51st Annual Meeting of the Japanese Circulation Society  
March 30, 1987, Tokyo (President: Hirokazu Niitani, M.D.)

President Lecture

CLINICOPATHOLOGIC STUDIES ON VARIOUS HEART DISEASES
—Light and Electron Microscopic Analysis of Autopsied and Biopsied Human Heart Tissue Specimens—

Hirokazu Niitani, M.D.

It has long been emphasized that comparison of clinical and morphologic findings of diseased heart tissue obtained by autopsy and biopsy is a very important way for physicians to investigate various diseases in the branch of cardiology. Recent advances in medicine have given rise to a variety of excellent diagnostic measures, but the basic importance of clinical pathology has never been decreased.

In many clinical occasions as the patients are not fatal, biopsy technique is available as a very useful method of diagnosis. It gives large amount of histopathologic informations which cannot otherwise be obtained although biopsy unlike autopsy is considerably restricted in its applicability.

Attentions have long been drawn to comparison of electrocardiogram and autoptic findings of heart diseases in the aged. In recent years, many investigators have routinely been involved in light and electron microscopic studies on autopsied and biopsied heart tissue specimens in various heart diseases. In this President Lecture some of the results of these studies will be discussed.

I. Complication of Arrhythmias and Impairment of Conduction System in Acute Myocardial Infarction (AMI)

Among the causes of death in the early myocardial infarction, severe arrhythmias, such as ventricular tachycardia (VT) and fibrillation (VF), and atrioventricular block (AVB), occupied in about 50% before coronary care unit (CCU) was introduced in 1968 in Showa University Hospital. After the establishment of treatment of patients with AMI in CCU, fatal episodes due to arrhythmias decreased markedly to about 50% of the initial incidence, and instead, cardiogenic shock and pump failure have become the major causes of death. However, incidence of a variety of arrhythmias in early AMI is still higher. Complete absence of arrhythmia is seen in 11.2% of the patients of Classes I and II of the Killip’s classification, and in only 0.7% of the cases of Classes III and IV, as shown in Fig. 1. In cases of Classes III and IV, the incidence of arrhythmias and their mortality rate are considerably higher than those of patients of mild to moderate severities. Fig. 2 illustrates the relation between the causes of death and the incidence of severe arrhythmias. Patients died of heart failure and cardiogenic shock also had severe arrhythmias of various types similarly to those died of arrhythmias.

Heart tissue specimens obtained at autopsy from 65 cases of myocardial infarction were histopathologically examined. Serial sections was made for the observation of the conduction system according to the method of Lev. These

Key words:
- Myocardial infarction
- Myocarditis
- Dilated cardiomyopathy
- Conduction disturbances
- Endomyocardial biopsy

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65 cases consisted of 37 patients who died of the first attack of AMI, 23 of recurrent attacks, and 5 with chronic MI. In terms of the site of infarction, there were 37 cases of anterior wall infarction, 18 of posterior, and 10 of nontransmural infarctions.

Electrocardiographic evidence was atrial fibrillation (af) in 13 patients, AVB of second degree or above in 25, left bundle branch block (LBBB) in 8, right bundle branch block (RBBB) in 19, and intractable VT or VF in 15.

In 6 out of 10 cases in whom af appeared after the onset of AMI, infarction site was posterior and all had complication of complete ABV. In these cases necrosis was found in the atrial muscles and in the approach to the AV node. The anterior wall was affected in 6 patients, and necrosis was observed only in one case in the approach to the AV node. These 6 patients with anterior infarction complicated with complete AVB. RBBB preceded AVB in 5 patients, and VF developed 3 of them. In all cases, both bundle branches were affected by edema, degeneration and necrosis. In patients with severe septal lesions, cardiac function was lower, and prognosis was poor in general.

Figure 3 shows lesions of the conduction system in 16 cases of posterior wall infarction complicated with complete AVB. The localization of infarct was the highest in the interatrial septum, followed by the approach to the AV node and atrial myocardium. The AV node itself was affected only in one case. In 9 patients, right ventricular infarction was complicated. Cardiogenic shock developed in 7 of them, cardiac rupture in one, and septal...
Fig. 2. Incidence of arrhythmias in fatal cases in acute myocardial infarction. Complication of arrhythmias are presented in each cause of death. Abbreviations are the same as those in Fig. 1.

