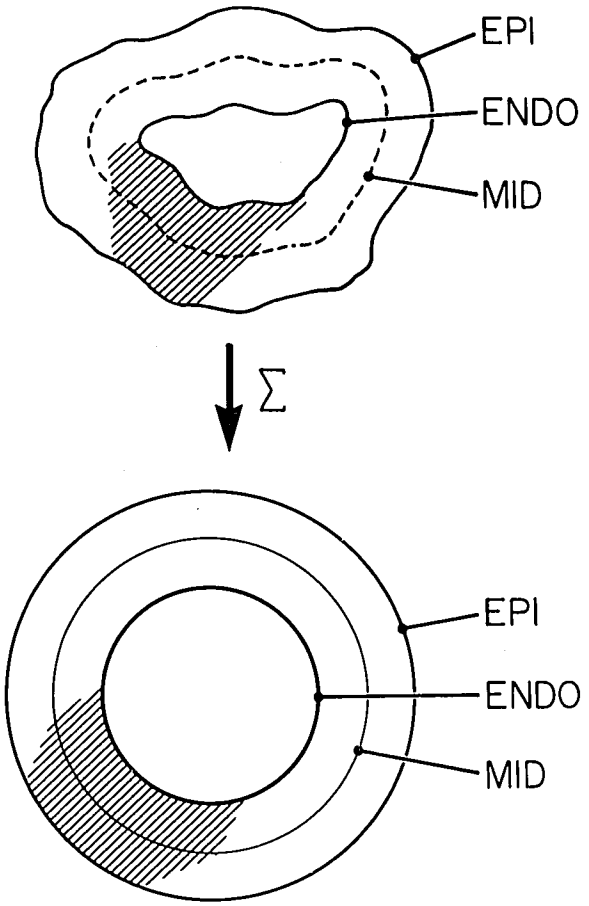

FIG. 2. The figure is a representative tracing of one surface of a left ventricular section (*above*) and a schematic representation of the summation of all tracings from one heart (*below*), showing the extent of infarction (*shaded area*) on the epicardial (EPI), midmyocardial (MID), and endocardial (ENDO) circumferences.

cupied by infarct were measured by using a planimeter to follow the convolutions of the tracing. These data from individual myocardial sections were summed for each heart to permit a statistical construction of the "average" extent of epicardial, midmyocardial, and endocardial infarction for each dog. This procedure is illustrated schematically in figure 2. Data thus obtained from the 10 dogs treated with halothane were pooled and statistically compared with similar data from the eight control dogs.

GROUP B: HEMODYNAMIC AND RMBF PROTOCOL

In 10 additional dogs, catheters were placed into the left atrial appendage for microsphere injection and into the femoral artery for arterial blood sampling after the initial preparation described above. The left ventricle was cannulated at the apical dimple with a 6-in rigid polyethylene catheter connected directly to a transducer system to measure left ventricular pressure. Thirty minutes after ligation of the LAD at the previously determined location and, with the chest closed, hemodynamic measurements were obtained concurrent with the injection of approximately 1.5×10^6 (4 ml solution) 9-μ diameter radionuclide-labeled microspheres[9] (isotopes of tin, ^{113}Sn, and cobalt, ^{57}Co, in random sequence) into the left atrial appendage over 20 s, followed immediately by flushing the injecting syringe and tubing with 20 ml of normal saline. The reference sample of arterial blood was aspirated from the femoral artery at a constant rate (15.3 ml/min) by using a Harvard pump, beginning 15 s before microsphere injection and continuing for 2 min after injection.

Immediately after the initial microsphere flow determination (30 min after LAD ligation), the dogs randomly were assigned to treatment (n = 5) and control (n = 5) subgroups. The treatment group received halothane, 1.0% inspired, in room air via a previously calibrated Fluotec Mark II vaporizer with controlled ventilation. The control group was treated identically, except that halothane was omitted from the ventilator circuit. After 15 min of treatment (or 45 min after LAD ligation in control dogs), microspheres were injected again and hemodynamic variables measured simultaneously, followed immediately by removal of the heart.

