Contractility and Stiffness of Noninfarcted Myocardium After Coronary Ligation in Rats

Effects of Chronic Angiotensin Converting Enzyme Inhibition

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Background. Previous studies have shown that global left ventricular function is depressed after myocardial infarction. However, little is known about the effects of myocardial infarction on contractility and the passive-elastic properties of residual myocardium.

Methods and Results. We evaluated isometric function and passive myocardial stiffness in isolated, noninfarcted left ventricular papillary muscle from rats 6 weeks after sham operation or myocardial infarction. Maximal developed tension and peak rate of tension rise (+dT/dt) were significantly decreased in untreated rats with large myocardial infarction compared with controls (3.3±1.1 versus 4.3±0.6 g/mm² and 49.5±17.5 versus 72.5±10.5 g/mm²/sec, respectively). Time to peak tension was prolonged (120±8 versus 102±4 msec) and myocardial stiffness was increased in untreated myocardial infarction rats compared with controls (35.2±4.9 versus 24.2±3.7). Rats with smaller myocardial infarctions differed from controls only with respect to a prolongation of time to peak tension. Papillary muscle myocyte cross-sectional area was increased by 44% (p<0.05), and myocardial hydroxyproline content was increased by 160% (p<0.05) in rats with large myocardial infarctions compared with controls. To determine whether treatment that improves left ventricular function after myocardial infarction also improves myocardial function, rats were treated with captopril beginning 3 weeks after myocardial infarction and continuing for 3 weeks. Treatment with captopril attenuated the prolongation in time to peak tension in the myocardial infarction rats; however, developed tension, +dT/dt, and muscle stiffness remained abnormal. Compared with untreated myocardial infarction rats, captopril-treated myocardial infarction rats had a 9% decrease in myocyte cross-sectional area (p=0.1) but a persistent increase in myocardial collagen content. In summary, large myocardial infarction in rats causes contractile dysfunction, increased stiffness, myocyte hypertrophy, and increased collagen content in the residual noninfarcted myocardium. Treatment with captopril alters the process of cardiac remodeling and hypertrophy and improves one parameter of contractility in noninfarcted myocardium; however, myocardial collagen content and myocardial stiffness remain abnormal.

Conclusions. These findings suggest that angiotensin converting enzyme inhibition in the rat infarct model of heart failure improves global cardiac performance via combined effects on myocardial function and the peripheral circulation. (Circulation 1991;83:1028–1037)

After large myocardial infarction, there is progressive left ventricular dilatation and depression of global left ventricular performance. These changes occur even in the absence of additional ischemic insult. Global cardiac function after myocardial infarction is influenced by several factors, including contractility of residual myocardium, ventricular geometry, mechanical properties of the scar tissue and residual myocardium, and ventricular loading conditions. Although a significant body of data have accumulated that describe the influence that several of these factors have on left ventricular performance, surprisingly little is known about the function of the noninfarcted myocardium. The question of whether there is intrinsic dysfunction of the noninfarcted myocardium is of great importance.

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because efforts to improve global cardiac function with inotropic agents are unlikely to succeed if subnormal muscle function is not contributing to “whole organ” dysfunction.

Intrinsic myocardial function after myocardial infarction cannot be deduced from evaluation of indexes of global ventricular function because these indexes represent the combined changes in the residual noninfarcted myocardium and scar tissue. Thus, there is inherent difficulty in quantifying both systolic and diastolic properties of the residual myocardium in infarcted hearts. Methods of assessing myocardial wall stress in vivo rely on mathematical models that assume that the ventricle has a symmetrical shape (ellipsoid or spheroid), uniform wall thickness, homogeneous myocardial elasticity, and a constancy of forces from epicardium to endocardium. This clearly is not applicable to the infarcted heart because it contains thin areas of scar and other areas of compensatory hypertrophy. Because of the limitations of previous techniques, contractile state and passive stiffness of noninvolved myocardium after myocardial infarction are not known.

