

Autonomic function in hypertrophic cardiomyopathy

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Abstract

Background—Autonomic dysfunction has been found to be a powerful predictor of arrhythmic events and sudden death after myocardial infarction. Hypertrophic cardiomyopathy carries a risk of sudden death and this risk is increased by the occurrence of syncope.

Objectives—To determine if autonomic dysfunction occurs in patients with hypertrophic cardiomyopathy and if it is associated with the occurrence of syncope.

Patients and methods—Autonomic function was measured in 30 patients with hypertrophic cardiomyopathy, 15 with and 15 without a history of syncope, and in 28 healthy volunteers.

Results—Tests of parasympathetic activity showed that the mean (SD) variation in heart rate during deep breathing was reduced in patients compared with controls, 17 (9) v 22 (9) beats/min, $p = 0.03$, the Valsalva ratio was also reduced in patients, 1.52 (0.33) v 1.70 (0.36), $p = 0.05$ but the immediate heart rate response to standing, the 30:15 ratio, was similar in both groups. Tests of sympathetic activity—namely the diastolic blood pressure response to sustained handgrip and the change in systolic blood pressure on standing—did not differ between patients and controls. There was no significant difference in autonomic function between patients with and without a history of syncope. A secondary predetermined analysis showed that the degree of impairment in variation of heart rate with breathing was correlated with the severity of left ventricular hypertrophy, $r = 0.39$, $p = 0.03$.

Conclusions—Patients with hypertrophic cardiomyopathy have a selective impairment of variability of heart rate with deep breathing and the Valsalva manoeuvre indicating decreased cardiac parasympathetic activity. The data suggest that the afferent limb of these reflexes is impaired and that the severity of impairment is related to the degree of left ventricular hypertrophy.

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The prevalence and importance of autonomic nervous dysfunction in cardiovascular disease has been increasingly recognised in the past

decade. In general, ventricular arrhythmia is facilitated when cardiac parasympathetic activity is reduced and sympathetic activity increased.^{1,2} In clinical studies, a number of tests of heart rate variability that reflect cardiac parasympathetic activity, such as the heart rate variation with breathing, are impaired after myocardial infarction.³⁻⁵ This impairment is associated with subsequent arrhythmic events and sudden death.³⁻⁵ A similar reduction in heart rate variability has been reported in patients with chronic stable angina,⁶ congestive cardiac failure,⁷ and aortic stenosis,⁸ but the prognostic importance of this finding remains uncertain in these groups.

A history of syncope,⁹ a family history of hypertrophic cardiomyopathy and sudden death,⁹ ventricular tachycardia on Holter monitoring,^{10,11} and inducible ventricular tachycardia at electrophysiological study¹² each indicate an increased risk of sudden death in patients with hypertrophic cardiomyopathy but the accurate identification of high risk patients remains imprecise.¹³ The question of whether autonomic dysfunction occurs in patients with hypertrophic cardiomyopathy and if so whether it is important in the genesis of ventricular arrhythmia or the risk of sudden death has not yet been answered. We therefore undertook a systematic investigation of autonomic function in patients with hypertrophic cardiomyopathy. To gain insight into the role of any autonomic disturbance in cardiovascular collapse in these patients we studied patients with and without a history of syncope. Secondary predetermined analyses were to compare autonomic function in patients with and without ventricular tachycardia on Holter monitoring, with and without a family history of sudden death, and to correlate autonomic function with the important echocardiographic features of the disease.