From each heart, three transmural samples of left ventricular myocardium (1–1.5 g each) were obtained from normal-appearing myocardium outside the distribution of the occluded vessel, and three similar samples were taken from cyanotic myocardium within the distribution of the occluded vessel. Each myocardial sample was divided into its endocardial and epicardial halves and weighed. Cardiac output and RMBF were calculated from the emission data obtained from the arterial blood sample and myocardial samples by using a protocol previously described by this laboratory.[10] The amount of injected radioactivity was assessed by counting an aliquot of microsphere solution of known volume together with the blood and tissue samples. For each heart, endocardial and epicardial RMBFs were calculated for normal and ischemic myocardium as weighted averages of the RMBF of each individual tissue sample. Tissue from cyanotic myocardium was considered ischemic only if the tissue sample had an RMBF less than or equal to 25% of the corresponding nonischemic RMBF for the first microsphere injection (before randomization). The endocardial-to-epicardial RMBF ratio was calculated for both the normal and the ischemic myocardium for each dog by using these weighted mean data.

The hemodynamic variables measured were heart rate, aortic pressure (systolic, diastolic, and mean), left ventricular end-diastolic pressure (post "A" wave), and the peak rate of change of left ventricular pressure. The latter was measured as the slope of the steepest line tangent to the left ventricular pressure curve. Hemodynamic variables calculated from measured variables and microsphere flow data measured by using standard formulae were cardiac index, stroke index, left ventricular stroke work index, systemic vascular resistance, coronary vascular resistance (in normal myocardium), tension-time index, and the product of heart rate and peak left ventricular systolic pressure.

All intravascular (and left ventricular) pressures were measured by using calibrated Statham P23Db transducers in conjunction with a Gould polygraph. Connections between transducers and the intravascular site were with 6-in rigid, saline-filled polyethylene tubing. Transducers were calibrated with a mercury manometer and checked for drift before each measurement. The directly visualized left atrium was taken as the zero reference level for calibration.

