

Hemodynamic Determinants of Ischemic Myocardial Dysfunction in the Presence of Coronary Stenosis in Dogs

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The effects of arterial blood pressure and heart rate on myocardial contraction were studied in a canine model of coronary stenosis. Systolic thickening of a region of myocardium supplied by a cannulated coronary artery was used as a measure of oxygen shortage. A glass stenosis in an external perfusion circuit that provided blood to the cannulated vessel was used to limit coronary flow. Mean arterial pressure was controlled by a blood reservoir and phenylephrine infusion and stabilized at four levels: 60, 80, 100, and 120 mmHg. At each blood pressure level, heart rate was increased by ventricular pacing in steps from 50 to 150 beats/min. Systolic thickening was measured at each of the resulting 20 combinations of blood pressure and heart rate. Measurements were made before cannulation, to serve as an unstenosed control, and following cannulation in the presence of moderate and severe stenoses. In the presence of the severe stenosis, ischemic dysfunction occurred when mean arterial pressure was decreased to 60 mmHg. At this pressure, dysfunction was most dramatic at rapid heart rates. In contrast, hypertension to a mean arterial pressure of 120 mmHg was well tolerated in these nonfailing hearts. Importantly, no single value of either blood pressure or heart rate was found to be associated with ischemia. The threshold for rate-induced ischemia depended on the coexisting value of blood pressure and *vice versa*. Ischemia was absent if mean arterial pressure exceeded heart rate, that is, if the pressure-rate *ratio* exceeded one. (Key words: Anesthesia; cardiovascular. Arteries: coronary. Blood pressure. Heart: blood flow; coronary stenosis; myocardial function; myocardial ischemia; pulse rate. Hemodynamics.)

A SIGNIFICANT PROPORTION of this country's aging population has coronary heart disease and often requires cardiac or noncardiac surgery. An important aim of the anesthetic and perioperative management of these patients is to avoid myocardial ischemia, since arrhythmias, ventricular failure, and infarction can result. The primary technique used to avoid ischemia is manipulation of arterial blood pressure and heart rate, yet many fundamental issues remain unresolved. In anesthetizing a patient with stable angina pectoris and good left ventricular function: Should hypotension be avoided? Is hypertension harmful? What is the ideal heart rate? Which hemodynamic index or value best predicts myocardial ischemia?

Current anesthetic management is far from perfect. Clinical studies have found that 40-70% of patients with coronary artery disease have episodes of myocardial isch-

emia during anesthesia.¹⁻³ In addition, a strong association between intraoperative ischemia and myocardial infarction has been demonstrated.⁴

A better understanding of the hemodynamic conditions that produce myocardial ischemia is needed. The aim of this study was to determine the effect of blood pressure and heart rate, as independent variables, on myocardial ischemia in the presence of a coronary stenosis. Myocardial ischemia was assessed by measurement of regional contraction, since this is a sensitive, quantitative indicator of oxygen shortage.⁵

Methods

SURGICAL PREPARATION

Sterile surgery was performed to implant piezoelectric crystals in the myocardium and to produce a permanent A-V heart block. Mongrel dogs weighing 24-32 kg were anesthetized with amobarbital and intubated. Anesthesia was maintained with halothane in oxygen. The left thorax was entered through the fifth intercostal space. The pericardium was opened and the heart suspended in a pericardial cradle. A suture was passed around the left circumflex artery proximal to the first marginal branch. Traction on this suture temporarily occluded the artery so that the extent and location of epicardial cyanosis could be observed. Obvious epicardial collateral arteries connecting the circumflex and anterior descending arteries were ligated.

A 1-2-mm-diameter, lensed piezoelectric crystal was inserted through a stab wound in the epicardium and tunneled tangentially to a position at the endocardial surface in the center of the region displaying cyanosis. A 2-3-mm-diameter, lensed crystal was sewn to the epicardium at the location that minimized distance between the crystals. The pair of crystals measured wall thickness. A temporary occlusion once the crystal pair was in place confirmed that the set was located in ischemic tissue. At autopsy, the inner crystal was located by blunt dissection. All inner crystals were within 3 mm of the subendocardium. The orientation of the crystal sets was checked as well to be certain that the set was perpendicular to the epicardium. Three animals with crystal sets not meeting these geometric criteria were excluded from analysis.

Following crystal placement, the suture around the cir-

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cumflex artery was removed, the pericardium was closed, and the chest was closed. The dog was turned, and an incision was made on the right side. The chest was entered through the fourth intercostal space. An 8–10-cm-long incision in the pericardium gave access to the right atrium and ventricle. An instrument was passed through a stab wound in the atrium, and the A-V node was located by palpation of landmarks. Electrocautery or formalin injection was used to create a permanent A-V heart block.⁶ A unipolar pacemaker lead was sutured to the epicardial surface of the right ventricle. The ventricle was paced at a constant rate of 76–80 beats/min by a demand pacemaker located in a subcutaneous pocket on the flank. The pericardium and chest were closed, and the animal was allowed to recover for at least 6 days.

GENERAL PREPARATION

Eighteen closed-chest dogs were studied a minimum of 6 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 alpha-chloralose (100 mg/kg, iv). Anesthesia was maintained with a continuous infusion of alpha-chloralose ($10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, iv) during the experiment.⁷ The animals were ventilated with a positive-pressure pump (Harvard) operating with a 10 cmH₂O end-expiratory back pressure (Boehringer). Oxygen enrichment of room air was adjusted by means of a variable demand valve so that arterial blood oxygen tension was kept between 100 and 200 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, $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, iv. Arterial blood was sampled periodically and pH, P_{CO₂}, and P_{O₂} determined (Instrumentation Laboratory, 813). Arterial hemoglobin concentration was determined by use of a Co-oximeter[®] (Instrumentation Laboratory, 202). Rectal temperature was held at 37° C with a heating pad and temperature controller (Yellow Springs, 73A). Blood coagulation in the extracorporeal circuits was prevented by infusion of sodium heparin (750 U/kg, iv bolus plus $250 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, iv).

