PROGNOSTIC SIGNIFICANCE OF CONDUCTION DISTURBANCE
AND REDUCTION OF LEFT PRECORDIAL VOLTAGE OF
ELECTROCARDIOGRAM IN HYPERTROPHIC CARDIOMYOPATHY

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To clarify the prognostic significance of electrocardiographic changes in hypertrophic cardiomypathy, we retrospectively evaluated serial electrocardiograms in 77 patients with hypertrophic cardiomypathy who were followed for more than 1 year. The electrocardiographic features analyzed were conduction disturbance and left precordial QRS voltage. There were 4 sudden deaths. Various conduction disturbances appeared in 32 (44%) of the remaining 73 patients. Intraventricular conduction delay was the most common (47%). The left precordial voltage decreased in 19 (26%), increased in 3, and did not change in 51. The left ventricular end-diastolic pressure at the initial investigation was significantly higher and clinical deterioration was more frequently seen in patients with a conduction disturbance or reduction of QRS voltage than in those without these electrocardiographic changes. Also, echocardiographic analysis showed that left ventricular dimensions increased significantly (from 4.4 ± 0.6 to 4.8 ± 0.7 cm in end-diastole and from 2.6 ± 0.6 to 3.1 ± 0.8 cm in end-systole; p < 0.01, respectively) and left ventricular fractional shortening was reduced (from 41 ± 8 to 36 ± 11%; p < 0.01) in the 32 patients with conduction disturbance during the follow-up period although absolute cavity size remained normal in 26 of these patients. These parameters did not change in those without conduction disturbance. Histopathological analysis of endomyocardial biopsies showed that myocardial fibrosis in the left ventricle was frequently associated with these electrocardiographic changes. However, such changes were not present in the sudden death patients. It is concluded that conduction disturbance and the reduction of QRS voltage are significant parameters which suggest a poor prognosis in patients with hypertrophic cardiomypathy, but are not predictors of sudden death.

Key words: Hypertrophic cardiomypathy
Electrocardiographic changes
Conduction disturbance
Natural history

(Received January 26, 1989; accepted March 20, 1989)
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This study was supported in part by a research grant for intractable diseases from the Ministry of Health and Welfare of the Japanese Government.
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reported to be very rare, but the development of congestive heart failure in association with thinning of the wall, dilatation of the cavity, and poor systolic function has been reported recently as one of the terminal manifestations of hypertrophic cardiomyopathy. The majority of patients who have symptoms of congestive heart failure in this disease have normal systolic function, normal cavity size and hypertrophied myocardium with or without atrial fibrillation. The pathophysiology of the former can be classified as systolic failure and that of the latter as diastolic failure.

Recently, we have observed the development of conduction disturbance and/or the reduction of left precordial QRS voltage in electrocardiograms of patients with hypertrophic cardiomyopathy during follow-up, and noticed that symptoms of clinical deterioration are frequently associated with these electrocardiographic changes. The presence of left ventricular conduction delay is the most powerful predictor of poor prognosis in patients with dilated cardiomyopathy. However, no studies have evaluated the clinical significance of conduction disturbance or of the reduction of left precordial voltage in patients with hypertrophic cardiomyopathy. The purpose of this study is to clarify the relationship between these electrocardiographic changes and symptoms of clinical deterioration in patients with hypertrophic cardiomyopathy.

METHODS

Patients

We evaluated retrospectively electrocardiographic changes in 77 patients with hypertrophic cardiomyopathy (59 men and 18 women) who were followed for more than 1 year at our institute. Their diagnosis was established after complete cardiac examination, including echocardiography and cardiac catheterization. The patients' profiles at the initial investigation are listed in Table 1. Eleven patients had a family history of hypertrophic cardiomyopathy.

Follow-up studies

Follow-up examinations included electrocardiography and echocardiography during the past 2 years (as of December, 1987) except in the patients who died. Clinical deterioration was defined as the appearance of severe heart failure (New York Heart Association functional class 3–4) or symptomatic paroxysmal or persistent atrial fibrillation.

