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Halothane-induced Decrease in Experimental Myocardial Ischemia in the Non-failing Canine Heart

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The effect of halothane on net myocardial oxygen balance of ischemic myocardium was studied in the non-failing canine heart. Myocardial ischemia was produced by repeated reversible occlusions of a coronary artery; the severity of ischemia was estimated by summating ST-segment elevations (ΣST) obtained by epicardial ECG mapping at 15 to 18 sites. Control measurements were obtained before and after administration of halothane (0.75 per cent) to six dogs with chloralose–urethane basal anesthesia. Halothane was associated with significant decreases of systemic arterial pressure ($P < .001$), heart rate ($P < .01$), and the product of systolic arterial pressure × heart rate ($P < .01$), an indirect index of myocardial oxygen consumption, while left atrial pressure remained unchanged at normal levels. ΣST during occlusion was less ($P < .001$) during halothane (26.5 ± 7.4 {SD} mv) than before (36.6 ± 5.4 mv) or after (34.4 ± 8.2 mv) its administration. Thus, halothane decreased the severity of experimentally-induced myocardial ischemia in the non-failing canine heart. The data suggest that, in the absence of ventricular failure, halothane influences the relationship between myocardial oxygen supply and demand in a favorable direction when coronary blood flow is limited. (Key words: Heart, coronary blood flow; Heart, oxygen consumption; Anesthetics, volatile, halothane.)

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GENERAL ANESTHESIA for the patient who has severe coronary-artery disease is becoming increasingly commonplace. The increased perianesthetic mortality associated with this disease has been emphasized by many investigators.[1–3] However, there is no systematic study that evaluates the effects of specific anesthetics on the ischemic heart. There are also no data relating the effects of anesthetics on the major determinants of myocardial oxygen demand in the ischemic myocardium. These deficiencies may reflect the previous lack of an appropriate animal model of ischemic heart disease. The present studies define the effect of 0.75 per cent halothane anesthesia in a canine model of experimental myocardial ischemia that has proven applicable to man[4,5] and demonstrate that the severity of experimental myocardial ischemia in the non-failing canine heart is decreased by halothane administration.

Methods

Six mongrel dogs weighing between 18 and 22 kg were anesthetized with intravenously-administered chloralose (90 mg/kg) and urethane (900 mg/kg). The trachea was intubated and the animal ventilated with oxygen using a Harvard animal ventilator. A left thoracotomy was performed, and the heart exposed and suspended in a pericardial cradle. A branch of the left anterior descending coronary artery was isolated 3 to 5 mm from its origin, and a reversible tourniquet placed loosely around it. A polyethylene cannula was placed in the left atrium for pressure recording and another in a femoral artery for pressure recording and blood sampling.

Myocardial ischemia was produced and its severity estimated according to the method described by Maroko and associates.[4] Briefly, a diagram of the visible coronary arterial cir-

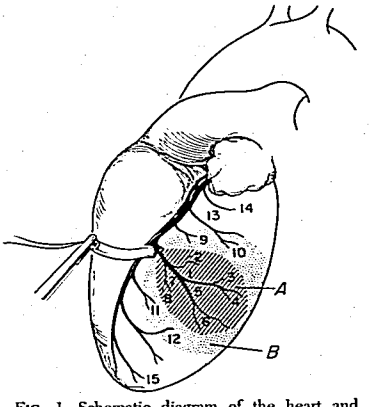

FIG. 1. Schematic diagram of the heart and coronary circulation with a tourniquet shown around a branch of the left anterior descending coronary artery. Numbers 1 through 15 represent sites selected for epicardial mapping. Sites 1 through 8 (Area A) are directly within the area supplied by the temporarily occluded branch, and sites 9 through 12 (Area B) are in the adjacent or "border" zone. Sites 13, 14 and 15 are remote from the site of occlusion and are used to monitor stability of the preparation. The total ST-segment elevation (ΣST) was calculated from individual values recorded at each site.

culation was drawn and 15 to 18 sites selected for epicardial electrocardiographic mapping (fig. 1). Some sites were directly within the area supplied by the branch that had been selected for occlusion, some in the immediately adjacent area, and some in areas remote from the occluded artery. The epicardial electrode, a needle with a rounded tip (diameter 1 mm) attached to the "V" lead of the ECG, was standardized to 1 mv/mm. For each recording, the epicardial ECG was obtained consecutively at each of the pre-selected sites. Severity of ischemia was considered to be the sum of the S-T-segment elevations (ΣST) of the epicardial electrocardiogram at the selected sites.

