Inclusion of electric disturbance type cardiomyopathy in the classification of cardiomyopathy: A current review

Morie Sekiguchi∗, Atsuyo Hasegawa, Michiaki Hiroe, Shinichiro Morimoto, Toshio Nishikawa

International Cardiomyopathy Study Section, Japan Research Promotion Society for Cardiovascular Diseases, 8-1 Kawada-cho, Shinjuku, Tokyo, 162-8666 Japan

Received 12 February 2008; accepted 13 February 2008
Available online 14 March 2008

KEYWORDS
Endomyocardial biopsy; Cardiomyopathy; Arrhythmias and conduction disorders; ECM; Atrial cardiomyopathy

Summary
There are cases of cardiomyopathy which are not easily classifiable into hypertrophic, dilated or restrictive type. They often show ventricular arrhythmia, right or left bundle branch block, intraventricular conduction disturbance, atrioventricular conduction disturbance, and sinus node dysfunction (sick sinus syndrome). Endomyocardial biopsy in such cases reveals advanced myocardial disease, for which we propose the simpler term "electric disturbance type cardiomyopathy (ECM)". In our consecutive series of studies of cardiomyopathy employing endomyocardial biopsy in 573 cases, 264 (46%) were hypertrophic, 224 (39%) were dilated, and 85 (14.8%) were classified into the ECM.

© 2008 Published by Elsevier Ireland Ltd on behalf of Japanese College of Cardiology.

Contents
Introduction .................................................................................................. 82
Proposal for the inclusion of ECM (electric disturbance type cardiomyopathy) in cardiomyopathy classification ................................................................................................................. 82
Features of the electric disturbance type cardiomyopathy (ECM) [1,2] .......................................................................................................................... 82
Some reference points in diagnosis ................................................................ 83
Frequency of occurrence and significance ..................................................... 84
Acknowledgements ......................................................................................... 87
References ................................................................................................. 87
Introduction

The proposal in the title of this review article was originally presented in 1985 at the AHA (American Heart Association) annual meeting [1], and was thereafter presented in a monograph series book entitled "Cardiomyopathy Update 3" [2]. It was also planned to be submitted later as an original paper submission with the addition of new data. Since then, years have passed because of the authors' time and circumstances, postponing publication until this day. On the occasion of this newly arranged international cardiology journal, the authors were asked to present a review article, which seemed to be a good opportunity to contribute this paper at long last.

The reason for repeating the contents of this proposal today is that although our concept appeared over 20 years ago, it has yet to be cited in any scientific journals or cardiology textbooks, possibly due to its initial submission to a monograph book with a limited distribution and indexed format. Therefore, it will appear again with a revised title and contents, and hopefully shed more light on the classification of cardiomyopathies [6].

Proposal for the inclusion of ECM (electric disturbance type cardiomyopathy) in cardiomyopathy classification

It is a generally accepted functional concept that there are two major types of cardiomyopathy: hypertrophic type, which is characterized by thickening of the interventricular septum or the free wall of the left ventricle, and dilated type, characterized by a reduced left ventricular ejection fraction [3,4]. However, we have frequently experienced cases of myocardial disease, often associated with cardiac arrhythmias or disorders of conduction, which do not belong to either of the two major functional categories [1–10].

In many cases of cardiomyopathy, there is neither thickening of the interventricular septum or the ventricular free wall nor is there an apparent decrease in the left ventricular ejection fraction. In our studies using endomyocardial biopsy over the past 40 years [11–27], including right atrial biopsy [6,17,38], we have encountered cases where the histopathologic changes are confined to the right atrial myocardium without functional or anatomical changes in the right ventricle. Accordingly, we have termed such cases "atrial cardiomyopathy" [17].

In our investigation of patients with right bundle branch block as the only clinical feature, we have found fairly advanced pathology in the right ventricular biopsy specimens [2,7,8]. Similarly in sarcoidosis [30,31], where right bundle branch block and atrioventricular block are the predominant features of this cardiac disorder, it is not possible to functionally categorize such cases as either the hypertrophic or dilated type of heart muscle disease. We therefore propose an additional category of cardiomyopathy, namely "non-hypertrophic and non-dilated" and characterized by cardiac arrhythmias or conduction (electric) disturbances as the predominant clinical manifestation [1,2]. In this way, both clinical and pathologic features can be more easily reconciled. An analysis of this third category of cardiomyopathy is presented with our proposed term "electric disturbance type cardiomyopathy (ECM)" [1,2,9].

Fig. 1 illustrates background of understanding ECM which has been taken from our own experience of myocardial sarcoidosis [30,31].

