AGE-ASSOCIATED MYOCARDIAL CHANGES IN VARIOUS HEART DISEASES
A Clinicopathologic Analysis in Biopsied and Autopsied Myocardium

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Age-associated changes in histopathologic and ultrastructural aspects of cardiac myocytes were systematically compared with clinical problems. The study material consisted of 1,515 endomyocardial biopsies; 150 normal and 50 diseased cardiac myocytes from pediatric autopsy specimens; 34 intra-operative endomyocardial biopsy specimens from the left ventricle and 28 surgical biopsy specimens from the right or left atrium. The following results were obtained:

1) The myocytes developed to adult size by the age of 15 years. Thereafter, the size did not change up to the age of 59.
2) Short-term hemodynamic overloading to the ventricle caused reactive hyperfunction and hypertrophy of myocytes. Stable hypertrophy resulted in long-term overloading.
3) In cardiomyopathy, compensated or stable hypertrophy occurred, but progression to decompensated or gradual exhaustion and progressive cardio-sclerosis (Meersson) took place. Progress of endocardial thickening was often observed during the course of the disease.
4) In the right and left atrial myocardium, extremely advanced pathology was observed and changes were related to the duration of the disease rather than to the severity of the hemodynamics.

There are various methods for investigating the age-associated changes of the myocardium in forecasting the prognosis of various heart diseases.1-3 We have been performing endomyocardial biopsy during the past 20 years and have observed myocardial changes during the progression from pediatric to geriatric age.4-32,40 Our study on surgically-excised atrial muscle was based on work on right atrial endomyocardial biopsy40 in which correct interpretation of the atrial muscle disease is always necessary.33-39 In order to understand the atrial muscular changes in various heart diseases,33-35 either the right or left atrial muscle was studied in specimens taken during cardiac surgery.36-39 It was found that far more advanced myocardial changes were present in the atrial muscle.

In this report, the results of the following three subjects in our series of studies are presented and discussed in a review form and results of some additional studies are presented.

1) Aging changes of cardiac myocytes from the pediatric age17

Key Words:
Atrial muscle
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Tetralogy of Fallot

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TABLE I  BREAKDOWN OF THE INTRAOPERATIVE BIOPSY

1. Left ventricular endomyocardial biopsy
   AR of short duration (less than 10 months after the onset) ........................................ 6
   Infective endocarditis .................................................. (2)
   AR due to dissecting aneurysm ............................................. (3)
   AR due to the rupture of the sinus of Valsalva .............................. (1)
   AR of long duration .......................................................... 10
   MR of short duration (less than 3 years after the onset) ......................... 8
   Infective endocarditis ........................................................ (3)
   Ruptured chordae tendineae ................................................. (5)
   MR of long duration .......................................................... 10

2. Right ventricular biopsy in cases with tetralogy of Fallot ....................... 11

3. Right atrial biopsy
   Atrial septal defect .................................................. (20)
   Right atrial myxoma ......................................................... (2)

4. Left atrial biopsy ........................................................... 6
   Left atrial myxoma .......................................................... (6)

AR = aortic regurgitation;  MR = mitral regurgitation

2) Acute and chronic effects of volume or pressure loading to the atrial36–39 or ventricular muscles in various heart diseases31,32

3) Some concepts on age-associated clinicopathologic aspects in various heart muscle diseases.

MATERIALS AND METHODS

The breakdown of the studies and the methods employed is as follows: 1. A study on the development of the myocardial cells from birth to up to 15 years old. One hundred and fifty autopsied hearts which were regarded as normal were studied using conventional histopathologic methods17 2. An endomyocardial biopsy study was done in the following:5 (1) idiopathic cardiomyopathy and allied cardiac diseases (n = 701), (2) specific heart muscle diseases (n = 240), (3) arrhythmia or conduction disturbance (n = 303), (4) myocardial disease in various valvular or congenital heart diseases (n = 237), and (5) others (n = 34). 3. Intraoperative endomyocardial biopsy study from the left or the right ventricle, surgical biopsy of the right ventricle, and from the right or left atrial muscle. The breakdown of the case material is presented in Table I. 4. Analysis of cases by serial endomyocardial biopsy. Cases with acute viral or

