

Mechanisms of improving regional and global ventricular function by preload alterations during acute ischemia in the canine left ventricle

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ABSTRACT We examined the influence of left ventricular end-diastolic pressure (LVEDP) on the mechanical interaction between ischemic and nonischemic areas during acute myocardial ischemia. Circumferentially oriented ultrasonic segment gauges were implanted in the midwall of the anterior apex and posterior apex of the left ventricle in seven anesthetized dogs. Stroke volume was measured with a flow probe around the ascending aorta in five of these animals. We varied LVEDP with vena caval occlusion and dextran infusions to three matched levels (7, 12, and 19 mm Hg) before and 30 min after complete occlusion of the mid left anterior descending coronary artery. With acute ischemia, the anterior apex or ischemic zone demonstrated marked segmental lengthening during isovolumetric systole (end-diastole to aortic valve opening) and akinesis during the ejection phase (aortic valve opening to closure). In the posterior apex or nonischemic area, isovolumetric shortening increased and ejection phase shortening decreased during acute ischemia when compared with those under control conditions at the same LVEDP. Thus, a portion of the shortening generated by the nonischemic area was expended in stretching the ischemic zone during isovolumetric systole, thereby reducing the amount of ejection phase shortening. As LVEDP was increased, there was a parallel decrease in both the amount of isovolumetric lengthening in the ischemic zone and the isovolumetric shortening in the nonischemic area. As a result, acute ischemia produced less of a reduction in ejection phase shortening in the nonischemic area and in stroke volume at high as compared with low LVEDP. We conclude that the ischemic zone imposes a mechanical disadvantage on the nonischemic area, the magnitude of which is directly proportional to the amount of isovolumetric lengthening or bulge in the ischemic zone. An increase in LVEDP during acute ischemia improves regional and global ventricular function by both the Frank-Starling mechanism in the nonischemic (but not the ischemic) area and by reducing the mechanical disadvantage that the ischemic zone imposes on the nonischemic area.

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IN PATIENTS with acute myocardial infarction, therapeutic alteration of the left ventricular filling pressure to an "optimal" level improves stroke volume while minimizing adverse hemodynamic effects.¹⁻⁶ Although much of this improvement is due to the Frank-Starling mechanism in nonischemic areas, additional alterations in regional function may be involved. Accordingly, this study was designed to examine the effects of preload manipulation during acute ischemia on

regional function in the ischemic zone and on the mechanical interaction between ischemic and nonischemic areas.

Recently, we postulated that a mechanical interaction between ischemic and nonischemic areas occurs during acute myocardial ischemia.⁷ After occlusion of a coronary artery, paradoxical lengthening during isovolumetric systole was observed in the ischemic zone. In nonischemic areas, end-diastolic segmental length increased due to the increase in left ventricular end-diastolic pressure (LVEDP), and total segmental shortening (from end-diastole to aortic valve closure) increased due to the Frank-Starling mechanism. However, all of the increase in nonischemic area shortening occurred during isovolumetric systole (from end-diastole to aortic valve opening), and developed coincident with the development of paradoxical isovo-

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lumetric lengthening in the ischemic zone. Therefore, we suggested that a significant portion of the shortening generated by the nonischemic segments was expended in stretching the ischemic zone during isovolumetric systole. Although there was hyperfunction of nonischemic areas, there was no significant "compensatory" increase in nonischemic area shortening during the ejection phase (aortic valve opening to closure).

The current study was designed to more completely explore the mechanical interaction between ischemic and nonischemic areas and its consequences. First, we hypothesized that during acute ischemia, the ischemic zone imposes a mechanical disadvantage on the nonischemic areas, due to the regional intraventricular unloading effect during isovolumetric systole. However, this mechanical disadvantage may be masked by the increased effect of the Frank-Starling mechanism in nonischemic areas. Thus, we proposed to examine the effects of acute ischemia under conditions in which LVEDP and end-diastolic segmental length of nonischemic areas do not change. Under these conditions, we predicted that the shortening expended by the nonischemic areas to stretch the ischemic zone during isovolumetric systole would result in an actual decrease in ejection phase shortening by nonischemic areas.

Second, we hypothesized that the magnitude of the mechanical disadvantage imposed by the ischemic zone is directly proportional to the amount of its paradoxical isovolumetric lengthening, which in turn is inversely proportional to its stiffness. We postulated that when LVEDP is increased during acute ischemia, the ischemic segment is placed at a steeper (stiffer) position on its passive pressure-length curve, and thus offers greater resistance to passive (paradoxical) isovolumetric lengthening. If less shortening is expended by the nonischemic areas in stretching the ischemic zone during isovolumetric systole, the reduction in nonischemic area ejection phase shortening with acute ischemia would be less severe. This reduction in the mechanical disadvantage imposed by the ischemic zone on nonischemic areas would be an additional mechanism by which an increase in LVEDP to an "optimal" level improves regional and global ventricular function during acute myocardial ischemia.