Treatment with angiotensin converting enzyme inhibitors has been shown to decrease left ventricular dilatation, improve global hemodynamics, and improve survival in the rat infarct model of heart failure. There are also data that suggest that angiotensin converting enzyme inhibition may slow the rate of left ventricular dilatation in humans after myocardial infarction. Whether these salubrious effects of angiotensin converting enzyme inhibition are attributable to alterations in the peripheral circulation or changes in muscle function is unknown. The purpose of the present study was to measure active and passive properties of isolated, noninfarcted papillary muscle in rats after large myocardial infarction with no treatment or after treatment with captopril. We hypothesized that contractility would be depressed and that muscle stiffness would be increased after large myocardial infarction. We further speculated that treatment with captopril would in part correct these abnormalities. Finally, we performed morphometric and biochemical analyses of the myocardium to determine whether changes in myocyte size or myocardial collagen content were associated with changes in systolic and diastolic functions after myocardial infarction.

Methods

Myocardial infarction was produced in male Sprague-Dawley rats (Harlan, Indianapolis, Ind.) weighing 220–260 g. All studies conformed to the animal care guidelines of the American Physiological Society. Rats were screened for evidence of large myocardial infarction 21 days after surgery using surface electrocardiographic recording. Previous studies have shown that most rats identified in this manner have infarction of more than 40% of the left ventricle, elevated left ventricular end-diastolic pressure and volume, and impaired systolic function.

Animals meeting electrocardiographic criteria for large infarcts were randomly assigned to receive no treatment (n=11) or treatment with captopril (E.R. Squibb, Princeton, N.J.) (n=11). Rats from these groups were compared with rats with moderate-sized infarctions (n=5) and a control group of rats that underwent surgery but did not sustain a myocardial infarction (n=4). Because of the low rate of failed infarction, normal animals (n=7) were included in the control group. Treatment with captopril was started immediately after electrocardiographic screening and continued for 21 days. This time course was chosen because histological healing of the infarct region is complete at 21 days, and there is preliminary evidence that initiation of angiotensin converting enzyme inhibition soon after myocardial infarction is not superior to therapy initiated 3 weeks after myocardial infarction. Captopril (2 g/l) was put into the animals’ drinking water. This route of delivery has been shown to produce consistent hemodynamic responses in rats with myocardial infarctions. The fifth group comprised normal, age-matched rats treated with captopril for 21 days (n=6).

Production of Myocardial Infarction

After induction of anesthesia with 2.4 mg/kg acepromazine maleate (TechAmerica, Kansas City, Mo.) and 125 mg/kg i.m. ketamine HCl (Parke-Davis, Morris Plains, N.J.), a left anterior thoracotomy was performed under sterile conditions. The heart was expressed through the incision, and a 7-0 synthetic ligature was secured snugly around the proximal left anterior descending coronary artery. The lungs were inflated to reduce the pneumothorax, and the muscle layer and skin were closed separately.

