Alterations of Myocardial Function during Early Stages of Mild Experimental Ischemia in Dogs Determined by Left Ventricular Pressure-Wall Thickness Loop

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Summary

Alterations of regional left ventricular myocardial function immediately after coronary artery branch ligation as related to the total left ventricular function were determined by utilizing left ventricular pressure-wall thickness loop in 6 anesthetized open-chest dogs. End-diastolic wall thickness was decreased immediately from 11.54 ± 0.50 mm (standard error of the mean) of control to 10.99 ± 0.50 mm in 5 to 10 min after ligation ($p < 0.05$), while regional myocardial work calculated as the loop area, was also decreased from 27.5 ± 6.1 to $19.3 \pm 5.8 \times 10^3$ dyn/cm ($p < 0.05$), indicating that the local Frank-Starling curve at the myocardium was depressed during ischemia. At the site where the ligation did not have effect, end-diastolic wall thickness and the regional work did not change significantly. Analysis of the shape of the loop revealed that the myocardial shortening was incomplete during the systolic ejection phase, and that the myocardial relaxation occurred very early in the ventricular relaxation phase after ischemia without alterations in the isovolumic contraction phase. These findings are compatible with those reported on isolated cardiac muscle strips during anoxia. The left ventricular pressure-wall thickness loop is superior to the pressure-length loop in that the former can be applied easily for clinical purposes and that the former utilizes a more direct relationship of pressure to its generator than the latter. Thus, primary alterations of myocardial function during ischemia were clarified accurately by utilizing the present method in the left ventricle in situ.

Additional Indexing Words:

Local Frank-Starling curve Regional myocardial work Stroke work Extent of shortening Diastolic thickness Myocardial relaxation

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LOCAL myocardial ischemia may arise in coronary artery disease, in which the morbidity in the left ventricular wall is localized. When the ischemic focus is large enough, cardiogenic shock may ensue. However, this does not always manifest an abnormal cardiac function; since various compensatory mechanisms in the circulatory system are activated to keep left ventricular function apparently unchanged. To find out the extent of the damage which has occurred in the myocardium during what we call compensatory cardiac failure, it is necessary to measure directly the severity and spread of local lesions. The contractile abnormalities of ischemic myocardium have been the subject of study since 1935 when Tennant and Wiggers first demonstrated systolic bulging of an ischemic segment of myocardium.[1] Recently, attention has been paid even to the function of non-ischemic site of the left ventricle. Some investigators[2),3)] noted that control segment showed no apparent changes during regional ischemia in terms of developed tension and systolic wall thickening. In contrast to this, Theroux et al[4)] observed a hyperdynamicity in the control area.

There is as yet no effective therapeutic means established for power failure syndrome once it has occurred. In approaching this disease state, we must first examine closely how left ventricular function is related to local function in ischemic heart disease and what effects therapeutic methods have on this relationship. As a sensitive method for simultaneous assessment of total cardiac and regional myocardial function during systole and diastole, the pressure-length loop method has been described.[4)-7)] On the other hand, the regional myocardial contractile abnormality induced by the ischemia was well assessed by the dynamic measurement of left ventricular wall thickening and thinning.[3),8)-12)] These authors emphasized that myocardial wall thickness was more sensitive than ventricular pressure[8)] or overall left ventricular function[11)] as a measure of the abnormality due to ischemia.

In order to judge the degree of contribution of the myocardium affected by the ischemia to the total left ventricular pressure generating function, the present authors have developed a new method that relates changes in wall thickness to left ventricular pressure. The purpose of the present study was to determine local myocardial function in the early stage of the ischemic disorder and relate this to total left ventricular function by using pressure-wall thickness loop method in acute ischemia in the canine left ventricle. The findings are to be compared to those reported on the isolated cardiac muscle.[13)]

The second purpose is to clarify whether these minimal ischemic changes may accompany normal or altered function in the non-ischemic site.

