Myocyte Disarray Develops in Papillary Muscles Released from Normal Tension After Mitral Valve Replacement

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SUMMARY Normal papillary muscles are typified by a cellular architecture in which myocytes are arranged in orderly arrays, whose alignment is approximately parallel to the lines of tension within the muscle. To examine the contribution of directed tensile force to the maintenance of myocyte architecture within the papillary muscle, we studied the histologic effects of abrupt disruption of tension on the myocytes of the left ventricular papillary muscles in 84 patients who died after mitral valve replacement. Focal contraction band necrosis or coagulation necrosis was seen in 57 cases (68%) and fibrosis in 71 cases (85%). Zonal lesions — sarcoplasmic condensations adjacent to intercalated discs — were present in 49 cases (58%) and correlated negatively with survival time. Myocyte disarray in 26 cases (31%) was more frequent with longer survival and became an interconnecting random network of myocytes. All 10 patients who survived more than 1 year had disarray, as did eight of 10 patients who survived 1 month to 1 year. Myocyte atrophy in 19 cases (23%) correlated with the degree of acquired disarray. Multivariate regression analysis of these five histologic features showed significant prediction of survival time by myocyte disarray only. This finding demonstrates that the development and progression of disarray is not significantly associated with any of the other lesions studied. Since surgical disruption of normal lines of tension causes papillary muscles to function in a setting that approaches idealized isotonic contraction, it appears that myocyte disarray may be acquired over time in such a physical state. The findings support the concept that while myocyte orientation usually arises during development as a direct consequence of force distribution within the myocardium, disarray may also be acquired postnatally in regions of myocardium in which force distribution is altered.

MOST of the cardiac muscle cells of the left ventricular myocardium are aligned in an orderly, nearly parallel array so as to reduce chamber size during contraction. In several cardiac conditions, this normal architecture is replaced by a seemingly random network of myocytes. In idiopathic hypertrophic subaortic stenosis, extensive disarray is often seen among the hypertrophic myocytes of the interventricular septum and was once regarded as a relatively specific feature. Disarray is also seen in some congenital malformations, such as right- or left-heart syndrome, in which the myocardium of the respective ventricular wall is typically involved. The presence of myocyte disarray is not confined to pathologic settings, however; it is observed in specific areas of the normal heart; for example, at the juncture of the right ventricular free wall, interventricular septum and the left ventricular free wall both anteriorly and posteriorly. These features are present during the embryonic and fetal stages of cardiac development. Hutchins and Bulkeley suggested that the salient feature of the varied cardiac settings, including idiopathic hypertrophic subaortic stenosis, is a disruption of the force distribution within the myocardium. Typically, this disruption of force distribution subjects the areas of observed disarray to isometric contraction.

While the connection between isometric contraction and fiber disarray has been documented, we were intrigued by the possibility that an approximately isotonic state imposed on regions of myocardium after completion of cardiac development might result in acquired cellular disarray. Accordingly, we studied the papillary muscles of patients who survived for varying times after mitral valve replacement. In this circumstance, the normal forces applied to the myocardium of the papillary muscles have been removed. The cellular architectures observed in the postoperative papillary muscles we studied seem to suggest that postdevelopmental disruption of contractile force distribution leading to isotonicity may generate a pattern of disarray distinct from that in isometric developmental settings, and in marked contrast to the appearance of normal papillary muscle.

Materials and Methods

The autopsy files of The Johns Hopkins Hospital listed 84 adult patients who had undergone mitral valve replacement and whose hearts were studied after postmortem coronary arteriography and fixation in distention. These 84 patients form the basis of this study. Blocks of papillary muscle tissue were taken along the longitudinal axis of both anterior and posterior papillary muscle bodies and included papillary muscle from the apical stump through the left ventricular myocardium at the base of the muscle body. Blocks were taken from normal myocardium of the right and left ventricular free wall and the interventricular septum in each of the abnormal hearts and in normal hearts with intact...
mitral valves and papillary muscles. Tissue blocks were routinely processed and sectioned at 5 μ. The sections were stained with hematoxylin-eosin and Verhoeff-van Gieson’s elastic stain.