Features of the electric disturbance type cardiomyopathy (ECM) [1,2]

1. There is no evidence of hypertrophic cardiomyopathy (HCM), in that there is no thickening of the left ventricular wall or at the apex.
2. There are no clinical signs suggestive of dilated cardiomyopathy (DCM), and the echocardiogram, left ventriculogram and radionuclide ventriculography show left ventricular ejection fraction exceeding 50%.
3. There are no clinical features suggestive of mitral valve prolapse.
4. There is the presence of non-specific electrocardiographic abnormalities including complete right or left bundle branch blocks, A-V block, intraventricular conduction disturbance, sick sinus syndrome [34], primary ST-T wave changes, and ventricular arrhythmias as the main clinical features.
5. When the above four criteria are satisfied and when secondarily occurring myocardial disorders can be excluded, this strongly suggests that cardiomyopathy with electric disturbance is present (Table 1).
6. To establish the diagnosis in such circumstances, it is useful to perform endomyocardial biopsy [11–16]. Findings of myocardial degeneration or fibrosis, when prominent, should be regarded as significant evidence of myocardial disease [11,12]. When hypertrophy of the myocytes is the only feature, it may be
Figure 1 A diagrammatic representation of electric (arrhythmia and/or conduction disturbance) disorders in specific heart muscle diseases. Cardiac sarcoidosis represents this type of heart muscle disease. Without cardiomegaly in the chest X-ray (A), various forms of electric disturbance occur because of infiltration of sarcoidosis (dotted area). With a more diffuse infiltration, ventricles may develop dilatation, resulting in cardiac dysfunction (B). SSS: sick sinus syndrome; Af: atrial fibrillation; RBBB: right bundle branch block; PVC: premature ventricular contraction; VT: ventricular tachycardia; Vf: ventricular fibrillation; TR and MR: tricuspid and mitral regurgitation (from Sekiguchi et al. [31], with permission).

Table 1 Definition of electric disturbance type cardiomyopathy (ECM) [1,2]

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient shows evidence of A-V block, CRBBB, CLBBB, IVCD, ventricular arrhythmia, and/or atrial arrhythmia</td>
</tr>
<tr>
<td>2</td>
<td>Significant pathology in RV, LV, and/or RA endomyocardial biopsy</td>
</tr>
<tr>
<td>3</td>
<td>Non-hypertrophic, non-dilated form is recognized</td>
</tr>
<tr>
<td>4</td>
<td>Non-significant coronary angiogram is seen</td>
</tr>
</tbody>
</table>

IVCD: intraventricular conduction disturbance.

difficult to determine a basis of myocardial disease. Therefore, only in those cases which show severe grades (more than 2) for either degeneration or fibrosis of the myocardium should a positive diagnosis be made (Table 2) [7,8,15].

Some reference points in diagnosis

It is helpful to obtain a history of an influenza-like illness within about 10 days prior to the

Table 2 Histopathologic criteria for defining significant pathology [7,8,14,15,23]

<table>
<thead>
<tr>
<th>A. Parameters</th>
<th>B. Criteria for Determining Significant Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypertrophy</td>
<td>At least one of $A^2$ should exceed grade 2.</td>
</tr>
<tr>
<td>2. Degeneration</td>
<td>Sum of $A^{1-4}$ should exceed a score of 4.</td>
</tr>
<tr>
<td>3. Interstitial fibrosis</td>
<td></td>
</tr>
<tr>
<td>4. Disarrangement</td>
<td></td>
</tr>
</tbody>
</table>

Grading: | 0 | 1 | 2 | 3 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Grading for each parameter of the endomyocardial biopsy findings is determined using our own histopathologic diagnosis panel.
Figure 2 This 33-year-old male patient with sick sinus syndrome who suffered from diphtheria during childhood (A and B) underwent a right atrial (RA) and right ventricular (RV) endomyocardial biopsy. The RA biopsy revealed more advanced interstitial fibrosis (F) than the RV biopsy, leading to the clinical diagnosis of atrial cardiomyopathy. Results of his electrophysiologic examination is shown in (B). Bars in the RA and RV pictures indicate 20 μm. SNRT: sinus node recovery time.

onset of cardiac symptoms [19]. In such a setting, viral myocarditis may be suspected. Familial occurrence of heart disorders should also be considered [5]; arrhythmia and conduction disturbance type of cardiomyopathy may be present intrafamilially [6]. Radionuclide studies using thallium or technetium may reveal abnormality in scintigraphic or in wall motion in cases of suspected cardiomyopathy. Thereafter, a diagnosis can be finalized only by recourse to cardiac biopsy [11—15,21—27]. Arrhythmogenic right ventricular cardiomyopathy/dysplasia [27—29] showing a defect in thallium scintigraphy may also be differentiated by endomyocardial biopsy [26].

**Frequency of occurrence and significance**

Through analysis of our case material, we have come to the conclusion that cases with cardiomyopathy of the arrhythmia and conduction disturbance type are not infrequent [8,9]. Case examples are presented in Figs. 2—6, and the results of our case analysis are presented in Tables 2 and 3. In our series of endomyocardial biopsy in 573 consecutive cases [9], 264 (46%) were hypertrophic, 224 (39%) were dilated and 85 (14.8%) were classified as ECM (Table 4).

