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EXPERIMENTAL STUDIES

Comparison of Early Systolic and Early Diastolic Regional Function During Regional Ischemia in a Chronically Instrumented Canine Model

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Depressed left ventricular function during the early part (first third) of both systole and diastole in the resting state have been reported to be sensitive indicators of coronary artery disease in patients with normal global function at rest. To evaluate the possible mechanisms of these findings, 11 dogs were chronically instrumented with segmental function sonomicrometers in the left circumflex and left anterior descending coronary artery distribution, circumflex coronary flow probes and cuff occluders, aortic flow probes and ventricular pressure transducers. Percent segmental function during the first third of systole and diastole was measured in the control state and with graded circumflex artery flow reductions. Significant decreases in early systolic function with ischemia in the circumflex artery distribution were partially offset by compensatory augmented shortening in the left anterior descending artery distribution. With ischemia in the circumflex distribution, there was prolonged contraction into diastole manifested as impaired relaxation. Simultaneously, in the left anterior descending artery distribution, there was minimal compensatory enhanced relaxation.

These results suggest that early systolic dysfunction in ischemic segments may be offset by enhanced function in nonischemic segments, rendering minimal, if any, change in global systolic function. Early diastolic dysfunction in ischemic segments exceeds compensatory changes in nonischemic areas by two-to four-fold. Hence, early diastolic functional indexes may be more sensitive indicators of ischemia at rest than early systolic functional indexes.

Several previous reports (1,2) suggested that rest ejection fraction determinations in the early (first third) period of systole predict with adequate sensitivity and specificity patients with significant coronary disease. Subsequently, this finding was disputed by two studies in similar numbers of patients. Denenberg et al. (4) found no difference between the ventricular emptying curves of normal subjects and patients with coronary disease, whether volumes were measured angiographically or with equilibrium gated radionuclide ventriculography. Thus, early ejection phase indexes, especially in patients with normal global ejection fraction, may be insensitive as indicators of coronary artery disease despite earlier reports.

Incomplete diastolic relaxation has been described in experimental animal preparations (5) that have been subjected either to hypoxia or to ischemia followed by reperfusion or reoxygenation. This observation led to investigations of ventricular performance during early diastole in human subjects. Bonow et al. (6) found an abnormal left ventricular filling rate in 86% of patients with coronary disease and a normal rest ejection fraction. Reduto et al. (7) found that a significant number of patients with coronary disease and a normal rest ejection fraction had a depressed filling fraction (percent of filling during the first third of diastole).

Thus, previous reports suggest that both early systolic and early diastolic dysfunction occurs at rest in patients with coronary artery disease. However, the temporal sequence and relative importance of early systolic versus early diastolic dysfunction and the mechanisms involved have not been determined. In an attempt to understand the physiologic mechanisms involved in this important clinical prob-

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lem, we developed a chronically instrumented canine preparation to study regional early systolic and diastolic function during graded circumflex flow reductions.

Methods

Experimental preparation. Eleven conditioned mongrel dogs weighing 22 to 32 kg underwent a sterile left thoracotomy under general anesthesia for implantation of transducers. The aortic root was mobilized and an electromagnetic flow probe (Zepeda Instruments) was placed at the base of the ascending aorta. The left circumflex coronary artery was dissected and fitted with an electromagnetic coronary flow probe (Zepeda Instruments) and two hydraulic cuff occluders. A Konigsburg P22 micromanometer and polyethylene catheter were inserted into the left ventricular chamber through a stab wound in the left ventricular apex. One pair of piezo-electric sonomicrometer crystals was implanted midwall in the ventricle in the hoop direction in the circumflex coronary artery distribution, and a second pair was implanted in the left anterior descending artery distribution. Sonomicrometer crystals were also implanted on the subendocardium and epicardium in the circumflex artery distribution and positioned at a minimal separation distance for measuring instantaneous wall thickness in the circumflex artery distribution. Left ventricular radius crystals were inserted through a stab wound to the subendocardium at the level of the origin of the first diagonal branch of the left anterior descending artery and the origin of the posterior descending coronary arteries. Atrial pacing wires were sutured onto the right atrial appendage. At closure, the wires and tubing were tunneled to the dorsal chest and exited from the skin. The chest was closed, air and fluid were evacuated from it and the dog was allowed to recover for 7 to 10 days.

