HISTOLOGICAL FINDINGS OF THE RIGHT AND LEFT VENTRICULAR MYOCARDIUM AND CLINICAL FOLLOW UP IN IDIOPATHIC VENTRICULAR TACHYCARDIA

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In order to evaluate the etiology of so-called idiopathic ventricular tachycardia, endomyocardial biopsies were performed in four patients with electrocardiographically documented recurrent and sustained ventricular tachycardia. During the episodes of ventricular tachycardia, standard ECG showed a QRS pattern of right bundle branch block with left axis deviation in two patients and left bundle branch block in two patients. The episodes were associated with palpitation, dyspnea and hypotension in all cases. No organic heart disease was detected by physical examination, chest X-ray films, echo cardiograms, left ventriculograms or coronary cineangiograms. His bundle electrograms showed blocks at various sites in the atrioventricular conduction system. The biopsy specimens revealed nonspecific myocardial degeneration in the right and left ventricles. These findings suggest mild but wide-spread myocardial damage in both the working myocardium and the conduction system.

The clinical course of these patients appeared benign according to follow-up data of one to nine years' duration. None developed overt clinical signs of dilated, hypertrophic or restrictive cardiomyopathy.

It is well known that there are some patients who have recurrent episodes of ventricular tachycardia (VT) and whose underlying heart disease cannot be detected by conventional non-invasive and invasive methods. These patients have been diagnosed as "idiopathic"1–3 "primary"4 "functional" VT5 or with other terms6,7 Although some electrophysiological characteristics of this disease have been reported, histological findings of the myocardium have not been described until recently, when Strain et al8, Vignola and associates9 and Surgue and coworkers10 reported chronic myocarditis, small vessel disease and myocardial degeneration as possible causes of recurrent VT.

This paper describes the histopathological findings of biopsy specimens obtained from both right (RV) and left ventricular (LV) myocardium in four patients with "idiopathic" VT, and reports the follow-up data of these patients.

METHODS

Over the past ten years we performed endomyocardial biopsy in 175 patients with cardiomyopathies, and in more than 42 patients with various types of primary arrhythmias11,12 among which were included four patients with "idio-
### TABLE I CLINICAL CHARACTERISTICS

<table>
<thead>
<tr>
<th>Case</th>
<th>Age on admission</th>
<th>of onset</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Ventricular tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Frequency</td>
</tr>
<tr>
<td>1</td>
<td>27</td>
<td>10</td>
<td>M</td>
<td>Palpitation</td>
<td>6 episodes</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>29</td>
<td>M</td>
<td>Palpitation dyspnea</td>
<td>4 episodes</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>33</td>
<td>M</td>
<td>Palpitation syncope</td>
<td>3 episodes</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>14</td>
<td>M</td>
<td>Palpitation dyspnea</td>
<td>16 episodes</td>
</tr>
</tbody>
</table>

$LAD = \text{left axis deviation}; LBBB = \text{left bundle branch block}; M = \text{male}; RBBB = \text{right bundle branch block}$

**H.O. 33yr. Male**

**Ventricular tachycardia**  
**Sept. 25, 1978**

![Electrocardiogram](image)

Fig.1. Electrocardiogram during an attack of ventricular tachycardia taken from case 3. The QRS pattern shows left bundle branch block with left axis deviation.

Idiopathic VT. They were all male and their ages ranged from 19 to 33 years (mean 27). Recurrent and sustained VT was manifested as QRS patterns of right bundle branch block (RBBB) with left axis deviation (LAD) in two patients and left bundle branch block (LBBB) in two patients. The age of onset was between 10 and 33 years. The number of VT attacks was three to 16 episodes by the time of admission. The maximum rate of VT ranged from 146 to 220 beats per minute (mean 184). Emergency electrical cardioversions were performed in three patients. In the remaining case, intravenous injection of lidocain and disopyramide was effective for the termination of sustained VT. The cases had various degrees of symptoms during the episodes, but were completely symptom-free during normal sinus rhythm.

