Active Stiffness of the Intact Canine Left Ventricle
WITH OBSERVATIONS ON THE EFFECT OF ACUTE AND CHRONIC MYOCARDIAL INFARCTION

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ABSTRACT
Three methods were employed to measure the overall active stiffness of the intact left ventricle in anesthetized dogs. In two of these, isovolumic contractions of the ventricle were examined, and in the third the response to a minor increase in afterload was analyzed. The average modulus of active stiffness of the normal left ventricle by all three methods was found to be lower than that reported for the cat papillary muscle (57-76%).

Myocardial infarction studied 1 hour and 2 to 3 weeks following ligation of the anterior descending coronary artery did not alter active stiffness of the left ventricle. When sufficient time had elapsed, however, for complete scarring and thinning of the infarction to occur, active stiffness was significantly reduced. It is suggested that a functional defect of the overall active stiffness (series elasticity) of the ventricle may be operative in the pathogenesis of congestive failure due to ventricular aneurysm.

ADDITIONAL KEY WORDS
muscle mechanics series elasticity force-velocity relations myocardial performance
aneurysm pathogenesis of congestive failure

As first suggested by A. V. Hill (1, 2), the mechanical components of active muscle may be represented by an active contractile element (CE) in series with a stiff, passive spring (series elastic component, SEC). The major characteristic of the CE is the force-velocity relationship that has been demonstrated by varying the afterload of isotonic contractions of isolated skeletal and cardiac muscle (1-6). The characteristics of the SEC have been examined by measuring the force-displacement relationship following the sudden release of tension of active muscle (3, 7). While the CE and the SEC can be separated functionally, no attempt has been made to assign each component a specific anatomic location within the contractile apparatus.

Abbott and Mommaerts measured the series elasticity of the cat papillary muscle and found it to be significantly more compliant than that of isolated skeletal muscle (3). More recently, Sonnenblick has made a careful study of series elasticity in the cat papillary muscle and has presented evidence to suggest that much of the SEC is associated closely with the CE system itself, rather than the passive connective tissue within a muscle (8). In addition, he has examined the amount of work the CE performs in shortening the fiber (external or isotonic work) and that which it performs in stretching the SEC (internal or isometric work) over the entire range of afterload. Because of its greater compliance, the SEC of heart muscle captures a greater fraction of the total CE work (as internal work) in isotonic contractions than does skeletal muscle (8). This has also been demon-
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Stratified in auxotonic contractions of the intact dog heart (9). The implication of this observation is that the external mechanical efficiency of heart muscle should be less than that of skeletal muscle. However, this has yet to be shown (10, 11).

In the intact heart there is reason to believe that internal shortening of the contractile elements may be influenced by passive factors other than the series elasticity of cardiac muscle itself. Thus, the overall stiffness of the contracting ventricle (active stiffness) may not be the same as the series elasticity of homogeneous cardiac muscle. During the isovolumic period of contraction, for example, changes in ventricular geometry prevent the muscle fibers from contracting in a truly isotropic fashion (12, 13). In addition, fibrous valves in series with heart muscle alter the overall active stiffness of the ventricle. Asynchronous activation of the heart, too, may permit active muscle to contract in series with resting muscle during the early part of systole, and in this way alter active stiffness of the intact ventricle.

It is the purpose of this paper to describe three methods for measuring the overall active stiffness of the intact left ventricle, and to examine possible mechanisms by which changes in active stiffness may influence the performance of the heart.

Methods

Thirty-five mongrel dogs, weighing 15 to 25 kg were anesthetized with sodium pentobarbital, 25 mg/kg i.v. Respirations were driven by a Harvard pump connected to auffed endotracheal tube. Large-bore polyethylene cannulae were placed in a carotid artery and femoral vein, and cardiac output was measured by the indocyanine dye technique. A thermistor was passed into the heart through the left atrial appendage into the body of the left atrium and a cold bolus of saline was injected into the left ventricle just prior to cross-clamping the aortic root. In no instance was a fall in left atrial blood temperature observed during the isovolumic beat. Cardiac output and three to five thermal dilution curves were recorded immediately before each series of interventions, and the average values for control stroke volume and end-diastolic volume were calculated (14). The tracings of each pair of beats were examined; some were discarded because of premature contractions, early or late placement of the afterload, or unstable flow curve base line.