Measurements during segmental ischemia. The dogs were trained to lie quietly on the right side for experiments. Data were recorded on an Electronics for Medicine VR-16 recorder. Phasic aortic flow immediately above the aortic valve was used to identify onset and end of ventricular ejection. Zero baseline for the coronary electromagnetic flowmeter was verified by brief (10 seconds) total occlusion of the circumflex artery, before and after each phase of data collection and during periods of stable ischemia. Graded circumflex coronary blood flow reductions were produced by applying constant air pressure to the hydraulic occluder through a regulator system and monitoring the change in flow recorded by the electromagnetic flowmeter.

Ultrasonic crystal segmental shortening measurements were made with a Norland sonomicrometer. The piezoelectric crystals were pulsed at 5 MHz frequency, with a theoretical resolution of 0.01 mm. Experimental measurements were referenced to the distance between each pair of crystals at the onset of ejection for each beat.

During data collection, atrial pacing was initiated at a heart rate 10% greater than the rest heart rate. Control data were taken for 30 seconds and included aortic flow, coronary flow, circumflex distribution segmental shortening, left anterior descending distribution segmental shortening, circumflex distribution wall thickness, left ventricular radius and left ventricular pressure. A partial occlusion was then produced to reduce circumflex flow to approximately 25, 50 or 75% of the level at rest. A stable flow reduction was produced in 30 seconds and maintained for an additional 30 to 120 seconds while left ventricular function data with this flow reduction were recorded.

After flow reduction data were obtained, the occlusion was released and the animal was allowed to recover for a minimal period of 10 minutes. After segmental shortening and coronary flow returned to baseline, a second stenosis was produced to cause a different level of flow reduction and data were recorded again. Each animal was studied daily for approximately 10 days with no more than three levels of flow reduction. Data collection was terminated when the transducers failed or when coronary blood flow failed to show a normal hyperemic response to a 10 second total occlusion. All animals had postmortem examinations to verify depths and orientation of sonomicrometer crystals. Data obtained from malpositioned sonomicrometers were excluded. A total of seven dogs had transducer positions acceptable for data interpretation.

Analysis of data. Continuous recordings on Electronics for Medicine paper for each experiment were entered into a Digital Equipment Corporation VAX-11/780 computer with a Tectronics digitizing tablet and graphics terminal. For each flow level, a group of three consecutive beats was selected when noise and motion artifacts were minimal. The Q wave of the electrocardiogram was used to indicate the start of each cardiac cycle and determine the heart rate for the complete cycle. The middle beat was traced and digitized at 10 ms intervals. Appropriate calibration factors, flow levels and timing of ejection were also entered for each beat analyzed. Segmental shortening at the time of the first third of systole was calculated as percent change from the absolute separation distance of the two crystals at the onset of ejection. Segmental relaxation at the first third of diastole was defined as the percent change from the absolute crystal separation at end ejection. The ejection period was defined as the period of contraction delimited by positive ascending aortic flow.

Experiments were classified into three groups: 1) ischemia with circumflex flow less than 33% of control level, 2) ischemia with flow between 33 and 66% of control level and 3) ischemia with flow equal to or greater than 66% of control level. Within each group, data for segmental shortening were tabulated and compared using paired t test analysis. Data entered into the computer were also graphically displayed and replotted to superimpose recordings during

ischemia and nonischemic control cycles for qualitative comparison.

Results

Segmental ischemia in circumflex artery distribution (Fig. 1). The maximal extent of shortening in the left anterior descending coronary artery segment and in the circumflex coronary artery segment occurred during the period of positive aortic flow. With circumflex flow reduced to 33% of the control level, shortening in the circumflex segment was slightly diminished. Toward the end of ejection, systolic bulging occurred followed by continued contraction after ejection was over. Circumflex wall thickness was also decreased at end-diastole and end-systole. This suggests that wall stress in the circumflex distribution is increased during this period of time. Segmental shortening in the left anterior descending distribution was enhanced during circumflex ischemia.

Percent segmental shortening during circumflex ischemia. To quantitatively and qualitatively evaluate these changes, percent shortening in the left anterior descending distribution and circumflex distribution were compared (Fig. 2). In this particular preparation, circumflex flow was reduced to 54% of the control value. With circumflex ischemia, systolic function was augmented in the left anterior descending distribution both at end-systole and during the first third of systole. During the first third of diastole, however, the relaxation in the left anterior descending distribution was only slightly augmented during circumflex ischemia compared with the control value. In the circumflex distribution, modest systolic dysfunction developed during the first third of systole in an amount almost equal and opposite to the increase seen in the left anterior descending distribution. However, during the first third of diastole, shortening appeared to continue and, in fact, exceeded that achieved during ejection. Therefore, contraction is prolonged with ischemia (relaxation is delayed) in the circumflex distribution, and rather than occurrence of relaxation, there is active persistent shortening during the first third of diastole in the circumflex distribution.

