The Effect of Acute Changes in Coronary Blood Flow on Left Ventricular End-diastolic Wall Thickness

An Echocardiographic Study

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SUMMARY The effect of acute alterations in coronary blood flow (CBF) on left ventricular (LV) end-diastolic wall thickness was measured by reflected ultrasound in twelve anesthetized dogs. During five minutes of coronary ligation, wall thickness decreased from a control of 9.0 ± 0.3 mm to 8.1 ± 0.3 mm (P < 0.001); during reperfusion (reactive hyperemia), wall thickness was greater than control (10.2 ± 0.2 mm at one minute, P < 0.001). Increased CBF produced by intracoronary nitroglycerin or papaverine resulted in transient increases in wall thickness from 8.9 ± 0.1 mm to 9.7 ± 0.2 at one minute (P < 0.001) and 10.0 ± 0.6 mm to 11.2 ± 0.7 mm at one minute (P < 0.001), respectively. The observed direct relation between CBF and wall thickness suggests a dynamic role for CBF in calculations of LV mass, diastolic wall stress, and myocardial stiffness constants.

LEFT VENTRICULAR WALL THICKNESS is a determinant of diastolic chamber compliance in patients with chronic heart disease and diastolic wall thickness has been shown to correlate with diastolic compliance in acute studies in canine hearts.1, 2 The present study was designed to determine if moment to moment changes in coronary blood flow result in significant changes in LV wall thickness; if so, coronary blood flow itself might be considered a dynamic variable influencing LV mass, wall stress, and chamber compliance.

Methods

Instrumentation and Measurements

Twelve mongrel dogs weighing 20–30 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg). Respiration was maintained with a Harvard pump anduffed endotracheal tube using an appropriate oxygen-nitrogen mixture; arterial blood gases and pH were monitored throughout each experiment and were maintained in a physiologic range. A median sternotomy was performed and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery (the distal portion of its proximal 1/3) was dissected free for placement of a coronary blood flow probe (Carolina Medical Electronics, model 501) and a balloon occluder (fig. 1). A small branch of the coronary artery was cannulated distal to the flow probe in six animals for regional infusion of nitroglycerin or papaverine. Left ventricular (LV) pressure was measured with a Statham P23Db transducer by means of a short catheter inserted through the apex of the heart. The electrocardiogram, mean coronary blood flow, and arterial and/or LV pressure were recorded on a Sanborn 560 photographic recorder.

LV wall thickness was measured with an Aerotech model CIT 5 MHz transducer and a Smith-Kline Echoline 20A ultrasmscope. The transducer was sutured directly to the epicardium of the left ventricle within the distribution of the left anterior descending coronary artery, using 5-0 silk sutures. Prior to suturing the transducer in place, minimal adjustments in position were necessary to obtain a continuous signal from the endocardium; the ultrasonicoscope was adjusted to define optimally the endocardium throughout the cardiac cycle and then position and gain adjustments were not repeated during any experiment. The ECG and the ultrasonic LV wall thickness signal (and in some cases LV pressure) were recorded on a second photographic recorder (Irex model 150). The ultrasound signal was magnified so that 17 mm of paper was equal to 10 mm of muscle; measurements were made to the nearest 0.5 mm paper (0.3 mm muscle) and were averaged over eight to ten beats. In three dogs the LV endocardial signal was verified by injecting 3–6 ml of saline into the ventricle and observing the endocardial-blood interface. The injected saline produces ultrasound reflections which fill the chamber and outline the endocardium. An example of a simultaneous recording of LV pressure and LV wall thickness is shown in figure 2.

LV end-diastolic wall thickness was measured throughout the interventions at a constant point on the QRS complex (generally at the peak of the R wave). End systolic wall thickness, shown in figure 2, was measured at the end of LV ejection. The percent change in wall thickness from end diastole to end systole was determined as end-systolic minus end-diastolic wall thickness divided by end-diastolic wall thickness.