Isometric Muscle Function

Six weeks after myocardial infarction, the animals were killed by decapitation, and the hearts were rapidly excised. The left ventricle was opened from the septum to expose the papillary muscles. The muscles could be distinguished from adjacent or underlying scar tissue, which is white. Figure 1 is a cross section of a left ventricle from a rat 6 weeks after myocardial infarction. It shows the clear delineation between scar tissue and viable posterior papillary muscle. Under a dissecting microscope, the noninfarcted posterior papillary muscle was dissected free in a bath containing oxygenated modified Krebs bicarbonate buffer (mM): NaCl 120, KCl 5.9, dextrose 5.5, NaHCO3 25, NaH2PO4 1.2, MgCl2 1.2, and CaCl2 2.5. The ends of the muscle were grasped with spring clips, and the muscle was suspended vertically from an isometric force transducer (Metrigram Mtm., Gould Instruments, Cleveland, Ohio) in a tissue bath containing the Krebs-Henseleit solution. The bath was bubbled with 95% O2-5% CO2 and maintained at a constant temperature of 33±0.5°C. Field stimulation at 0.5 Hz was delivered through a pair of platinum wire electrodes placed parallel to the muscle. We used 5 msec square wave pulses approximately 10% above threshold (S44, Grass Instruments,
Quincy, Mass.) to produce isometric contractions. The muscle was allowed to stabilize for 1–2 hours with a resting tension of approximately 1 g/mm². The muscle was then stretched to the length at which maximum tension development occurred (L_max). Muscle length was measured at L_max using a calibrated telemicroscope (M101AT, Gaertner Scientific Corp., Chicago). Tension was recorded on a physiological recorder (Gould Recording Inc., Cleveland, Ohio), and digitized data points recorded at 500 Hz were stored on-line onto an IBM AT computer using customized software. A force-frequency relation was determined in a subgroup of muscles by recording contractions at stimulation frequencies of 0.20, 0.33, and 0.50 Hz.

**Myocardial Stiffness**

After the above measurements were completed, the muscle was passively stretched at a constant rate (1.4 mm/min) to a maximum stress of 3 g. A slow rate of stretch was chosen to avoid viscous effects. Tension was recorded as above, except the acquisition rate was 50 Hz. Natural strain (ln L/L₀), where L is instantaneous length and L₀ is length at 0.1 g/mm² stress, was calculated from digitized data points on the tension–time curve. Three separate stretches of each muscle were done to confirm reproducibility. Muscle length was measured at a stress of 3 g. Muscle length at each digitized point was calculated from the known rate of stretch and the time. Myocardial stiffness was calculated using a modification of previously described methods. Natural strain was then plotted against stress, and the curve was fitted to the following exponential equation:

\[ \sigma = \sigma_0 e^{\kappa \epsilon} + B \]  

(1)

where \( \sigma \) is instantaneous stress, \( \sigma_0 \) is stress at \( L_0 \), \( e \) is the base of the natural logarithm, \( \kappa \) is the muscle stiffness constant, \( \epsilon \) is natural strain, and \( B \) is a constant. Differentiating Equation 1 yields:

\[ \frac{d\sigma}{d\epsilon} = \kappa (\sigma - B) \]  

(2)

The term \( \frac{d\sigma}{d\epsilon} \) represents the elastic stiffness and is plotted against instantaneous stress to give a straight line (mean correlation coefficient \( r = 0.998 \)). \( \kappa \) is the slope of this line. \( \kappa \) can be used to compare the passive-elastic properties of different muscles because it is independent of stress and muscle diameter. At the conclusion of each study, the muscle was gently blotted dry and weighed. Assuming cylindrical geometry and a specific gravity of 1.05, papillary muscle cross-sectional area (CSA) was calculated as:

\[ \text{CSA} = \frac{\text{muscle mass}}{1.05/L_{\text{max}}} \]  

(3)
Histological Studies

After the papillary muscle was removed, the heart was separated into right ventricle and left ventricle plus septum, weighed, and immersion-fixed into 10% buffered formalin. The left ventricle was later cut into four transverse slices and embedded into paraffin. Thin sections of the ventricle were stained with Masson’s trichrome, and infarct size was measured by tracing the outlines of the infarcted and noninfarcted regions of the ventricle at each of the four levels.34 Infarct size is given as the mean percent of epicardial and endocardial circumferences occupied by scar tissue for the four sections.

At the conclusion of the functional studies, the papillary muscle was immersion-fixed into 10% buffered formalin and processed as above. Cross-sectional slices were made at three different levels. These sections were stained with hematoxylin and eosin and Masson’s trichrome. Morphometric analysis of the tissue was performed using a modification of previously described methods.11 Briefly, the trichrome stain of each section was projected at a magnification of ×1,100 using a binocular microscope attached to a video camera. This system is interfaced to an AT compatible personal computer equipped with morphometric software (Bioquant TM system IV, R and M Biometrics Co., Nashville, Tenn.). The circumferences of approximately 35 myocytes cut cross-sectionally were traced and digitized. Mean myocyte CSA was calculated for each of the three sections. Thus, approximately 100 myocytes cut into cross sections were measured for each papillary muscle. Portions of the muscle where cell borders could be clearly identified and myocytes were the most round in shape were used for all measurements. The operator was blinded to the experimental group during the analysis.

