Functional Significance of Hypertrophy of the Noninfarcted Myocardium After Myocardial Infarction in Humans

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Hypertrophy of the noninfarcted left ventricle as a chronic response to myocardial infarction has been demonstrated in animals and at autopsy in humans. However, the functional significance of postmyocardial infarction hypertrophy is a subject of dispute. The purpose of this study was to determine the time course of development of postmyocardial infarction hypertrophy of the noninfarcted myocardium in humans and to assess its functional significance. Subcostal view, two-dimensional echocardiograms were recorded at rest and during peak exercise, 6 and 40 weeks postmyocardial infarction in 45 patients (16 anterior, 20 inferior, nine non-Q wave infarcts), for measurement of left ventricular mass and ejection fraction. The left ventricular mass index increased from 94±30 to 118±27 g/m² (p<0.01) during the time of the two studies. There was a significant correlation between the change in left ventricular mass index and improved resting ejection fraction (r=0.48, p<0.001) and exercise ejection fraction (r=0.48, p<0.001) at the follow-up study. Of the 32 patients who increased their left ventricular mass index >7%, 18 improved their rest ejection fraction >0.05 units and 17 improved their exercise ejection fraction >0.05 units. Conversely, of the 13 patients who failed to increase their left ventricular mass index, only three improved their rest ejection fraction and one improved the exercise ejection fraction (Fisher’s exact test, p<0.05). We reached three conclusions. First, in humans, significant hypertrophy of the noninfarcted myocardium can be detected by two-dimensional echocardiography, 9 months postmyocardial infarction. Second, patients who demonstrate hypertrophy of the noninfarcted myocardium are more likely to demonstrate improved rest and exercise ejection fraction than those who do not. Third, postmyocardial infarction left ventricular hypertrophy may, therefore, represent a beneficial chronic adaptation to the loss of myocardium after myocardial infarction. (Circulation 1989;80:816–822)
been well documented at autopsy in patients with coronary artery disease,\textsuperscript{10-12} and thickening of the noninfarcted left ventricular wall assessed by echocardiography has been reported in humans,\textsuperscript{13,14} there are no studies that have reported serial changes in left ventricular mass in patients recovering from myocardial infarction. Thus, it is not known whether humans adapt to loss of myocardium by developing hypertrophy of the remaining myocardium to the same degree and time course as do other species. It is also unknown whether such hypertrophy is related to improvement in either resting or exercise left ventricular function (physiologic hypertrophy) or has adverse effects on left ventricular function (pathologic hypertrophy). The purpose of this study, therefore, was 1) to determine the time course of hypertrophy of the noninfarcted myocardium following acute myocardial infarction in humans and 2) to assess the functional significance of the postinfarction hypertrophy by relating its development to changes in ejection fraction at rest and at peak exercise.

Methods

Population

Forty-five patients recovering from an acute myocardial infarction (as documented by clinical history and serial electrocardiograph and cardiac enzyme changes) comprised the study population. They included all patients discharged from Harbor-UCLA Medical Center who met inclusion criteria for this study. Patients were excluded if they had unstable angina pectoris (one patient), congestive heart failure refractory to medical therapy (two patients), malignant uncontrolled ventricular arrhythmias (one patient); if they were unable to exercise for orthopedic or neurologic reasons; or if they had two-dimensional echocardiograms of inadequate quality (six patients excluded because of inadequate echocardiograms). Patients with multiple infarctions and patients with compensated congestive heart failure were not excluded. The population had a mean age of 53±10 (mean±1 SD) years with a range from 27 to 73 years of age. There were 36 men and nine women. Thirty-seven patients had no prior history of myocardial infarction, and eight patients had a clinical history of at least one prior myocardial infarction. The locations of their myocardial infarctions according to 12-lead electrocardiographic criteria were anterior in 16, inferior in 20, and non-Q wave infarctions in nine patients. Informed consent was obtained from all patients prior to entry into the study, according to a protocol approved by the Research Committee and Human Subjects Committee at Harbor-UCLA Medical Center.

Echocardiograph Protocol

Subcostal, four-chamber, two-dimensional echocardiograms were recorded in the upright position at rest just prior to exercise and at the peak of symptom-limited graded upright bicycle exercise as described herein, using a protocol previously reported by this laboratory.\textsuperscript{15} Briefly, the echocardiographic transducer was placed in the subcostal position, just inferior to the left of the xiphoid process, and gently angled upward and posteriorly to visualize the left ventricular cavity. Using the mitral valve plane as a guide, the longest possible axis of the left ventricular cavity was then visualized by angling and sweeping the transducer slightly from side to side. The images of the left ventricle were obtained during quiet respiration or on held, partial inspiration, as close as possible to atmospheric intrathoracic pressure. The Mueller and Valsalva maneuvers were carefully avoided. Using this protocol, reproducible measurements of left ventricular mass,\textsuperscript{16-19} cavity volume,\textsuperscript{20-23} ejection fraction,\textsuperscript{22} and regional endocardial motion\textsuperscript{15,24} can be made and have been validated previously. The two-dimensional echocardiographic images were recorded on ½-in. VHS videotape.