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idiopathic myocardiitis \( (n = 10)^{10,22,24} \) right ventricular dysplasia \( (n = 2) \), dilated cardiomyopathy \( (n = 4) \), and hypertrophic cardiomyopathy \( (n = 3) \) were studied. 5. A comparative study of endomyocardial biopsy and autopsy findings in 63 cases with various heart muscle diseases and an analysis of age-associated changes was made\(^{18} \). The heart muscle was studied using conventional histopathologic procedures, and in 2, 3, and 4, a conventional ultrastructural study was concomitantly performed in most of the cases. The diseased heart muscle condition was assessed at the histopathologic\(^{11} \) and/or ultrastructural\(^{12} \) level by our own method of semi-quantitative study. Three histopathologic features, i.e. degeneration and/or lysis of myocytes, fragmentation of muscle bundles, and interstitial fibrosis that contribute to contractility failure, were scored from 0 (indicating no pathology) to 3+ (indicating severe changes) and the severity of the morphologic changes was assessed by adding the three scores together. We termed this scoring system "histopathologic contractility failure index\(^{25} \)". The severity of the morphologic changes was compared with the clinical findings or prognosis. For the ultrastructural assessment of the progression of the myocardial hypertrophy, Meerson's classification\(^{41} \) into three stages, i.e. the first or damage stage of isometric hyperfunction, the second stage or stage of relatively stable hyperfunction, and the third stage or gradual exhaustion and progressive cardioclerosis was applied and incorporated in the interpretation of our results. Statistical analysis was made using

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**Fig. 2.** Breadth of right ventricular myocytes of various ages in cases with tetralogy of Fallot. Breadth (diameter) is expressed by mean ± S.D. It is noted that the diseased myocytes increase in size according to age similar to normal healthy myocytes.

**Fig. 3.** Breadth of the left ventricular myocytes in aortic regurgitation (AR) and in mitral regurgitation (MR). It can be seen that the breadth of myocytes (mean ± S.D.) is smaller in cases with short-term (less than 10 months) overloading (short) than in those with long-term overloading (long) in AR.
RESULTS

Results in each study are as follows:

1) Development of myocytes during pediatric age in normal hearts and in tetralogy of Fallot: Within one week after birth, the breadths of the right ventricular myocytes were greater than those of the left ventricular myocytes, but later, the left ventricular myocytes became larger and continued to grow until the age of 15\(^17\) Thereafter, the size did not change up to 59 years of age (Fig. 1). Also in tetralogy of Fallot, the size of the right ventricular myocytes became larger according to age, up to 15 years (Fig. 2).

2) Left ventricular myocardial changes in cases with left ventricular overloading: When cases where the volume overloading was of short duration (less than 10 months), such as cases of infective endocarditis or ruptured chordae tendineae, were compared with a group of long-term overloading cases, the myocyte size was found to be greater in the latter group (Fig. 3). An ultrastructural analysis of both groups revealed that the total ultrastructural score was greater in the short-term overloaded group than in the long-term overloaded group (Fig. 4). In the former group, development of rough-surfaced endoplasmic reticulum, ribosomes and Golgi apparatus was more pronounced. Similar changes were seen in cases with tetralogy
Fig. 5. Ultrastructural findings of hyperplasia of the cardiac myocytes observed in the right ventricular endomyocardial biopsy specimen in a juvenile patient (11-year-old boy) with tetralogy of Fallot. Note A: Numerical increase in mitochondria (M) (mitochondriosis). B: Proliferation of the Golgi apparatus (G) around the nucleus (N). C: Increase in rough-surfaced endoplasmic reticulum (rER) at the perinuclear portion. Bars indicate 1μ.

Fig. 6. Ultrastructural findings of the right ventricular myocytes showing stable hypertrophy. This picture was taken from an older case (17-year-old male) with tetralogy of Fallot, and shows that the appearance at a glance looks like that of a normal cardiac myocyte. There is, however, an increase in the development of the T-system (T) and in glycogen deposition (G1).