Methods

Instrumentation. Seven mongrel dogs of both sexes and weighing between 20 and 33 kg were anesthetized with intravenous pentobarbital (25 mg/kg) and intubated. Respiration was supported with a Harvard respirator. A midline sternotomy and bilateral fifth interspace thoracotomy were performed in each and the heart exposed and supported in a pericardial cradle. An inflatable occlusion cuff was placed around the inferior vena cava and a large-bore cannula was placed in a femoral vein for

administration of intravenous fluids. A fluid-filled pigtail catheter, attached to a Statham P23 DB transducer, was placed into the left ventricle through a femoral artery. The zero level was established at the level of the right atrium. A Konigsberg P20 high-fidelity micromanometer catheter was placed into the left ventricle through a stab wound in the apex and secured in place with a purse-string suture. After the left ventricular pressure waveform from the micromanometer was matched to that of the fluid-filled catheter, the fluid-filled catheter was withdrawn into the ascending aorta just above the aortic valve for measurement of central aortic pressure. A limb-lead electrocardiogram was recorded throughout.

The mid left anterior descending coronary artery was isolated just distal to the first or second acute diagonal branch and dissected free over a 3 to 5 mm course. Any large visible collateral vessels from the right coronary or left circumflex systems supplying the anterior wall were ligated near the ventricular apex.

Regional ventricular function was measured with ultrasonic segmental length gauges comprised of two 5 MHz piezoelectric crystals (2 mm diameter). The crystals were implanted approximately 1 cm apart through small stab wounds into the midwall of the left ventricle (4 to 6 mm below the epicardial surface) and oriented in the circumferential direction of the midwall hoop axis fibers.⁸ One gauge was placed in the anterior apex within the perfusion bed of the mid left anterior descending coronary artery so it would be within the ischemic zone after acute coronary artery occlusion. This gauge was placed at a level approximately one-third of the distance from the apical dimple to the bifurcation of the left coronary artery along an external (epicardial) long axis. The second midwall segmental length gauge was placed in the posterior apex in a region that would remain nonischemic. This gauge was approximately one-third to one-half of the distance from the apex to the inferior pulmonary veins along the posterior wall. The circumferential orientation and midwall depth of the gauges were confirmed on postmortem examination.

In five of the seven animals, a Biotronix electromagnetic flow probe attached to an electromagnetic flowmeter (Biotronix Model BL620) was placed around the ascending aorta. The aortic flow signal was integrated on-line such that the area under the flow curve was proportional to the stroke volume. The aortic flow curve was calibrated over several cardiac cycles by determining the simultaneous stroke volume. Cardiac output was determined with thermodilution techniques (Instrumentation Laboratory Cardiac Output System 601) by the use of a No. 7F balloon-tipped catheter (Instrumentation Laboratory Model 44166) introduced through the right jugular vein, through the right heart, and placed into the pulmonary artery. Cardiac output was divided by heart rate to obtain the average stroke volume, which was compared with the average area from the integrated aortic flow curve over the same cardiac cycles. At least three cardiac output and calibration determinations were made and the results were averaged.

The electrocardiogram, central aortic pressure, left ventricular pressure, ultrasonic segmental length signals from the anterior and posterior apices, and the central aortic flow signal (in five animals) were recorded on an eight-channel forced-ink polygraph (Brush Clevite) at a paper speed of 200 mm/sec (figure 1) and on FM magnetic tape for subsequent playback. All measurements were obtained under steady-state conditions with respiration suspended at end-expiration; at least 20 consecutive beats were recorded.

Experimental protocol. LVEDP was varied by a combination of inferior vena caval occlusion by inflatable cuff and infusion of 6% dextran dissolved in 0.9% saline. Control measurements were obtained under steady-state conditions at three

