Histopathological Study on the Effects of Aging in Myocardium of Hypertrophied Hearts

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To clarify the effects of aging in myocardium of hypertrophied hearts, 555 autopsied hearts were studied histopathologically. Degrees of myocyte hypertrophy, disarrangement and fibrosis and lipofuscin deposits were estimated light-microscopically in tissue specimens taken from the anterior wall of the left ventricle. Myocyte hypertrophy was assigned to one of four classes from 0 to 3+ according to size. Other findings were estimated using the conventional three classes. All cases were divided according to heart weight, into the following groups: severe hypertrophy (Group I; more than 450g for males and 400g for females), mild hypertrophy (Group II; 450 > HW > 350g for males and 400 > HW > 300g for females) and no hypertrophy (Group III; less than 350g for males and 300g for females).

Lipofuscin deposits increased with aging, but in Group I the increase was delayed in comparison to that in other groups. As a rule, myocyte size in the outer layer was equal to or smaller than that in the inner layer (outer-layer-selective atrophy). This was particularly true in pressure-overloaded hypertrophy and less so in volume-overloaded hypertrophy. Myocyte disarrangement was observed in the inner and median layers in the oldest group. Peri-vascular fibrosis became thick with aging, and perimysial fibrosis increased with age. The fibrotic process was accelerated in hypertrophied myocardium. As to the mode of hypertrophy, aging appears to result in a kind of myocardial asymmetry of layer-selective atrophy. This atrophy may be the result of an unequal distribution of myocyte disarrangement, causing unregressed hypertrophy and the development of fibrosis resulting from wear and tear of the support system against persistent mechanical stress in the overloaded myocardium.

CHANGES resulting from aging are observed in all elements of the heart: the myocardium, valves, conduction system and coronary arteries. These elements may be modified in the hypertrophied heart, as compared to the normal heart. This study is aimed at clarifying aging changes in the myocardium from a histopathological viewpoint and comparing them in normal and hypertrophied human autopsied hearts. Hearts with different grades of myocyte hypertrophy, disarrangement and fibrosis and lipofuscin deposits were selected for microscopic observation.

Key Words:
Aging myocardium
Myocyte hypertrophy
Myocyte atrophy
Layer-selective atrophy
Myocardial fibrosis
Lipofuscin

MATERIALS AND METHODS
Three hundred fifty five male and 200 female autopsied hearts, excluding those with cardiomyopathy or cor pulmonale, were randomly selected for pathohistological study. Ages

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reanged from 20 to 99 years. Hypertrophy was defined as a heart weight above 350 g for males and 300 g for females. Hypertrophied hearts were further subdivided into severe (Group I) and mild (Group II) groups. Group I consisted of cases with heart weights above 450 g for males and 400 g for females. Hypertrophied hearts weighing less were assigned to Group II. Nonhypertrophied hearts made up Group III. Tissue specimens were taken from the midportion of the anterior wall of the left ventricle for light microscopic examination. After fixation in 10% formalin and embedding in paraffin, they were cut into 7 μ-thick slices and stained with hematoxylin-eosin, elastica-van Gieson or azan stain. The lipofuscin deposits were determined as none, poor or rich. Ventricular myocardium was microscopically divided into three layers according to orientation of myocytes, i.e. inner oblique, median circular and outer oblique. Myocyte size was evaluated in each layer and classified as atrophy, normal or hypertrophy. The grade of hypertrophy was subdivided into 3 classes as mild, moderate or severe. Consequently, the myocyte size was divided into five classes from atrophy to severe hypertrophy. The disarrangement of myocytes was estimated as none, mild or severe.

Myocardial fibrosis was classified as perivascular, perimysial or focal and each type was graded as none, mild or severe. Peri-vascular fibrosis was subdivided into two types. “T type” was tight fibrosis consisting of thick collagen fibers, and “t type” was loose fibrosis consisting of thin collagen fibers. Fibrosis containing both thick and thin collagen fibers was classified as “mixed type”.

We also divided all these cases into four groups by the following: valvular disease (V), hypertension (H), ischemic heart disease (I) and other diseases (O).

Age division for all cases was young (from 20 to 49 years), middle (50–69) or old (70–99). Statistical significance was estimated using the chi-square test.

RESULTS

Mean heart weight was not significantly different among the young, middle and old age groups, as shown in Fig. 1. In the old age H and O groups, the number of cases in group III was higher than in the other groups.

Figure 2 shows three representative cases. The light microscopic findings in the inner, median and outer layers are shown from top to bottom. Case 1 (left column) is a 40-year-old female who died of fulminant hepatitis. Heart

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Fig. 2. Histological features of three representative cases. 100 x, H-E stain.
Case 1 (left column) 40 y.o. F. Typical “young” myocardium.
Case 2 (middle column) 99 y.o. M. Typical “old” myocardium.
Case 3 (right column) 72 y.o. M. “Old” myocardium with hypertension.
Inner, middle and outer layers are shown from top to bottom.