Patients and methods

PATIENTS

The study was approved by the hospital research ethics committee. All subjects gave written, informed consent. Thirty outpatients (16 female) with hypertrophic cardiomyopathy were studied, mean (SD) age 42 (16) (range 16-71) years. The diagnosis of hypertrophic cardiomyopathy was based on the presence of typical clinical and electrocardiographic findings in association with a hypertrophied, non-dilated left ventricle on cross

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sectional echocardiography, in the absence of hypertension, valvar disease, or any other systemic cause of hypertrophy. Fifteen patients were in New York Heart Association functional class I, 10 in class II, and five in class III. Of the 30 patients, 22 were not receiving medication and in eight, who were receiving a β blocker ($n = 6$) or verapamil ($n = 2$), the medication was discontinued for five drug half lives before the tests. The patient group was selected to include 15 consecutive patients with a history of one or more episodes of syncope during the preceding five years and 15 age and sex matched patients without syncope. Patients were excluded in the presence of (a) atrial fibrillation or permanent pacemaker, (b) cardiac medication that could not be withdrawn, (c) definite history or clinical suspicion of autonomic neuropathy, (d) diabetes mellitus, alcohol abuse, or any other systemic disorder that might affect autonomic function.

Twenty eight healthy volunteers were also selected for study to match the patient group with similar numbers and sex distribution in each decade of age. Their mean age was 40 (13) (range 18–69) years and 18 were female. Normal controls had no significant medical illness (including hypertension); they were not receiving any medication, and had a normal cardiovascular examination and resting electrocardiogram.

AUTONOMIC FUNCTION TESTS

Subjects fasted for at least four hours after their usual breakfast and came to the laboratory in the early afternoon. On arrival, they rested in a seated position for 30 minutes. A three lead electrocardiogram was monitored with trunk electrodes. For the measurement of changes in heart rate, a continuous electrocardiographic record was printed at 25 mm/s and measurements were performed manually. Blood pressure was recorded by auscultation and a standard sphygmomanometer. Autonomic function tests were performed according to the protocols described by Ewing and Clarke and are:¹⁴ (a) heart rate response to deep breathing (seated). After instruction and practice, the subject performed six respiratory cycles during one minute, inspiratory and expiratory phases lasting five seconds each and moving at least 50% of vital capacity with each breath. The result was calculated as the average difference in beats/min between the maximum heart rate during inspiration and the minimum rate during expiration over six respiratory cycles; (b) heart rate response to the Valsalva manoeuvre, Valsalva ratio (seated). After instruction and one to three practice attempts, the subject performed a Valsalva manoeuvre by blowing into a mouthpiece connected to a modified sphygmomanometer and maintaining a pressure of 35 mm Hg for 15 seconds. Care was taken to ensure that subjects used expiratory effort to perform the manoeuvre and did not block the mouthpiece with their tongue. Three Valsalva manoeuvres were performed with two minute rest periods between each. The result was cal-

culated as the average ratio of the longest RR interval after release to the shortest RR interval during strain; (c) heart rate response to standing, 30:15 ratio. This was calculated as the ratio of the longest RR interval about the 30th beat after standing from a supine position to the shortest RR interval about the 15th beat after standing. The average of three ratios was taken. The supine heart rate was allowed to return to baseline between each measurement; (d) systolic blood pressure response to standing. This was calculated as the difference between the supine systolic blood pressure and the systolic blood pressure immediately on standing. An average of three values was obtained; (e) diastolic blood pressure response to handgrip (seated). A handgrip dynamometer was used. The subject's maximum grip strength was determined in his or her dominant arm. Resting diastolic blood pressure was taken as the average of three readings in the non-dominant arm. The subject then maintained sustained handgrip at one third of maximum grip strength for three minutes or until fatigue, whichever was the shorter. Blood pressure and heart rate were recorded each minute.

Tests were always performed in the same order ((a), (b), (e), (c), (d)) with sufficient rest between tests to allow heart rate and blood pressure to return to a stable baseline. Tests (a), (b), and (c) have been shown to primarily reflect cardiac parasympathetic efferent activity, whereas tests (d) and (e) reflect sympathetic efferent activity.¹⁴