Segmental shortening changes related to percent decrease in circumflex flow. Data for all the experiments were grouped according to the percent decrease in circumflex flow during ischemia. Figure 3 depicts changes in segmental shortening during the first third of systole. In 17 experiments with flow reductions to 0 to 33% of control

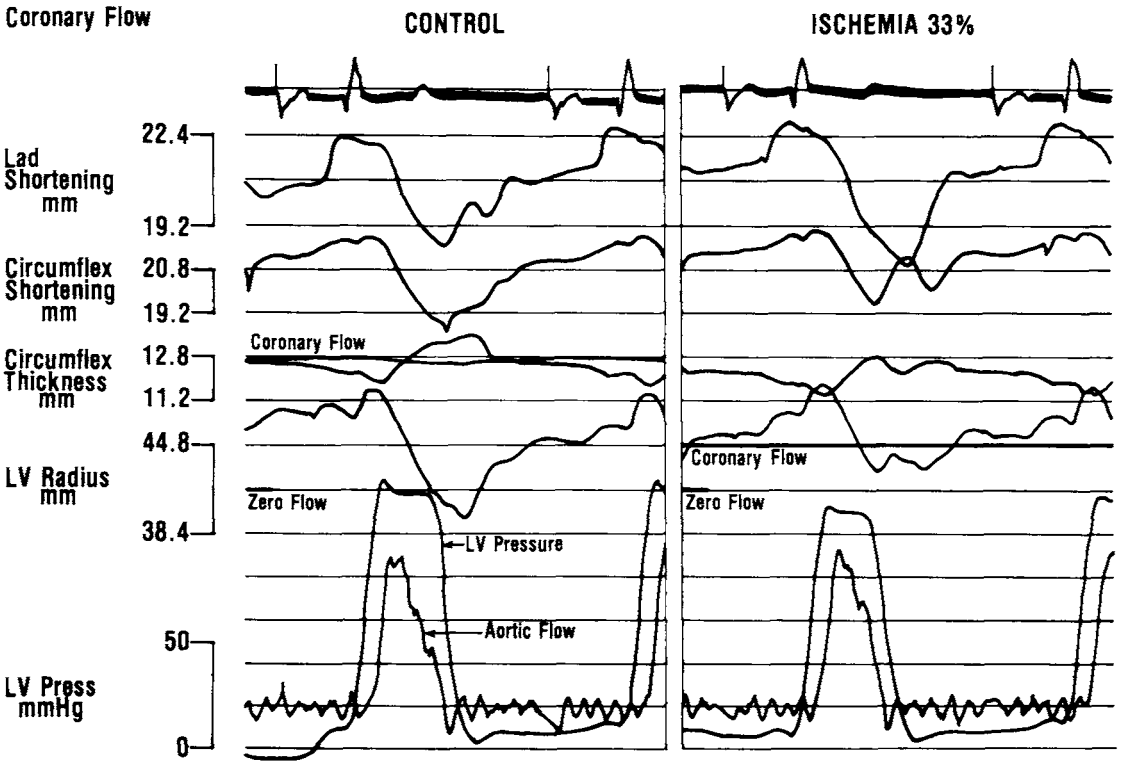

Figure 1. Physiologic traces obtained during the control state **(left)** and with circumflex coronary flow reduced to 33% of control level **(right).** From **top to bottom,** the panels demonstrate an electrocardiogram with atrial pacing artifact, left anterior descending (Lad) segmental shortening, circumflex segmental shortening, coronary blood flow, circumflex segmental thickness, left ventricular (LV) radius, left ventricular pressure and phasic aortic flow.