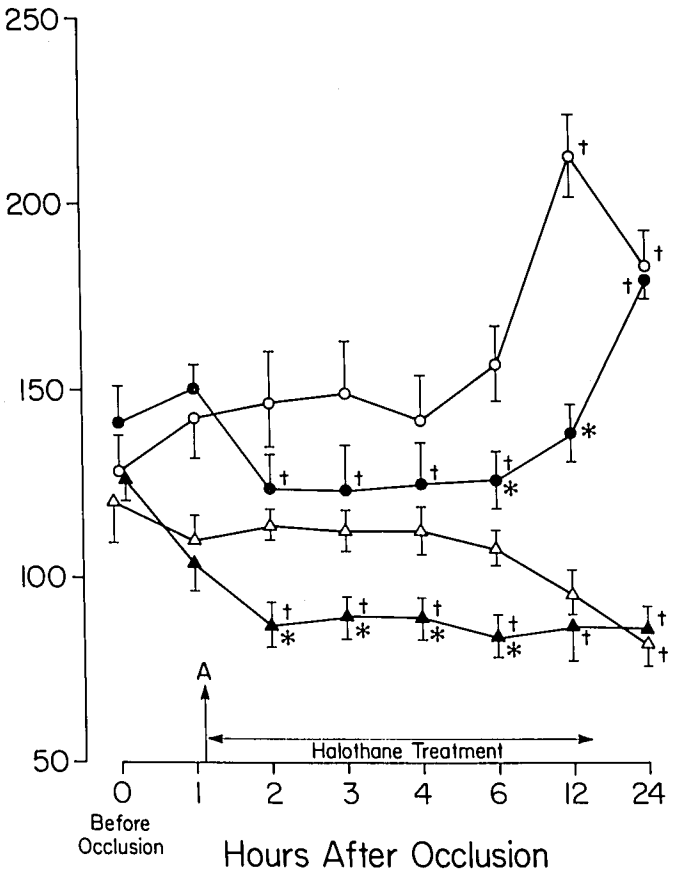

FIG. 3. The figure shows the response of heart rate (circles), beats/min, and mean arterial pressure (triangles), mmHg, of dogs treated with halothane (closed symbols) and of controls (open symbols) over 24 h. Dogs were assigned randomly to either group at A, immediately after 1-h measurements. The asterisk indicates $P < 0.05$ when compared with corresponding control value and the dagger indicates $P < 0.05$ when compared with the value obtained 1 h after left anterior descending (LAD) ligation. Data points are mean values ± 1 SEM.

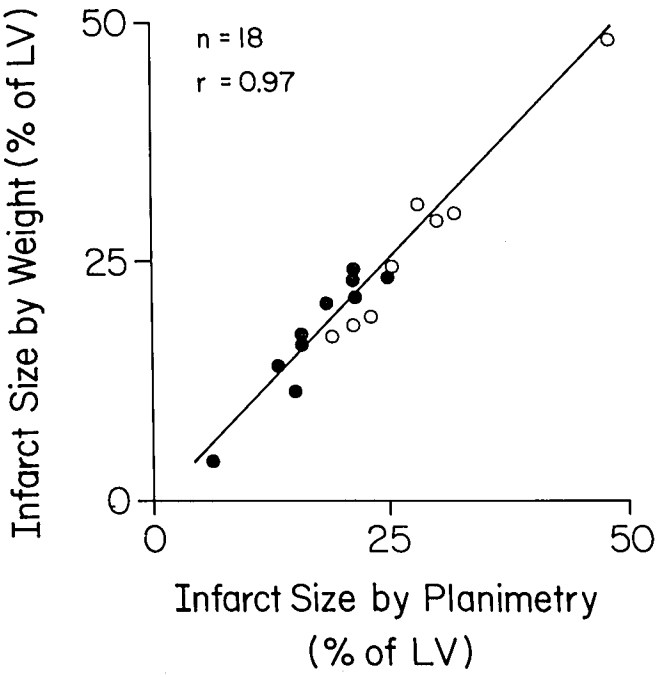

FIG. 4. The figure is a comparison of infarct size measured by planimetry on the abscissa and by tissue weight on the ordinate; both are expressed as percentage of left ventricle (LV) for all 18 dogs in Group A. The solid circles represent data from halothane-treated dogs and the open circles from control dogs. Infarct size (weight) = 1.03 (infarct size [planimetry]) − 0.57; 4 = 0.97.

Statistical Methods

For both protocols, data from individuals were pooled to allow grouped comparison of halothane-treated and control subgroups. Intergroup comparisons were made by using Student's t test for grouped data, while intragroup comparisons were by Student's t test for paired data (Group B) and analysis of variance (Group A). The two measurements of infarct size (planimetry and tissue weight) were compared by using linear regression analysis. Results are expressed as the mean ± 1 standard error of the mean. A probability of chance occurrence of less than 5% ($P < 0.05$) was considered significant.

Results

Group A: Infarct Size Protocol

Heart rate and mean arterial pressure obtained over the 24-h study period are shown in figure 3. Heart rate

