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Impaired Systolic Thickening Associated with Halothane in the Presence of a Coronary Stenosis Is Mediated by Changes in Hemodynamics

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Myocardial ischemia results when halothane is administered to animals with severe coronary stenosis. This study was done to separate the effect of halothane, *per se*, on myocardial ischemia from indirect cardiovascular effects, primarily hypotension, that might cause ischemia by altering the oxygen supply–demand balance. Eight dogs underwent sterile surgery for implantation of sonomicrometer crystals and atrioventricular (A-V) heart block. One week later, each dog was anesthetized with morphine and chloralose. Heart rate was controlled by ventricular pacing and altered in five steps from 50 to 150 beats/min. Arterial blood pressure was controlled by blood withdrawal or phenylephrine infusion at four levels of arterial pressure (60 to 120 mmHg). Regional myocardial contraction was measured at each of the resulting 20 points as an indicator of myocardial ischemia. Twenty points were collected under each of four conditions in each animal: control, halothane (1% inspired), stenosis, halothane plus stenosis. Systolic thickening in the presence of stenosis was divided, on a point-by-point basis, by values obtained in the absence of stenosis to obviate the direct effects of blood pressure and heart rate on thickening. A separate normalization was done for data obtained in the presence of halothane. The normalized data demonstrate impaired systolic contraction at low arterial pressures and high heart rates. Multiple regression analysis failed to demonstrate a significant effect of halothane on systolic contraction once the effects of blood pressure, heart rate, and the negative inotropic effect of halothane were taken into account. Thus, the contraction failure that occurred during halothane and severe stenosis was mediated by changes in hemodynamics. Halothane, *per se*, did not cause myocardial ischemia in this nonfailing canine model of acute coronary artery stenosis. (Key words: Anesthesia: cardiovascular. Anesthetics, volatile: halothane. Blood pressure. Complications: myocardial ischemia; hypotension. Heart: blood flow; coronary stenosis; myocardial function; myocardial ischemia; pulse rate. Hemodynamics. Monitoring. Surgery: cardiac.)

THE SAFETY OF halothane as an anesthetic for patients with coronary stenoses remains controversial. Recently, three well-done animal studies have all convincingly demonstrated that the combination of halothane and severe stenosis produces myocardial ischemia.[1–3]

In contrast, a number of clinical studies provide evidence that halothane does not produce ischemia in patients with coronary artery disease[4–6] and may, in fact, be useful in the treatment of stress-induced ischemia.[7]

A possible resolution of these discrepant results is suggested by the clinical study of Lieberman *et al.*[8] All patients received halothane for coronary artery surgery, and two-thirds of them had at least one episode of myocardial ischemia, as judged by electrocardiographic criteria. Ischemia was more frequent during periods of hypotension or tachycardia than during hypertension. These findings suggest that ischemia associated with halothane may be an indirect result of halothane's cardiovascular effects operating through changes in blood pressure and heart rate. This possibility is supported by the observation that systemic blood pressure was considerably lower (mean pressures around 50 mmHg) in the animal studies showing ischemia than in the clinical studies (mean pressures of 75 to 90 mmHg) that did not.

A recently developed canine model of coronary stenosis[9] allows independent control of blood pressure and heart rate and can thereby separate myocardial ischemia caused by halothane, *per se*, from ischemia caused indirectly by the cardiovascular effects of halothane. The strategy of the present experiment was to hold the concentration of halothane constant (none or approximately 1%, inspired) and vary blood pressure and heart rate over clinically relevant ranges in the presence of a severe coronary stenosis. Identical measurements were made in the absence of stenosis to calibrate the effects of halothane on regional contraction, the measure of myocardial ischemia. Loss of systolic contraction in a hypoperfused region is a sensitive, quantitative indicator of relative oxygen shortage,[10–13] but contraction is also influenced by the well-known negative inotropic effect of halothane.[14]

The results suggest that myocardial ischemia occurring when halothane is added to a severe coronary stenosis is mediated by changes in blood pressure and heart rate.

Methods

SURGICAL PREPARATION

A detailed description of several of the methods used in this study has been published previously.[9] In summary: Dogs weighing 25–30 kg were anesthetized and prepared for sterile surgery. The left thorax was entered and a permanent heart block created by injection of formalin into the atrioventricular (A-V) node.[15] The ventricles were

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paced (80 beats/min) during recovery to prevent congestive failure.

One set of piezoelectric crystals was used to measure wall thickness in the center of the territory supplied by the circumflex coronary artery. A lensed crystal (1–2 mm in diameter) was tunneled tangentially through the myocardium to a spot not more than 3 mm from the endocardial surface. A second crystal (2–3 mm in diameter) was sewn to the epicardium at the spot that minimized the distance between the crystals. The location of the inner crystal and perpendicular orientation of the set was confirmed at autopsy. Following crystal placement, the pericardium and chest wall were closed, and the animal was allowed to recover for at least six days.

