

An Analysis of Segmental Ischemic Dysfunction Utilizing the Pressure-Length Loop

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SUMMARY

Left ventricular (LV) pressure and myocardial segment length, determined by an epicardial mercury-in-silastic length gauge, were plotted simultaneously to obtain a pressure-length loop before and after left anterior descending artery (LAD) occlusion in 11 dogs. Previous studies have indicated that the area within this loop is a sensitive and reproducible means of quantitating regional myocardial performance. Immediately following ligation, systolic performance deteriorated as indicated by progressive reduction in the pressure-length loop area. Within approximately 30 sec a zero area for the pressure-length loop was observed, indicating no effective work was being performed by the ischemic segment. During the ensuing 3-5 min the pressure-length loop moved into a clockwise orientation which indicated work was being done *on* rather than *by* the segment. The magnitude was approximately 50% of that amount previously generated by the segment. In addition, during this latter period of repetitive passive stretch, the end-diastolic pressure-length relationship shifted to the right indicating increased diastolic compliance. Restoration of perfusion after 30 min produced variable results. Substantial return of function was observed in two animals, but recovery in the majority of animals was limited to the elimination of paradoxical expansion without restoration of active contraction. Therefore, the pressure-length loop method allows quantitation of regional myocardial performance, and indicates that a predictable pattern of significant changes in both systole and diastole accompanies acute myocardial ischemia.

Additional Indexing Words:

Coronary artery ligation Reperfusion Compliance Paradoxical expansion
Starling curve Cardiac function Myocardial segment length

ALTHOUGH cardiac mechanical dysfunction resulting from ischemia has been recognized since the classical observations of Tennant and Wiggers,¹ there are important deficiencies in current knowledge relative to the effects of ischemia upon cardiac function. Thus, alterations of performance have been qualitatively described by

many methods in experimental animals^{2,3} and similar phenomena have been observed in patients with ischemic heart disease,^{4,5} but methodologic limitations in all these studies have precluded any quantitative conclusion regarding the amount of energy wasted by ischemic dysfunction.

In addition, the effects of ischemic changes on diastolic compliance are still in the process of being defined. Since cardiac function may be significantly altered by changes in diastolic compliance, it is necessary to determine the time course and the magnitude of these changes in diastolic compliance during ischemia.

The purpose of this study is twofold: first, to describe a method for quantification of regional cardiac function during systole and diastole in ischemia; second, to describe the nature and time course of such regional changes that accompany the onset of ischemia.

Methods

Eleven mongrel dogs (22-27 kgm) were anesthetized

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with morphine sulphate (2.2 mgm/kgm, i.m.) and ethyl carbamate (1.1 gm/kgm, i.v.). A left thoracotomy was performed via the fourth interspace. A 1 cm long mercury-filled silastic length gauge (Parks Electronics, Beaverton, Oregon) was fixed to the antero-lateral surface of the left ventricle near the apex by four sutures. The gauge was oriented in a direction parallel to the direction of the superficial myocardial fibers and placed within the distribution of the distal left anterior descending (LAD) coronary artery. In some experiments, a second gauge was fixed to a normally perfused segment. The artery was dissected free near its midpoint and a snare was placed for subsequent occlusion. Left ventricular (LV) pressure was recorded by a solid state pressure transducer (Model BT-7F2, Bio-Tech, Pasadena, California) mounted on an 8F double lumen cardiac catheter passed retrograde across the aortic valve into the left ventricle. Accuracy of measurements of diastolic pressure was assured by comparison of the magnified signal from the catheter-tip transducer with that recorded via the second lumen from an external manometer (P23Db, Statham Instruments, Hato Rey, Puerto Rico) and referenced to the level of the mid left ventricle. Aortic pressure was recorded via a catheter advanced through the femoral artery to the arch of the aorta. Ascending aortic flow was recorded by means of an electromagnetic flowmeter (Model RC 1000, Micron Instruments, Los Angeles, California). These signals were recorded for visual examination (Visicorder, Model 1505, Honeywell, Incorporated, Denver, Colorado) and recorded on magnetic tape for subsequent analysis (Model GR-2800, Consolidated Electrodynamics Corporation, Pasadena, California). In addition, an instantaneous display of LV pressure (ordinate) against epicardial segment length (abscissa) was continuously monitored.