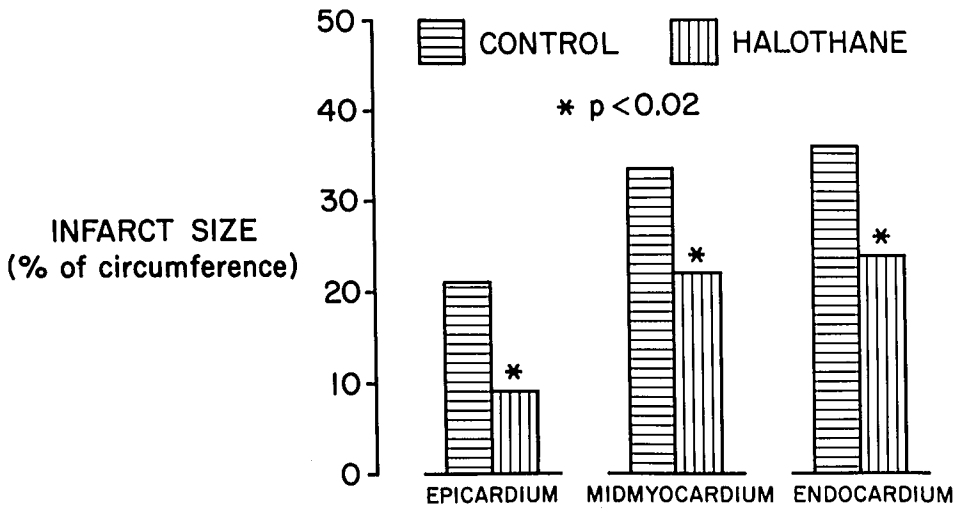

FIG. 5. The figure is a comparison of infarct size in halothane-treated and control dogs. Data are expressed as a percentage of the circumference occupied by infarction in the epicardium, mid-myocardium, and endocardium. Asterisk indicates $P < 0.05$ when compared with corresponding control value. Numerical values are 21.6 ± 3.5 *vs.* 8.9 ± 1.9% for epicardium, 33.4 ± 4.0 *vs.* 21.7 ± 2.7% for midmyocardium, and 35.9 ± 4.2 *vs.* 23.1 ± 2.9% for the endocardium when control data are compared with halothane data, respectively (mean values ± 1 SEM).

declined with the onset of halothane treatment and then remained relatively constant until halothane was discontinued after 12 h. The prominent tachycardia seen in control dogs at 12 and 24 h and in halothane-treated dogs at 24 h is due to the appearance of ventricular tachydysrhythmias. In halothane-treated dogs, mean arterial pressure declined with the administration of halothane, remained stable for the remainder of the protocol, and was less than in control dogs 2, 3, 4, and 6 h after LAD ligation. By 12 h, pressure in the control group had declined so that, despite stable values in the halothane group, the groups did not differ.

The distance from the left coronary ostium to the site of occlusion was the same in halothane-treated and control dogs (2.5 ± 0.2 *vs.*2.6 ± 0.3 cm, respectively). Similarly, the percentage of the left ventricle below (distal to) the occlusion, determined by planimetry or tissue weight, was similar between the groups (75 ± 1 *vs.* 77 ± 2%). Infarct size measured by tissue weight, expressed directly as weight, was 16.2 ± 2.4 g for the halothane-treated

TABLE 1. Measured and Derived Hemodynamic Data for Control and Halothane-treated Dogs 30 Minutes after Coronary Occlusion but before Randomization (A) and Again 15 Minutes later during Treatment, 45 Minutes after Coronary Occlusion (B)

	Control			Halothane		
	A	B	%	A	B	%
Heart rate (beats/min)	152 ± 8	153 ± 6	0	162 ± 8	138 ± 3*†	−15 ± 6†
Mean arterial pressure (mmHg)	107 ± 6	106 ± 6	0	116 ± 8	83 ± 7*†	−28 ± 2†
Peak left ventricular (LV) dP/dt (mmHg/s)	2,151 ± 191	2,054 ± 132	−3 ± 8	1,999 ± 231	1,336 ± 147*†	−33 ± 2†
LVEDP (mmHg)	7 ± 1	8 ± 1	5 ± 5	9 ± 1	9 ± 1	0
LV tension-time index ($mmHg \cdot s \cdot min^{-1}$)	2,569 ± 154	2,712 ± 187	6 ± 4	2,950 ± 230	1,794 ± 107*†	−38 ± 2†
Heart rate X LV systolic pressure ($\times 10^3$)	19.1 ± 0.6	20.2 ± 0.6	6 ± 6	24.3 ± 2.1	13.4 ± 1.1*†	−45 ± 3†
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	2,701 ± 335	2,565 ± 385	−14 ± 8	3,013 ± 492	1,990 ± 225*	−31 ± 5†
Stroke volume index ($ml \cdot beat^{-1} \cdot m^{-2}$)	17 ± 3	16 ± 3	−4 ± 12	18 ± 2	15 ± 2*	−19 ± 5†
LV stroke work index ($g \cdot m^{-1} \cdot beat^{-1}$)	28 ± 5	27 ± 4	−6 ± 5	31 ± 5	16 ± 3*†	−48 ± 2†
Systemic vascular resistance ($mmHg \cdot l^{-1} \cdot min^{-1}$)	51 ± 8	55 ± 11	8 ± 1	53 ± 10	54 ± 7	4 ± 5