The end-diastolic (onset of the electrocardiographic ORS) wave and end-systolic (smallest left ventricular cavity just prior to mitral valve opening) frames were identified by slow motion and frame-by-frame review of the videotape, in which all or nearly all of the endocardial and epicardial contours could be visualized on a single stop-frame image. Patients, in whom images of adequate quality could not be obtained at rest, were excluded from the study. Patients, in whom an adequate resting study could be obtained at the initial study, uniformly had adequate images obtainable at peak exercise and at the follow-up study. The endocardium was identified as the interface between the myocardial echoes and the cavity echoes, and the epicardial echoes were defined as the middle of the brightest pericardial echoes. The endocardial and epicardial borders were identified visually and traced manually for transfer to a microcomputer, using an XY digitizer directly overlaid on the video image (Dextra D-100). Left ventricular end-diastolic and end-systolic volume and the left ventricular end-diastolic muscle mass were calculated by the microcomputer using a previously validated single-plane Simpson’s Rule algorithm.\textsuperscript{19,22,25,26} Calculation of ventricular volumes and muscle mass were done separately for the initial and follow-up studies with the observer blinded to the clinical status of the patient and the results of the initial study.

Exercise Protocol

Exercise was performed in the upright position on a bicycle ergometer. Work was begun at 0 kilopond meters (kpm)/min and increased at increments of 75 kpm/min each minute until maximally tolerated exercise was achieved. During exercise, the electrocardiogram was monitored continuously. Sphygmomanometric blood pressures and 12-lead electrocardiograms were obtained at rest, every 3 minutes during exercise, and at peak exercise. The patients were exercised to the point of exhaustion.
(38 patients in study 1; 41 patients in study 2), moderately severe angina (five patients in study 1; four patients in study 2), or ST-segment depression on the 12-lead electrocardiogram that exceeded 0.2 mV in any lead (one patient in study 1; none in study 2). The test was discontinued because of hypotension in one patient in study 1 and none in study 2.

Sequential Studies

The patients were studied on two occasions. The first was 4–6 weeks (mean, 5.5 weeks) following their myocardial infarction. The protocol was repeated 6–9 months postinfarction (mean, 8.5±2.5 months). During the intervening period between the first and second exercise echocardiograms, the physician caring for the patient had no knowledge of the results of the first echocardiogram and the investigators did not attempt to influence any clinical decisions regarding changes in therapy or other diagnostic evaluations.

Statistical Analysis

All data are expressed as mean±1 SD. The statistical significance of changes in left ventricular volume, ejection fraction, heart rate, blood pressure, and left ventricular mass between the two studies was tested by analysis of variance. The significance of changes in heart rate and systolic pressure from rest to peak exercise was tested using the Student’s t test for paired data. The significance of correlations between changes in left ventricular mass and changes in ejection fraction was tested using least-squares linear regression formulae and Fisher’s exact test for data conforming to a 2×2 table. A p value of 0.05 or less was considered statistically significant.

Results

All of the 45 patients who entered the study were available for the follow-up study. There were no deaths in the patient population during this time and only one patient required coronary artery bypass grafting. There were no significant differences in the dosage of oral nitrates, β-adrenergic-blocking agents, or calcium channel-blocking agents taken by the patients between the first and second studies. There were no significant differences between the initial and following studies in exercise duration (7.5±1.8 vs. 7.9±2.3 minutes, p>0.10), maximum exercise heart rate (132±23 vs. 136±24 beats/min, p>0.20), or maximum exercise systolic blood pressure (172±31 vs. 177±28 mm Hg, p>0.20).

Changes in Left Ventricular Mass Index

During the 9 months postmyocardial infarction, the patient left ventricular mass index increased from 94±30 to 118±27 g/m² (p<0.01). Because there was no change in resting end-diastolic volume index between the two studies (78±29 vs. 79±31 ml/m²), the end-diastolic-volume/left-ventricular-mass ratio decreased significantly, as the hypertrophy developed (0.45±0.11 to 0.36±0.11, p<0.001). The 37 patients recovering from their first myocardial infarction had a significant increase in left ventricular mass index (91±25 to 116±26 g/m², p<0.001), as did the eight patients with multiple infarcts (104±47 to 125±23 g/m², p<0.02). Similar degrees of increased left ventricular mass index were demonstrated when patients were subgrouped by the electrocardiographic location of their myocardial infarction (anterior, inferior, and non-Q wave infarct) (Figure 1). Patients taking a β-adrenergic-blocking agent had the same change in left ventricular mass index as those not taking the blocking agent (98±35 to 123±33 g/m² vs. 90±25 to 114±20 g/m², p=0.84).