The length gauge was calibrated at the beginning and end of the experiment by fixing the ends of the gauge to the jaws of a vernier caliper and extending the gauge by fixed increments.

After the initial control determinations the LAD artery was ligated by means of a snare for a period of 30 min. Data were recorded continuously during the first 5 min after occlusion and at 5 min intervals thereafter. After 30 min the snare was removed and data were continuously recorded for five minutes. Observations continued at increasing intervals throughout the recovery period which always exceeded one hour and usually extended to two hours. During control, occlusion, and recovery periods a range of end-diastolic pressures from approximately 0 to 25 mm Hg was traversed by rapid volume expansion via a large bore catheter in a jugular vein using blood from a donor dog.

Data were analyzed using a specially developed interactive program on the Xerox Data Systems Sigma-3 digital computer. The area of the pressure-length loop was determined by summing the incremental rectangular elements of area $1/2(P_1 + P_2)(l_1 - l_2)$ through the course of one cardiac cycle. To normalize for variations in gauge length, placement, and blood pressure, pressure-length loop area was expressed as a percentage of the pressure-length loop area recorded

during the control period when the LV end-diastolic pressure equalled 10 mm Hg. Similarly, end-diastolic segment length was expressed as a percentage of the end-diastolic segment length during the control period at LVEDP = 10 mm Hg. The significance of differences in end-diastolic segment length following occlusion was evaluated by means of the paired Student's *t* test.

Results

The upper panels of figure 1 show epicardial segment lengths, aortic flow, aortic pressure, and LV pressure recorded as a function of time; and the lower panels show instantaneous X-Y plots of LV pressure as a function of segment length (recorded from the gauge fixed in the area made ischemic). In the control state (left hand panels), pressure-length loops of this configuration were regularly recorded

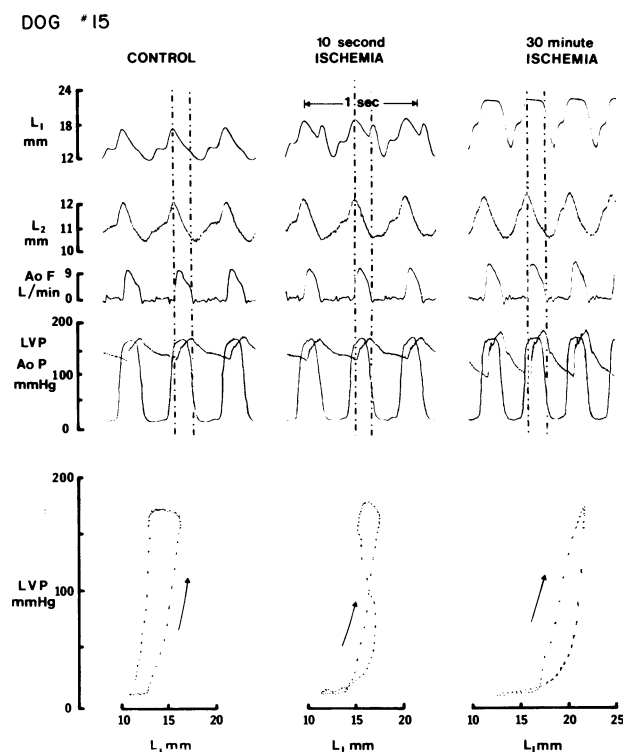


Figure 1

Ischemic alterations in segmental shortening and in the morphology of the pressure length loop in a typical experiment. The top panels show the length (L_1) of an epicardial segment perfused by the left anterior descending artery (later occluded). In this experiment a second gauge (L_2) was attached to a segment perfused normally throughout the experiment. Below are ascending aortic flow velocity (AoF), left ventricular (LVP) and aortic (AoP) pressures. The bottom panels show instantaneous X-Y plots of LVP versus segmental length. Early (center panel) and late (right panel) ischemic changes are discussed in the text.

when the gauge was oriented parallel to the direction of the superficial fibers. Within a few beats after occlusion of the coronary artery (center panels), the configuration of the length tracing was altered. Characteristically, the earliest change observed was a late systolic lengthening and delayed shortening. This resulted in a collapsed pressure-length loop of the shape shown. After 1–3 min of ischemia, no shortening occurred until pressure fell to near diastolic values (upper right panel). Since, at each value of segment length, the LV pressure was greater during lengthening than during shortening, an open *clockwise* loop was described. The sign of the area of this loop is the negative of that of the control loop and indicates that energy is being expended on the passive, incompletely elastic segment.