General Preparation

Eight closed-chest dogs were studied a minimum of six days following surgery when they were afebrile and active. Approximately 1 h after sedation with morphine sulfate (2.5 mg/kg, sc), each dog was anesthetized with an initial injection of α-chloralose (100 mg/kg, iv). Anesthesia was maintained with a continuous infusion of α-chloralose (10 $mg \cdot kg^{-1} \cdot h^{-1}$, iv) during the experiment.[16] The animals were ventilated with a positive-pressure pump (Harvard) operating with a 10 cmH_2O end-expiratory back pressure (Boehringer). Oxygen was delivered to a semiclosed circuit containing a soda lime cannister, and arterial blood oxygen tension was between 300 and 450 mmHg throughout the experiment. End-expiratory carbon dioxide was monitored continuously with an infrared device (Beckman LB-1®) and was held between 4.5% and 5% by adjustment of rate of ventilation and tidal volume. Metabolic acidosis caused by chloralose anesthesia was prevented by infusion of 150 mM sodium bicarbonate, 5 $ml \cdot kg^{-1} \cdot h^{-1}$, iv. Arterial blood was sampled periodically, and *p*H, P_{CO_2}, and P_{O_2} were determined (Instrumentation Laboratories, 813). Arterial hemoglobin concentration was determined by use of a CO-oximeter® (Instrumentation Laboratories, 282). Rectal temperature was held at 37° C with a heating pad and temperature controller (Yellow Springs, 73A). Blood coagulation in the extracorporeal circuit was prevented by infusion of sodium heparin (750 U/kg, iv bolus plus 250 $U \cdot kg^{-1} \cdot h^{-1}$, iv).

Arterial blood pressure was measured with a catheter introduced into the arch of aorta *via* the right brachial artery. A solid state, catheter-tip transducer (Millar) introduced *via* the left carotid artery was used to measure left ventricular pressure. The first derivative of left ventricular pressure with respect to time was derived with an analog circuit (Honeywell Accudata®, 132).

Coronary Blood Flow Measurements

A stainless steel cannula[17] was advanced into the root of the aorta *via* the right carotid artery. The tip of this cannula was wedged into the left circumflex coronary artery. Arterial blood from a femoral artery was supplied to this cannula by an external perfusion circuit. Coronary pressure was measured at the cannula tip *via* a small, internal, stainless steel tube. The seal at the tip was tested by a 10-s period of stopped flow; coronary pressure fell below 25 mmHg if the seal was complete. Total flow into the circumflex coronary artery was measured with an electromagnetic flowmeter (Zepeda SWF-3rd®) located in the extracorporeal circuit. Flow per gram was calculated by dividing total flow by total weight of the perfused area. This area was defined by injection of 3–4 ml of india ink into the cannula at the end of the experiment. The flowmeter was calibrated with the dog's blood by timed collection after each experiment.

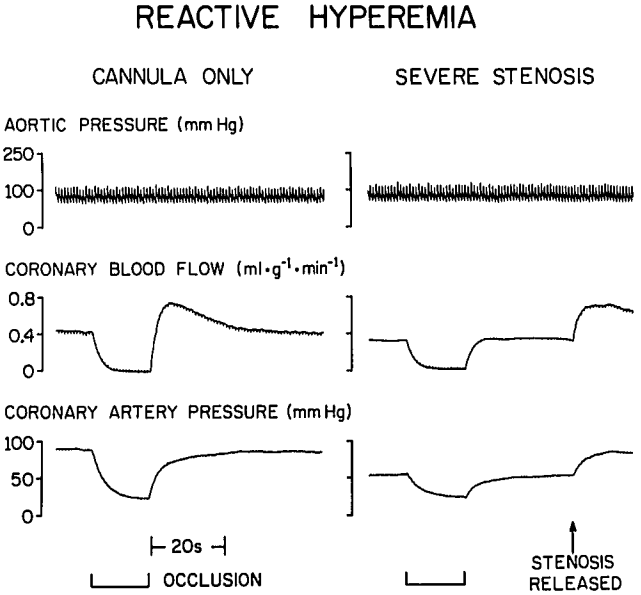

FIG. 1. Hyperemic response to a 15-s coronary occlusion is shown for two conditions in one dog. *Left panel,* flow was delivered to the coronary circulation by an external perfusion circuit that resulted in a 5–15 mmHg aorto-coronary pressure gradient and limited reactive hyperemia to a two- to three-fold increase above resting flow. The addition of a severe coronary stenosis (*right panel*) produced a 30–60 mmHg pressure gradient, reduced resting coronary flow by 15–20%, and abolished reactive hyperemia. This degree of flow restriction is comparable to an atherosclerotic lesion that reduces coronary vessel diameter 90–95%.