Histologic features were graded semiquantitatively on a scale of 0 to 4, with 4 corresponding to greater than 40% involvement of the area of tissue studied microscopically. Myocyte contraction band or coagulation necrosis, zonal lesions and replacement fibrosis were evaluated to assess their possible contribution to the development of disarray and atrophy. Myocyte atrophy was quantitatively confirmed by independent microscopic measurement of myocyte diameters in foci of disarray and myocyte diameters in normally arranged, immediately adjacent myocardium using an ocular graticule and 100 × objective. Standardization was achieved by computing myocyte diameter ratios (diameter in foci of disarray/diameter in normal myocardium). The data were organized by survival group, and all patients were in one of five survival categories: operation to 1 day, more than 1 day to 1 week, more than 1 week to 1 month, more than 1 month to 1 year, more than 1 year to 15 years. Means, standard deviations and correlation coefficients (Pearson’s r) were calculated among variables of interest. Histologic predictors of postoperative survival were analyzed by forward, stepwise, multivariate regression.9

Results
The postoperative survival time for the 84 patients is shown in table 1. The patients were 25–74 years old (average 55 years). There were 56 female patients and 15 black patients. The mitral valve disease was rheumatic in 56 patients, bacterial endocarditis in three, congenital in two, ischemic papillary muscle dysfunction in four and floppy mitral valve in two. In 21 patients, the cause of the valvular disease was uncertain, but eight of them had mitral stenosis, 10 had mitral insufficiency and three had both.

Myocyte necrosis (fig. 1) of both coagulation and contraction band types was seen in the left ventricular papillary muscles of 57 cases (68%). Contraction band necrosis, which results from rapid reflow in areas of previously ischemic myocardium,10,11 was the most frequent necrotic lesion and was seen in 54 cases (64%). It was most common in patients who survived less than 1 day and correlated negatively with survival time (p < 0.05). It also correlated with postoperative hypotension (p < 0.005). Contraction band necrosis in late survivors was associated with acute events during their terminal course. Coagulation necrosis, present in seven cases (8%), did not occur in patients who survived longer than 1 month and correlated negatively with survival time (p < 0.05). Zonal lesions — reversible sarcolemal condensations adjacent to the intercalated discs — were observed in 49 cases (58%) and also correlated negatively with survival time (p < 0.01); zonal lesions were seen most frequently in patients who survived less than 1 week. Although zonal lesions correlated with postoperative hypotension (p < 0.01), we do not know whether their development is equivalent to the lesions previously associated with hemorrhagic shock.12,13 While the lesions seen in such situations are typically found in the subendocardial myocardium, the zonal lesions seen in our patients were almost entirely restricted to the ends of the papillary muscles. Replacement fibrosis was present in 71 cases (85%) and was seen in all survival groups; the incidence of replacement fibrosis was slightly higher in later survival groups, but did not correlate with survival time.

Myocyte disarray (table 2) was present in 26 cases (31%), and the degree of disarray correlated linearly with postoperative survival time (p < 0.001). The foci of disarray ranged from 0.5 to more than 1 cm along at least one dimension and were located at the apical parts of the papillary muscles. Myocyte atrophy was present in 19 cases (23%), and the degree of atrophy correlated with both postoperative survival time (p < 0.01) and the degree of acquired myocyte disarray (p < 0.001). Cell diameters were 7.4 ± 2.1 μ (mean ± sd) for atrophic cells in foci of disarray and 9.6 ± 0.9 μ for cells in areas of adjacent normally arranged myocardium (p < 0.001). In addition to reduction of myocyte diameters, cell length was markedly reduced, but this could not be reliably measured because of the difficulty in locating intercalated discs. Examples of myocyte disarray and myocyte atrophy are shown in figure 2. Deviation, usually angular, from the normal parallel array was occasionally seen very early. This initial disorganization was replaced in later weeks by disarray showing increasing angles of orientation and concomitant decrease in cell size. In patients who survived longer, the patterns of disarray varied. In some papillary muscles, foci of disarray were typified by extensively branching cells of small diameter with prominent interstitial tissue (fig. 2C). In other papillary