For each experimental run we obtained readings of control pressures and heart rate, and the epicardial ECG was recorded in duplicate; the snare was then tightened, occluding the selected branch of the coronary artery, and all measurements repeated 3, 6, 9, and 12 minutes later. The snare was then loosened, re-establishing flow in the branch, and measurements repeated again after 3, 6, 9, and 12 minutes.

Each dog was subjected to a "pre-halothane" control run during basal anesthesia with chloralose and urethane; a "halothane" run after at least 20 minutes of exposure to 0.75 per cent halothane, when heart rate and systemic arterial and left atrial pressures were stable; and a "post-halothane" control run, performed a minimum of 20 minutes after discontinuation of halothane when heart rate and systemic arterial and left atrial pressures approximated the values of the pre-halothane run.

Arterial and left atrial pressures were measured by Sanborn 267 BC transducers and recorded continuously on a Hewlett-Packard recorder. Mean pressures were obtained by electronic integration and the heart rate was calculated from the ECG tracing. Severity of ischemia was estimated by the sum of the ST-segment (ΣST) elevations of the epicardial electrocardiogram of the mapping sites. Systolic arterial pressure × heart rate product was calculated by multiplication of these two values. Inspired halothane concentration was measured with a Beckman LB-2 medical gas analyzer. Intermittent analysis of arterial blood documented normality of arterial blood gases and pH.

Data were analyzed by Student's t test for paired data. Pre-halothane data were compared with post-halothane data, and halothane data with the mean of the pre-halothane and post-halothane data.

Results (Table 1)

No change in heart rate, systemic arterial blood pressure, or left atrial pressure occurred when the coronary arterial branch was occluded. However, a prompt increase in ΣST occurred each time the coronary branch was occluded. ΣST decreased promptly with release of the tourniquet and re-establishment of flow.

Mean arterial pressure, heart rate, and systolic arterial pressure × heart rate product decreased significantly during halothane anesthesia, whereas left atrial pressure remained

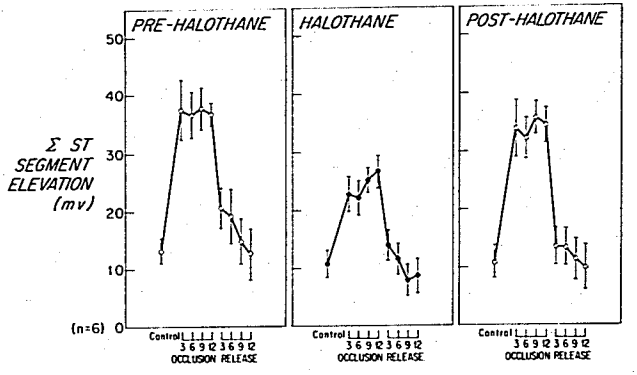

FIG. 2. Sum of ST-segment elevations (ΣST) before, during and after 0.75 per cent halothane administration in six dogs. The severity of ischemia produced by occlusion of the identical branch of the left anterior descending coronary artery was significantly ($P < .001$) less during halothane anesthesia. I = mean and SEM.

unchanged. The ΣST was significantly ($P < .001$) less during occlusion of the coronary arterial branch when halothane was administered, compared with the pre- and post-halothane values obtained during occlusion (fig. 2). Figure 3 shows typical epicardial electrograms obtained at one site during these studies, and demonstrates the decrease in ST-segment elevation consequent to coronary occlusion during halothane anesthesia.

All values obtained in pre- and post-halothane periods were comparable, except for the ΣST 3 minutes after release of the tourniquet in the post-halothane period, which was significantly less than the corresponding pre-halothane value.

Discussion

These studies demonstrate that the severity of experimental myocardial ischemia produced by transient occlusion of a major branch of the canine coronary artery is decreased substantially during administration of 0.75 per cent halothane. This effect may be due not specifically to halothane, but to its influence on the determinants of myocardial oxygen demand.

A direct relationship between S-T-segment elevation of the epicardial ECG early after

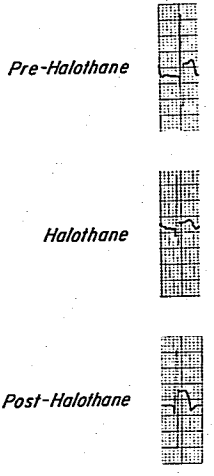

FIG. 3. Representative epicardial electrograms taken at the same site within the area of ischemia during coronary-arterial occlusion before, during and after administration of 0.75 per cent halothane. The ST segment is raised 2 mm during administration of halothane compared with 4 mm in the pre-halothane period and 4.5 mm in the post-halothane period.

