HISTOPATHOLOGICAL STUDY OF THE PAPILLARY MUSCLES AND APEX CORDIS OF THE HYPERTROPHIED LEFT VENTRICLE

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Hypertrophy of the papillary muscle and apex cordis of the left ventricle was studied histopathologically using 84 hearts obtained at autopsy. The hearts were divided into three groups: a hypertrophy group (heart weight more than 350g); a borderline group (heart weight between 350 and 300g) and a control group (heart weight less than 300g).

The size of the papillary muscle increased with increase in heart weight. Derangement of myocyte linings and fibrosis at the papillary muscle base became apparent with hypertrophy. In addition derangement and fibrosis extended from the internal to middle layers of the free wall with progressing hypertrophy. Derangement seemed to precede hypertrophy and fibrosis. A cluster of huge myocyte-like Purkinje's cells were associated with the center of the derangement. At the apex, criss-cross derangement developed from right and left side derangement with increasing hypertrophy.

It is speculated that the focal derangement plays an important role in producing hypertrophy in response to mechanical stress with subsequent development of hypertrophy and fibrosis with some asymmetry.

INTEREST in morphological studies on hypertrophy of the left ventricle has so far been limited to the free wall and ventricular septum. Hypertrophy of the papillary muscle (Pm) and apex cordis (Apex) seemed to progress in parallel with that of either the free wall or ventricular septum, and was thought to be a nonspecific phenomenon. Recently, in cases of a specific type of hypertrophic cardiomyopathy with apical hypertrophy, a disproportionate hypertrophy of the Apex and Pm was demonstrated in echocardiographic or ventriculographic recordings.¹⁻⁵

The aims of the present work are to study the

mechanism of hypertrophy of the Pm and Apex histopathologically. Hearts obtained at autopsy with left ventricle hypertrophy of known etiologies are used. This study examines the effect of increased hemodynamic load on the Pm and Apex and attempts to explain the significance of hypertrophy.

MATERIALS AND METHODS

Eighty-four hearts obtained at autopsy showing no recognizable ischemic myocardial lesions were selected for this study. Table I shows the classification of the materials by sex ratio, age distribution and range of heart weight. The hearts were classified by weight: the hypertrophy group (heart weight greater than 350g), the borderline group (heart weight between 300 and

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TABLE I MATERIALS

Group	Sex		Age (yr.)		Heart weight (g)	
	Male	Female	Range	Average	Range	Average
Control (n = 34)	16	18	38 to 78	62.7	130 to 290	253
Borderline (n = 18)	10	8	34 to 82	60.6	305 to 345	329
Hypertrophy (n = 32)	26	6	44 to 85	63.0	360 to 600	446

Control group: Heart weight less than 300g. Borderline group: Heart weight between 300 and 350g. Hypertrophy group: Heart weight more than 350g.

Fig.1. Sampling sites for tissue blocks. Left ventricle was opened longitudinally and viewed from the left inferior side. Sup: superior; Inf: inferior; Ant: anterior; Post: posterior

350g) and the control group (heart weight less than 300g). The etiology of the hypertrophy was clinically proved hypertension in most cases. Under macroscopic observation all hypertrophied hearts were found to have increased left ventricle wall thickness and absence of or slight dilatation of the left ventricle cavity. The length of the Pm body from the base to tip, and the cross-sectional areas at levels of the base and upper third of both the anterior and posterior Pm of the left ventricle were measured. Where the Pm consisted of double or triple bodies, the largest one was selected for measurement.

Five tissue blocks were taken from each heart, as illustrated in Fig. 1, i.e., two transverse sections each at the bases of the anterior and posterior Pm groups, including the bodies of the Pm and transmural free wall, and one transverse

section at the Apex, containing the apical vortex.

The tissue specimens were fixed in 10% formalin and embedded in paraffin according to a routine procedure. After taking thin-sections of 4 μ thickness, hematoxylin-eosin (H-E), elastica-van Gieson's (EvG) and azan stains were applied for microscopic examination. The grade of myocyte hypertrophy, myocardial fibrosis and derangement of myocyte linings were estimated using four classes, i.e., —, +, ++, and +++, for which scores of 0, 1, 2, and 3, respectively, were given for the calculation of statistical significance using the t test.

