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Parasympathetic dysfunction in hypertrophic cardiomyopathy assessed by heart rate variability: comparison between short-term and 24-h measurements

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Summary

In this study, we evaluate cardiac autonomic function in hypertrophic cardiomyopathy (HCM) by assessing heart rate variability (HRV), comparing a short-term laboratory method with an ambulatory (24-h) method, in patients with and without beta-blockade. Reduced HRV is a risk factor for adverse events in some cardiac diseases, but is not a proven risk indicator in HCM. Analysis of HRV has been based on either short- or long-term electrocardiographic recordings and previous studies in HCM have shown conflicting results. There is no consensus on which method to prefer, and we evaluate, for the first time, both short- and long-term analyses in patients with HCM. Long- and short-term HRV analyses were performed in 43 patients with HCM. They were divided in two groups, 22 patients on beta-blockade and 21 non-treated patients. As controls, 121 healthy subjects were used. Young patients without beta-blockade showed a reduction in HRV parameters reflecting parasympathetic function, both in the short- and long-term registrations, which was attenuated by beta-blockade. Parasympathetic autonomic regulation was found to be impaired in young patients with HCM. This may be of clinical relevance as abnormal autonomic function might be a substrate for malignant dysrhythmias. The impairment was attenuated by beta-blockade, which might indicate a clinically useful effect. We also show that short- and long-term methods yield similar results, suggesting that a short-term registration might be sufficient to assess HRV in patients with HCM.

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Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by left and/or right ventricular hypertrophy, with predominant involvement of the interventricular septum, in the absence of other causes of hypertrophy, such as hypertension or valvular heart disease (Towbin & Roberts, 1994). Typical morphological changes include myocyte hypertrophy and sarcomere disarray surrounding areas of increased connective tissue. The prevalence in the general population is about 0·2% (Maron *et al.*, 1995). The clinical manifestations of HCM are diverse, ranging from asymptomatic cases to severe heart failure and sudden cardiac death (Towbin & Roberts, 1994; Maron, 2002). Symptomatic patients may exhibit dyspnoea, chest pain, palpitations and sometimes syncope. Atrial fibrillation and non-sustained ventricular tachycardia (NSVT) are relatively common dysrhythmias. Recognized risk factors for sudden death are family history of sudden death, recurrent syncope, NSVT, abnormal blood pressure response during exercise and severe left ventricular hypertrophy (LVH, wall thickness over 30 mm) (Elliott & McKenna, 2001). The disease is an important cause of sudden cardiac death in children and young adults, often due to ventricular dysrhythmia.

Spectral analysis of heart rate variability (HRV) is now a commonly used method for evaluation of the autonomic modulation of the heart rate. Analysis of HRV is either based on ambulatory long-term recordings (up to 24 h) or short-term recordings (30–60 min) performed in laboratories and then often combined with physiological or pharmacological tests (Malik *et al.*, 1996). Both methods have empirically been shown to give an estimate of the overall function of the cardiac autonomic nervous system (ANS) and also information on the function of the sympathetic and parasympathetic components

respectively. Abnormal autonomic modulation, assessed as an alteration in HRV, is present in various heart diseases and may be associated with increased mortality rates. Thus, reduced HRV is found in patients with heart failure and dilated cardiomyopathy (Guzzetti *et al.*, 1995; Fauchier *et al.*, 1997; van de Borne *et al.*, 1997). After myocardial infarction, decreased HRV is a risk factor for cardiac dysrhythmia and death (Fei *et al.*, 1996; Malik *et al.*, 1996) (Kleiger *et al.*, 1987).

Assessment of HRV has previously been used to evaluate the autonomic function in patients with HCM. However, different studies have shown conflicting results, with evidence of dysfunction in both sympathetic and parasympathetic activities (Ajiki *et al.*, 1993; Counihan *et al.*, 1993; Fei *et al.*, 1995; Tanabe *et al.*, 1995; Bonaduce *et al.*, 1997; Limbruno *et al.*, 1998; Doven *et al.*, 2001). In the present study, autonomic cardiac modulation in patients with HCM was assessed by analyses from both a 24-h ambulatory ECG and a short-term ECG registration with provocation of the autonomic reflexes.

The aim of the present investigation was to assess the autonomic modulation of heart rate in a cross-sectional study of well-defined HCM patients, compared with controls. The congruence of short- and long-term HRV methods was evaluated in patients with and without beta-blockade.

Methods

Study group

The region of northern Sweden has a population of 883 000 inhabitants. Specialized cardiac care is provided by the Heart Center at Umeå University hospital. The Hospital Discharge Register of the National Board of Health and Welfare in Stockholm was used to identify patients who had been hospitalized with HCM. Moreover, the physicians in charge of cardiology at the 12 other hospitals in the region were contacted to obtain information about known patients with HCM. The diagnosis was based on the presence of LVH, ≥15 mm on echocardiographic examination (Richardson *et al.*, 1996). Exclusion criteria were arterial hypertension, defined as blood pressure >160/90 mmHg or ongoing antihypertensive treatment, significant valvular disease or known systemic disease capable of producing cardiac hypertrophy. A total of 53 patients with HCM were initially available for the study. Both sporadic and hereditary cases were included. Ten patients (nine patients >60 years old) were excluded because of dysrhythmias that made HRV interpretation impossible (six patients with supraventricular/ventricular dysrhythmia, three patients with atrial fibrillation, one with a pacemaker). The clinical characteristics of the remaining 43 patients are described in Table 1. They were divided into two groups, 22 patients treated with beta-blockade and 21 patients who were not treated with any drug that might affect the cardiovascular reflexes for at least 6 months prior to the investigation.