ECHOCARDIOGRAPHY

Cross sectional echocardiography and Doppler were performed within one week of the autonomic function tests with the Toshiba 65A imaging system and methods already described for our laboratory.¹⁵ As well as the standard measurements of septum and posterior wall, the degree of left ventricular hypertrophy was assessed by measurement of wall thickness in a total of 10 segments at three different short axis planes: four segments at mitral valve level (anterior and posterior septum, inferior and lateral walls), four segments at papillary muscle level (anterior and posterior septum, inferior and lateral walls), and two segments at the apex (anterior and posterior). A total hypertrophy score was calculated from the sum of all 10 segmental thicknesses and the single maximum wall thickness was noted. Doppler measurements of the peak early (E) and late (A) transmitral flow velocities and the peak left ventricular outflow tract velocity were measured as previously described.¹⁵ All studies were recorded on videotape and measurements were made by one observer without knowledge of the results of the autonomic function tests.

HOLTER MONITORING

Twenty four hour Holter monitoring was also performed (Tracker recorders, Reynolds Medical) within one week of autonomic function tests as previously described.¹⁵ Ventricular tachycardia was defined as three

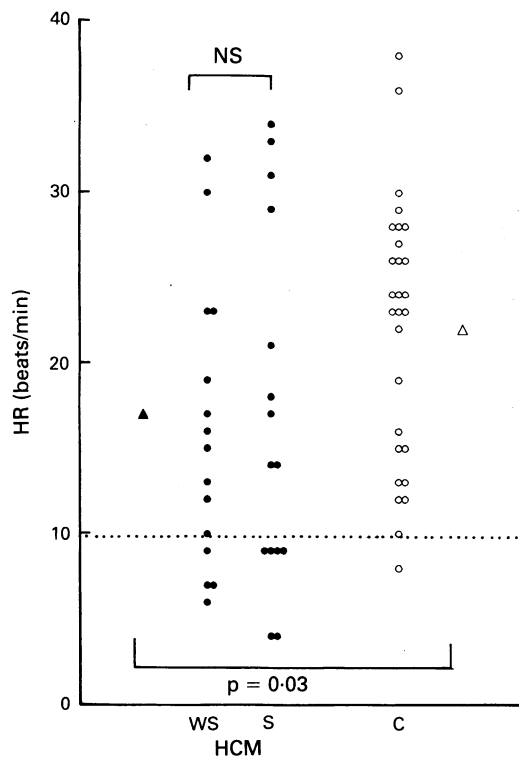


Figure 1 Heart rate (HR) variation with deep breathing in 30 patients with hypertrophic cardiomyopathy (HCM), 15 with a history of syncope (S) and 15 without (WS), compared with 28 normal controls (C). Values ≤ 10 beats/min are considered diagnostic of autonomic neuropathy.¹⁴

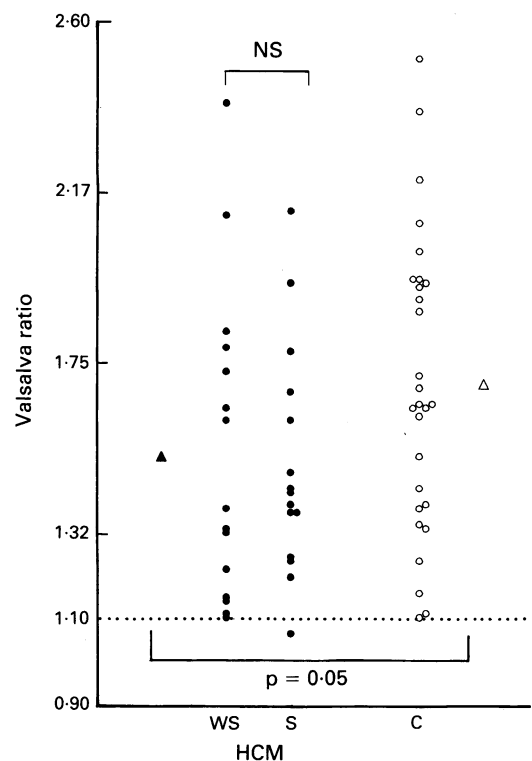


Figure 2 Valsalva ratio (ratio of longest RR interval after release to shortest RR interval during strain) in 30 patients with hypertrophic cardiomyopathy (HCM), 15 with a history of syncope (S) and 15 without (WS), compared with 28 normal controls (C). Values ≤ 1.10 are considered diagnostic of autonomic neuropathy.¹⁴

or more consecutive extrasystoles at a rate of ≥ 120 beats/min.

