

## *Regional Ischemic Ventricular Dysfunction in Myocardium Supplied by a Narrowed Coronary Artery with Increasing Halothane Concentration in the Dog*

Edward Lowenstein, M.D.,\* Pierre Foëx, M.D., D. Phil.,† C. Mark Francis, B.A.,‡ W. Lynn Davies, Ph.D.,§ Salim Yusuf, M.B., D. Phil.,¶ W. Alan Ryder\*\*

The effects of increasing inspired halothane concentration (0.5, 1.0, 1.5, 2.0 per cent) upon left ventricular myocardium supplied by a critically narrowed coronary artery and a normal coronary artery were studied in 11 open-chested dogs. Regional ventricular function was measured by continuous recording of ventricular segment length using pairs of implanted miniature ultrasonic length detectors in the left anterior descending coronary artery (LAD) and left circumflex coronary artery (LC) territories before and during critical stenosis of the LAD by a micrometer-controlled snare. Critical narrowing was documented by ischemic regional ventricular function (*i.e.*, post-systolic shortening; systolic lengthening) limited to the LAD territory when  $\text{FI}_{\text{O}_2} = 0$  for 90 seconds. Hemodynamic variables (aortic, left atrial and left ventricular pressure, and heart rate) were measured, ECG lead II was recorded, and the first derivative of left ventricular pressure (LV dP/dt) and coronary perfusion pressure derived for each halothane concentration before and during LAD narrowing. Increasing halothane was associated with equivalent progressive depression of global ventricular function before and during LAD constriction. Prior to LAD constriction, no ischemic changes in regional function occurred. Regional ventricular function was normal during 0.5 percent halothane in the presence of LAD constriction. With increasing halothane during LAD constriction, ischemic regional ventricular function was observed in the LAD territory in eight of eleven hearts, whereas regional ventricular function remained normal in the LC territory. The epicardial ECG was recorded in three dogs and was insensitive as an indicator of ischemia, becoming abnormal only after severe ischemic changes were established. In these studies, in which heart rate remained constant, ar-

terial blood pressure and LV dP/dt decreased, and left ventricular end-diastolic pressure increased, decrease in blood flow and oxygen delivery due to a lower perfusion pressure distal to the coronary artery narrowing appears to be primarily responsible for the observations. The authors hypothesize that clinically unapparent episodes of regional myocardial ischemia distal to narrowed coronary arteries may be an important cause of perioperative myocardial infarction. (Key words: Anesthesia. Complications: myocardial infarction. Heart: coronary artery disease; electrocardiography; regional myocardial ischemia; regional ventricular function.)

THE RESPONSE OF THE HEART with an occluded coronary artery,<sup>1,2</sup> analogous to an acute myocardial infarction, to anesthetic drugs has been previously investigated, whereas the response of the heart muscle supplied by a narrowed coronary artery has not. The present studies were therefore initiated to begin to define the response to anesthetic drugs of myocardium supplied by a narrowed coronary artery, as present in patients with ischemic heart disease not suffering an acute myocardial infarction. We administered increasing concentrations of halothane to define the effect upon an area of left ventricle whose nutrient artery had been constricted, and to determine whether halothane has an effect other than dose-dependent myocardial depression in the presence of coronary artery narrowing. In order to document any differences in response of such an area to that in a normally vascularized area, regional ventricular function was assessed by continuous recording of ventricular segment length. In addition, regional electrical activity was recorded in some animals. Studies were performed both prior to and following mechanical narrowing of a coronary artery. Measurements were obtained simultaneously in an area of the heart supplied by an artery which had not been constricted and in an area supplied by the narrowed coronary artery.

### Materials and Methods

Studies were performed in eleven mongrel dogs weighing between 14 and 30 kg. The dogs were premedicated with intramuscular morphine sulfate (0.3 mg/kg). Anesthesia was induced with thiopental (15 mg/kg) and the trachea intubated. Constant-volume intermittent posi-

\* Anesthetist, Massachusetts General Hospital; Professor of Anesthesia, Harvard Medical School.

† Clinical Reader and Honorary Consultant (Clinical Physiology), Nuffield Department of Anaesthetics.

‡ MCR Student, Nuffield Department of Anaesthetics.

§ Senior Electronics Engineer, Nuffield Department of Anaesthetics.

¶ Registrar in Medicine, Oxford University.

\*\* Chief Technician, Nuffield Department of Anaesthetics.

Received from the Nuffield Department of Anaesthetics, Oxford University, Oxford, England, and Cardiac Anesthesia Group, Department of Anesthesia, Anesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts 02114. Accepted for publication April 28, 1981. Supported in part by Grant GM 15904, US PHS and the Dalton Foundation. Reported in part at the annual meeting of the American Society of Anesthesiologists, October, 1979.

Address reprint requests from North America to Dr. Edward Lowenstein: Department of Anesthesia, Massachusetts General Hospital, Boston, Massachusetts 02114; and reprint requests from Europe to Dr. Pierre Foëx: Nuffield Department of Anaesthesia, Oxford OX2 6HE, England.

tive-pressure ventilation was instituted at a rate of 12 breaths/min with a mixture of 70 per cent oxygen and 30 per cent nitrogen to which sufficient carbon dioxide was added to maintain end-tidal carbon dioxide concentration at 5.3 per cent. Anesthesia was maintained during preparation with 0.7 per cent inspired halothane supplied by a Fluotec® vaporizer (Fraser/Sweatman Incorporated), calibrated with a refractometer. Temperature was measured in the mid-esophagus and maintained between 37°C and 38°C by a heating element incorporated in the operating table.

The left common carotid artery was exposed in the neck and a stiff 14-gauge polyethylene catheter introduced and advanced to within 1 cm of the aortic valve for measurement of systemic arterial pressure by a Statham® pressure transducer and withdrawal of blood samples. An intravenous cannula was threaded into the inferior vena cava via a femoral vein and 0.9 per cent saline administered at constant rate of  $4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ .

A left thoracotomy was performed, the fifth and sixth ribs excised and the heart exposed and suspended in a pericardial cradle. A miniature Konigsberg® pressure transducer was inserted into the left ventricle via a stab wound in the apical dimple. A cannula was inserted into the left atrium and connected to a Statham® pressure transducer. The two Statham® transducers were calibrated with a mercury manometer. The signal of the Konigsberg transducer was calibrated by matching peak left ventricular pressure to peak aortic pressure, and left ventricular end-diastolic pressure to left atrial pressure.<sup>3</sup>

The left anterior descending coronary artery was dissected free distal to the second major diagonal branch and a woven OO Dacron® suture loosely placed around it. The suture was attached to a micrometer-controlled, spring-suspended snare which could be tightened or loosened in increments of 0.001 inch.