Protocol

LV end-diastolic wall thickness and coronary blood flow (CBF) were measured during several interventions.

In six dogs (10 experiments), measurements were made during a control period, during five minutes of LAD coronary artery occlusion (at three and five minutes of ischemia), and at 30 seconds, one, two, three, and five minutes of reperfusion (during reactive hyperemia). In seven experiments the coronary occlusion was partially released to allow reflow without reactive hyperemia. This was accomplished by manually releasing the occlusion while adjusting the occluder to maintain coronary blood flow at the control level (labeled partial reflow in fig. 5). After five

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minutes of partial reflow, the occlusion was completely released (labeled full reflow in fig. 5).

In three dogs (seven experiments) measurements of coronary blood flow and wall thickness were made during an injection of nitroglycerin into the coronary artery. The nitroglycerin was given in a 2 ml bolus (0.08 mg/ml) of normal saline. In three dogs (seven experiments) similar measurements were made during the injection of 2 ml of papaverine (0.1 mg/ml) into the coronary artery. Two ml of normal saline injected into the coronary artery produced a slight and very transient increase in CBF (3-8 ml/min); however, there was no associated change in wall thickness during this "control" intervention.

Data are presented as the average ± one standard error. Data obtained after each intervention were compared to the pre-intervention control using the Student's paired t-test.

Results

An example of the alterations in LV end-diastolic wall thickness produced by coronary artery ligation and release is shown in figure 3. During the control period, at a coronary blood flow of 26 ml/min, the end-diastolic wall thickness was 9.7 mm; a gradual increase in wall thickness during systole was recorded. During ischemia, end-diastolic wall thickness fell to 8.8 mm and systolic thinning of the LV wall developed. After one minute of reperfusion (during reactive hyperemia) coronary blood flow was 74 ml/min, the end-diastolic wall thickness had increased to 11.1 mm, and systolic thickening was again present. Fifteen minutes later the coronary blood flow and wall thickness had returned to control levels.

The average values for LV end-diastolic wall thickness and coronary blood flow during occlusion and during reflow in ten experiments are shown in figure 4. The average end-diastolic wall thickness during the control period was 9.0 ± 0.3 mm. In every experiment, thinning of the LV wall (at end diastole) occurred during ischemia; at five minutes of ischemia the end-diastolic wall thickness was 8.1 ± 0.3 mm (P < 0.001). During early reperfusion (labeled reflow in fig. 4) the LV end-diastolic wall thickness increased to values which were significantly greater than the control values; at 30 seconds of reperfusion the end-diastolic wall thickness was 9.6 ± 0.3 mm (P < 0.005) and at one minute the end-diastolic wall thickness was 10.2 ± 0.2 mm (P < 0.001). This "overshoot" in wall thickness was associated with a fivefold increase in coronary blood flow (from 21 ± 3 ml/min to 103 ± 16 ml/min). Five minutes after reperfusion, coronary blood flow did not differ significantly from the control value; however, the end-diastolic wall thickness remained significantly greater than control values (9.4 ± 0.3 mm, P < 0.025). Wall thickness had returned to normal at ten minutes of reperfusion. In seven experiments, coronary blood flow was maintained at the control level during early reperfusion by careful adjustment of the occluder. In the absence of reactive hyperemia, the overshoot in wall thickness during early reperfusion was abolished (labeled partial reflow on fig. 5). After five minutes of partial reflow, the occlusion was fully released; a small but significant increase in coronary blood flow occurred at 30 seconds (P < 0.005) and at one minute (P < 0.01), but the changes in end-diastolic wall thickness during full reflow were not significantly greater than control. In these ischemia-reperfusion experiments, there were no significant changes in heart rate or arterial blood pressure, nor were there changes in LV end-diastolic pressure.