Mean values ± 1 SEM.

* $P < 0.05$ when compared with the preceeding value in the same treatment group.

† $P < 0.05$ when compared with the control value for the same time.

TABLE 2. Regional Myocardial Blood Flow (RMBF) Data for Normal and Ischemic Myocardium 30 Minutes after Coronary Occlusion before Assignment to Groups (A) and 15 Minutes later during Treatment, 45 Minutes after LAD Occlusion (B)

	Control			Halothane		
	A	B	%	A	B	%
Transmural RMBF						
Normal	90 ± 9	96 ± 13	8 ± 8	117 ± 18	66 ± 5*†	−38 ± 4†
Ischemic	9 ± 3	8 ± 3	−18 ± 4	14 ± 4	10 ± 3*	−25 ± 13
Ischemic (as % of normal)	11 ± 3	10 ± 3	−11 ± 7	12 ± 3	17 ± 6	29 ± 14
Endocardial to epicardial RMBF ratio						
Normal	1.1 ± 0.1	1.2 ± 0.1	4 ± 4	1.1 ± 0.1	1.0 ± 0.1	4 ± 7
Ischemic	0.8 ± 0.1	0.8 ± 0.1	−1 ± 3	0.6 ± 0.2	0.5 ± 0.2*†	−21 ± 10†

Mean values ± 1 SEM.
* $P < 0.05$ when compared with the preceeding value in the same treatment group.
† $P < 0.05$ when compared with the control value for the same time.

dogs and 29.2 ± 6.1 g for control dogs (17.8 ± 2.0 and 27.3 ± 3.3% of the left ventricle, respectively; $P < 0.05$). The relationship between infarct size determined by planimetry and by tissue weight is shown in figure 4. The correlation of the two methods ($r = 0.97$; regression line slope near unity, and y-intercept close to zero) supports the examination of the geometry of infarction by the more indirect method of planimetry.

There was less infarction at all layers of the myocardium in halothane-treated dogs compared with controls (fig. 5). Infarction was greater on the endocardial than on the epicardial surface in both halothane-treated and control dogs. However, in halothane-treated dogs, the epicardial extent of infarction (as a percentage of that on the endocardium) was less than in controls, 39% *versus* 61%, respectively ($P < 0.05$).

GROUP B: HEMODYNAMICS AND RMBF PROTOCOL

The hemodynamic and RMBF data for the 10 dogs in this protocol are shown in tables 1 and 2. No hemodynamic or flow parameter changed significantly in control animals. In contrast, halothane treatment significantly altered hemodynamics and flow. Heart rate and arterial pressure in halothane-treated dogs were reduced by an amount similar to that in Group A. Halothane also significantly reduced peak left ventricular dP/dt, tension-time index, and left ventricular stroke work index. Systemic vascular resistance did not change in either control or halothane-treated dogs. The microsphere blood flow data document a reduction in cardiac index with halothane due to the combined effects of a reduced heart rate and a lower stroke volume index.

Halothane was associated with a 38% decline in RMBF to the normal myocardium but no significant change in flow to the ischemic myocardium (table 2). RMBF remained constant in both the normal and ischemic regions in control dogs. The endocardial-to-epicardial RMBF ratio was unchanged for the normal myocardium during halothane treatment. However, this ratio declined for the ischemic myocardium during halothane but was unchanged for this region in controls at the same time periods.