The 12-lead electrocardiograms recorded at the initial investigation and during follow-up examinations were evaluated retrospectively in the survey of conduction disturbance and left precordial QRS voltage. The conduction disturbances were atioventricular block, bundle branch block, intraventricular conduction delay and left fascicular block, according to the criteria of the WHO/ISFC task force. The left precordial voltage was measured as the sum of the S wave in lead V₁ and the R wave in V₅ (SV₁ + RV₅). The lowest amplitude was used if there were beat to beat variations. The voltage of the initial investigation was compared with that of the last follow-up, and we defined the changes of the voltage in the following three categories: increase, an increment of more than 1 mV; decrease, a decrement of more than 1 mV; and no significant changes, a change of less than 1 mV. In a few patients, who developed complete right bundle branch block, the voltage of RV₅ was evaluated.

Echocardiographic examinations were performed repeatedly during the follow-up period. As echocardiographic data, left ventricular end-diastolic and end-systolic dimensions, end-diastolic thickness of the interventricular septum and of the left ventricular free wall were measured, and left ventricular fractional shortening (FS) was calculated according to the previous protocol and these data were compared between the initial investigation and the last follow-up.

Cardiac catheterization and endomyocardial biopsy

The cardiac catheterization procedure and hemodynamic characteristics of these patients

Japanese Circulation Journal Vol. 33, September 1989
Fig. 1. The clinical course of 77 patients with hypertrophic cardiomyopathy.

Fig. 2. The incidence of conduction disturbance during follow-up in 73 patients (4 sudden death cases excluded). Seven patients had conduction disturbances at the initial investigation: two of them developed an additional disturbance during follow-up. Of the 66 patients without a conduction disturbance at the initial investigation, 25 developed one during follow-up.
TABLE II  CONDUCTION DISTURBANCES IN PATIENTS WITH HYPTERTROPHIC CARDIOMYOPATHY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrioventricular block</td>
<td>4</td>
</tr>
<tr>
<td>Complete right bundle branch block</td>
<td>3</td>
</tr>
<tr>
<td>Left anterior fascicular block</td>
<td>3</td>
</tr>
<tr>
<td>Intraventricular conduction delay</td>
<td>15</td>
</tr>
<tr>
<td>Atrioventricular block + right bundle branch block, left fascicular block</td>
<td>5</td>
</tr>
<tr>
<td>or intraventricular conduction delay</td>
<td></td>
</tr>
<tr>
<td>Left anterior fascicular block + intraventricular conduction delay</td>
<td>2</td>
</tr>
</tbody>
</table>

have been described in detail elsewhere. The left ventricular end-diastolic pressure was evaluated as the hemodynamic parameter.

In the majority of these patients, left and right ventricular endomyocardial biopsies were performed at the end of catheterization with a Konno-Sakakibara bioprome through the brachial artery and the femoral vein, respectively. The specimens were obtained from the free wall of the left ventricle and the interventricular septum of the right ventricle, fixed, embedded and stained according to the method described in the previous reports. The degree of the proliferation of collagen fibers in the myocardium was classified by the semiquantitative scoring system into 5 ranks (grades 0–4) by one of the investigators (YN), and into two groups: no significant fibrosis (grades 0 and 1) and significant fibrosis (grades 2–4).

Statistics

Unpaired Student's t test and chi-square analysis were used.

RESULTS

Clinical course

The clinical course of 77 patients is diagrammed in Fig. 1. The follow-up period ranged from 1 to 22 years (mean 6.0); 28 patients were followed for more than 10 years. There were 4 sudden deaths; 2 patients died of congestive heart failure, 1 after 10 and 1 after 4 years; and 2 patients died of noncardiac causes. Calcium blocking agents and/or beta blocking agents were administered to 33 patients for various mild cardiac symptoms, such as

Fig. 3. The prevalence of conduction disturbance and the changes of left precordial QRS voltage in the 73 patients with hypertrophic cardiomyopathy.

Among the 73 patients with hypertrophic cardiomyopathy (4 sudden death cases excluded), various conduction disturbances developed in 32 (44%), and reduction of left QRS voltage was seen in 19 (26%). Also, reduction of left ventricular voltage occurred more frequently in the patients with conduction disturbance than in those without it.