In seven experiments an intracoronary injection of nitroglycerin resulted in a fourfold increase in coronary blood flow (from a control of 21 ± 5 to 76 ± 16 ml/min) which was maximum at 15 seconds after the drug was administered and returned to control by one minute (fig. 6). The average value for end-diastolic wall thickness during the control period was 8.9 ± 0.2 mm. Fifteen seconds after intracoronary nitroglycerin, end-diastolic wall thickness increased to 9.7 ± 0.2 (P < 0.001); wall thickness remained above control values at 30 seconds and at one and two minutes, but was not significantly greater than control at three minutes (9.1 ± 0.1). There were no changes in systemic arterial pressure recorded at 15 seconds following the nitroglycerin. At 30 seconds mean arterial pressure had fallen from a control of 115 ± 5 mm Hg to 102 ± 6 mm Hg (P < 0.01); at one minute arterial pressure was 96 ± 7 mm Hg (P < 0.005); there was a gradual return to control by five
Thus, intracoronary heart rate one minute the nitroglycerin increases in minutes. Heart rate was unchanged at 15 and 30 seconds; at one minute the heart rate had increased from a control of 156 ± 9 beats/min to 167 ± 11 beats/min (P < 0.025); heart rate gradually returned to control by five minutes. Thus, intracoronary nitroglycerin produced significant increases in coronary blood flow and diastolic wall thickness prior to the systemic effects of the drug (prior to the reduction in arterial pressure and the subsequent increase in heart rate).

In six experiments intracoronary papaverine was administered and a pattern which was qualitatively similar to the nitroglycerin experiments was observed (fig. 6).

However, the duration of the augmented coronary blood flow and increased wall thickness appeared greater following papaverine than after nitroglycerin. Coronary blood flow increased from a control of 18 ± 4 ml/min to 99 ± 11 ml/min at 15 seconds and returned to control by ten minutes. Diastolic wall thickness increased from a control of 10.0 ± 0.7 mm to 10.5 ± 0.6 mm (P < 0.05) at 15 seconds; maximum wall thickness (11.3 ± 0.7) occurred at two minutes; wall thickness remained significantly above control for ten minutes (9.9 ± 0.8). There was no change in heart rate or arterial pressure at 15 seconds; at 30 seconds arterial pressure had fallen from a control of 136 ± 7 mm Hg to

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**FIGURE 3.** An example of the changes in left ventricular end-diastolic wall thickness produced by coronary artery ligation (ischemia) and by reperfusion. End-diastolic wall thickness is indicated by the arrows and varies from 9.7 mm (control) to 8.8 mm (ischemia) to 11.1 mm (reactive hyperemia). End-diastolic wall thickness was measured at the peak of the R wave of the electrocardiogram; a large P wave precedes each QRS complex. Compared to the normal pattern of wall motion shown in figure 2, tracings show variable degrees of abnormal thickening. Values for coronary blood flow (CBF) are shown at the top of each panel and the wall thickness calibration (10 mm) is shown by the dark dots in the lower right of each panel.

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**FIGURE 4.** Left ventricular (LV) end-diastolic wall thickness and coronary blood flow data. During coronary ligation (ischemia) wall thickness fell by 10%; following release of the ligature (reflow) a marked reactive hyperemia was associated with an overshoot in wall thickness to values which were greater than control. Data are presented as the average ± SEM.
121 ± 8 (P < 0.01) and heart rate increased from a control of 162 ± 5 beats/min to 175 ± 8 beats/min (P < 0.05). Heart rate and arterial pressure returned to control by two minutes. As in the nitroglycerin studies, the changes in wall thickness (and coronary blood flow) preceded the systemic effects of the papaverine.

The average increase in wall thickness from end diastole to end systole was 32 ± 5% (range 20 to 45%) in the control state (N = 12). Following coronary occlusion there was an abrupt reduction in the extent of thickening and within one minute the LV wall thickness recordings commonly revealed systolic thinning; this abnormal pattern returned to control within ten to fifteen minutes after reperfusion. Intra-coronary nitroglycerin did not alter the fractional increase in wall thickness from end diastole to end systole. Papaverine variably reduced the extent of systolic thickening; in three studies paradoxical systolic thinning was recorded and in the other four experiments systolic thickening at 30 seconds ranged from 4% to 24%. These effects were transient and wall motion returned to control within five minutes.