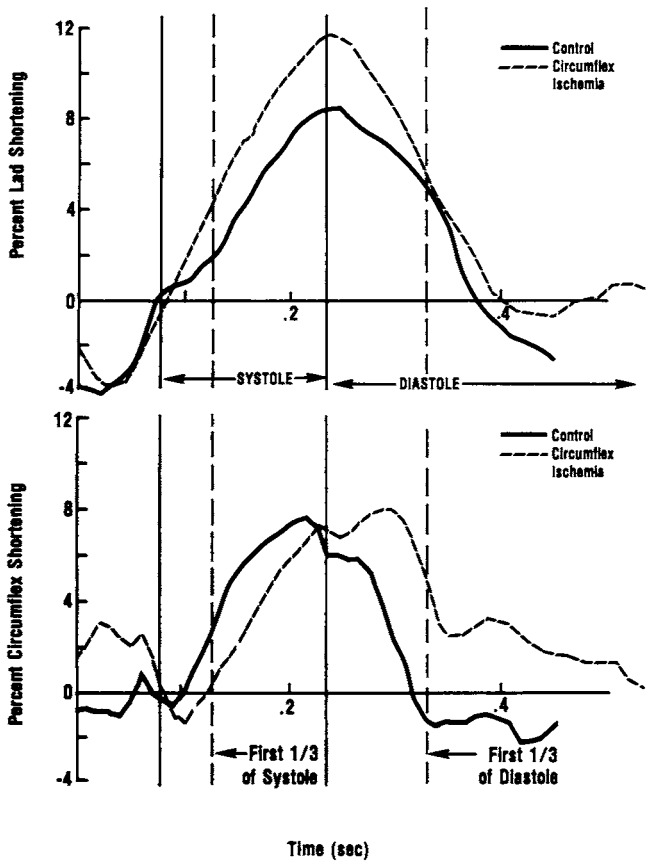

Figure 2. Top, Percent segmental shortening in the left anterior descending artery distribution is demonstrated. The **solid lines** show shortening during control period and the **dotted lines** demonstrate shortening during circumflex artery ischemia. The **dotted vertical lines** indicate the first third of systole and the first third of diastole. **Bottom,** Percent circumflex shortening during control and ischemic periods.

flow, percent shortening in the left anterior descending distribution during the first third of systole increased from 2.0 ± 1.4 to 3.8 ± 1.8% (probability [p] <0.001). In the circumflex distribution, however, segmental shortening during the first third of systole decreased from 3.0 ± 1.8 to 0.38 ± 1.3% (p<0.001). These changes are similar in magnitude but opposite in direction. With flow reductions to 33 to 66% of control flow, shortening in the left anterior descending distribution during the first third of systole increased from 2.4 ± 1.3 to 3.3 ± 1.3% (p<0.001). In the circumflex distribution for the same flow reduction, shortening decreased from 3.2 ± 1.6 to 1.3 ± 1.4% (p<0.001). Again, the decrease in function in the circumflex distribution is offset by an increase in function in the left anterior descending distribution. For coronary flow greater than 66% of the control flow, the differences in function, although occasionally dramatic were not constantly significant.

Changes in segmental relaxation during the first third of diastole (Fig. 4). Percent relaxation during the first third of diastole was referenced to end-ejection segment length and compared in the left anterior descending and circumflex distributions. Continued contraction after ejection would result in negative percent relaxation. With flow reduction to less than 33% of control flow in the circumflex distribution, percent diastolic relaxation decreased from 5.3 ± 2.6 to −2.4 ± 2.8%. Thus, during early diastole shortening rather than relaxation was occurring. Conversely, relaxation in the left anterior descending distribution was slightly augmented, although not nearly to the same degree. For flow levels at 33 to 66% of control, diastolic relaxation in the circumflex distribution decreased from 3.9 ± 3.5 to −0.32 ± 2.9% (p<0.001), compared with increases in relaxation