An additional endomyocardial biopsy study of 103 asymptomatic individuals detected as having heart disease by electrocardiogram, heart murmur, and/or cardiomegaly in chest X-rays during a health examination was performed by Kitajima [10] for a 10-year period from 1988 to 1998. In the

<table>
<thead>
<tr>
<th>S-A</th>
<th>A-H</th>
<th>H-V</th>
<th>SNRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>130</td>
<td>30</td>
<td>8200 msec.</td>
</tr>
</tbody>
</table>
103 cases in which clinical diagnosis of cardiomyopathy was finally established with the help of a biopsy, 36 cases (35%) of hypertrophic cardiomyopathy, 6 cases (5.8%) of dilated cardiomyopathy, and 17 cases (16.5%) of ECM were found. Another 41 (39.8%) of the 103 cases were diagnosed as heart disease of either specific or idiopathic nature.

It is to be reminded here that the above breakdown was obtained only from asymptomatic cases, and differs from Hasegawa’s report [9] where ECM was found in both symptomatic and asymptomatic subjects (Table 4).

In our studies of cardiac involvement in sarcoidosis, we found many cases with atrioventricular conduction disturbance or bundle branch block [30]. Autopsy revealed sarcoid granulomas distributed throughout the ventricular wall and especially in the interventricular septum. It was also confirmed at autopsy that cardiac sarcoidosis is not always functionally classifiable into either the hypertrophic or dilated types of cardiomyopathy. While it is agreed that cardiac sarcoidosis is a specific heart muscle disease [3,4], it should be regarded as a pathologic model of myocardial disorder with arrhythmia or conduction disturbance as the major clinical manifestation [30]. It may, therefore, be inferred that a similar clinico-pathologic presentation may occur in other non-specific or idiopathic myocardial diseases, such as cardiomyopathy (Fig. 1).

In muscular dystrophy, the finding of increased amplitude of R waves in lead V1 in the ECG could be...
This 41-year-old man was found to have left axis deviation (presumed to be of left anterior hemiblock) with an associated intraventricular conduction delay (IVCD) of 120 ms in an ECG (A). History taking and ophthalmologic examination suggested that he had suffered from toxoplasmosis. Endomyocardial biopsy from the right ventricle (B) showed a marked fibrocellular endomyocardial lesion (EM), suggesting the presence of preceding endomyocarditis. In this case, IVCD type of ECM was suggested. Two crossmarks in (B) may indicate artifacts. Bar in (B) indicates 20 μm. M: myocytes.

Explained by regression of the myocardium in the posterolateral region of the ventricle [32]. Again, heart muscle disease of muscular dystrophy type cannot be classified as the dilated type of heart muscle disease.

In our 30-year study of viral myocarditis, we have been able to recognize changes of acute myocarditis in biopsied specimens at a very early stage of the disease [18–25]. In those cases which have been followed for several years, right bundle branch block or left axis deviation persists even when the patient has clinically recovered and returned to full activity [20]. Patients who have recovered from myocarditis may also show persistent minor electrocardiographic changes or arrhythmias and various conduction disturbances [22]. A few of these cases may progress to dilated cardiomyopathy [22]. When a biopsy is performed in cases of ventricular arrhythmia or bundle branch block as the main presenting features, postmyocarditic changes [23–27] are often observed. A diagnosis of viral myocarditis is suggested on review of a history of an acute viral illness preceding the development of cardiac symptoms.

It is generally considered that sick sinus syndrome [34] and advanced A-V block or fascicular block are diseases of the conduction system only and regarded as a gerontologic disorder, as in Lev’s disease [33,35,36]. Lenegre’s disease is considered a disease of the conduction system in the young [37]. Both Lev’s and Lenegre’s disease can be differentiated from what we call ECM [1,2].

In a case of nonsustained left bundle branch block type of ventricular tachycardia in a 42-year-old man, right ventricular endomyocardial biopsy revealed fibrofatty change (FF) of the myocardium quite similar to that of arrhythmogenic right ventricular cardiomyopathy (ARVC). It is to be reminded that this patient did not show dilatation of the right and left ventricles, and therefore we diagnosed ECM of idiopathic VT type without ventricular dilatation. Bar in (B) indicates 20 μm.
because we define ECM to be restricted to those cases where diffuse involvement of heart muscle disease is confirmed by endomyocardial biopsy [1,2,7,8].

Following our report on right atrial endomyocardial biopsy and presentation on the concept of atrial cardiomyopathy [17,38], an Italian group has reported supporting evidence in a case of transient sinoatrial disease causing atrial myocarditis [39], and in 12 cases with lone atrial fibrillation [40]. In their laboratory, the biopsy was performed from the right atrial septum, contrary to our conventional method from the right atrial lateral free wall.

It is therefore necessary to discriminate the local characteristics of both normal and abnormal histologies for appropriate interpretation, especially in cases of endocardial thickening. To this aim, we have also comprehensively studied the nomogram at the biopsy sites using normal autopsied hearts [41].

Acknowledgements

This study was supported by a grant from the Japan Research Promotion Society for Cardiovascular Diseases.

The editorial assistance of Mr. Trevor Ralph is appreciated.

References