Sinus node Atrial septum
0 13

Atrial muscle Approach
7 8

His Bundle
3

AV node
1

Post. fascicle Ant. fascicle
3 2

Fig. 3. Incidence of complication of atioventricular block and histopathologic myocardial lesions in acute posterior infarction.

perforation in another patient. Fig. 4-A-D shows a cases of posterior infarction complicated with right ventricular infarction. This type of infarct did lead frequently to cardiogenic shock. The longitudinal section of the interventricular septum with a posterior infarct (Fig. 4-B) gave

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A case of acute inferior infarction complicated with right ventricular infarction 
(72-y-o, F)
A: Macroscopy of the heart. B: Longitudinal section of the interventricular septum. Infarction is extended to the top of the septum. C: Necrotic cells approach to the AV node. D: Myoglobin staining of the infarcted tissue. AV node is marked with dashed line, and stained deeply suggesting the ischemic changes are mild.

Evidence in general that in case of posterior wall infarction, the infarct extended to the top of the interventricular septum, forming a ventricular aneurysm. These histopathologic changes are conceivable of having adversely affected the cardiac function. Fig. 4-C shows necrotic cells making up the approach to the AV node of the conduction system. Ischemic changes in atrial cells and conduction system cells were more difficult to be observed than in ventricular cells. Then, myoglobin in the ventricular cells was stained by the enzyme-labelled antibody method as shown in Fig. 4-D, and AV node, marked with dashed line, was stained more deeply than the surrounding atrial myocardium, suggesting that the ischemic changes were milder in the conduction system than in the surrounding myocardium.

Left bundle branch block (LBBB) was seen in only one case shortly after the onset of MI. In 7 cases LBBB appeared in the chronic stage, several months to years after MI, suggesting that cardiac myocytes of the subendocardial LBB are fairy tolerable to acute ischemia, but rather vulnerable to chronic ischemia.

RBBB was detected in 19 patients (Table I), and in 7 cases advanced to complete AVB. With these patients cardiogenic shock was the most frequent cause of death, followed by cardiac rupture and septal perforation. Serious arrhythmias including VT and VF occurred frequently. Conduction system was affected mostly in RBB, and the lesion extended to the bilateral bundle branches in some cases. Fig. 5 shows a case of septal perforation in which a left anterior fascicular block was accompanied by RBBB. Perforation occurred at the outflow tract to the pulmonary artery. The infarct extended widely to the anterior wall including the anterior to thirds of the ventricular septum. RBBB seemed to have faithfully reflected the anatomical extent of infarction in the ventricular septum.

Intractable VT and VF were observed in 15 patients as shown in Table II. RBBB and bilateral bundle branch block were accompanied frequent-
TABLE I  RIGHT BUNDLE BRANCH BLOCK, PROFILES OF 16 CASES

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>ECG findings</th>
<th>Complications</th>
<th>AV node</th>
<th>His bundle</th>
<th>LBB Ant.</th>
<th>LBB Post.</th>
<th>RBB</th>
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<tr>
<td>71</td>
<td>F</td>
<td></td>
<td>Rupture</td>
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<td></td>
<td>Fibrosis</td>
<td>Edema</td>
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<tr>
<td>64</td>
<td>M</td>
<td></td>
<td>Sept perf</td>
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<td></td>
</tr>
<tr>
<td>57</td>
<td>M</td>
<td>af</td>
<td>Rupture</td>
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<td>Necrosis</td>
<td></td>
<td></td>
<td>Fibrosis</td>
</tr>
<tr>
<td>77</td>
<td>M</td>
<td>af + LAH</td>
<td>Sept perf</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Necrosis</td>
</tr>
<tr>
<td>59</td>
<td>M</td>
<td>VF + LAH</td>
<td>Shock</td>
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<td>Degener</td>
<td>Necrosis</td>
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<td>Edema</td>
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<tr>
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<td>M</td>
<td>VT, VF</td>
<td>CHF</td>
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<tr>
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<td>VT, VF + LAH</td>
<td>CHF</td>
<td></td>
<td>Degener</td>
<td>Fibrosis</td>
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<tr>
<td>78</td>
<td>M</td>
<td>PAT + LAH</td>
<td>CHF</td>
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<td>CAVB + LAH</td>
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<td>Edema</td>
<td>Edema</td>
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<tr>
<td>69</td>
<td>M</td>
<td>CAVB, VT</td>
<td>CHF</td>
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<td>Hemorrhage</td>
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<tr>
<td>86</td>
<td>F</td>
<td>CAVB, VT, VF</td>
<td>Shock</td>
<td></td>
<td>Necrosis</td>
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Posterior infarction