The classes of derangement and fibrosis were estimated using the standard panels (A-F) indicated in Fig. 2.

At the Apex, the locations of pathologic lesions were positioned according to an anti-clock mode, with 0 hour standing for the anterior, 3 hour for the left side, 6 hour for the posterior and 9 hour for the right side, as shown in Fig. 3A.

RESULTS

Table II shows the length and transverse areas of Pm bodies in each group. Both parameters increased with increase in heart weight. The parameters showed a greater increase in the anterior Pm than in the posterior Pm. Increases were statistically significant in all hypertrophy group. Less statistical significance is attached to increases in the control or borderline groups. An increase of the transverse area of both Pm's was more significant in the hypertrophy group compared to the control or borderline groups.

Figure 4 shows a low-power magnification of the anterior Pm base in a heart from the hypertrophy group. Irregularly scattered patchy peri-

Fig. 2. Microscopic pictures of the base of the anterior papillary muscle.

A: Control case with no derangement. B: Borderline case with derangement of ++ grade. C: Hypertrophy case with derangement of +++ grade. A, B and C. H-E stain, $\times 100$. D: Control case with no fibrosis. E: Borderline case with fibrosis of + grade. F: Hypertrophy case with fibrosis of +++ grade. D, E and F. Azan stain, $\times 40$.

vascular fibrosis are concentrated in the Pm body and trabeculae carneae. Derangement and less prominent small fibrotic foci are widely distributed from the internal to the middle layer of the free wall.

Figure 5 shows the grades of derangement and fibrosis in the Pm base and body in each group. Fibrosis was significantly more prominent in the borderline and hypertrophy groups than in the controls in both the base and body of the anterior Pm. Fibrosis was greater in the hyper-

trophy group than the control group in the posterior Pm. Derangement, however, was marked only in the borderline and hypertrophy groups in the base of the anterior and posterior Pm but not in the body of the Pm.

Fibrosis in the control and borderline groups was generally less marked and of the perivascular type, and also more prominent at the Pm base than the Pm body as shown in D and E of Fig. 2. Fibrosis in the hypertrophy group was widely distributed and consisted of perivascular, plexi-

Fig.3. Macro- and microscopic view of the apex cordis.

A: Transverse section of the apex viewed from the base side. A case of hypertrophy. Rt: right; Lt: left. Arrows indicate locations of derangement. B: Microscopic picture of locations of derangement. H-E stain, $\times 100$.

Fig.4. Microscopic picture of the transverse section of the base of the anterior papillary muscle of a case of hypertrophy. Irregular patchy fibrosis are scattered densely in the papillary muscle and trabeculae carneae to the subendocardial myocardium where derangement is marked. The top is the endocardial side and the bottom is the epicardial side. EvG stain, $\times 1.2$.

TABLE II MEASUREMENTS OF ANTERIOR AND POSTERIOR PAPILLARY MUSCLES

Group	Ant Pm			Post Pm		
	Length (mm)	Transverse area at		Length (mm)	Transverse area at	
		upper one third (mm ²)	base (mm ²)		upper one third (mm ²)	base (mm ²)
Control (n = 34)	15.7 $\pm$ 3.4	48.0 $\pm$ 22.2	42.9 $\pm$ 33.2	14.5 $\pm$ 3.3	30.7 $\pm$ 12.8	33.5 $\pm$ 16.6
Borderline (n = 18)	18.5 $\pm$ 2.9	55.8 $\pm$ 26.1	50.5 $\pm$ 37.4	16.7 $\pm$ 3.7	35.8 $\pm$ 15.6	37.9 $\pm$ 32.5
Hypertrophy (n = 32)	22.7 $\pm$ 4.1	66.8 $\pm$ 24.7	56.5 $\pm$ 24.5	19.9 $\pm$ 4.2	47.4 $\pm$ 15.8	47.8 $\pm$ 19.0