Table 1 Clinical characteristics of the patients.

Patients	Non-treated (n = 21)	With beta-blockade (n = 22)	P-value
Age (years)	48·7 (14·1)	56·6 (16·7)	0·11
Gender (M/F)	13/8	13/9	0·85
Blood pressure (mmHg), supine	132/82	130/79	0·42
Dyspnoea (%)	33	45	0·42
Chest pain (%)	19	14	0·63
LA (mm)	39·5 (4·8)	42·5 (6·0)	0·09
IVSD (mm)	17·8 (2·7)	19·3 (4·4)	0·19
LVPWD (mm)	11·1 (2·6)	13·5 (3·0)	0·01
LVEDD (mm)	44·7 (5·6)	45·4 (6·3)	0·68
LVM (g)	255 (49)	323 (91)	0·004
LVOT-obstruction (%)	19	23	0·77
LVH on ECG (%)	38	68	0·048

IVSD, interventricular septum thickness in end-diastole; LVPWD, left ventricular posterior wall thickness in end-diastole; LVEDD, left ventricular end-diastolic diameter; LVM, left ventricular mass (Devereux *et al.*, 1986); LA, left atrium; LVH, left ventricular hypertrophy as defined by Romhilt-Estes score >4; LVOT, left ventricular outflow track; LVOT-obstruction, >30 mmHg at rest or >50 mmHg under stress. Continuous data are given as mean (SD).

The patients underwent physical examination, echocardiography (M-mode, two-dimensional and Doppler), 12-lead ECG, short-term HRV recording and ambulatory 24-h HRV recording. Echocardiographic evaluation was performed with an Acuson xp/10 or Acuson Sequoia ultrasound system (Acuson, Mountain View, CA, USA). All echocardiographic examinations were made in accordance with the standards of the American Society of Echocardiography (Sahn *et al.*, 1978). Specifically, the myocardial wall thickness was measured by M-mode echocardiography, using the leading edge method (Sahn *et al.*, 1978). The present study is a part of an extensive investigation of patients with HCM in northern Sweden, including systematic genotyping and subsequent genotype–phenotype correlation studies.

Controls

The 121 control subjects (64 men and 57 women) were derived from a large local study focused on echocardiography in healthy individuals (aged 20–90 years). The subjects were randomly selected from the population register and examined with echocardiography, ECG, short-term and ambulatory 24-h HRV recording, dynamic spirometry and clinical investigation. They were not taking any medication known to interfere with cardiac function. Exclusion criteria were arterial hypertension (>160/90 mmHg), LVH on echocardiography, pathological spirometry or ECG (conduction defects or absence of sinus rhythm), pulmonary hypertension >35 mmHg and significant valvular heart disease. Informed consent was obtained from both patients and controls and the protocol was approved by the ethics committee of Umeå University.

Short-term HRV recording

Short-term recording of HRV was performed in the following manner: after 10 min supine rest, the blood pressure was measured and a continuous recording of ECG and respiration (using a thoracic belt) was started. Free spontaneous breathing was continued for 6 min, the subjects were then instructed to perform controlled breathing at a rate of 12 breaths per minute during 1 min. After passive tilting to 70 degrees head-up position, the recording was continued during 4 min, after which the blood pressure was measured again.

Spectral analysis was performed on segments without artefacts and arrhythmic beats. Recordings in the supine and upright positions were analysed as 2-min data, and as 1-min data in the sequence with controlled breathing. The R-R interval data was transformed to an evenly sampled (2 Hz) time series by cubic spline interpolation, and both the mean and linear trends were removed. The power spectral density (PSD) was estimated by autoregressive modelling (Malik *et al.*, 1996), consequently using 30 parameters. The recording and analysis software was developed at our laboratory.

The mean heart rate, the total spectral power (0·003–0·45 Hz) and the power of three different spectral components were calculated. The very low-frequency (VLF) component (0·003–0·04 Hz) is attributed to several physiological variables, such as thermoregulatory fluctuations in vasomotor tone and fluctuations in the renin-angiotensin system. The spectral power of the low-frequency (LF) component (0·04–0·15 Hz) is considered to be related to baroreceptor-mediated blood pressure control, reflecting both sympathetic and parasympathetic activity and its magnitude after postural change has been shown to provide a useful marker of sympathetic activity (Pumprla *et al.*, 2002). The power of the high-frequency (HF) component (0·15–0·45 Hz) is at normal breathing related to the respiratory rate and used as an estimate of parasympathetic activity (Malik *et al.*, 1996). The LF/HF ratio was calculated as an indicator of sympathovagal balance. The VLF component was considered to be of relevance only in the long-term study.

Ambulatory 24-h HRV recording

Twenty-four-hour recording of HRV was performed using continuous ECG monitoring with a two-channel tape recorder (Tracker 2, Reynolds Medical Ltd, Hertford, UK). The ECG data was digitized with a sampling rate of 128 Hz and transferred for computer analysis. A commercially available software (Danica Holter Replay Unit, Danica Biomedical, Borlange, Sweden) was used to detect pathological events, which were then manually edited and confirmed by a technician.