<table>
<thead>
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<th>Operative survival group</th>
<th>n</th>
<th>Myocyte necrosis</th>
<th>Zonal lesions</th>
<th>Replacement fibrosis</th>
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<tr>
<td>Operation to 1 day</td>
<td>35</td>
<td>28 (80%)</td>
<td>28 (80%)</td>
<td>27 (77%)</td>
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<td>19</td>
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<td>10</td>
<td>6 (60%)</td>
<td>3 (30%)</td>
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<tr>
<td>Over 1 month to 1 year</td>
<td>10</td>
<td>2 (20%)</td>
<td>2 (20%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Over 1 year to 15 years</td>
<td>10</td>
<td>3 (30%)</td>
<td>0 (0%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>57 (68%)</td>
<td>49 (58%)</td>
<td>71 (85%)</td>
</tr>
</tbody>
</table>
muscles, myocyte branching was equivalent, but the cells retained more normal diameters combined with greatly reduced cell length (fig. 2D). The histologic appearance of mature forms of myocyte disarray and atrophy and prominent interstitial connective tissues in the papillary muscle tips resembled the normal appearance of the sinoatrial and atrioventricular nodes. Multivariate regression analysis was performed using each of the histologic features as independent variables as predictors of postoperative survival. Only papillary muscle disarray entered as a significant predictor, and the regression was significant at the 0.001 level ($r = 0.57$). Although other histologic features were significantly correlated with postoperative survival (atrophy, $p < 0.001$; contraction band necrosis, $p < 0.05$), these features did not give significant addi-

**FIGURE 1.** (A) Contraction band necrosis with irregular transverse sarcoplastic condensation of contractile elements in the dead myocytes. This type of injury occurs from reflow after periods of no flow. (B) Coagulation necrosis with cells showing preservation of the sarcoplasmic elements in their usual positions in the dead myocytes. Fixed coronary artery obstructions are generally associated with this type of injury. (C) Zonal lesions appear as dense sarcoplasmic condensates, located at the ends of the myocytes adjacent to intercalated discs. They are somewhat similar to contraction bands, which are not present in the area. The cells are still viable, as indicated by the presence of preserved nuclei and sarcoplasm in the center of the cells. (D) Replacement fibrosis with dense collagenous tissue and a few interspersed fibroblasts and blood vessels. Hematoxylin-eosin stain; original magnification × 500.
tional predictive value after disarray had entered the regression.

**Discussion**

The striking aspect of the acquired myocyte disarray was its localization in areas of myocardium experiencing isotonic contraction. That the isotonicity within papillary muscle bodies results from surgical intervention during mitral valve replacement may be seen by examining the pre- and postoperative morphology of the mitral valve/papillary muscle system. In the normal (or unoperated) heart (fig. 3A), the papillary muscle is attached to the mitral valve leaflets by chordae tendineae and at its base fuses with the trabeculae carneae of the left ventricular cavity. In this state, lines of tensile force are directed longitudinally through the papillary muscle, corresponding to the tension experienced by the papillary muscle during systole. Most of the myocytes of such normal papillary muscles are arranged in a parallel array aligned with the direction of tension of the chordae on the valve. During surgical resection, portions of the mitral valve leaflets are removed and most of the chordae tendineae are detached from the apical tip of the papillary muscle (fig. 3B).

