Quantitation of Left Ventricular Myocardial Fiber Hypertrophy and Interstitial Tissue in Human Hearts with Chronically Increased Volume and Pressure Overload

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SUMMARY Using new techniques, we quantitated left ventricular myocardial fiber hypertrophy and interstitial tissue in four groups of autopsied hearts free of coronary disease: 1) 22 normal hearts, 2) 20 hearts from patients with mitral incompetence (NYHA Class II-III) who died early after mitral valve replacement from causes other than cardiac failure, 3) 22 hearts from patients with mitral incompetence (NYHA Class III-IV) who died early after mitral valve replacement from cardiac failure with low cardiac output syndrome, and 4) 22 hearts from patients with hypertensive heart disease (NYHA Class II-III). Myocardial fiber hypertrophy was quantitated by measuring cross-sectional myocardial fiber diameter; the proportion of interstitial tissue was quantitated by using a computerized, high-resolution video image-digitizing system.

Myocardial fiber average diameter in groups 2, 3 and 4 was significantly higher than group 1. The proportion of interstitial tissue was significantly increased in group 3. In chronic mitral incompetence an increase in left ventricular interstitial tissue may play a role in the development of severe cardiac failure.

THE MANAGEMENT OF PATIENTS with advanced cardiac failure secondary to chronic valvular heart disease remains one of the most challenging problems encountered by the cardiologist and cardiac surgeon. Despite the surgical correction of the valvular lesions, a number of these patients die of cardiac failure in the early and late postoperative periods.1-3 Our primary objective was to quantitate certain histologic features of the myocardium of these patients in an attempt to explain such irreversible cardiac conditions.

Cardiac muscle is composed of myocardial fibers and interstitial tissue. The development of fiber hypertrophy is one of the fundamental mechanisms that permit the heart to maintain cardiac output in the early stages of chronically increased volume or pressure overload.4 However, little information is available regarding the relative influence of myocardial fiber hypertrophy and of interstitial tissue when cardiac failure develops. In the present study we describe two methods that have enabled us to quantitate and evaluate the possible influence of interstitial tissue and of myocardial fiber hypertrophy in patients who have different degrees of cardiac failure secondary to chronically increased volume or pressure overload.

Material and Methods

Retrospective quantitation of left ventricular myocardial fiber diameter and of interstitial tissue was done in four groups of autopsied hearts uniformly preserved with 10% formalin, matched by patient’s age, sex, and date of autopsy (from 1962 to 1972). Hearts with significant coronary artery disease were excluded from the study.

Group 1 was composed of 22 grossly normal control hearts (mean weight 287 ± 68 g) from individuals who died of a noncardiac cause, most of them from cranial trauma.

Group 2 consisted of 20 hearts (mean weight 560 ± 136 g) from patients with left ventricular volume overload, in the form of chronic predominant mitral incompetence and preoperative moderate left ventricular failure, who had symptoms of dyspnea only with more than ordinary or with ordinary activity (NYHA Class II-III), and who died early after mitral valve replacement (mean 5.13 days) from causes other than cardiac failure. The majority died from bleeding or thromboembolism.

Group 3 comprised 22 hearts (mean weight 622 ± 123 g) from patients with left ventricular volume overload, in the form of chronic predominant mitral incompetence and preoperative severe left ventricular failure, who had symptoms of dyspnea with ordinary activity plus episodic or persistent dyspnea at rest (NYHA Class III-IV), and who died early after mitral valve replacement (mean 5.04 days) from left ventricular failure with low cardiac output syndrome.

Group 4 was composed of 22 hearts (mean weight 574 ± 166 g) from patients with left ventricular pressure overload, in the form of chronic systemic diastolic hypertension and moderate left ventricular failure (NYHA Class II-III), who died from causes other than cardiac failure. The majority died from intracranial hemorrhage or apparent cardiac dysrhythmia.

In each heart, quantitative analysis of left ventricular myocardial fiber cross-sectional diameter and of interstitial tissue was performed from the two myocardial specimens taken from the lateral aspect of the left ventricular wall, one from the base and the other from the apex. Four histologic preparations (two from each specimen) were made and stained with hematoxylin and eosin and with Heidenhain-Weigert-van Gieson stain. Photographs of the histologic preparations at a magnification of ×1,200 were then taken from the cross-sectional areas at the subendocardial and subepicardial regions of both basal and apical specimens. Analysis of the photographs was performed in a blind manner without knowledge of the origin of the histologic preparations.
Quantitation of Myocardial Fiber Hypertrophy

In each heart myocardial fiber diameter was obtained by measuring from the photograph of the stained cross-sectional areas the shortest diameter at the level of the nucleus of at least four myocardial fibers from each of the four histologic preparations and then taking the average results (fig. 1). The fibers measured in each preparation were those considered to be the most representative and easiest to measure. For this reason, and despite the variation of the fiber diameters, we believe that measuring a larger number of fibers in each preparation would result in decreased sensitivity. Variation of the mean diameter among histologic preparations from the same cardiac region was 0.4 μm.