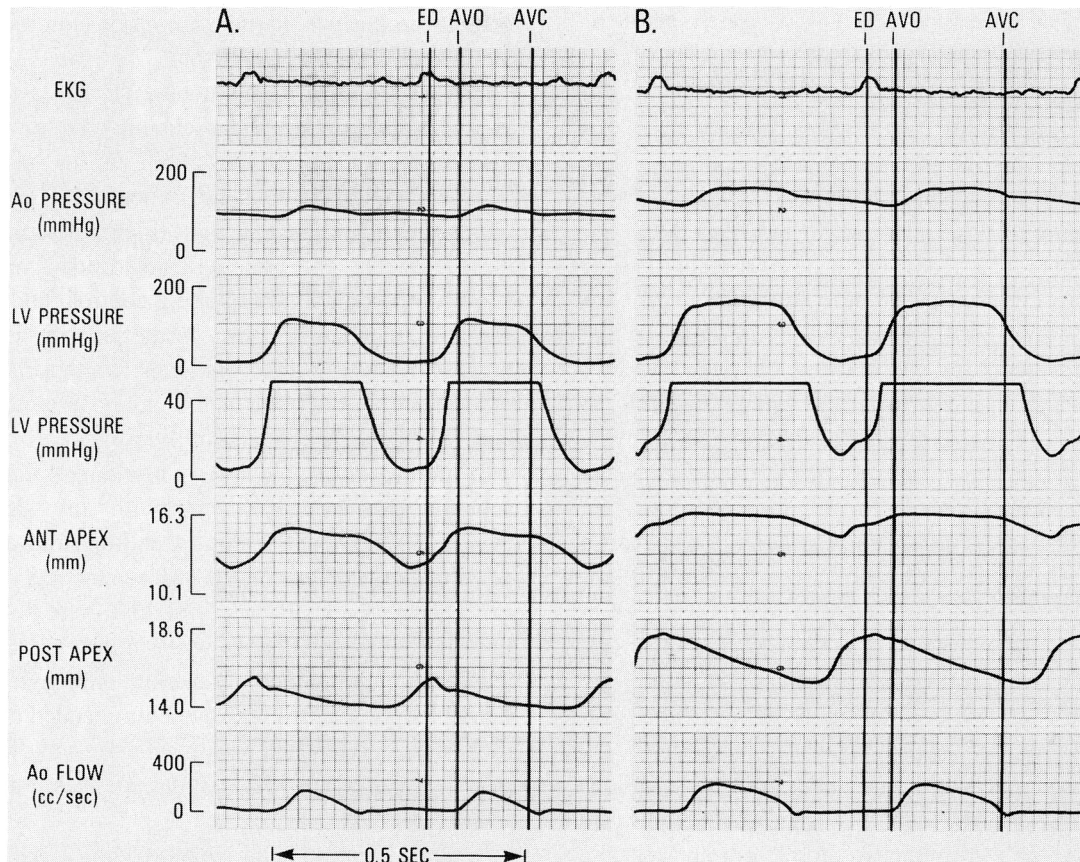


FIGURE 1. A typical tracing obtained after 30 min of ischemia including the electrocardiogram (EKG), central aortic (Ao) pressure, left ventricular (LV) pressure low and high gain, segmental length signals from the anterior (ANT) and posterior (POST) apices, and the aortic flow signal (Ao FLOW). The time scale is at the bottom. The vertical lines denote the time of end-diastole (ED), aortic valve opening (AVO), and aortic valve closure (AVC). A, Low LVEDP; B, high LVEDP. Note in A that the anterior apex or ischemic zone demonstrates marked segmental lengthening during isovolumetric systole (from ED to AVO) and akinesis during the ejection phase (from AVO to AVC). The posterior apex or nonischemic area demonstrates a significant amount of shortening during early isovolumetric systole. When LVEDP is increased (from A to B), there is a significant decrease in the amount of isovolumetric lengthening or bulge in the ischemic zone and a parallel decrease in the amount of isovolumetric shortening in the nonischemic area. Although an increase in LVEDP increased ejection phase shortening in the nonischemic area, there is no improvement in the akinesis of the ischemic zone during the ejection phase.

levels of LVEDP (7, 12, and 19 mm Hg). After a recovery period of at least 30 min, acute anterior wall ischemia was induced by occluding the mid left anterior descending coronary artery with a Schwartz clamp. Although the majority of changes in regional function and hemodynamics occurred within the first 5 min, the animals were allowed to stabilize for at least 30 min after occlusion of the coronary artery to ensure that nearly steady-state conditions had been achieved. Repeat measurements then were made during ischemia at the three levels of LVEDP, which were chosen to closely simulate those under control conditions.

Data analysis. The aortic and left ventricular pressures and anterior and posterior apical lengths and aortic flow signals were all played back from FM tape and converted from analog to digital data at 5 msec intervals. Data from 20 consecutive cardiac cycles were averaged. Thus, in each animal, averaged data were obtained at the same three levels of LVEDP (7, 12, and 19 mm Hg) under control conditions and after 30 min of ischemia.

Regional segmental lengths were determined at three times during the cardiac cycle: at end-diastole, at aortic valve opening, and at aortic valve closure (figure 1). End-diastole was

determined from the high-gain left ventricular pressure tracing by the trough following atrial contraction. If this was not obvious, the peak of the R wave on the electrocardiogram was used. In the five animals with aortic flow probes, the time of zero crossover of the aortic flow tracing was used to time aortic valve opening and closure (figure 1). In the other two animals, the central aortic pressures at the onset of ejection and at the dicrotic notch were transposed onto the high-fidelity left ventricular pressure tracing to time aortic valve opening and closure, respectively.

Total segmental shortening, defined as the percent change in segmental length from end-diastole to aortic valve closure, was subdivided into isovolumetric shortening (from end-diastole to aortic valve opening) and ejection phase shortening (from aortic valve opening to closure), as in our previous study.⁷ The times from end-diastole to aortic valve opening (isovolumetric time) and from aortic valve opening to closure (ejection time) were measured from the original tracings, and the intervals from five cardiac cycles were averaged.

Statistical analysis. Hemodynamic and timing data, segmental lengths, and segmental shortening were compared for

the same region at the same LVEDP before and after acute ischemia by a repeated-measure analysis of variance and Tukey's test for comparing mean values. A *p* value of less than .05 was considered to indicate statistical significance.