Two pairs of ultrasonic piezo-electric crystals, each approximately 1.5 mm in diameter, were inserted in sub-endocardial myocardium. One pair was located within the area supplied by the left anterior descending coronary artery (LAD) distal to the isolated arterial segment, and the other pair within myocardium supplied by the left circumflex coronary artery (LC). Both pairs of crystals were implanted parallel to the short axis of the heart. The technique of insertion was as follows: Two sites were selected approximately 10 mm apart and a 3-mm linear epicardial incision made at each site. A tract for each crystal was made by inserting a mosquito hemostat through the incision perpendicular to the surface until the resistance offered by the endocardium was felt. The crystals, directed by removable Teflon® sleeves, were advanced to the endocardial area and the Teflon® sleeves

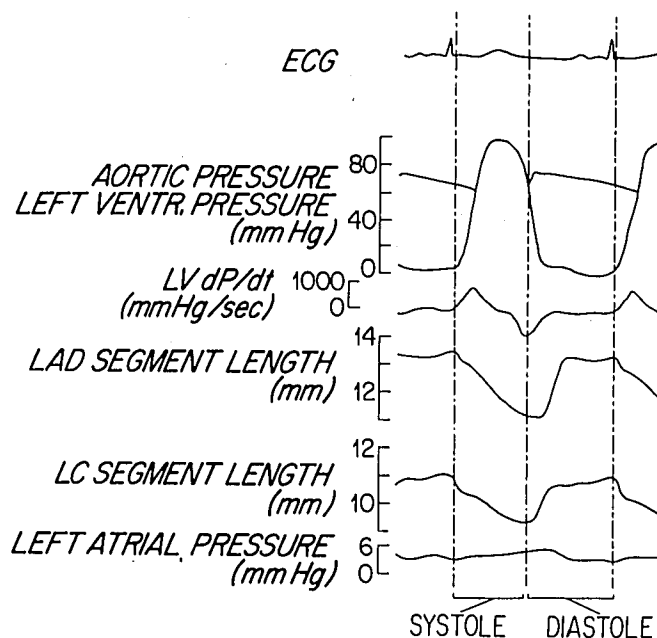


FIG. 1. Representative recording of hemodynamic variables and two normal ventricular segment lengths. Systole and diastole are indicated by the vertical lines. LAD: ventricular segment length recording in the area supplied by the left anterior descending coronary artery. LC: ventricular segment length recording in the area supplied by the left circumflex coronary artery.

withdrawn. The subendocardial position of the crystals was confirmed at autopsy.

#### REGIONAL MYOCARDIAL FUNCTION

Regional myocardial function was assessed by obtaining a continuous measurement of segment length between each pair of crystals based on the measurement of ultrasonic transit time.<sup>4,5</sup> One member of a pair of 5 MHz piezo-electric crystals acts as an emitter and the other as a receiver. The emitter crystal is excited by a 10-nanosecond 180-volt pulse to produce a longitudinal ultrasound-wave front that travels through the myocardium. The receiver crystal detects this wave front, and this allows the transit time to be measured. The transit-time signal may be converted into a length signal since ultrasound travels through the myocardium at a constant velocity of  $1.56 \text{ mm}/\mu\text{s}$ .<sup>5</sup> The emitter crystal is stimulated at a repetition rate of 1 kHz to provide a continuous analogue signal of dynamic segment length.

#### ANALYSIS OF THE ULTRASONIC LENGTH SIGNAL

The signals for analysis were recorded at a paper speed of 100 mm/s. Figure 1 shows length tracings in relation to the hemodynamic variables recorded. End-diastole was defined as the time of the beginning of the sharp upslope

TABLE 1. Effect of Changes in Contractility and Myocardial Ischemia Upon Ventricular Segment Length

	Myocardial Stimulation (↑ Contractility)	Myocardial Depression (↓ Contractility)	Myocardial Ischemia	
			Mild	Severe
End-diastolic length, Maximum length-systole	↓	↑	—↓	↑ to ↑↑↑
Minimum length-systole	↓	↑	↑	↑↑↑
Systolic shortening	↑	↓	↓ or ↓↓	↑↑↑ or none
Velocity of systolic shortening	↑	↓	↓ or ↓↓	↑↑↑ or none
Diastolic shortening	absent	absent	present	prominent

of the first derivative of left ventricular pressure (LV dP/dt) signal, and end-systole as the time of closure of the aortic valve as indicated by either the dicrotic notch on the aortic pressure tracing or by the minimum deflection of LV dP/dt. In preliminary experiments utilizing an aortic flowmeter, we have established that these events occur within 0.01 s of cessation of aortic flow.

As figure 1 illustrates, in a normal segment length recording, the distance between the two crystals is shortest at the end of systole or beginning of diastole. There is a rapid lengthening as the heart fills and then a plateau. A small increase in length occurs due to atrial contraction just prior to the beginning of ventricular systole and may continue during the early phase of systole. During isovolumic systole, as the left ventricle assumes a more spherical configuration, there is shortening in the minor axis of the heart. The greatest proportion of shortening takes place during ejection.

End-diastole length (EDL), maximum length during systole (L max S), and minimum length during systole (L min S) were obtained from the calibrated traces. The following formulas were used for derivations of lengths:

$$\text{Systolic shortening } (\Delta L_s) = L \text{ max S} - L \text{ min S}$$

$$\text{Per cent shortening} = \frac{\Delta L_s}{L \text{ max S}} \times 100$$

Changes observed during enhanced contractility, depressed contractility, moderate ischemia and profound ischemia are outlined in table 1. With enhanced contractility there is a decrease in end-diastolic length and an increase in the velocity and magnitude of shortening. With myocardial depression, the end-diastolic length is increased and the velocity and magnitude of shortening are decreased. With moderate ischemia there may be no change or a small increase in end-diastolic length, while the velocity of shortening is decreased, and postsystolic shortening appears. As ischemia worsens progressively and becomes severe, systolic lengthening, rather than shortening, is observed. Furthermore, all shortening oc-

curs in diastole, *i.e.*, after the closure of the aortic valve, so this shortening does not contribute to the pumping function of the heart. End-systolic length may be greater than end-diastolic length, indicative of paradoxical expansion. Figure 2 schematically illustrates a length tracing without and with progressively more severe ischemia.

#### HEMODYNAMIC AND ELECTROCARDIOGRAPHIC MEASUREMENTS

In addition to segment length measurements, we recorded lead two of the electrocardiogram in all dogs and the epicardial electrogram midway between each pair of crystals in three dogs. We also recorded arterial blood pressure, left ventricular pressure, and left atrial pressure. We derived LV dP/dt by on-line differentiation, heart rate from RR interval, and coronary perfusion pressure (diastolic arterial pressure — left atrial pressure). ST segment elevation was quantitated in mV in those dogs in which epicardial electrocardiograms were obtained.

#### PROTOCOL

The aim of the experiment was to expose the myocardium to stepwise increases in inspired halothane concentration before and after critical constriction of the left anterior descending coronary artery. Exposure to each concentration was 10 min in duration. (Preliminary studies demonstrated that circulatory stability was always achieved within 7 min. The expired concentration was not measured nor assumed to have achieved a steady state.) After the surgical preparation of the animal was complete, a one-hour period of stabilization was allowed to elapse. The experiments were initiated a minimum of four hours after the administration of thiopental.