These effects of coronary occlusion on segmental systolic function are immediate and profound. Alterations in the phasic pattern of segmental length, which rapidly develops into “paradoxical” systolic expansion, translate into marked changes in the configuration of the pressure-length loop (see fig. 1). Figure 2 shows the transition between normal contraction and ischemic dysfunction in a single experiment. Throughout the first minutes

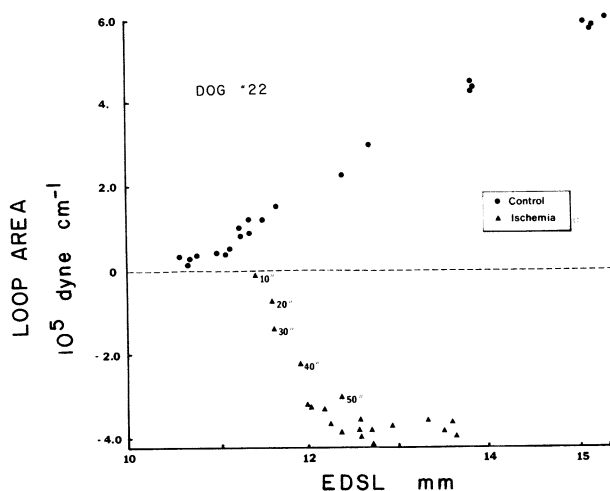


Figure 2

Time course of ischemic alterations in segmental function during coronary artery ligation. Circles indicate the segmental function curve generated by measuring pressure-length loop area and end-diastolic segment length (EDSL) during volume expansion prior to occlusion. After LAD ligation segmental function declined rapidly through the first minute (triangles labelled with seconds elapsed after ligation) to negative levels. After segment function stabilized at one minute, it became entirely unresponsive to changes in end-diastolic segment length (triangles without subscripts).

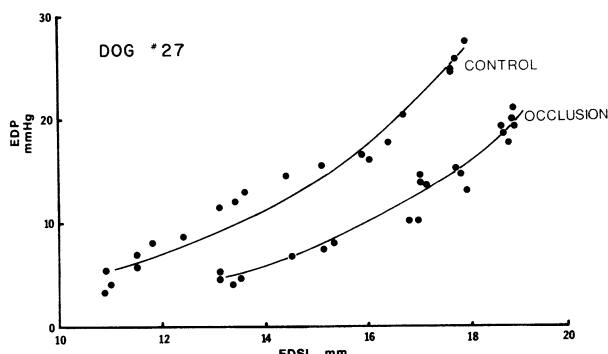


Figure 3

End-diastolic pressure-segment length relation before (upper line) and during a 30 min coronary artery ligation (lower line) in a single animal. The lines were constructed from the equations derived by a least-squares fit from each set of volume loading data. The data indicate that acute ischemia results in a “shift to right” of the diastolic pressure-length relationship, i.e., an increase in segment compliance.

after occlusion, the area of the loop progressively decreases. After this time, loop area remained constant and was completely unresponsive to alterations in end-diastolic length, suggesting that the segment no longer responded in terms of its Starling function curve.

To study segmental diastolic compliance, the end-diastolic pressure-length relationship was constructed from the end-diastolic coordinates of loops described during rapid volume loading sufficient to raise EDP to 20–30 mm Hg. Figure 3 shows such curves inscribed during the control period and during the period of ischemia in a representative experiment. During the first few minutes after occlusion, a shift to the right (i.e., greater segment length for a given end-diastolic pressure) was observed. After approximately five minutes, no further changes in diastolic compliance were noted. Figure 4 shows the results of 11 such experiments. The top graph shows a small but consistent shift to the right of approximately 5% increase in segment length at each end-diastolic pressure. The lower figure demonstrates the analysis of the difference in relative end-diastolic segment length before and after coronary artery occlusion.

When the occlusion was released after 30 min, the changes in the pressure-length loop were variable (fig. 5). In the two animals compared in this figure, even though the configuration of the pressure-length loop during ischemia was similar, the degree of recovery of function was qualitatively different.