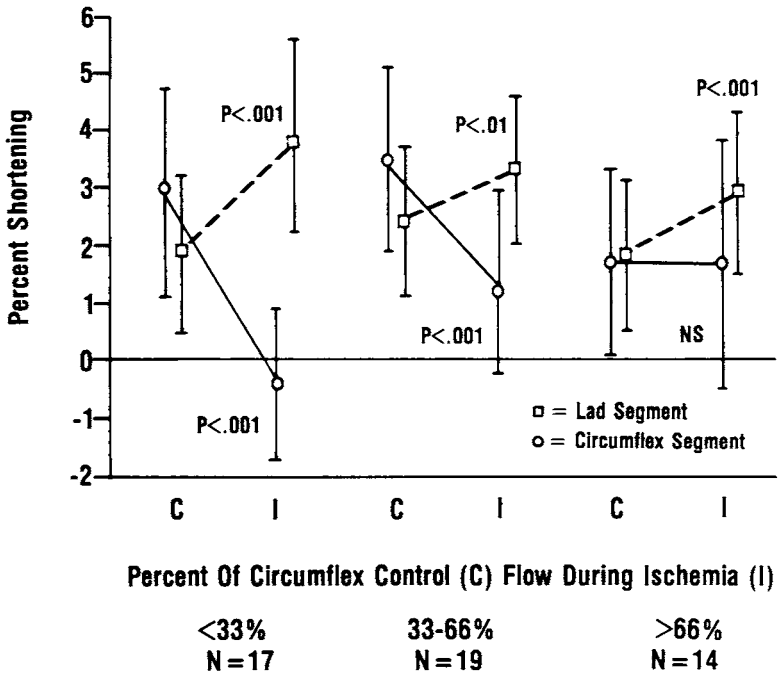

Figure 3. Percent segmental shortening during the first third of systole in the circumflex and left anterior descending coronary artery distributions during three stages of circumflex artery ischemia.

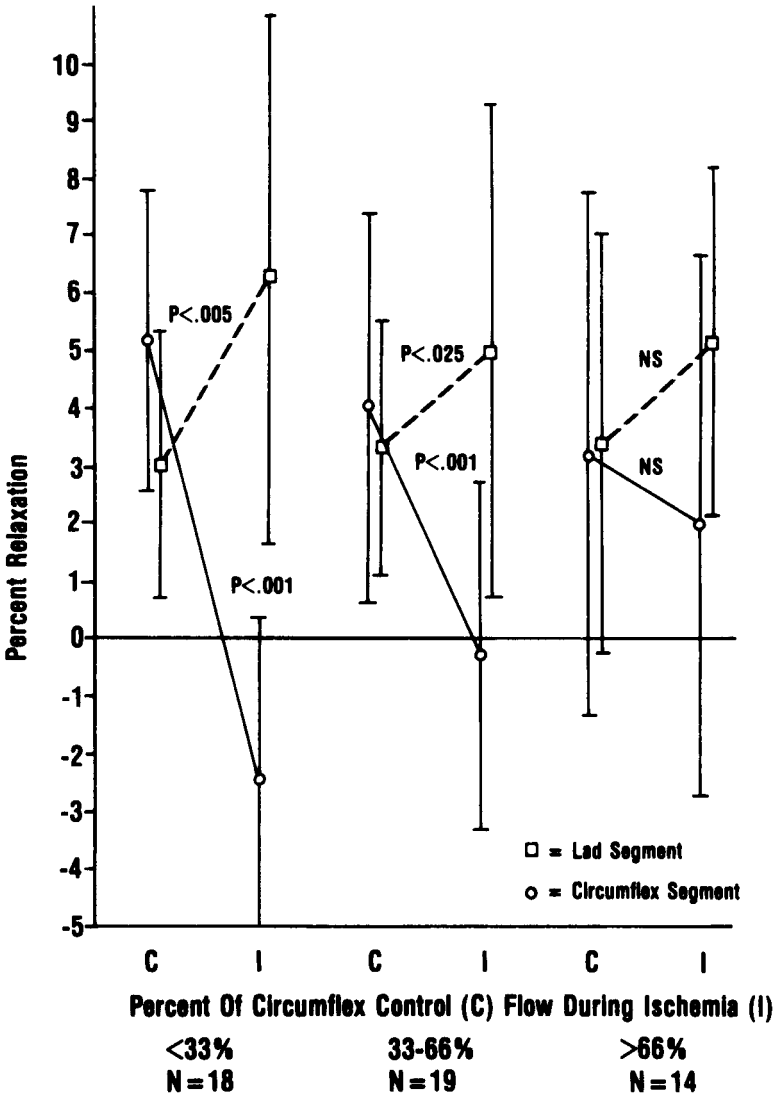

Figure 4. Percent segmental relaxation during the first third of diastole during three stages of circumflex artery ischemia. Relaxation is referenced to segment length at end ejection and depicted by **circles** for the circumflex segment and **boxes** for the left anterior descending segment.

in the left anterior descending distribution of 3.4 ± 2.2 to 5.0 ± 4.4% ($p<0.025$). Again, for flow reductions to 66% of control flow, minimal changes in function occurred.

