HISTOPATHOLOGICAL STUDY ON MYOCARDIAL HYPERTROPHY ASSOCIATED WITH ISCHEMIC HEART DISEASE

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The mode and causes of myocardial hypertrophy occurring in association with ischemic heart disease were studied. The investigation involved autopsied hearts (15 cases of subendocardial infarction, 27 of transmural infarction, 20 of non-infarcted three vessel disease and 17 controls) and biopsied materials obtained during coronary-aorta bypass graft surgery (23 patients with angina pectoris and 46 with myocardial infarction). The subendocardial infarction group showed most marked myocardial hypertrophy that reflected extensive infarction and fibrosis, dilatation of the left ventricular cavity and the loss of myocytes. Despite a marked decrease in the number of myocyte layers, the residual myocardium of the left ventricle was uniformly hypertrophic, accompanied by an increase in the heart weight. The larger the area of fibrosis, the more marked was myocardial hypertrophy irrespective of the luminal diameter of the responsible coronary artery. These finding indicate that myocardial hypertrophy associated with ischemic heart disease is enhanced by the compensatory mechanisms for a decrease in the contractile myocardium due to fibrosis.

A heart with myocardial infarction is known to show an increase in weight, myocardial hypertrophy, which is generally considered compensatory for diffuse fibrosis resulting from the loss of myocytes. However, the onset of myocardial hypertrophy in the presence of ischemic heart disease is thought to be closely related to the presence of infarction, the size and extent of infarction, severity of cardiac dilatation, severity of coronary artery stenosis and the presence or absence of obstruction. In particular, myocardial hypertrophy associated with typical subendocardial infarction is characterized by circumferential infarction on the endocardial side, increased heart weight and a specific pathomorphological form, but remains unclarified in many other aspects.

Furthermore, patients with ischemic heart-disease without infarction also develop myocardial hypertrophy. However, there is no morphometric report on autopsied hearts showing myocardial hypertrophy, and the question of whether myocardial hypertrophy associated with ischemic heart disease is caused by ischemia alone remains unsolved.

The present study histologically examined myocardial hypertrophy associated with ischemic heart disease in autopsied hearts and biopsied materials. The aim was to achieve pathomorphological clarification of the factors of myocardial hypertrophy and to analyze the involvement of the ischemic factors in stenosis of the responsible coronary vessels(s).

SUBJECTS AND METHODS

1. Autopsied Hearts

A total of 79 autopsied hearts were
cases of subendocardial infarction, 13 showed significant (75—100%) stenosis of three coronary vessels, and 2 showed stenosis of 50—70%.

Transmural infarction showed 5 cm or more infarction of all layers of the left ventricular wall. Anterior wall infarction was observed in 9 of the 27 cases, and posterior wall infarction in 18. Lateral wall infarction was not included in the present study to determine responsible coronary vessels.

Of the 9 cases showing anterior wall infarction, 1 had complete obstruction of the left anterior descending branch (LAD); 6 had significant stenosis of 75—99%; and 2 had stenosis of 50—75%. Five of the 9 cases with anterior infarction had significant stenosis of LAD, the left circumflex branch (LCx) and right coronary artery (RCA); 1 case had both LAD and LCx lesions; 2 cases had that of the LAD alone.

Of the 18 cases of posterior wall infarction, complete obstruction of the RCA was observed in 9; significant stenosis in 7; stenosis of 50—75% in 1; and stenosis of 0—25% in 1. Six of the 18 cases with posterior infarction had significant stenosis of both the LAD and LCx; 7 cases had that of either LAD or LCx; and 5 cases had that of the RCA.

The 3VD group showed significant (75% or more) stenosis of the proximal portion of the three vessels, LAD, LCx and RCA, but no myocardial infarction.

For macroscopic and histological examinations, both ventricles of each autopsied heart were cross-sectioned from the apex to the base at intervals of 1 cm, and the coronary artery was cross-sectioned at intervals of 5 mm. Stenosis was rated on a 5-point scale: 0—25%, 25—50%, 50—75%, 75—99% and 100%, and stenosis of 75% or more was considered significant.