The following time-domain variables were calculated. The average R-R interval value was calculated from accepted beats (mean RR). The overall HRV was determined by the standard deviation of all the NN (normal-to-normal) R-R intervals (SDNN), and the baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of NN intervals (TINN). The long-term HRV was quantified by the standard deviation of all 5-min NN interval mean values (SDANN). Finally, the beat-to-beat HRV was estimated by the square root of the mean squared differences of successive NN intervals (RMSSD), and the ratio of NN interval differences of successive NN intervals greater than 50 ms to the total number of NN intervals (pNN50).

Power spectral analysis was performed on the R-R interval data by means of fast Fourier transformation. Spectral components (as defined above) were calculated as average data over 24 h, as well as hour by hour (e.g. from 08:00 to 09:00 h). The PSD was estimated using the Welch technique, i.e. as the average of the PSD for successive blocks of data with a length of 205 s. Missing values, e.g. due to long episodes with poor signal quality of the Holter recording, were replaced by linear interpolation using the previous and next available hourly averages.

Statistical analyses

To test the null hypothesis that the two patient groups had similar HRV patterns as the controls, ANOVA or ANOVA of repeated measurements was applied (short-term HRV: three different procedures; long-term HRV: 24 hourly mean values). However, because of differences in the age dependency for several HRV parameters between patients and controls, the analysis was performed for three different age groups: young (below 40 years), middle-aged (40–60 years) and old subjects (above 60 years). All frequency-domain HRV indices were log transformed because of skewed distribution. Short-term HRV variables with a statistically significant interaction between the group and time factors, were reanalysed by ANOVA for each of the three procedure separately. Otherwise, *post-hoc* tests for statistically significant group differences were performed using the least significant difference correction, as it was predetermined that the main focus was on differences between non-treated patients and controls.

The relation between clinical variables (echocardiographic data and symptoms) and HRV measures was investigated within the non-treated patient group by multiple linear regression, with age as a covariate. Differences in clinical characteristics between beta-blocked and untreated HCM patients were analysed by Student's *t*-test or chi-square test when appropriate. The level of statistical significance was defined as a two-tailed *P* value $<0·05$.

Results

Short-term HRV

The main findings are shown in Table 2. Young HCM patients (<40 years) without beta-blockade had statistically significantly lower total spectral power in the three procedures (supine rest, controlled breathing and upright tilt) compared with controls, whereas HR was found to be significantly higher during all procedures. The HF power was also significantly reduced in this

Table 2 Short-term heart rate variability in the supine position, during controlled breathing and upright tilt.

	Controls			Untreated HCM			Beta-blocked HCM			ANOVA	
	Supine	12/min	Upright	Supine	12/min	Upright	Supine	12/min	Upright	Group *P*-value	Group-time *P*-value
Young subjects											
HR (b min^{-1})	60 (11)	64 (11)	73 (11)	72 (15)*	77 (16)*	84 (17)*	56 (10)	60 (6)	62 (12)	0·02	0·22
P_{tot} (ms^2, log)	3·4 (0·4)	3·6 (0·5)	3·4 (0·3)	2·9 (0·4)*	3·0 (0·6)*	3·1 (0·4)*	3·1 (0·1)	3·2 (0·6)	3·3 (0·2)	0·01	0·67
P_{LF} (ms^2, log)	2·9 (0·4)	2·6 (0·4)	3·2 (0·4)	2·4 (0·4)	2·3 (0·7)	2·8 (0·5)	2·5 (0·2)	2·7 (0·7)	2·8 (0·3)	0·06	0·08
P_{HF} (ms^2, log)	3·0 (0·6)	3·4 (0·6)	2·5 (0·5)	2·3 (0·6)**	2·5 (0·7)**	2·2 (0·7)	2·7 (0·3)	2·8 (0·5)	2·5 (0·4)	0·02	0·04
log P_{LF}/P_{HF}	−0·1 (0·4)	−0·8 (0·6)	0·6 (0·4)	0·2 (0·4)	−0·2 (0·5)**	0·6 (0·6)	−0·1 (0·3)	−0·1 (0·6)	0·3 (0·5)	0·23	0·001
Middle-aged subjects											
HR (b min^{-1})	67 (9)	67 (8)	77 (10)	64 (9)	66 (11)	74 (8)	59 (5)	63 (5)	68 (5)	0·19	0·38
P_{tot} (ms^2, log)	2·9 (0·4)	2·9 (0·4)	2·9 (0·5)	2·8 (0·4)	2·8 (0·5)	2·91 (0·5)	2·6 (0·4)	2·6 (0·3)	2·8 (0·2)	0·49	0·67
P_{LF} (ms^2, log)	2·4 (0·5)	2·2 (0·5)	2·5 (0·5)	2·4 (0·4)	1·8 (0·6)**	2·56 (0·5)	2·2 (0·3)	1·7 (0·5)**	2·4 (0·3)	0·30	0·03
P_{HF} (ms^2, log)	2·3 (0·5)	2·6 (0·5)	1·9 (0·5)	2·1 (0·4)	2·3 (1·2)	1·80 (0·5)	2·0 (0·5)	2·3 (0·4)	1·8 (0·5)	0·21	0·94
log P_{LF}/P_{HF}	0·0 (0·4)	−0·3 (0·5)	0·6 (0·4)	0·4 (0·2)	−0·5 (0·6)	0·77 (0·4)	0·2 (0·4)	−0·6 (0·5)	0·7 (0·6)	0·57	0·07
Old subjects											
HR (b min^{-1})	66 (10)	65 (10)	75 (11)	64 (8)	64 (8)	74 (10)	55 (10)*	56 (8)*	62 (10)*	0·01	0·77
P_{tot} (ms^2, log)	2·7 (0·4)	2·7 (0·4)	2·6 (0·4)	2·8 (0·5)	2·5 (0·5)	2·6 (0·4)	3·0 (0·7)	2·9 (0·5)	2·9 (0·5)	0·23	0·29
P_{LF} (ms^2, log)	2·1 (0·5)	1·9 (0·6)	2·0 (0·5)	2·3 (0·7)	1·5 (0·7)	2·2 (0·4)*	2·6 (0·8)	2·1 (0·7)	2·2 (0·6)	0·31	0·09
P_{HF} (ms^2, log)	1·9 (0·5)	2·4 (0·5)	1·5 (0·5)	1·9 (0·6)	2·2 (0·6)	1·6 (0·7)	2·3 (0·9)	2·4 (0·6)	1·8 (0·7)	0·57	0·19
log P_{LF}/P_{HF}	0·2 (0·4)	−0·4 (0·6)	0·5 (0·5)	0·3 (0·4)	−0·7 (1·0)	0·5 (0·6)	0·3 (0·2)	−0·3 (0·5)	0·4 (0·2)	0·83	0·42