Coronary vascular resistance (mean aortic diastolic pressure minus left ventricular end diastolic pressure divided by RMBF) for the normal myocardium was not changed for either treatment group. Coronary vascular resistance data for ischemic regions are not presented, because the driving pressure was not measured directly either in the collateral vascular channels or in the LAD distal to the occlusion site.

Discussion

EXPERIMENTAL MODEL

Several aspects of the experimental model used in this study require consideration concerning the interpretation of our data. Barbiturate anesthesia alters the hemodynamic state of dogs,[11] and the combination of halothane and barbiturate anesthesia produces a different hemodynamic state than induction of halothane anesthesia from a conscious state. For example, Merin *et al.* showed a heart rate of 105 beats/min in dogs with 0.79% end-tidal concentration of halothane, compared with the conscious, unmedicated heart rate of 67.[12] Similarly, Vatner and Smith[13] induced halothane anesthesia (1% end-tidal) in unmedicated dogs, and showed an initially increased heart rate, from 76 to 101 beats/min, followed by a decline with continued anesthesia to 84 beats/min (not significantly different from the conscious baseline level). Thus, the significant decrease in heart rate that we observed with halothane in both protocols may have been influ-

enced by the underlying barbiturate anesthetic and the associated tachycardia. Furthermore, the difference in heart rate comparing (protocol A) halothane-treated dogs with control dogs also may have resulted, in part, from discomfort associated with this "awake" control; and the lower heart rate in the treated group very probably was a significant component of the infarct size reduction observed.

The observed arterial pressure change produced by halothane also may have influenced our findings. However, in a similar experimental model, the extent of ischemia varied inversely with arterial pressure, hypotension increasing the ischemic region and hypertension having the opposite effect.[14] Therefore, the depressor effect of halothane noted in both protocols in this study may have biased our data against the infarct size reduction that we show with halothane. Conversely, a reduction in aortic pressure as observed with halothane may have improved regional myocardial oxygenation by allowing a reduced left ventricular (LV) intracavitary pressure and wall tension. Further studies are needed to examine the effect of halothane on infarct size and RMBF when arterial pressure is maintained at control level, as would be the case clinically.

Although arterial gas tensions were not measured in the present study, several comments relative to ventilatory management are pertinent to a consideration of the experimental model. Previous studies from this laboratory have documented the absence of arterial hypoxemia in dogs, prepared as in the present study, spontaneously breathing room air at 3 and 24 h after coronary occlusion, and no difference in oxygen tension comparing data obtained immediately before coronary occlusion during mechanical ventilation with that obtained during spontaneous ventilation at 3 and 24 h after occlusion.[15] The mechanical ventilatory technique used (tidal volume of 15 ml/kg, frequency of 8 breaths/min and ambient end-expiratory pressure) may have predisposed the halothane-treated group to increasing ventilation/perfusion inequality, leading to a decline in arterial oxygenation, which likely established a moderately hypocarbic state. Both conditions, hypoxemia and hypocarbia,[16,17] in halothane-treated dogs would have worsened the status of the treated group relative to control and biased the study against the observed infarct size reduction. Therefore, the argument that hypoxemia and hypocarbia may have occurred in the halothane-treated dogs strengthens the primary finding of the study, namely that in this animal model, halothane anesthesia is associated with a reduced myocardial infarct size.

Another important point regarding interpretation of our data is the different protocols for each group. In order to assess the effect of halothane on myocardial necrosis after acute coronary occlusion, Group A was observed for 24 h. Additionally, the control for Group A was an "awake" control to obviate the potential influence of sedative or analgesic drugs.[15] In contrast, in Group B 1% inspired halothane (or no agent in control) was superimposed on a basal barbiturate anesthetic. Thus, any mechanistic interpretation of Group B data vis-a-vis Group A must be undertaken cautiously.