Methods

Six adult mongrel dogs weighing between 14 and 28 Kg were anesthetized with intravenous sodium pentobarbital (25 mg/Kg). Respiration was maintained oxygen-mixed room air, so that arterial blood gases and pH were maintained in a physiological range. The chest was opened bilaterally at the fifth intercostal space. The pericardium was incised, and the heart was suspended in a pericardial cradle.

Left ventricular (LV) wall thickness was measured with a specially designed strain gauge device (Fig. 1). The principle of measuring wall thickness is the same as described originally by Feigl and Fry[14] and subsequently modified by van der Meer et al.[15] A thin (0.5 mm) needle of stainless steel (length 20 cm) is fitted with a polyurethane end piece (8×8 mm, 4 mm thick) at the proximal end. This needle was introduced into the LV cavity through the incised left atrial appendage and through the mitral valve under digital manipulation. When the needle is pushed through the LV wall, the end-plate unfolds inside the heart just located on the endocardial surface, forming a catch so that the shaft cannot be withdrawn. The shaft of the needle moves through a small base plate, which is a part of, and an end of flexible plate of phosphor bronze (8×40 mm, 0.2 mm thick).

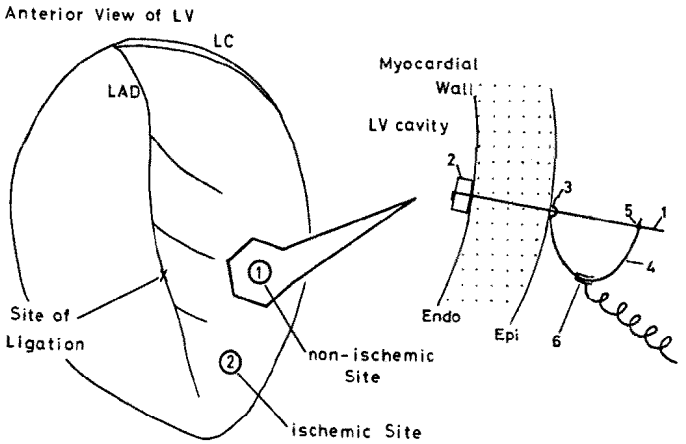

Fig. 1. Schematic drawing of our wall thickness measuring device (right) and of sites where these gauges are placed in the left ventricular wall (left). Wall thickness was measured at 2 sites (① and ②). Site ① was at the left ventricular free wall midway between apex and base which was non-ischemic throughout the experiments and served as control. Site ② was in the apical area where the ligation made ischemic.

1: a thin stainless steel needle; 2: a poly-urethane end-piece; 3: a small base plate of phosphor bronze; 4: the major part of the flexible plate acting as a spring; 5: the point where the end of the spring is fixed on the needle shaft with an adjustable stop; 6: 2 etched foil strain gauges mounted on both sides of the spring.

Abbreviations: Epi and Endo=epicardial and endocardial surfaces of the myocardial wall, respectively; LV=left ventricle; LAD=left anterior descending coronary artery; LC=left circumflex coronary artery.

It seems that this material is of the most satisfactory quality to date in its elasticity. The other end of this flexible plate is fixed on the shaft with an adjustable stop. The end plate was held against the inside of the ventricle by a light compression produced by the phosphor bronze plate acting as a spring between the base plate and the adjustable stop. The to-and-fro motions of the shaft with respect to the base plate were sensed by the flexure of the phosphor bronze plate, which had one end fixed to the base plate and the other to the stop on the shaft. Two etched foil strain gauges were mounted on both sides of the phosphor bronze plate and form 2 arms of a resistance bridge. The changes in the bridge resistance resulting from motions of the shaft were sensed and amplified with a carrier amplifier.

The transducer was calibrated following each run with a test stand, applying a Harvard pump (Infusion/Withdrawal Pump, Model-915) to move the shaft by a known distance. The instrument was linear throughout the ranges encountered. The drift was negligible (less than 6% of the peak-to-peak deflection) for the effect was cancelled out by the 2 strain gauges with each other. The dynamic response was satisfactory (flat up to 20 Hz) and no hysteresis was observed with this instrument.

