Myocarditis and Arrhythmia:
A Clinico-pathological Study of Conduction System Based
on Serial Section in 65 cases

SHIN INOUE, M.D., FUMIO SHINOHARA, M.D., TETSUO SAKAI, M.D.
HIROKAZU NIITANI, M.D., TSUKASA SAITO, M.D.*, JOKO HIROMOTO, M.D.*
AND TOSHIHIKO OTSUKA, M.D.*

We studied the conduction system of 65 cases of proven active or healed myocarditis and related diseases among 7120 autopsy samples. For this purpose, we prepared serial sections by Lev's method. The pathological diagnoses were idiopathic acute myocarditis (5), giant cell myocarditis (3), chronic myocarditis (13), healed myocarditis (22), sarcoidosis (4), collagen or autoimmune disease (13) and complication of cachexia (5). Among all the autopsy cases, Fiedler’s myocarditis was found in only one case, but myocarditis was revealed in 19 out of 30 cases of dilated cardiomyopathy, and 15 out of 25 cases of sick sinus syndrome. Conduction system lesions were divided into two groups. In older cases manifesting mainly arrhythmia, the SA node, atrial muscle and AV node were involved concomitantly with perimyocarditis. In younger cases mainly showing heart failure, the RBB, LBB and Purkinje fibers were damaged by endomyocarditis. Histologically, interstitial myocarditis was observed in the former group and parenchymatous myocarditis in the latter.

From a clinical standpoint, myocarditis was formerly thought to be a relatively rare heart disease with a good prognosis which may occur after symptoms of virus infection. However, the recent development of endomyocardial biopsy technique has revealed various clinical manifestations of myocarditis, i.e. chest discomfort, brady- or tachyarrhythmia and congestive heart failure. Nevertheless, biopsy specimens can only provide information about a very limited portion of the endomyocardial layer, despite their availability throughout the clinical course of the disease. In autopsy hearts, we can examine the regions of pathogenesis if sufficient pains are taken. In this study, we attempted to reconstruct the relationship between clinical manifestation and histopathological findings of myocarditis observed in autopsy samples. In particular, we examined the conduction system using serial sections and compared the result with ECG findings.

SUBJECTS AND METHODS

The subjects used in this study were 65 cases (ranging from 18 to 88 years of age) of autopsy-proven active or healed myocarditis and related disease detected in 7120 serial autopsy samples in the Pathology Department of Showa University from January 1967 to December 1986. The

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Third Department of Internal Medicine: *Second Department of Pathology, Showa University School of Medicine.
Tokyo, Japan
Mailing address: Shin Inoue, M.D., Third Department of Internal Medicine, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan

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### TABLE I CLINICAL VERSUS PATHOLOGICAL DIAGNOSIS

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<td>Dilated cardiomyopathy</td>
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<td>Hypertrophic cardiomyopathy</td>
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<td>Pneumonia</td>
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### TABLE II ECG FINDINGS

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<th>ECG Finding</th>
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<td>Sick sinus syndrome</td>
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<td>AV block (&gt; 2ND degree)</td>
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<tr>
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</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
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<tr>
<td>RBBB</td>
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</tr>
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</tr>
<tr>
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**Abbreviations:** RBBB = right bundle branch block; LBBB = left bundle branch block; LAH = left anterior hemiblock; LPH = left posterior hemiblock; BBBB = bilateral bundle branch block; IVCD = intra-ventricular conduction disturbance.

The incidence of myocarditis was 0.9%. However, accurate clinical diagnosis of myocarditis had been made only in 5 cases (Table I). The most frequent clinical diagnoses were dilated cardiomyopathy (DCM) (19 cases), sudden death of young males (5 cases), valvular heart disease (4 cases) or sarcoidosis (1 case), while the others were diagnosed as ECG abnormalities or arrhythmia. The most typical ECG findings were recurrent sequences of brady- and tachyarrhythmia, and the breakdown was as follows (Table II): AV block of second degree or above (23 cases), sick sinus syndrome (13 cases), atrial fibrillation or flutter (23 cases), intraventricular conduction disturbance (25 cases) and recurrent ventricular tachycardia or fibrillation (9 cases).