Results

Hemodynamic and timing measurements (table 1). Measurements before and after acute ischemia were obtained at three matched levels of LVEDP (table 1). For convenience, these levels will be subsequently referred to as LVEDP 7, 12, and 19 mm Hg. When compared with control conditions at the same LVEDP, acute ischemia was not associated with any significant change in heart rate at any of the three matched levels of LVEDP. The heart rate was significantly higher at LVEDP 7 mm Hg than at 12 or 19 mm Hg during acute ischemia, but not under control conditions. Aortic pressures at the time of aortic valve opening and closure at control and during acute ischemia differed significantly at only one of the matched LVEDP levels: the aortic valve closure pressure at LVEDP 7 mm Hg was significantly lower during acute ischemia than during control.

When compared with that under control conditions at the same LVEDP, there was a slight but significant increase in the isovolumetric time (from end-diastole to aortic valve opening) after acute ischemia at LVEDP 7 and 19 mm Hg, but not at LVEDP 12 mm Hg. Both at control and after acute ischemia, isovolumetric time decreased similarly as LVEDP increased. The left ventricular ejection time (from aortic valve opening to closure) did not differ under control conditions and after acute ischemia at any of the matched LVEDP levels. With increasing LVEDP, ejection time in-

creased similarly both under control conditions and after acute ischemia.

Regional segmental lengths (table 2). Regional segmental lengths before and after ischemia were obtained at three matched LVEDP levels (table 2). In the anterior apical or ischemic zone, acute ischemia was associated with a significant increase in segmental length at end-diastole, aortic valve opening, and aortic valve closure when compared with those under control conditions at the same matched LVEDP. In the anterior apex, the increase in end-diastolic segmental length for the same increase in LVEDP was significantly less after ischemia than under control conditions.

In the posterior apical or nonischemic area, acute ischemia was not associated with any significant change in segmental length at end-diastole or aortic valve closure at any of the three matched levels of LVEDP. As LVEDP increased, the increase in end-diastolic segmental length was similar under control conditions and after acute ischemia. Although the segmental length at aortic valve opening tended to be less after ischemia than under control conditions (particularly at low LVEDP), this difference was not statistically significant.

Regional segmental shortening (figures 2 and 3). Regional isovolumetric and ejection phase shortening measurements obtained at different LVEDPs before and after ischemia are shown in figure 2. Under control conditions, segmental shortening occurred predominantly during the ejection phase, with minimal motion during isovolumetric systole in both the anterior and posterior apices. In both the anterior and posterior apices, the ejection phase shortening increased sig-

TABLE 1
Hemodynamic and timing measurements for three levels of LVEDP before (control) and after acute ischemia in seven animals

LVEDP (mm Hg)	HR (beats/min)	AVO P (mm Hg)	AVC P (mm Hg)	ISOVOL T (msec)	EJECT T (msec)
Control					
6.8 ± 0.7	118 ± 17	94 ± 11	108 ± 10	60 ± 11	185 ± 28
12.3 ± 1.1	117 ± 15	98 ± 7	118 ± 12	51 ± 10	207 ± 27
19.1 ± 2.5	115 ± 12	103 ± 11	126 ± 18	52 ± 10	227 ± 25
Ischemia					
7.3 ± 1.2	124 ± 23	83 ± 19	93 ± 22 ^A	65 ± 12 ^A	186 ± 44
12.3 ± 1.3	112 ± 14	94 ± 19	113 ± 18	55 ± 7	224 ± 40
19.1 ± 2.3	109 ± 14	102 ± 13	122 ± 12	58 ± 11 ^A	240 ± 40

Measurements are given as mean ± 1 SD.

HR = heart rate; AVO P = aortic pressure at the time of aortic valve opening; AVC P = aortic pressure at aortic valve closure; ISOVOL T = isovolumetric time interval; EJECT T = ejection phase time.

^ASignificantly different from control measurements at the same LVEDP (*p* < .05). See text for additional statistical analysis and discussion.

TABLE 2
Regional segmental lengths (mm)

LVEDP (mm Hg)	Anterior apex			Posterior apex		
	ED	AVO	AVC	ED	AVO	AVC
Control						
7	12.7 ± 2.6	12.5 ± 2.4	10.5 ± 2.7	15.0 ± 4.5	14.9 ± 4.6	13.3 ± 4.0
12	14.7 ± 2.2	14.8 ± 2.2	11.8 ± 2.6	16.3 ± 5.0	16.4 ± 5.0	14.2 ± 4.4
19	15.7 ± 1.7	15.8 ± 1.6	12.6 ± 2.1	17.0 ± 5.2	17.0 ± 5.1	14.6 ± 4.4
Ischemia						
7	15.0 ± 2.4 ^A	16.9 ± 2.3 ^A	16.7 ± 2.3 ^A	14.9 ± 3.8	14.2 ± 3.7	13.0 ± 3.5
12	16.5 ± 2.5 ^A	17.6 ± 2.4 ^A	17.4 ± 2.4 ^A	16.4 ± 4.6	16.1 ± 4.5	14.2 ± 4.0
19	17.1 ± 2.3 ^A	17.9 ± 2.3 ^A	17.6 ± 2.3 ^A	17.1 ± 5.0	16.9 ± 4.9	14.7 ± 4.2

Segmental lengths (mean ± 1 SD) from the anterior apex and posterior apex are given at three levels of LVEDP before (control) and after acute ischemia in seven animals.