Two such wall thickness gauges were attached to the LV free wall in each dog; one to the apical area and the other to the free wall of LV midway between apex and base, in order to observe the effect of mild ischemia not only in the apical (ischemic) segment, but also on the basal (non-ischemic) segment.

In one dog the LV endocardial border was verified by injecting 3–6 ml of indocyanine green solution (5 mg/ml saline) into the ventricle and observing wall thickening and thinning by using an ultrasonic cardiograph (San-ei, UC101B) with a 5 MHz transducer. These findings indicated that the gauge worked as a measuring device of LV wall thickness very accurately as judged from the movement of endocardial border demonstrated by the ultrasonic method.

LV pressure was measured by introducing a 5 cm long KIFA tube at the apex and connecting this to a Statham transducer (P23Db). Time lag can be ignored with this equipment. Aortic pressure and aortic blood flow were measured with an electromagnetic flow meter (Narco, RT-500), and electrocardiogram was recorded simultaneously with changes in wall thickness at the 2 sites on a direct pen-recorder (Nihon Kohden Polygraph, RM-85). LV pressure and wall thickness were also recorded on a 4-channel magnetic data recorder (Sony, DFR-3515). Simultaneous records on a magnetic tape were later replayed on a storage oscilloscope (Tektronics, 5103 N), and displayed LV pressure-wall thickness loop and photographed with a 35-mm camera (Fig. 2).

The loop area was calculated from those reproduced on the tracing paper and measured by the weighing method. LV external stroke work (SW) was calculated from the aortic mean pressure (Ao_m) and stroke volume (SV, planimetered from the aortic flow tracings) as follows;

$$SW\ (dyn/cm) = SV\ (ml) \times Ao_m\ (mmHg) \times 1{,}332$$

After recording of control data, one of the branches of the left anterior descending coronary artery was ligated in such a way as to cause a lesion in the part of the apex where one of the wall thickness gauges was attached. Observation was made immediately after ligation for a period of 20 min. Data obtained in 5 to

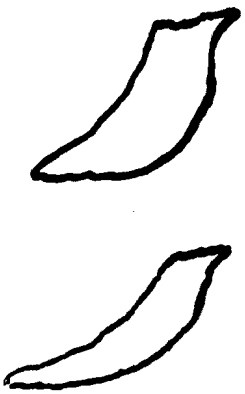

Fig. 2. Typical change in left ventricular pressure (ordinate)—wall thickness (abscissa) loop before (upper) and 5 min after (lower) coronary arterial branch ligation as shown on the same scale.

10 min after ligation were compared to the values obtained during the control period, and each difference of the means was tested statistically using Student's paired t-test.

Results

I. Changes in left ventricular pressure and wall thickness immediately after ligation (Fig. 3)

Fig. 3 shows the changes in the left ventricular pressure, wall thickness at the affected area by the induced ischemia, aortic flow and aortic pressure as well as ECG before and immediately after ligation in a typical experiment. An increase in wall thickness was observed immediately after ligation, but approximately 20 sec later, wall thickness movement slackened, mostly, showing a slight temporal alternation, which did not usually lead to pulsus alternans; after a while systolic and diastolic wall thickness recovered to the control level; and, after 3 min end-diastolic wall thickness gradually decreased (as described below and seen in the following Figures 2, 3, 5 and Table I). Endsystolic LV pressure remained unchanged throughout the period of observation, but aortic flow tended to decrease in this very early tracing.

II. Comparison of pressure-wall thickness loops before and 5 min after ligation (Figs. 2 and 4)

Fig. 2 shows actual pressure-wall thickness loops obtained from the oscilloscope: the upper photograph is obtained before ligation; lower one is a loop at 5 min after ligation. The change in shape of the loop before and after ligation is shown schematically in Fig. 4. The principal effects of ligation occurred i) in the ejection phase (the increase in wall thickness was