The pathological diagnoses were idiopathic acute myocarditis (5), giant cell myocarditis (3), chronic myocarditis (13), healed myocarditis (22), cardiac sarcoidosis (4), myocarditis accompanied with collagen or autoimmune disease (13) and complication of cachexia (5).

**Methods:** The autopsied heart was measured after formalin fixation and the conduction system was removed and embedded by Lev's method, after which serial sections were prepared! The other parts of the myocardium were cut into 7–20 blocks. The prepared conduction system was paraffin embedded and cut into 6 μ serial sections, and every tenth section was stained. The main stains used were Elastica-van-Gieson's or hematoxilin-eosin, and Azan-Marolly, while PAS and PTAH were added as required. The histological extent of conduction tissue injury was divided into 5 stages between 0 and 100%, and lesions were regarded as significant when reduction of conducting cells was 50% or more. As controls we used 65 autopsied hearts from cases of death due to myocardial infarction, including a nearly equal number of dysrhythmias.

**RESULTS**

Damage caused by myocarditis was more frequent and severe than myocardial infarction, because conducting cells are resistant to ischemia.

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Fig. 1. a: Fulminant myocarditis (Fiedler type). A 64-year-old man with fatal ventricular standstill, resisting temporary pacing after influenza-like symptoms. Microscopically, degeneration and disappearance of conducting cells was observed, especially in the left bundle branch and Purkinje fibers. (hematoxylin-eosin stain \( \times 100 \))

b: Giant cell myocarditis. A 35-year-old woman who had complained of palpitation and died with heart failure. Inflammatory regions with giant cells were observed in the atrial septum and the epicardial sites of both ventricles. Epithelioid cells were not observed. (hematoxylin-eosin stain \( \times 100 \))

c: Chronic myocarditis. A 37-year-old woman who died of heart failure and cerebral embolism. ECG recording exhibited RBBB and LAH. Diffuse infiltration of lymphocytes was accompanied by severe interstitial fibrosis. (hematoxylin-eosin \( \times 100 \))

d: Healing endomyocarditis. A 18-year-old girl who had experienced severe congestive heart failure, and died of recurrent ventricular tachycardia. Endomyocardial fibrosis with mononuclear infiltrates was found. The surface of the thickened endocardium was partially shared by organizing thrombi. (hematoxylin-eosin \( \times 100 \))

Abbreviation: En = endocardium; Pu = Purkinje fibers; My = myocardium; Th = thrombus; Fi = fibrosis; Pe = pericardium; Ca = calcification.

1. Fulminant Myocarditis

Among all 7120 autopsy hearts, death caused by fulminant myocarditis (Fiedler type) was found in only 1 case. This 64-year-old male manifested Adams-Stokes syndrome after common cold symptoms. The ECG exhibited complete AV block. The patient died of cardiogenic shock with ventricular standstill resistant to temporary pacing. Autopsy revealed pronounced lymphocytic infiltration in the myocardial interstitium accompanied by myocardial degeneration and necrosis, and both bundle branches as well as Purkinje fibers were affected by inflammation (Fig. 1-a).

2. Acute Myocarditis

In most clinically diagnosed myocarditis, the prognosis is good and fatal cases of myocarditis
are quite rare. Main causes of death in cases of acute myocarditis are due to complications of arrhythmia (i.e. cerebral embolism) or primary disease. Acute myocarditis was found in one patients with chronic renal failure undergoing hemodialysis, and in another patient with fever of unknown origin. Both of these patients displayed complete AV block. Also, acute myocarditis was observed in one patient of cerebral hemorrhage suffering from atrial fibrillation, whose heart rate was difficult to control by medication. One case of acute perimyocarditis in the convalescent stage was autopsied after death due to chronic bronchitis, but the myocardium was almost intact except for a slight interstitial fibrosis.

3. Dilated Cardiomyopathy

Histological observation including conduction system showed that most cases of autopsy-proven myocarditis had manifested heart failure or various arrhythmias without evident clinical signs.
of infection or inflammation. Among 30 autopsy cases diagnosed as DCM during their lifetime, we found three cases of giant cell myocarditis, 7 cases of chronic myocarditis and 9 cases of healed myocarditis.