Quantitation of Interstitial Tissue

The photographs of the stained cross-sectional areas were enhanced by using a black pen to darken the myocardial fiber and a white pen to lighten the interstitial space (fig. 2). These photographs were then analyzed by a modified operator-interactive, computer-controlled system developed for high-speed, high-resolution digitization of video images. In this system, a television camera scans each photograph, and the video image of the cross section is digitized into an array of numbers that are mathematically processed to delineate the number of light points (interstitial space) from the number of dark points (myocardial fibers). This delineation of white and black points is performed on each television line during the video scan (fig. 3). When the histologic photograph has been completely scanned, the computer displays the result as a proportion of interstitial space present in the scan preparation. Mean variation among histologic preparations from the same cardiac region was 4%.

Results

Group 1. Normal Control Hearts

Normal control hearts showed a myocardial fiber diameter of 5.8 ± 0.535 μm (mean ± SD) (fig. 4). The proportion of interstitial tissue to myocardial fiber space was 32.2% (fig. 5). In each heart, the left ventricular myocardial fiber diameter and degree of interstitial tissue were similar in the left ventricular basal and apical regions, in both the subendocardial and the subepicardial areas (fig. 6).
Figure 4. Left ventricular myocardial fiber diameter in normal control hearts, in hearts with chronic mitral incompetence and preoperative moderate left ventricular failure, and in hearts with chronic mitral incompetence and preoperative severe left ventricular failure with postoperative low cardiac output syndrome (LCOS). Observe that the two groups with mitral incompetence show significant myocardial fiber hypertyrophy when compared with the normal control hearts.

Group 2. Mitral Incompetence and Moderate Left Ventricular Failure

Hearts from patients with chronic mitral incompetence and preoperative moderate left ventricular failure (NYHA Class II-III) showed a significant ($P = 0.0035$, rank $\Sigma$ test) increase in myocardial fiber diameter (6.4 ± 0.738 μm) representing hypertrophy when compared with the normal hearts (fig. 4). However, the proportion of interstitial tissue was only slightly increased (35.7%) when compared with the normal hearts (fig. 5). In each heart, the degree of left ventricular myocardial fiber hypertrophy and of interstitial tissue was similar in the left ventricular basal and apical regions, both the subendocardial and the subepicardial areas (fig. 6).

Group 3. Mitral Incompetence and Severe Left Ventricular Failure

Hearts from patients with chronic mitral incompetence and preoperative severe left ventricular failure (NYHA Class III-IV) with postoperative low cardiac output syndrome showed a significant ($P = 0.0035$, rank $\Sigma$ test) increase in myocardial fiber diameter (6.8 ± 0.935 μm) representing hypertrophy when compared with the normal hearts (fig. 4). The degree of hypertrophy was not significantly different from the hearts with mitral incompetence and moderate left ventricular failure (group 2). However, the proportion of interstitial tissue was significantly ($P < 0.001$, rank $\Sigma$ test) increased in these hearts with mitral incompetence and severe left ventricular failure (50%) (fig. 5). In each heart, the degree of left ventricular myocardial fiber hypertrophy and of interstitial tissue was similar in the left ventricular basal and apical regions, both the subendocardial and the subepicardial areas (fig. 6).

Group 4. Systemic Hypertension and Moderate Left Ventricular Failure

Hearts from patients with systemic hypertension and moderate left ventricular failure (NYHA Class II-III) showed a significant ($P < 0.001$, rank $\Sigma$ test) increase in myocardial fiber diameter (7.1 ± 0.801 μm), representing hypertrophy, when compared with the normal hearts (fig. 7). However, the proportion of interstitial tissue was not significantly increased in the group with systemic hypertension (31.5%) when compared with the normal group.

The hearts with pressure overload were also similar in myocardial fiber hypertrophy and interstitial tissue when comparison was made between the left ventricular basal and apical regions, both the subendocardial and the subepicardial areas.