*: $p < 0.001$; ☆: $p < 0.01$; #: $p < 0.05$
Values are mean $\pm$ standard deviation

Fig.5. Grade of derangement and fibrosis. Derangement is conspicuous in the base of both the anterior and posterior papillary muscles with hypertrophy and it seems to be a prelude to fibrosis.

form and perimysial types, as shown in Fig. 2. (F)

Derangement was clearly associated with myocyte hypertrophy at the Pm base in the internal layer of the free wall around the Pm-free wall junction. Derangement appeared in the middle layer of the free wall at later stages of hypertrophy. Clusters of large myocytes (maximal diameter $> 50 \mu\text{m}$) were observed in some cases in the center of derangement at both the anterior and posterior Pm base (Fig. 6.)

Table III shows the maximal diameters of the enlarged myocytes in each group. The diameters increased with increase in heart weight. The increase in myocyte diameter was more marked on the anterior Pm base than on the posterior Pm base, and on the anterior Pm base was more significant in the hypertrophy group than in the

control or borderline groups. On the posterior Pm base, myocyte enlargement was significantly greater in the borderline and hypertrophy groups than in the control group. In the hypertrophy group, it was significantly larger on the anterior Pm base than on the posterior Pm base.

Shown in Fig. 3A is a macroscopic view of the apex showing hypertrophy. Focal derangement and fibrosis are positioned at 0, 3, 6 and 9 hours (according to our convention). Figure 3B shows the apex under magnification. Viewing the apex of the left ventricle-free wall from upper side (Fig. 3A), it appears that the derangements follow the direction of muscle bundles in a anti-clockwise spiral path towards the center of the vortex of muscle bundles.

Table IV shows the distribution of derangement at the Apex. In the control group, 21%

Fig.6. Microscopic pictures at the base of the papillary muscle with hypertrophy.
A: Base of the anterior papillary muscle; B: Base of the posterior papillary muscle. A cluster of huge myocytes mimicking Purkinje's cells. H-E stain, $\times 400$.

TABLE III MAXIMAL DIAMETERS OF HUGE MYOCYTES

Group	Ant Pm base (μ)	Post Pm base (μ)
Control (n = 34)	29.9 ± 5.34	29.7 ± 4.36
Borderline (n = 18)	34.0 ± 4.62	33.3 ± 5.13
Hypertrophy (n = 32)	37.0 ± 6.92	33.9 ± 4.16

*: $p < 0.005$; #: $p < 0.05$

Values are mean $\pm$ standard deviation.

and 9% of the cases had right side and left side apical derangement, respectively. In the borderline group, 47%, 12% and 6% of the cases had right side, posterior and left side derangement, respectively. And in the hypertrophy group, 53%, 41%, 19% and 16% of the cases had right side, left side, posterior and anterior derangement in a criss-cross direction, respectively.

In the area surrounding the derangement, and in the derangement itself, hypertrophy of myocytes and proliferation of loose connective tissue surrounding the muscle bundles were common

features. Derangements are generally located in areas of contact between muscle bundles and particularly in the sharp-angled direction of the muscle bundle.

DISCUSSION

Hypertrophy is often more prominent in the Pm and Apex than in the free wall or ventricular septum, particularly in cases where asymmetrical apical hypertrophy is associated with a giant negative T-wave.¹ Asymmetrical hypertrophy of the heart has also been reported in other cases of hypertension.⁶ In addition Pm hypertrophy can be reproduced in experimentally hypertensive rats.⁷

The hypothesis that hypertrophy is caused by increased stretch stress in the Pm during systole, is supported by the finding that hypertrophy of the Pm in the hypertensive heart is associated with increase in heart weight. By this mechanism of hypertrophy, stretch stress would have to be transmitted to the Pm-free wall myocardium junction since this is where derangement is found in the borderline and hypertrophy groups. Derangement at the Pm base is assumed to have similar significance to the derangement found