In a previous study of the variability of left ventricular mass measurements in dogs, using the equipment and procedures described in the present study, we reported that an increase in calculated left ventricular mass of 7% must occur for the 95% confidence limits of the measurement (defined as 1.96×SD/the square root of the sample size) to be exceeded. Thus, in this study, we defined a change in calculated left ventricular mass of at least 7% as significant hypertrophy. By this definition, 32 of the 45 patients in the present study had a significant increase in left ventricular mass between the initial and follow-up studies. There was no significant difference between the patients who did or did not develop hypertrophy with regard to medications taken (nitrates, β-blockers, or calcium channel blockers).

Changes in Rest and Exercise Ejection Fraction

At the time of the initial study, the patients with a non-Q wave infarction had a higher resting ejection fraction (0.53±0.16) than did the patients with anterior myocardial infarction (0.38±0.13, p=0.002) or the patients with inferior infarcts (0.42±0.14, p=0.002). However, there were no significant changes between the initial and follow-up studies in either rest (Figure 2) or exercise (Figure 3) ejection...
fraction for the anterior, inferior, or non-Q wave infarct patients.

Relation of Increased Left Ventricular Mass Index to Changes in Rest and Exercise Left Ventricular Function

There were significant differences in improvement in rest and exercise ejection fraction between the patients who increased their left ventricular mass and those who did not. Of the 32 patients who significantly increased their left ventricular mass as previously defined, 18 increased their resting ejection fraction by at least 0.04 units (the 95% confidence limits, as defined for a normal population, as previously reported by this laboratory)23 (Figure 4), and 17 increased their peak exercise ejection fraction (Figure 5) from the initial study to the follow-up study. In contrast, of the 13 patients who failed to increase their left ventricular mass, only one improved their rest ejection fraction and one improved the peak exercise ejection fraction (Fisher’s exact test, p=0.05, for resting ejection fraction changes, and p=0.01, for exercise ejection fraction changes) (Figures 4 and 5).

For the entire patient population, the increase in left ventricular mass index correlated significantly with increases in both resting (r=0.48, p < 0.001) (Figure 4) and the peak exercise (r=0.48, p < 0.001) (Figure 5) ejection fraction between the two studies.

Patients with a single infarct had a significant correlation between left ventricular mass increase and improved rest (r=0.54, p=0.001) and exercise (r=0.51, p < 0.001) ejection fraction. In the eight patients with multiple infarcts, the relation between development of hypertrophy and improved ejection fraction did not attain significance. For the entire group, there was no significant relation between increased left ventricular mass and changes in ejection fraction from rest to peak exercise between the two studies.

Discussion

Hypertrophy of the noninfarcted myocardium has been demonstrated to occur as a chronic response to acute myocardial infarction in several animal studies.1-4 Some authors have hypothesized that this response represents a beneficial “compensatory” adaptation to the loss of myocardium from the acute myocardial infarction.2,6,7 However, others have questioned whether the hypertrophy is a beneficial response and have observed that the hypertrophied myocardium in rats has reduced cap-
illarity density and altered epicardial-to-endocardial blood-flow ratios compared with normal myocardium. These investigators have suggested that the hypertrophy that occurs postmyocardial infarction may be a deleterious response leading to chronic ischemia and recurrent infarctions.  

There is, unfortunately, a paucity of data relating the postmyocardial infarction hypertrophy to left ventricular function, and the functional significance of the hypertrophy is a matter of dispute. Using serial, two-dimensional echocardiograms to measure left ventricular mass and ejection fraction in dogs recovering from an acute anterior myocardial infarction, this laboratory has reported that the development of hypertrophy of the noninfarcted myocardium of the canine left ventricle is associated with improved resting ejection fraction, suggesting that the hypertrophy may be a beneficial chronic adaptation to the myocardial infarction.  

However, there are no data regarding the relation of the postmyocardial infarction left ventricular hypertrophy to left ventricular function during stress.  