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\(^{1}\)Model 300, Carolina Medical Electronics, Winston-Salem, North Carolina.
Acute myocardial infarction was produced by single-stage ligation of the anterior descending coronary artery approximately 2.5 cm from the left coronary ostium. Subacute and chronic myocardial infarction was achieved by two-stage ligation of the same artery according to the method of Harris (15). Following each experiment the left ventricle with the intraventricular septum was dissected from the remaining chambers, valves and chordae tendineae and was weighed.

**Calculations**

Cardiac output, heart rate and average stroke volume were calculated in the usual fashion, and end-diastolic volume was determined from the ejection fraction and the stroke volume (14). Calibration of the flowmeter was achieved in each experiment by using the average stroke volume and the average area under the control flow rate curves as described previously (9). Volume decrement (dV) for each 20-msec interval of systole was derived by integration of the flow rate curve. The following calculations were also made at 20-msec intervals and have been derived previously (9):

\[
V = \text{end-diastolic volume} - dV, \text{in ml;}
\]

\[
V = r^2h, \text{in ml;}
\]

\[
r = \sqrt{\frac{V}{2.39}}, \text{in cm;}
\]

\[
\text{fiber shortening rate (FSR)} = \frac{\text{flow rate}}{2\pi r^2}, \text{in cm/sec;}
\]

\[
\text{force (F)} = \pi r^2P, \text{in dynes;}
\]

\[
\text{fiber shortening power (FSP)} = F \times \text{FSR}, \text{in dyne-cm/sec;}
\]

\[
\frac{dF}{dt} = \pi r^2 (\frac{dP}{dt}) - rP (\text{FSR}), \text{in dynes/sec.}
\]

Total fiber shortening work was calculated by integration of the FSP-time plot. The above calculations were performed after appropriate conversion of data to digital form on an IBM 1620 computer. 2

**Calculation of Active Stiffness**

**Method 1.** It has been shown that the total contractile element work (CEW) of a ventricle, when the end-diastolic fiber length and inotropic environment are both constant will be determined by its afterload (9). It has further been shown that the normal ventricle during a steady state generally functions at the peak of the CEW-load curve, somewhere near 60% of the isometric load. Although a major increase in afterload is associated with a decrease in CEW of the normal systole, a small increase in afterload can be produced which will not significantly alter the total CEW, but will cause a redistribution of CEW between fiber-shortening work (FSW) and force-generating work (FGW). This redistribution of CEW is manifest grossly as a rise in intraventricular pressure and a fall in stroke volume. Thus, if a sufficiently small increase in

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1 Computation Center, Tufts University, Medford, Massachusetts.

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Afterload is produced, CEW of the control and adjacent beat may be assumed to be equal. Thus, CEW$_1$ = CEW$_2$, and since CEW = FSW + FGW (16), then FSW$_1$ + FGW$_1$ = FSW$_2$ + FGW$_2$. Since FGW = $F_p/S$ (16), where $F_p$ = peak force in dynes and $S$ = the linear slope of the (dF/dl)-F relation in cm$^{-1}$, the above equation may be rewritten as follows: $(F_p)_1/S + FSW_1 = (F_p)_2/S + FSW_2$. Solving for $S$, the modulus of active stiffness may then be normalized (Sn) by multiplying by end-diastolic fiber length.$^3$

There proved to be several disadvantages of this type of analysis, however. Firstly, if the intervention is too small, changes in $F_p$ and FSW are so small that a large error is introduced in attempting to measure their difference. If, on the other hand, the intervention is too large, one may not assume that CEW has not changed significantly in the afterloaded beat. In an attempt to obviate this problem, beats were selected in which changes in $F_p$ and flow rate could be accurately measured, but in which the calculated CEW did not change by more than 2% when an average normal value of active stiffness was used to calculate CEW. These limitations, however, led to a search for other methods for calculating functional active stiffness of the ventricle.