After resection of the valve leaflets, the remaining basilar portions of the papillary muscles experience no opposing tension during systole and accordingly function in a contractile state that approaches idealized isotonic contraction. The cellular disarray that develops with time in such a contractile state may be explained as a consequence of the sudden interruption of forces that normally serve to coordinate and align the direction of myocyte contraction. The localization of disarray within the tips of the papillary muscles, as well as the distribution of such areas of disarray in discrete foci, are apparently a manifestation of the trabecular nature of the myocyte bundles that compose the papillary muscles. Although the majority of the postsurgical papillary muscle body is suspended within the left ventricle, the extensive basilar fusion of the papillary muscle with the trabeculae carneae of the left ventricular cavity may allow for the persistence of an approximately normal force distribution through many of the cellular bundles within the papillary muscle body. Accordingly, only portions of the ends of the muscle actually experience an isotonic environment, and it was only there that we found foci of disarrayed and atrophic myocytes. We found no evidence that necrosis, zonal lesions or fibrosis played a role in the development or distribution of disarray and atrophy.

That isotonicity should give rise to acquired myocyte disarray equivalent to that in the developmental isometric setting seemed unusual to us, and subsequent comparisons of the myocodes in both situations re-
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Figure 3. (A) Normal posterior papillary muscle complex with discrete heads that histologically have a predominant pattern of parallel myocytes. (B) View toward the apex of the left ventricular cavity from the basilar aspect showing the anterior (right) and posterior (left) papillary muscle complexes from a patient who had undergone mitral valve replacement 2 years before death. The chordae tendineae have been sectioned. Myocyte disarray and atrophy were found in the tips of the papillary muscles. In the portions of the papillary muscles that retained their interconnections with the trabecular muscle, myocyte arrangement and size were normal. IVS = interventricular septum; LV = left ventricle; MV = mitral valve.

Figure 4. (A) Disarrayed and hypertrophied myocardium from the septum of a patient with IHSS compared with (B) disarrayed and atrophic myocardium in the tip of a papillary muscle of a patient who survived 21 months after mitral valve replacement. The myocardium in the lower left of panel B has myocytes of normal pattern and size. Hematoxylin-eosin stain; original magnification × 100.

A striking difference in cellular morphology. While myocytes located in foci of isometric disarray (such as the interventricular septum in idiopathic hypertrophic subaortic stenosis and the right ventricular free wall in hypoplastic right-heart syndrome) are typically hypertrophied, the disarrayed myocytes in isotonic postoperative papillary muscle tips were markedly atrophied, and both the diameter and the cell length were reduced (fig. 4, table 3). Thus, although disarray may depend only on the disruption of organizing forces within the myocardium, concomitant myocyte atrophy appears unique to the isotonic contractile state, and may be acquired in adult life.

Zonal lesions, which have been associated with hemorrhagic shock in experimental animals,12,13 were commonly found in the papillary muscle tips of patients who died early after operation. The common denominator of the reduced left ventricular cavity size in hemorrhagic shock and the papillary muscle released from its attachments could be a relative length reduction of the affected myocytes; the zonal lesions

Table 3. Comparison of Two Types of Cardiac Myocyte Disarray

1. Isometrically contracting areas of myocardium (septum in idiopathic hypertrophic subaortic stenosis, respective ventricular walls in right- and left-heart syndromes)
   - A. Disarray (developmental)
   - B. Hypertrophy (acquired)

2. Isotonically contracting areas of myocardium (papillary muscle tips after mitral valve replacement)
   - A. Disarray (acquired)
   - B. Atrophy (acquired)
are a compensatory condensation of sarcoplasm at the ends of the cells to reduce their length. Replacement fibrosis was common in all survival groups and did not correlate with survival time. Histologic study showed that the acquired atrophy and disarray in the papillary muscle tips was not confined, or even particularly associated with, regions of replacement fibrosis.

The contractile state established in the papillary muscle body after mitral valve replacement appears to be a unique setting for observing the myocyte response to prolonged periods of contraction after disruption of the normal tensile force distribution within the myocardium. The disarray that appears to develop with time in this setting supports the concept that myocyte orientation is a direct consequence of force distribution in the myocardium.

References
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