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palpitation or fatigue. Digitalis and/or diuretics were prescribed in 20 patients for atrial fibrillation and/or heart failure. Antiarrhythmic agents were also used in some patients for atrial or ventricular arrhythmias. One patient had two documented episodes of ventricular fibrillation with successful resuscitation although he usually had only mild symptoms. One patient at the initial investigation and 3 during follow-up had pacemaker implantation because of lazy sinus or complete atrioventricular block.

**Electrocardiographic findings**

Among the 73 patients (4 sudden deaths excluded) conduction disturbance was present at the initial investigation in 7, two of whom had additional new conduction disturbances during follow-up. In 25 patients, conduction disturbances started during follow-up (Fig. 2). The conduction disturbances of these 32 patients are listed in Table II. There was no difference in mean age at the time of initial investigation between patients with and without conduction disturbance (42 ± 15 and 47 ± 13 years, respectively). However, the follow-up period was significantly longer in the patients with conduction disturbance (mean 7.5 years) than in those without it (mean 4.7 years). There was no relationship between the occurrence of these conduction disturbances and medications because they occurred before the administration of medications, such as digitalis, calcium channel blockers or beta adrenergic blocking agents.

In these 73 patients, the left precordial QRS voltage of SV₁ + RV₅ at the initial investigation was compared with that at the last follow-up examination. It decreased in 19 patients (26%), increased in 3 (4%) and did not alter significantly in 51 (70%) (Fig. 3). Follow-up periods were significantly longer in patients with reduced left precordial voltage (mean 8.5 years) than in those without it (mean 5.2 years). In the group with conduction disturbances, the left precordial voltage decreased in 15 of the 32 patients (47%), but it decreased in only 4 of the 41 patients without conduction disturbances (10%) (Fig. 3). Also, of the 19 patients with reduced voltage
Fig. 5. Representative electrocardiograms of a patient with hypertrophic cardiomyopathy who developed reduction of left precordial QRS voltage. These electrocardiograms were recorded at the initial investigation in 1977 (at age 36: a) and at the last follow-up in 1987 (b) in a patient with hypertrophic nonobstructive cardiomyopathy and a history of paroxysmal supraventricular tachycardia. Left ventricular end-diastolic pressure was 19 mmHg at the time of the initial investigation. He is in heart failure (NYHA functional class 3) and has been treated with digitalis for the past 4 years. The voltage of SV₂, RV₄₅ is markedly decreased during follow-up (6.0 to 1.7 mV) and the QRS duration is somewhat prolonged with notching.

**TABLE III** ECHOCARDIOGRAPHIC DATA OF PATIENTS WITH AND WITHOUT CONDUCTION DISTURBANCE (mean ± standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>EDD (cm)</th>
<th>ESD (cm)</th>
<th>FS (%)</th>
<th>IVS (cm)</th>
<th>FW (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduction disturbance (+)</td>
<td>(a)</td>
<td>4.4 ± 0.6</td>
<td>2.6 ± 0.6</td>
<td>41 ± 8</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*4.8 ± 0.7</td>
<td>*3.1 ± 0.8</td>
<td>*36 ± 11</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>Conduction disturbance (-)</td>
<td>(a)</td>
<td>4.4 ± 0.5</td>
<td>2.4 ± 0.5</td>
<td>42 ± 7</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.4 ± 0.5</td>
<td>2.4 ± 0.5</td>
<td>45 ± 7</td>
<td>1.8 ± 0.6</td>
</tr>
</tbody>
</table>

*a: at the initial investigation, b: at the last follow-up, EDD: left ventricular end-diastolic dimension, ESD: left ventricular end-systolic dimension, FS: left ventricular fractional shortening, FW: left ventricular free wall thickness, IVS: thickness of interventricular septum.* *p < 0.01

13 had concomitant prolongation of QRS duration due to right bundle branch block or intraventricular conduction delay. Consequently, the alterations of left precordial voltage were correlated with the development of conduction disturbances during follow-up. The two representative electrocardiograms are shown in Figs. 4 and 5.