Myocardial Hydroxyproline Content

In a separate group of rats, hydroxyproline content of noninfarcted left ventricular wall was measured using previously described methods.12 Briefly, the scar was removed from the left ventricle, and the tissue was frozen. At a later time, the tissue was dried, weighed, and hydrolyzed in 6N HCl at 105°C. Hydroxyproline content of the samples was determined using spectrophotometry at 557 nm.

Statistical Analysis

All reported values are given as mean±SD, except where specified. Isometric parameters are means of three to five twitches, and muscle stiffness values are the mean of at least three stretches for each muscle. Muscle stiffness constants and correlation coefficients were calculated by the method of least-squares. Differences between groups were detected with one-way analysis of variance, and intergroup comparisons were performed using the Student’s-Neuman-Keul’s test where differences were found. Significance was defined as a probability of less than 0.05.

Results

At the time of the papillary muscle studies, two rats in the captopril-treated infarct group were noted to have moderate-sized rather than large infarctions. Subsequent histological studies revealed infarct size of approximately 20% of the left ventricle in these rats. Because of the small size of this group, their data were not included in the analysis. Five untreated rats had moderate-sized myocardial infarctions, and their data are included as a separate group.

Body weight tended to be higher in the untreated control rats (p=NS) than in the other groups of rats (Table 1). Therefore, it was necessary to normalize left ventricular weight for body weight for purposes of intergroup comparisons. Left ventricular weight and the ratio of left ventricular weight to body weight were not changed in the untreated large or moderate-sized infarct groups compared with controls; however, captopril treatment decreased left ventricular weight in control and infarct rats and decreased the ratio of left ventricular weight to body weight in control rats. In contrast, right ventricular weight and the ratio of right ventricular weight to body weight were markedly increased in the infarct rats. The development of right ventricular hypertrophy in myocardial infarction rats was diminished by captopril treatment. In contrast, right ventricular weight was not changed in the captopril-treated control rats compared with untreated control rats. Infarct size was comparable in treated (n=6) and untreated (n=6) rats (45% versus 45%) with the ranges being

| Table 1. Heart Weights, Body Weights, and Infarct Sizes in Untreated and Captopril-Treated Control and Infarct Rats |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Control rats    | Moderate-sized  | Large infarct   | Captopril-treated | Captopril-treated |
|                 | (n=11)          | infarct rats    | rats (n=6)      | control rats     | large infarct   |
| BW (g)          | 376±36          | 355±5           | 355±23          | 323±23           | 335±31          |
| LV (mg)         | 798±68          | 749±97          | 734±28          | 571±48*          | 645±75†         |
| RV (mg)         | 226±25          | 267±46‡         | 424±97‡         | 199±13           | 334±82‡         |
| LV/BW           | 2.09±0.07       | 2.19±0.13       | 2.08±0.14       | 1.77±0.11*       | 1.95±0.35       |
| RV/BV           | 0.61±0.07       | 0.70±0.06‡      | 1.19±0.22§      | 0.62±0.03        | 1.00±0.27†      |
| INF             | ...             | 20±2            | 45±6            | ...             | 45±4            |

BW, body weight; LV, left ventricular weight; RV, right ventricular weight; INF, infarct size (% left ventricular circumference).