Arterial blood pressure was measured with a catheter introduced into the arch of aorta via the left brachial artery. A solid-state catheter-tip transducer (Millar[®]) 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

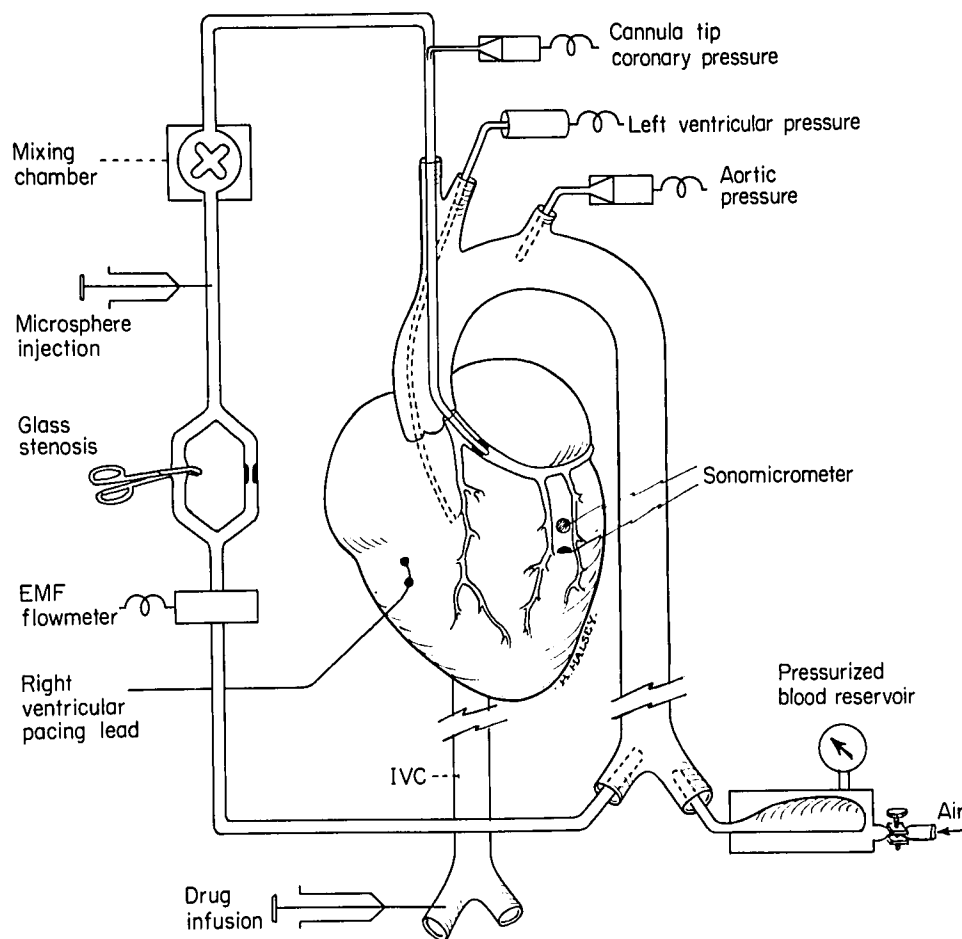
132[®]). Pulmonary artery wedge pressure was measured through a balloon-tip catheter inserted into the pulmonary artery via the left external jugular vein. A schematic diagram of the experimental preparation appears in figure 1.

CORONARY BLOOD FLOW MEASUREMENTS

A stainless steel cannula⁸ 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 the perfusion circuit shown in figure 1. 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.

Regional myocardial blood flow was measured with radioactive microspheres.⁹ Microspheres ($9 \pm 1 \mu\text{m}$) labeled with ⁴⁶Sc, ⁹⁵Nb, ¹⁰⁵Ru, ¹¹³Sn, ⁵¹Cr, or ¹⁴¹Ce were injected into the tubing that supplied blood to the left coronary artery. Approximately 2×10^5 microspheres were injected over a 30- to 45-s period. The injection site was upstream of a mixing chamber. The mixing chamber was cylindrical in shape and 1–2 mm larger in all dimensions than the 8-mm fluted magnetic stir bar that was rapidly rotated inside it. Following the experiment, 3–4 ml of India ink was infused in the cannula, staining the perfused area. This area was dissected free, weighed, and placed in a 4% solution of formaldehyde for at least 48 h. The central region containing the crystals was subdivided into four transmural sections that were, in turn, divided into inner, middle, and outer layers. Epicardial fat and vessels and endocardium were trimmed from the sections before the final division. Each resulting piece was weighed and counted in a well-type NaI Packard[®] scintillation counter. The spectrum from 0.01 to 1.0 MeV was divided into five regions corresponding to the major peaks of the isotopes used. Following correction for background counts and Compton scatter from higher energy isotopes, the counts were divided by tissue weight (corrected for dehydration by formaldehyde). The average coefficient of variation of 60 separate microsphere injections was 21%. Tissue samples containing fewer than 400 microspheres were excluded from analysis. A total of four sections in

FIG. 1. Diagram of the experimental preparation. Blood from a femoral artery was delivered to the left circumflex coronary artery of closed-chest dogs via a passive, external perfusion circuit. This circuit incorporated an electromagnetic flowmeter to measure total coronary flow and provision for microsphere injection and mixing. A bypass in the circuit contained a glass stenosis, created by narrowing a 6-mm OD Pyrex® glass tube. Coronary pressure at the tip of the stainless steel coronary cannula was measured through a small internal tube. Aortic pressure was measured in the arch of the aorta and controlled by use of a pressurized blood reservoir and phenylephrine infusion. Left ventricular pressure was measured by use of a catheter-tip transducer introduced through the left carotid artery. Implanted piezoelectric crystals measured thickness. Right ventricular pacing was used to control heart rate following permanent A-V block.



three animals were excluded because of low microsphere density. The inner-outer blood flow ratio was calculated by dividing counts per gram in the inner layer of each section by the counts per gram in the outer layer and averaging the values for all four sections.

CORONARY STENOSIS

The perfusion circuit that delivered blood to the circumflex bed contained a bypass with a glass stenosis that could be placed in the blood path. The stenosis was formed by a 10–12-mm-long constriction in a 6-mm OD Pyrex® glass tube. Two stenoses were used in each experiment: one moderate and one severe. The stenosis severity was assessed by the relationship between stenosis pressure gradient and coronary blood flow (fig. 2). The moderate stenosis did not alter resting coronary flow but blunted reactive hyperemia. The severe stenosis decreased resting flow by 20–30% and eliminated the hyperemic response to a 15-s total occlusion. The perfusion circuit itself re-

stricted blood flow to a degree comparable to a mild stenosis: pressure gradients of 10–20 mmHg between femoral and coronary artery were noted.