ANOVA results: *P<0·05 *post-hoc* test for statistically significant group factor; **P<0·05 *post-hoc* test for group–time interaction. Data are given as mean (SD). HCM, hypertrophic cardiomyopathy.

group, and the LF/HF ratio was higher during controlled breathing. In Fig. 1 is depicted the dynamics of the three procedures for all subjects. Instead of presenting data for the three age groups separately, only mean values corrected for age (to 50 years) are presented, for the sake of clarity. Group differences given in Fig. 1 refer to the statistical analyses on data from the specific groups versus controls in Table 2. In controls, most HRV measures declined with increasing age. However, old HCM patients tended to have similar or, for some variables, even higher values than young subjects (both patients and controls) (Fig. 2). Therefore, the age dependency was handled in the statistical analysis by dividing patients and controls into three age groups.

Patients treated with beta-blockade had lower heart rate than controls as expected, which reached statistical significance only in the old patients (>60 years). None of the age groups showed any significant differences in total power, HF power or LF/HF ratio compared with controls (Table 2 and Fig. 1). The findings indicate a decreased parasympathetic activity in the young patients, the signs of which were attenuated in the group treated with beta-blockade.

24-hour HRV

The main findings are shown in Table 3 and Fig. 3. The results are presented as hourly averages (Fig. 3) as well as a total average for all 24 h (Table 3). Spectral analysis of both the hourly averages and the 24-h average showed that young HCM patients without beta-blockade had statistically significantly lower total-, HF- and LF-power compared with controls, whereas the middle-aged and old subjects did not show any significant differences in these parameters. There were no statistically significant group differences in the LF/HF ratio between patients without beta-blockade and controls. However, it was observed that young HCM patients had a higher circadian LF/HF ratio than the corresponding controls, whereas old patients had a tendency towards a lower daytime LF/HF than controls (Fig. 3). Analysis of time-domain indices over 24 h showed statistically significantly lower values for NNmean, SDNN, TINN, RMSSD and pNN50 only in the young HCM patients without beta-blockade compared with controls (Table 3). Only statistically significant group differences in the *post-hoc* tests are shown in Fig. 3 and Tables 2 and 3, i.e. for variables where there was a statistically significant overall difference (P<0·05 for the group factor). No significant interaction between the time and group factors was found for any of the hourly averages.

Patients treated with beta-blockade showed no significant differences in time-domain indices in young or middle-aged patients, compared with controls. In the spectral analysis, only LF- and HF-power remained significantly lower in young patients, both in the hourly averages and the average over 24 h. The HRV findings in both short-term and 24-h registrations in young HCM patients remained statistically significant after adjustments for mean HR, sex and body mass index.

Relation to echocardiography and symptoms

The echocardiographic data are summarized in Table 1. Spectral power and time-domain indices did not correlate