Coronary Stenosis

The perfusion circuit that delivered blood to the circumflex artery restricted blood flow to a degree comparable to a mild coronary stenosis. Aorto-coronary pressure differences of 5–20 mmHg were noted, and hyperemic flow following a 20-s complete occlusion was limited to two to three times resting flow (fig. 1). Although the cannula and perfusion circuit limited coronary reserve,

TABLE 1. Systolic Thickening

	Mean Arterial Pressure—120 mmHg					Mean Arterial Pressure—100 mmHg				
Heart Rate	50	75	100	125	150	50	75	100	125	150
Control	28 ± 2	25 ± 2	22 ± 2	21 ± 1	19 ± 2	30 ± 2	25 ± 2	23 ± 2	22 ± 2	20 ± 2
Stenosis	29 ± 3	25 ± 2	22 ± 2	18 ± 2	15 ± 3	32 ± 3	27 ± 2	23 ± 2	18 ± 3	14 ± 2
Halothane	24 ± 3	22 ± 2	22 ± 2	20 ± 2	19 ± 2	27 ± 2	24 ± 2	22 ± 2	21 ± 1	19 ± 2
Halothane and stenosis	25 ± 3	23 ± 2	21 ± 2	17 ± 2	13 ± 3	28 ± 3	24 ± 2	22 ± 1	16 ± 2	11 ± 3

no evidence of myocardial ischemia in the absence of the severe stenosis was noted. In addition, a reactive hyperemic response remained even at a mean arterial pressure of 60 mmHg and heart rate of 150 beats/min. This finding indicates that vasodilator reserve was not exhausted by the perfusion system. In contrast, the severe stenosis used in this experiment reduced resting flow by 20–30% and abolished reactive hyperemia. A stenosis with such severe hemodynamic impact is probably comparable to a atherosclerotic lesion that reduces coronary artery diameter 90–95%.[18] The stenosis was formed by making a "vacuum seal" in a 6 mm O.D. piece of Pyrex® glass tubing.

HALOTHANE

Halothane was administered from a calibrated Vernitrol® vaporizer into a semiclosed circuit. Two per cent halothane in oxygen was administered for 10 min, and then 1.0% halothane was administered for an additional 30–40 min. End-tidal gas was sampled from the trachea *via* a small tube. Halothane concentrations were measured using a gas chromatograph.[19] Known concentrations of halothane in oxygen were used to calibrate the chromatograph prior to each determination. Duplicate samples were withdrawn at the end of each run. End-tidal halothane concentrations ranged from 0.67 to 0.87%. If halothane was administered first, a 50–60 min period of ventilation with a nonrebreathing circuit was allowed for elimination of halothane prior to the nonhalothane runs.

EXPERIMENTAL PROTOCOL

Heart rate was controlled by ventricular pacing (Medtronics). Arterial pressure was controlled by infusion of phenylephrine (Sigma) and by use of a pressurized blood reservoir connected to a femoral artery. This device withdrew arterial blood from the animal if arterial pressure was above chamber pressure. Blood was infused if *vice versa*. The reservoir and phenylephrine infusion (40–200 μg/min iv) were used to stabilize mean arterial pressure at four levels: 60, 80, 100, and 120 mmHg, while measurements were made at each of five heart rates: 50, 75, 100, 125, and 150 beats/min. Following an increase in heart rate, sufficient time was allowed for all hemodynamic and dimension gauge measurements to reach a steady state. Usually a 30–60 s period was sufficient, but occasionally 2–3 min were required. Dysfunction in the circumflex region occurred primarily with rapid heart rates. If dysfunction was apparent from inspection of the oscillograph record, then the stenosis was relieved and wall motion allowed to recover prior to measurements at the next mean arterial pressure level. In this fashion, 20 points, each representing a different combination of blood pressure and heart rate, were obtained. The order in which the 20 points were obtained was the same in each set in all experiments.

Four sets of 20 points were obtained in each animal. In four of the animals, the order of conditions was: control, stenosis, halothane alone, halothane plus stenosis. In four other animals, the order was: halothane alone, halothane plus stenosis, control, stenosis. An hour was allowed between conditions 2 and 3 for uptake or elimination of halothane.