Giant Cell Myocarditis
The three cases of giant cell myocarditis ranged from 35 to 70 years of age, and the duration of their illness had been 14 months to 4 years. In ECG findings, all three cases showed atrioventricular block of the second degree or above, resulting from intraventricular conduction disturbances. Microscopically, giant cells were observed in the atrial septum and the pericardial layer of both ventricles (Fig. 1-b). Conduction disturbances were chiefly due to bilateral bundle branch block caused by inflammatory lesions in the ventricular septum. The main cause of heart failure and ventricular dilatation was degeneration and disappearance of ventricular myocardial cells. Most of the giant cells were suggestive of myogenic origin, and myocardial degeneration and necrosis were not necessarily accompanied with inflammatory infiltrate. We regarded this type of phenomenon as “parenchymatous myocarditis”, because it occurred principally in the myocardial parenchyma, i.e. the myocardial cells.

Chronic Myocarditis
Chronic myocarditis without giant cells was found in 7 cases of DCM, with ages ranging from 18 to 88 years. Various type of myocardial degeneration and fibrosis were revealed, and parenchymatous change was also an essential feature of this condition, as in giant cell myocarditis (Fig. 1-c, 1-f). The ECG findings were atrial fibrillation (2 cases), third degree AV block (5 cases) and intraventricular conduction disturbances (6 cases). Damage to the conduction system caused by endomyocarditis was observed at the left and right bundle branches in young cases, and at the SA node, atrial muscle and AV node concomitant with perimyocarditis in elderly cases.

Healed Myocarditis
Healed myocarditis was found in 9 cases of DCM, and 7 cases showed atrioventricular or intraventricular conduction disturbances. The main histological findings were segmental fibrosis of myocardium unrelated to the coronary circulation (Fig. 1-d). Inflammatory infiltrates had disappeared from the myocardial interstitium but small foci remained beneath the epicardium. Epicardial thickening or endocardial fibroelastosis with myocardial fibrosis were interpreted as healed peri- or endomyocarditis. The distribution of conduction system lesions due to myocarditis was identical with that observed in chronic myocarditis.

4. Sick Sinus Syndrome
Sick sinus syndrome is one of the clinical
manifestations of myocarditis. Among 25 autopsied hearts diagnosed as sick sinus syndrome, including atrial fibrillation with bradycardia, 15 cases showed histological evidence of chronic or healed perimyocarditis (Fig. 1-e). Twelve cases were Rubenstein type III, one case was type I and 2 cases were atrial fibrillation with bradycardia. Their main causes of death were cerebrovascular disorders (7 cases). Conduction system lesions were essentially in pericardial sites, i.e., in the SA node, atrial muscle, AV node and in some cases the His bundle. One case showed neuritis, and one case revealed angitis of a branch of the SA nodal artery. Interstitial infiltrates were relatively predominant, rather than damage to the myocardial parenchyma. We used the term "interstitial myocarditis" to describe such a condition. The conduction system beneath the His bundle was well preserved.

5. Atrio-Ventricular Conduction Disturbances
Among the 10 cases manifesting atrioventricular block, 2 cases were complications of cachexia and one case was endomyocarditis accompanied by hemopathy. However, in cases suggesting idiopathic conduction disturbances, we found involvement of myocarditis not only in cases of acute onset, but also in chronically progressive cases with histories of several years; their ECG findings indicated complications of various atrial arrhythmias and atrioventricular block. The major sites of damage were the AV node and its approach, caused by perimyocarditis.

6. Sudden Deaths of Young Males
In cases of sudden death of young adults, the main causes of death were presumed to be lethal arrhythmias, e.g., ventricular fibrillation. We found myocarditis and its sequelae in 5 of these cases. Recurrence of myocarditis with thrombotic angitis was observed in one case, lymphocytic infiltration in the sino-atrial junctional area and loop formation of the left bundle branch was in 1 case, neutrophilic infiltration and fibrosis in the AV nodal approach in 1 case, and healed myocarditis in 2 cases, which exhibited fibrosis of both bundle branches.

7. Collagen or Autoimmune Diseases
Myocarditis associated with collagen or autoimmune diseases, including rheumatic pancarditis, was observed in 14 cases; among these 2 cases of SSS, 7 cases of atrial fibrillation, one case of AV block and 4 cases of intraventricular conduction disturbance had been recorded in ECGs. Histologically, the SA node together with its junction and atrial muscle were damaged by perimyocarditis but the other parts of the conduction system such as the AV node, His bundle and Purkinje fibers were relatively well preserved.