The precontraction halothane exposure was performed as follows: Control recordings were obtained at a halothane concentration of 0.5 per cent. If inspired halothane concentration had been greater than 0.5 per cent, it was decreased to that concentration for 10 min. The inspired halothane concentration was then increased

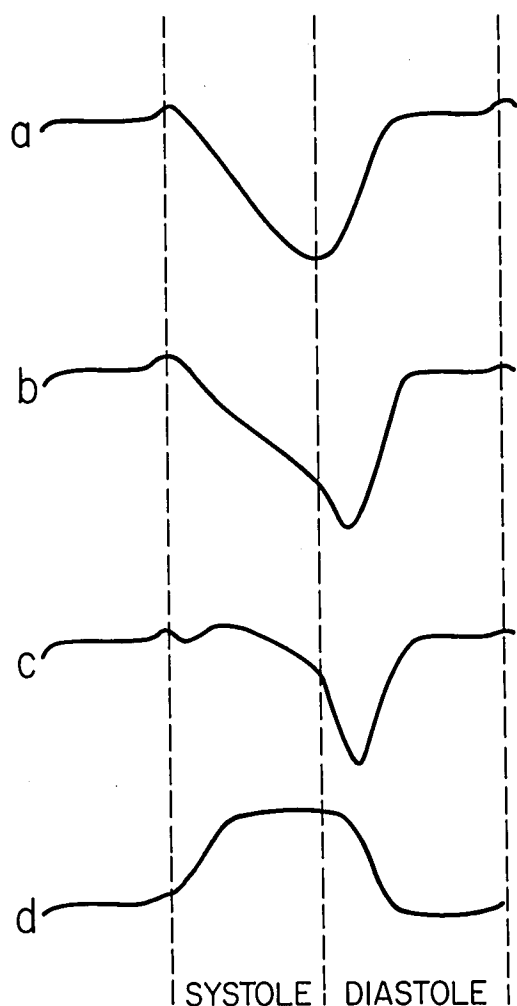


FIG. 2. Schematic representation of the effect of ischemia upon the configuration of ventricular segment length recordings. Normal (a): Shortening occurs during systole, lengthening during diastole. Mild ischemia (b): Postsystolic shortening appears. Magnitude and velocity of systolic shortening may be decreased. Moderate ischemia (c): Little net shortening occurs during systole. There is transient mid-systolic lengthening. Postsystolic shortening becomes pronounced. Severe ischemia (d): Lengthening occurs throughout systole, so that end-systolic length exceeds end-diastolic length. All shortening occurs after aortic valve closure.

in steps of 0.5 per cent to a concentration of 2 per cent. Each level of inspired halothane concentration was maintained for 10 min, when recordings were obtained. The halothane concentration was then returned to 0.5 per cent and recordings obtained after 15 min. All recordings were obtained during a 20-s period of apnea at end-expiration.

A critical constriction of the left anterior descending coronary artery was then imposed: the snare was tightened by increments of 0.025 in at 30-s intervals until

changes indicative of ischemia were observed in the LAD segment unaccompanied by such changes in the LC segment. The snare was then loosened by 0.025 to 0.050 in until the ischemic changes resolved. After a variable recovery interval, the micrometer was retightened by 0.005-in increments until early changes of LAD contraction again occurred. The snare was then re loosened by 0.005 in until these changes resolved, and a 20-min period allowed to elapse. A 90-s exposure to nitrogen (without change of inspired  $\text{CO}_2$ ) was then imposed upon the animal. Previous work has demonstrated that this results in a  $\text{PaO}_2$  of  $31 \pm 5$  torr.<sup>6</sup> If ischemic changes in LAD contraction occurred unaccompanied by similar changes in LC contraction, this degree of narrowing was considered a critical constriction, as illustrated in figure 3. If not, further narrowing was imposed in 0.0025- to 0.005-in increments until a differential response to hypoxia was obtained. Only animals which demonstrated this differential response were studied further.

A further recovery period of 20 min was allowed to elapse after the establishment of critical constriction. The halothane exposure during constriction was then carried out in the same fashion as previously described for the prestriction exposure.

Statistical analysis was performed by Student's *t* test for paired and unpaired data. Results are expressed as mean  $\pm$  SEM.

## Results

### HEMODYNAMIC DATA (TABLE 2)

There were no significant differences between the pre-constriction and constriction exposures in any measured or derived hemodynamic variable at any halothane concentration.

However, all measured and derived variables except heart rate (systolic and diastolic arterial pressure, left ventricular end-diastolic and left atrial pressure, coronary perfusion pressure, and LV dP/dt max) changed progressively and significantly in a dose-dependent fashion with increasing inspired halothane concentration before and after critical constriction of the LAD.

### LENGTH MEASUREMENTS (TABLE 3)

#### Prestriction

There were significant dose-dependent reversible increases in EDL, L max S, L min S, and decreases in  $\Delta L_s$  and percentage shortening. Though the percentage of shortening in the two areas of the heart (LAD and LC) differed, the percentage of increase in end-diastolic

TABLE 2. Hemodynamic Effects of Increasing Halothane Concentration without and during Constriction of the Left Anterior Descending Coronary Artery in Dogs (n = 11)

	Preconstriction Halothane Concentration (Per Cent)					During Constriction Halothane Concentration (Per Cent)				
	0.5	1.0	1.5	2.0	0.5	0.5	1.0	1.5	2.0	0.5
Heart rate (b/min)	113 ± 7	114 ± 7	114 ± 7	110 ± 6	110 ± 7	113 ± 8	115 ± 7	116 ± 8	116 ± 7	114 ± 7
Systolic arterial pressure (torr)	95 ± 3	85 ± 3‡	76 ± 2‡	62 ± 2‡	93 ± 3	97 ± 3	89 ± 3‡	80 ± 2‡	61 ± 4‡	96 ± 3
Diastolic arterial pressure (torr)	70 ± 3	61 ± 3‡	52 ± 3‡	41 ± 3‡	67 ± 3	72 ± 4	64 ± 3‡	56 ± 3‡	39 ± 4‡	69 ± 4
LVEDP (torr)	5.1 ± 0.6	5.3 ± 0.7	5.9 ± 0.7*	6.6 ± 0.7‡	5.6 ± 0.7	5.4 ± 0.7	5.5 ± 0.6	6.3 ± 0.7	7.3 ± 0.8*	5.6 ± 0.7
Coronary perfusion pressure (torr)	65 ± 3	56 ± 3‡	46 ± 3‡	34 ± 3‡	61 ± 3	67 ± 4	59 ± 3‡	50 ± 3‡	32 ± 4‡	63 ± 4
LV dP/dt max. (torr/s)	1380 ± 55	1155 ± 45‡	930 ± 35‡	685 ± 40‡	1265 ± 60‡	1285 ± 65	1090 ± 65‡	945 ± 65‡	640 ± 65‡	1250 ± 70

\* P &lt; 0.05 compared to preconstriction control or postconstriction control.