DATA ANALYSIS

Dimension gauge (Triton) and hemodynamic data were recorded on an oscillograph (Gould 260) and an F.M. tape recorder (Sanborn). Paper speeds of 125 mm/min were used except for short periods of 25 mm/s or 125 mm/s at each point. These faster speeds allowed accurate timing of the start and end of systole. The beginning of systole was taken as the time when left ventricle maximum rate of pressure development (LV dP/dt) first left the baseline prior to peak positive LV dP/dt. The end of systole was assumed to occur 25 ms prior to peak negative LV dP/dt.[12] Values for four to six beats of end-systolic thickness (EST) and end-diastolic thickness (EDT) were averaged and per cent thickening computed as [(EST − EDT)/EST] × 100. Systolic and diastolic arterial pressure was averaged over six to eight beats. Mean arterial pressure was obtained by electronic averaging. Heart rate was obtained from a cardiotachometer triggered from left ventricular pressure.

Experimental control of blood pressure and heart rate was not always exact; therefore, values of systolic thickening obtained during various conditions could not be directly compared. To eliminate this covariance, the surface formed by heart rate (X), mean arterial pressure (Y), and systolic thickening (Z) under each condition in each

(per cent) ($\bar{X} \pm 1$ SEM)

Mean Arterial Pressure—80 mmHg					Mean Arterial Pressure—60 mmHg				
50	75	100	125	150	50	75	100	125	150
29 ± 3	25 ± 2	23 ± 2	21 ± 2	19 ± 2	25 ± 2	23 ± 2	21 ± 2	19 ± 2	17 ± 1
25 ± 2	23 ± 2	19 ± 2	14 ± 2	9 ± 2	25 ± 2	21 ± 2	15 ± 2	9 ± 2	6 ± 1
28 ± 2	24 ± 2	22 ± 2	22 ± 2	20 ± 2	26 ± 2	23 ± 2	22 ± 2	20 ± 1	18 ± 1
23 ± 3	21 ± 1	18 ± 2	13 ± 2	9 ± 2	22 ± 2	20 ± 2	14 ± 2	9 ± 2	4 ± 2

dog was fit by a polynomial equation by means of a computer graphics program (Surface II®, Kansas Geological Survey, Lawrence, Kansas).[20].

After the surface was fit, 20 interpolated values at the coordinate intersections of mean arterial pressure 60, 80, . . . 120 mmHg and heart rate 50, 57, . . . 150 beats/min were calculated. The interpolated values at each of these intersections during each condition were averaged over all eight dogs to obtain the data in table 1 that are also plotted in figure 2. The interpolated values during control and halothane conditions in the presence of stenosis were divided, on a point-by-point basis in each dog, by the respective values obtained with the cannulation alone. These normalized data were expressed as a per cent and averaged for all dogs. These data form the basis of the contour maps presented in figure 3. The normalization was done to obviate differences between dogs in the absolute values for systolic thickening and to take into account the direct mechanical effects of heart rate and afterload on systolic thickening.

Normalized systolic thickening in the presence and absence of halothane was also plotted against the ratio of mean arterial pressure to heart rate (fig. 4).

Statistical Analysis

A multiple regression analysis was used to define the relationships between systolic thickening and blood pressure and heart rate.[21] The presence or absence of halothane and of stenosis were also added to the regression model as well as an interaction term for these two variables. This interaction term tested whether or not halothane potentiated the impairment of systolic contraction caused by stenosis. In addition, variables indicating time and the order of treatment (halothane or control first) were included.

The stepwise analysis was carried out using a standard statistical package (SPSS, version 9.1, May, 1982). A probability of less than 0.05 was considered significant. Similar regression analyses were carried out for end-diastolic thickness and coronary flow. In each analysis, the combination of independent variables explained 85–97% of the variability in the dependent variable.

Results

Contour maps of systolic thickening as a function of both mean arterial pressure and heart rate are shown in figure 2. The data from which the plots were constructed appear in table 1.

Systolic thickening ranged from 17% to 30% of end-diastolic thickness during control conditions. A definite decrease in thickening with increasing heart rate was observed. A similar pattern was noted with the addition of halothane, although the absolute values for systolic thickening were somewhat reduced. A dramatic decrease in

TABLE 2. Results of Multiple Regression Analysis

Dependent Variables	Independent Variables						
	Arterial Pressure	Heart Rate	Stenosis	Halothane	Interaction Stenosis × Halothane	Time	Order
Systolic thickening (%)							
P	<0.0001	<0.0001	<0.001	<0.01	NS	<0.001	NS
Regression coefficient*	(+)	(−)	(−)	(−)		(−)	
End-diastolic thickness (mm)							
P	<0.0001	<0.0001	NS	<0.001	NS	<0.001	<0.0001
Regression coefficient	(−)	(+)		(−)		(−)	(−)
Coronary flow ($ml \cdot g^{-1} \cdot min^{-1}$)							
P	<0.0001	<0.0001	<0.0001	NS	<0.01	NS	NS
Regression coefficient	(+)	(+)	(−)		(−)		

P = probability that an independent variable influences the dependent variable; NS = not significant.