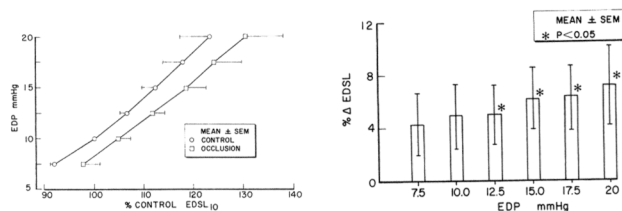


Figure 4

Left: The relationship of left ventricular end-diastolic pressure and relative segment length during the control (circles) and occlusion (squares) periods (mean \pm SEM) in 11 dogs demonstrating increased compliance during acute ischemia. End-diastolic segment length was normalized by dividing each absolute value by the length of the segment during the control period at LVEDP = 10 mm Hg. Right: Differences between normalized end-diastolic segment length during the periods of occlusion and control (mean \pm SEM). The significance of these differences was evaluated by the paired Student's *t* test (**P* < 0.05).

Figure 6 shows the summarized results of segmental systolic function during the control, occlusion, and reperfusion states. As with the compliance results, data recorded less than five minutes after occlusion and release were not included. Coronary artery occlusion resulted in a profound depression in segmental function. At every end-diastolic pressure, the average area of the pressure-length loop was negative, and no increase in function with increasing end-diastolic pressure was noted. After reperfusion the mean segmental pressure-length loop area at each value of end-diastolic pressure was more positive than during the ischemic period (*P* < 0.05) although these values were not significantly different from zero. As noted above (see fig. 5), the degree of recovery of mechanical function after 30 min of coronary artery occlusion was not uniform. During the reperfusion period two of the 11 animals developed positive segmental pressure-length loops larger than 45% of their respective controls in area. This improved degree of recovery was correlated with less severely depressed function during the period of occlusion. The relative areas of these pressure-length loops during the period of occlusion were approximately two standard errors above the mean.

Discussion

Employing an analysis of the loop formed by an instantaneous plot of LV pressure and epicardial segment length, this study quantitates the relative changes in segmental mechanical performance

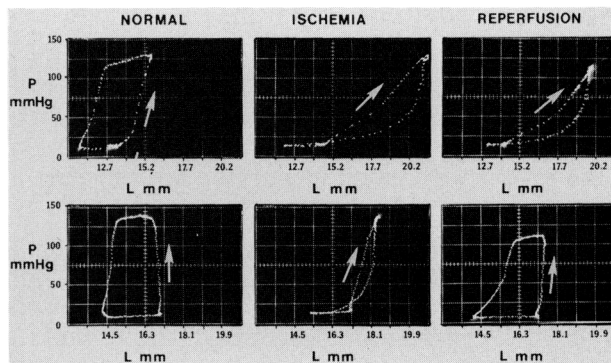


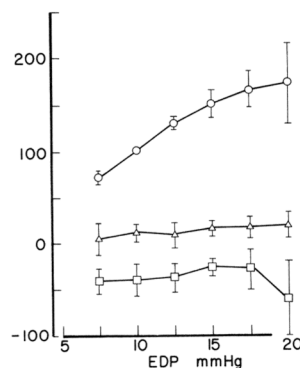
Figure 5

Variable recovery of segmental function after coronary artery occlusion. The top panels show the pressure-length loop during control (left), ischemic (center), and reperfusion (right) periods in an animal that showed little recovery of segmental function upon reperfusion. In the experiment illustrated in the bottom panels, reperfusion resulted in substantial restoration of mechanical function, despite the fact that the morphology of the pressure-length loop during the ischemic period was similar to that observed in non-reversible dysfunction.

following coronary artery occlusion and subsequent release and reperfusion. This analysis is based on the fact that the quantity of energy expended on, or by, a material is proportional to the integral of stress with respect to strain. Use of the pressure-length loop area as an easily instrumented index to

Figure 6

Relative segmental systolic function during control (circles), ischemic (squares), and reperfusion (triangles) periods in 11 dogs (mean \pm SEM). Data were normalized by dividing each value by the value of the pressure-length loop area inscribed during the control period at LVEDP = 10 mm Hg. In the control period segmental function increased with increased preload. During 30 min of ischemia segmental function was negative and independent of preload. After 1-2 hours of reperfusion, mechanical energy was neither consumed nor produced by the segment.



approximate the stress-strain integral derives from two considerations: first, as a first approximation, intraventricular pressure varies with stress except late in the ejection period;⁷ second, the change in length is proportional to the change in strain. Therefore, the integral of pressure with respect to length is approximately proportional to the integral of stress with respect to strain, or to mechanical energy. Consequently, the area enclosed by this loop, described over the entire course of one cardiac cycle, tends to reflect the net mechanical work of the myocardial segment during that cycle.