CORONARY SINUS BLOOD LACTATE

A Sones® catheter (USCI No. 007538) was advanced into the coronary sinus via the right jugular vein and right atrium with the aid of a fluoroscope. The location of the catheter tip, measured postmortem, ranged from 25 to 40 mm into the coronary sinus. Blood was withdrawn from the coronary sinus catheter at a rate of 12 ml/min to prevent contamination of the coronary sinus sample with blood from the right atrium.¹⁰

Plasma lactate extraction or production across the coronary circulation was determined by measurements of simultaneously drawn arterial and coronary venous samples. Samples were promptly chilled, precipitated with 8% perchloric acid, and centrifuged at 3° C. Lactate concentration was determined photometrically by an enzymatic

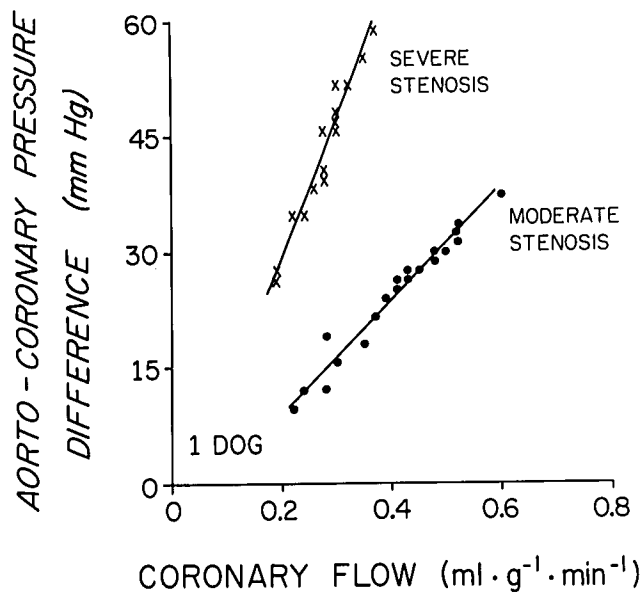


FIG. 2. The pressure drop from aorta to coronary artery versus coronary flow is shown. Filled circles show the relationship when a moderate glass stenosis was added to the external perfusion circuit. The result with a severe glass stenosis (*crosses*) indicate pressure gradients of 30–60 mmHg at low coronary flows. The data are derived from simultaneously measured mean aortic and coronary pressures and mean electromagnetic flow obtained during the experiment in one dog.

method. The myocardial lactate extraction was calculated as the ratio of arterial–coronary venous concentration difference divided by the arterial concentration and expressed as a per cent.

EXPERIMENTAL PROTOCOL

Heart rate was controlled by ventricular pacing (Medtronic®). Arterial pressure was controlled by infusion of phenylephrine (Sigma) and by use of a pressurized blood reservoir connected to a femoral artery (fig. 1). 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 $\mu\text{g}/\text{min}$ 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 before 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. The first set of points was obtained before cannulation of the coronary artery and served as a control. The second set was obtained following cannulation with the moderate coronary stenosis in the perfusion system and a third set, with the severe stenosis.

Arterial and coronary sinus blood was sampled for lactate measurement and microspheres were injected at six points. These points included the four combinations of lowest and highest blood pressure and heart rate as well as a measurement at mean arterial pressure 80 mmHg and heart rate 75 beats/min. All of these measurements were made in the presence of a severe coronary stenosis except a baseline set at mean arterial pressure 80 mmHg heart rate 75 beats/min that was made with the coronary cannula and perfusion system alone.

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 LV dP/dt first left the baseline before peak-positive LV dP/dt . The end of systole was assumed to occur 25 ms before peak-negative LV dP/dt . Values for 4–6 beats of end-systolic thickening (EST) and end-diastolic thickness (EDT) were averaged and per cent thickening computed as $[(\text{EST}-\text{EDT})/\text{EST}] \times 100$. Systolic and diastolic arterial pressure was averaged over 6–8 beats. Mean arterial and mean pulmonary wedge pressures were obtained by electronic averaging. Heart rate was obtained from a cardiachometer triggered from left ventricular pressure.

Experimental control of blood pressure and heart rate was not always exact, and so 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 dog was fit by a polynomial equation by means of a computer graphics program (Surface II®, Kansas Geological Survey, Lawrence, Kansas).¹¹ The goodness of fit of each surface to the original data was assessed by comparing observed values of systolic thickening with those predicted by the equation. A correlation coefficient (r) of 0.95 to 0.99 was obtained in all cases.

After the surface was fit, 20 interpolated values at the coordinate intersections of mean arterial pressure 60, 80, . . . 120 mmHg and heart rate 50, 75, . . . 150 beats/min were calculated. The interpolated values at each of these intersections were averaged over all dogs to obtain figure 3. The interpolated values in the presence of stenosis were divided, on a point-by-point basis in each dog, by those obtained before cannulation, and expressed as a per cent. These normalized data were averaged for all dogs and form the basis of the contour maps presented in figure 4. The normalization was done to obviate differences between dogs in the absolute values for systolic thickening and take into account the direct mechanical effects of heart rate and afterload on systolic thickening.

An identical method of analysis was used to obtain the contour maps for the five time control animals shown in figure 5.

TIME CONTROL SERIES

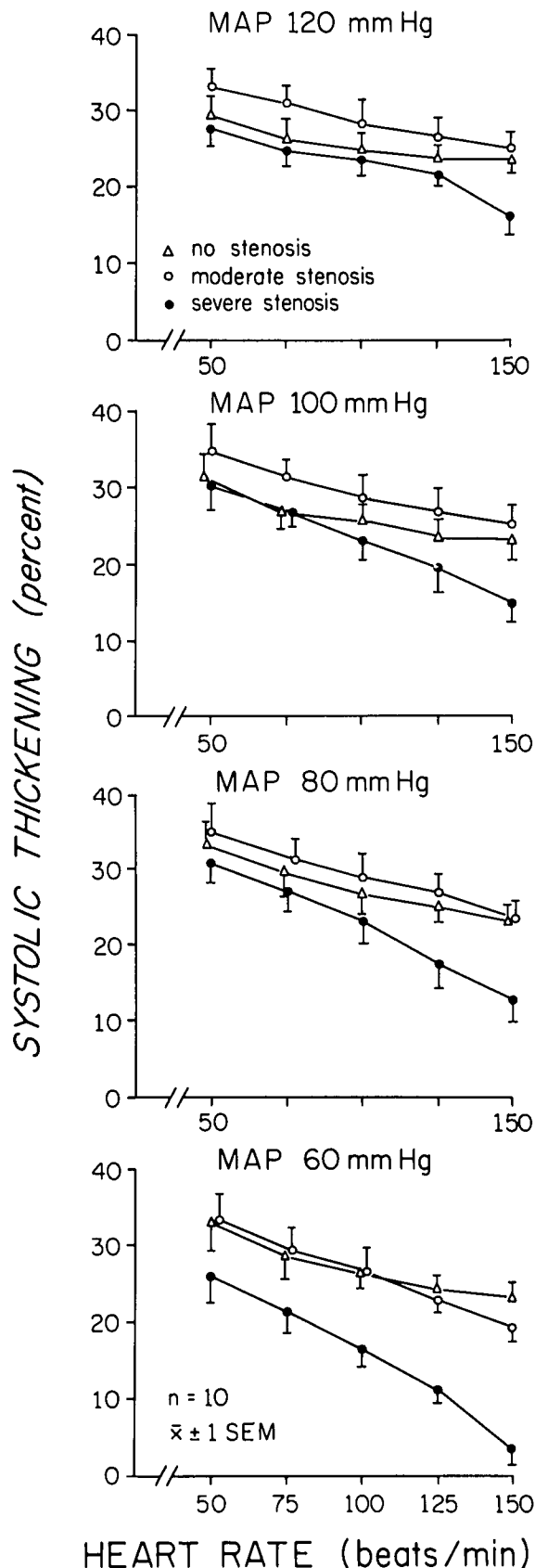
Five additional animals served as time controls. Surgery and the experimental preparation were identical to the stenosis animals except that the coronary artery was not cannulated. Data were obtained in exactly the same fashion as in the animals with stenosis except that no microsphere or electromagnetic coronary flows were measured. Myocardial lactate extraction was measured during the second time control, that is, during collection of the third set of data.