STATISTICAL ANALYSIS

The results of autonomic function tests in the patient and control groups and in the patient subgroups were compared with the two tailed Student's *t* test for unpaired data. The relations between autonomic function and age, and between autonomic function and echocardiographic values were assessed by plotting the data and performing linear regression analysis. A correlation coefficient and *p* value were subsequently calculated. All group data are expressed as mean (SD).

Results

AUTONOMIC FUNCTION IN PATIENTS *V*

NORMAL CONTROLS

The heart rate variation with deep breathing

was significantly lower in patients compared with controls (fig 1, table 1), with 10 patients (33%) falling in the range defined as definite autonomic neuropathy.¹⁴ The heart rate variation with the Valsalva manoeuvre was also reduced in patients compared with controls (fig 2), but to a lesser degree and only one patient was in the autonomic neuropathy range.¹⁴ The heart rate variation with breathing correlated positively with the Valsalva ratio, $r = 0.51$, $p = 0.004$, in patients. The 10 patients with a depressed heart rate variation with breathing also had a lower Valsalva ratio compared with the 20 remaining patients (1.36 (0.18) *v* 1.60 (0.37), $p = 0.02$). There were no differences between patients and controls in the third parasympathetic test, the 30:15 ratio, nor in the two tests of sympathetic function, the diastolic blood pressure increase with handgrip, and the systolic blood pressure change from lying to standing.

Table 1 Results of autonomic function tests in patients and controls

| | HC patients (n = 30) | Normal controls (n = 28) | 95% CI of difference | <i>p</i> Value |
|----------------------------------------------|----------------------|--------------------------|----------------------|----------------|
| Age (yr) | 42 (16) | 40 (13) | (-5 to 10) | 0.54 |
| Resting heart rate, seated (beats/min) | 78 (12) | 78 (6) | (-5 to 5) | 0.99 |
| Resting systolic BP, seated (mm Hg) | 124 (21) | 125 (15) | (-11 to 9) | 0.86 |
| Resting diastolic BP, seated (mm Hg) | 83 (11) | 85 (10) | (-8 to 4) | 0.49 |
| HR variation with deep breathing (beats/min) | 16.5 (9.2) | 22.0 (9.2) | (-10.4 to -0.7) | 0.03 |
| Valsalva ratio | 1.52 (0.33) | 1.70 (0.36) | (-0.36 to 0.003) | 0.05 |
| HR lying to standing, 30:15 ratio | 1.24 (0.25) | 1.24 (0.11) | (-0.11 to 0.12) | 0.93 |
| Systolic BP change lying to standing (mm Hg) | -7 (11) | -7 (8) | (-6 to 5) | 0.89 |
| Diastolic BP response to handgrip (mm Hg) | 19 (14) | 18 (8) | (-6 to 7) | 0.85 |

HC, hypertrophic cardiomyopathy; HR, heart rate; values are mean (SD).

Table 2 Results of autonomic function tests in patients with and without a history of syncope

| | Syncopal patients (n = 15) | Non-syncopal patients (n = 15) | 95% CI of difference | p Value |
|----------------------------------------------|----------------------------|--------------------------------|----------------------|---------|
| Age (yr) | 47 (15) | 37 (15) | (-1 to 21) | 0.08 |
| HR variation with deep breathing (beats/min) | 17 (10) | 16 (8) | (-7.8 to 6.1) | 0.8 |
| Valsalva ratio | 1.5 (0.3) | 1.5 (0.4) | (-0.22 to 0.29) | 0.79 |
| HR lying to standing, 30:15 ratio | 1.24 (0.19) | 1.24 (0.31) | (-0.19 to 0.2) | 0.95 |
| Systolic BP change lying to standing (mm Hg) | -6 (14) | -7 (10) | (-10 to 8) | 0.81 |
| Diastolic BP response to handgrip (mm Hg) | 20 (20) | 19 (6) | (-13 to 10) | 0.79 |

HR, heart rate; values are mean (SD).

