SCIENTIFIC LETTER

Heart rate variability in children with hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) carries an increased risk of sudden death, especially in children and young adults. We investigated heart rate variability (HRV) in children with HCM, in order to evaluate its prognostic value.

METHODS

Seventeen patients (9 males and 8 females) with non-obstructive HCM were prospectively enrolled in the study. The diagnosis of HCM had been made between the ages of 1 month and 13 years (mean (SD) 71 (54) months). At the time of the study their ages ranged from 16 months to 16.5 years (mean 123 (70) months). HCM was defined by the presence of a hypertrophied, non-dilated left ventricle, in the absence of underlying cardiac, systemic disease or syndromic conditions. Four patients had a family history of HCM and two had a family history of premature (less than 50 years) sudden cardiac death of a first degree relative. At the time of the study, no patients were receiving treatment.

Seven patients complained of moderate exertional dyspnoea; no patient had a history of chest pain or syncope. Standard 12 lead ECG showed that seven patients had abnormal repolarisation. On 24 hour monitoring, all patients were in stable sinus rhythm, and no arrhythmia was recorded. Ten patients underwent exercise testing and none had hypotension, arrhythmias or ischaemia during exercise. Five patients underwent catheterisation and none of them had myocardial bridge. Of the 17 patients studied, 5 have since died suddenly, 80 (25) months after the HRV investigation; their age at death ranged from 102 months to 165 months (mean 116 (50) months).

Eighteen healthy children (9 males, mean age 132 (30) months) referred to our institution for evaluation of a history of palpitations were studied as control group. There were no differences in age, sex distribution, and mean heart rate between patients and controls.

All subjects underwent 24 hour Holter monitoring and analysis of HRV.

Time domain analysis included the following indices: mean duration of RR intervals (RR, ms); standard deviation of all RR intervals (SD, ms); square root of the mean squared differences of successive RR intervals (r-MSSD, ms); percentage of differences between adjacent RR intervals > 50 ms (pNN50, %).

Frequency domain analysis allowed the identification of two major peaks: a low frequency component (LF, 0.04–0.15 Hz) and a high frequency peak centred around the respiratory frequency (HF, 0.15–0.4 Hz). The total power spectrum (0.01–0.4 Hz) and LF/HF ratio were computed.

Differences between groups were tested as appropriate. The effect on prognosis of age, sex, family history, New York Heart Association (NYHA) functional class, echocardiographic parameters, abnormalities of repolarisation on ECG, and HRV indices, were tested by multivariate logistic regression analysis. The Kaplan-Meier method was used to examine differences in survival rate according to prognostic factors.

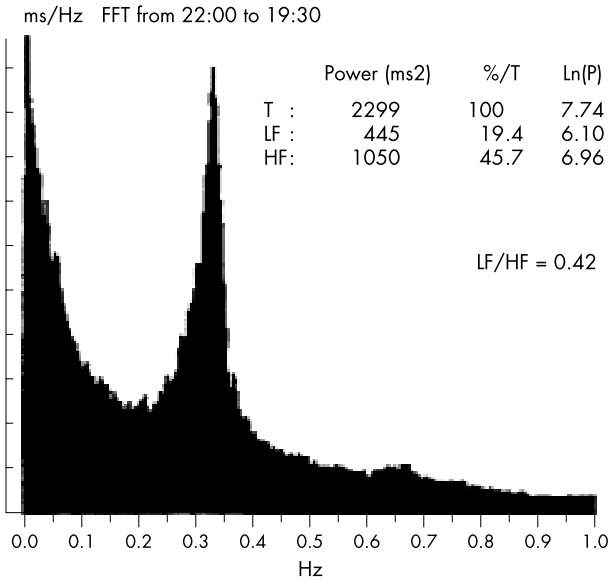

Figure 1 Frequency domain analysis in a patient who died suddenly.

Comparisons between groups were based on the log rank test. All tests were two sided. A probability value of $p < 0.05$ was considered significant.

RESULTS

The results are presented in table 1. There were no differences in HRV indices according to family history, ECG abnormalities, and NYHA class.