Values are given as mean±SD. *p<0.05 captopril-treated control versus control; †p<0.05 captopril-treated large infarct versus large infarct; §p<0.05 moderate-sized infarct versus large infarct; ¥p<0.05 large infarct versus control.
<table>
<thead>
<tr>
<th>TABLE 2. Papillary Muscle Characteristics</th>
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<tr>
<td>Control rats</td>
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<tr>
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</tr>
<tr>
<td>PMW (mg)</td>
</tr>
<tr>
<td>PMA (mm²)</td>
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<tr>
<td>Lo (mm)</td>
</tr>
<tr>
<td>L_max (mm)</td>
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<tr>
<td>Diameter (μm)</td>
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<td>Area (μm²)</td>
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PMW, papillary muscle weight; PMA, papillary muscle area; Lo, length at 0.1 g/mm²; L_max, length at maximal developed tension; Diameter, myocyte diameter; Area, myocyte cross-sectional area.

* p<0.05 captopril-treated control versus control; †p<0.05 large infarct versus control.

37–49% and 33–51%, respectively. Mean infarct size in the moderate-sized myocardial infarction group was 20% (range, 19–22%).

Papillary muscle lengths, weights, and CSAs are given in Table 2. Compared with control rats, papillary muscle weight was significantly decreased in the captopril-treated control rats, and L_max was decreased in the untreated large myocardial infarction rats. Otherwise, there were no differences in papillary muscle size among the experimental groups. Compared with the control group, mean myocyte CSA was increased by 44% (p<0.05) in the untreated infarct rats. This finding confirms the presence of myocyte hypertrophy in the papillary muscles from myocardial infarction rats. Captopril treatment resulted in a 9% reduction in myocyte CSA in the large myocardial infarction rats and a 22% reduction (p=0.1) in myocyte CSA in the control rats. Histological examination of the papillary muscles revealed a qualitative increase in interstitial fibrosis in the untreated and captopril-treated myocardial infarction rats (Figure 2). In addition, collagen content of the noninfarcted left ventricular myocardium was significantly increased (p<0.05) in rats with large myocardial infarctions (n=5) compared with control rats (n=5) (8.5±2.7 versus 3.3±1.05 μg hydroxyproline/mg dry left ventricular wt). This elevation of myocardial collagen was also seen in the captopril-treated myocardial infarction rats (n=3) (7.2±0.5 μg hydroxyproline/mg dry left ventricular wt). Captopril-treated control rats (n=4) did not differ from untreated controls with respect to this parameter (3.9±0.8 μg/mg dry wt).

There were no differences in papillary muscle mechanics between the sham-operated and the unoperated rats; therefore, these were analyzed together as the control group. Papillary muscle function was characterized by decreases in contractility in the untreated large myocardial infarction rats, defined as decreases in developed tension and peak rate of tension rise and prolongation of time to peak tension (Table 3). Captopril-treated large infarct rats also had depression of developed tension and rate of tension rise, but time to peak tension was restored to normal. Representative twitches from untreated control and untreated myocardial infarction muscles are shown in Figure 3. Rats with moderate myocardial infarctions showed only a prolongation of time to peak tension. Muscles from all groups exhibited a negative force–frequency relation (Figure 4). The time to 50% tension decline (t1/2 R) was not changed in either of the myocardial infarction groups, but the peak rate of tension decrease was depressed in both untreated and captopril-treated large myocardial infarction rats. k was significantly increased in untreated and treated large myocardial infarction groups but unaltered in rats with moderate myocardial infarctions. The only significant change in papillary muscle mechanics that occurred in the captopril-treated control rats compared with the untreated controls was an increase in passive muscle stiffness. The passive stress-strain relations for all of the groups are displayed graphically in Figure 5.