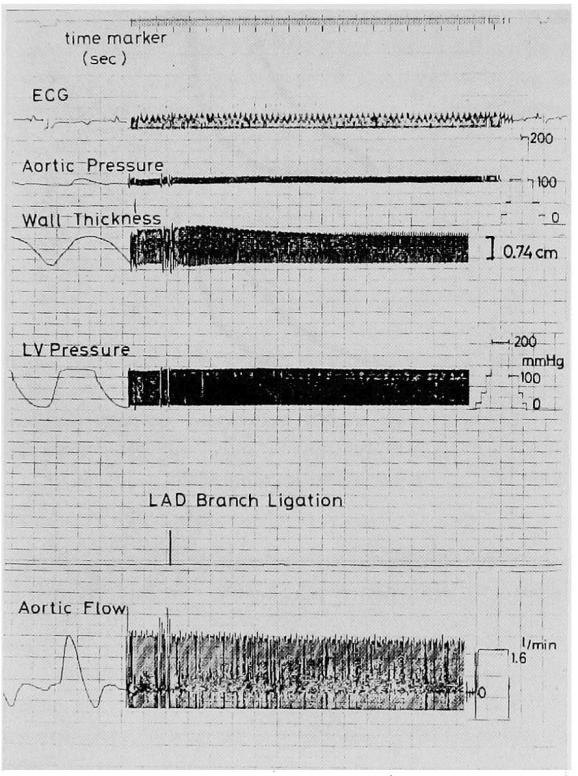

Fig. 3. Typical record (from upper to lower panels) of electrocardiogram (ECG), aortic pressure, wall thickness at the affected site by the induced ischemia, left ventricular (LV) pressure, and aortic blood flow, before and after the ligation of a branch of the left anterior descending (LAD) coronary artery (see text).

incomplete during peak pressure) and ii) in the diastole (the reduction in wall thickness appeared already at the moment when systolic pressure was halved). There was no apparent change during the isometric contraction phase of the loop. As a result of the 2 former effects, the loop area diminished following ischemia, and a reduction in regional work was suggested.

III. Changes in left ventricular and regional myocardial functions after ligation (Figs. 5 and 6, Table I)

Fig. 5 shows percent changes from the pre-ligation values in left ventricular end-diastolic pressure, systolic pressure and stroke work, over a 20 min period. After ligation, the end-diastolic pressure increased, and systolic pressure, as shown in Table I, remained unchanged throughout the period. Stroke work was reduced by about 20% immediately after ligation, and continued at this reduced level. This reflected a drop in stroke volume.

Changes in regional work after ligation observed in ischemic and non-

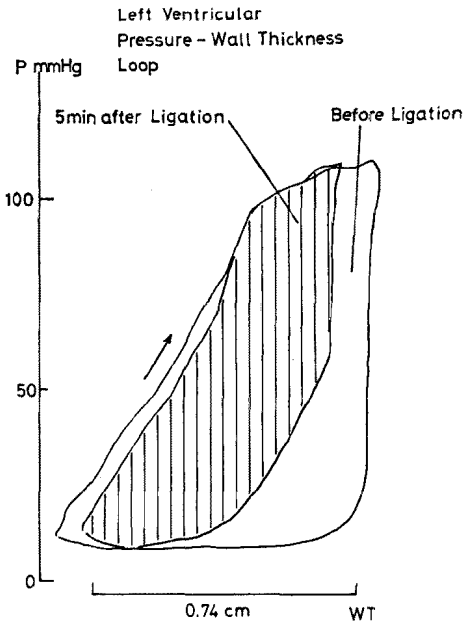

Fig. 4. Schematic drawing of the distortion of left ventricular pressure-wall thickness loop after ischemia. Normally the loop is clockwise in rotation as indicated by arrow.