**Method 2.** Two adjacent cardiac systoles were examined; one an auxotonic control beat and the other an isovolumic contraction of the ventricle at the same end-diastolic volume (Fig. 1). The force-time curves of the two beats were plotted and superimposed as illustrated in Figure 2. The time course of force development before the onset of ejection in the auxotonic beat can be seen to be identical in the two beats. At any given moment in systole in the two beats, it was assumed that the intensity of the active state was the same and the instantaneous difference in wall force and circumferential fiber length of the two beats was measured to derive active stiffness (dF/dl). Thus, dF/dl was calculated as $(F_1 - F_2)/(l_1 - l_2)$ (Fig. 2). For this measurement the point of peak force of the auxotonic beat was chosen for two reasons: First, the series elastic velocity of the auxotonic beat is zero at this moment. Secondly, at this time in the auxotonic beat, the change in fiber length is large enough to minimize the error of this measurement. Assuming a linear relationship between dF/dl and $F$ (8), the modulus of active stiffness ($S$) was derived by dividing dF/dl by the wall force that existed in the isovolumic beat at the moment of measurement ($F_1$). This value in turn was normalized for unit fiber length by multiplying by end-diastolic fiber length and the normalized modulus of functional active stiffness (Sn) is expressed as cm$^{-1}$ per cm of muscle length. One theoretical disadvantage of this analysis is that the instantaneous length of the CE may be

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$^3$Since the addition of series elastic elements in parallel with one another is associated with the addition of an equal number of force-generating sites in parallel, the force generated by a single contractile unit will be reduced pari passu with the addition of parallel SE elements. Since dF/dl varies linearly with force (8), normalization for cross-sectional area of muscle is not required.
shorter at \( F_2 \) than at \( F_1 \). If so, the \( dl \) measured will include some shortening of the CE as well as shortening of the SEC. For this reason, a third method for measuring active stiffness of the ventricle was devised.

**Method 3.** The experimental design is the same as for method 2, and the force-time curves of an auxotonic and adjacent isovolumic contraction are plotted in like fashion (Fig. 2). At the point of peak force of the auxotonic systole (\( F_2 \)) the instantaneous fiber shortening rate (FSR) is measured. As the series elastic velocity is zero at this moment, FSR is equal to CE velocity. The rate of force development (\( dF/dt \)) of the isovolumic beat is then measured at the same level of wall force (point A, Fig. 2). Assuming that the intensity of the active state of the ventricle is the same at A as it is at \( F_2 \) (see below), one may conclude that CE velocity is the same at these two points since wall force is the same. Thus, FSR at \( F_2 \) may be equated to series elastic velocity at point A, and \( dF/dl \) is derived as follows: \( dF/dl = (dF/dt)/FSR \). The modulus of active stiffness is calculated by dividing \( dF/dl \) by \( F_2 \) and is then normalized as described under method 2.

**Results**

The results are summarized in Table 1. Twenty-two pairs of auxotonic beats from 10 normal dogs were analyzed by method 1; contractile element work of the afterloaded beat differed by less than 2% of that of the control beat. The normalized modulus of active stiffness (\( Sn \)) in this group averaged \( 18.2 \pm 4.9 \) cm\(^{-1} \) per cm of muscle length. Fifty isovolumic interventions were analyzed in 16 normal dogs by method 2, and the average value for \( Sn \) was found to be \( 24.3 \pm 7.0 \) cm\(^{-1} \) per cm of muscle length. The average \( Sn \) of

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**Table 1**

<table>
<thead>
<tr>
<th>Functional Active Stiffness</th>
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<tbody>
<tr>
<td>No. of dogs</td>
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<td>-----------------------------</td>
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<tr>
<td><strong>Control</strong></td>
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<tr>
<td>Method 1</td>
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<tr>
<td>SD</td>
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<td>Method 2</td>
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<tr>
<td><strong>Acute myocardial infarction</strong></td>
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<td>Method 1</td>
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<td>SD</td>
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<td>Method 2</td>
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<td>SD</td>
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<td>Method 3</td>
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<tr>
<td>SD</td>
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<tr>
<td><strong>Subacute myocardial infarction</strong></td>
</tr>
<tr>
<td>Method 2</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Method 3</td>
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<tr>
<td>SD</td>
</tr>
<tr>
<td><strong>Chronic myocardial infarction</strong></td>
</tr>
<tr>
<td>Method 1</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Method 2</td>
</tr>
<tr>
<td>Method 3</td>
</tr>
</tbody>
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\( sd \) = standard deviation. The determinations on each dog were averaged and treated as one observation.