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Fig. 7. Changes of clinical features during the long follow-up (7 years) in a case with dilated cardiomyopathy (36 years old at the initial examination). When first seen, in 1977, this patient showed fairly good compensation and only slight cardiomegaly, electrocardiographic (ECG) signs of left ventricular hypertrophy, and right ventricular endomyocardial biopsy findings of myocardial hypertrophy. The patient was relatively well until 6 months prior to death, when he began to develop severe congestive heart failure with cardiomegaly, poor r wave progression in ECG, and worsening of the right ventricular endomyocardial biopsy findings. Interstitial fibrosis is evident.

of Fallot and this was especially so in patients less than 15 years old (Fig. 5). In contrast, in the long-term overloaded group, the ultrastructure of the myocytes did not show prominent changes and the pictures were similar to that of Meerson's Stage 2 (Fig. 6). In tetralogy of Fallot, the total ultrastructural scores in a younger patient group (10–15 year old; 12.7 ± 2.0 (mean ± S.D.), n = 7) and an older patient group (16–39 year old; 25.2 ± 7.1 (mean ± S.D.), n = 7) were 6.7 ± 1.9 and 3.4 ± 1.1, respectively, showing a higher score in the former (p < 0.005).

3) When 65 cases with dilated cardiomyopathy (DCM) were analyzed, the histopathologic contractility failure score (HCFS) that was obtained from the right ventricular endomyocardial biopsy findings was higher in the deceased group than in the survivors. It was noteworthy that the cases with score 5 or more, all died within 3 years.

The general clinical analysis of the cases with DCM showed that the important factors which
related to the death of the patients were an increase in cardiothoracic ratio, worsening of the NYHA grading, and electrocardiographic changes. An example of a case with DCM is presented in which the decrease in amplitude and the widening of QRS is clearly seen as well as the worsening of the biopsy findings (Fig. 7).

4) We performed a clinicopathologic study in cases with atrial septal defect in 20 cases in order to determine whether there is any correlation between age and both the degree of pathologic changes of the atrial myocardium and the presence of atrial fibrillation. The regression coefficient between the age and degree of the semiquantitatively assessed histopathologic score was $y = 0.12x - 1.69$ ($r = 0.95$). Similar results were obtained in the ultrastructural analysis ($y = 0.45x - 5.29$, $r = 0.95$). It was noted that with the duration of the disease, development from hypertrophy of the cardiac muscle to severe degenerative changes occurred, and the patients finally developed atrial fibrillation (Fig. 8). The degree of left to right shunt did not influence the pathology. A correlated clinical, pathological and ultrastructural study of atrial myocardium in atrial myxoma (6 cases with left and 2 cases with right) revealed that the extent of light or electronmicroscopically-assessed pathology revealed no correlation with pulmonary capillary wedge pressure or right atrial pressure but showed correlation with increase in age.

5) Myocardial changes after suffering from diseases affecting the heart muscle.

a) During our observation in performing serial endomyocardial biopsy in cases with viral or idiopathic myocarditis, we found that in 5 out of the 13 cases, recovery of the electrocardiographic changes was striking and it returned to a normal configuration. Another 7 cases showed either persistent A-V conduction disturbance or complete right bundle branch block plus left axis deviation. The patients are doing fairly well in their daily activities with (2 cases) or without (11 cases) permanent pacemakers.

A radionuclide follow-up study by Iwagami revealed that in 8 out of the 10 cases, there was either depression or no rise of the ejection fraction after the ergometer exercise testing and also there were defects in thallium scintigraphy in 3 cases. This indicated that sub-clinical heart failure was present. These clinical pictures correlated well with the improvement in morphology seen in the biopsied specimens from the serial endomyocardial biopsy study which were assessed by both histopathology and electronmicroscopy.