Previous studies have shown that left ventricular hypertrophy can be demonstrated in patients with ischemic heart disease at autopsy, and several small series and case reports have suggested that thickening of the contralateral wall, as demonstrated by M-mode echocardiography, occurs in at least some patients who have sustained a myocardial infarction. However, the time course for the development of the hypertrophy, the frequency with which it occurs, and its functional significance are unknown. The data from this study demonstrate that significant hypertrophy of the noninfarcted myocardium occurs in approximately 70% of patients within 8 months of the infarction, regardless of the site of infarction. The data also suggest that the observed hypertrophy is a beneficial adaptation. The magnitude of hypertrophy attained correlates significantly with improved resting and exercise left ventricular function (Figures 4 and 5). The hypertrophy appears to be most beneficial in patients sustaining a first myocardial infarction, raising the possibility that patients who have sustained multiple infarcts may have too little remaining viable myocardium to compensate with a functional hypertrophic response.

In this study, the correlation between the observed left ventricular hypertrophy and improved rest and exercise ejection fraction was only moderate, although highly significant. There are several potential reasons for the observed correlation. First, the patient population was heterogeneous, with variable age, gender, infarct location, multiplicity of infarcts, and previous hypertension. In addition, patient activity levels were not controlled during the study, and it is possible that some patients may have engaged in significantly higher levels of exercise training than others. However, the fact that the correlation between the hypertrophy and improved left ventricular function was significant indicates that at least part of the improved ejection fraction was related to hypertrophy of the noninfarcted myocardium, even though the pathogenesis of the improved ejection fraction clearly is multifactorial.

There are abundant clinical and animal data to suggest that improvements in ejection fraction following myocardial infarction are multifactorial, with both acute and chronic adaptations. Ejection fraction in patients often spontaneously improves during the first 2 weeks postinfarction, independent of specific therapy. Early in acute infarction, plasma catecholamine levels increase markedly, but this is followed by down-regulation of beta-receptors resulting in a blunted response to inotropic stimulation during recovery. In animal studies, acute protein synthesis is preferentially shifted toward increased mitochondria and other elements necessary for contractile function, and, days to weeks later, shifts to enhanced production of myofilaments. Thus, recovery from an acute myocardial infarction is facilitated by multiple mechanisms that are different in the acute and chronic phase. Hypertrophy of the noninfarcted myocardium appears to be an important chronic factor leading to improved rest and exercise left ventricu-
lar function, but which probably has little or no role as an early adaptation to the myocardial infarction.

Critique of Methodology

In this study the accuracy and reproducibility of the measurements of left ventricular mass and ejection fraction are important to the conclusions reached. We have reported, in a previous study,\(^1^9\) on the accuracy and reproducibility of two-dimensional echocardiographic estimates of left ventricular mass compared to autopsy left ventricular weight in dogs with and without myocardial infarction. The reproducibility of echocardiographic left ventricular mass estimates using the equipment and methods described here was significant \((r=0.88, p=0.001, \text{ in 12 normal dogs; and } r=0.84, p=0.005, \text{ in 10 dogs three months postinfarction}).\) However, the SEE was approximately 12%, making a 7% change in estimated left ventricular mass a requirement for exceeding the 95% confidence limits of the test. For this reason, an increase of at least 7% in left ventricular mass was used in this study as the point at which we concluded that detectable hypertrophy had occurred in an individual patient (32 of the 45 patients had hypertrophy by this criterion). Other laboratories have recently reported accuracy and reproducibility measurements similar to this study.\(^1^8,2^1^\)

This laboratory has also compared the two-dimensional echocardiographic measurements of left ventricular ejection fraction at rest and exercise in coronary artery disease patients with first-pass radionuclide angiography \((r=0.91, p=0.001).\)\(^2^2\) The 95% confidence limit reproducibility of two-dimensional echocardiographic measurements of ejection fraction in this laboratory is 0.04 units. This also is similar to the reproducibility reported by other laboratories.\(^1^8,2^1^\) Thus, in this study, changes in both left ventricular mass and ejection fraction were observed that were significantly greater than may be expected solely on the basis of methodologic variability.

Medications taken, the presence of hypertension, and differences in exercise capacity, potentially, could affect the magnitude of hypertrophy observed in this study. However, there were no significant differences between the initial and follow-up studies in any of these parameters, and there was no correlation between these parameters and the magnitude of hypertrophy observed. Significant obstruction of coronary arteries in other portions of the left ventricle may conceivably result in chronic ischemia and may significantly affect the development of left ventricular hypertrophy. Unfortunately, cardiac catheterization was not a routine part of the study protocol; hence, the potential significance of chronic ischemia cannot be addressed by this study.

Conclusions

Our study has demonstrated that hypertrophy of the noninfarcted myocardium occurs in humans and can be detected by two-dimensional echocardiography within 9 months after incurring a myocardial infarction. Patients who develop hypertrophy of the noninfarcted myocardium are more likely to develop improved rest and exercise left ventricular function than those who do not. Post-infarction hypertrophy of the noninfarcted myocardium, therefore, appears to represent a beneficial chronic adaptation to the loss of myocardium following an acute myocardial infarction.

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