TABLE 1. Hemodynamic and Epicardial Electrocardiographic Mapping Data before, during and after 0.75

	Control	Minutes of Occlusion 3	6	9	12
A. Pre-halothane*					
ΣST (mv)	13.3 ± 8.4	37.5 ± 13.7	36.6 ± 10.5	37.8 ± 9.5	36.6 ± 5.5
HR (beats/min)	160.4 ± 31.5	156.6 ± 31.4	153.7 ± 30.4	157.0 ± 32.8	159.3 ± 31.6
MAP (mm Hg)	118.6 ± 17.3	123.0 ± 13.6	120.4 ± 16.9	121.1 ± 12.7	123.0 ± 12.6
M LAP (mm Hg)	5.8 ± 1.9	6.1 ± 2.0	6.3 ± 1.8	6.5 ± 1.8	6.6 ± 2.0
PRP/100	255 ± 77	244 ± 73	243 ± 68	248 ± 73	258 ± 71
B. Halothane					
ΣST (mv)	10.8 ± 9.0	22.8 ± 8.2¶	22.0 ± 7.9¶	25.1 ± 5.7¶	26.5 ± 7.4¶
HR (beats/min)	138.7 ± 30.1†	138.6 ± 29.5†	137.0 ± 29.4§	135.6 ± 27.3§	136.1 ± 27.1§
MAP (mm Hg)	108.0 ± 13.6§	102.7 ± 10.9¶	102.3 ± 10.5¶	101.4 ± 9.9¶	101.1 ± 10.2¶
M LAP (mm Hg)	6.6 ± 2.2	6.8 ± 2.1	6.9 ± 2.0	6.9 ± 2.0	6.9 ± 2.0
PRP/100	199 ± 52§	199 ± 49§	186 ± 47§	185 ± 46§	183 ± 44§
C. Post-halothane					
ΣST (mv)	10.9 ± 11.5	33.8 ± 13.1	32.1 ± 9.1	35.6 ± 7.4	34.4 ± 8.2
HR (beats/min)	145.1 ± 40.4	150.0 ± 36.4	150.7 ± 37.2	150.7 ± 37.2	150.1 ± 37.8
MAP (mm Hg)	122.3 ± 11.0	121.6 ± 7.9	122.0 ± 10.1	122.7 ± 10.7	121.6 ± 9.8
M LAP (mm Hg)	6.9 ± 2.4	6.6 ± 2.4	6.6 ± 2.4	6.3 ± 2.4	6.1 ± 2.3
PRP/100	243 ± 100	243 ± 95	243 ± 93	241 ± 86	239 ± 88

* ΣST = sum of ST segment elevation. HR = heart rate. MAP = mean arterial pressure. M LAP = mean
† Less than A ($P < .01$).
‡ Less than the mean of A + C ($P < .05$).
§ Less than the mean of A + C ($P < .01$).
¶ Less than the mean of A + C ($P < .001$).

coronary arterial occlusion and the later development of cellular damage and death evidenced both by electron microscopy and by depression of creatine phosphokinase activity has been demonstrated by Maroko *et al.*[4] Interventions that improve net myocardial oxygen balance decrease the severity of myocardial ischemia and ΣST during coronary occlusion, while those that worsen net myocardial oxygen balance have the opposite effect. Watanabe has shown that a given intervention may have an opposite effect on myocardial oxygen balance, depending upon the underlying condition of the heart.[6] For instance, increasing mean arterial blood pressure by peripheral vasoconstriction produces greater ischemia in the failing heart subjected to experimental occlusion of a coronary arterial branch, whereas peripheral vasoconstriction improves myocardial oxygen balance and decreases ΣST in the non-failing heart.

The major determinants of myocardial oxygen demand (or consumption) are 1) left ventricular wall tension, which is proportional to the left ventricular systolic or systemic systolic arterial pressure and the volume of the left ventricle; 2) the contractile state of the heart, *i.e.*, velocity of contraction; and 3) heart rate.[7] When a coronary artery is occluded, a portion of the heart muscle is totally deprived of blood and oxygen. Adjacent to this area is a border zone which is the recipient of collateral flow from the vasculature of surrounding muscle. Interventions that increase collateral flow or decrease oxygen demand of this area would be expected to improve myocardial oxygen balance and decrease the severity of ischemia, while those that have the opposite effect would increase ischemia.