b) Progress of the myocardial changes in cardiac sarcoidosis. We observed a patient in whom the ECG change progressed gradually to that of complete right bundle branch block with left axis deviation. Development of premature ventricular contraction and ventricular tachycardia also occurred and we realized that the myocardial changes occur insidiously. In a nationwide Japanese study, a follow-up ECG in 242 of 963 cases with sarcoidosis revealed that there were high incidences of right bundle branch block, left axis deviation and ventricular prema-
tecture beats for up to 5 years. In a radionuclide study in 21 cases with sarcoidosis there were defects in thallium myocardial scintigraphy in 4 of 7 cases (57%) where the ECG changes were distinctly observed, but out of 16 cases without ECG change, the defect was present in only 1 case (6%) (p < 0.001).

c) In a study of 74 cases with sick sinus syndrome a history of diphtheria was present in 24% of the cases. Symptoms and signs suggesting the presence of cardiac disease were not evident at the time of the infection, but sick sinus syndrome was recognized after many years of a silent clinical condition.

d) A study on the correlation between the endomyocardial biopsy and autopsy findings during the course of the disease in 63 cases revealed that the essential diagnoses made from the biopsy and autopsy findings were identical in 80% of the cases with hypertrophic cardiomyopathy (n = 5) and 100% with DCM (n = 21). However, the endocardial thickening seemed to have increased with the progression of the disease, as the endocardium observed at autopsy was more thickened than that seen in the biopsy. Hypertrophy of myocytes and interstitial fibrosis had increased as well.

DISCUSSION

In summarizing the data from various aspects of the heart diseases presented above, the following assessment can be made.

1) The right ventricular myocytes are bigger than those of the left for one week immediately after birth. However, the left ventricular myocytes develop with age and reach adult size by the age of 15.

2) Cardiac myocytes show reactive hypertrophy in the acute stage of the disease and various intracellular hyperfunctional morphological changes can be seen ultrastructurally. After passing through the acute stage of the disease, the morphology of the myocytes becomes more stabilized and shows stable hyperfunction, or in other words, a compensated appearance, in the chronic stage of the disease.

3) In dilated cardiomyopathy (DCM), myocardial degeneration and interstitial fibrosis increase with age, which is reflected by the progression of the ECG changes. This clinical experience is applicable in deciding which patients with DCM would be good candidates for cardiac transplantation. However, it should always be remembered that patients may die suddenly, even if the clinical or pathologic changes are mild, because of the occurrence of malignant arrhythmias.

4) Atrial muscle shows much more advanced pathology than ventricular muscle. This may be because the ventricular muscle becomes severely damaged as the disease progresses, so the patients may eventually die. However, changes of atrial muscle can continue to a much more advanced pathology as the patients do not die because of the progress of the atrial disease.

5) Even though the myocardium may be extensively diseased by inflammation, cardiac myocytes can recover to a great extent and show capability of complete recovery. However, in about 80% of the cases, some residual changes may exist and become a potential factor for the development of congestive heart failure, which is sometimes not clinically evident. Exercise testing may show the existence of such subclinical heart failure.

Our experience suggests that the age-associated changes of myocardium contribute to the advancement of the heart disease and do not necessarily indicate that some immune process is ongoing. However, in immune-mediated diseases such as sarcoidosis, collagen disease, and eosinophilic heart disease the progression of the disease may be more rapid and extensive than the age-related changes.

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REFERENCES

1. HAMER J: Cardiovascular Aging. In Geriatric Heart Disease, ed by COODLEY EL, PSG Publishing Company, 1985, p 1

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NII-Electronic Library Service


18. MORIMOTO S, SEKIGUCHI M, HIROE M, NISHIKAWA T, NIWA K, HASUMI M, HIROSAWA K, KAJITA A: Compatibility of biopsy and autopsy findings from the same heart. An autopsy study on 63 out of 1255 cases where endomyocardial biopsy had been performed. Jpn Circ J 46: 861, 1982 (abstract)


21. HASUMI M, SEKIGUCHI M, MORIMOTO S, TAKE M, HIROE M, OHNISHI S, KASANUKI H, HIROSAWA K: Catheter biopsy assessed cardiomyopathic and postmyocarditic changes in cases with atrioventricular or intraventricular conduction disturbance. In Cardiac Pacing, ed by STEINBACH K et al., Steinkopf Verlag, Darmstadt, 1983, p 101


JF GOODWIN. Heart and Vessels (Suppl 1): 199, 1985