Early systolic versus early diastolic changes in segmental shortening. With reduction in circumflex blood flow from control values to between 0 and 66% of control flow, the percent decrease in segmental shortening in the circumflex distribution was −88 ± 52% compared with the compensatory increase in the left anterior descending distribution of 102 ± 127%. The relative difference is 14%, which is not significant (Fig. 5). The early diastolic change in the circumflex distribution was twice as great as the early diastolic changes in relaxation in the left anterior descending distribution. The absolute mean change was 76%, which is highly significant.

Thus, acute regional ischemia may produce regional early systolic dysfunction that is offset, in part, by hyperfunction in the nonischemic area. These counterbalancing changes are present but to a much smaller degree during early diastole.

Discussion

In a chronically instrumented canine preparation, we demonstrated that early (first third) systolic regional dysfunction exists in the ischemic segment. However, in the nonischemic zone, early systolic shortening is augmented. These changes are similar in magnitude and proportional to the severity of ischemia induced. We also demonstrated that early (first third) diastolic dysfunction exists in the ischemic segment. Relaxation is slightly augmented in the nonischemic segment; however, there is a two- to four-fold difference in early diastolic function comparing ischemic with nonischemic zones.

Pressure-diameter relation during diastolic relaxation. Relaxation in the intact ventricle is a complex process affected by both metabolic and hemodynamic factors. Early ventricular diastolic relaxation is thought to be an energy-dependent process. According to Sabbah and Stein (8), the pressure-diameter relation during the rapid phase

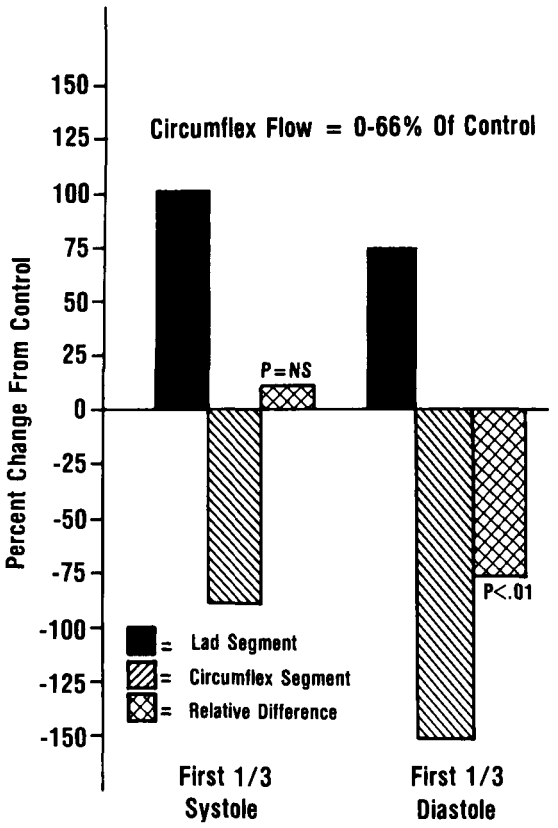

Figure 5. Percent change in segmental function from control with graded circumflex occlusion during early systole and diastole. Lad = left anterior descending.

of ventricular filling suggests that rapid filling occurs secondary to active left ventricular dilation, creating a negative pressure gradient across the mitral valve. During end-diastole, however, with atrial contraction, the pressure-diameter relation suggests that the left ventricle undergoes passive distension.

This concept is supported by the work of Stein et al. (9), who measured intramyocardial pressures in the subendocardium and subepicardium during diastole in the beating and arrested heart. Classic mechanics theory predicts that the intramyocardial pressure in the epicardium would be less than that in the endocardium. However, in the beating heart, during diastole, epicardial pressure exceeded endocardial pressure which, in turn, was higher than the intracavitary pressure. This observation suggests that coronary pressure, in the absence of restrictive stenosis, provides structural support of the left ventricular wall during the early phase of ventricular filling. In other words, the myocardium is inflated in a manner similar to inflation of the space between two tethered concentric balloons. Thus, during early diastole, rapid pressurization of the ventricular wall would serve to distend the ventricle creating an "erectile" effect. Early rapid filling may be partly due to rapid filling of the coronary bed distending the ventricular wall.

Role of decreased wall distension secondary to limited inflow. One would expect that the rapid increase in left ventricular radius during early ventricular filling would be obscured by restricted coronary inflow secondary to a coronary stenosis. Figure 1 illustrates this concept; the left ventricular radius shows a sharp upswing during early diastole with normal circumflex artery flow. With circumflex artery stenosis, however, this sharp upswing is markedly attenuated, suggesting that rapid relaxation (ventricular dilation) did not occur.