ED = end-diastole; AVO = aortic valve opening; AVC = aortic valve closure.

^ASegmental lengths during ischemia that are significantly different from control values at the same LVEDP ($p < .01$). The trends also differed in the anterior apex. For the same increase in LVEDP, end-diastolic segmental length in the anterior apex increased significantly less after ischemia than under control conditions ($p < .01$).

nificantly when LVEDP increased from 7 mm Hg to 12 or 19 mm Hg. In neither region was there a significant difference in ejection phase shortening at LVEDP 12 and 19 mm Hg. Isovolumetric shortening in both regions tended to decrease as LVEDP increased, but this was not a statistically significant change.

After acute ischemia, there was virtual akinesis during the ejection phase in the anterior apex or ischemic zone and most of the changes in segmental length occurred during isovolumetric systole, with marked paradoxical lengthening or bulge (figure 1). With acute ischemia, ejection phase shortening in the anterior apex decreased significantly for all three levels of LVEDP. During ischemia, there was no significant change in ejection phase shortening of the ischemic zone as LVEDP increased. However, there was a significant decrease in the amount of isovolumetric lengthening or bulge in the ischemic zone as LVEDP increased from 7 mm Hg to 12 or 19 mm Hg. The amount of isovolumetric lengthening in the ischemic zone was not significantly different between LVEDP 12 and 19 mm Hg.

In the posterior apex or nonischemic area, acute ischemia was associated with a significant increase in isovolumetric segmental shortening when compared with that under control conditions at the same LVEDP. This was true at all three levels of LVEDP. During ischemia, the amount of isovolumetric shortening in the nonischemic posterior apex decreased significantly as LVEDP increased from 7 mm Hg to 12 or 19 mm Hg. There was no significant difference in isovolumetric shortening at LVEDP 12 and 19 mm Hg.

The amount of isovolumetric shortening in the non-

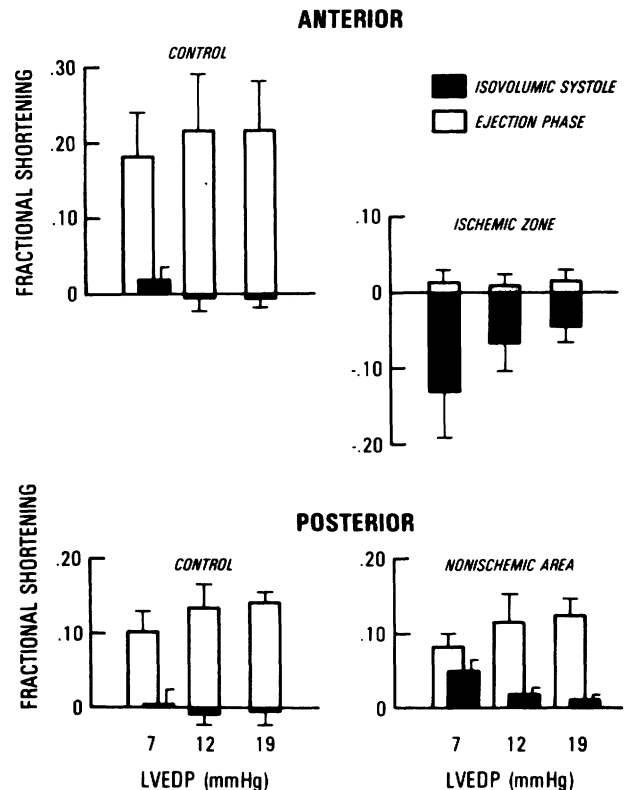


FIGURE 2. Regional segmental shortening in the seven animals. Values are with error bars denoting one standard deviation. The filled bars represent isovolumetric shortening (measured as the fractional change in segmental length from end-diastole to aortic valve opening) and the open bars are ejection phase shortening (from aortic valve opening to closure). Within each panel, three sets of bars are given for the three levels of LVEDP of 7, 12, and 19 mm Hg. The two top panels represent shortening in the anterior apex and the two bottom panels illustrate shortening in the posterior apex. In each case, the panel on the left is during control conditions and the panel on the right is after 30 (or more) min of acute ischemia when the anterior apex becomes the ischemic zone (top right) and the posterior apex is the nonischemic area (lower right). See text for statistical analysis and discussion.