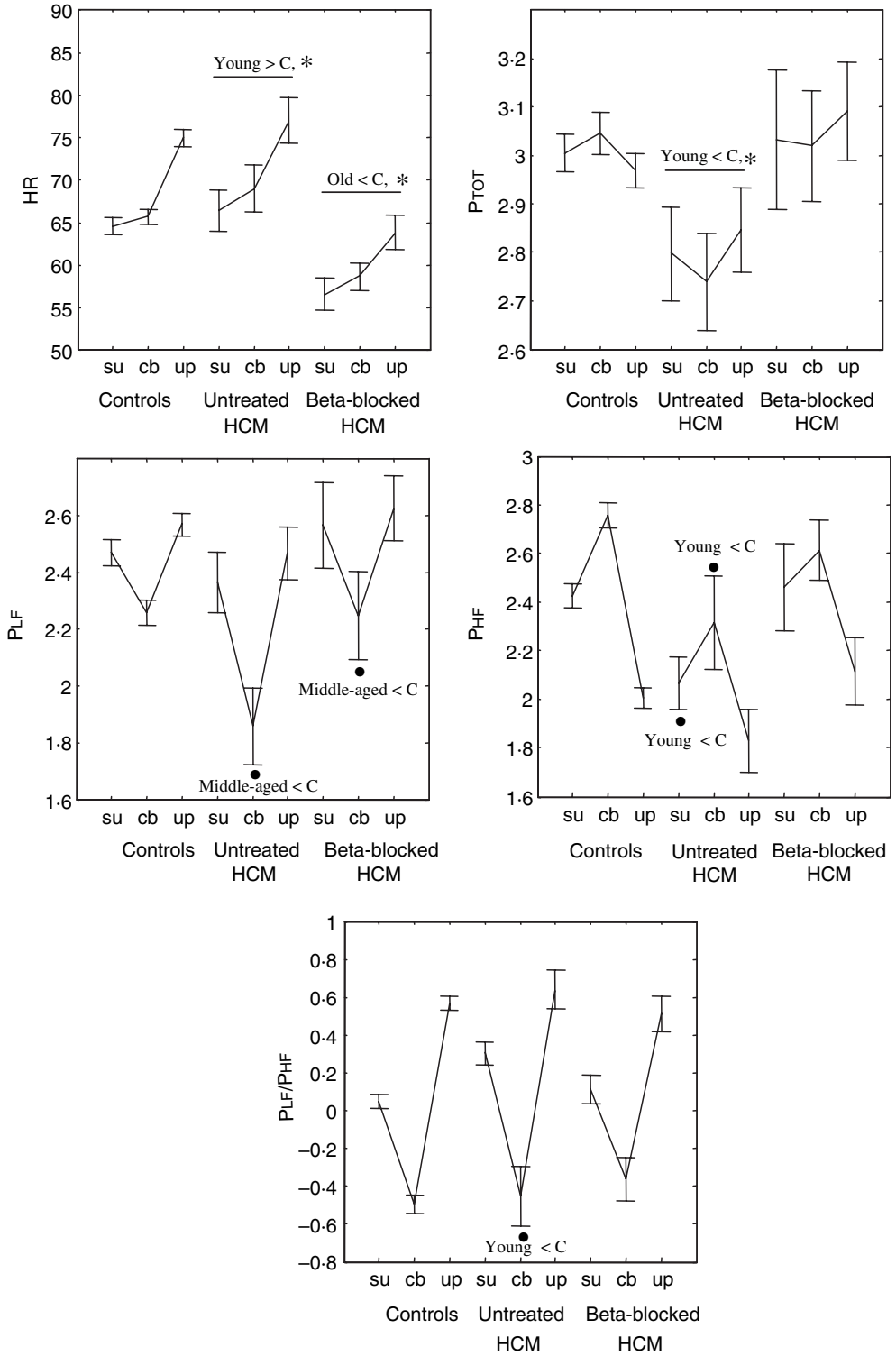

Figure 1 Short-term heart rate variability. Age-corrected mean values (to 50 years). Statistically significant differences (as given in Table 2) are shown for the age groups indicated in the figure. *, $P<0{\cdot}05$ for overall difference of the three procedures, non-treated/beta-blocked patients versus controls; ●, $P<0{\cdot}05$ for difference between non-treated/beta-blocked patients and controls at the corresponding procedure. su; supine rest; cb; controlled breathing; up; upright tilt; HR, heart rate. Data are given as mean (SEM) for all subjects in each group.

in a systematic way with either echocardiographic findings or symptoms. However, septal thickness had a positive correlation to SDNN ($P = 0{\cdot}004$) and SDANN ($P = 0{\cdot}02$) in the long-term registration, but not to the other HRV parameters measured. No significant correlation was found between the different HRV parameters and left atrial

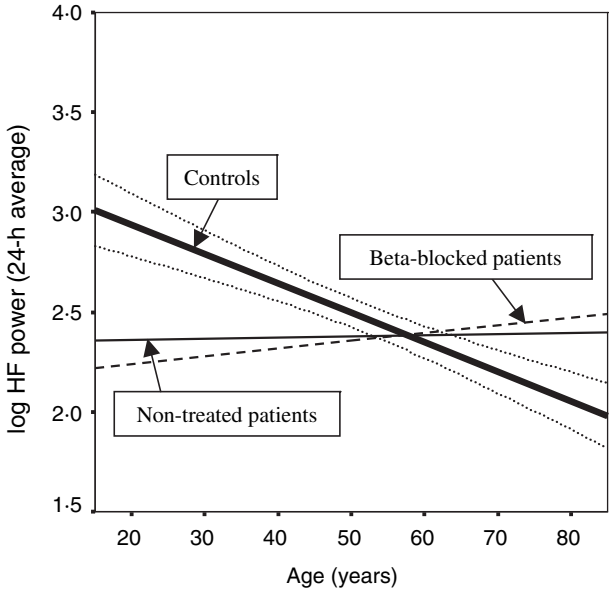

Figure 2 24-Hour heart rate variability, log HF versus age. Regression and 95% CI for mean of control group (thick line and dotted lines), for non-treated patients and for beta-blocked patients.

size, left ventricular end-diastolic diameter and left ventricular mass.