‡ P &lt; 0.01 compared to preconstriction control or postconstriction control.

‡ P &lt; 0.001 compared to preconstriction control or postconstriction control.

length and percentage decrease in shortening were similar in the two areas. Thus, the effect of increasing halothane concentration was the same in the two segments under study prior to constriction of the artery supplying one of the areas. No changes consistent with ischemia, *i.e.*, systolic lengthening or postsystolic shortening, were observed in any myocardial segment.

### Constriction

*Left circumflex segment.* In the LC area there were no statistically significant differences between the preconstriction and constriction data.

*Left anterior descending segment.* At 0.5 per cent halothane, the end-diastolic length and L max S were unchanged during the constriction period as compared to the preconstriction period. The minimum length (L min S) was slightly greater when compared to preconstriction control, though not significantly different from the preconstriction recovery (*i.e.*, 0.5 per cent halothane). Systolic shortening ( $\Delta L_s$ ) and per cent shortening were reduced significantly from the preconstriction control period by 10.2 per cent and 10.5 per cent, respectively. Thus, a modest decrease of regional ventricular performance was evident at 0.5 per cent halothane. The only evidence suggestive of ischemia at 0.5 per cent halothane was the presence of minimal postsystolic shortening.

During 1.0 and 1.5 per cent halothane, EDL was unchanged from preconstriction, though L min S was greater and  $\Delta L_s$  and per cent shortening were decreased. At 2 per cent halothane, EDL and L max S were increased significantly compared to preconstriction, in addition to worsening of the above changes. Fifteen min after returning the halothane concentrations to 0.5 per cent all these variables had recovered to the constriction control values. Figure 4 shows the per cent shortening of the two segments normalized to the beginning of each halothane exposure. There is a greater degree of depres-

sion with increasing inspired halothane concentration in the LAD territory during constriction than prior to constriction. At 2 per cent halothane the difference is significant.

Eight of eleven LAD segments demonstrated changes indicative of myocardial ischemia during the postconstriction halothane exposure. Four segments showed frank paradoxical motion, with increased end-systolic length relative to end-diastolic length (fig. 5). All eight demonstrated postsystolic shortening. Figure 6 shows the increase of end-diastolic length of the LC segment plotted against the LAD segments, expressed as the per cent of increase at 2 per cent halothane compared to 0.5 per cent halothane. Seven of eight muscle segments demonstrating ischemia had greater increases in end-diastolic length of the LAD than the LC, whereas the increases in length of the non-ischemic LAD segments were similar to those of the LC segments.

### Epicardial Electrocardiogram

Three hearts were studied. No ST segment changes indicative of ischemia were observed at any time in the LC segment or in the LAD segment prior to constriction. Minor ST segment elevation (maximal 1.5 mV) occurred in all three LAD segments, but only after frank paradox was established.

### Discussion

The single most important finding of this study is that an inspired concentration of halothane, tolerated well by myocardium supplied by a normal coronary artery, commonly produces dysfunction and paradox, changes characteristic of myocardial ischemia,<sup>7-10</sup> in an area supplied by a critically narrowed coronary artery. Ischemic regional ventricular dysfunction occurs despite anesthetic-concentration appropriate systemic hemodynamics, nor-

TABLE 3. Effect of Increasing Halothane Concentration upon Regional Ventricular Function before and during Constriction of the Left Anterior Descending Coronary Artery in Dogs (n = 11)

	Precontraction Halothane Concentration (Per Cent)					During Constriction Halothane Concentration (Per Cent)				
	0.5	1.0	1.5	2.0	0.5	0.5	1.0	1.5	2.0	0.5
LAD										
L max S (mm)	13.08 ± 0.81	13.11 ± 0.80	13.23 ± 0.80	13.49 ± 0.80	13.21 ± 0.83	13.22 ± 0.86	13.28 ± 0.83	13.47 ± 0.81	14.01 ± 0.81*	13.28 ± 0.81
EDL (mm)	12.97 ± 0.80	13.01 ± 0.79	13.15 ± 0.79	13.41 ± 0.79	13.15 ± 0.81	13.10 ± 0.85	13.18 ± 0.82	13.40 ± 0.80	13.96 ± 0.80*	13.15 ± 0.79
L Min S (mm)	10.45 ± 0.66	10.63 ± 0.65	11.02 ± 0.64	11.55 ± 0.65	10.68 ± 0.64	10.86 ± 0.73*	11.15 ± 0.70‡	11.70 ± 0.69*	13.00 ± 0.74‡	11.06 ± 0.65*
ΔL <sub>s</sub> (mm)	2.63 ± 0.23	2.48 ± 0.23	2.21 ± 0.25	1.94 ± 0.25	2.54 ± 0.23	2.36 ± 0.22*	2.13 ± 0.22‡	1.77 ± 0.24*	1.01 ± 0.33§	2.22 ± 0.25‡
Per cent Shortening	20.0 ± 1.3	18.8 ± 1.3	16.5 ± 1.4	14.1 ± 1.5	19.0 ± 1.3	17.9 ± 1.3‡	16.0 ± 1.3‡	13.0 ± 1.4*	6.9 ± 2.1§	16.5 ± 1.3‡
LC										
L max S (mm)	10.75 ± 0.64	10.82 ± 0.62	10.89 ± 0.63	11.08 ± 0.63	10.82 ± 0.61	10.84 ± 0.66	10.92 ± 0.68	11.01 ± 0.70	11.35 ± 0.77	10.90 ± 0.73
EDL (mm)	10.69 ± 0.63	10.75 ± 0.61	10.88 ± 0.62	11.05 ± 0.63	10.77 ± 0.60	10.80 ± 0.65	10.87 ± 0.67	10.98 ± 0.70	11.33 ± 0.76	10.85 ± 0.71
L min S (mm)	9.37 ± 0.56	9.50 ± 0.56	9.66 ± 0.56	10.01 ± 0.56	9.44 ± 0.53	9.49 ± 0.57	9.56 ± 0.58	9.70 ± 0.61	9.70 ± 0.62	9.49 ± 0.61
ΔL <sub>s</sub> (mm)	1.38 ± 0.10	1.32 ± 0.09	1.23 ± 0.10	1.06 ± 0.12	1.38 ± 0.09	1.35 ± 0.10	1.35 ± 0.12	1.31 ± 0.11	1.24 ± 0.18	1.41 ± 0.13
Per cent Shortening	12.8 ± 0.5	12.3 ± 0.6	11.3 ± 0.6	9.5 ± 0.9	12.7 ± 0.5	12.4 ± 0.5	12.3 ± 0.5	11.9 ± 0.5	10.9 ± 1.1	12.8 ± 0.6

Values are means ± SEM.

L max S = maximum length during systole; EDL = End-diastolic length; L min S = minimum length during systole; ΔL<sub>s</sub> = decrease of length during systole.

