Heart Rate Variability and Ambulatory Blood Pressure Monitoring in Young Patients With Hypertrophic Cardiomyopathy

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Background Sudden cardiac death commonly occurs in young patients with hypertrophic cardiomyopathy (HCM); however, their heart rate variability (HRV) and blood pressure (BP) response to daily activities is not well known.

Methods and Results HRV and ambulatory BP monitoring were performed in 20 patients (age range: 7–21 years) and 57 age-matched healthy volunteers (age range: 10–22 years). Time domain variables and spectral data were obtained at hourly intervals throughout the day. To determine the BP response to daily life activities, the ratios of the mean BP and pulse pressure in the morning, afternoon, and night to those during sleeping were calculated. The association between the BP level and HRV was also evaluated. The HCM patients showed significantly increased sympathovagal imbalance and decreased parasympathetic activity in the early morning, around noon, and in the early evening. This abnormality was independent of cardiac symptoms. Symptomatic patients showed a significantly lower systolic BP response in the morning, and a higher incidence of dissociation between sympathetic activity and BP response than asymptomatic patients.

Conclusion An abnormal BP response in the presence of impaired HRV appears to be predictive for cardiac events in young patients with HCM. (Circ J 2004; 68: 757–762)

Key Words: Ambulatory blood pressure monitoring; Autonomic activity; Children; Heart rate variability; Hypertrophic cardiomyopathy; Prognosis

The major causes of death of patients with hypertrophic cardiomyopathy (HCM) include sudden death, progressive heart failure, and HCM-related stroke associated with atrial fibrillation. Of these, sudden cardiac death is the most common in young patients1–4. Sudden death in HCM is associated with many factors: a family history of sudden death, the presence of an obstructive region, abnormal blood pressure (BP) response during exercise, increased left ventricular wall thickness, and the presence of an increased QT interval, ventricular arrhythmia, or myocardial bridging of the left anterior descending artery3,4

A study on sudden death in patients with HCM and a mean age of 28 years demonstrated a circadian pattern over a 24-h period, with a prominent midmorning peak and a less striking early-evening peak5. The peak frequency of sudden death after awakening in the morning is similar to adult subjects with or without coronary artery disease6–8.

The data regarding circadian variability suggest that the autonomic nervous system plays an important role in the genesis of sudden cardiac death, not only in coronary artery disease6,9,10 but also in HCM11–16. Many indices using 24-h Holter monitoring have been evaluated in HCM and those reports have described altered sympathetic and/or vagal activity;2,5,10,14,16,19 the results, however, are controversial, and the data for children are scant, despite the fact that sudden death primarily occurs in children and adolescents.

An abnormal BP response during exercise has been reported as one of the predictive factors of sudden cardiac death in HCM20–22, especially in young patients23, but sudden death also occurs during sedentary periods or mild activity2. Recently, ambulatory BP monitoring has been used to manage childhood hypertension24,25, with results showing that BPs in childhood are quite different for the various time periods (resting, at school, at home, and sleeping)26. These results suggest that the BP response to daily life activities should be investigated in children with HCM.

Therefore, the purpose of this study was to determine the presence or absence of altered autonomic activity and abnormal BP response to daily life activities, and to predict sudden cardiac death in young patients with HCM.

Methods

Subjects

All patients with a diagnosis of HCM made before 19 years of age, and who were being treated at the Depart-
Table 1 Characteristics of the Subjects With Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age at Dx (years)</th>
<th>Sex</th>
<th>Symptom &amp; outcome</th>
<th>Arrhythmia</th>
<th>IVSTh (mm)</th>
<th>LVPWTh (mm)</th>
<th>Pressure gradient (mmHg)</th>
<th>Treatment (mg/kg per day)</th>
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Treatment, the β-adrenoceptor blocking dose in propranolol-equivalents.
IVSTh, thickness of interventricular septum; LVPWTh, thickness of left ventricular wall; Dx, diagnosis; Noonan, Noonan syndrome; MVR, mitral valve replacement; AF, atrial flutter; VT, ventricular tachycardia; LV, left ventricle; RV, right ventricle.

Heart Rate Variability (HRV)

All subjects underwent 2-channel 24-h ambulatory electrocardiographic (ECG) monitoring and the HRV was analyzed on a Holter analysis system (SCM-2000, Fukuda Denshi). After classification of the QRS configuration, only normal-to-normal intervals were included. The power spectral density was computed as low-frequency (LF: 0.04-0.15 Hz) and high-frequency (HF: 0.15-0.40 Hz) components in 10-min segments with a 512-point fast Fourier transform algorithm and a frequency resolution of 0.008 Hz. The logarithmic values of these component values were used to normalize the data. The log (HF) component was used as an index of parasympathetic activity. The ratio between the log (LF) and log (HF) components [log (LF)/log (HF) ratio] was calculated as an index of sympathovagal balance of the heart. Time domain variables considered in this study were standard deviation of R-R intervals (SDNN) and the percentage of cycle differencing from the preceding one by more than 50 ms (pNN50).

