JACC Vol. 31, No. 6
May 1998:1377–82

Reduced Cardiopulmonary Baroreflex Sensitivity in Patients With Hypertrophic Cardiomyopathy

HELEN L. THOMSON, MBBS, JAYNE MORRIS-THURGOOD, PhD,* JOHN ATHERTON, MBBS,* MICHAEL FRENNEAUX, MD, FACC*

Cardiff, Wales, United Kingdom

Objectives. **We sought to assess baroreflex function in patients with hypertrophic cardiomyopathy (HCM).**

Background. **We have previously demonstrated a specific abnormality in the afferent limb of the cardiopulmonary baroreflex in patients with vasovagal syncope. Patients with HCM exhibit abnormal control of their vasculature during exercise and upright tilt; we therefore hypothesize a similar abnormality in the afferent limb of the cardiopulmonary baroreflex arc.**

Methods. **We investigated 29 patients with HCM and 32 control subjects. Integrated baroreceptor sensitivity was assessed after administration of phenylephrine. Cardiopulmonary baroreceptor sensitivity was assessed by measuring forearm vascular resistance (FVR) during lower body negative pressure (LBNP). Carotid artery baroreflex sensitivity was assessed by measuring the in RR interval during manipulation of carotid artery transmural pressure. The integrity of the efferent limb of the reflex arc was determined by studying responses to both handgrip and peripheral alpha-receptor sensitivity.**

Results. **During LBNP, FVR increased by only 2.36 ± 9 U in patients, compared with an increase of 12.3 ± 8.76 U in control subjects ($p = 0.001$). FVR paradoxically fell in eight patients, but in none of the control subjects. Furthermore, FVR fell by 4.9 ± 5.6 U in patients with a history of syncope, compared with an increase of 4.7 ± 7.2 U in those without syncope ($p = 0.014$). Integrated and carotid artery baroreflex sensitivities were similar in patients and control subjects (14 ± 7 vs. 14 ± 6 ms/mm Hg, p = NS and −3 ± 2 vs. −4 ± 2 ms/mm Hg, p = NS, respectively). Similarly, handgrip responses and the dose/response ratio to phenylephrine were not significantly different.**

Conclusions. **This study suggests that patients with HCM have a defect in the afferent limb of the cardiopulmonary reflex arc.**

(J Am Coll Cardiol 1998;31:1377–82)

We previously reported (1,2) that exercise hypotension occurs in ~30% of patients with hypertrophic cardiomyopathy (HCM) as a result of an exaggerated fall in systemic vascular resistance. This is associated with impaired forearm vasoconstriction or paradoxic vasodilation during dynamic leg exercise (1,2). A possible mechanism is exaggerated activation of left ventricular (LV) mechanoreceptors during exercise.

This observation may be clinically important when considered in light of a recent prospective study showing an association between abnormal blood pressure responses to exercise and an increased risk of sudden death in young patients (<25 years) with HCM (3). One group has also reported a high incidence of syncope and hypotension during tilt-table testing in HCM (4). Activation of ventricular mechanoreceptors in the setting of a small hypercontractile ventricle has been proposed as a mechanism of vasovagal syncope during tilt-table testing (5). Patients with HCM typically have relatively small LV cavities and increased LV ejection fractions.

There is evidence of an abnormality in the autonomic control of the cardiovascular system in patients with HCM. One group reported reduced heart rate variability during deep breathing and a decreased Valsalva ratio in patients with HCM compared with control subjects (where the Valsalva ratio is defined as the ratio of the longest RR interval after the maneuver to the shortest before the maneuver) (6). Studies assessing heart rate variability in patients with HCM have yielded conflicting results (7–9). We assessed integrated baroreceptor sensitivity, cardiopulmonary sensitivity and carotid artery baroreflex sensitivity in control subjects and patients with HCM. Using a similar protocol, we recently demonstrated a specific abnormality of cardiopulmonary baroreceptor function in patients with vasovagal syncope (10), located in the afferent limb of the reflex arc. We hypothesised that patients with HCM would have a similar abnormality.

From the Department of Medicine, University of Queensland and *Department of Cardiology, University of Wales College of Medicine, Cardiff, Wales, United Kingdom. Drs. Frenneaux, Morris-Thurgood and Atherton were supported by the British Heart Foundation, London. This study was supported in part by Project Grant 665 941193 and Scholarship Grant 948220 from the NH&MRC of Australia.

Manuscript received April 21, 1997; revised manuscript received February 3, 1998, accepted February 5, 1998.

Address for correspondence: Dr. Michael Frenneaux, Department of Cardiology, University of Wales College of Medicine, Heath Park, Cardiff, Wales, CF4 4XN, United Kingdom.

0735-1097/98/$19.00
PII S0735-1097(98)00102-8

Abbreviations and Acronyms

FVR = forearm vascular resistance
HCM = hypertrophic cardiomyopathy
LBNP = lower body negative pressure
LV = left ventricular

Methods

Patients. Thirty-six consecutive patients with HCM were selected from the Cardiomyopathy Clinic at the Royal Brisbane Hospital. The diagnosis of HCM was based on typical clinical, echocardiographic and hemodynamic features (11). Two-dimensional echocardiography was used to determine LV hypertrophy (>1.4 cm) in the absence of cardiac or systemic disease that could have caused such hypertrophy. Patients were excluded from the study 1) if blood pressure exceeded 160/90 mm Hg, 2) if there was a definite history or clinical suspicion of autonomic failure; or 3) if the cardiac rhythm was other than sinus. Twenty-nine patients satisfied these criteria and consented to take part in the study (Table 1).