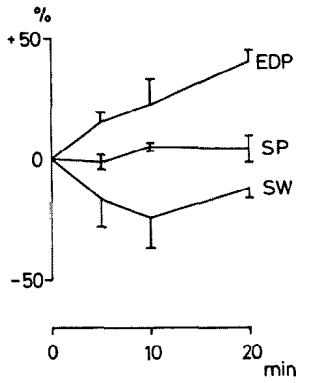

Fig. 5. Serial changes in left ventricular end diastolic pressure (EDP), systolic pressure (SP), and stroke work (SW) over 20 min after ligation, showing percent changes from the pre-ligation values. Vertical bar indicates one standard error of the mean.

ischemic regions are shown in Fig. 6. Change for a 20 min period is shown on the vertical axis of the diagram with respect to the values before ligation. Changes in loop area, in other words in regional external work, were approximately 40% reduction immediately after ligation in the ischemic region, but very slight reduction at first, and rather hyperdynamic condition after

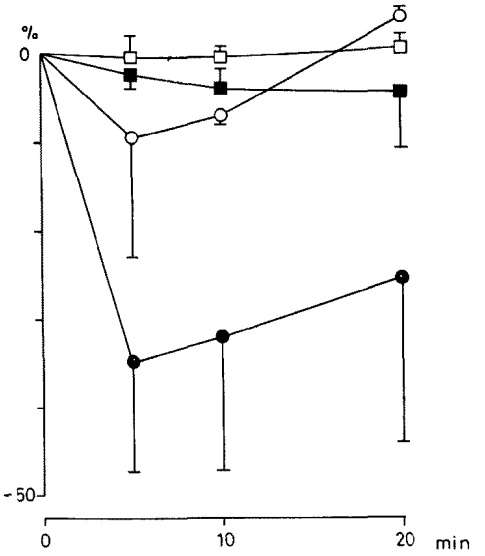

Fig. 6. Serial changes in loop-area (which means regional myocardial work, indicated by sign of circle ○), and in diastolic wall thickness (indicated by sign of square □) after ligation, in the ischemic (closed signs) and non-ischemic (open signs) regions. Shown are changes for a 20 min period on the vertical axis from the values before ligation (see text).

20 min in the non-ischemic region. At this time, end-diastolic wall thickness showed a gradual reduction in the ischemic region, in contrast to the non-ischemic region where it remained unchanged. Increase or decrease in end-diastolic wall thickness can be considered to indicate reduction or elongation of end-diastolic fiber length, respectively. Consequently, a preload increase in the ischemic region accompanies a drop in stroke work which indicates a depressed condition of the function in terms of Frank-Starling mechanism. The changes in stroke work shown in Fig. 5 can be thought to occur as the summation of the regional work changes shown in Fig. 6 in ischemic and non-

Table I. Changes in Left Ventricular and Regional Myocardial

	Regional Myocardial			
	Loop-area $\times 10^3$ dyn/cm		Extent of shortening mm	
	Ischemic site	Non-ischemic site	Ischemic site	Non-ischemic site
before	27.5 (±6.1)	18.5 (±5.7)	1.95 (±0.38)	1.76 (±0.29)
after	19.3* (±5.8)	19.3 (±3.6)	1.51 (±0.91)	1.86 (±0.28)

The value in the parentheses is SE.

* denotes the difference is significant ($p<0.05$) as compared to the values before ligation.

ischemic regions.

Table I summarizes changes in regional myocardial and total left ventricular function in 5 to 10 min after ligation as compared with each control value. As evidenced in Fig. 5, stroke volume and stroke work were reduced, and left ventricular systolic and end-diastolic pressures were elevated by ischemia, but these changes were not significant statistically. Loop area considered as local myocardial work and diastolic wall thickness were significantly decreased ($p<0.05$) in the ischemic site, whereas these variables were not altered in the control area, although a tendency of increase in loop area was apparent in the control site as seen in Fig. 6. Extent of wall thickening decreased or increased in the ischemic or non-ischemic site, respectively. However, these differences were not significant.

Discussion

Ischemia not only reduces the supply of oxygen and substrates to the myocardium but also inhibits the elimination of the metabolites out of the cells. As a result, aerobic metabolism is curbed, ATP becomes deficient, and, at the same time, anaerobic metabolism is invigorated, bringing about acidosis, which seems mainly related to the drop in myocardial contractility following ischemia.[16] When the fact is taken into account, however, that a certain amount of time is required for the lactic acid to accumulate, it can be surmised that ischemia does not immediately weaken contraction; there could be a period without change or even a temporary overwork condition (Fig. 3) could be brought about by some reflex.