Ambulatory Blood Pressure Monitoring

All subjects were monitored for BP at the same time as HRV using the same system (SCM-2000, Fukuda Denshi). The recorder measured BP every 15 min during the day, and once every h between 23.00 and 06.00 h. The children were asked to keep their arms still during the BP measurements. All readings were accepted, unless the systolic BP was >250 or <70 mmHg, and the diastolic BP was >130 or <30 mmHg. The day was divided into 4 periods: sleeping, morning (from waking to 12.00 h), afternoon (12.00-18.00 h), and night (18.00 h to bedtime). Bedtime was defined by a sharp drop in heart rate (HR) at night, and the time of waking was defined as a sudden increase in HR in the morning, based on the 24-h ambulatory ECG. The mean values of the systolic BP were calculated for each period. To determine the BP response to daily life activities, the ratios of the mean systolic BP, diastolic BP, and pulse pressure in the morning, afternoon, and night to those during sleeping were calculated. The mean value of the HRs at the time of the BP measurements were also calculated for each period to determine the presence or absence of a compensatory increase in HR to daily life activities.

Echocardiographic Parameters

Left ventricular posterior wall thickness, interventricular septal wall thickness, the sum of the left ventricular posterior wall and interventricular septal wall thicknesses, and...
the pressure gradients across the left and right outflow tract of the ventricles were obtained at each hospital or clinic.

**Statistical Analysis**

Differences in mean values between the groups were analyzed using the Mann-Whitney U-test. The HRV is known to differ according to age, and BP is influenced by age, sex, and the index of obesity. Therefore, to determine the impact of the presence of disease (HCM) on the HRV or BP in children, stepwise regression analyses were carried out. In these, the HRV or the ratio of the mean BP during the day period to the mean BP during sleeping was used as a dependent variable, and the presence or absence of the disease, age, sex, the ß-blocker in propranolol-equivalents/kg of body weight, and the index of obesity (percent relative body weight) were used as independent variables.

Because HRV and BP may be influenced by the baroreceptor reflex, the correlation between spectral data and systolic BP was analyzed after both parameters were averaged for each h throughout the day in each subject. A p-value of <0.05 was considered statistically significant.

**Results**

**Characteristics of Subjects**

Characteristics of the subjects are shown in Table 1. Case 6 died suddenly 11 months after the HRV and BP monitoring, while climbing the stairs at school. Case 7, a younger sister of Case 6, experienced a rescued cardiac event 1 month before these characteristics were recorded, and a cardioverter defibrillator was implanted after her brother’s death. Case 11 experienced a rescued cardiac event 26 months after the characteristics were recorded. Cases 4 and 9 underwent surgical treatment at ages 7 and 5 years, respectively, because of severe left ventricular outflow obstruction and inability to participate in physical activities. Case 5 experienced syncope. These 6 cases were classified as symptomatic HCM.

**Spectral Data Analysis**

HRV in terms of the log (HF) and the \( \frac{\log (LF)}{\log (HF)} \) ratio of normal children and those with HCM is shown in Figs 1 and 2. In determining the exact impact of the presence of the disease on the log (HF), stepwise regression analysis revealed that in the patients, as compared with the normal children, the presence of the disease had a significant impact on decreases in the log (HF) all day long, except at 07.00, 08.00, 09.00, 14.00, and 15.00 h (Fig 1). The log (HF) values did not differ between the symptomatic and asymptomatic patients, or between the patients who were receiving a ß-blocker and the patients who were not (data not shown). The daily dose of ß-blocker did not correlate with the log (HF) values.

The log (HF) at 06.00 h, at which time the presence of the disease showed the highest impact in the stepwise test, was found to have a weak negative correlation with the...
sum of the left ventricular posterior wall and interventricu-
lar septal thicknesses (r=0.385, p=0.0850).

Patients with HCM showed a higher \( \frac{\log (LF)}{\log (HF)} \) ratio than the normal controls throughout the day. Stepwise regression analysis revealed that the presence of the disease had a significant impact on increases in the \( \frac{\log (LF)}{\log (HF)} \) ratios from 22.00 to 07.00, 11.00, 13.00 h, and from 16.00 to 20.00 h (Fig 2). The \( \frac{\log (LF)}{\log (HF)} \) ratio did not differ between the symptomatic and asymptomatic patients. In the HCM patients, the presence of a \( \beta \)-blocker had a significant impact on decreases in the \( \frac{\log (LF)}{\log (HF)} \) ratios only at 08.00 and 12.00 h (data not shown). The daily dose of \( \beta \)-blocker showed a significantly negative correlation with the \( \frac{\log (LF)}{\log (HF)} \) ratios at 08.00 h in patients with HCM (p=0.0190).

Of the echocardiographic parameters studied in the HCM patients, the \( \frac{\log (LF)}{\log (HF)} \) ratio at 06.00 h was also found to have a weak positive correlation with the sum of the left ventricular posterior wall and interventricular septal thicknesses (r=0.396, p=0.0753).