8. Cardiac Sarcoidosis
Four cases of cardiac sarcoidosis were found among all the samples, but only one of these cases had been clinically diagnosed as such, and had received cortico-steroid hormone therapy. ECG findings exhibited third or higher degree AV block in all cases, consistent with the fact that the most frequent site for the occurrence of sarcoid granuloma is in the atrial or ventricular septum.
9. Clinico-Pathological Classification

For the purpose of classifying the differences between clinical manifestations and pathological findings, we divided the cases into 2 age groups: younger subjects under 59 years of age and older subjects over 50 years of age (Table III).

The younger age group (28 cases) had mainly suffered from congestive heart failure and had been clinically diagnosed as having dilated cardiomyopathy (13 cases). Cases of sudden death were not rare (8 cases). In ECG recordings, intraventricular conduction disturbance (16 cases) and incurable ventricular tachycardia or fibrillation (7 cases) were noted. Macroscopically, the main site of the lesions was the left ventricular myocardium and since these lesions were not concomitant with pericarditis, we referred to such cases as "isolated myocarditis". However, endocardial thickening or fibroelastosis, considered as sequelae of endomyocarditis, was frequently observed. Microscopically, degeneration and reduced numbers of myocytes with consequent fibrosis were characteristic of this type of case, which we referred to as "parenchymatous myocarditis". Formation of aneurysms in the postero- or anterolateral area of the left ventricular myocardium was also conspicuous. Conduction system lesions were mainly in endocardial sites, left or right bundle branches and Purkinje fibers (Fig. 2).

In the older group (37 cases), the major manifestations were various arrhythmias, i.e., atrial fibrillation (20 cases), sick sinus syndrome (11 cases) and AV block (15 cases), and the main causes of death were congestive heart failure and cerebral embolism. Histopathological examination revealed perimyocarditis involving the right atrium or right ventricle, but the left ventricular myocardium was relatively hypertrophied. Microscopically, interstitial inflammatory infiltrates were more predominant than in the younger group, and pericarditis or focal endocarditis was also observed. However, degeneration or disappearance of myocytes was relatively slight and hypertrophy and disarrangement of residual myocytes were frequently seen. Lesions of the conduction system occurred in pericardial sites such as the SA node, atrial muscle and AV node. The lower part of the conduction system, i.e. left and right bundle branches were significantly better preserved than in the younger group.

DISCUSSION

Since it was described by Fiedler in 1899, myocarditis has been considered to exhibit acute onset and occasionally lead to a fatal course due to pump failure accompanied by brady- or tachyarrhythmia. However, Saphar and his colleagues, on the basis of their studies of serial autopsy samples, suggested that myocarditis was not a rare occurrence in autopsied hearts but that the correct diagnosis of this condition is very difficult in living patients. The incidence of myocarditis is vague, and estimates ranging from 9% to 0.15%, since the diagnosis of myocarditis depends on the sensitivity, and criteria of the observer. On the other hand, there has been a discrepancy between clinical manifestations and autopsy findings as regards the diagnosis of myocarditis, since patients regarded as suffering from acute myocarditis have a good prognosis and fatal cases are quite rare. However, recent advances in endomyocardial biopsy technique have revealed the presence of unexpected and latent myocarditis in various heart diseases, particularly in patients suffering from various arrhythmias or congestive heart failure.

Fibrosis of the conduction system has been proposed as the cause of conduction disturbances and arrhythmias by several researchers, e.g. Lenègre et al. However, the origin of fibrosis of conducting tissue has not been made clear. As for the pathogenesis of atrioventricular block, Davies has also attributed this condition to idiopathic bundle branch fibrosis and ischemic injury, and suggests that inflammatory disease is relatively rare. Nevertheless, we believe that conduction tissue possesses greater resistance to ischemia and other degenerating disorders than working muscle. On the other hand, in dilated cardiomyopathy, participation of viral myocarditis has been strongly suggested by endomyocardial biopsy studies subsequent to its acute stage. In our autopsy samples, the fulminant type of myocarditis was quite rare, especially in its acute stage, but chronic myocarditis was frequently found, and healed myocarditis free from infiltration of inflammatory cells was more frequent occurrence in various heart diseases. We found that some cases of dilated cardiomyopathy preserved the normal structure of the myocardium without fibrosis or inflammatory infiltrate, hence, we considered this type to be a genuine form of dilated cardiomyopathy.