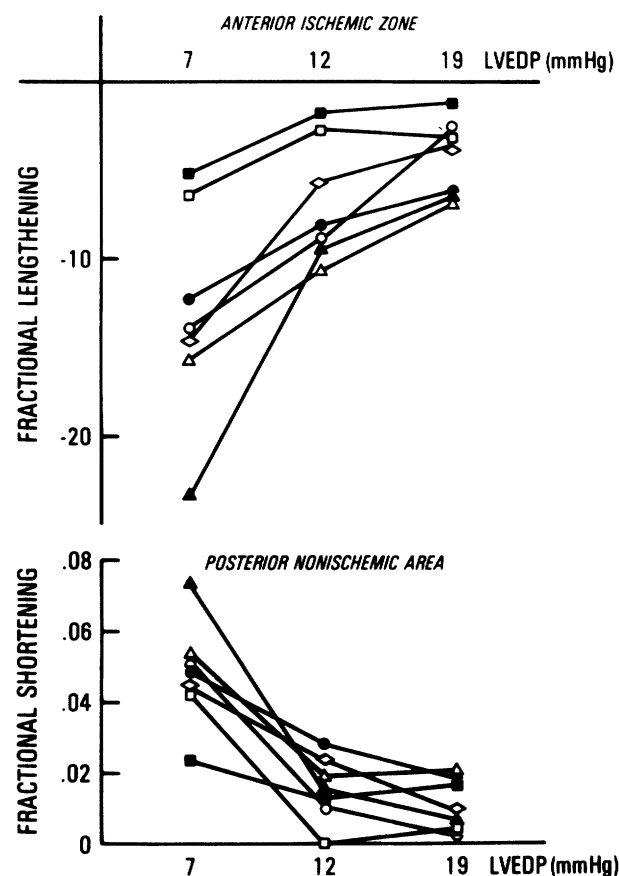


FIGURE 3. The simultaneous isovolumetric lengthening in the ischemic zone and isovolumetric shortening in the nonischemic area during acute ischemia are shown individually for each of the seven animals with the use of seven different symbols. For each animal, the symbols are connected by lines to demonstrate the change in isovolumetric shortening or lengthening as LVEDP is increased from 7 to 12 to 19 mm Hg. See text for discussion.

ischemic area directly paralleled the amount of isovolumetric lengthening in the ischemic zone. Figure 3 illustrates the regional isovolumetric data during acute ischemia for each of the seven animals at three levels of LVEDP. At LVEDP 7 mm Hg, the animals with the greatest amount of isovolumetric lengthening in the ischemic zone also had the greatest amount of isovolumetric shortening in the nonischemic areas (as shown with the filled and open triangles). Conversely, the animals with the least amount of isovolumetric lengthening in the ischemic zone were the same ones with the least amount of isovolumetric shortening in nonischemic areas (as shown with the filled and open boxes). As LVEDP increased, there was a significant decrease in isovolumetric lengthening of the ischemic zone that was directly paralleled by a significant decrease in isovolumetric shortening in nonischemic areas in each of the seven animals. An example of these changes is shown in figure 1.

The relationship between changes in isovolumetric

length in the anterior and posterior apices was examined by linear regression analysis. We defined x as the change in fractional isovolumetric shortening or lengthening in the anterior apex as LVEDP increased from 7 to 12 mm Hg, or from 12 to 19 mm Hg, and y as the change in fractional isovolumetric shortening in the posterior apex, also as LVEDP increased from 7 to 12 mm Hg or from 12 to 19 mm Hg. During the control period, there was no statistically significant correlation between x and y , i.e., between the fractional changes in isovolumetric shortening in the anterior apex and posterior apex. The correlation coefficient was .44. After acute ischemia, there was a significant ($p < .01$) correlation between the change in isovolumetric lengthening or bulge in the ischemic zone and the change in isovolumetric shortening in the nonischemic area. This was defined by the regression equation $y = -0.32x + 0.49$. The correlation coefficient was $-.64$. Thus, during acute ischemia, there was a direct correlation between the decrease in isovolumetric lengthening or bulge in the ischemic zone and the decrease in isovolumetric shortening in the nonischemic area as LVEDP increased.

In the posterior apex or nonischemic area, acute ischemia was associated with a significant decrease in ejection phase shortening when compared with that under control conditions at the same LVEDP. This was true at all three levels of LVEDP. However, the reduction in ejection phase shortening was less at high than at low LVEDP. When compared with that under control conditions at the same LVEDP, the reduction in ejection phase shortening in the nonischemic area with acute ischemia was $10 \pm 8\%$ at LVEDP 19 mm Hg, significantly less than the $21 \pm 10\%$ reduction at LVEDP 7 mm Hg.

Stroke volume and cardiac output (table 3). Stroke volume and cardiac output were measured in five of the seven animals (table 3). When compared with control conditions at the same LVEDP, acute ischemia was associated with a significant reduction in stroke vol-

TABLE 3

Stroke volume and cardiac output (mean \pm 1 SD) at three levels of LVEDP before (Control) and after acute ischemia (Ischemia) in five animals

LVEDP (mm Hg)	Stroke volume (ml/beat)		Cardiac output (l/min)	
	Control	Ischemia	Control	Ischemia
7	24 ± 3	16 ± 4	2.9 ± 0.5	1.9 ± 0.3
12	40 ± 8	30 ± 6	4.9 ± 1.0	3.3 ± 0.7
19	49 ± 11	38 ± 10	5.9 ± 1.5	4.2 ± 1.1

See text for statistical comparisons.

ume and cardiac output. However, the magnitude of this reduction was less at high than at low LVEDP. When compared with that under control conditions at the same LVEDP, there was a reduction in stroke volume of $21 \pm 16\%$ during acute ischemia at LVEDP 19 mm Hg, which was significantly less than the $32 \pm 15\%$ reduction at LVEDP 7 mm Hg. This milder impairment of stroke volume with acute ischemia at high as compared with low LVEDP occurred in each of the five animals.