**Discussion**

Acute alterations in coronary blood flow (produced by coronary occlusion or reactive hyperemia or by phar-
macologic interventions) are associated with changes in the thickness of the LV wall at end diastole. This direct relation between coronary blood flow and diastolic wall thickness most likely represents a relation between intravascular volume (rather than flow) and wall thickness. The time lag between coronary blood flow and wall thickness during reperfusion (figs. 4, 5 and 6) is likely related to flow returning to control levels before vascular engorgement (volume) decreases. In studies relating coronary perfusion pressure to LV chamber compliance, Salisbury et al. noted a similar time lag; they discussed the "erectile" nature of the myocardium and postulated that the volume of blood in the coronary vessels influences myocardial distensibility. Our experimental preparation did not allow measurements of LV compliance, but the thickness data coupled with Salisbury's conclusions suggest that during periods of increased coronary blood flow there is vascular engorgement, followed by an increase in wall thickness and a consequent decrease in LV compliance.

Although it seems likely that engorgement and stiffening of the coronary vessels would lead to a reduction in LV compliance, Templeton et al. were unable to effect a change in elastic or viscous stiffness by altering coronary perfusion (coronary blood flow increased 16-71% above control). The differences in these studies may be due in part to different coronary blood flow alterations; in the present study coronary blood flow increased 500% above control during reactive hyperemia. Our observations in the isolated, isovolumic (balloon in LV) blood perfused dog heart reveal a decrease in wall thickness and an increase in chamber compliance within the first few minutes of global ischemia. At physiologic filling pressures (average 5 mm Hg) changes in compliance are small (1-2 mm Hg), while damaged preparations with unphysiologically high filling pressures may show marked changes in compliance during alterations in coronary blood flow. These different findings in "normal" and "abnormal" hearts may explain the different conclusions of Templeton and Salisbury and others.

LV diastolic wall thickness and LV mass have been related to diastolic chamber compliance in patients with chronic heart disease and in ischemic dog hearts. While calculations of LV mass vary only by about 10% when wall thickness is measured during control and ischemic states, values for LV mass may vary by as much as 30% if a calculation made during ischemia is compared to a calculation made during reactive hyperemia. Such changes in diastolic wall thickness likewise may affect calculation of ventricular preload (end-diastolic stress) and myocardial stiffness constants.

A potential limitation of these methods is the lack of information regarding ventricular volume during the interventions. Our previous experience with this model suggests that segmental ischemia similar to that produced in this study does not result in global LV dysfunction (increased end-diastolic pressure). This is important since generalized ischemia may result in chamber dilatation with subsequent thinning of the wall. On the other hand, a vasodilator might reduce arterial pressure and heart size, and consequently the measured wall thickness would increase. In the present studies, changes in thickness occurred before the systemic effects of the drugs were observed.

Left ventricular wall thickness (with emphasis on systolic thickening) has been measured under a variety of clinical and experimental conditions. In the present study, LV wall thickness increased by an average of 32% from end diastole to end systole. This fractional change in wall thickness is essentially the same value obtained by others in the instrumented (ultrasonic crystals) conscious dog. However, it is greater than the value (10%) found by Goldstein and de Jong who used a harpoon-like device coupled to a mercury in silastic resistance bridge, and it is less than the value (60%) obtained by Hugenholz et al. using angiocardiography. Echocardio graphic measurements of LV wall thickening in man likewise give higher values (average 50%) than those observed in the present study. Excellent correlations exist between the percent increase in wall thickness throughout systole and the overall ventricular performance (in the absence of segmental disease). These correlations provide a firm basis for the use of wall thickness measurements as indices of ventricular performance in clinical echocardiography.