* + indicates a direct relationship between dependent and independent variables; − indicates an inverse relationship between dependent and independent variables.

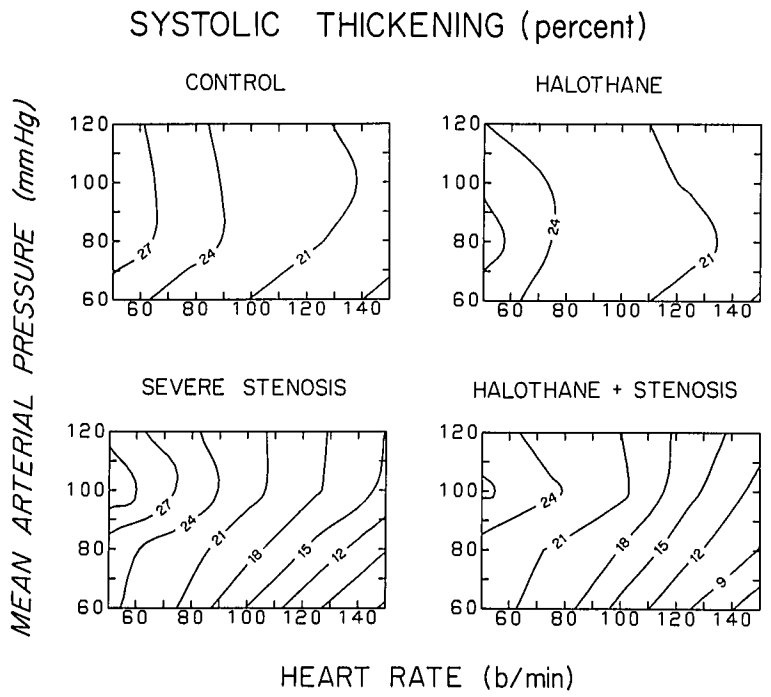

FIG. 2. Contour plots of systolic thickening as a function of heart rate and mean arterial pressure during four experimental conditions. Data were gathered in all conditions in each of eight animals. No indication of variability is shown in the figure, but the appropriate standard errors appear in table 1. Heart rate had a pronounced effect on systolic thickening. Coronary stenosis produced ischemic dysfunction during the combinations of high heart rates and low arterial pressures. Halothane produced a slight reduction in systolic contraction, but this effect did not augment (or reduce) the amount of depression seen with stenosis. A simple additive effect was observed.

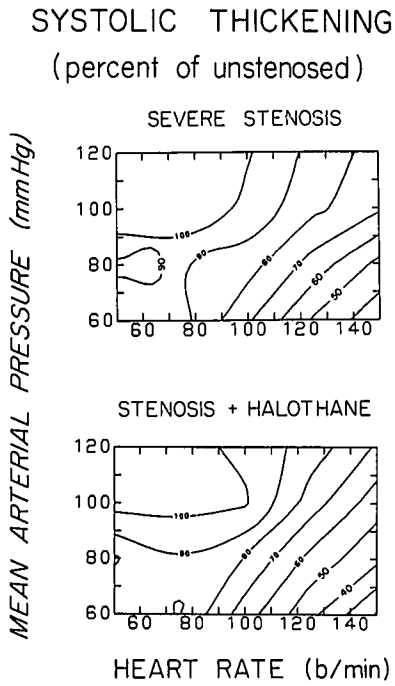

FIG. 3. Contour plots of normalized systolic thickening as a function of both heart rate and blood pressure. Raw values in the presence of stenosis were normalized (and converted to per cent) by division, on a point-by point-basis, by the values obtained in the absence of stenosis. Separate normalizations were done for data in the presence and absence of halothane. The normalizations were done to factor out the direct effects of heart rate, blood pressure, and end-diastolic thickness on systolic function so as to produce a pure measure of ischemia. The similarity of the contour plot obtained in the presence of halothane and that obtained in the absence of halothane is apparent. Indeed, regression analysis failed to find a significant halothane effect.

systolic thickening occurred with increased heart rate and low arterial pressures in the presence of the severe stenosis. The addition of halothane to the severe stenosis produced little change.

The independent effects of blood pressure, heart rate, stenosis, halothane, time, and order of treatment on systolic thickening were assessed by multiple regression. The results for systolic thickening shown in table 2 indicate highly significant effects for all primary variables with the exception of the order of treatments. In contrast, the interaction term for halothane and stenosis was not a significant predictor of systolic thickening. This finding indicates that a simple additive effect was operative and that halothane did not potentiate the impairment of systolic contraction caused by stenosis.