STATISTICAL ANALYSIS

Data were subjected to a two-stage statistical analysis. First, a global test of the independent effect of stenosis, time, heart rate, and blood pressure was done using multiple regression analysis of raw data (SPSS, Version 9) (table 1). A probability of less than 0.05 was considered significant. Second, means and standard errors were calculated for normalized systolic thickening values at each of the 20 heart rate–blood pressure combinations. These measures of variability allow calculation of the confidence interval at each point and testing of the hypothesis that a given value differs from 100%, the expected value under



FIG. 3. Systolic myocardial thickening as a function of heart rate at four mean arterial pressures. The values are from 10 dogs (mean \pm 1 SEM). The results before cannulation (*triangle*) suggest that heart rate had a direct effect on thickening. In the presence of a moderate stenosis (*open circles*), thickening was slightly impaired by tachycardia at a mean pressure of 60 mmHg. Thickening was enhanced with moderate stenosis at high arterial pressures. In the presence of a severe stenosis (*filled circles*), thickening was reduced at a mean pressure of 60 mmHg, indicating myocardial ischemia. This decrement was most dramatic at high heart rates. Hypertension at low heart rates was well tolerated.



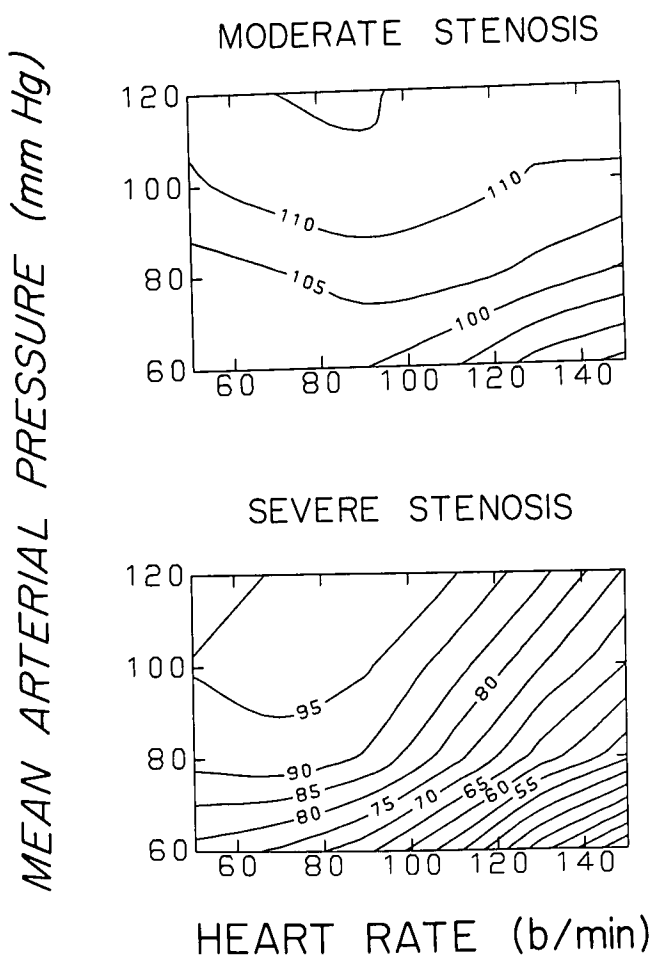


FIG. 4. Contour maps relating systolic myocardial thickening to mean arterial pressure and heart rate. The contour lines are isopleths of thickening expressed as a per cent of the value obtained in the absence of stenosis. Contour maps for moderate and severe stenoses are shown. The values are the average of those obtained in 10 dogs. The values from which these contour plots were constructed are shown in tables 4 and 5. The changes caused by the severe stenosis are more dramatic than those caused by the moderate stenosis. Ischemic dysfunction was most prominent with the combination of hypotension and tachycardia. Hypertension at a slow heart rate was not associated with dysfunction. The heart rate at which ischemia occurred depended importantly on the coexisting mean arterial pressure, and *vice versa*. Ischemia was absent if mean arterial pressure exceeded heart rate.

the null hypothesis. Myocardial lactate extraction data in the presence of a severe stenosis (table 2) were compared with data obtained during the time control experiments (table 3) by use of unpaired *t* tests.

Results

Cannulation and coronary perfusion via the external circuit altered systolic thickening, although heart rate (60 ± 5 beats/min) (mean ± 1 SD) and mean arterial pressure

(96 ± 13 mmHg) were not affected. Systolic thickening increased from 32 to 35% ($P < 0.05$ by paired *t* test) with cannulation. End-diastolic thickness increased from 11.6 ± 2.0 to 12.2 ± 2.2 mm and end-systolic thickness increased from 15.2 ± 2.8 to 16.5 ± 3.0 mm with cannulation.