Echocardiographic findings
Echocardiographic data are listed in Table III. In the 32 patients with conduction disturbances, left ventricular end-diastolic and end-systolic dimensions increased significantly and fractional shortening was reduced during follow-up; however, in 26 of the 32, absolute cavity size remained within normal limits (≤ 5.0 cm) at the last follow-up examination. On the other hand, these parameters did not change significantly in the patients without them. Also, wall thickness did not alter during the follow-up in either
TABLE IV  THE INCIDENCE OF CLINICAL DETERIORATION RELATED TO CHANGES OF LEFT PRECordial QRS VOLTAGE IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

<table>
<thead>
<tr>
<th>Clinical deterioration</th>
<th>Decrease</th>
<th>Increase or no change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11/19</td>
<td>9/54</td>
</tr>
<tr>
<td></td>
<td>(58%)**</td>
<td>(17%)</td>
</tr>
</tbody>
</table>

**: p < 0.005

TABLE V  THE INCIDENCE OF MYOCARDIAL FIBROSIS IN LEFT AND RIGHT VENTRICLE OBSERVED BY ENDOMICRORDIAL BIOPSY IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY WITH AND WITHOUT CONDUCTION DISTURBANCE

<table>
<thead>
<tr>
<th>Myocardial fibrosis</th>
<th>Conduction disturbance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>7/15</td>
</tr>
<tr>
<td></td>
<td>(47%)***</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>12/25</td>
</tr>
<tr>
<td></td>
<td>(48%)</td>
</tr>
</tbody>
</table>

***: p < 0.025

**Sudden death**

The four sudden death patients had no conduction disturbances or voltage reduction during the follow-up, although the left ventricular end-diastolic pressures were markedly elevated in three of them (34, 26, 18 mmHg; normal in one, 11 mmHg).

**Correlation between symptoms and electrocardiographic changes**

In the 32 patients with conduction disturbances, the development of atrial fibrillation or congestive heart failure was observed in 17 (53%), but the deterioration was less frequent in those without them (3/41: 7%) (p < 0.005) (Fig. 6). Among the 19 patients with reduction of the left precordial voltage, symptomatic deterioration developed in 11 (58%), while in the 54 patients without voltage reduction it occurred in 9 (17%) (p < 0.005) (Table IV). Thus, the appearance of conduction disturbances and the
reduction of left precordial voltage show significant positive correlations with symptomatic deterioration or progression of the disease process in patients with hypertrophic cardiomyopathy.

**Histopathological findings**

Biopsy specimens were obtained from the right ventricle of 52 patients and from the left ventricle of 39 patients. In the left ventricle, proliferation of collagen fibers could be detected in 7 of the 15 (47%) patients with conduction disturbances, but in only 3 of the 24 (13%) patients without them (Table V). Also, in the left ventricle proliferation of collagen fibers could be detected more frequently in the patients with reduced precordial voltage (4/7; 57%) than in those without it (6/32; 19%) (p < 0.05). However, in the right ventricle there was no difference in the prevalence of proliferation of collagen fibers between the patients with and without conduction disturbances, and between those with and without reduced precordial voltage. Thus, these two electrocardiographic features are positively correlated with proliferation of collagen fibers in the left ventricle, but not in the right ventricle.

In the 4 sudden death patients, biopsy specimens were obtained from two right ventricles and from two left ventricles. There was no relationship between sudden death and the degree of proliferation of collagen fibers.

**DISCUSSION**

It is well known that sudden cardiac death, presumably due to ventricular tachycardia, is by far the most common cause of death in patients with hypertrophic cardiomyopathy. Predictable parameters for the sudden death are reported to be the following: young age at the time of diagnosis, family history of sudden death, documented ventricular tachyarrhythmias and echocardiographic evidence of poorly contracting interventricular septum with decreased systolic thickening. Furthermore, it has been reported that a combination of the following indexes: young age, the presence of heart failure and syncope at the time of diagnosis, the development of severe dyspnea at the last follow-up, electrocardiographic evidence of conduction disturbance (especially bundle branch block) and left or right atrial enlargement, is predictive for either sudden death or death due to heart failure.