Significant inverse relationships were found between systolic thickening and heart rate, stenosis, halothane, and time. The decrease in systolic thickening with increasing heart rate is apparent in figure 2. The decrease in thickening with halothane is consistent with halothane's well-known negative inotropic effect.[14] The decrease in thickening with time was observed in a previous experiment[9] in which a 5–10% decrease occurred over the same period. The lack of effect of treatment order on systolic thickening suggests that long-lasting effects of halothane were not present.

A primary determinant of systolic contraction is initial length. End-diastolic thickness is an indicator of this state because the ventricular wall thins as fibers elongate. Values for end-diastolic thickness in the present experiment are given in table 3. An inverse relationship with mean

arterial pressure ($P < 0.0001$) probably reflects the effects of afterload on the extent of shortening. A direct relationship with heart rate ($P < 0.0001$) may be the result of incomplete ventricular filling as heart rate increased. The wall was also thinner at end-diastole in the presence of halothane ($P < 0.001$). The increased fiber length that is implied by this measurement would enhance systolic thickening, an effect in the wrong direction to explain the observed decrease in thickening with halothane. Finally, end-diastolic thickness was decreased by time ($P < 0.001$) and influenced by the order of treatments ($P < 0.0001$). The explanation for these effects is not clear.

Coronary flow into the cannulated zone in the absence of stenosis increased with increasing blood pressure ($P < 0.0001$) and heart rate ($P < 0.0001$), probably because of increased myocardial oxygen demand (table 4). The severe stenosis decreased flow ($P < 0.0001$), a predictable effect. Halothane, time, and order had no effect on coronary flow, but interaction between halothane and stenosis was of borderline significance ($P < 0.01$). The lack of effect of halothane on coronary flow suggests that halothane had no direct effects on coronary autoregulation in these experiments. Note that coronary flow was largely pressure-dependent in the presence of stenosis. Increasing heart rate did not decrease flow even though the diastolic period must have become shorter.

The contour maps shown in figure 3 were constructed from normalized data obtained in the following manner: data in the presence of stenosis (no halothane) were divided by those obtained with the cannula system alone (no halothane) on a point-by-point basis in each dog. The values were then averaged over all eight dogs. Data obtained with halothane present were normalized in an identical fashion. This normalization factored out the direct effects of heart rate and blood pressure on systolic thickening. Values of 100 (per cent) mean that the region's mechanical capabilities were not affected by stenosis. Values less than 100% reflect ischemic dysfunction.

The data from figure 3 were used to construct plots of (normalized) systolic thickening *versus* the *ratio* of mean arterial pressure to heart rate (fig. 4). The rationale for this plot results from the observation that systolic thickening isopleths (fig. 3) can be mathematically modeled as radial lines from the origin. The slope of each line is the ratio of mean arterial pressure to heart rate. Use of this ratio simplifies the data presentation and emphasizes that the combination of increased arterial pressure and low heart rate (high ratio) did not produce ischemia, whereas the combination of low pressure and high heart rate (low ratio) was associated with impaired contraction. This relationship may not hold outside of the range of pressure and rate investigated.

Hemoglobin concentration was stable throughout the experiment. A value of 14.4 ± 0.3 g/dl ($\bar{X}$ ± 1 SEM) was measured during control conditions and 14.0 ± 0.3 g/dl with stenosis. During halothane administration, hemoglobin concentration was 14.1 ± 0.4 g/dl in the absence and 14.2 ± 0.4 g/dl in the presence of stenosis. These values were not significantly different by analysis of variance.