Discussion

During the last decades, analysis of HRV has become an accepted method for assessing autonomic modulation of the heart rate. The relationship between the ANS and cardiovascular mortality has been extensively studied (Lown & Verrier, 1976; Zipes & Jalife, 1990). There is experimental evidence for an association between a propensity for lethal dysrhythmias and signs of changes in sympathetic and/or parasympathetic activity, which has encouraged the development of quantitative markers of autonomic activity, such as HRV (Malik *et al.*, 1996). Reduced HRV is a predictor of mortality in patients with myocardial infarction and is associated with sudden death in chronic heart failure (Kleiger *et al.*, 1987; Fei *et al.*, 1996; Malik *et al.*, 1996; La Rovere *et al.*, 2003). Sudden cardiac death is a major problem, particularly in young individuals with HCM, and it is therefore of interest to investigate the autonomic function in different age groups of the disease.

In the evaluation of HRV, different methods can be applied, either time-domain or frequency-domain analysis. The methods are non-invasive and thus useful in clinical studies. Frequency-domain analysis facilitates a more precise evaluation of direction and magnitude of changes in sympathovagal balance than is possible with time-domain analysis (Pumprla *et al.*, 2002). Only frequency-domain methods (spectral analysis) have been recommended when investigating short-term recordings but there is still no general agreement or recommendation when short-term or long-term HRV registrations should be used (Malik *et al.*, 1996). Although 24-h recordings are often used for HRV studies, the optimal time period required to obtain useful data has not been determined (Pumprla *et al.*, 2002). Short-term recordings have the advantage of being performed under standardized laboratory conditions, whereas long-term recordings bring about the possibility to study circadian patterns. Because of lack of comparative studies, we evaluated short-term and long-term HRV registrations in the same patients with HCM.

Table 3 Time-domain and frequency-domain indices of 24-h HRV.

	Controls	Untreated HCM	Beta-blocked HCM	ANOVA group *P*-value
Young subjects	n = 33	n = 6	n = 5	
Time-domain indices				
NNmean (ms)	829 (115)	714 (96)*	932 (175)	0·02
SDNN (ms)	187 (49)	142 (42)*	143 (40)	0·05
TINN	798 (251)	525 (88)*	593 (176)	0·02
SDANN(ms)	166 (44)	133 (48)	123 (38)	0·08
RMSSD (ms)	53 (25)	26 (7)*	35 (12)	0·02
PNN50 (%)	19 (12)	4 (3)*	10 (7)	0·02
Frequency-domain indices				
P_{tot} (ms^2, log)	3·8 (0·2)	3·4 (0·1)*	3·6 (0·2)	0·001
P_{VLF} (ms^2, log)	3·5 (0·2)	3·2 (0·2)*	3·4 (0·2)	0·004
P_{LF} (ms^2, log)	3·3 (0·2)	2·8 (0·1)*	3·0 (0·2)*	0·001
P_{HF} (ms^2, log)	2·9 (0·4)	2·3 (0·3)*	2·4 (0·2)*	0·002
log P_{LF}/P_{HF}	0·4 (0·2)	0·6 (0·2)	0·6 (0·2)	0·22
Middle-aged subjects	n = 46	n = 9	n = 6	
Time-domain indices				
NNmean (ms)	802 (73)	875 (134)*	860 (115)	0·05
SDNN (ms)	187 (49)	153 (45)	129 (27)	0·38
TINN	631 (155)	769 (357)	587 (121)	0·12
SDANN(ms)	131 (32)	137 (48)	115 (31)	0·49
RMSSD (ms)	32 (13)	35 (10)	23 (3)	0·15
PNN50 (%)	7 (8)	7 (4)	2 (1)	0·24
Frequency-domain indices				
P_{tot} (ms^2, log)	3·5 (0·2)	3·5 (0·2)	3·5 (0·5)	0·95
P_{VLF} (ms^2, log)	3·3 (0·2)	3·2 (0·2)	3·4 (0·5)	0·54
P_{LF} (ms^2, log)	3·0 (0·3)	2·9 (0·3)	2·8 (0·4)	0·44
P_{HF} (ms^2, log)	2·4 (0·3)	2·5 (0·2)	2·2 (0·2)	0·16
log P_{LF}/P_{HF}	0·6 (0·2)	0·5 (0·2)	0·6 (0·3)	0·33
Old subjects	n = 41	n = 6	n = 11	
Time-domain indices				
NNmean (ms)	835 (73)	840 (79)	951 (127)*	0·003
SDNN (ms)	142 (35)	156 (41)	137 (42)	0·57
TINN	619 (159)	573 (233)	633 (205)	0·8
SDANN(ms)	129 (33)	139 (31)	119 (39)	0·56
RMSSD (ms)	31 (20)	38 (22)	47 (32)	0·11
PNN50 (%)	5 (8)	6 (5)	14 (16)*	0·03
Frequency-domain indices				
P_{tot} (ms^2, log)	3·4 (0·3)	3·3 (0·2)	3·5 (0·6)	0·36
P_{VLF} (ms^2, log)	3·2 (0·3)	3·1 (0·2)	3·3 (0·6)	0·77
P_{LF} (ms^2, log)	2·7 (0·3)	2·6 (0·2)	2·8 (0·5)	0·54
P_{HF} (ms^2, log)	2·2 (0·4)	2·4 (0·4)	2·5 (0·5)	0·23
log P_{LF}/P_{HF}	0·4 (0·3)	0·3 (0·4)	0·3 (0·3)	0·26

ANOVA results: *P<0·05 *post-hoc* test for statistically significant group factor. Data are given as mean (SD).