The decreased infarct size observed in this investigation does not reflect necessarily a specific pharmacologic property of halothane. Similar results have been reported with heavy sedation using a "lytic cocktail"[18] and with specific hemodynamic interventions such as verapamil[18] and propranolol.[14] The data reported in the present investigation do not distinguish the direct effects of an inherent pharmacologic property of halothane from the indirect effects of the anesthetic state that it produces. Further studies are required to provide this distinction.

The canine model of myocardial infarction also deserves consideration. Although there is an abundant epicardial collateral network for coronary circulation in humans,[19,20] its functional significance is controversial in the absence of coronary stenoses.[21] However, in the presence of high-grade coronary stenoses or occlusion, regional flow through the collateral channels does occur[22,23] and this flow has been reported to support improved ventricular function[24] and increased survival[25] after coronary occlusion. The canine coronary circulation, with its abundant epicardial collateral network, therefore may be a suitable model of human chronic coronary artery disease with superimposed acute coronary occlusion.

The significant variability of canine coronary anatomy complicates this model by necessitating grouped comparisons, which reduces the sensitivity to various interventions.[26] Occlusion of the coronary artery at the same distance from the coronary ostium does not ensure an equal "at-risk" volume of myocardium from one animal to another as documented by Jugdutt *et al.*[27] However, since the present study was completed, methods have been described for delineating the "at-risk" area in each animal,[27,28] thereby improving the sensitivity of this method.

Infarct Size Protocol (24 h)

The most important finding of this portion of our study is that inhalation of halothane at an approximately 1 MAC concentration substantially reduced (35%) myocardial necrosis produced by a standardized coronary artery occlusion in this canine model of acute myocardial infarction. This reduction in infarct size occurred despite the 1-h

lapse between the coronary occlusion and the onset of halothane inhalation. Myocardial salvage was present transmurally, although it was most pronounced in the epicardial layer (fig. 5). Furthermore, myocardial salvage occurred in the presence of a significant reduction in mean arterial pressure, compared with control values, throughout halothane inhalation. These results are consistent with the reports of several previous investigators. Bland and Lowenstein,[29] using an epicardial ST-segment mapping technique, reported a reduction of the sum of ST-segment elevation during coronary occlusion with halothane inhalation at a concentration of 0.75%. Similarly, Gerson *et al.*,[30] using a similar model, showed that halothane (1.1% end-tidal) more effectively reduced epicardial ST-segment signs of ischemia than the combination of sodium nitroprusside and propranolol titrated to produce a similar hemodynamic state. Smith *et al.*[31] reported an increased ratio of oxygen availability to oxygen consumption in ischemic myocardium as compared with normal myocardium during 1% halothane inhalation in a canine model using coronary artery ligation. Clinically, Roizen *et al.*[32] described a reduction in the "stress-induced" elevation of pulmonary capillary wedge pressure, a sign consistent with early myocardial ischemic dysfunction, by increasing anesthetic depth with halothane. Thus, halothane has been shown repeatedly to reduce electrocardiographic and hemodynamic indexes of myocardial ischemia in both clinical and experimental circumstances. The results of the present study amplify these reports by documenting a reduction in the actual tissue mass of necrotic left ventricular myocardium produced by administering halothane beginning 1 h after coronary artery occlusion and by showing that the amount of salvage is more prominent in epicardial regions than in the endocardium.

Hemodynamics and RMBF Protocol (Acute)

The major hemodynamic and RMBF finding of the present study is that halothane was associated with significant reduction of hemodynamic indexes of myocardial oxygen consumption and a proportionate reduction in RMBF to the normal myocardium, but RMBF to the ischemic myocardium was not changed. Halothane did not affect the intramyocardial distribution of blood flow (endocardial to epicardial RMBF ratio) for the normal myocardium but did reduce relative endocardial flow in the ischemic region (table 2). This observation is consistent with the relatively greater salvage of epicardium than endocardium in halothane-treated dogs compared with control dogs.