\* P &lt; 0.05 compared to same period precontraction.

† P &lt; 0.01 compared to same period precontraction.

‡ P &lt; 0.001 compared to same period precontraction.

§ P &lt; 0.0001 compared to same period precontraction.

mal global left ventricular function, and minor changes in the epicardial electrocardiogram. The cause of the dysfunction appears to be a localized decrease in coronary perfusion, most probably associated with a pressure gradient across the constriction in the coronary artery. Since prolonged ischemia may lead to myocardial tissue death, we hypothesize that clinically unsuspected intra-anesthetic compromise of such an area may be an important cause of perioperative myocardial infarction despite the absence of an identifiable episode of ischemia or hemodynamic instability.

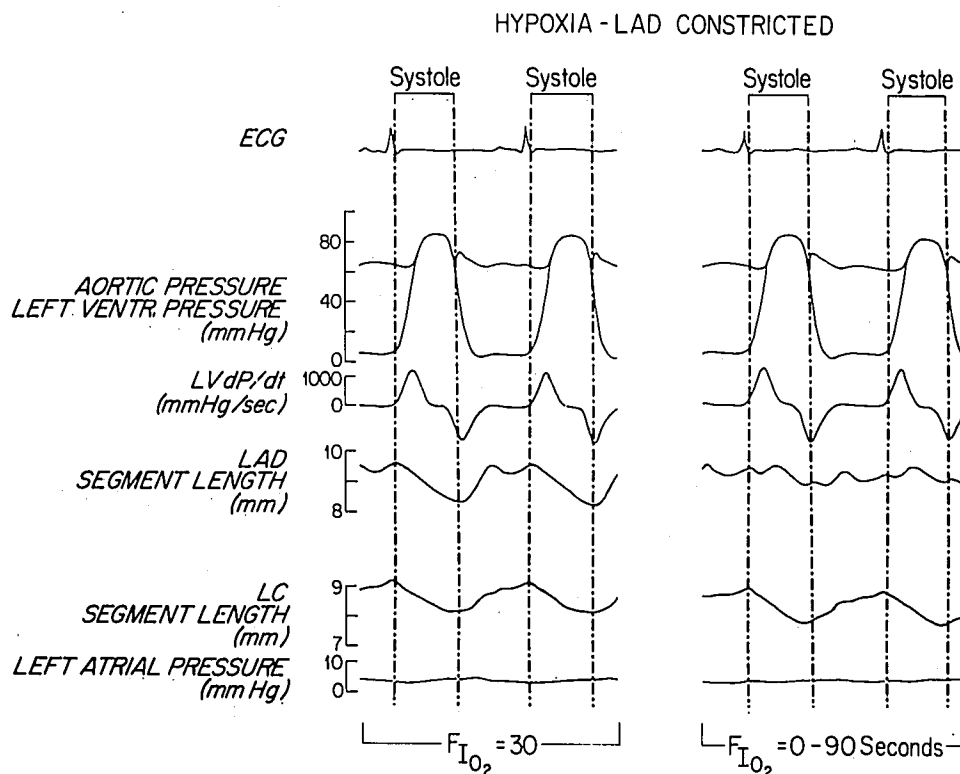
Studies employing occlusion of a canine coronary artery,<sup>11</sup> which mimics a recent myocardial infarction, have conclusively shown that some anesthetic drugs, *i.e.*, 0.7 per cent halothane and a morphine-based "lytic cocktail," may importantly decrease the magnitude of myocardial tissue death.<sup>1,2,12</sup> Individuals with recent myocardial infarction constitute a small subgroup of patients with coronary artery disease presenting for anesthesia and surgery. Patients with narrowed rather than recently occluded coronary arteries, constitute a far larger group of patients. Thus we believe it is important to study the effect of anesthetics when a coronary artery is narrowed.

The model we have employed in the present study does have a narrowed coronary artery. Under control conditions, the function is normal in both the control segment and the segment supplied by the narrowed coronary artery. Moreover, we demonstrated that the area supplied by the constricted artery is unable to contract

normally when the arterial oxygen content is decreased by hypoxic hypoxia. We believe that the constriction prevents the coronary artery flow from increasing sufficiently to meet the increased flow requirement. Thus, this area would appear to be comparable to an area causing angina pectoris, in which the available vascular supply is able to meet basal oxygen demands but is unable to respond normally to stress.

Flow across a constriction is dependent upon the pressure difference across that constriction and the duration of flow (diastole). In the normal coronary circulation, the vascular bed dilates (*i.e.*, autoregulates) progressively in response to a decreased driving pressure in order to maintain the flow constant.<sup>13</sup> When a critical pressure is reached, flow becomes proportional to pressure. The driving pressure required to maintain a given flow across a tube with a constriction is greater than that required to maintain the flow in the absence of that constriction. These studies were performed in the presence of increasing inspired halothane concentrations, constant heart rate, and decreasing arterial blood pressure. It is therefore reasonable to assume that heart segments which demonstrated dysfunction and paradox did so because the blood flow and oxygen delivery were insufficient to meet oxygen demands, though other contributory factors can not be excluded. Figure 7 supports the assumption that flow was important. In this dog the ventricular premature beat, with its very short time for coronary flow, is paradoxical in the narrowed segment, indicative of

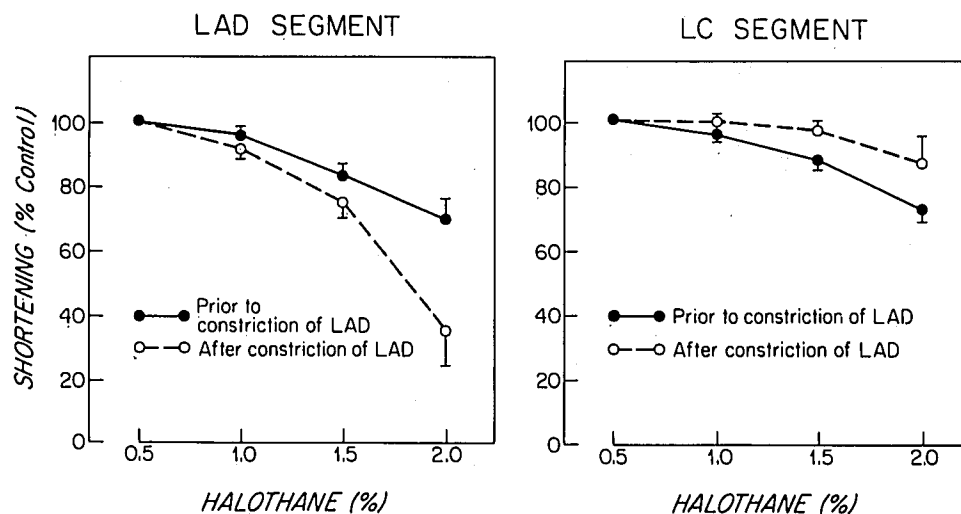
FIG. 3. Effect of hypoxic hypoxia imposed by inhalation of  $N_2$  for 90 seconds. Prior to hypoxia (left panel). Shortening occurs normally in both the LAD and LC segments. During hypoxia (right panel). Little systolic shortening occurs in the constricted (LAD) area, and mid systolic lengthening is present. In the LC segment, the pattern of shortening remains normal, the velocity and magnitude of shortening are greater than prior to hypoxia, and the end diastolic length is less. These changes are indicative of enhanced contractility.