The single epicardial transducer used in the present study offers little advantage over methods which utilize ultrasonic transit time between two implanted miniature crystals except that readily available, clinical ultrasonoscopes and recorders may be used. Our recordings reveal a pattern which is similar to those reported by Sassayama et al. (implanted crystals): both methods allow measurement of wall thickness without damage to intervening tissue; changes in thickness during isovolumic contraction and relaxation are minimal; and the extent of systolic thickening in our studies closely resembles their data. We have found that the small epicardial transducer, sutured directly to the epicardium, produces a cleaner signal and less motion artifact than our clinical transducers which must be held in place with a ring stand apparatus. These methods provide a relatively simple and inexpensive approach to the analysis of regional myocardial function in the experimental animal.

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A New, Noninvasive Technique for Inducing Post-extrasystolic Potentiation during Echocardiography

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SUMMARY Left ventricular function was evaluated in 34 patients with the echocardiogram, and an external mechanical cardiac stimulator was used to induce a ventricular premature contraction (VPC) noninvasively. Extent of post-extrasystolic potentiation (PESP) was determined by comparing systolic dimensional shortening and ejection fraction of the sinus beat preceding the VPC to that of the potentiated beat which followed it. Using this technique, a VPC could be introduced into the cardiac cycle of 30 of the 34 patients, six of whom were free of obvious cardiac disease and 24 of whom had valvular, coronary or myopathic heart disease. The only complication observed was mild breast ecchymosis in a female patient. Systolic dimensional shortening and ejection fraction increased from control values by an average of 21% and 17% respectively, with a range of 0–100%. The degree of PESP was very reproducible in repeat studies and when the same patients were subsequently evaluated during a spontaneously occurring or catheter-induced VPC. This technique can safely and reliably induce post-extrasystolic potentiation during echocardiography and is a potentially important adjunct to the noninvasive evaluation of left ventricular function.

THE AUGMENTATION OF MYOCARDIAL CONTRACTILITY that occurs in the normally conducted beat following a ventricularextrasystole is referred to as post-extrasystolic potentiation (PESP). Evaluation of the effect of PESP on ventricular contraction (determined by ventriculographic study of left ventricular wall motion) has demonstrated that areas of ventricular wall that exhibit absent or diminished motion during regular cardiac cycles often exhibit augmented contraction during the postextrasystolic beat. In patients with coronary artery disease, the degree of regional and global improvement of left ventricular function with PESP (measured by augmentation of axis shortening and ejection fraction) has proven useful in predicting: 1) which areas of myocardium supplied by stenosed coronary arteries are reversibly rather than irreversibly damaged, and hence suitable for myocardial revascularization; and 2) which patients with depressed ventricular function have the greatest amount of contractile reserve, and thus are more likely to tolerate myocardial revascularization. The effects of PESP in other forms of heart disease have also been studied by ventriculography in our laboratory, but no firm conclusions as to the clinical value can be made at present.

If a technique were available to measure the effects of PESP on left ventricular function noninvasively, it could complement — and hopefully replace — similar ventriculographic studies in some patients. Such a technique would have to combine noninvasive methods both for evaluating left ventricular function and introducing ventricular premature contractions safely into the cardiac cycle. At present, echocardiography is one of the most widely used noninvasive techniques for evaluating left ventricular function, but until recently no noninvasive method for consistently and safely eliciting ventricular premature contractions has been available. In 1976, Zoll et al. reported studies utilizing an external mechanical stimulator capable of introducing ventricular beats into the cardiac cycle. They used the device as an external emergency pacemaker, but in the present report it was employed to induce ventricular premature contractions, thereby allowing evaluation of the effects of PESP on left ventricular function. Specifically, in these initial studies, the effects of PESP were determined during echocardiography by measuring induced changes in systolic dimensional shortening and ejection fraction. We were concerned not only with whether or not PESP could be induced, but also with the safety of the device and its reliability in

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