Both coronary perfusion pressure and coronary flow have been shown to produce a rather dramatic effect on instantaneous wall thickness (10–12). Because end-diastolic wall thickness is directly correlated with coronary flow, instantaneous wall stress would be inversely proportional to wall thickness (and coronary flow), independent of metabolic derangement. We have confirmed these findings in dogs by the discovery that peak instantaneous wall stress was inversely related to percent segmental shortening. Thus, partial coronary stenosis was associated with wall thinning and decreased segmental shortening, while hyperemia caused end-diastolic wall thickening, decreased wall stress and augmented segmental shortening (13).

It would appear, therefore, that ventricular wall distension secondary to coronary pressurization and actual blood volume within the coronary vasculature plays a significant role in both active shortening and active relaxation. Intracoronary pressurization or flow may have a mechanical effect on early diastolic filling.

Both calcium fluxes and high energy phosphate concentrations are affected by hypoxia in papillary muscle preparations. Increased loading, increased calcium concentration, paired pacing and hypoxia also prolong contraction (14,15). Prolongation of contraction appears to occur in the intact preparation with ischemia, as demonstrated by left circumflex artery shortening in Figures 1 and 2.

Wiegner et al. (16) coupled a papillary muscle preparation to a computer-controlled tension generator, allowing the computer-developed tension to mimic a normally contracting segment while the papillary muscle itself was made hypoxic to various degrees. This would be analogous in our preparation to a partial circumflex occlusion causing dysfunction in a circumflex segment, which in turn was loaded by a normally contracting left anterior descending segment. The shortening curve demonstrated in the right panel of Figure 1 (in the circumflex distribution) is virtually identical to that predicted by the computer-papillary muscle preparation reported by Wiegner et al. (16). Thus, prolonged contraction in ischemic areas caused by increased loading and hypoxia impedes left ventricular filling during early diastole. This effect is additive to that caused by decreased wall distension secondary to limited coronary inflow.

Causes of compensatory increased systolic function in nonischemic zone. Yet to be explained, however, is the

increase in function seen during systole in the nonischemic zone. Certainly, the afterload found in segments within the left ventricular wall circumference is directly related to left ventricular pressure and radius and inversely related to wall thickness. In any given segment in the left ventricular midwall, circumflex shortening and tension development will serve as an additional load on the left anterior descending regional segments. The converse would obviously also be true. Hence, when shortening is impaired, as is tension development in an ischemic zone, the nonischemic segment may be effectively unloaded. This internal unloading would enable the normal nonischemic segment to shorten to a greater degree than it would under the control situation. This effect is also nicely demonstrated in Figures 2 and 3. The left anterior descending segmental shortening increases during the first third of systole by an amount almost equal to the decreased shortening seen in the circumflex distribution.

The importance of compensatory changes in regional shortening is well illustrated in acute myocardial infarction. Enhanced function is seen in myocardium contralateral to the infarcted area (17). With successful early coronary reperfusion, improvement in regional function occurs in the infarct zone and hyperfunction in the contralateral zone diminishes. Thus, although apparent salvage of jeopardized myocardium occurs, global ejection fraction may not change.

Clinical implications. Although our experiments involving acute episodes of ischemia may not be directly comparable with clinical findings in chronic ischemia, they suggest that global ischemic dysfunction may be more pronounced in early diastole than early systole. Global indexes of left ventricular function during systole may not be sensitive enough to detect minor regional dysfunction secondary to enhanced function in nonischemic areas. Our results suggest that with a severe stenosis of one or two coronary vessels, regional dysfunction may exist during the first third of systole at rest. However, this dysfunction may be offset by increased shortening in a nonischemic zone. In the presence of severe stenoses of three major vessels, however, there would be no possible compensation and, hence, one would expect depressed global function in the first third of systole. If the early reports of depressed ejection fraction during the first third of systole were obtained in a patient population with predominantly severe three vessel disease and the later series included predominantly single or double vessel disease, the discrepancy in first third ejection fraction sensitivity and specificity could be explained (1–4). Regional dysfunction exists during the first third of systole in ischemic segments and, hence, examination of early regional systolic function should be a more sensitive technique than global techniques reported for clinical use (1,2). Regional diastolic dysfunction, however, is only minimally compensated for by uninvolved segments. Early diastolic global functional indexes should be more sensitive than early systolic global functional indexes as indicators of ischemia.

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