Multiple regression models for the six conditions of the study showed a highly significant effect of heart rate on systolic thickening ($P < 0.0001$; table 1). This effect is apparent in plots of heart rate *versus* raw systolic thickening (fig. 3). Thickening decreased as heart rate increased at each mean arterial pressure, regardless of the degree of stenosis. Values for thickening were significantly altered by the presence of a moderate ($P < 0.0001$) or severe stenosis ($P < 0.0001$) and were altered by the pas-

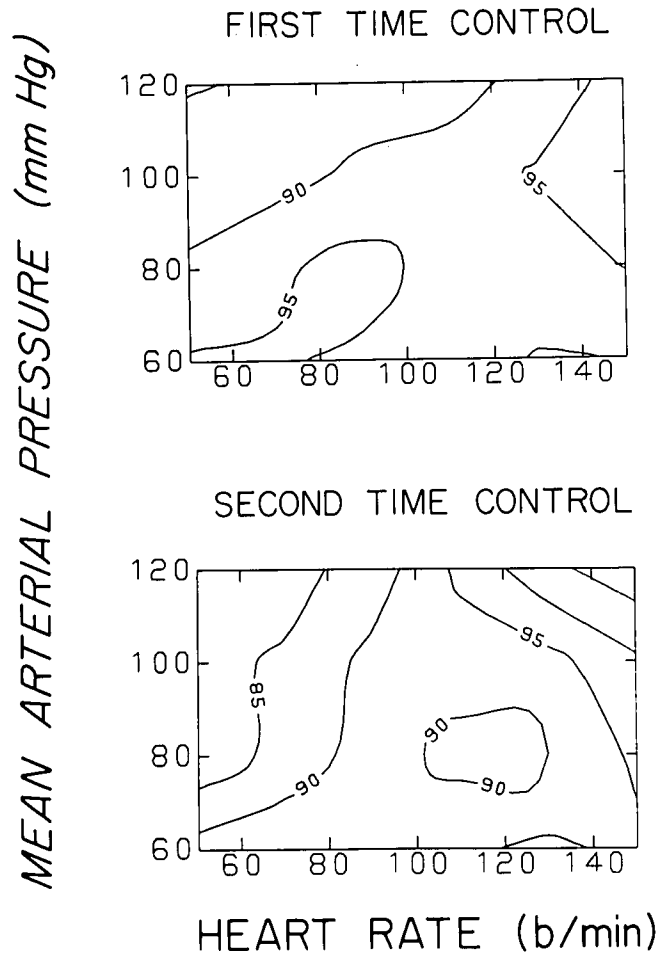


FIG. 5. Normalized systolic thickening for animals without cannulation or stenosis (time control series) (per cent of control). Data obtained during a first and second time control were divided by those obtained during the initial control and expressed as a per cent. Contour lines represent isopleths of systolic thickening. A mild but significant decrement in function with time was observed. The values from which these contour plots were constructed are shown in tables 6 and 7.

TABLE 1. Probabilities, Derived from Multiple Regression Models, that Certain Variables are Significant, Independent Predictors of Systolic Thickening during Six Conditions

Condition	Variable		
	Mean arterial pressure	Heart rate	Stenosis
No stenosis	NS	<0.0001	—
Moderate stenosis	NS	<0.0001	<0.0001*
Severe stenosis	<0.0001	<0.0001	<0.0001*
	Mean arterial pressure	Heart rate	Time
Initial control	NS	<0.0001	—
First time control	NS	<0.0001	<0.0001†
Second time control	NS	<0.0001	<0.0001†

* Relative to "No stenosis."
† Relative to "Initial control."

sage of time in the time control series ($P < 0.0001$). Mean arterial pressure was a significant, independent predictor of thickening only in the presence of a severe stenosis ($P < 0.0001$).

The results of the regression models indicate that blood pressure and heart rate influenced systolic thickening in addition to the presence of stenosis. In order to account for the direct effects of heart rate and mean arterial pressure, thickening values in the presence of stenosis were divided by values obtained at exactly the same heart rate and blood pressure but before cannulation (see "Methods"). Normalized values in each dog were converted to per cent and averaged for all 10 dogs in the stenosis experiment and all five dogs in the time control group. The average values and standard errors are shown in tables 4-7. Contour maps of these normalized data are shown in figures 4 and 5. No indication of variability is given for the contour maps because three-dimensional confi-

TABLE 3. Systolic Wall Thickening and Myocardial Lactate Extraction during the Second Time Control Measurements in Dogs without Cannulation or Stenosis

Mean Arterial Pressure (mmHg)	Heart Rate (beats/min)	Thickening (Percent of control)	Lactate Extraction (%)
80 ± 3	75 ± 1	91 ± 8	60 ± 2*
63 ± 1	53 ± 1	89 ± 4	58 ± 5*
59 ± 3	150 ± 1	96 ± 9	56 ± 1*
122 ± 2	50 ± 1	83 ± 3	52 ± 5*
121 ± 2	149 ± 1	113 ± 18	54 ± 4*

$\bar{X} \pm 1$ SEM, $n = 4$ (lactate extraction was not measured in one dog).
* Different from values obtained during severe stenosis ($P < 0.001$) by unpaired t test.

dence limits are difficult to represent. The standard error of the normalized values at each heart rate-blood pressure combination can be used to construct confidence intervals and to test whether or not a value differs from 100%, the expected value under the null hypothesis.

Inspection of figure 3 demonstrates that ischemic myocardial dysfunction occurred primarily in the presence of a severe stenosis. Values for systolic thickening reached 10-15% of control with the combination of high heart rates and low arterial pressures. On the other hand, hypertension and bradycardia were associated with normal thickening in the presence of the severe stenosis and with increased thickening in the presence of the moderate stenosis. This effect was most likely caused by cooling of blood in the external perfusion circuit (see "Discussion").

Figure 4 demonstrates that at any given heart rate in the presence of the severe stenosis, regional function was better with high arterial pressures than with low. An increase in heart rate caused dysfunction at any arterial pressure, but the heart rate at which dysfunction occurred depended importantly on coexisting arterial pressure.

TABLE 2. Flow Distribution, Myocardial Metabolism, and Ischemic Wall Thickening at the Time of Microsphere Injection in Dogs with Severe Stenosis ($\bar{X} \pm 1$ SEM, $n = 10$)

Mean Arterial Pressure (mmHg)	Heart Rate (beats/min)	Total Coronary Flow ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	Mean Coronary Pressure (mmHg)	Thickening (Percent of control)	Inner-Outer Flow Ratio	Lactate Extraction (%)	Mean Pulmonary Wedge Pressure (mmHg)
Cannula Only 79 ± 1	75 ± 1	0.46 ± 0.02	63 ± 1	107 ± 7	1.13 ± 0.05	42 ± 6	8 ± 1
Severe Stenosis							
81 ± 1	76 ± 1	0.28 ± 0.02	44 ± 1	98 ± 7	1.10 ± 0.04	42 ± 6*	8 ± 1
59 ± 1	54 ± 2	0.19 ± 0.02	36 ± 2	80 ± 4	1.14 ± 0.06	37 ± 5*	7 ± 1
58 ± 1	147 ± 2	0.20 ± 0.02	34 ± 2	23 ± 11	1.00 ± 0.06	23 ± 8*	8 ± 1
119 ± 2	54 ± 2	0.30 ± 0.02	76 ± 3	88 ± 6	1.50 ± 0.10†	29 ± 5*	10 ± 1
118 ± 1	149 ± 1	0.38 ± 0.02	63 ± 3	80 ± 11	0.95 ± 0.05	30 ± 4*	10 ± 1

* Different from time control data ($P < 0.001$ by unpaired t test).