It has been reported recently[12),17] in the experiments using ultrasonic cardiography, and we have demonstrated (Fig. 6 and Table I) by using wall thickness measuring device, that end-diastolic wall thickness in ischemic regions decreased. This wall thickness decrease has been asserted to reflect

Functions in 5 to 10 min after Coronary Arterial Ligation

Function		Left Ventricular Function			
Diastolic thickness mm		LVSP mmHg	LVEDP mmHg	SV ml	SW $\times 10^5$dyn·cm
Ischemic site	Non-ischemic site				
11.54 (±0.46)	11.64 (±0.22)	100.7 (±6.4)	6.0 (±0.6)	5.8 (±0.7)	8.0 (±1.2)
10.99* (±0.50)	11.63 (±0.27)	102.1 (±5.8)	7.0 (±0.7)	4.5 (±0.5)	6.0 (±0.8)

Abbreviations: LVSP=left ventricular systolic pressure: LVEDP=left ventricular end-diastolic pressure; SV=stroke volume; SW=stroke work.

a decrease in coronary blood volume.[17] but it seems to us difficult to explain all by this alone. It could be thought that, in part, a probable increase in myocardial compliance caused increased preload. If myocardial volume is assumed to be fixed throughout systole and diastole, and we believe that this assumption holds good even when we take into account the changes in coronary blood volume that accompany systole,[18] then a decrease in LV wall thickness is considered as an extension of myocardial length. There are several reports that wall thickness characteristics exhibited an inverse behavior to corresponding myocardial segments.[3),10),11] Therefore, it is thought that the decrease in diastolic thickness in the ischemic region seen in Fig. 5 shows an increase in preload.

The cardiodynamic significance of the configuration and area of the left ventricular pressure-wall thickness loop can be considered as follows; the starting slope of this loop during early systole (isovolumic contraction phase) is related to the tension-generating speed (dT/dt) of that region, and the area enclosed by the loop is correlated to the regional work. Taking account of such fiber orientation across the left ventricular myocardial wall as studied by Streeter et al,[19] the muscle thickens in the process of shortening since total volume of the muscle unit remains constant. Thickening requires energy and the work thereby done by the muscle may be calculated as the product of thickening and side-pressure. This is related to the radial component of element work considered by Gould et al.[20] Thus, the integral of pressure with respect to wall thickening and thinning (i.e., the area of the pressure-wall thickness loop) represents a crude first approximation of the mechanical work done by (or on) the segment. In this study, during observation of the ischemic region, a drop (Fig. 6) was observed in regional work accompanying increased preload; this proved the depression of the Frank-Starling curve more directly. The depressed local function curve during ischemia has been suggested by other investigators.[6),21] For example, Tyberg et al[6] have shown that an increase in pressure-length loop area which was observed on increasing end-diastolic pressure in dog left ventricle was eliminated after ischemia. Since left ventricular end-diastolic pressure changes have an inverse effect on end-diastolic wall thickness,[24] the latter finding of Tyberg et al may be explained by an abolishment of Frank-Starling relationship in the presence of ischemia.

As to the non-ischemic region of the ischemic ventricle, Theroux et al[4] observed a hyperdynamicity, and this is considered as the Frank-Starling effect, caused by increased preload. In contrast, other investigators[2),3),12] have reported that the control segment did not change. Our results show no significant change, either in preload or in contraction at the non-ischemic

region (Fig. 6). The reason for the discrepancy is not clear as yet. Since Theroux et al caused more extensive ischemia, the change in preload in non-affected area would depend on the extent of the ischemia.