In the period following HRV analyses, 5 of the 17 patients with HCM died suddenly. There were no differences between patients who died and survivors, according to age at the time of diagnosis and the study, family history, sex distribution, NYHA class, mean heart rate, ECG abnormalities or echocardiographic indices. Patients who died suddenly were found to have a lower LF/HF ratio than survivors (0.9 (0.2) *v* 2.5 (1.3), $p = 0.03$). Compared to patients with an LF/HF ratio more than 1.2, those with an LF/HF ratio less than 1.2 had a higher incidence of sudden death (80% *v* 10 %, $p = 0.02$)(figs 1 and 2). The sensitivity of this threshold was 80% and its specificity 90%. The positive predictive value was 80%, and the negative predictive value 90%. In the Kaplan-Meier survival curve patients with an LF/HF ratio less than 1.2 had a poorer prognosis (1 year 83%; 5 years 42%; 10 years 42%; log rank test

Abbreviations: LF/HF, low frequency/high frequency; HCM, hypertrophic cardiomyopathy; HRV, heart rate variability; NYHA, New York Heart Association

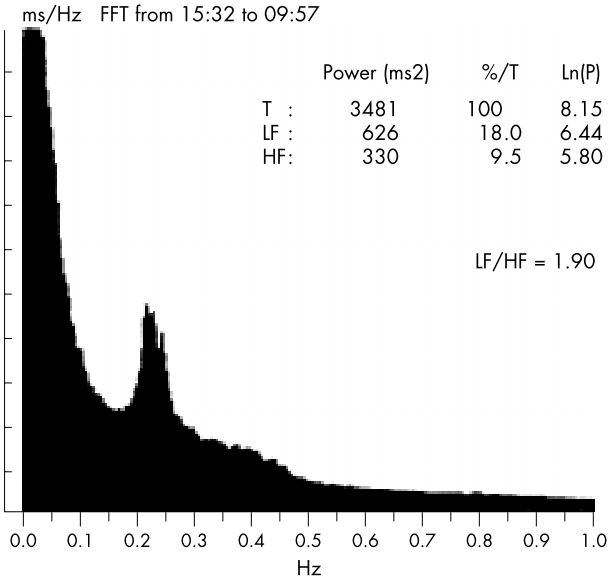

Figure 2 Frequency domain analysis in a survivor.

Table 1 Heart rate variability indices

	HCM patients	Healthy controls	p Value
SD (ms)	130 (40)	170 (43)	0.03
PNN50 (%)	21 (13)	32 (12)	0.05
LF (ms^2)	1027 (900)	1862 (1400)	0.03

HCM, hypertrophic cardiomyopathy; LF, low frequency component; PNN50, percentage of differences between adjacent RR intervals >50 ms; SD, standard deviation of all RR intervals.

p = 0.03). This effect of the LF/HF ratio on prognosis was independent of age, sex, NYHA class, family history, and echocardiographic indices.

DISCUSSION

Main markers of increased risk of sudden death in patients with HCM are a positive family history of sudden death and previous syncope.[1 2] Arrhythmias and haemodynamic factors such as an abnormal blood response to exercise, and myocardial bridging have been suggested as risk factors. However, accurate identification of high risk children is difficult, and sudden cardiac death often occurs in children with no symptoms or clinical risk factors, as was the case in our population.

Previous studies in adult populations with various cardiac diseases have shown that HRV, which gives information about cardiac autonomic nervous inputs, could predict arrhythmic events and sudden death.[3] However, analysis of HRV in adults with HCM did not add to the predictive accuracy of conventional risk stratification.[3]

In our paediatric population, we found an important correlation between clinical evolution and alterations in HRV. In fact, all our patients who died suddenly had a low LF/HF ratio, with a cut-off value of 1.2. This finding is probably related to the fact that mechanisms of sudden death are different between children and adults.

A recent study by Yetman and colleagues[4] showed that myocardial ischaemia and arrhythmias are probably responsible for sudden death in these children. In adults with non-obstructive HCM, exercise induced abnormal blood pressure response, positive family history, and a history of syncope are strong predictors of sudden death. These risk factors suggest that a haemodynamic mechanism could be related to sudden death in adults. In patients surviving a myocardial infarction, reduced HRV is a strong independent risk factor of sudden death related to arrhythmic events. Hypothesising that sudden death in children with HCM could be related to arrhythmic events, it is probable that HRV analysis could be predictive in children despite not being so in adults. Finally, Shusterman and colleagues[5] have pointed out that changes in the dynamics of RR intervals, rather than the absolute values of the indices, facilitate arrhythmogenesis. For this reason, we think that the LF/HF ratio—an index of sympathovagal balance—rather than the absolute value of single indices, is a more powerful predictor.

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