**Natural course**

Of the 77 patients with hypertrophic cardiomyopathy followed at our institution over the past 20 years, 8 have died. The cause of death was sudden death in 4, heart failure in two and noncardiac causes in two. Among the remaining 69 patients who are currently alive, physical activity is severely limited in 20 because of congestive heart failure (New York Heart Association functional class 3–4) or atrial fibrillation. The development of cardiac symptoms in patients with hypertrophic cardiomyopathy is related to two major physiological problems, systolic and diastolic dysfunction. The basic physiology of hypertrophic cardiomyopathy suggests that the progression of this disease results in congestive heart failure due to increased stiffness of the left ventricle, i.e., diastolic failure, and may be related to advanced myocardial fibrosis. Recently, it has been reported that a hypertrophied and well contracting left ventricle may become dilated and poorly functioning as dilated cardiomyopathy in some patients with hypertrophic cardiomyopathy. This alteration suggests that the ventricular myocardium has been replaced by advanced fibrosis.

**Electrocardiographic changes and clinical course**

Of the 73 patients with hypertrophic cardiomyopathy, 32 (44%) developed various conduction disturbances, and 19 (26%) had reduced left precordial QRS voltage, during follow-up. The left ventricular end-diastolic pressure at the initial investigation was significantly higher in the patients with conduction disturbances than in those without them, and in the patients with reduced left precordial voltage than in those without it. Conduction disturbances were frequently seen in the patients with reduction of left precordial voltage, and their prognosis tended to be worse than that of those without them. In the patients with conduction disturbances or reduction of left precordial voltage, myocardial fibrosis was frequently detected in the left ventricle, and the left ventricle was more dilated and less efficient. However, the sudden death patients did not develop these electrocardiographic changes.

**Electrocardiographic changes and histological or hemodynamic evaluation**

Electrocardiographic evaluations of hypertrophic cardiomyopathy have shown a high incidence of various atroventricular or His-Purkinje conduction disturbances.
McKenna noted that an increase of voltage is associated with a poor prognosis and a decrease of voltage is rare, but QRS voltage variability has been reported during follow-up. The QRS voltage becomes reduced with the regression of ventricular hypertrophy, as has been shown after therapy for hypertension or surgery for valvular heart disease. However, in most of the patients with reduction of left ventricular voltage, ventricular wall thickness remains hypertrophied. In a few patients with cavity dilatation and poor function, the ventricular wall becomes thin, and the voltage is markedly reduced. Thus, voltage reduction or conduction disturbances may develop because of myocardial fibrosis, especially interstitial fibrosis. In some patients with the physiology of dilated cardiomyopathy, these changes may indicate progression from interstitial fibrosis to replacement fibrosis. Also, it may be that these electrocardiographic changes are strongly related not only to diastolic but also to systolic dysfunction.

The diagnosis of ventricular hypertrophy in the presence of intraventricular conduction disturbance is difficult, and the development of conduction disturbance affects left precordial voltage. The significant correlation between conduction disturbances and reduced left precordial voltage may be due to the above reasons.

In previous investigations of hypertrophic cardiomyopathy, it has been concluded that elevated left ventricular end-diastolic pressure is clearly not related to sudden death or severe functional limitations. In this study, left ventricular end-diastolic pressure was significantly higher in the patients with than in those without conduction disturbances and in the patients with than in those without reduced precordial voltage, although there was considerable overlap between them. From the hemodynamic aspect, left ventricular end-diastolic pressure may be a significant parameter in predicting the clinical course to some extent, but not in predicting sudden death. The reason that these electrocardiographic changes do not appear before sudden death may be that they are related not only to the stage of the disease at the initial examination, but also to the changes of this disease with time.

As for the clinical implications, it may be that electrocardiographic changes in patients with hypertrophic cardiomyopathy, such as conduction disturbance and/or a reduction of left ventricular voltage, are significant predictors of a poor clinical course. However, these electrocardiographic changes are not predictors of sudden death in this disease.

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