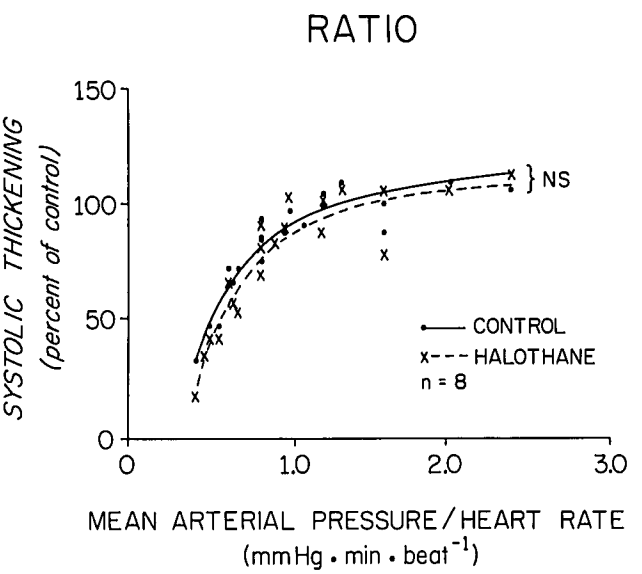

FIG. 4. Normalized systolic thickening is shown as a function of the *ratio* of mean arterial pressure to heart rate. See "Results" section for the rationale for such a plot. Normalized data from fig. 3 are plotted. Each point is the average of data from eight dogs. No indication of variability is shown. The correlation coefficients between systolic thickening and the ratio were >0.90. These data illustrate that the *combination* of high mean arterial pressure and low heart rate was associated with normal systolic contraction but that the *combination* of low arterial pressure and high heart rate produced myocardial ischemia. This relationship may not hold outside the range of absolute pressure and rate studied.

Discussion

The results of this study indicate that impaired systolic thickening associated with halothane in the presence of stenosis is mediated by changes in hemodynamics. Virtually all of the impaired systolic contraction observed in the presence of a severe coronary stenosis could be accounted for by changes in blood pressure and heart rate. Halothane caused a small decrease in contractile function in the absence of stenosis, but this negative inotropic effect was not enhanced by ischemia. These results confirm and extend the findings of several previous studies.[1,2]

Assumptions

A primary assumption of this study is that decreases in systolic contraction quantitatively reflect myocardial ischemia. Several recent studies have addressed this issue.[10–13] Each of these studies has found a significant relationship

TABLE 3. End-diastolic Thickness, Ischemic

	Mean Arterial Pressure—120 mmHg					Mean Arterial Pressure—100 mmHg				
Heart Rate	50	75	100	125	150	50	75	100	125	150
Control	11.0 ± 0.8	11.4 ± 0.7	11.7 ± 0.6	11.8 ± 0.7	11.9 ± 0.7	11.1 ± 0.7	11.6 ± 0.6	11.8 ± 0.7	12.0 ± 0.7	12.2 ± 0.7
Stenosis	11.0 ± 0.6	11.5 ± 0.6	11.7 ± 0.6	11.8 ± 0.7	11.9 ± 0.7	11.0 ± 0.7	11.6 ± 0.7	12.0 ± 0.7	12.1 ± 0.7	12.2 ± 0.7
Halothane	10.8 ± 0.6	11.2 ± 0.5	11.4 ± 0.5	11.5 ± 0.6	11.6 ± 0.6	10.8 ± 0.6	11.2 ± 0.5	11.5 ± 0.5	11.6 ± 0.5	11.8 ± 0.5
Halothane and stenosis	10.7 ± 0.6	11.1 ± 0.5	11.3 ± 0.6	11.4 ± 0.6	11.4 ± 0.7	11.0 ± 0.7	11.3 ± 0.6	11.4 ± 0.6	11.4 ± 0.6	11.4 ± 0.6

TABLE 4. Coronary Flow (ml · 100 g^{-1} ·

	Mean Arterial Pressure—120 mmHg					Mean Arterial Pressure—100 mmHg				
Heart Rate	50	75	100	125	150	50	75	100	125	150
Control	45 ± 6	46 ± 6	52 ± 6	54 ± 5	59 ± 5	36 ± 2	37 ± 2	40 ± 3	44 ± 3	48 ± 3
Stenosis	31 ± 2	31 ± 2	32 ± 2	34 ± 1	36 ± 2	29 ± 2	29 ± 2	30 ± 2	32 ± 2	32 ± 2
Halothane	42 ± 5	48 ± 5	52 ± 5	53 ± 5	58 ± 4	31 ± 4	36 ± 4	40 ± 4	45 ± 4	50 ± 4
Halothane and Stenosis	28 ± 2	29 ± 2	32 ± 2	34 ± 2	34 ± 2	25 ± 2	27 ± 2	29 ± 2	29 ± 2	30 ± 2

between regional contraction (either subendocardial shortening or transmural thickening) and coronary flow. A decrease in myocardial lactate extraction was found to parallel the decrease in function in one study.[10] Alterations in lactate metabolism are considered by many the gold-standard measure of ischemia.[22]

Although loss of contractile function is a primary result of myocardial ischemia, regional contraction is clearly influenced by alterations in preload, afterload, heart rate, and contractility. In the present experiments, the effects of afterload and rate were taken into account in the regression models and by the normalization procedure. End-diastolic thickness (a reflection of regional preload) was not influenced by stenosis and indicated increased fiber length during halothane, an effect in the wrong direction to explain the decrease in function caused by halothane in the absence of stenosis. By dividing the values obtained in the presence of stenosis by the appropriate control (halothane or no halothane), these effects of preload and contractility as well as the direct effects of blood pressure and heart rates could be factored out. Once these factors were taken into account, only a barely perceptible (and statistically insignificant) difference between thickening values obtained with stenosis in the presence and absence of halothane remained (figs. 3 and 4).