**Discussion**

Major changes in systolic and diastolic functions occur after myocardial infarction in humans and experimental animals. These changes are often progressive and may culminate in the syndrome of congestive heart failure, even in the absence of further ischemia or infarction. It is unclear whether the decline in cardiac performance is an immediate consequence of the loss of contractile tissue or whether there are ongoing alterations in the anatomical, mechanical, and functional properties of the remaining viable myocardium that account for the deterioration. Unfortunately, it is very difficult to separate in human subjects the relative contributions of the akinetic scar and the residual myocardial tissue to overall left ventricular function. To overcome this problem, we studied the properties of isolated, noninfarcted papillary muscle from rats. Our results indicate that noninfarcted myocardial tissue develops contractile dysfunction and increased passive stiffness within 6 weeks after large myocardial infarction, but there are minimal functional changes after smaller myocardial infarction. Treatment with captopril improved time to peak tension but not passive stiffness of the muscles from large myocardial infarction rats. This suggests that previously reported propitious hemodynamic effects of angiotensin converting enzyme inhibition in the rat infarct model of
heart failure are results of a combination of improved myocardial function and more favorable ventricular loading conditions.

Many previous investigators have relied on papillary muscle studies to obtain information about intrinsic myocardial function. Because regional cardiac function is different from global cardiac function in segmental disease processes, we used isolated papillary muscles to assess function of the noninfarcted myocardium. Measurements of muscle stiffness done on isolated papillary muscles have been found to correlate well with muscle stiffness derived from stress–strain analyses of intact normal ventricles.10,13 Previous morphometric studies have confirmed that

**TABLE 3. Isometric Function and Muscle Stiffness in Papillary Muscles From Control, Infarct, Captopril-Treated Control, and Infarct Captopril-Treated Rats**

<table>
<thead>
<tr>
<th></th>
<th>Control rats (n=11)</th>
<th>Moderate-sized infarct rats (n=5)</th>
<th>Large infarct rats (n=11)</th>
<th>Captopril-treated control rats (n=6)</th>
<th>Captopril-treated large infarct rats (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT (g/mm²)</td>
<td>4.3±0.6</td>
<td>4.0±1.1</td>
<td>3.3±1.1*</td>
<td>4.3±0.7</td>
<td>3.2±0.5</td>
</tr>
<tr>
<td>+dT/dt (g/mm²/sec)</td>
<td>72.5±10.5</td>
<td>65.0±18.0</td>
<td>49.5±17.5*</td>
<td>70.1±9.9</td>
<td>51.8±5.9</td>
</tr>
<tr>
<td>−dT/dt (g/mm²/sec)</td>
<td>46.6±6.2</td>
<td>40.1±12.0</td>
<td>33.8±9.1*</td>
<td>40.5±6.0</td>
<td>32.2±6.9</td>
</tr>
<tr>
<td>TPT (msec)</td>
<td>102±4</td>
<td>113±6†</td>
<td>120±8*</td>
<td>105±5</td>
<td>109±8‡</td>
</tr>
<tr>
<td>T₁/₂R (msec)</td>
<td>71±6</td>
<td>77±7</td>
<td>77±10</td>
<td>83±10</td>
<td>77±10</td>
</tr>
<tr>
<td>Kₘ</td>
<td>24.2±3.7</td>
<td>27.6±8.2</td>
<td>35.2±4.9*</td>
<td>36.7±7.3§</td>
<td>36.6±9.0</td>
</tr>
</tbody>
</table>

DT, developed tension; +dT/dt, peak rate of tension increase; −dT/dt, peak rate of tension decrease; TPT, time to peak tension; T₁/₂R, time to 50% tension decline from maximal tension; Kₘ, muscle stiffness constant.

Values are given as mean±SD.

*p<0.05 large infarct versus control; †p<0.05 moderate-sized infarct versus control; §p<0.05 captopril-treated infarct versus large infarct; ¶p<0.05 captopril-treated control versus control.

**FIGURE 2.** Photomicrographs of histology of papillary muscle in control (A) and infarct (B) rats. Trichrome stain (×350) shows evidence of increased interstitial fibrosis and myocyte hypertrophy in infarct muscle. Magnification bar, 20 μm.
processes that cause hypertrophy of the ventricular free wall cause qualitatively similar changes in the papillary muscles. Our own morphometric studies also demonstrate the presence of myocyte hypertrophy in the papillary muscles. Furthermore, histological examination showed that none of the muscles studied had evidence of infarction (Figures 1 and 2). These data support the use of papillary muscle studies to define the active and passive properties of residual viable myocardium after myocardial infarction.