Halothane anesthesia in this study was associated with a decrease in left ventricular systolic pressure and no change in left atrial pressure. While the left ventricular volume was not measured directly, the lack of change in left atrial pressure and the published data of Rusy *et al.*,[8] which documented the lack of change in left ventricular end-diastolic volume during anesthesia with 1 per cent

Per Cent Halothane in Six Dogs Subjected to Temporary Occlusions of a Coronary Artery (Mean ± SD)

Minutes after Release of Occlusion			
3	6	9	12
20.6 ± 9.5	19.1 ± 12.3	14.8 ± 10.5	12.6 ± 11.7
158.7 ± 31.6	160.6 ± 31.0	158.4 ± 30.5	159.6 ± 29.2
123.0 ± 11.0	125.0 ± 12.2	125.3 ± 12.2	126.3 ± 12.1
6.5 ± 2.4	6.3 ± 2.3	6.0 ± 2.4	6.1 ± 2.3
262 ± 74	273 ± 72	267 ± 72	273 ± 72
13.9 ± 6.9	11.6 ± 7.2	7.9 ± 7.0	8.7 ± 7.8
135.3 ± 28.1§	135.3 ± 27.8§	137.9 ± 32.8§	135.9 ± 30.0§
100.7 ± 10.4§	100.7 ± 10.7§	100.0 ± 10.1§	100.1 ± 9.4§
6.7 ± 2.0	6.6 ± 2.1	6.6 ± 2.1	6.6 ± 2.1
180 ± 44§	182 ± 47§	183 ± 52§	179 ± 49§
13.6 ± 8.6†	13.6 ± 8.6	11.3 ± 9.5	9.9 ± 10.3
152.0 ± 38.0	151.4 ± 39.5	153.0 ± 38.3	154.6 ± 36.8
121.9 ± 10.0	122.7 ± 9.8	124.6 ± 9.0	122.6 ± 10.8
6.1 ± 2.6	6.1 ± 2.7	5.9 ± 2.6	5.9 ± 2.5
242 ± 88	243 ± 89	242 ± 87	242 ± 87

left atrial pressure. PRP = systolic arterial pressure × heart rate product.

halothane in dogs, argue strongly for the absence of change in left ventricular volume in the present study. Accordingly, left ventricular wall tension was presumably decreased by halothane in our study. We did not measure the second major determinant of myocardial oxygen consumption, *i.e.*, contractile state. However, Prys-Roberts[9] previously documented a decrease in velocity of left ventricular contraction when 1 MAC halothane was administered to dogs during basal chloralose–urethane anesthesia. The third major determinant of myocardial oxygen consumption, heart rate, was also decreased in the present studies. Thus, it appears that the magnitudes of all three major determinants of myocardial oxygen demand declined during halothane administration in the present study, and therefore that myocardial oxygen consumption was decreased. The decrease of approximately 25 per cent in systolic arterial pressure × heart rate product, an indirect index of myocardial oxygen consumption,[10] supports this hypothesis. Our data are in accord with those of Theye,[11] who reported a 35 per cent reduction in myocardial oxygen consumption when halothane concentration was increased from 0.2 to 0.8 per cent in dogs.

Coronary blood flow occurs principally during diastole, and the coronary perfusion pressure is equal to the difference between aortic diastolic pressure and left ventricular diastolic (left atrial) pressure.[12] Coronary perfusion pressure was modestly decreased by halothane in the present studies, since aortic diastolic pressure decreased and left atrial pressure remained constant. Whether total coronary flow or its distribution changed in proportion to the decrease in coronary perfusion pressure was not measured. Coronary blood flow and distribution when coronary perfusion pressure is decreased may depend, at least in part upon the ability of the coronary vasculature of the individual experimental animal to autoregulate. The observed decline in heart rate increases the proportion of time available for coronary flow, which may offset the effect of the change in coronary perfusion pressure. Regardless of these considerations, the lesser ΣST

consequent to coronary occlusion during halothane administration indicates that the decrease in oxygen demand exceeded the potential decrease in oxygen supply, with a net improvement in myocardial oxygen balance.