<table>
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<th>Age</th>
<th>Sex</th>
<th>ECG findings</th>
<th>Complications</th>
<th>AV node</th>
<th>His bundle</th>
<th>LBB Ant.</th>
<th>LBB Post.</th>
<th>RBB</th>
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<td>Fibrosis</td>
</tr>
<tr>
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<td>F</td>
<td>VT, VF</td>
<td>Shock</td>
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<td></td>
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<td>Fibrosis</td>
</tr>
<tr>
<td>92</td>
<td>F</td>
<td>CAVB</td>
<td>Shock</td>
<td></td>
<td></td>
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<td></td>
<td>Necrosis</td>
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Abbreviations: RBB = right bundle branch; LBB = left bundle branch; Sept perf = septal perforation; af = atrial fibrillation; LAH = left anterior hemiblock; VF = ventricular fibrillation; VT = ventricular tachycardia; PAT = paroxysmal atrial tachycardia; CAVB = complete AV block; CHF = congestive heart failure

ly in such cases. Ventricular aneurysm concurred in the cases where 1 week or more had passed after the onset of MI.

Discussion of Section I:

Incidence of variety of arrhythmias in early myocardial infarction is still higher, especially in severe cases such as those with pump failure or cardiogenic shock, even though the number of fatal cases has been decreased after the institution of CCU.

And it has been difficult to elucidate the mechanism of generation of severe arrhythmias on a viewpoint of histopathology even in the autopsied cases. Utilizing the method of Lev? impairment of conduction system has been detected in connection with the morphologic standpoint.

Atrial heart muscle was often affected in acute myocardial infarction followed by the approach to the AV node and the portion distal to the bundle-branching, however, AV node and His bundle were rarely affected. Atrial fibrillation was frequently accompanied by pump failure, but did not always correspond with infarction area. Focal small infarctions were found in atrial wall in relatively high incidence rather than past report? and this phenomenon would be regarded as moderate ischemic changes caused by extension of infarcted area.

AVB in anterior infarction was a rare complication, because conducting cells in left bundle branch tore latch well in the ischemic state. Only one case developed left bundle branch block in acute stage, resulting from broad necrosis of ventricular septum. AVB in posterior infarction was a common finding and showed good prognosis. All of fatal cases with AVB were due to cardiogenic shock complicating right ventricular infarction. Previous reports3,4 pointed out edema in AV junctional area, and equally we found cellular infiltration in atrial septum.

RBBB was frequently seen in the cases of cardiogenic shock, reflecting transmural necrosis of anterior ventricular septum. In the cases
A 77-year-old male, died on the 3rd day after onset of acute anteroseptal infarction. Note the extension of infarction to the anterior portion of the interventricular septum (shown by an arrow).