RELATIONS OF AUTONOMIC FUNCTION TO OTHER MEASUREMENTS

In the control group, increasing age was associated with a reduction in the heart rate variation with deep breathing ($r = -0.42$, $p = 0.03$) and with a reduction in the Valsalva ratio ($r = -0.46$, $p = 0.01$). In patients with hypertrophic cardiomyopathy the relation of age to the Valsalva ratio persisted ($r = -0.43$, $p = 0.02$) but the correlation of age to heart rate variation with breathing was less noticeable ($r = -0.33$, $p = 0.07$). There were no differences in autonomic function between the sexes in either the patient or control groups.

The primary predetermined subset analysis in the patient group was a comparison of autonomic function in patients with and without a history of syncope. This analysis showed no significant difference between these two groups (table 2).

A number of secondary predetermined analyses were performed. Autonomic function test results were not significantly different between patients with a family history of sudden death ($n = 6$) and those without ($n = 24$) nor between patients with ventricular tachycardia on Holter monitoring ($n = 6$) and those without ($n = 24$). Five echocardiographic features were examined for a correlation with autonomic function; left atrial diameter, maximum wall thickness, total hypertrophy score, a left ventricular outflow tract pressure gradient ≥ 30 mm Hg ($n = 12$), and the E/A ratio. The only significant correlation was a negative association between maximum wall thickness and the heart rate variation with deep breathing ($r = -0.39$, $p = 0.03$) (fig 3).

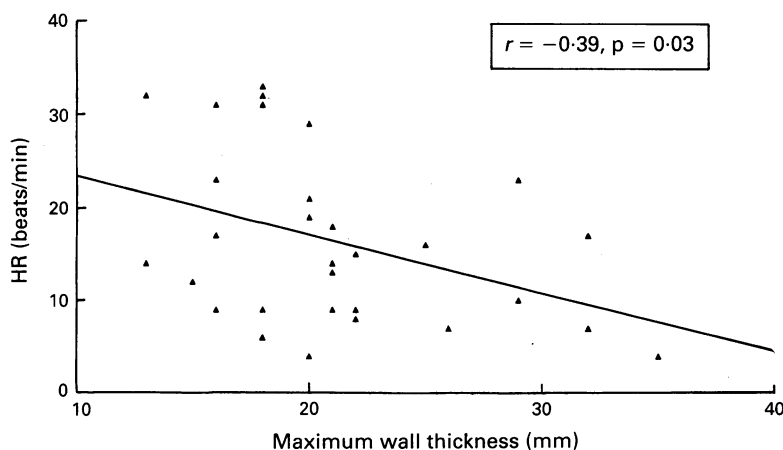


Figure 3 Relation between the maximum left ventricular wall thickness and the heart rate variation with deep breathing in 30 patients with hypertrophic cardiomyopathy.

Discussion

In this study we used three autonomic function tests that reflect efferent cardiac parasympathetic activity; the heart rate variations with deep breathing, the Valsalva manoeuvre, and immediately on standing. These heart rate responses are blocked by atropine.¹⁶ These tests have been developed and validated in normal populations and in the study of diabetic autonomic neuropathy.¹⁴ Our normal controls showed the described decline of these indices with age and this finding emphasises the importance of age matched groups when comparing autonomic function.¹⁷ This correlation with age, particularly for heart rate variability with deep breathing, was less pronounced in the patient group probably due to the impairment in young patients.