Discussion

The characteristic alterations in regional ventricular function that develop with acute ischemia include paradoxical systolic lengthening or bulge in the ischemic zone⁹⁻¹⁵ and an increase in segmental shortening,^{13, 14, 16-19} wall thickening,²⁰⁻²² or endocardial wall motion²³ in nonischemic areas. The concept that the ischemic zone may impose a mechanical disadvantage on the nonischemic area has evolved from theoretical studies of regional ischemia,²⁴⁻²⁶ studies placing hypoxic and normal muscle strips in series,^{27, 28} and studies of ventricular aneurysms.²⁹ It has been proposed that the magnitude of the mechanical disadvantage imposed by a "weak" ischemic²⁴⁻²⁶ or aneurysmal muscle²⁹ is directly proportional to its size and inversely proportional to its stiffness.

Recently, we postulated that a mechanical interaction between ischemic and nonischemic areas occurs during acute ischemia in the intact ventricle.⁷ We found an increase in segmental shortening in nonischemic areas during acute ischemia due to the increase in LVEDP and the Frank-Starling mechanism. However, all of the increase in nonischemic area shortening occurred during isovolumetric systole (end-diastole to aortic valve opening) and developed with a time course that paralleled the development of paradoxical isovolumetric lengthening or bulge in the ischemic zone. These findings suggested that all of the increase in nonischemic area shortening was expended in stretching the ischemic zone during isovolumetric systole. Although the hyperfunction of nonischemic areas has been thought to "compensate" for the loss of systolic function in the ischemic zone, we did not find any significant "compensatory" increase in ejection phase shortening (aortic valve opening to aortic valve closure) in the nonischemic areas.

The current study was designed to further examine the mechanical interaction between ischemic and nonischemic areas. We used techniques to measure regional ventricular function similar to those used in our previous study.⁷ Ultrasonic segmental length gauges

were implanted in the midwall and oriented in the circumferential direction. Thus, gauges were in line with the direction of local midwall fibers⁸ and could detect the maximal amount of midwall segmental shortening.³⁰ Measuring regional function in the circumferential direction is important since there are many more circumferential than longitudinal fibers across the ventricular wall⁸ and the predominant direction of left ventricular shortening and work is circumferential.^{31, 32} This is also a sensitive method for the detection of alterations in regional function, as occurs with ischemia. For example, a circumferentially oriented segmental gauge in the subepicardium will be more sensitive to impairments in subendocardial blood flow and function than a segmental gauge placed in line with the local subepicardial fiber direction.³³ Thus, midwall circumferential segmental length gauges measure maximal midwall segmental shortening under normal conditions, and provide a sensitive measure of functional alterations induced by even mild degrees of myocardial ischemia.

The first hypothesis examined in the current study was that the ischemic zone imposes a mechanical disadvantage on the nonischemic areas. We postulated that this was due to the regional intraventricular unloading effect during isovolumetric systole that was observed in our prior study.⁷ However, the increase in LVEDP with acute ischemia increases end-diastolic segmental length in the nonischemic area and may mask any mechanical disadvantage. Thus, to examine the first hypothesis, we compared regional function before and after acute ischemia at the same matched LVEDP. We found a significant increase in isovolumetric shortening and a decrease in ejection phase shortening in the nonischemic area under these conditions of acute ischemia at a matched LVEDP. These findings were present at each of the three matched levels of LVEDP (7, 12, and 19 mm Hg). The reduction in ejection phase shortening in the nonischemic area was primarily due to the significant amount of shortening that had been expended in stretching the ischemic zone during isovolumetric systole. Thus, the regional intraventricular unloading effect during isovolumetric systole resulted in a decrease in ejection phase shortening in the nonischemic area, a manifestation of the mechanical disadvantage imposed by the ischemic zone.

The second hypothesis examined in this study was that the magnitude of the mechanical disadvantage imposed by the ischemic zone is directly proportional to the amount of its paradoxical isovolumetric lengthening, which in turn is inversely related to its stiffness.

We found a direct parallel between the isovolumetric behavior of the ischemic zone and the nonischemic area in this study (figure 3). As LVEDP increased during acute ischemia, the amount of isovolumetric lengthening or bulge in the ischemic zone and the amount of isovolumetric shortening in the nonischemic area decreased in parallel. Since less shortening generated by the nonischemic area was expended in stretching the ischemic zone during isovolumetric systole at a high LVEDP, relatively more shortening was available during the ejection phase. Therefore, the reduction in ejection phase shortening in the nonischemic area during acute ischemia was less severe at high than low LVEDP. This was also reflected by a less severe reduction in stroke volume with acute ischemia at high than at low LVEDP (when compared with that under control conditions at the same matched LVEDP). These findings support the concept that the magnitude of the mechanical disadvantage imposed by the ischemic zone is directly related to the amount of its isovolumetric lengthening or bulge.