TABLE II  VENTRICULAR TACHYCARDIA AND VENTRICULAR FIBRILLATION. PROFILES OF 15 CASES

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>ECG findings</th>
<th>Complications</th>
<th>Course</th>
<th>His</th>
<th>LBB</th>
<th>RBB</th>
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<tr>
<td>64</td>
<td>M</td>
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<td>Hemorrhage</td>
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</tr>
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<td>56</td>
<td>M</td>
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<td></td>
<td></td>
<td>4 hrs</td>
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<tr>
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<td>M</td>
<td>CAVB</td>
<td></td>
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<td>59</td>
<td>M</td>
<td>RBBB + LAH</td>
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<td>17 days</td>
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<td>M</td>
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<td>RBBB</td>
<td>Rupture</td>
<td>3 days</td>
<td>Congest</td>
<td>Necrosis</td>
<td>Edema</td>
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<td>7 days</td>
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<td>77</td>
<td>M</td>
<td>RBBB + LAH</td>
<td>Sept perforat.</td>
<td>8 days</td>
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<td>68</td>
<td>M</td>
<td>CAVB + RBBB</td>
<td>Vent aneurysm</td>
<td>14 days</td>
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</tr>
<tr>
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<td>M</td>
<td>CAVB + RBBB</td>
<td>Vent aneurysm</td>
<td>23 days</td>
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<td>RBBB + LAH</td>
<td>Vent aneurysm</td>
<td>39 days</td>
<td>Degen. + Fibr.</td>
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<tr>
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<td>F</td>
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<td>2 days</td>
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<tr>
<td>72</td>
<td>F</td>
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<tr>
<td>88</td>
<td>F</td>
<td>RBBB</td>
<td>Reattack</td>
<td>4 hrs</td>
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<td>Fibrosis</td>
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Abbreviations are as follows: CAVB = complete AV block; RBBB = right bundle branch block; LAH = left anterior hemiblock; af = atrial fibrillation; Congest = congestion; Degenerat. = degeneration; Fibr. = fibrosis

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complicated with intractable VT and VF serial section of conducting tissue exhibited hemorrhage, vacuolar degeneration or broad fibrosis especially in left bundle branch. Norris et al.\textsuperscript{5} mentioned that early VT in 24 hours showed good prognosis, but late VT did poor one causing VF or pump failure. In this study, we could not find out significant changes in conducting cells in very early infarction. But various degenerative changes were seen in left bundle branch 24 hours after the onset, which seemed to be responsible to intractability of arrhythmias.

Summary of Section I:
1. The incidence of deaths by severe arrhythmias in patients with AMI decreased markedly by the establishment of the treatment in CCU. But extensive infarction has still been complicated with fatal arrhythmias in no small numbers of patients.
2. The conduction system was affected frequently in the atrial myocardium, the approach to the AV node, and the portions distal to the bundle-branching portion in accordance with the anatomical extension of the infarct.
3. Lesions in the AV node and His bundle were relatively mild.

4. In cases with intractable VT or VF, extension of infarction and ventricular aneurysm were frequent.

II. Myocardial Biopic Findings of Patients with Various Arrhythmias
It is well known that many heart diseases such as ischemic heart diseases (IHD), valvular heart diseases (VHD), cardiomyopathy, and myocarditis may lead to various arrhythmias, but some of them have been considered to be idiopathic. When arrhythmia is fatal, its cause can histologically be investigated at autopsy, but it may largely remain unknown in less than fatal cases. Histologic investigations were made on heart tissues obtained by endomyocardial biopsy in patients with various arrhythmias.

Patients and methods: 146 patients with various arrhythmias were examined except those having evident IHD. 38 patients had sick sinus syndrome (SSS), 43 AVB, 50 supraventricular tachycardia (SVT) including atrial flutter (AF), and 15 VT with average age of 51.5 years. Patients were categorized into 80 individuals without underlying diseases (idiopathic arrhythmias) and 66 individuals with underlying diseases.
or complications.

Endomyocardial biopsy was carried out with consent of the patients after explaining the significance of bioptic investigation and safety of the method at the cardiac catheterization utilizing a Machida type biopome. Biopict findings were categorized into following 4 groups; 1) Histologically normal or near-normal myocardium (normal group), 2) Myocardial tissue with 5 or more inflammatory cells per highly magnified field in light microscopy (myocarditis group), 3) Postmyocarditic tissue suspected from interstitial fibrosis and increased vascularization (postmyocarditic group), and 4) Myocarditis-unrelated changes including myocardial hypertrophy, coarseness, and irregular cell arrangement (non-specific abnormality group)⁶ The typical histologic features for each of 4 groups are shown in Fig. 6. Fig. 6-A shows a typical findings of acute myocarditis, with apparent inflammatory cells. Fig. 6-B represents those in the chronic stage from the same patient. Perivascular focal fibrosis, increased vascularization and small remaining inflammatory cell infiltration were noted being considerable to postmyocarditic state. Fig. 6-C shows a tissue with non-myocarditic changes. It shows non-specific myocardial hypertrophy, coarseness, and diffuse interstitial fibrosis. And a normal myocardium is shown in Fig. 6-D.