Resting electrocardiogram (ECG), chest X-ray, and 2 dimensional and M mode echocardiographic examination were performed in all patients. Graded maximal exercise test was performed with a treadmill (model ML-300, Fukuda) using Bruce’s protocol in three patients. His bundle electrograms were recorded via the femoral approach with the standard technique using an optical recording system (4588D-Hewlet-Packard with an amplifier 8811).

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Cardiac catheterization was performed with a brachial approach under fasting conditions. Left ventricular cineangiograms were recorded in a 30° right anterior oblique projection. After electrophysiological and hemodynamic evaluations, endomyocardial biopsies were obtained from the lower portion of the septum of the right ventricle via the right femoral vein with the sheath technique in all patients and from the apical portion of the left ventricle via the left brachial artery with a Konno-Sakakibara bioprome in three patients. Specimens were fixed with 10% formalin, dehydrated with a series of ethanol, and embedded in paraffin. The specimens were cut into 3–5μ thick sections and stained with hematoxylin and eosin, Mallory-azan, elastica-van Gieson, and periodic acid-Schiff reagent for light microscopic observation.

The histology specimens were reviewed by two independent investigators (Y.N. and K.K.) for the following findings: 1) hypertrophy of myofibers, 2) reduction in the number of myofibrils, 3) nuclear changes, 4) vacuolization, 5) disarray of myofibers, 6) endocardial thickening, 7) proliferation of collagen fibers, 8) interstitial edema, 9) cell infiltration and 10) fatty infiltration, graded from zero to four according to Noda's criteria. Degenerative substance or vascular change was counted as positive.

These patients were followed in our outpatient department. Ambulatory ECG was repeatedly recorded with Oxford Medilog and analyzed with Pathfinder II (Reynolds Medical) in three patients during the follow-up period. One of the four patients (case 2) could not visit our hospital after February 1981. Information on this case was obtained by telephone by one of the authors (H.N.).

**RESULTS**

Cardiovascular evaluations (Table II): No patients had obvious heart disease on physical examination. Serum electrolytes, thyroid hormone, serum immunological test for collagen diseases and serum viral antibody titers were in normal ranges in all patients. The resting ECG was normal in two patients, and left A-V block and right ventricular hypertrophy were present in the other two, respectively. The rate-corrected QT interval was normal in all patients and no patient had advanced A-V block, sinoatrial block, abnormal Q wave or ischemic ST, T wave changes. Two patients showed T wave inversion for hours to days after the cessation of VT. The chest X-ray films showed mild cardiomegaly in two patients. The cardiothoracic ratio of case 3 was 68% on admission immediately after termination of VT, and it decreased to 52% after

**TABLE II CARDIOVASCULAR EVALUATIONS**

<table>
<thead>
<tr>
<th>Case</th>
<th>ECG</th>
<th>CTR (%)</th>
<th>Exercise test</th>
<th>HBE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>45</td>
<td>Negative</td>
<td>1° H-V</td>
</tr>
<tr>
<td>2</td>
<td>1° A-V block</td>
<td>42</td>
<td>Negative</td>
<td>1° BH</td>
</tr>
<tr>
<td>3</td>
<td>RVH</td>
<td>68**</td>
<td>—</td>
<td>2° A-H***</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>51</td>
<td>Negative</td>
<td>1° A-H</td>
</tr>
</tbody>
</table>

* degree and site of block  
** two days after the termination of VT, CTR decreased to 52%.  
*** induced by right atrial pacing at the rate of 93 beats per min.  
A-V = atrioventricular; CTR = cardiothoracic ratio;  
HBE = His bundle electrogram; RVH = right ventricular hypertrophy

**TABLE III HEMODYNAMIC DATA**

<table>
<thead>
<tr>
<th>Case</th>
<th>Pressure (mmHg)</th>
<th>CI (L/min/m²)</th>
<th>EDVI (ml/m²)</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAm</td>
<td>RVEDP</td>
<td>PAm</td>
<td>PCW</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>7</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>6</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>9</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Normal value (mean ± SD)</td>
<td>5.0 ± 2.5</td>
<td>7.0 ± 2.2</td>
<td>14.6 ± 5.5</td>
<td>8.6 ± 4.6</td>
</tr>
</tbody>
</table>