The mean heart rate variation with deep breathing was clearly depressed and the mean heart rate variation with the Valsalva manoeuvre was slightly depressed in patients with hypertrophic cardiomyopathy in this study. In one third of patients, the heart rate variation with breathing fell into the range described as frank autonomic neuropathy¹⁴ and the Valsalva ratio was also relatively reduced in this group. By contrast, the heart changes on standing (the 30:15 ratio) were normal. This pattern of abnormality on autonomic function tests has been described in other cardiac diseases.^{6,8,18} These findings contrast with studies of diabetic autonomic neuropathy where the results of the three tests tend to be in parallel and where the 30:15 ratio is a sensitive test of parasympathetic neuropathy.¹⁶ The results, therefore, suggest that the autonomic impairment found in patients with cardiac disease does not lie in the parasympathetic efferent system, but rather the afferent limb or central integration of these reflexes is abnormal.

Afferent information for the heart rate variations with breathing and the Valsalva manoeuvre comes from vascular baroreceptors and pulmonary stretch receptors whereas the immediate heart rate changes on standing result mainly from stimulation of muscle afferent receptors in response to movement.¹⁹ Therefore an alteration in afferent information from baroreceptors is a possible explanation for the findings in this and similar studies of autonomic dysfunction in cardiac disease.

Although haemodynamic, neurohumoral, and other mechanisms cannot be ruled out, the most likely cause of impaired afferent input from cardiac baroreceptors is damage to cardiac afferent nerves. This hypothesis is

based on experimental studies in which infarction reduces baroreflex sensitivity in dogs.²⁰ Infarction damages both those cardiac afferent nerves arising in the area of infarction and those coursing through it.²¹ This damage may lead to an alteration of the neural feedback to higher centres and produce the abnormalities found.⁵ The extensive myocardial pathology of hypertrophic cardiomyopathy could similarly damage afferent autonomic nerves in the heart. It has been shown that hypertrophy may impair cardiopulmonary baroreceptor reflexes even in athletes,²² and we have evidence that these reflexes are impaired in some patients with hypertrophic cardiomyopathy.²³ Also, the association, albeit weak, between the severity of hypertrophy and the degree of parasympathetic impairment in this study supports a local mechanism within the heart.

The tests of sympathetic function used in this study did not show any difference in the amount of stimulated sympathetic activity between patients and controls. Exaggerated sympathetic activity or responsiveness has been suggested as a pathogenic factor in the development of hypertrophic cardiomyopathy.²⁴ Our initial data did suggest a correlation between septal thickness and a lesser fall of blood pressure on standing (that is, greater sympathetic activity)²⁵ but after completion of the study there was no correlation with the measurements of hypertrophy.

Reduced heart rate variability is strongly associated with subsequent ventricular arrhythmia and sudden death after myocardial infarction.³⁻⁵ It is likely that such abnormal autonomic tone predisposes to the occurrence of sustained ventricular arrhythmia in patients who already have an arrhythmogenic myocardial substrate.^{1,25} This is the first study to show that cardiac parasympathetic activity is reduced in patients with hypertrophic cardiomyopathy. It raises the possibility that altered autonomic tone may have a role in the pathophysiology of hypertrophic cardiomyopathy. We did not find any correlation between a history of syncope and the presence of impaired heart rate variability. Syncope in patients with hypertrophic cardiomyopathy may result from a number of mechanisms, however—for instance, ventricular tachycardia—which would be facilitated by impaired parasympathetic activity,^{1,2} or reflex hypotension and bradycardia, which require an active autonomic system.²³ Thus syncopal patients as a group may not show a distinctive pattern. Because only six patients had ventricular tachycardia on Holter monitoring we cannot draw conclusions about its relation with autonomic function. Importantly, Counihan, *et al* have recently confirmed a similar impairment of autonomic function in a larger population of patients with hypertrophic cardiomyopathy and found it to be associated with both ventricular tachycardia and syncope.²⁶ Future studies must determine whether measures of heart rate variability can predict the risk of sudden death in patients with hypertrophic cardiomyopathy. If this proves to be the case, manipulation of autonomic tone may become

a valuable new treatment in this condition.²⁷

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