Figure 7 summarizes all of the biopict findings. Histologic findings of heart muscles were near-normal in 25% and more or less degenerated in 75%. The latter consisted of myocarditis in 12%, postmyocarditis in 32%, and non-specific abnormalities in 31% (Fig. 7-A). One half of the cases of AVB were affected by non-specific abnormalities, and VT was frequently associated with the microscopic findings suggesting myocarditis or postmyocarditic state. None of the patients in whom myocarditis was histopathologically diagnosed showed typical clinical symptoms of myocarditis. The only previous clinical symptoms observed suggested the common cold in some patients.

No evident underlying diseases were found in 80 out of 146 patients (55%) in clinical practice, however, normal myocardium was suspected only in 26% of the 80 patients, and in the remaining 74% of the cases some degeneration of cardiac myocytes was observed (Fig. 7-B). Postmyocarditis was the most frequent (40%), myocarditis in 15%, and non-specific abnormalities in 19%.

On the other hand, in 66 patients who had arrhythmias related to underlying diseases or having complications including hypertension, diabetes mellitus, VHD, cardiomyopathy, and heart failure, 24% had near-normal myocardium, and 76% had some myocardial abnormality. Non-specific abnormalities was the most frequent, followed by postmyocarditis and myocarditis (Fig. 7-C).

Discussion of the Section II:
Histopathologic features of myocardial biopsies obtained from patients with various arrhythmias were categorized into normal, active myocarditis, postmyocarditis, and non-specific abnormalities⁶. Myocarditis was not clinically evident, but remained subclinical in all of the cases. In the patients with myocarditis to whom endomyocardial biopsies could be carried out in
the chronic stage, diagnosis of postcardiotic state was settled on the basis of the presence of interstitial focal fibrosis, increased vascularization, and myocardial hypertrophy. Myocarditis was found in 12% of 146 patients, and postmyocarditic state in 32%. In total, myocarditis was thought to have developed in a portion as large as 44% of the patients. It was reported that viral infection is accompanied by myocarditis at a rate of 5 to 15%. Thus, myocarditis seems to remain subclinical in no small number of cases, and it seems most likely that myocarditis is more or less responsible for the development of various arrhythmias.

This tendency was more evident in arrhythmias without underlying diseases or complications. In 55% of such cases, myocarditis or postmyocarditis were recognized, suggesting a strong likelihood that subclinical myocarditis was involved in the development of arrhythmias. Among the cases of arrhythmias with underlying diseases or complications, however, non-specific myocardial abnormalities were the most frequent histopathological finding, and they included cardiomyopathy-like, arteriosclerotic, pressure and volume overload-induced alterations, and other various abnormalities.

Summary of the Section II:

1. Myocardial biopsy demonstrated histologic abnormalities in 75% of the cases, in which myocarditis was observed in 12%, postmyocarditis in 32%, and non-specific abnormalities in 31%.

2. Among the cases of probably idiopathic arrhythmias biopic findings were abnormal in 74%. Postmyocarditic state was most frequently observed (40%). The incidence of myocarditis plus postmyocarditic state was as high as 55%, suggesting that subclinical myocarditis might be involved in the development of arrhythmias.

3. Among the cases of arrhythmias with underlying diseases or complications, non-specific myocardial abnormalities were the most frequent. Thus, a considerable number of cases of arrhythmias were accompanied with histopathologic alterations in the heart tissue, suggesting that these myocardial alterations might be involved in the development of arrhythmias.