In this study the middle portion of the ventricle was examined macroscopically and microscopically. Routine light microscope slides, 5 μm thick, were prepared from each of the paraffin embedded sections. The slides were stained with hematoxylin-eosin, azan, and elastica-van Gieson’s stains (Fig. 1).

Morphometrical determination:

(1) Left Ventricular Cavity Size:
After fixation, the surface of the middle transverse section of the ventricle was photographed at actual size. The internal circumference (excluding the trabecular layer) of the left ventricle was traced with IBAS-2000 (Zeiss) and converted to a complete circle to determine its diameter.

(2) Diameter of Myocytes
For determination of the diameter of myocytes, the myocardium of the middle circular layer was magnified 200 times under Prepara Micro Viewer M-200 (Hoken Shizai Hanbai, K.K.). The minimum diameter of the myocyte in the nuclear area was measured in 150 cells in each region by using Muto Image Analyzing System (Muto Industrial Co., Ltd.) and the mean was used as the diameter of the myocytes in each case.

Myocardial Diameter of Infarcted Area and Non-Infarcted Area: In the subendocardial infarction group, diameter of the myocytes of the infarcted area (within 5 mm from the fibrotic focus) and that of the non-infarcted area (the distal portion of the infarction; posterior wall in the heart with anterior wall infarction and anterior wall in those with posterior wall infarction) were measured.

(3) Area of Fibrosis (%):
Using a 25-point eye-piece (Integrating eye-piece I of Zeiss), the compact layer of the left ventricle in the azan-stained specimens was completely scanned in a 40-fold field (Olympas BH-2). The number of points on definite collagen fibers were divided by the sum of the number of points on myocardial cells and that of points on collagen fiber to obtain % area of fibrosis.

(4) Number of Myocyte Layers
The number of myocardial cells comprising the wall was examined by a modification of Suwa's method.\textsuperscript{15,16} Three sampling lines perpendicular to the compact layer were drawn from the outer to inner layers, and the number of myocardial fibers intersecting the lines was determined by using IBAS-1 (Zeiss). Determinations were carried out at two sites, the anterior and posterior walls of the left ventricle and the mean was used.

(5) The weight of each heart was measured at autopsy.

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2. Biopsied Materials of the Myocardium

Biopsy specimens of the myocardium were obtained from 69 patients undergoing coronary-aorta bypass graft surgery (CABG) to LAD at Anjo Kosei Hospital: 23 with angina pectoris (20 males and 3 females; 14 with angina pectoris on effort, 4 with angina pectoris at rest and 5 with angina pectoris on effort and at rest; ranging in age between 28 and 68 y, with a mean of 56.3 y) and 46 with old myocardial infarction (40 males and 6 females; 37 – 73 y, with a mean age of 57.9 y).

Preoperatively, all patients underwent left ventricularography followed by coronary arteriography following the administration of nitroglycerin preparation.

Transmural biopsy samples of the anterior wall of the left ventricular myocardium were obtained with a Tru-cut needle (Travenol Laboratories) during CABG (Fig. 2). All patients had LAD lesions. Preoperative coronary arteriography revealed stenosis of 75% or more of the LAD in 19 cases of angina pectoris and 39 of old myocardial infarction. The remaining 11 cases showed stenosis of 50 – 75%.

According to the procedure of histological measurement used for autopsied hearts, the diameter of 120 myocytes each in the inner, middle and outer layers were determined, and the area of fibrosis was determined by the point count method.

Statistical analysis: Values are presented as mean ± SD. A multiple comparison test with one-way analysis of variance and Student’s t-test were used. P values of less than 0.05 were considered significant.

RESULTS

A) Autopsied Hearts

Table I shows histopathological findings.