The reduction in RMBF to normal myocardium observed with halothane in the present investigation is consistent with observations in previously published reports.[12,13,33-35] This reduction has been reported to be proportional to the reduced myocardial work and oxygen utilization produced by halothane in experimental animals[12,13,24,26,36] and in humans.[37] The effect of halothane on RMBF to ischemic myocardium is less well understood. Smith *et al.*[31] measured coronary perfusion distal to occlusion and oxygen tension (arterial and venous) in the ischemic region to calculate regional oxygen consumption in the ischemic myocardium. Their results with halothane show a decline of oxygen consumption in the ischemic region proportional to that in the normal myocardium but an unchanged ischemic region coronary perfusion pressure. The net result was an improved ratio of oxygen availability to oxygen consumption in ischemic myocardium during halothane administration.

Verrier *et al.*[38] reported the coronary pressure–flow relationship in a canine preparation by using a variable circumflex coronary artery constriction. Halothane produced a left shift of the pressure–flow relationship during maximal vasodilation, which lowered the distal coronary artery pressure at which flow stopped. These investigators postulated that the lower "zero-flow" pressure with halothane reflects a lower intramyocardial pressure with a consequent lower vascular waterfall pressure in the left ventricle during halothane administration. However, they also stated that the observed effect may have been more related to heart rate than to halothane.

Lowenstein *et al.*[39] described a dose-dependent impairment of segmental left ventricular function within a region perfused by a critically stenosed coronary artery associated with increasing inspired concentration of halothane from 0.5% to 2.0%. This was not seen in normally perfused regions. The observed ventricular dysfunction was attributed to ischemia produced by the diminished driving pressure associated with halothane and the concomitant inability of the stenosed vessel to maintain flow at the reduced pressure. In another investigation, hypotension induced by halothane in dogs was reported not to produce myocardial ischemia in the presence of "moderate" coronary stenosis but did so with "severe" coronary stenosis.[40]

All of these studies are consistent with the data in the present investigation, however, in most (including the present study) halothane is superimposed on a basal anesthetic, which may have influenced the findings. In contrast to the conditions associated with a stenotic coronary artery, perfusion distal to a complete coronary occlusion depends on collateral channels from adjacent normal coronary vessels. Thus, an intervention after coronary occlusion that tends to maintain resistance in the normal vascular bed, as reported for halothane by Merin *et al.*[12]

and by Vatner and Smith,[13] and tends to shift the pressure–flow relationship in the direction of improved flow at lower pressure, as shown for halothane by Verrier *et al.*,[38] potentially could improve perfusion and oxygen availability in the portion of the ischemic region of myocardium best supplied by collateral blood flow, *i.e.*, the peripheral margins. While the present study does not provide RMBF data for the periphery of the ischemic region, the salvage of myocardium at the lateral and epicardial margins of the infarction in halothane-treated dogs supports this interpretation.

It is important to emphasize that our data were gathered from dogs with an isolated coronary occlusion, with the remaining coronary vasculature and the baseline cardiac function being normal, while patients with atherosclerotic coronary artery disease frequently have multiple, lengthy, and sequential stenoses with impaired underlying ventricular function. Furthermore, canine coronary circulation may provide better immediate epicardial collateral flow after acute coronary artery occlusion than human circulation, although the chronicity of human coronary artery disease enhances the development of collateral channels. The present study supports the continued use of halothane as a component of anesthesia for patients with coronary artery disease; however, detailed attention to the maintenance of hemodynamic parameters within "acceptable" ranges remains the goal of the perioperative anesthetic management of actual or potential myocardial ischemia.

The authors gratefully acknowledge the technical assistance of Ms. Sharon Hale and Mr. John Tumas, the secretarial assistance of Mrs. Kathy Angell, Ms. Pearl Short, and Mrs. Nancy Hanner, University of Florida College of Medicine, the editorial assistance of Ms. Lynn Carroll, University of Florida College of Medicine, and the administrative support of Dr. R. Brian Smith, Professor and Chairman of the Department of Anesthesiology, The University of Texas Health Science Center at San Antonio.

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