**Time Domain Variables**

Stepwise analyses revealed that the presence of the disease had a significant impact on the decrease in the SDNN only at 06.00 h, and a significant impact on the decrease in the pNN50 from 23.00 to 06.00 h, at 10.00 h, and 11.00 h. The significance between the HCM patients and normal controls was greater in the spectral data than in the time domain variables.

**Blood Pressure**

Asymptomatic HCM patients showed similar systolic BP ratios to the normal volunteers (Fig 3); however, symptomatic patients showed significantly lower BP ratios. After determining the BP ratios, stepwise regression analysis, using the various parameters described in earlier as independent variables, revealed that the presence of symptoms had a significant impact on the BP ratio in the morning (p<0.05), and that \( \beta \)-blocker had a significant impact on the ratio in the afternoon (p<0.001) (Fig 3). The same method was performed using the diastolic BP ratio and the pulse pressure ratio, but there were no differences in the ratios between symptomatic and asymptomatic patients (data not shown). The ratios of the mean HR to that during sleeping were not significantly different between the symptomatic and asymptomatic patients at any time.

The mean BP in the afternoon to that during sleeping appeared to have a negative correlation with the left ventricular pressure gradient (–0.447, p=0.0471).

**Association Between BP and Spectral Data Analysis**

Among the spectral data, the LF/HF ratio showed a significant positive correlation with the level of systolic BP in 34 (60%) of the 57 control subjects, whereas a significant correlation was present only in 6 of the 20 (30%) patients with HCM (p=0.0363) (Fig 4). Of the 6 symptomatic patients, 5 did not have a correlation between the LF/HF ratio and systolic BP, compared with 9 of the 14 asymptomatic patients who did not show a correlation,
suggesting that an abnormal systolic BP response to sympathetic activities is present in symptomatic patients, although the values were not significant (symptomatic vs control subjects, p=0.0811).

Discussion

The present study showed decreased log (HF) values and increased \( \frac{\log (HF)}{\log (LF)} \) ratios in young HCM patients compared with normal controls. Only patients with cardiac symptoms showed an abnormal systolic BP response compared with asymptomatic patients.

The present study showed that decreased parasympathetic activity and alteration of the autonomic balance toward sympathetic predominance were present in pediatric HCM with or without symptoms, and Ajiki et al\(^{31} \) and Oben et al\(^{32} \) reported the same result in adult HCM. The mechanism of these phenomena may be alteration of the baroreflex sensitivity of both the parasympathetic and sympathetic nervous systems.\(^{33} \) Sudden cardiac death in HCM patients occurs in the first peak at midmorning between 07.00 and 13.00 h\(^{5} \) and the second peak occurs in the early evening, between 20.00 and 22.00 h.\(^{5} \) Impaired autonomic activity during sleep may also be important, because some patients have been found dead in bed early in the morning.\(^{5} \) Their data suggest that suppression of sympathetic activity is associated with the prevention of sudden cardiac death in HCM children. In the present study, \( \beta \)-blocker was used. Exercise-induced hypotension is a well-recognized feature of HCM\(^{20–22} \). A prospective study has revealed that an abnormal BP response to treadmill-exercise testing is associated with an increased risk of sudden cardiac death in HCM, especially in young patients;\(^{23} \) however, because treadmill-exercise testing has a risk of cardiac event in patients with HCM, we examined the BP response to daily life activities among HCM patients with and without symptoms. In the present study, the systolic BP in daily life was significantly lower in HCM, especially in the HCM patients with symptoms, than in the control group. The data suggested that the HCM patients with symptoms showed an abnormal BP response not only during stress exercise but also during daily life. The ratio of the mean HR in the morning to that during sleeping did not differ between asymptomatic and symptomatic patients, suggesting that a compensatory increase in HR was present in both groups. The reason for the lower BP response may be linked to a decrease in stroke volume and/or inappropriate peripheral vasodilatation.\(^{35} \)

In recent study using cardiac \( ^{125} \)I-metiodobenzylguanidine (MIBG) scintigraphy, the reduction of catecholamine uptake correlated with disease progression and malignant ventricular tachycardia\(^{40,41} \). Schafers et al reported the presence of myocardial \( \beta \)-adrenoreceptor downregulation in patients with HCM, which was associated with decreased catecholamine reuptake and increased local catecholamine.\(^{42} \) The presence of a dissociation between the LF/HF ratio and the levels of systolic BP in 5 of 6 symptomatic patients suggests the presence of autonomic dysfunction in symptomatic patients with HCM.

Study Limitations

Only a small number of children with HCM were studied, and we did not include data about diastolic function, MIBG scintigraphy or genetic diagnosis. Further study is thus needed, because diastolic dysfunction and abnormal MIBG imaging are features of patients with HCM, and the age of appearance and severity of cardiac symptoms are genetically determined.

Conclusion

Impaired autonomic activity in the early morning, around noon, and in the early evening is a feature of young HCM patients. An abnormal BP response in the presence of impaired autonomic activity appears to be a predictive factor for cardiac events in young patients with HCM. Whether a high dose of \( \beta \)-blocker improves these abnormalities is an issue that requires further investigation.

References