(1) Heart Weight

The heart weight of the subendocardial infarction group was greatest, with a significant difference from the control group (p<0.001), and that of the transmural infarction group also showed an increase with a significant difference from the control group (p<0.01). The non-infarcted 3VD group showed no significant increase in heart weight. The heart weight of the subendocardial infarction group was slightly

<table>
<thead>
<tr>
<th>TABLE I. HISTOPATHOLOGICAL FINDINGS</th>
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<tr>
<td>% Area of fibrosis (X%)</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Whole LV</td>
</tr>
<tr>
<td>Non-infarcted area</td>
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<td>Infarcted area</td>
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greater than that of the transmural infarction group, with no significant difference.

(2) Left Ventricular Cavity Size

As an indicator of the degree of left ventricular dilatation, the left ventricular cavity sizes of the subendocardial and transmural infarction groups were significantly larger than that of the control group (p<0.001 for both), but the non-infarcted 3VD group showed no expansion of the cardiac cavity. The dilatation of the cardiac cavity in the subendocardial infarction group was more marked than that in the transmural infarction group, with no significant difference.

(3) Diameter of Myocytes

In the subendocardial infarction group, the infarcted area and the distal portion of infarction showed no difference in the diameter of myocytes, with uniform hypertrophy in the anterior, lateral, posterior and septal regions, with a significant difference from the control group (p<0.001). In contrast, the transmural infarction group showed area differences in the diameter of myocytes, the infarcted area being significantly more hypertrophic than the distal portion of infarction (p<0.005). The diameter of myocyte in the subendocardial infarction group was significantly larger than that in the transmural infarction group (p<0.05). The non-infarcted 3VD group also showed significant hypertrophy compared with the control group (p<0.001).

(4) Area of Fibrosis:

The area of fibrosis representing the extent of infarction or fibrosis was largest in the subendocardial infarction group, followed by the transmural infarction group and the non-infarcted 3VD group. All disease groups showed significant differences from the control group (p<0.001). Fibrosis was significantly more advanced in the subendocardial infarction group than in the transmural infarction group (p<0.05). In the subendocardial and transmural infarction groups, fibrosis involved 12.4±1.6% and 10.1±17% respectively, of the non-infarcted area, being significantly more severe than that in the control group (4.2±1.5%).

(5) Number of Myocyte Layers

The number of myocyte layers constituting the left ventricular wall was significantly decreased in the subendocardial infarction group alone (p<0.001).

(6) There was a definite correlation between the diameter of myocytes and fibrotic area in all groups (Fig. 3).

(7) The relationships between the severity of coronary artery stenosis and the diameter of myocytes and fibrotic area were examined in the transmural infarction group. There was no significant difference in the diameter of myocytes in the infarcted or non-infarcted area between the significantly stenotic subgroup (75−100%) and insignificantly stenotic subgroup (0−75%). The area of fibrosis showed no significant difference either.

**Examination of Biopsied Materials**

The myocardial infarction group showed a significantly greater diameter of myocytes (p<0.005) and a significantly greater fibrotic area (p<0.001) than those of the angina pectoris group.

The biopsy materials in each group were divided depending on the presence or absence of significant stenosis of the responsible coronary vessel(s). In both the myocardial infarction and angina pectoris groups, the diameter of myocytes and fibrotic area were slightly greater in the significantly stenotic subgroup, with no significant differences (Table II).

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TABLE II  CORRELATION BETWEEN CORONARY ARTERY STENOSIS AND HISTOPATHOLOGICAL FINDINGS IN BIOPSY MATERIALS

<table>
<thead>
<tr>
<th></th>
<th>Old myocardial infarction</th>
<th>Angina pectoris</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No (µm)</td>
<td>Diameter</td>
</tr>
<tr>
<td>Coronary stenosis (++)</td>
<td>39</td>
<td>23.4 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Coronary stenosis (--)</td>
<td>7</td>
<td>21.5 ± 3.3</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>22.9 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.005</td>
<td>p &lt; 0.005</td>
</tr>
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</table>

Coronary Stenosis: (++) significant stenosis of 75-100%  
(-- ) not significant stenosis of 50-75%

DISCUSSION

Badeer17 reported that the pathogenesis of cardiac hypertrophy is initiated by a sustained increase in mean contractile "stress" (or tension) or, more likely, by a sustained increase in stroke energy expenditure causally related to dyssynergy and dilatation of the cardiac chamber in myocardial infarction.