The similarity of giant cell myocarditis to
cardiac sarcoidosis has been a controversial subject, but epithelioid cells were not observed in our cases and giant cells were suggestive of myogenic origin. Particularly in the residual myocardium, the degeneration and disappearance of myocytes was conspicuously different from that seen in cardiac sarcoidosis. In cardiac sarcoidosis, lesions of the myocardium tended to be confined to the interstitium and degeneration of myocytes appeared to be slight. That is, sarcoidosis was considered to be primary interstitial myocarditis and giant cell myocarditis as parenchymatous myocarditis. A specific form of myocardial degeneration was found in one case diagnosed as dilated cardiomyopathy (a 45-year-old male). Microscopically, calcification and necrosis of myocytes were the essential findings and inflammatory infiltrates were slight (Fig. 1-f). Also we applied the term “parenchymatous myocarditis” to this case. Healed myocarditis diagnosed as dilated cardiomyopathy was characterized by fibrosis of the myocardial parenchyma and partial aneurysm formation; its main features were disappearance of myocytes and scar formation. These types of illnesses suggest the relationship of acute and chronic viral hepatitis, the former having a good prognosis and the latter often having a bad one.

In myocarditis accompanied by clinical manifestations of arrhythmia, the effect of pericarditis upon the SA nodal area has been mentioned by James, and the occurrence of pericarditis in sick sinus syndrome was pointed out by Rossi. The SA node and AV node were formerly regarded as primarily pericardial organs, and anatomically their close relationship to the pericardium is apparent. Myocarditis frequently involves damage at pericardial sites in the myocardium, and this tendency has already been pointed out in the literature. On the other hand, the left and right bundle branches and Purkinje fibers are considered to be subendocardial organs, and although they may be affected by endocarditis, the pure form of endocarditis is rarely fatal, and accompanying conduction disturbance has not been frequently reported. However, in myocarditis of the parenchymatous type, the main lesions are in the left ventricle, and endocardial thickening results from necrosis of the subendocardium. The same phenomenon is observed in myocardial infarction, but infarction occurs in regions limited by the blood supply. Myocarditis damages broader areas, and interstitial response accompanied by endocardial thickening is more severe than in myocardial infarction.

In the conduction systems observed in cases of sudden death of young males, scattered fibrosis with mild inflammatory infiltrates have already been mentioned in the literature. Some researchers have suggested that damage to the conduction system is caused by myocardial ischemia, but our experience of infarcted hearts indicates that this is unlikely, because conducting cells are more resistant to ischemia than working myocardial cells. Moreover, in myocarditis, since conducting cells exist in the subepicardium or subendocardium, inflammation easily affects conduction tissue, and since the conduction system contains rich interstitial tissue, such as vascular tissue, elastic and collagen fibers, adipose tissue and nerves, interstitial inflammation is also likely to damage the conduction system. However, in the parenchymatous type of myocarditis, the conduction system lesions are secondary results of necrosis in the left ventricle, so bilateral bundle branch block or intraventricular conduction disturbances result from concomitant endomyocardial fibrosis. We believe that the extent of activity and tissue damage in myocarditis is difficult to assess from clinical examination or symptoms. The severity and activity of inflammation may be reflected by the ratio of CD4/8 in peripheral blood. Elevation of its level suggests decline of suppressor T cell activity and may result in tissue damage due to autoimmune mechanisms.

Myocarditis displays a broad spectrum of varied cardiac symptoms, hence, it is important to detect latent myocarditis, which may be involved in the pathogenesis of various disorders. If myocarditis, especially of the chronic type, is discovered, then immunosuppressive therapy should be instituted.

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REFERENCES


2. JARCHO S: Fiedler on acute interstitial myocarditis (1899)I and II. Am J Cardiol 58: 221, 1973

4. SAPHER O, COHEN NA: Myocarditis in Infancy. *Arch Path* 64: 446, 1957