CI = cardiac index; EDVI = end-diastolic volume index; EF = ejection fraction; LVEDP = left ventricular end-diastolic; PAm = mean pulmonary arterial; PCW = pulmonary capillary wedge; RAm = mean right atrial; RVEDP = right ventricular end-diastolic
2 days bed rest. Echocardiograms were normal in all patients and no patient showed abnormal wall motion, dilatation or hypertrophy of ventricles. Two patients (cases 1 and 4) had one and two false tendons, respectively, passing from the mid-septum to the posteroapical portion in the left ventricle. In three patients, first degree AV block was present: between the atrium and His bundle, in the His bundle, and between the His bundle and the ventricle, respectively. The remaining patient (case 3) showed second degree (Mobitz type 1) block proximal to the His bundle during right atrial pacing at low rate (93 beats per minute).

Hemodynamic data are shown in Table III with the normal values of our laboratory. Pressure gradients across the cardiac valves, valvular regurgitation, or significant shunts could not be detected by diagnostic cardiac catheterization, which was performed in all of the patients during normal sinus rhythm. Coronary arteries were free of sclerotic lesions, and LV end-diastolic volume was normal in three patients, and ejection fraction was low normal in two and subnormal in one patient.

**Histological Findings:** The histological findings are summarized in Table IV, and photographs are shown in Figs. 2 to 4. In case 1, right ventricular biopsy (RVB) (Fig. 2A) showed marked deformity of nuclei, moderate disarray of myofibers, moderate collagen fiber proliferation and moderate interstitial edema; left ventricular biopsy (LVB) (Fig. 2B) showed moderate deformity of nuclei, slight reduction in the number of myofibers, mild disarray of myofibers, and mild vacuolization. In patient 2, RVB (Fig. 3A) showed marked cellular hypertrophy (24.54 ± 9.55 μm in diameter) with slight reduction in the number of myofibers, mild nuclear deformity, mild vacuolization, mild disarray of myofiber, basophilic degeneration, and moderate collagen fiber proliferation; LVB (Fig. 3B) showed reduction in the number of myofibers, deformity of nuclei, vacuolization, and moderate disarray of myofibers. In case 3, RVB (Fig. 4A) showed marked disarray of myofibers, moderate deformity of nuclei and moderate fatty infiltration which was less than

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**TABLE IV THE HISTOPATHOLOGICAL FINDINGS OF ENDOMYOCARDIAL BIOPSIES***

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr) of biopsy</th>
<th>Hypertrophy of myofibers (diameter in μm)**</th>
<th>Reduction of myofibrils</th>
<th>Deformity of nuclei</th>
<th>Vacuolization</th>
<th>Disarray of myofibers</th>
<th>Degenerative substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV</td>
<td>1</td>
<td>28</td>
<td>0 (12.19 ± 2.89)</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>29</td>
<td>3 (24.54 ± 9.55)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>33</td>
<td>1 (17.68 ± 3.91)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>20</td>
<td>1 (17.43 ± 3.03)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>LV</td>
<td>1</td>
<td>28</td>
<td>0 (13.93 ± 3.03)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>29</td>
<td>0 (15.73 ± 3.07)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>33</td>
<td>4 (32.51 ± 10.36)</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**The histological findings are graded according to severity as: 0, no apparent change; 1, mild; 2, moderate; 3, marked and 4, excessively marked.

**Mn ± SD of one hundred myocytes
LV = left ventricle; RV = right ventricle**
Fig. 2. Light micrographs of endomyocardial biopsies from case 1. A. Right ventricular biopsy showed interstitial edema, deformity of nuclei, disarray of myofibers and collagen fiber proliferation. H & E stain. B. Left ventricular biopsy showed less conspicuous changes in myofibers and interstitial tissue than right ventricular biopsy. H & E stain. Bar scales: 50 μm.