The mechanism for the reduction of the mechanical disadvantage imposed by the ischemic zone by an increase in LVEDP may be related to the passive properties of the ischemic zone. At higher LVEDP, the ischemic segment is at a steeper (stiffer) position on its passive pressure-length relationship. Less isovolumetric shortening would be expended by the nonischemic area in stretching an ischemic segment that offers greater resistance to passive (paradoxical) isovolumetric lengthening. Thus, the reduction in nonischemic area ejection phase shortening with acute ischemia would be less severe at high than at low LVEDP. This inverse relationship between the stiffness of the ischemic zone and its mechanical disadvantage supports the conclusions drawn from the theoretical studies examining "weak" and "strong" muscles in series.^{24-26, 29}

The ischemic zone may also be particularly sensitive to changes in LVEDP since the end-diastolic pressure-length relationship is steeper after acute ischemia. Our findings are consistent with prior studies that have demonstrated an increase in ischemic zone stiffness with acute regional ischemia^{13, 14, 34, 35} and an increase in global left ventricular stiffness with global hypoxia³⁶ or global ischemia.³⁷ However, these findings remain controversial because some investigators have found no change^{25, 38} or a decrease^{39, 40} in left ventricular stiffness with acute ischemia. Furthermore, it is difficult to use measurements of regional segmental length to assess regional myocardial stiffness or its change with ischemia. Elastic stiffness is more precisely defined by the stress-strain relationship than by the pressure-

length relationship. Estimates of regional wall stress frequently are derived from mathematic models that require several assumptions that are controversial and difficult to validate.^{41, 42} These calculations require a measure of the local radius of curvature, which cannot be accurately assessed from local measurements of segmental length. Furthermore, with myocardial ischemia, there are local shape changes that will significantly alter the local radius of curvature, particularly in the ischemic zone. Thus, segmental length data cannot be used reliably to describe changes in regional shape or wall stress that occur with ischemia, or the resultant change in myocardial wall stiffness.

The ischemic zone may not behave as a strictly passive tissue during isovolumetric systole. Studies with theoretical models^{24, 27, 28} and in the intact ventricle⁴³ suggest that the ischemic zone retains some residual contractile function. If this were the case, then an increase in LVEDP could conceivably improve residual contractile function in the ischemic zone. A Frank-Starling effect has been demonstrated in the ischemic zone in a model of coronary stenosis,⁴⁴ but not with complete coronary occlusion.⁴⁵ If the ischemic zone is able to generate active tension during early isovolumetric systole, as in the model of Elings et al.,²⁴ then greater tension may develop with an increased LVEDP. This would be an additional mechanism by which the ischemic zone resists passive stretch during isovolumetric systole at high LVEDP. However, an increased LVEDP did not improve the akinesis of the ischemic zone during the ejection phase. Therefore, it is unlikely that the ischemic zone can utilize the Frank-Starling mechanism sufficiently to make any direct or effective contribution to ventricular ejection.

The results of our study can be related to the clinical setting of acute myocardial infarction. Bedside hemodynamic estimates of left ventricular filling pressure are frequently obtained in patients with acute myocardial infarction to guide therapy and to provide prognostic information.^{5, 6, 46, 47} At an "optimal" left ventricular filling pressure, stroke volume is optimized while adverse hemodynamic effects are minimized.¹⁻⁶ Ventricular filling pressures above this optimal level are associated with pulmonary venous congestion, exacerbation of myocardial perfusion deficits, a possible decrease in stroke volume, and a poor prognosis.^{5, 6, 38, 46, 47, 48} When ventricular filling pressure is below the optimal level, a significant increase in stroke volume can be obtained by therapy designed to increase LVEDP. The current study demonstrates that therapeutic preload manipulations to increase LVEDP to an optimal level during acute ischemia results in

increased utilization of the Frank–Starling mechanism in the nonischemic area but not in the ischemic zone. In addition, at an optimal LVEDP, the ischemic zone imposes less of a mechanical disadvantage on the nonischemic area. As a result, acute ischemia is associated with a less severe reduction in nonischemic area ejection phase function and in stroke volume at high as compared with low LVEDP.

We conclude that during acute myocardial ischemia, the ischemic zone imposes a mechanical disadvantage on the nonischemic area due to the regional intraventricular unloading effect during isovolumetric systole. This mechanical disadvantage results in a reduction in ejection phase shortening in the nonischemic area, a finding that may be masked if the increase in LVEDP that normally accompanies acute ischemia occurs. The magnitude of the mechanical disadvantage of the ischemic zone is directly related to the amount of its paradoxical isovolumetric lengthening. Increases in LVEDP to an optimal level during acute ischemia improve regional and global ventricular function as a result of the Frank–Starling mechanism in the nonischemic (but not the ischemic) area, and by reducing the mechanical disadvantage that the ischemic zone imposes on the nonischemic area.

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