† $n = 8$.

TABLE 4. Normalized Systolic Thickening for Moderate Stenosis ($\bar{X} \pm 1$ SEM) Expressed as a Per Cent of Unstenosed (n = 10)

Mean Arterial Pressure (mmHg)	Heart Rate (beats/min)				
	50	75	100	125	150
120	112 ± 4	117 ± 3	114 ± 5	112 ± 7	114 ± 6
100	109 ± 4	114 ± 4	114 ± 3	110 ± 5	109 ± 5
80	102 ± 5	106 ± 7	108 ± 8	106 ± 6	100 ± 6
60	102 ± 5	101 ± 5	99 ± 5	91 ± 6	84 ± 8

Hemodynamic, metabolic, and flow distribution data at the times of microsphere injections are shown in table 2. With cannulation alone, an average 16-mmHg pressure drop occurred across the perfusion system. Normal values for systolic thickening, inner-outer flow ratio, and lactate metabolism data suggest that cannulation alone did not produce ischemia. The imposition of the severe stenosis increased the pressure gradient from aorta to coronary artery to 37 mmHg and reduced coronary flow by approximately 28%. Measures of ischemia were similar following imposition of the stenosis. The combination of low arterial pressure and high heart rate produced dysfunction in the area supplied by the stenosed artery, and a reduction in lactate extraction was observed. Lactate production under these hemodynamic conditions was observed in several animals in which the tip of the coronary sinus catheter was located in a small vein draining the ischemic region rather than in the coronary sinus. Global ventricular preload as reflected in pulmonary wedge pressure was similar during all experimental conditions (table 2).

Arterial hemoglobin concentration was 14.4 ± 0.5 g/dl during control, 14.5 ± 0.5 g/dl during moderate stenosis, and 14.4 ± 0.4 g/dl during severe stenosis. Arterial oxygen tension was between 100 and 200 mmHg throughout all experiments.

Time Control Animals

Five animals served as time controls. Data were collected in a fashion identical to that used for the animals with stenosis except that the coronary artery was not can-

TABLE 5. Normalized Systolic Thickening for Severe Stenosis ($\bar{X} \pm 1$ SEM), Expressed as a Per Cent of Unstenosed (n = 10)

Mean Arterial Pressure (mmHg)	Heart Rate (beats/min)				
	50	75	100	125	150
120	93 ± 4	98 ± 5	98 ± 6	93 ± 8	74 ± 12
100	95 ± 4	99 ± 5	92 ± 6	82 ± 8	65 ± 10
80	92 ± 5	95 ± 8	84 ± 8	69 ± 7	51 ± 8
60	78 ± 5	72 ± 7	60 ± 8	42 ± 8	15 ± 10

TABLE 6. Normalized Systolic Thickening for First Time Control ($\bar{X} \pm 1$ SEM) Expressed as a Per Cent of the Initial Control (n = 5)

Mean Arterial Pressure (mmHg)	Heart Rate (beats/min)				
	50	75	100	125	150
120	90 ± 7	88 ± 4	86 ± 6	89 ± 6	97 ± 6
100	87 ± 4	89 ± 5	93 ± 5	93 ± 3	98 ± 3
80	91 ± 3	97 ± 6	97 ± 7	90 ± 6	95 ± 3
60	96 ± 5	95 ± 5	94 ± 4	90 ± 2	90 ± 4

nulated. Normalized data, the result of dividing the first and second time control by initial values, are presented as contour maps in figure 5. Thickening values ranged from 83 to 113% of the initial control, and time, *per se*, was a significant independent predictor of thickening in the regression models.

A major reason for the time control series was to assess indirect effects of the experimental maneuvers on myocardial lactate extraction. Data presented in table 3 suggest that heart rate and phenylephrine had little effect on myocardial lactate extraction. However, the values observed in the time control series were significantly higher than the lactate extractions observed in the stenosis experiments.

Discussion

ASSUMPTIONS

A major assumption of this study is that mechanical dysfunction was caused by, and quantitatively reflects, myocardial ischemia. Studies by Waters *et al.*,⁵ Gallagher *et al.*,¹² and Vatner¹³ support this assumption. Two other measures of ischemia were made at five separate times when the severe stenosis was in place. Myocardial lactate extraction, regarded by many as the gold standard measure of ischemia, decreased in parallel with function. However, lactate production rarely was observed, possibly because dysfunction is a more sensitive indicator of ischemia and occurs prior to overt anerobiasis. More likely, lactate produced by the ischemic region was diluted by

TABLE 7. Normalized Systolic Thickening for Second Time Control ($\bar{X} \pm 1$ SEM) Expressed as a Per Cent of the Initial Control (n = 5)

Mean Arterial Pressure (mmHg)	Heart Rate (beats/min)				
	50	75	100	125	150
120	85 ± 4	81 ± 4	93 ± 7	99 ± 8	108 ± 13
100	84 ± 8	87 ± 4	96 ± 7	89 ± 4	99 ± 6
80	81 ± 4	92 ± 6	92 ± 9	85 ± 8	96 ± 6
60	92 ± 5	94 ± 5	92 ± 6	97 ± 5	94 ± 7

blood from nonischemic myocardium in the coronary sinus. Since the myocardial venous samples were drawn from the coronary sinus, this dilution probably led to an underestimation of the actual rate of glycolysis in the ischemic tissue. Myocardial lactate extraction values obtained during the second time control were significantly higher than those obtained during severe stenosis. The reason for these differences during conditions that produced no ischemic dysfunction is not apparent.

Inner-outer myocardial blood flow ratios decreased in parallel with systolic wall thickening. The proper comparison for these ratios would be the value observed in the absence of stenosis. No such measurements were made in this study except at a mean arterial pressure of 80 mmHg, heart rate of 75 beats/min because of the limited number of isotopes per experiment.