III. Pathology of Myofibrils in Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is a disease accompanied by myocardial degeneration and fibrosis of unknown etiology, resulting in progressive and refractory heart failure that leads finally to death. Thus the prognosis of the disease is recognized to be very poor. The common feature of DCM is contraction failure and cardiac dilatation with the development of myocardial hypertrophy, degeneration, and degradation. In secondary cardiac hypertrophy such as VHD, on the other hand, similar changes as myocardial hypertrophy and cardiac dilatation will also develope and precipitate contraction failure.

We have studied the biopsied heart tissues...
from patients with various heart diseases with morphometry of the densities of myofibrils and other organellae in the myocytes, utilizing electron microscopy. And structural proteins were also extracted from the biopsied specimens, and fractionated by polyacrylamide gel electrophoresis to compare myocardium of the heart affected by DCM with normal myocardium or myocardium of secondary hypertrophied heart.

Endomyocardial specimens were obtained by biopsy as described in Section II of this lecture with a Machida type bioprome and were prepared for electron microscopic observations in an usual manner. Control heart muscles were obtained from 12 patients who were hospitalized for close examination for arrhythmic or other cardiac diseases, and proved to be hemodynamically and histologically not abnormal by cardiac catheterization or light microscopy. Biopsied specimens of secondary hypertrophied heart were from 12 patients with HHD, aortic valvular diseases, etc., and of DCM were from 17 patients who were definitely diagnosed according to the criteria of the Research Group of the Ministry of Welfare of Japan.

To quantify ultrastructural changes, electron micrographic morphometry was carried out by the point count method according to Weibel et al. A 7500 X electron micrograph for each patient was analyzed at random for 4080 points to measure the volume densities of myofibrils and mitochondria.

Structural proteins of myofibrils were also extracted from a piece of biopsy specimen in a crude fraction and analysed quantitatively by electrophoresis. Biopsied specimens were immersed in a solution containing 50% glycerine and 0.1M NaCl at -20°C for 14 days, homogenized, and centrifuged. Crude fraction containing total structural proteins was obtained as the precipitate of the last centrifugation and the subunits of structural proteins were separated by polyacrylamide gel electrophoresis in the presence of SDS.

In biopsied cardiac myocytes from patients with DCM, myofibrils were coarse and fragmented, and glycogen granules in the cytoplasm increased markedly. Irregularly arranged Z-bands, unequally sized mitochondria, and myofibrils consisting exclusively of thin filaments were observed. These findings seemed to suggest the lack of myocardial contractility. Most of the changes found above were not specific with DCM, because these ultrastructural changes were also observed in some degrees in secondary hypertrophic cardiac myocytes.

Morphometry of the myofibrils were summarized in Fig. 8. Myofibrils constituted 60.7 and 61.4% of the cell of the right and left ventricles, respectively, and mitochondria 23.5 and 23.9%, respectively in the normal control group. In secondary hypertrophic heart, volume

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densities of myofibrils and mitochondria were similar to those in the normal heart, suggesting that myofibrils increased correspondingly as myocardial cells were enlarged. On the contrary in DCM, the volume density of myofibrils decreased significantly to 52.7 and 50.9% in the right and left ventricles, respectively, and the volume densities of mitochondria also decreased significantly with increasing the cytosole.

Normal myocardial cells have mean diameters of 12.7 and 14.2 μm in the right and left ventricles, respectively, and myofibrils constituted a volume density of about 61% of the cell. In the secondary hypertrophic heart, the cell diameter increased to mean of 19.4 and 20.2 μm in the overloaded right and left ventricles, respectively, but the volume density of myofibrils was similar to that in the normal heart muscle. In DCM, the mean cell diameter increased significantly to 22.2 and 24.2 μm in the right and left ventricles, respectively, but the volume density of myofibrils decreased markedly as the cell diameter increased. This inverse correlation was significant in the myocardium of the left ventricle (Fig. 9).

Increases in enddiastolic volume of the left ventricle accompanied with decreases in the volume density of myofibrils, and this inverse relation was significant in the left ventricle. Ejection fraction was decreased in parallel with the volume density of myofibrils in the left ventricle as shown in Fig. 10.