The shape of the segmental pressure-length loop closely resembles that of the intact heart pressure-volume loop (fig. 1, left-hand panels), i.e., there is shortening during systole and lengthening during diastole, resulting in a counterclockwise, rectangular loop. Evidence collected in this laboratory has indicated this measure of segmental systolic function is reproducible, and that the area of the pressure-length loop closely parallels ventricular stroke work in the uniformly contracting ventricle in a variety of conditions.⁶

The pressure-length loop provides a sensitive means of examining the synchrony of contraction of a given segment with respect to the total left ventricle. Left ventricular pressure reflects the time course of contraction in the mass of normal ventricle, while local segment length reflects the time course of the contraction of the ischemic segment interacting with the adjacent normal myocardium. In the presence of regional myocardial ischemia, ventricular contraction was not uniform and the configuration of the pressure-length loop obtained from ischemic myocardium reflected these changes. Within a few beats of the moment of coronary occlusion, the ischemic muscle segment began to lengthen late in systole (fig. 1, center panels). As ischemia continued, this lengthening occurred progressively earlier until there was no shortening during systole. These changes represent the progressive decline in the capacity of the ischemic muscle to shorten during systole against the stress developed by normal segments of the left ventricle. The observed change in contraction pattern of an ischemic muscle segment is parallel to those described in the hypoxic isolated cat papillary muscle. In these studies, the time to peak tension and the relaxation time declined very promptly after the induction of hypoxia.⁸ Such alterations in the time course of contraction may partially explain the earliest ischemic changes in the pressure-length loop. Shortening of time-to-peak tension and the

relaxation time would result in a considerably abbreviated duration of contraction in the ischemic muscle in comparison to that of the normal muscle. Thus, the normal muscle would stretch the ischemic muscle during the relaxation phase. Coincident with early stretching during systole, end-diastolic length increased at every end-diastolic pressure, suggesting an increase in diastolic compliance (*vide infra*).

As ischemia became profound, the affected muscle segment lengthened passively as ventricular pressure and wall stress increased (fig. 1, right-hand panels). The segment remained at this extended length during ventricular ejection and shortened only late in the ventricular relaxation phase. Of particular interest is the fact that the pressure-length loop became clockwise, such that at every value of segment length the LV pressure was actually greater during lengthening than it was during shortening. This evident hysteresis implies that effective mechanical energy generated by normal muscle was being dissipated into the ischemic segment in the process of repetitive stretching and relaxation.

During reoxygenation, changes in the morphology of the pressure-length loop were variable. In general, however, moderate lengthening during isometric systole was observed. This phenomenon may be related to the prolongation of time-to-peak tension and reduced capacity to develop force observed in ischemic papillary muscles early after reoxygenation.⁸ As the force generating capacity of the ischemic segment returned, shortening during systole progressively increased. During reoxygenation, shortening characteristically continued in the recently ischemic segment during the isometric relaxation phase of the ventricle (fig. 5, lower right-hand panel). This is compatible with the significant prolongation in relaxation time observed in reoxygenated papillary muscles.

With the pressure-length loop method of muscle segment analysis, the relative magnitude of energy loss into an expanding ischemic segment may be quantitated. A segment which contracts during systole produces a positive loop area, one whose contraction is negated by expansion produces zero loop area, and one that shortens at a lesser pressure than that at which it lengthens produces a negative loop area. Thus, the relative magnitude of energy which the contracting heart loses with an expanding ischemic segment is represented by the area of the clockwise (i.e., negative) pressure-length loop. Figure 6 demonstrates that the magnitude of energy dissipated by this segment is on the order of one-

half of its previous energy production. These data complement the studies of Parmley et al.,⁹ in which the distensibility of human ventricular aneurysms removed at surgery was measured. They hypothesized that no significant amount of mechanical energy would be dissipated in distending chronic fibrous aneurysms. In the acute aneurysm with relatively normal compliance, however, a significant fraction of the stroke volume of the normal ventricular wall would be compromised by paradoxical systolic expansion. Figure 6 also demonstrates that an expanding ischemic segment did not respond to volume loading. Since performance of these fibers was not enhanced by increased fiber length, any increase in total cardiac function observed during volume loading must have occurred only in those fibers capable of contracting normally.