As has been reported11-15,7 the myocardial infarction group showed a significant increase in the weight of the heart, and the mean heart weight of the subendocardial infarction group was about 50% greater than that of the control group. No weight increase of the heart was observed in the non-infarcted 3VD group.

Left ventricular cavity size, representing the degree of left ventricular dilatation, was significantly larger in the myocardial infarction group, and larger by about 70% in the subendocardial infarction group than in the control group. The left ventricular dilatation in the myocardial infarction group may be due to expansion of infarction, an increase in mechanical load, or changes in the architecture of myocytes that constitute the ventricular wall.8-25 None of the non-infarcted 3VD cases exhibited dilatation of the left ventricular cavity.

In the subendocardial infarction group, both the myocardium of the outer layer and the middle circular layer showed uniform hypertrophy, with no area difference. It seems that in the dilated hearts with subendocardial infarction, the hypertrophic factors acted on both the myocardium of the outer layer and that of the middle layer resulting in decrease in the elevated tension17. In the transmural infarction group, the diameters of myocytes in both the infarcted area and the distal portion of infarction indicated hypertrophy, but the two diameters were significantly different, reflecting less elevated stress in the non-infarcted area.

The area of fibrosis, an indicator of the severity of fibrosis or the extent of infarction, was largest in the subendocardial infarction group, accounting for 26.7% of the cross-sectioned surface of the left ventricle. The fibrotic area in the transmural infarction and non-infarcted 3VD groups was 22.3% and 17.8%, respectively. The fibrosis in the last group was attributable to progress in the loss of myocytes and interstitial fibrosis that resulted from chronic ischemia due to significant stenosis of the coronary artery.17

The number of myocyte layers was decreased by about 36% only in the subendocardial infarction group, which indicated an extensive myocyte loss due to circumferential subendocardial infarction.

In the biopsy specimens, the myocardial infarction group showed a significantly larger diameter of myocytes and fibrotic area than those of the angina pectoris group, which were consistent with the results of measurement in the hearts obtained by autopsy in the transmural group and non-infarcted 3VD group. Comparison between the significantly and insignificantly stenotic

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subgroups revealed no significant difference in the diameter of myocytes and the fibrotic area both in the myocardial infarction group and the angina pectoris group. If ischemia due to coronary artery stenosis in a major determinant of myocardial hypertrophy, a heart showing significant stenosis of three coronary vessels should show myocardial hypertrophy of similar severity to that in an infarcted heart. Therefore, the grade of coronary artery stenosis is not a major factor in the development of myocardial hypertrophy. On the other hand, the diameter of myocytes increased in proportion to the fibrotic area (Fig. 3). Even in a small amount of specimens such as biopsy materials, there was good correlation between the fibrotic area and the diameter of myocytes, regardless of the presence of significant coronary artery stenosis (Table II).

Because the diameter of myocytes in the subgroup showing significant coronary artery stenosis was slightly larger than that in the subgroup showing less severe stenosis, with no significant difference, it is thought that myocardial hypertrophy associated with ischemic heart disease depends largely on the presence or absence and the extent of fibrosis, rather than ischemia, which is nevertheless also an important factor17,27.

Myocardial hypertrophy was most advanced in the subendocardial infarction group, which seemed to be due to extensive infarction, a marked decrease in the residual myocytes, marked fibrosis and dilatation of the left ventricular cavity.

These findings indicate that myocardial hypertrophy associated with ischemic heart disease is enhanced by the compensatory mechanisms for a decrease in the contracting capacity of myocardium due to fibrosis.

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