The content of the structural proteins are shown in Table III. Myosin heavy chain/actin ratio was 1.26 on the average, and α-actinin/actin ratio 0.18 in the normal heart. In the secondary hypertrophic heart, the respective

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**TABLE III COMPOSITIONS OF STRUCTURAL PROTEINS OF BIOPSIED HUMAN HEART TISSUES**

<table>
<thead>
<tr>
<th></th>
<th>Myosin heavy chain / actin</th>
<th>α-actinin / actin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 6)</td>
<td>1.26 ± 0.44</td>
<td>0.18 ± 0.03</td>
</tr>
<tr>
<td>Secondary hypertrophy (n = 5)</td>
<td>1.13 ± 0.11</td>
<td>0.18 ± 0.03</td>
</tr>
<tr>
<td>Dilated cardiomyopathy (n = 6)</td>
<td>0.48 ± 0.20</td>
<td>0.08 ± 0.04</td>
</tr>
</tbody>
</table>

**p < 0.01, ***p < 0.001, mean ± S.D.**

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values were 1.13 and 0.18 on the average, being similar to those in the normal heart muscle. In DCM, however, decreases in myosin and α-actinin were recognized as indicated by significant decreases in myosin heavy chain/actin and α-actinin/actin ratios to 0.48 and 0.08, respectively.

Discussion of the Section III:

Poor prognosis of patients with DCM is attributable mainly to refractory heart failure. The morphologic observation exhibited in this lecture reflects the impaired contractility. Even though the morphologic findings in DCM are non-specific in quality, quantitative and biochemical myofibrillar alterations show the DCM specific findings. Cardiac hypertrophy occurs both in DCM and in secondary cardiac hypertrophy, but the volume density decreased in DCM in proportion to an increase in myocellular diameter. But in secondary cardiac hypertrophy the volume density of myofibrils increased with an increase in myocellular diameter. In addition to a decrease in the volume density of myofibrils, reductions in myosin and α-actinin of the structural proteins were noted in DCM in good contrast to the retainment of the structural proteins in secondary cardiac hypertrophy.

These morphologic and biochemical alterations in myofibrils in DCM indicate that the style of hypertrophy in DCM will be quite different from that in the secondary hypertrophy, and may be an expression of impaired protein synthesis in DCM.

Summary of the Section III:

1. Ultrastructural alterations found in DCM were generally similar to those in secondary hypertrophy of the heart. In DCM, however, the volume density of myofibrils in cardiac cells decreased significantly giving rise to the difference between secondary cardiac hypertrophy.

2. Decreases in the volume density of myofibrils in myocardial cells from patients with DCM was related with the left ventricular dysfunction, and likely to be a reflection of morphologic changes for impaired myocardial contractility.

3. Biochemical analysis of the structural proteins in DCM demonstrated that myosin heavy chain and α-actinin were predominately decreased, suggesting primary degeneration and degradation of myofibrils in DCM.

Conclusion:

It is still true that morphologic investigation is the most important and valuable way for the clinical researches of various diseases. In the recent years the analysis of the function of each diseased organ and of the intrinsic character of diseases have been becoming possible with the improvement and development of various diagnostic measures. Morphologic way of researches, on the contrary, has been considered to be the basic but classical one, however, it will make it also possible even to examine the functional and etiological investigations by the application of new applicable methods.

In this President Lecture, three fields of clinical researches made by the combinations of clinical practice and morphologic methodologies in which the author has long been engaged.

Notwithstanding many new diagnostic measures including the study of genes, the importance of clinicopathologic studies has never been decreased, and should be more important in the future.

Acknowledgement

I would like to express my sincere thanks to Professor Yasumitsu Nakai and Professor Kouji Tashiro of the Showa University School of Medicine for their generous help for these studies. I am also deeply grateful to Associate Professor Takashi Katagiri, Assistant Professor Youichi Takeyama and Drs. Hidemichi Goto, Shin Inoue, Youichi Kobayashi, Tohru Kitsu, and other fellow researchers in the Third Department of Internal Medicine, Showa University School of Medicine, for their collaboration.

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Japanese Circulation Journal Vol. 54, January 1990