\( l_0 \) = Circumferential end-diastolic fiber length.

\( S \) = Modulus of active stiffness.

\( Sn \) = Modulus of active stiffness, normalized for unit fiber length.

LV = Left ventricular.
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50 determinations in 20 dogs by method 3 was $24.0 \pm 5.6 \text{ cm}^2/\text{cm}$.

Active stiffness was measured by all three methods 1 hour following ligation of the anterior descending coronary artery. Eleven such determinations were made in 3 dogs by method 1, 13 determinations in 5 dogs by method 2, and 14 measurements in 6 dogs by method 3. Ventricular arrhythmias were transient, and despite visible loss of contractility of that area of the myocardium rendered ischemic, left ventricular end-diastolic pressures remained normal (0 to 5 mm Hg) during the period of study. The average left ventricular end-diastolic volume was 80 ml before and 88 ml after coronary ligation, but in some experiments this volume fell following coronary ligation. Four dogs were studied 2 to 3 weeks after two-stage surgical ligation of the anterior descending coronary artery. Active stiffness was studied by methods 2 and 3 in each animal. An irregular, transmural, anteroseptal myocardial infarction with slight thinning of the ventricular wall in the region of the infarction was found at autopsy in all 4 dogs. Two dogs with a similar two-stage coronary artery ligation were studied 9 and 11 months later, but in these postmortem examination of the heart demonstrated a thin-walled, pale, fibrous aneurysm 4 cm in diameter. Six determinations of active stiffness were made in these 2 dogs by method 1, and two analyses by methods 2 and 3 were performed in 1 of these animals.

The data were tested for homogeneity of variance. With all three methods, the variance in the control group was not significantly different from the variance in the acute or subacute groups. Similarly, with method 1, the variance in the control group can be assumed equal to the variance in the chronic group. Under the assumption of equal variance, $t$-tests were applied for the difference between the means of the above groups. There was a significant difference between the chronic and control group with method 1 ($P < .02$). The differences between the acute, subacute and control groups was not significant. The two determinations by method 2 and the two by method 3 in the dog with chronic infarction were not analyzed statistically, but averaged 57% and 55%, respectively, of the means of the control group.

Discussion

The elasticity of active muscle is far less than that of resting muscle. Under experimental conditions in which nonuniformity of activation of muscle has been minimized by mass electrode stimulation, the elasticity of isolated, active heart muscle is approximately three times that of active skeletal muscle (3, 8). In the intact heart, there is good reason to believe that the overall active stiffness will be different from that in isolated heart muscle. The entire myocardium is not activated simultaneously, and if inactive muscle is present in series with active muscle, the overall active stiffness of the ventricle will be decreased both early and late in systole when wall force is low. In addition, fibrous valves and chordae tendineae contribute to the passive series elements during systole and will thus modify the active stiffness of a ventricle. Also, of great importance is the fact that the methods used in estimating active stiffness in the intact heart are different from those used in isolated-muscle studies, and this alone may be responsible for differences in results. It should be emphasized that the mechanical component which we refer to as the series elastic component of the entire ventricle is not functionally homogeneous. Its lengthening is equal but opposite in sign to all shortening of the CE except that amount of CE shortening which ejects blood from the ventricle. For the above reasons, a measure of the active stiffness of this spring will represent the overall stiffness of what in reality is a number of springs with differing stiffness. Although it may be difficult to compare measurements of active stiffness in the intact heart to those in isolated muscle, the former have direct bearing on the performance of the intact heart and provide a basis for examining the role of passive elements of the myocardium during systole which may not be apparent in studies of isolated muscle. For example, the mechanical
abnormalities produced by myocardial infarction, ventricular aneurysm or abnormal activation of the heart can be properly assessed only in the intact heart.

**Sources of Error**

Practical and/or theoretical objections can be found to each of the three methods described in this paper. With method 1, it was difficult to predict the optimal afterload which would produce small but easily measurable changes in fiber-shortening work and force-generating work. Furthermore, this method is based on the assumption that small increases in afterload do not alter CEW, and to determine whether a significant change in CEW had been produced by an increase in afterload it was necessary to assume an average value of active stiffness.