Fig. 3. Light micrographs of endomyocardial biopsies from case 2. A. Right ventricular biopsy showed cellular hypertrophy, reduction in the number of myofibrils, deformity of nuclei and collagen fiber proliferation. H & E stain. B. Left ventricular biopsy showed reduction in the number of myofibrils, deformity of nuclei, vacuolization and disarray of myofibers. H & E stain. Bar scales: 50 μm.
Fig. 4. Light micrographs of endomyocardial biopsies from case 3. A. Right ventricular biopsy showed subendocardial fatty infiltration, deformity of nuclei and disarray of myofibers. Erythrocytes in interstitium probably represent bleeding artifact during biopsy. H & E stain. B. Left ventricular biopsy showed cellular hypertrophy (diameter = 32.51 ± 10.36 micrometer) with marked nuclear deformity and collagen fiber proliferation. H & E stain. Bar scales: 50 μm.

<table>
<thead>
<tr>
<th>Case</th>
<th>Observation period (months)</th>
<th>Symptoms</th>
<th>Antiarrhythmic agents</th>
<th>ECG</th>
<th>CTR (%)</th>
<th>Holter ECG (24 hrs)</th>
<th>Echocardiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>none</td>
<td>(−)</td>
<td>Normal</td>
<td>45</td>
<td>one PVC</td>
<td>Normal**</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>none</td>
<td>(−)</td>
<td>Normal</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>Thumping sensation</td>
<td>(+)*</td>
<td>RVH</td>
<td>57</td>
<td>Occasional single PVCs</td>
<td>Mild RVE</td>
</tr>
<tr>
<td>4</td>
<td>108</td>
<td>none</td>
<td>(−)</td>
<td>Normal</td>
<td>48</td>
<td>Normal</td>
<td>Normal**</td>
</tr>
</tbody>
</table>

* mexiteline, disopyramide and procainamide
** normal except for left ventricular false tendon
CTR = cardiothoracic ratio; PVC = premature ventricular contraction;
RVE = right ventricular enlargement

50% of the whole specimen; LVB (Fig. 4B) showed marked cellular hypertrophy (32.51 ± 10.36 μm in diameter) with marked nuclear deformity and moderate reduction in the number of myofibrils and collagen fiber proliferation. In case 4, RVB showed moderate deformity of nuclei, vacuolization, disarray of slightly hypertrophied myofibers and interstitial edema. There was no interstitial cellular infiltration or vascular change in any case. These findings do not correspond to any specific disease entity.

Follow-up data (Table V): These patients were followed in our outpatient department for 12 to 108 months (average: 59.5 ± 40.2 months). None of them died or developed congestive heart failure during this period. Cases 1 and 2 have been free of attacks for 12 and 34 months, respectively, without any antiarrhythmic agents, and cases 3 and 4 experienced several episodes of VT after discharge which necessitated emergency admissions to our hospital or other hospitals. Case 3 is currently receiving mexiteline, pro-
cainamide and disopyramide, and still complains of an occasional precordial thumping sensation. In case 4 all available antiarrhythmic drugs were ineffective in preventing VT attacks. However, their frequency has gradually decreased in later follow-up period.

Resting ECG remained unchanged in all patients. Echocardiograms were normal except for one with mild right ventricular enlargement (case 3), but without abnormal segmental movement of the right ventricular wall. Twenty-four-hour ambulatory ECG revealed no premature ventricular contractions (PVC) in case 4, occasional single PVCs in case 3 and only one PVC in case 2.

DISCUSSION

It has been reported that there is no identifiable cause in 10 to 12 percent of the patients with paroxysmal VT.\textsuperscript{16,17} Latent coronary artery disease or other diseases might have been included in series reported earlier, but there is a certain group of patients whose underlying heart disease cannot be identified by conventional noninvasive and invasive techniques without endomyocardial biopsy.

In the four patients described here with recurrent and sustained episodes of VT, organic heart disease could not be identified even after a thorough work-up, including coronary cine-angiography. The RV and LV biopsies of these four patients showed disarray of myofibers, interstitial fibrosis, myocardial hypertrophy of various degrees, and other degenerative changes (Table IV, Figs. 2 to 5). Although these changes are non-specific and do not indicate any specific disease, they are definitely abnormal and might be called cardiomyopathic, if cardiomyopathy is defined as heart muscle disease.