Fig. 3. Relationship of lipofuscin deposits, hypertrophy and aging.
White areas represent no deposits of lipofuscin, hatched areas mild deposits and black areas severe deposits.
Lipofuscin deposits increase with age but in severe hypertrophy they are less prominent than in the other groups.

weight is 250g. Histologically, the difference in myocyte size between the inner and outer layer is small. The grades of lipofuscin deposits, myocyte disarrangement and fibrosis are mild. These findings are typical for “young” myocardium. Case 2 (middle column), a 99-year-old man, died of pneumonia. Heart weight is 340g. Myocyte size in the outer layer is obviously smaller than that in the inner layer. Myocyte disarrangement with hypertrophy in the inner layer is prominent. Rich lipofuscin deposits and mild perimysial fibrosis can also be observed. As a rule, prominent myocyte atrophy in the outer layer and disarrangement with hypertrophy in the inner or median layer appear to be characteristic of the aged heart. Case 3 (right column) is a 72-year-old male with hypertension. Heart weight is 260g. The size of the myocytes in the inner and median layers is normal or mildly hypertrophied. But in the outer layer, they are smaller than normal. Myocyte disarrangement is mild, even in the inner layer.

The amount of lipofuscin in the myocytes increases with age in all three groups, as shown in Fig. 3. Moreover, in the same decade, the amount is less in Group I than in Groups II and III; the increase of lipofuscin tends to occur in old age when hypertrophy becomes severe.

The size of myocytes in the outer layer tends to be equal to or smaller than that in the inner layer, as shown in Fig. 4. It is noteworthy that relative myocyte atrophy in the outer layer.
Fig. 4. Outer layer selective atrophy
Each section represents the following: myocyte size in inner layer is larger (black section), equal to (white section) or less than (dotted ones) that in the outer layer. Myocyte size is less in the outer layer in all three age groups. This tendency is accelerated in non-hypertrophied hearts, but it is mild in severe hypertrophy, even in older cases.

Fig. 5. Disarrangement of myocytes
White sections represent no disarrangement, hatched sections mild disarrangement and black sections severe disarrangement. Almost no disease-related difference in grade is seen in the "old" age group.
H = hypertension; V = valvular diseases; I = ischemic heart diseases; O = other diseases

Fig. 6. Aging changes in peri-vascular (left and middle) and perimysial (right) fibrosis.
Black bars represent "T" type, hatched bars "mixed" type and white bars "t" type.
Both types of fibrosis increase with age. The collagen arrangement tends to be loose in peri-vascular fibrosis in the young H group, but there is almost no difference in the quality of fibrosis in the V group.
M = male; F = female; Y = young; M = middle; O = old age

exists even in the hypertrophied heart, especially in the H group. This phenomenon is most prominent in the middle age division group III.

Figure 5 shows age- and disease-related differences in the grade of disarrangement of myocytes. It is more prominent in the inner and median layers than in the outer layer. In the old age group, the differences among the diseases become less remarkable.

Perimysial fibrosis becomes more severe with age and as hypertrophy progresses. The collagen fiber framework becomes thick in aged cases with peri-vascular fibrosis, as shown in Fig. 6.

DISCUSSION
Lipofuscin is a yellowish-brown pigment which accumulates around the myocyte nuclei and increases with aging. But even in younger cases exposed to malnutrition, its accumulation was reported to be increased. This condition is known as brown atrophy. Our data indicate that the amount of lipofuscin increases with age in both hypertrophied and non-hypertrophied hearts but the rate of increase is delayed in hearts with severe hypertrophy. These data suggest that the hypertrophy works to reverse the increase of lipofuscin deposits associated with aging. Sandritter et al. reported that lipofuscin deposits increased in proportion to heart weight, but in hearts weighing over 500g, deposits decreased. Their results are compatible with ours.

It is interesting to note that the size of myocytes is smaller in the outer layer than in the inner one in most cases. This phenomenon "Outer-layer-selective atrophy" is found in all four groups. As a rule, this tendency is weaker in hypertrophied hearts, than in non-hypertrophied hearts. Moreover, this phenomenon can be modified by basic diseases. For example, this tendency is rather mild in a volume-overloaded
heart, but is prominent in a pressure-overloaded heart, such as those in the H group. This phenomenon gives a kind of asymmetry to aged hearts when atrophy progresses as a counterpart to asymmetrical hypertrophy which is well known in cases with hypertrophic cardiomyopathy.

The disarrangement of myocytes with aging is obvious in the inner and median layers. At the adjacent area to infarction or fibrosis, the disarrangement is widely spread and is frequently accompanied by myocyte hypertrophy, as in case 2. It is possible that the disarrangement protects myocytes against atrophy, and maintains adequate hypertrophy for reserved capacity. Disparities of myocyte size must be caused by differences in myocardial structure or in the intra-myocardial stress distribution in each layer.

Perimysial fibrosis progresses with age and increases when hypertrophy becomes severe. In peri-vascular fibrosis, the collagen fiber framework becomes thicker with age. The amount of fibrosis reflects wear and tear in the intramyocardial support system resulting from persistent mechanical stress during cardiac performance.

From our data, we conclude that the features of aging in the myocardium are increased lipofuscin deposits, outer-layer-selective atrophy, myocyte disarrangement and fibrosis. Lipofuscin deposits and outer-layer-selective atrophy become milder in severely hypertrophied hearts than those which are mildly hypertrophied or non-hypertrophied, while perimysial fibrosis becomes more prominent.

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