The average modulus of active stiffness found by method 1 was lower than that found by methods 2 and 3, and a consistent error would be introduced in method 1 if the CEW of the afterloaded beat were less than the control beat. However, the direction of this error would be such as to give a spuriously high value of the modulus of active stiffness, and since most normal systoles function at the peak of the CEW-load curve (9), it is unlikely that the CEW of the afterloaded systole was consistently greater than the control beat.

Several sources of error in method 2 warrant consideration. One is that systolic coronary blood flow has been ignored. While this would vary insignificantly in two similar auxotonic beats, the analysis by method 2 assumes that an isovolumic contraction has been produced. Consideration of this error would indicate that both $dF$ and $dl$ have been slightly underestimated and the resultant $dF/dl$ would not be altered in a predictable fashion. Furthermore, it has been estimated that the ratio of systolic coronary blood flow to stroke volume (flowmeter) in these experiments is not greater than 1:40 (14). Thus, it is unlikely that an important source of error would be introduced by this factor. Since the ratio of systolic coronary flow per beat to end-diastolic volume would be approximately 1:120, the error in the calculation of wall force would be miniscule. A second problem concerns the slight delay in the flow signal (maximum 2.5 msec) relative to the measurement of intraventricular pressure. While this delay would be constant during consecutive auxotonic beats, $dl$ would be underestimated and therefore $dF/dl$ overestimated by the present calculations. However, in six determinations, correction for this delay was made and the value for $dF/dl$ was decreased by only 2 to 3%.

The major objection to method 2 is that the calculated $dl$ of the SEC (1, -1, Fig. 2) may well include some shortening of the CE, which has not been possible to estimate. While the close agreement between the results of methods 2 and 3 suggests that this error is small, there still remains a basic difference between this in vivo method and in vitro methods for measuring series elasticity (7, 8).

The theoretical basis for method 3 on the other hand more closely resembles the isotonic technique used by Sonnenblick for determining series elasticity of cat papillary muscle (8). As described, however, method 3 differs from the in vitro technique in two respects. The measurement of CE velocity in the in vivo method is made somewhat later than that of $dF/dt$ (approximately 40 msec). Therefore, the instantaneous muscle length at which CE velocity is measured is slightly shorter than that at which $dF/dt$ is measured. Since velocity is a function of instantaneous muscle length, CE velocity will be slightly less at $A$ than at $A$ and thus the modulus of active stiffness will be slightly overestimated by this method. However, since FSR is measured early in the ejection period, at a time when the average fiber shortening is only 1.25% of end-diastolic fiber length, the magnitude of this error should be small. The second problem in method 3 concerns a possible difference in the intensity of the active state of muscle at $F_2$ and $A$ (Fig. 2). The studies of Brady (17) and of Sonnenblick (18) indicate that in isolated heart muscle at 20° to 30°C, the intensity of the active state rises gradually, and that this

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FIGURE 3

Relationship of external mechanical efficiency (FSW/myocardial \( \cot \theta \)) to FSW/CEW of the dog left ventricle. A, In this plot CEW was calculated using the modulus of series elasticity found in studies of cat papillary muscle (16) (reproduced with permission of the Journal of Clinical Investigation). B, The data in A were recalculated using the mean value for active stiffness found in the present study (method 1). While the relationship in A is best described by a quadratic equation, that in B is best described by a linear equation. See text.

is abbreviated by increases in temperature. In the intact dog heart (36° to 38°C), however, there is reason to believe that the intensity of the active state is near maximum and quite constant from 40 msec to more than 100 msec after the onset of pressure rise. The evidence for this is as follows: if the instantaneous force-velocity relations throughout an isovolumic systole are calculated (9), a plot of \((F_0 - F)/V\) vs. \(F\) remains linear from 40 msec to greater than 100 msec after the onset of pressure rise (H. J. Levine, manuscript). This would indicate a single hyperbolic relationship between force and velocity during this period and suggests that a detectable change in the intensity of the active state has not occurred during this time. Thus, in method 3 there is reason to believe that the intensity of the active state of the ventricle is essentially the same at A and at \(F_2\) (Fig. 2).

Of the three methods presented, method 3 is practical and perhaps the least objectionable conceptually. An additional advantage of this method is that since \(dF/dt\) is calculated relatively early in systole, the small error introduced by unmeasured systolic coronary blood flow is lessened even further.