The etiology of idiopathic VT is not known, and little is known about the histopathologic changes of the myocardium in this disease. Gault et al.\textsuperscript{18} reported that postmortem examination in a patient who died suddenly with paroxysmal VT revealed no gross pathology; however, the histopathologic studies showed degenerative changes in the atrioventricular conduction system, main left bundle and myocardium. Strain et al.\textsuperscript{19} described the RV endomyocardial biopsy findings of 18 such patients. The biopsy specimens were abnormal in 16; nine had hypertrophy of myocytes, interstitial fibrosis and vascular sclerosis which they called cardio-

myopathy changes, three had subacute myocarditis, and two patients each had small artery disease and arrhythmogenic right ventricular dysplasia, respectively. A recent report by Vignola et al.\textsuperscript{20} described 12 patients with histological evidence of chronic lymphocytic myocarditis presenting as "primary ventricular tachycardia", and Surge and coworkers\textsuperscript{10} also reported that histological abnormalities were detected in 11 out of 12 patients with life-threatening ventricular arrhythmias. Our observations also confirmed various degrees of degenerative process in both RV and LV endomyocardium. As these patients had various sites of atrioventricular block identified by His bundle electrocardiography, they seem to have diffuse myocardial disease involving not only working muscle, but also the specialized conduction system.

It is not yet known whether these myocardial changes preexist and are responsible for the episodes of VT or the sequellae of hypotension and subendocardial ischemia during episodes of VT. Two of our patients (cases 1 and 4) showed inversion of T wave in leads II, III, aVF, V4, V5 and V6 after VT attacks without elevation of cardiac enzymes. To explain this post-tachycardia T wave inversion, Levine\textsuperscript{19} postulated post-tachycardia heart muscle fatigue or relative local anoxia. However, Rakov\textsuperscript{20} ruled out significant ischemic myocardial necrosis, and Rosenbaum et al.\textsuperscript{21} suggested that post-tachycardia syndrome was due to electrotonic modulation of ventricular reporalization with accumulation and memory. In our four patients there was no clear difference in myocardial biopsy between patients with and without post-tachycardia T wave inversion.

From this observation, it is not clear whether the myocardial degeneration seen in the biopsy specimens is the focus of VT and is responsible for the attacks. It is certainly possible, however, that these histological changes contribute to the mechanism of VT; the formation of reentry or enhanced triggered automaticity. Two patients showing right bundle branch block and left axis deviation during VT (cases 1 and 4) had false tendons in the left ventricle. Whereas we reported high incidence of premature ventricular contractions in apparently healthy patients with left ventricular false tendon\textsuperscript{22} the relation between VT and false tendon is not known. Another patient (case 3) might have an atypical type of arrhythmogenic RV dysplasia, but the
definite diagnosis could not be made because there was no abnormal wall motion of RV by two-dimensional echocardiography and angionigraphy. The RV endomyocardial specimen in this case showed interstitial fatty infiltration which occupied less than 50% of the area.

There is no extensive documentation of the natural history and prognosis of nine patients with idiopathic VT followed for 18 years, and Buxton et al. reported that none of 30 patients with idiopathic VT of RV origin died or experienced cardiac arrest during a mean follow-up period of 30 months. On the other hand, pulmonary edema, congestive heart failure, and sudden death have been reported by some authors.

Strain et al. and Vignola et al. did not perform the long follow-up of their patients with idiopathic VT and cardiomyopathic myocardial changes. Our patients enjoy a relatively asymptomatic life between attacks, and none have developed congestive heart failure or echocardiographic deterioration of systolic function during the follow-up period. LV hypertrophy is also absent on repeated echocardiographic examinations. Therefore, these patients should be separated from the three known categories of idiopathic cardiomyopathies: dilated, hypertrophic or restrictive, though they had cardiomyopathic changes in the myocardium.

In conclusion, our data and previous reports show that the majority of patients with idiopathic VT have abnormal biopsy findings. Although the definite relation between VT and histopathologic abnormalities is unknown, it is apparent that idiopathic VT is not a primary electrical heart disease. Histological findings of the biopsy specimens from our patients were compatible with those of dilated cardiomyopathy, but these patients did not show clinical profile of cardiomyopathy during the follow-up period. Those patients with non-specific myocardial degeneration whose only symptom is ventricular tachycardia may be regarded as a new clinical entity or as another subtype of cardiomyopathy.

REFERENCES


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