severe ischemia. After a compensatory pause, which allows for added diastolic duration, that segment shortens normally. This is compatible with sufficient flow across the constriction to satisfy the oxygen requirement for normal contraction. The initial beats, with an intermediate RR interval and filling time, show impaired, though present, systolic shortening and postsystolic shortening,

indicative of moderate ischemia. In contrast, shortening is normal in all beats in the segment fed by the normal coronary artery. This isolated observation is a dramatic example of the beat-to-beat dependence of heart muscle function upon adequate oxygen supply.<sup>14</sup> Thus, although the regional ischemia observed in these studies, in which heart rate remained constant, appeared to be due prin-

FIG. 4. Effect of increasing halothane concentration upon systolic shortening of the LAD and LC segments prior to and during constriction of the LAD segment (mean  $\pm$  SEM). The results have been normalized to the beginning of each halothane exposure. Shortening in the two segments is decreased similarly with increasing halothane concentration prior to constriction of LAD. During constriction, the LAD segment shortens less at each concentration of halothane. This becomes significant at 2 per cent. In contrast, function of the control (LC) segment is preserved. See text for details.



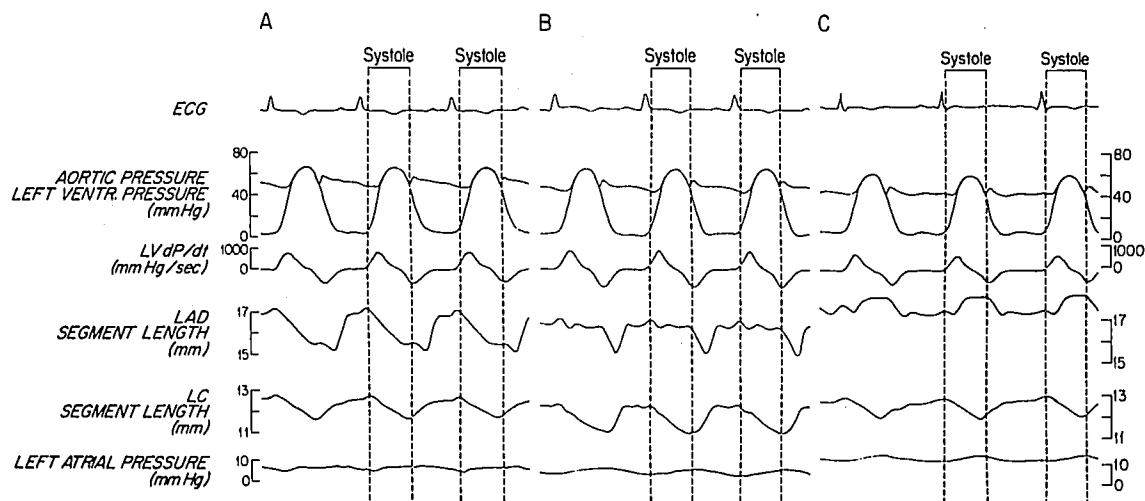


FIG. 5. The spectrum of ischemic ventricular segment dysfunction associated with 2 per cent inspired halothane in LAD segments supplied by a narrowed coronary artery. A. Mild dysfunction, with most shortening taking place during systole. Postsystolic shortening is apparent. B. Hypokinesis, little systolic shortening occurs. Postsystolic shortening is prominent. C. Frank paradox, with systolic lengthening and all shortening occurring after aortic valve closure. Note that LC segment contraction is normal in all three panels.

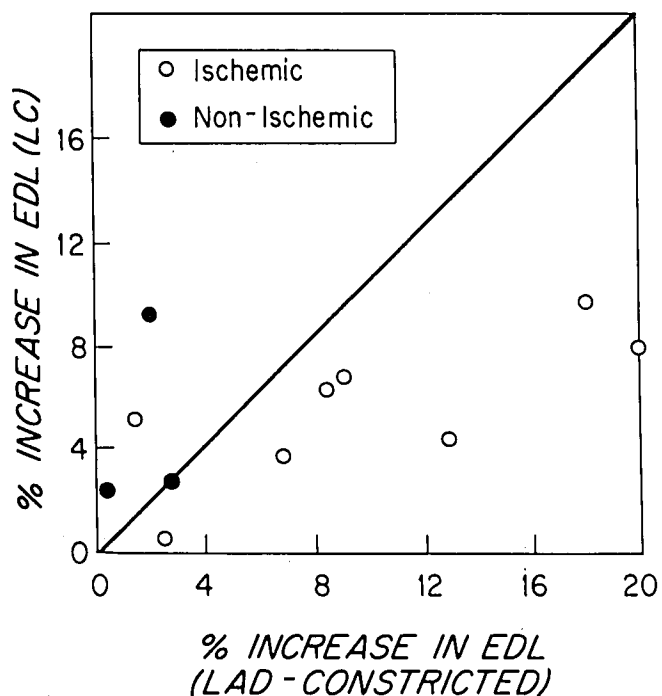


FIG. 6. Increase in end-diastolic length of LAD (constricted) and LC (unconstricted) segments associated with increasing halothane concentration from 0.5 per cent to 2.0 per cent. In 7 of 8 LAD segments which became ischemic, the halothane-associated increase of EDL was greater than the increase of EDL of the LC segment. In the LAD segments which did not become ischemic, the EDL did not increase disproportionately. Thus the greater elevation of EDL appears to be related to ischemia rather than being a direct effect of the halothane. See text for details.

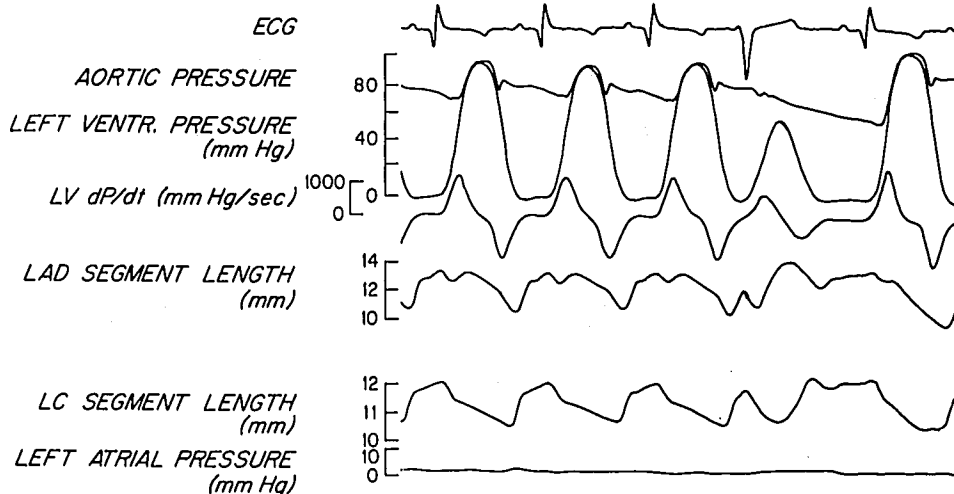
cipally to pressure-mediated decrease in coronary blood flow distal to the narrowing, we believe it would be misleading to emphasize the pressure dependence to the exclusion of the factors regulating myocardial oxygen balance in the interpretation of our data.