Insertion of the coronary cannula was associated with a small (10–12%) but statistically significant increase in systolic thickening in the perfused zone. This increase probably was caused by cooling of blood in the external circuit, since a previous study has demonstrated a 10% increase in systolic shortening for every degree (C) decrease in myocardial temperature.¹⁴ This effect may account for the seeming paradox that moderate stenosis increased systolic thickening at low heart rates and high pressures. This temperature effect is in the wrong direction to explain the dysfunction that resulted from the combination of low arterial pressure and high heart rate.

Because the severe stenosis was always applied after the moderate stenosis rather than in random order, it is possible that the ischemic dysfunction observed during the severe stenosis was influenced or augmented by mild ischemia occurring during the previous period.

INTERPRETATION

Should hypotension be avoided during anesthesia in a patient with coronary artery disease? On one hand, reduced coronary perfusion pressure might lead to reduced coronary flow and ischemia. On the other hand, reduced arterial pressure decreases the heart's need for oxygen, an effect that might outweigh the decrease in oxygen supply.¹⁵ A major finding of the present study is that decreases in arterial pressure caused or worsened ischemic dysfunction in the presence of a severe stenosis (figs. 3 and 4). This finding suggests that oxygen supply was, in fact, reduced more than oxygen demand by the decrease in arterial pressure. These findings are consistent with previous studies involving hypotension in animal models of coronary stenosis.^{16–18}

Uncertainty exists about the net effect of hypertension on myocardial oxygen balance. An increase in arterial pressure increases myocardial oxygen demand, since peak

ventricular wall tension during systole is a major determinant of oxygen use. On the other hand, increases in arterial pressure provide greater coronary flow and oxygen delivery. The results of the present study suggest that a mean arterial pressure of 120 mmHg was well tolerated at low heart rates, and increases in mean arterial pressure were associated with improved regional contraction at any heart rate between 50 and 150 beats/min. This finding is consistent with previous studies in both animals and humans.^{19–22}

Care must be used in extrapolating these results to the clinical setting. It must be emphasized that the beneficial effect of increased arterial pressure occurred in a non-failing heart. If increases in afterload had led to ventricular failure, then it is possible that ischemia may have worsened rather than improved. Ventricular dilation accompanying failure increases the oxygen cost of pressure generation and reduces oxygen delivery into an ischemic zone.²³ Reversal of these effects by afterload reduction with a resultant improvement in ischemia is well documented.²⁴ In addition, the beneficial effect of hypertension may not hold for very high levels of arterial pressure, even in the absence of ventricular failure.²⁵

The ability of tachycardia to cause or worsen myocardial ischemia in the presence of a coronary stenosis has been reported previously.^{26,27} Conversely, drugs that cause bradycardia lessened ischemic dysfunction in a canine model of coronary stenosis.²⁸ Ischemia occurs because an increase in heart rate increases oxygen demand and simultaneously decreases oxygen supply by decreasing the duration of diastole.²⁹ In the present study, an increase in heart rate caused or worsened ischemic dysfunction at any arterial pressure, but the absolute heart rate at which ischemia occurred depended importantly on the existing level of arterial pressure: higher heart rates were tolerated without ischemia at higher mean arterial pressures.

The combined effects of mean arterial pressure and heart rate on ischemic dysfunction suggest that the combination of hypotension and tachycardia was associated with the most severe ischemia and that the combination of hypertension and bradycardia was well tolerated. These observations suggest that the ratio of mean arterial pressure to heart rate might predict ischemic dysfunction. The bottom panel of figure 6 is a plot of this ratio versus systolic thickening for dogs with severe stenosis. The data are taken from figure 4, and each point is the average value for 10 dogs. Ischemic dysfunction did not occur if the ratio was above 1.0 mmHg · min/beat. Thus, ischemia was not observed if mean arterial pressure exceeded heart rate.

The present results correspond closely to observations made in the clinical setting. Lieberman *et al.* studied 30 patients with coronary artery disease to determine the

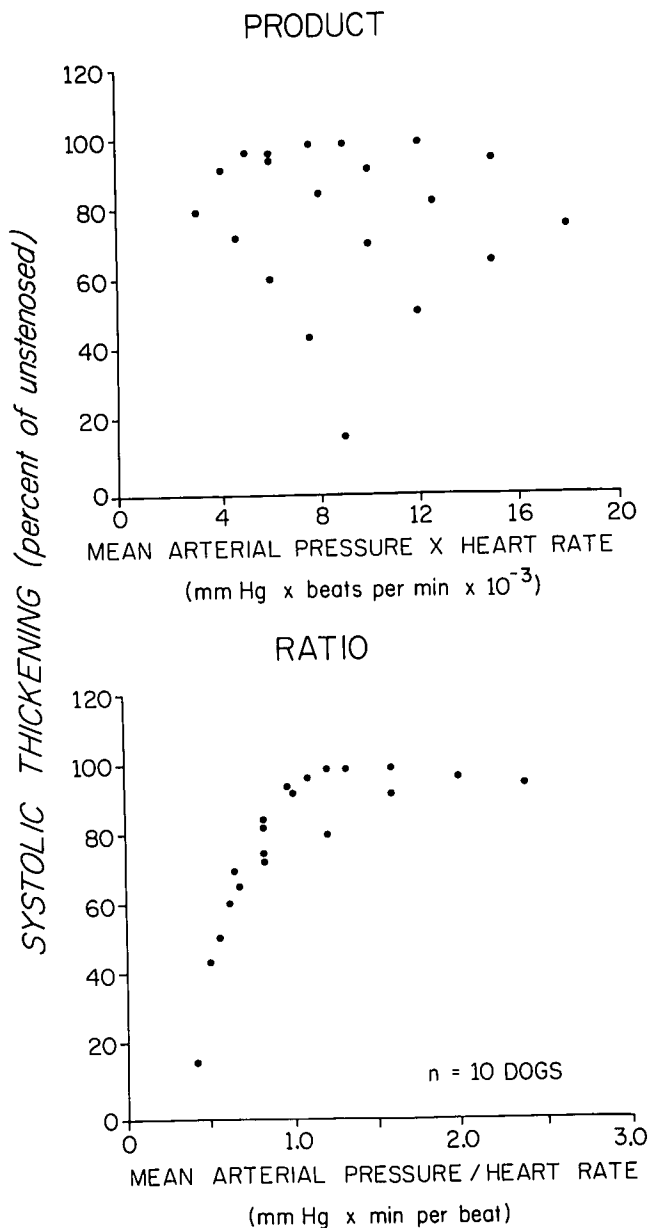


FIG. 6. Plots of systolic thickening versus the product (top panel) and ratio (bottom panel) of mean arterial pressure and heart rate. The data were obtained in the presence of a severe stenosis. Each point is the average of values obtained in 10 dogs. No indication of variability is shown. The failure of the (mean) pressure-rate product to predict ischemic dysfunction is evident. In contrast, the pressure-rate ratio is an improved predictor of regional ischemia in nonfailing hearts. These data suggest that ischemic dysfunction with a severe stenosis was unlikely if mean arterial pressure exceeded heart rate.

best hemodynamic predictors of intraoperative ischemia.³⁰ They found that hypotension to a mean arterial pressure less than 65 mmHg and tachycardia to a heart rate greater than 80 beats/min were each associated with myocardial ischemia. In contrast, hypertension with systolic arterial

pressure as high as 200 mmHg was not associated with ischemia.