It is possible that, in addition to its effects upon the major determinants of myocardial oxygen demand, a specific effect of halothane upon myocardial oxygen consumption may exist. For instance, the inhibition by halothane of calcium uptake by the sarcoplasmic reticulum described by Price may represent such an "oxygen-sparing" effect.[13] We have not examined that thesis. To do so, it would be necessary to maintain at control levels all major determinants, *i.e.*, heart rate, contractile state, systemic blood pressure, and left ventricular volume, during halothane anesthesia, a goal that may be impossible to achieve in the intact animal. In several animals, however, we did administer phenylephrine during halothane anesthesia in an attempt to increase systemic arterial pressure to pre-halothane control levels, and to quantitate that part of the beneficial effect dependent upon decreasing left ventricular systolic pressure and wall tension. In each animal, this led to ventricular failure and circulatory collapse, emphasizing the importance of the myocardial depression associated with halothane administration.

The present studies were performed in the non-failing heart. It is possible that halothane anesthesia in the failing heart would accentuate heart failure and further elevate ventricular diastolic pressure and size. Increased ventricular diastolic volume and pressure are associated with greater left ventricular wall tension and increased myocardial oxygen demand, as well as to impaired coronary circulation to the subendocardial region due to increased intramural pressure. They lead to deterimental changes in myocardial oxygen balance, in contrast to the changes observed in the non-failing heart.

The clinical implications of the present studies are intriguing. Approximately 5 per cent of the adult population of the United States has clinical evidence of coronary-artery disease. Increasing numbers of individuals with coronary-artery disease are candidates for a variety of surgical procedures. Recent data suggest that perioperative morbidity and mortality rates of general surgical patients who have severe coronary-artery disease have not improved over the last 15 years.[1–3] The present studies indicate that the myocardial oxygen balance of the jeopardized myocardium in the non-failing heart may be altered beneficially by halothane, an anesthetic that has myocardial depressant characteristics and was associated in these studies with moderate reductions of blood pressure and heart rate. The data suggest that the circulatory effects of anesthetics must be evaluated in terms of their effects upon the determinants of myocardial oxygen supply and demand, particularly when coronary blood flow is limited. The studies imply that choice of anesthetics, as well as their proper administration, may be important in management of patients who have coronary-artery disease. It also appears necessary to consider other drugs administered during anesthesia, such as muscle relaxants and adrenergic agonists and antagonists, in terms of their effects upon myocardial oxygen balance.

These data must be applied with caution to the failing heart. They emphasize the importance of clinical estimation of left ventricular filling pressure obtained by means of a flow-guided pulmonary-artery catheter.[4] The studies further emphasize the importance of considering all major determinants of myocardial oxygen consumption during the entire perioperative period in management of patients who have coronary-artery disease.

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Spinal Anesthesia

REGIONAL ANESTHESIA AND RENAL TRANSPLANTATION In 1962, the first report of anesthesia for renal transplantation was published. It was felt that continuous spinal anesthesia was a technique of choice. The use of regional anesthesia for this procedure has declined in recent years. Even when the patient is under adequate control, potential hazards for both general and regional anesthesia exist. Lack of renal drug excretion (neuromuscular blockers), potential electrolyte and acid–base abnormalities, bleeding disorders, peripheral neuropathy, increased incidence of serum hepatitis, hypertension, and anemia must all be considered. The authors report the use of single-dose high spinal anesthesia in 64 patients undergoing renal transplantation. Tetracaine and dextrose were used: 18–20 mg tetracaine were used in tall patients, 14–16 mg in shorter patients (usually female or teenaged). Epinephrine (0.2–0.4 mg) was also used. A level of T4–T6 was sought. Thirty-three patients required intravenous sedation; 2–5 ml of Innovar and 5–10 mg diazepam produced adequate sedation without loss of consciousness. Supplementation was necessary in all procedures lasting longer than two hours. An additional 27 patients received N_2O by mask; they were drowsy but easily aroused. General anesthesia was needed by only four patients (three with thiopental–N_2O and one with halothane). Although arterial blood pressures decreased by more than 25 per cent at some time during the procedure in 33 patients, this posed no difficulty. The only neurologic sequel was urinary retention lasting one month in a single patient. The authors conclude that this technique provides a number of major advantages: 1) Worry about untoward effects of neuromuscular blockers is avoided; 2) Lack of need for tracheal intubation while excellent surgical conditions are maintained; 3) Ease in the management of patients who have full stomachs; 4) Lack of interaction of acidosis and hyperkalemia with anesthetic and adjuvent drugs; 5) A conscious, reactive, comfortable patient in the postoperative period. (*Linke CA, Merin RG: A regional anesthetic approach for renal transplantation. Anesth Analg (Cleve) 55: 69–73, 1976.*)