In studies where segment length in the ventricular wall was measured by using a mercury-in-silastic gauge and a pair of ultrasonic crystals,[4] the object was mainly to investigate bulging and ventricular dyssynergy, so the severity and extent of ischemia were greater than in the present study. Therefore, primary abnormalities in myocardial contraction caused by anoxia, similar to those shown by our study, cannot be observed in the pressure-length loop studies. Since the object of the present study was to cause the slightest possible ischemia in the restricted region of the left ventricle, it was possible to show the abnormality clearly at an early stage. Wyatt et al[7] examined the graded reduction in regional coronary perfusion upon segmental function and total ventricular function by using the pressure-length loop method. They described that as coronary perfusion pressure and flow were reduced to 50 to 65 mmHg and 25 to 55 ml/min per 100 Gm, respectively, regional myocardial function was decreased minimally, so that there was a characteristic change in the length tracings consisting of late systolic lengthening and delayed shortening. The result of this mild ischemia was eventually a decrease in the area of the pressure-length loop. Moreover, their late systolic lengthening was accompanied with an incomplete shortening during ejection period, so that the distortion found on the loop resembles ours (Figs. 2 and 4). The difference is that the delayed shortening was not found on our pressure-wall thickness loop. It may be postulated that this finding appears only on the epicardial fibers. Similar distortion of the pressure-length loop appears in the results reported by Theroux et al.[4]

According to a report regarding the influence of anoxia on the contractility of isolated myocardium,[13] the obstacles to myocardial contraction are: i) shortened contraction time (decrease in time to peak tension) and ii) increased speed of relaxation (decrease in time for peak tension to be halved). In this study, as we see in Figs. 2 and 4, the fact that the extent of increase in wall thickness during the systolic ejection phase was insufficient, and the fact that a reduction in wall thickness began in the protodiastolic phase, as well as other findings, coincide perfectly with data on anoxia in isolated myocardium. Pressure-wall thickness loop does not include time axis, but it is still possible to know from its configuration whether the timing of contraction or relaxation becomes earlier or delayed as compared to the intact and control segments. For example, wall thinning commences already when LV pressure becomes halved (Fig. 4) during diastole in the loop obtained at ischemic region. In the control loop, however, wall thinning does

not appear until LV pressure decreases to less than one third of the peak pressure. This means that wall thinning starts earlier with ischemia as compared to the control, because the pressure does not change with such a minimal regional ischemia as in the present study in its shape and time course. The fact that the loop's starting slope does not change during ischemia (Fig. 4) supports in situ the observation made on isolated myocardium that anoxia does not change the myocardial contraction state at least in the stage of early ischemia, but mainly curtails the duration of the active state.[13] In isovolumic phase, an increase in LV intracavitary pressure (ordinate) mainly takes place, while an increase in wall thickness (abscissa) is also evident (Figs. 2, 4). Looking at the figures of pressure-length loops reported by other investigators,[4)-7)] it is always obvious that segment length shortens in the isovolumic systole more or less in every case. As noted previously[22] and reported by others,[23] this phase and also isovolumic relaxation phase can not be strictly isometric even under the physiological conditions; onset and speed of shortening and lengthening vary depending on the region of left ventricle. This would be the reason why an increase in the wall thickness was observed during isovolumic systole in our study. In the ventricular ejection phase, pressure stays almost unchanged and wall thickening is only evident.

It has been reported by some workers[8),11)] that left ventricular wall thickness is a most sensitive index to ischemic disorders of contraction. Abnormal wall thickness variations in ischemic ventricles without change in left ventricular systolic pressure and left ventricular external stroke work have been clearly observed in this study (Fig. 5), which supports the contention of the latter authors. In addition, the fact that at that moment aortic peak flow also decreases (Fig. 3) means that this same change in flow velocity is also equally sensitive and merits attention in very early stage.

It is possible to point out the disadvantages of the pressure-length loop[4)-7)]: first, it is difficult to apply clinically, and second, since length is usually measured on the epicardium, tension of this part has a weak relationship to internal pressure. In the present study, wall thickness was used instead of epicardial length, and for this reason it can be said that it is more directly related to internal cardiac pressure.

In conclusion, by means of the left ventricular pressure-wall thickness loop, light has been shed upon abnormal contraction in the mildly ischemic region and its relationship to total left ventricular function. Research is also being conducted on the effects of the vasodilators. It is hoped that these observations will contribute to the elucidation of the mechanism of power failure and to the development of therapeutic methods.

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