Contraction

Papillary muscle function has been shown to be abnormal in the aged, spontaneously hypertensive rat with signs of heart failure and in cats with right ventricular failure after pulmonary artery banding. Only one study evaluated intrinsic function of surviving myocardium in an infarct model of heart failure. Findings in that study were similar to ours in that rats were found to have prolonged time to peak force; however, unlike our study, no difference in developed force or peak rate of force rise was seen 3 weeks after myocardial infarction. Our results suggest that there is progressive functional deterioration of uninvolved myocardium at a later duration (6 weeks) after myocardial infarction. The cellular basis of the contractile dysfunction remains speculative. It is possible that increased expression of fetal myosin isoforms or alterations in intracellular calcium handling may contribute to decreased contractility. The former is known to occur in this model of heart failure, whereas the latter is known to occur in other experimental models but has not been studied in the infarct rat.

Myocardial Stiffness

Analysis of myocardial stiffness has been done in humans and in several models of heart disease in which uniform ventricular geometry is maintained. These models include pressure overload of the right ventricle caused by pulmonary artery banding, left ventricular pressure overload resulting from valvular aortic stenosis or occurring after aortic banding, and pressure overload in the spontaneously hypertensive rat. The results of these studies suggest that myocardial stiffness depends on the characteristics of the muscle, not on the thickness of the wall. Most studies have found that myocardial stiffness is unchanged in early hypertrophy due to pressure overload, variably increased in the later stages, and significantly abnormal in the failing heart. In general, hypertrophy causing a less than 50% increase in left ventricular mass has not been associated with increased myocardial stiffness.

The only other report of changes in myocardial stiffness after healed myocardial infarction showed that resting muscle tension at $L_{max}$ was increased compared with controls; however, $L_{max}$ was not significantly changed. It is possible that muscle stiffness was not changed because the amount of collagen deposition that had occurred 3 weeks after myocardial infarction...
was less than that occurring 6 weeks after myocardial infarction. Interestingly, in addition to finding no change in muscle stiffness, papillary muscle force development also was not depressed in the study by Bing et al. Synthesizing the results of the previous study with those of the current one, it appears that changes in force development and myocardial stiffness develop in parallel and are present at 6 weeks but not 3 weeks after myocardial infarction. These findings are consistent with previous observations in spontaneously hypertensive rats. It should be noted that some investigators have found a closer correlation of myocardial stiffness with myocyte diameter than with amount of interstitial fibrosis. In the present study, there are both myocyte hypertrophy and collagen accumulation in the surviving portion of the ventricle after myocardial infarction. It is therefore difficult to determine which, if either, of these changes may be responsible for the increased passive stiffness of the tissue.

Effects of Captopril

Captopril has been shown to decrease left ventricular dilatation and mortality after myocardial infarction in animal studies. The reason for the improved survival is not known. In a relatively small series of patients, captopril has also been shown to decrease the rate of left ventricular dilatation after myocardial infarction. Our study is the first to report the effects of chronic captopril treatment on indexes of contractility and myocardial stiffness in residual myocardium after myocardial infarction. The major change in the captopril-treated infarct rats was a normalization of the prolonged time to peak tension. Changes in this parameter generally correlate closely with changes in peak unloaded shortening velocity and myosin ATPase activity. The latter is decreased as expression of fetal myosin isoforms (V,δ) increases. Converting enzyme inhibition in this model of heart failure has been shown to result in partial restoration of the normal isomyosin profile. This effect may explain the normalization of time to peak tension in the captopril-treated infarct rats.