Furthermore, our studies dramatically demonstrate the limitations of calculated coronary perfusion pressure in the presence of a coronary constriction. In the clinical setting, estimates of coronary perfusion pressure always employ aortic diastolic pressure. The coronary artery diastolic pressure in a patent arterial system does equal aortic diastolic pressure. With high-grade stenosis, as present in these studies and coronary arteriosclerosis, indirect estimation of coronary artery diastolic pressure is not possible, and may range anywhere between aortic diastolic pressure and zero. Thus, the presence of a "normal" or "anesthetic concentration appropriate" blood pressure gives no assurance of positive net regional myocardial oxygen balance or lack of regional ischemic dysfunction. In fact, use of this value may be detrimental by leading to a false sense of security.

The present studies confirm that halothane causes a significant dose-dependent reduction of myocardial performance similar to that reported previously.<sup>15,16</sup> The presence of a constriction of the LAD did not change the response to halothane of any measured hemodynamic variable, including LV dP/dT, an index of global myocardial performance.

Two reasons for the absence of global impairment of function in these studies may be suggested. The area

FIG. 7. Effect of changing diastolic filling period upon a constricted LAD segment and unconstricted LC segment during 2 per cent inspired halothane. Regular sinus beats (S) are associated with moderate ischemia in the LAD segment and normal contraction in the LC segment. The ventricular premature contraction (V) is associated with a shorter duration of coronary filling. The LC segment shortening pattern remains normal. However, the LAD segment is frankly paradoxical; *i.e.*, the LAD segment lengthens during ventricular contraction, and shortening occurs only with the decline of ventricular pressure during the relaxation period. The sinus beat after the subsequent compensatory pause (C) is associated with the longest diastolic filling period. This allows sufficient coronary flow so that the LAD contraction pattern normalizes, indicating the absence of ischemia in that previously ischemic LAD segment during that beat. The contraction pattern of the LC segment remains normal. See text for details.



supplied by the left anterior descending coronary artery distal to the second diagonal branch is relatively small. When dysfunction occurs in a small area of the left ventricular wall it may not cause detectable impairment of global function. A second reason for the absence of impairment of global function may be the behavior of the control (*i.e.*, LC) segment. Prior to constriction, the per cent shortening was similar in two segments. During the administration of halothane, as the LAD became more dysfunctional, LC segment shortening was preserved (fig. 4). This was most evident in those hearts with the most severe LAD segment dysfunction. Whether this is due to local compensation, decreased impedance of the ischemic segment, or another unknown mechanism has not been clarified.

As figure 6 shows, at 2 per cent halothane, seven of eight hearts which demonstrated ischemic dysfunction had a greater increase of end-diastolic segment length in the narrowed segment relative to the increase in the normal (LC) segment. This was not true of segments that did not become ischemic. Thus, it is reasonable to assume that this excess increase in end-diastolic length was caused by ischemia rather than by global left ventricular dilatation. Once established, diastolic segmental distension may help to perpetuate ischemia by increasing tissue pressure. This, in turn, may lead to a vicious cycle in which subendocardial perfusion is not adequate even though aortic diastolic pressure returns to normal. Tissue compression of subendocardial vessels and elevation of the minimum inflow pressure required for diastolic perfusion may be responsible for this phenomenon.<sup>13</sup>

We have termed the shortening that occurs following aortic valve closure "postsystolic shortening," since the end of systole is classically defined by aortic valve closure.<sup>17</sup> Kumada *et al.* referred to this as "late systolic shortening," despite the fact that it takes place after completion of systole.<sup>18</sup> It is unclear whether this shortening is active or passive (elastic recoil).<sup>8,18</sup> Regardless of the mechanism, however, it does not contribute to the ejection of blood into the aorta.

The absence of early and reliable changes in the epicardial electrocardiogram recorded from the site of malfunction is disappointing. The literature validating the correlation of epicardial ST segment elevation after coronary occlusion and subsequent tissue death is copious.<sup>19,20</sup> Our previous work demonstrating decrease by halothane of ischemia as estimated by electrocardiography was confirmed by recent work demonstrating decrease in anatomic infarct size by a 12-h halothane exposure after coronary occlusion.<sup>2</sup> Perhaps the epicardial electrocardiogram is most reliable in the presence of an occluded artery. Any coronary flow that does occur in the presence of a constriction may well be distributed primarily to the subepicardial area closest to the epicardial electrocardiographic lead.<sup>21</sup> Thus, the reasons for lack of detectable changes in the epicardial electrocardiogram may include preservation of epicardial flow across the constricted orifice, despite a decrease in endocardial flow. Guyton and associates have shown that the endocardial electrocardiogram reflects ischemia associated with decreased coronary perfusion pressure prior to changes in the epicardial electrocardiogram.<sup>21</sup>

Smith *et al.* have also shown that the epicardial and endocardial electrocardiographic ST segment elevation is similar after an occlusion duration of 5 min.<sup>22</sup> Thus, there appears to be a qualitative difference between the effects of an occlusion and a constriction in regard to epicardial electrocardiography, which may explain our findings. Further studies including both total coronary flow and coronary flow distribution plus simultaneous epicardial and endocardial electrocardiograms would appear to be necessary to further clarify this issue.

Three recent investigations of halothane and coronary artery narrowing have been published since these studies were performed. Verrier *et al.* showed a decreased perfusion pressure requirement at 1 MAC halothane compared to nitrous oxide.<sup>23</sup> Behrenbeck has shown that decrease of coronary blood flow to 25–30 per cent of control causes the same magnitude of impairment of ventricular wall thickening at 0.5 to 1.5 MAC halothane.<sup>24</sup> Hickey *et al.* demonstrated that canine heart muscle supplied by an artery with a “moderate” stenosis tolerated halothane-induced deliberate hypotension without becoming ischemic, whereas regional ischemia occurred despite a decreased oxygen requirement when hypotension was induced for two hours in the presence of a “severe” stenosis.<sup>25</sup> All of these studies are compatible with our data. A reason that three of our eleven dogs did not become ischemic may be that the degree of constriction in those arteries was comparable to Hickey’s moderate stenoses, whereas that constriction in the eight other dogs was equivalent to their severe stenoses.