Discussion

Left ventricular failure resulting in the low cardiac output syndrome is the principal cause of early death after mitral valve replacement for severe chronic mitral incompetence. Two explanations have been proposed for poor myocardial function following surgery. The first postulates anoxic damage to the myocardium during cardiopulmonary bypass when techniques such as hypothermia with prolonged ischemic arrest or continuous coronary perfusion with ventricular fibrillation were used in the past. However, even with more modern techniques of cardiopulmonary bypass such as preservation of the heart in the beating nonworking state, it is our experience and the experience of others that postoperative left ventricular failure with low cardiac output syndrome is still a leading cause of death in patients with
mitral incompetence. Therefore, other factors may also play a role in the development of this syndrome. A reasonable explanation might be that the low left ventricular reserve inherent in the preoperative state is inadequate to overcome the sudden increase in afterload (Anrep effect) caused by the mitral valve made competent at surgery. This hypothesis is further supported by the fact that a poor surgical result occurs much more commonly in patients with mitral incompetence than in patients with aortic valve disease.

It has been shown that, for patients with predominant mitral incompetence, the surgical outcome depends in large part on the severity of left ventricular failure before surgery. The fact that these hearts appear to show a gross increase in left ventricular fibrous tissue prompted us to consider the possibility that such an increase in interstitial tissue might play a role in the development of preoperative and early postoperative severe left ventricular failure. The development of video-computerized techniques has enabled us to quantitate and evaluate accurately the possible influence of interstitial tissue in patients with left ventricular failure, not only in failure secondary to chronic mitral incompetence but also in that due to systemic hypertension.

Hearts with chronic volume overload in the form of mitral incompetence showed a significant increase in left ventricular myocardial fiber diameter, representing hypertrophy. The degree of hypertrophy in the group with moderate preoperative left ventricular failure was similar to that in the group with severe failure. This suggests that factors other than hypertrophy play a role in decreasing left ventricular function. However, the proportion of interstitial tissue was significantly increased only in the group with severe preoperative left ventricular failure and postoperative low cardiac output syndrome (fig. 8). Thus, it is not unreasonable to think that such a pronounced increase in the noncontractile element may play a role in the development of preoperative and early postoperative severe cardiac failure. Furthermore, as suggested by nonquantitative histologic techniques, the increase in interstitial tissue might also explain the persistence of cardiomegaly in patients who had preoperative left ventricular failure but who survived the operation.

Hearts with chronic pressure overload in the form of...
FIGURE 8. Summary scheme. Quantitation of left ventricular myocardial fiber diameter (abscissa) and interstitial tissue (ordinate) in human hearts with chronically increased volume overload (top) and pressure overload (bottom). The results obtained with the four groups of hearts studied are represented within the respective lined areas. Observe that, depending on the degree of left ventricular failure, the hearts with volume overload tended to develop myocardial fiber hypertrophy and a very significant increase in interstitial tissue. The hearts with pressure overload showed a marked increase in myocardial fiber hypertrophy but not in interstitial tissue. M.I. = mitral incompetence.

systemic hypertension also showed a very significant increase in left ventricular myocardial fiber diameter, representing hypertrophy. When compared with the hearts having volume overload, these hearts did not show an increase in the amount of left ventricular interstitial tissue (fig. 8). A possible explanation might be that patients with hypertensive heart disease die before an increase in interstitial tissue and severe left ventricular failure develop. This is supported by the fact that we were unable to find a sufficient number of hearts with both hypertensive disease and severe chronic left ventricular failure unless coronary artery disease was present (in which case the heart was excluded from the study). Similarly, patients with pressure overload in the form of aortic stenosis tend to die early after the first symptoms of left ventricular failure develop.

In the four groups of hearts, the basal and apical myocardial fiber diameter and the degree of interstitial tissue were similar in each heart. This indicated that, in hearts with myocardial fiber hypertrophy and increased interstitial tissue, these changes developed in a uniform manner throughout the left ventricular myocardium. Thus there was no difference between the degree of subendocardial and of subepicardial myocardial fiber diameter and interstitial tissue. This suggests that, in hearts with myocardial fiber hypertrophy and increase in interstitial tissue, these changes were probably not due to any limitations in coronary blood flow or hypoxia.

With our techniques, the uniformity in the amount of interstitial space among the different areas of the left ventricular wall suggests that we are dealing with a diffuse developing process and not with focal areas of myocardial fibrosis such as are seen in coronary artery disease or as residua of rheumatic myocardial disease. We are not yet able to identify with certainty the material present in the interstitial space of the hearts with chronic mitral incompetence and severe preoperative and postoperative left ventricular failure.

References
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