LIMITATIONS

The data and conclusions from this study conflict with data obtained in other models of coronary artery disease. Bland and Lowenstein demonstrated a beneficial effect of halothane in an acute, total coronary-ligation model.[23] Gerson and co-workers subsequently demonstrated that this effect was independent of blood pressure and heart rate.[24] These studies suggest the possibility of a beneficial effect of halothane on collateral vessel flow or dynamics. In addition, a study using greyhounds with well-developed native collateral vessels demonstrated an improvement in oxygen supply relative to oxygen demand in collateral-dependent myocardium with halothane.[25] Such mechanisms would likely not apply to the present model of acute coronary stenosis.

The results of this study might have been different in the presence of left ventricular failure. Increased oxygen demand caused by ventricular dilation combined with decreased oxygen supply caused by increased diastolic intraventricular pressure would likely augment myocardial ischemia.[26] Importantly, halothane may cause global ventricular failure if hypotension accompanying its use leads to ischemia of a large, rather than small, zone of myocardium.[2] The clinical strategy of increasing arterial pressure by altering systemic vascular resistance in the presence of halothane would appear unwise if this strategy leads to ventricular failure in the patient with coronary artery disease. In this regard, several authors have reported acute ventricular failure when aortic constriction or phenylephrine was used in an attempt to increase arterial pressure during 1–2% halothane anesthesia in animals.[14,23,27,28]

The coronary flow data require brief comment. Flow through the stenosis was reduced, compared with the levels observed in the absence of stenosis. Flow with stenosis was remarkably pressure-dependent but relatively insensitive to heart rate. This finding is surprising because increases in heart rate decrease diastolic time per min and might be expected to reduce coronary flow.

Zone (mm) ($\bar{X} \pm 1$ SEM)

Mean Arterial Pressure—80 mmHg					Mean Arterial Pressure—60 mmHg				
50	75	100	125	150	50	75	100	125	150
11.4 ± 0.7	12.0 ± 0.7	12.3 ± 0.7	12.5 ± 0.7	12.6 ± 0.7	11.6 ± 0.6	12.4 ± 0.7	12.6 ± 0.8	12.8 ± 0.9	12.8 ± 0.8
11.4 ± 0.7	12.2 ± 0.7	12.4 ± 0.7	12.6 ± 0.7	12.5 ± 0.7	12.6 ± 0.8	12.6 ± 0.7	12.6 ± 0.7	12.6 ± 0.7	12.5 ± 0.7
11.1 ± 0.6	11.6 ± 0.6	11.8 ± 0.6	12.0 ± 0.7	12.1 ± 0.6	11.6 ± 0.6	12.1 ± 0.6	12.3 ± 0.6	12.4 ± 0.7	12.4 ± 0.7
11.3 ± 0.6	11.8 ± 0.7	11.9 ± 0.7	11.9 ± 0.6	11.8 ± 0.6	12.1 ± 0.7	12.2 ± 0.6	12.2 ± 0.6	12.2 ± 0.6	12.1 ± 0.6

min^{-1})($\bar{X} \pm 1$ SEM)

Mean Arterial Pressure—80 mmHg					Mean Arterial Pressure—60 mmHg				
50	75	100	125	150	50	75	100	125	150
28 ± 2	32 ± 2	35 ± 1	36 ± 2	39 ± 2	19 ± 2	23 ± 2	27 ± 2	28 ± 2	30 ± 2
22 ± 2	24 ± 2	26 ± 2	27 ± 1	27 ± 2	18 ± 1	18 ± 1	19 ± 1	20 ± 1	20 ± 2
29 ± 4	33 ± 3	38 ± 4	40 ± 4	44 ± 4	22 ± 3	25 ± 2	27 ± 2	30 ± 2	30 ± 2
22 ± 2	23 ± 1	25 ± 1	25 ± 1	25 ± 1	16 ± 1	17 ± 1	18 ± 1	18 ± 1	19 ± 1

SUMMARY

This study demonstrates that blood pressure and heart rate are major determinants of ischemic myocardial dysfunction. Changes in these variables can explain virtually all the dysfunction seen when halothane is superimposed on an acute coronary stenosis in a nonfailing heart. These findings emphasize the clinical importance of maintaining a low heart rate and normal or high arterial pressure in patients with severe coronary stenosis. The use of halothane to achieve these goals is reasonable in light of the present findings.

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