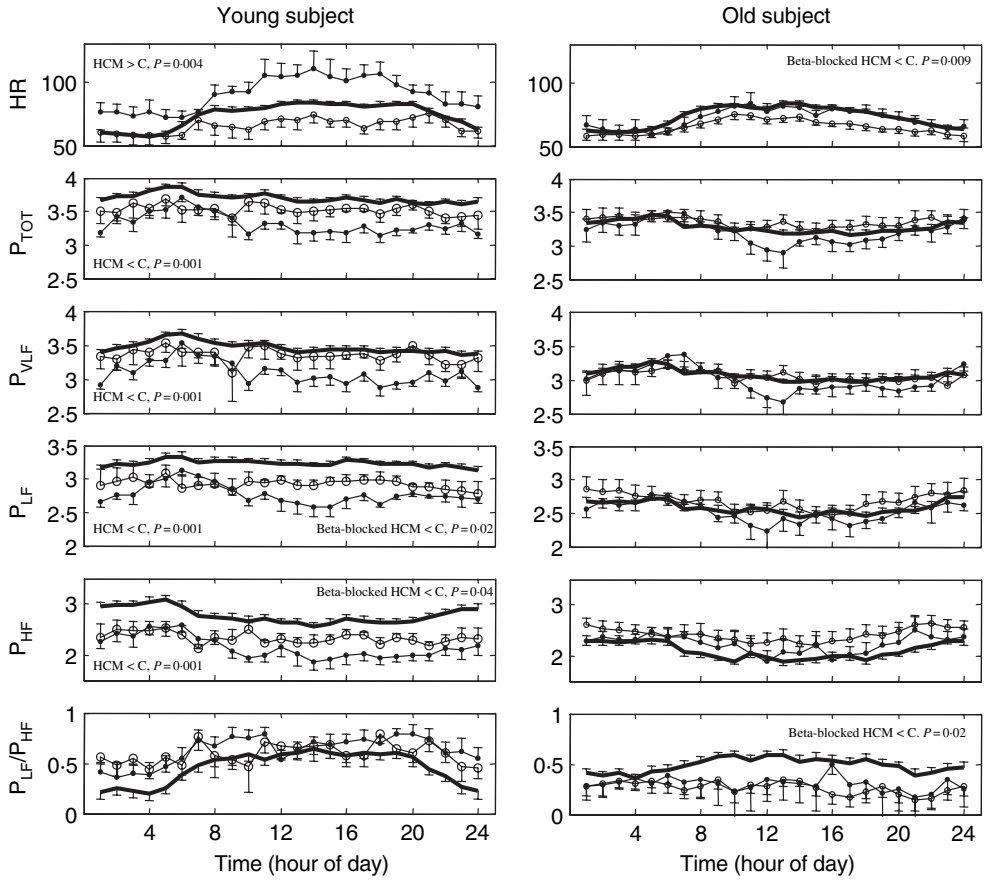

Figure 3 Long-term heart rate variability (hourly averages). Comparison of young and old hypertrophic cardiomyopathy (HCM) patients versus controls. C; controls (bold line), non-treated patients (dots) and beta-blocked patients (circles). Data are given as mean (SEM).

Main findings

Impairment of vagal autonomic regulation was found to be a prominent feature in HCM patients without beta-blockade. When short- and long-term registrations were compared, the frequency-domain indices yielded similar information, most importantly a decrease in total and HF power, as well as an increase in the LF/HF ratio in young patients. Time-domain measures were, as recommended (Malik *et al.*, 1996), only calculated from the long-term recordings, and showed a reduction in parameters reflecting overall and beat-to-beat variability in young patients, in coherence with the results from the frequency-domain analyses. The fact that HRV differed between patients and controls only in the young seems to be a reliable finding, as this was shown for a number of different analyses, such as repeated short-term measurements, as well as long-term frequency- and time-domain analyses.

Relation to beta-blockade

The HCM patients treated with beta-blockade showed higher HRV in parameters reflecting vagal tone, compared with non-treated patients. This effect of beta-blockade has also been shown in normal individuals, in heart failure and after myocardial infarction (Cook *et al.*, 1991; Sandrone *et al.*, 1994; Keeley *et al.*, 1996; Malik *et al.*, 1996; Aronson & Burger, 2001). Several mechanisms may contribute to this effect of beta-blockade, including a direct effect on beta-adrenoreceptors with inhibition of sympathetic over activity. It has been proposed that the relative increase in vagal tone contributes to the beneficial effect of beta-blockade treatment on prognosis in heart failure and after myocardial infarction (Sandrone *et al.*, 1994; Keeley *et al.*, 1996; Aronson & Burger, 2001). The patient group treated with beta-blockade had higher LV mass and more often showed signs of LVH in the ECG, but these factors were not found to influence the different HRV parameters in a significant way. The increase in HRV might be influenced by the reduction in heart rate caused by beta-blockade, but in this study the major findings were unaffected when corrected for heart rate.