A primary clinical approach to prevention of myocardial ischemia during anesthesia and surgery has been through use of the product of systolic blood pressure and heart rate.³¹ A threshold value of the pressure-rate product correlates with the onset of angina in exercising subjects with coronary artery disease.³² The rationale for this predictive ability is that the pressure-rate product is correlated with myocardial oxygen demand.³³ Since oxygen demand increases during exercise, and coronary flow is limited by the stenosis, myocardial ischemia results. This sort of logic has led to the adoption, by many anesthesiologists, of the pressure-rate product as a means of avoiding ischemia during anesthesia and surgery. It was reasoned that if the pressure-rate product were kept below a critical value, then oxygen demand would be low and ischemia should not result. Unfortunately, the strategy does not work: myocardial ischemia during anesthesia is poorly correlated with the pressure-rate product.³⁰ This failure apparently results from the fact that both pressure and rate increase in a reproducible fashion during exercise but may change in opposite directions (*e.g.*, low pressure, high rate) during anesthesia and surgery.^{31,34} This failure is illustrated in the top panel of figure 6. No correlation between systolic thickening and the *product* of mean arterial pressure and heart rate is evident.

LIMITATIONS

The findings of the present study clearly cannot account for all episodes of myocardial ischemia that occur in anesthetized patients with coronary artery disease. The glass stenosis used in these experiments provided a fixed resistance to coronary flow similar to that found in a rigid section of coronary artery affected by atherosclerosis. This sort of fixed lesion produces a stable clinical picture of angina with exertion. In contrast, many patients manifest symptoms such as angina at rest that are probably caused by dynamic changes in the severity of compliant coronary stenoses.³⁵ A compliant stenosis offers a variable, rather than fixed, resistance to blood flow. This type of stenosis is thought to have an eccentric atheroma that bulges into the lumen of the vessel across from an arc of relatively normal vascular wall. A recent postmortem study has shown a surprisingly high incidence of such eccentric lesions: 45% of moderate and severe stenoses were found to have an arc of at least 90 degrees of normal arterial wall.³⁶ This normal wall segment is capable of passive and active contraction and relaxation with the result that the stenosis severity can be altered substantially by intraluminal pressure as well as vasoactive drugs.³⁷ Stenosis severity has been shown to increase with decreased coronary pressure³⁸ and increased heart rate³⁹ in canine models of

compliant coronary stenosis. If such factors were operating in a patient with a compliant stenosis, then the results of the present study would likely underestimate the severity of ischemia during the conditions of hypotension and tachycardia.

Myocardial ischemia in patients with coronary artery disease frequently occurs during stressful events in clinical anesthesia such as laryngoscopy¹ or surgical stimulation.² Ischemia during these conditions in patients with compliant stenoses may be caused in part by active vasoconstriction at the site of the stenosis. Increases in stenosis resistance with isometric handgrip, a sympathetic stimulus, and attenuation of these resistance changes by nitroglycerin have been demonstrated.⁴⁰

It is clear that the present results do not apply to myocardial ischemia that results from active coronary vasospasm such as that responsible for Prinzmetal's angina.⁴¹ Ischemia in this circumstance is caused by an abrupt, transient decrease in coronary flow and may be treated by intravenous nitroglycerin infusion.⁴²

In addition, the present results may not apply to ischemia resulting from partial or total thrombotic occlusion of a coronary artery. Many dynamic factors influence coronary flow during these conditions.³⁵ Spasm of the vessel may make occlusion severity worse, and clot retraction or lysis may improve coronary flow and lessen ischemia independently of changes in arterial pressure and heart rate.

Nitroglycerin is an effective dilator of large coronary arteries,⁴³ it antagonizes stenosis vasoconstriction,⁴⁰ and is effective in coronary spasm.⁴¹ Because a significant proportion of patients have compliant coronary stenosis, it seems reasonable to use this drug during anesthesia to treat myocardial ischemia if increasing arterial pressure, decreasing heart rate, and adjusting ventricular filling pressure do not produce the desired result.

The pressure-rate-contraction surface uses mean arterial pressure and heart rate rather than systolic or diastolic arterial pressure. Mean arterial pressure was chosen for the analysis because it is a single value that estimates both coronary perfusion pressure and myocardial oxygen demand. Mean pressure was correlated ($r = 0.97$) with arterial pressure during diastole, the driving pressure for coronary flow in the present study. In addition, the correlation between the mean pressure-rate product and myocardial oxygen consumption ($r = 0.87$) differs only slightly from the correlation using peak systolic pressure ($r = 0.92$).⁴⁴ A pertinent clinical reason for using mean arterial pressure arises from measurement errors. Both invasive and noninvasive systems for measurement of arterial pressure provide more precise values for mean pressure than for systolic and diastolic pressure.⁴⁵

Numeric values from these experiments should be extrapolated to clinical practice with caution. These data

are from carefully controlled animal experiments, and the impact of other factors such as hematocrit, arterial oxygenation, collateral blood supply, left ventricular volume, and anesthetic and vasoactive agents have not yet been defined in this model.

In summary, the interdependent effects of heart rate and mean arterial pressure on the contractile function of myocardium served by a stenosed coronary artery have been studied in dogs. The results confirm the clinical impression that the combination of hypotension and tachycardia is best avoided in patients with coronary atherosclerosis. Hypertension in the absence of tachycardia or ventricular failure was not found harmful, but the combination of hypertension and tachycardia produced dysfunction. The results illustrate in a dramatic fashion why the pressure-rate product fails to predict myocardial ischemia and suggest that the mean arterial pressure-heart rate *ratio* may be a better predictor. The pressure-rate-contraction surface demonstrates that blood pressure and heart rate must be considered as coexisting determinants of myocardial ischemia when coronary flow is restricted.

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