TABLE IV LOCATIONS OF DERANGEMENT AT THE APEX

Group	cases (%)	Direction at			
		0°–1° cases (%)	3°–4° cases (%)	6°–7° cases (%)	9°–10° cases (%)
Control (n = 34)	10 (29.4)	0	3 (8.8)	0	7 (20.6)
Borderline (n = 17)	11 (64.7)	0	1 (5.9)	2 (11.8)	8 (47.1)
Hypertrophy (n = 32)	30 (93.8)	5 (15.6)	13 (40.6)	6 (18.8)	17 (53.1)

☆: $p < 0.01$; *: $p < 0.001$

Significant derangement appeared in 29.4% of the control group, 64.7% of the borderline group and 93.8% of the hypertrophy group.

in the anterior triangle of the ventricular septum⁶ i.e., it might act as a sensor for intramural stress and as a prompter of subsequent compensatory hypertrophy, since derangement was increased even in the borderline group. The assumption that increased derangement is a prelude to hypertrophy of the left ventricle-free wall is an attractive explanation of the morphogenesis of concentric hypertrophy. A thick wall does not necessarily lead to homogeneous stress distribution, which is widely believed to be responsible for stress-induced symmetrical hypertrophy. The fibrosis in and around the derangement area appears after derangement and hypertrophy have already progressed. The interpretation on this is that fibrosis may result from squeeze and tear stresses due to vigorous contraction of hypertrophic myocytes. Increased fibrosis, however, could promote more hypertrophy via increased inertial stress to myocytes, and vice versa^{8,9}

In the Pm body, derangement was less marked than in the Pm base. The Pm body is a uniform, simple structure connecting the chordae tendineae with the free wall and can unidirectionally transmit mechanical stress along its long axis. Relatively rich innervation in Pm systems^{10,11} indicates the presence of a built-in sensor system to compensate for intra-Pm stress changes.

In this study hypertrophied hearts generally resulting from clinical hypertension, were used. Hearts with hypertrophic cardiomyopathy were not used. In specific local regions, such as the bases of the anterior and posterior Pm and in the Pm bodies, both derangement and fibrosis were studied. Quantitative analysis of fibrosis has been studied but percentage areas of derange-

ment and fibrosis have not been calculated.^{12,13} In these regions of the hypertrophied hearts, disorder of myocyte lining arrangement is a common feature. This is called derangement in order to distinguish it from disarray of cardiomyopathy.

A cluster of huge Purkinje's cell-mimicking myocytes in the derangement area at the Pm base suggests two possibilities. The cells may represent hypertrophy in reaction to excess stimulus by squeezing contraction of disarrayed myocytes. Alternatively they may be specialized cells for rapid conduction of electrical stimulation to the Pm necessary, even from the early phase of systole, to support mitral valve closure. Either way, these complexes consisting of derangement, fibrosis, large cells and nervous elements should play an important role in the purposeful moderation of cardiac performance.^{14,15}

At the Apex, the vortex of muscle bundles acts to squeeze out blood during systole. The right and left side derangement could be associated with the anchoring site of the muscle bundle of the free wall to the ventricular septum. And also the site of strongest resistance to the left shift of the Apex. The criss-cross appearance of derangement in the hypertrophy group might be linked to the anterior and posterior Pm, which are located on the cross line against the above-mentioned right to left line. When the increased stress in the Pm system is transmitted to the muscle bundles orienting towards the Apex, a stress arises between and other muscle bundles around the Apex. This four-point support of the Apex is a self-protecting mechanism designed to resist buldge or slide of the Apex on the left side thus maintaining concentric hypertrophy in

hypertensive hearts. In both the Pm base and Apex, the presence of derangement seems important in producing hypertrophy appropriate to increased pressure load. The same view can be applied to derangement in the ventricular septum in disproportional hypertrophy in cor pulmonale, and hypertensive, ischemic and even normal hearts.¹⁶ The mechanism by which derangement modifies hypertrophy would be mediated by the nervous system. The septal triangle,¹⁷ Pm base and Apex are all heavily innervated. In particular, it promotes hypertrophy by sympathetic excitation via catecholamines.^{18,19}

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