Captopril may have advantageous hemodynamic effects in intact animals that exceed those that might be anticipated if the sole improvement was increased speed of contraction in the noninfarcted myocardium. Captopril is known to have marked effects on both venous and arterial circulations, the combination of which produces significant decreases in left ventricular end-diastolic pressure and volume in the failing heart. In addition to the beneficial effects on filling pressures, systolic function may be improved because of the afterload reduction. These effects are probably additive, or synergistic, with the improvement in myocardial contractility.

A final aspect of the present study deserves comment. Captopril treatment lowered left ventricular weight in normal and infarct rats. Right ventricular weight was also significantly decreased by captopril in the infarct group; this effect was not seen in the control captopril-treated rats. There are several possible explanations for these findings. First, by decreasing production of angiotensin II, both preload and afterload are reduced. Unloading the ventricle may decrease the stimulus for hypertrophy that occurs with left ventricular pressure overload. Second, there are data that suggest that angiotensin II acts directly as a trophic factor and that captopril might therefore inhibit hypertrophy by decreasing angiotensin II levels independent of changes in load. The combination of these factors results in decreased weight of the normal or infarcted left ventricle. Conversely, only in the setting of passive pulmonary hypertension due to severe left ventricular dysfunction does the right ventricle decrease in weight during captopril treatment.

It has been observed in the setting of chronic pressure overload that regression of myocardial hypertrophy is sometimes but not always associated with regression of myocardial fibrosis. This is in keeping with our finding that captopril-treated myocardial infarction rats had smaller myocytes than untreated myocardial infarction rats, but the two groups had similarly elevated myocardial collagen contents. This seems to suggest that the collagen content of the tissue is a more important determinant of passive stiffness than is myocyte size. However, the increased stiffness of muscle from normal rats treated with captopril cannot be explained solely on the basis of increased interstitial fibrosis. It is possible that qualitative changes in collagen (e.g., type, distribution, or weave) are more important than absolute amounts of collagen as mediators of passive myocardial properties. Our findings underscore the present lack of information about the structural basis of changes in myocardial passive-elastic properties.

Limitations of the Study

There are three potential limitations to this study. First, it is necessary to make certain geometric assumptions about the papillary muscle to calculate myocardial stiffness. Some investigators have proposed studying the mechanics of the central segment of papillary muscles to eliminate the effects of shape changes and possible structural damage caused by clamping the ends of the muscle. To our knowledge, it has not been shown that such techniques produce results directionally different than those obtained using conventional whole muscle measurements. Because damaged muscle ends tend to increase the series elasticity of the muscle, this would be expected to mask changes in stiffness of the infarct muscles. Therefore, we believe that our findings are valid and indicative of a true increase in passive stiffness of noninfarcted myocardium.

Second, we have assumed that papillary muscle function is representative of the remainder of the noninfarcted myocardium. This is difficult, if not impossible, to verify. The very problem of quantifying regional function in a segmental disease process is what led us to study the papillary muscle. As discussed previously, there are a number of indirect
pieces of evidence that support the use of papillary muscle studies to make inferences about myocardial function.

Finally, there is increasing interest in the existence and physiological importance of tissue renin-angiotensin systems. Our results do not allow us to draw any conclusions about potential changes in activity of a local renin-angiotensin system on myocardial function in this model of heart failure.

Conclusions

Our data indicate that contractile dysfunction and alterations of the passive-elastic properties of noninfarcted myocardium occur in the chronic phase of healed myocardial infarction. These functional changes develop in conjunction with, or possibly as a result, of anatomical and structural changes in the myocardium. These alterations are more pronounced in hearts after large than after moderate-sized myocardial infarction and may underlie the transition from compensated hypertrophy to congestive heart failure. Further studies will be required to delineate the mechanisms of these changes. The beneficial effects conferred by angiotensin converting enzyme inhibition in the post–myocardial infarction setting appear to be related to advantageous effects on the peripheral circulation and improvements in function of the residual myocardium.

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