INTACT HEART VS. PAPILLARY MUSCLE

Sonnenblick found the modulus of series elasticity of the cat papillary muscle to be 32 ± 3.9 cm\(^{-1}\) per cm of muscle length (8). While these studies were performed at 22° to 23°C, series elasticity has been shown to be unaffected by changes in temperature (3). Although the techniques used for the measurement of active stiffness in the intact ventricle differ from those used in isolated papillary muscle, it is noteworthy that all three methods reported here yielded results that were lower than those reported by Sonnenblick. By method 1, active stiffness of the ventricle was only 57% that reported in isolated heart muscle, while the average values observed by methods 2 and 3 were 76% and 75% of this figure. Whether these differences are real or due merely to unrecognized errors in methodology is not known. There is, however, evidence of a different sort which suggests that the true active stiffness of the ventricle is less than one would predict from the data obtained in isolated muscle. In a previous study (16), relating muscle mechanics to energetics in the intact canine left ventricle, the relationship between external mechanical efficiency and the ratio of fiber-shortening work to contractile-element work (FSW)/(CEW) was examined. For the calculation of CEW in these studies, Sonnenblick’s values for series elasticity of the cat papillary muscle were used (19). By regressing the plot through zero (Fig. 3A), it was found that a quadratic equation fit the points significantly better than a linear one \((P < .01)\). The implication of this finding is that the efficiency of the CE increases with increasing FSW/CEW. Since this would be
difficult to justify in terms of a simple series elastic model (16), another explanation was suggested; namely, that the modulus of series elasticity of the intact canine ventricle was overestimated by the in-vitro figures. To test this hypothesis, the data in Figure 3A were recalculated using the average modulus of active stiffness found in normal dogs by method 1. The new plot (Figure 3B) was examined in similar fashion, and it was found that the relationship was now best described by a linear equation and that this relationship was significant at the .01 level. It would appear likely, therefore, that the active stiffness of the intact ventricle is indeed less than that measured in isolated heart muscle.

**EFFECT OF MYOCARDIAL INFARCTION ON ACTIVE STIFFNESS**

No change in active stiffness was observed 1 hour and 2 to 3 weeks following coronary artery ligation, despite the observation that the ischemic muscle visibly lost contractility. This would suggest that either the functional impairment of the myocardium was not sufficiently large to detect these changes or that the ischemic muscle was viable enough to function qualitatively as active rather than passive or resting muscle. In the latter case, the overall contractile force of the ventricle may have decreased, but active stiffness was still commensurate with wall force. Thus, while a large variance was present in these groups, no significant change in active stiffness could be demonstrated by the present techniques.

Chronic infarction, with replacement of muscle by a thin fibrous scar, on the other hand, significantly reduced active stiffness of the entire ventricle. In this instance, it is presumed that the elasticity of the thin scar is greater than that of the normal active heart muscle it has replaced.

These data suggest that a significant decrease in overall active stiffness of the ventricle does not occur in experimental acute myocardial infarction and that the functional impairment which occurs in this situation is not likely to be due to changes in myocardial compliance during systole. However, when scarring has become complete, particularly where ventricular aneurysm has developed, active stiffness of the entire ventricle may be decreased substantially. The effect of this change is to increase the internal or force-generating work performed by the CE and thus reduce the ratio of external work to total CE work and the mechanical efficiency of the heart. It is conceivable, therefore, that the major mechanical defect in congestive heart failure, an inability of the myocardial fiber to shorten adequately (20, 21), may be brought about by a functional defect of active stiffness alone. In ventricular aneurysm, for example, a reduction in overall active stiffness diverts the work of the CE from fiber shortening to force generation. Whether this defect is present in other forms of myocardial failure remains to be shown.

**Acknowledgment**

The authors thank Miss Marcella Czarnecki for her valuable technical assistance and Mrs. Judith Goldberg for her secretarial aid.

**References**


\[^{4}\text{Since force-generating work equals } F/S (16), \text{ a reduction in the modulus of active stiffness } (S) \text{ will mean that the CE must generate more work to reach a given level of force.}\]

_Circulation Research, Vol. XIX, November 1966_
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*Circ Res.* 1966;19:970-979
doi: 10.1161/01.RES.19.5.970

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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