Most previous studies on HRV in HCM have included patients on beta-blockade, with termination of treatment only a few days before the examination, which is insufficient to abolish the beta-blocker effect. In a study by Rangno *et al.* (1982), acute withdrawal of metoprolol in hypertensive patients was associated with rebound phenomena up to 8 days after withdrawal. In the present study, two separate patient groups were therefore compared, one on continuous treatment with beta-blockade and one non-treated group.

Relation to age

The HRV decreases with age in normal individuals (Bonnemeier *et al.*, 2003), which was not the case for the HCM patients, who showed a more constant level, or even increase in many of the HRV parameters with age (Fig. 2). The reason for this is not clear. All ECG recordings were edited in the same way, to remove ectopic beats. Ten patients were excluded from the study because of obvious dysrhythmias interfering with the analysis, nine of them were >60 years old. It is possible that other dysrhythmias, such as supraventricular ectopic beats late in the cardiac cycle, which may not be classified as premature beats, could contribute to an increase in HRV and partly explain why the differences in HRV between patients and controls were not significant in middle-aged and old patients.

Comparison with previous studies

Previous studies on HRV in HCM have shown wide discrepancies and even contradictory results. Apparent problems in comparisons between HRV studies are the lack of standardization of the methods (Malik *et al.*, 1996), the varying severity of the disease in the patients from different studies and the possible residual effect of cardioactive drugs such as beta-blockade. In the present study, both short- and long-term registrations were used. Only one previous study utilized short-term registrations, where groups of obstructive and non-obstructive patients were compared and signs of sympathetic dysfunction was only found in the obstructive patients (Limbruno *et al.*, 1998). However, in our study, the subgroup of obstructive patients was very small and no such comparison was possible. In all other previous studies, long-term registrations were used and in only one of them, the findings were consistent with decreased sympathetic tone (Fei *et al.*, 1995). However, several authors have reported impaired parasympathetic modulation. In two studies, this was apparent only during the night hours (Ajiki *et al.*, 1993; Tanabe *et al.*, 1995). Bonaduce *et al.* (1997) also reported reduced parasympathetic control in 33 patients and Counihan *et al.* (1993) found that global and specific vagal influences on HRV were reduced in symptomatic patients compared with asymptomatic patients. Only time-domain variables were analysed in a study by Doven *et al.* (2001) and depressed global HRV and reduced parasympathetic modulation was found.

Thus, a decreased global and/or parasympathetic activity is the most frequent finding in previous studies, as in the present one. However, with these methods it is not possible to locate the anatomical level of the dysfunction, which might be within the brain, in peripheral ganglia or nerves or in the target organ receptors. The mechanisms by which HRV is altered in HCM are not defined but is likely to involve derangements in the neural activity of cardiac origin.

Autonomic nervous system

It has been hypothesized that the ANS may play a role in the development of HCM, with an increased sympathetic activity in the heart. A downregulation of myocardial beta adrenoreceptors has been observed in these patients (Lefroy *et al.*, 1993), probably due to locally increased levels of noradrenaline (Brush *et al.*, 1989), and was shown to be associated with a reduced catecholamine reuptake by myocardial sympathetic nerve terminals (Schafers *et al.*, 1998). Unlike patients with congestive heart failure, no significant increase in circulating cathecholamines has been found in patients with HCM (Lefroy *et al.*, 1993; Schafers *et al.*, 1998), which further supports the idea that locally increased neurotransmitter concentrations are important in the downregulation of myocardial beta adrenoreceptors. These pathophysiological findings suggest the presence of an increased sympathetic drive in the myocardium of patients with HCM. After myocardial infarction, there is evidence for a transient depression of vagal- and augmentation of sympathetic-cardiac outflow. It has been proposed that changes in the geometry of the heart due to necrotic and non-contracting segments may abnormally increase the firing of sympathetic afferent fibres by mechanical distortion of the sensory endings, thereby attenuating the efferent vagal outflow to the sinus node, causing a decrease in vagal activity (Eckberg & Sleight, 1992). This would be a rationale for treating HCM patients with beta-blockade for the same reason as in patients with myocardial infarction. A number of other factors may also influence the autonomic balance, such as LVH, myocardial ischaemia and the activity of mechanosensitive ventricular receptors (Sleight & Widdicombe, 1965; Gupta & Thames, 1983; Grassi *et al.*, 1990; Zipes, 1990; Hainsworth, 1991).

Conclusion

We show that parasympathetic activity is decreased in young patients with HCM. This may be of clinical relevance as abnormal autonomic function might be a substrate for lethal dysrhythmias, most often encountered in younger patients with HCM. However, the present study was not designed to assess long-term clinical consequences in terms of morbidity and mortality. For these purposes, a large prospective study would be needed to assess HRV as a risk factor in HCM and the possible protective effect of beta-blockade. The results from the short- and long-term registrations, as well as time- and frequency-domain indices were in coherence, suggesting that short-term HRV might be sufficient to assess cardiac autonomic function in patients with HCM.

Limitations of the study

There were relatively few patients in each age group, which affects the statistical power of the analyses. However, the main finding of decreased HRV in young patients was consistent with the different methods used. The treatment in the patient group with beta-

blockade was not standardized, leaving open the degree and type of beta-blockade in the individuals in this group.

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