This study has not directly addressed the definition of a prudent or adequate arterial pressure during clinical anesthesia. In patients with known ischemic heart disease, few anesthetists, (certainly including the authors) would be content with a diastolic arterial pressure of 40 torr! Our use of the terms “normal” and “anesthetic concentration appropriate” hemodynamics are employed to attempt to convey the message that regional ischemia may occur in areas supplied by stenotic coronary arteries despite an apparently benign anesthetic course with unimpressive deviations from normal hemodynamic values. It is likely that with lengthy and/or sequential stenoses, local coronary flow below that required to satisfy oxygen requirements may occur at a higher arterial pressure than in this study, particularly if the heart rate is elevated, the ventricle is distended, the hematocrit is decreased, etc. The assumption that hemodynamic values different from those present during the awake, non-ischemic state are safe may consequently be erroneous when coronary stenoses are present. Until on-line monitoring of regional myocardial ischemia is feasible, maintenance of intra-anesthetic hemodynamics within ranges known

to be associated with absence of myocardial ischemia in the awake individual appears to remain a reasonable goal and elusive ideal.

It is important to emphasize that no implication can be derived from these studies concerning the relative advantages or disadvantages of halothane over other anesthetic agents or regimens in the management of patients with coronary artery disease. These data neither confirm nor refute those data demonstrating a decrease of myocardial tissue death associated with halothane administration in the animal with an occluded coronary artery. Rather, they may establish the necessity for studying the interaction between anesthetic drugs and non-occlusive coronary artery disease in a model which has a coronary artery constriction rather than an occlusion. In addition, the implications of the changes in segmental wall motion must be confirmed by other studies documenting magnitude and distribution of coronary flow, metabolic consequences, tissue oxygen tensions, endocardial electrocardiograms, and other indices reflecting myocardial oxygen supply and demand. If the prevailing opinions are correct, the contraction abnormalities that we have observed are characteristic of and specific for ischemia.<sup>7-10</sup> Prolonged ischemia is associated with tissue death. We believe the major importance of our studies is that “normal” systemic hemodynamics and global ventricular function during anesthesia may be associated with regional myocardial ischemia. This may be an important mechanism for perioperative infarction despite the absence of clinically identifiable ischemia.

The authors acknowledge the contributions of Dr. Siegfried Hagl and Dipl. Ing. Werner Heimisch, Deutsches Herzzentrum, Munich, West Germany, who gave generously of their knowledge and technical skills.

## References

1. Bland JHL, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. *ANESTHESIOLOGY* 45:287–293, 1976
2. Davis RF, DeBoer LWV, Rude RE, et al: Beneficial effect of halothane anesthesia on myocardial infarction size in dogs. *Crit Care Med* 7:134, 1979 (abstract)
3. Roberts JG, Foex P, Clarke TNS, et al: Haemodynamic interactions of high-dose propranolol pretreatment and anaesthesia in the dog. I. Halothane dose-response studies. *Br J Anaesth* 48:315–325, 1976
4. Bugge-Asperheim B, Leraand S, Kiil F: Local dimensional changes of the myocardium measured by ultrasonic technique. *Scand J Clin Lab Invest* 24:361–371, 1969
5. Hagl S, Heimisch W, Meisner H, et al: The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. *Basic Res Cardiol* 72:344–364, 1977
6. Roberts JG, Foex P, Clarke TNS, et al: Haemodynamic interactions of high-dose propranolol pretreatment and anaesthesia in the dog. II: The effects of acute arterial hypoxaemia at increasing depths of halothane anaesthesia. *Br J Anaesth* 48:403–410, 1976

7. Forrester JS, Wyatt HL, Tyberg JV, et al: Functional significance of regional ischemic contraction abnormalities. *Circulation* 54:64-70, 1976
8. Theroux P, Franklin D, Ross J Jr, et al: Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. *Circ Res* 35:896-908, 1974
9. Wyatt HL, daLuz PL, Forrester JS, et al: Functional abnormalities in non-occluded regions of myocardium after experimental coronary occlusion. *Am J Cardiol* 37: 366-372, 1976
10. Waters DD, daLuz PL, Wyatt HL, et al: Early changes in regional and global left ventricular function induced by graded reduction in regional coronary perfusion. *Am J Cardiol* 39:537-543, 1977
11. Maroko PR, Kjekshus JK, Sobel BE, et al: Factors influencing infarct size following experimental coronary occlusions. *Circulation* 43:67-82, 1971
12. Ribiero LGT, Yasuda T, Lowenstein E, et al: Comparative effects on anatomic infarct size on verapamil, ibuprofen, and morphine-promethazine-chlorpromazine combination. *Am J Cardiol* 43:396, 1979 (abstract)
13. Rouleau J, Boerboom LE, Adrianata S, et al: The role of autoregulation and tissue diastolic pressure in the transmural distribution of left ventricular blood flow in anesthetized dogs. *Circ Res* 45:804-815, 1979
14. Boudoulas H, Rittgers SE, Lewis RP, et al: Changes in diastolic time with various pharmacologic agents: Implication for myocardial perfusion. *Circulation* 60:164-169, 1979
15. Vatner SF, Smith NT: Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and primates. *Circ Res* 34:155-167, 1974
16. Merin RG, Kumazawa T, Luka N: Myocardial function and metabolism in the conscious dog and during halothane anesthesia. *ANESTHESIOLOGY* 44:402-415, 1976
17. Hurst JW, Logue RB, Schlant RC, et al, eds: *The Heart*, New York, McGraw-Hill, 1974, p 1833
18. Kumada T, Gallagher KP, Shirato K, et al: Reduction of exercise-induced regional myocardial dysfunction by propranolol: Studies in a canine model of chronic coronary artery stenosis. *Circ Res* 46:190-200, 1980
19. Kjekshus JK, Maroko PR, Sobel BE: Distribution of myocardial injury and its relation to epicardial ST-segment changes after coronary occlusion in the dog. *Cardiovasc Res* 6:490-499, 1972
20. Maroko PR, Libby P, Bloor CM, et al: Reduction by hyaluronidase of myocardial necrosis following coronary artery occlusion. *Circulation* 46:430-437, 1972
21. Guyton RA, McClenathan JH, Newman GE, et al: Significance of subendocardial S-T segment elevation caused by coronary stenosis in the dog. *Am J Cardiol* 40:373-380, 1977
22. Smith HJ, Kent KM, Epstein SE: Relationship between regional contractile function and S-T segment elevation after experimental coronary artery occlusion in the dog. *Cardiovasc Res* 12:444-448, 1978
23. Verrier ED, Edelstein GE, Consigny PM, et al: Greater coronary vascular reserve in dogs anesthetized with halothane. *ANESTHESIOLOGY* 53:445-459, 1980
24. Behrenbeck T, Nugent M, Quasha A, et al: Halothane and ischemic regional myocardial wall dynamics. *ANESTHESIOLOGY* 53: S140, 1980
25. Hickey RF, Verrier ED, Baer RW, et al: Does deliberate hypotension produce myocardial ischemia when the coronary artery is stenotic? *ANESTHESIOLOGY* 53:S89, 1980