Changes in diastolic compliance associated with the onset of ischemia have been the subject of a number of recent studies; on superficial examination results appear to be contradictory. Barry et al.,¹⁰ studying the diastolic pressure-volume relationship during pacing-induced angina pectoris in man, demonstrated that LV end-diastolic pressure is increased at an unchanged LV end-diastolic volume immediately upon cessation of pacing, while angina was still present. Therefore, they concluded that LV compliance diminished with ischemia. The data of Diamond and Forrester¹¹ suggest increased myocardial wall stiffness following acute infarction in man, and Hood et al.¹² demonstrated similar results in intact dog hearts examined three to five days following infarction. In contrast, using a length gauge sutured to the myocardium, Hood also demonstrated that the compliance of an ischemic myocardial segment increased after 30 min of coronary artery occlusion but returned to normal after six hours.¹³ We have previously demonstrated that a decrease in wall stiffness is observed in the isolated intact canine ventricle one hour following coronary occlusion.¹⁴ The results of the current study are consistent with those of other studies which indicate that the earliest change following the onset of ischemia is an increase in LV compliance (table 1).

In these studies, LV diastolic compliance increased immediately after induction of ischemia, and remained increased for several hours. The mechanism for this initial increase might be repetitive passive stretch of the noncontracting fibers. Although the increase in compliance was statistically significant, the magnitude of segment

Table 1

Time Course of Compliance During Ischemia and Infarction

Author	Duration	Compliance
Current study	up to ½ hour	↑ (segment)
Forrester ¹⁴	1 hour	↑ (whole heart)
Ekong ¹³	6 hours	↔ (segment)
Hood ¹²	72-120 hours	↓ (whole heart)
Barry ¹⁰	pacing to angina	↓ (whole heart)

length increase was only 5% at an end-diastolic pressure of 10 mm Hg, and this change might be of little biological significance. By three to five days, infiltration of edema fluid and inflammatory cells led to increased stiffness of the then infarcted muscle segment. Since the magnitude of this change in stiffness might be relatively large, it might be of much greater biological significance as suggested by Swan et al.¹⁵

The reperfusion segment of this investigation demonstrates that return of contractile function is not observed within one hour after release of a 30 min occlusion in the majority of cases. In two animals, however, impairment of function during occlusion was less profound and recovery with reperfusion was more substantial. It may or may not prove possible to predict the degree of functional recovery from the ischemic pressure-length loop (fig. 5). Although this study was not designed specifically to assess the viability of ischemia myocardium, it seems likely that these differences may be due to one or more of several factors. First, it is well known that coronary collateral flow in the dog is extremely variable, and this may have affected the degree of dysfunction during occlusion and the degree of recoverability. Second, the gauge may not have been placed uniformly in the center of the ischemic area. Finally, if all factors affecting oxygen balance were identical, disparate results may simply reflect biologic variation in tolerance to ischemia. The conclusion that ischemic myocardium may be viable, although nonfunctioning after 30 min of ischemia, is consistent with recent observations in which mass of infarction increased from approximately 10% to 35% between 45 min and 24 hours of coronary artery occlusion,¹⁶ indicating myocardial infarction is a progressive process and that a substantial portion becomes infarcted after 45 min of occlusion.

In summary, the pressure-length loop method

provides a means for simultaneously evaluating total and segmental cardiac function in both systole and diastole. Although the area of the pressure-length loop is not precisely proportional to the integral of stress with respect to strain, and therefore not a precise, absolute measure of segmental, mechanical work, the analysis has been shown to be a convenient, sensitive and useful index of segmental systolic performance. With the onset of ischemia there is an immediate loss of contractile function, which is followed over several minutes by the development of paradoxical systolic expansion. In addition, changes in segmental diastolic compliance are observed during the first minutes and progressively increase until approximately five minutes, after which no further change in the segment pressure-length relationship is observed. Finally, the effect of one or two hours of reperfusion after 30 min of occlusion is to eliminate the mechanical disadvantage of paradoxical expansion, although on the average, normal contractile function is not restored. When this method is combined with methods to evaluate metabolic aspects of local myocardial ischemia, it should be possible to describe, quantitatively, the effect of currently employed therapy on myocardial energetics.

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