Thirty-two approximately age- and gender-matched control subjects with no history of cardiovascular disease and normal clinical examinations (electrocardiography and echocardiography) were recruited (Table 1). These control subjects were found in the endoscopy data base of the Department of Gastroenterology.

Table 1. Clinical Characteristics of Patients With Hypertrophic Cardiomyopathy (n = 29) and Control Subjects (n = 32)

Age (yr)	
Patients	43 ± 18
Control subjects	42 ± 17
Men/women	
Patients	11/18
Control subjects	8/24
Family history of HCM	17 (59%)
Family history of sudden death	6 (21%)
Concentric/asymmetrical septal hypertrophy	7 (37%)
NYHA functional class	
I	11
II	17
III	1
Syncope	7 (24%)
Presyncope	16 (55%)
Typical chest pain	10 (34%)
Atypical chest pain	5 (17%)
Palpitations	3 (10%)
LV wall thickness (mm)	23.2 ± 8.3
LV diastolic dimension (mm)	40.3 ± 13.1
LV systolic dimension (mm)	25.4 ± 8.8
Left atrial dimension (mm)	39.7 ± 12.0
Fractional shortening (%)	44.4 ± 8.3
Mean gradient >20 mm Hg	6 (21%)
Complete SAM of mitral valve	7 (24%)
Incomplete SAM of mitral valve	8 (28%)
NSVT/rate (beats/min)	7 (24%)/134 ± 34

Data presented are mean value ± SD or number (%) of patients with hypertrophic cardiomyopathy. HCM = hypertrophic cardiomyopathy; LV = left ventricular; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; SAM = systolic anterior motion.

Study protocol. The investigations were performed at the Royal Brisbane Hospital with the hospital's Ethical Committee approval. Written informed consent was obtained from all patients and control subjects. Subjects arrived at 8 AM having fasted from midnight. All cadioactive medications were withdrawn for at least five half-lives before the study, with the exception of amiodarone, which was continued in three patients. Patients and control subjects were randomly tested and fully familiarized with the protocol before initiation of each study. All participants rested for 30 min between studies.

Assessment of baroreceptor sensitivity. The assessment of cardiopulmonary, integrated and carotid artery baroreceptor sensitivities entailed recording the electrocardiogram and measuring blood pressure using a Finapress recorder (Ohmeda 2300, Anglewood). Both these signals and all physiologic variables recorded were acquired using the Acq Knowledge data acquisition program (Biopac Systems) on an Apple Macintosh IICI computer.

Cardiopulmonary baroreceptor sensitivity. Cardiopulmonary baroreflex sensitivity was assessed in all patients and in a subset of 18 control subjects. Cardiopulmonary receptors were deactivated by reducing central venous pressure. This was achieved by application of a mild lower body negative pressure (LBNP, −15 mm Hg) using a LBNP device. The blood pressure and heart rate were effectively unaltered by the mild negative pressure. This stimulus is believed to evoke forearm vasoconstriction predominantly through unloading of LV mechanoreceptors (12). Cardiopulmonary baroreceptor sensitivity was assessed during application of LBNP (−15 mm Hg) after stabilization for 2 min. The pressure within the lower body box was measured by a transducer (Dwyer [series 602] differential pressure transmitter integrated with Innotech current sensing controller and display). The following variables were measured both at rest and during LBNP: 1) Forearm blood flow was measured by a standard mercury-in-silastic strain gauge plethysmography technique (Hokanson) (13) and calculated from the mean of three slopes. 2) Forearm vascular resistance (FVR) was calculated as the quotient of the mean arterial pressure (mm Hg) and forearm blood flow (ml/min per 100 ml) and expressed in resistance units. 3) Central venous pressure was recorded using a Baxter transducer (Baxter Health Care Corp.) through a central line inserted from the antecubital vein.

Relation of cardiopulmonary sensitivity to LV outflow tract gradient. A subgroup of seven patients was studied during application of −15 mm Hg LBNP to determine whether dynamic increases in the LV outflow tract gradient might be responsible for activation of cardiopulmonary baroreceptors. We assessed changes in the LV outflow tract gradient, LV dimensions and fractional shortening. Two patients had a rest mean Doppler outflow tract gradient >20 mm Hg and complete systolic anterior motion of the mitral valve; two had

incomplete systolic anterior motion of the mitral valve but no significant outflow tract gradient; and three had no systolic anterior motion of the mitral valve or outflow tract gradient.

Integrated baroreceptor sensitivity. Integrated baroreceptor sensitivity was assessed using a standard phenylephrine ramp method (14). In brief, phenylephrine was injected into an antecubital vein at a dose sufficient to progressively increase systolic blood pressure by ~20 to 30 mm Hg, and hence increase the activity of the arterial baroreceptors. This induced a linearly related lengthening of the RR interval, which allowed the slope of the linear regression of the RR interval versus systolic blood pressure to be taken as the baroreflex sensitivity during baroreceptor stimulation.

The phenylephrine dose was given three times to increase the systolic blood pressure by 30 mm Hg. The three measurements of baroreceptor sensitivity were calculated, and the mean value represented phenylephrine baroreceptor sensitivity.

Carotid artery baroreceptor sensitivity. Carotid artery baroreceptor sensitivity was measured using a standard technique (15). In brief, the patients were fitted with a lead collar connected to an air source. This permitted the application of negative and positive pressures around the neck, increasing and decreasing carotid artery transmural pressure and selectively stimulating and inhibiting carotid artery baroreceptors, respectively. The negative and positive pressures were randomly applied in six separate steps ranging from −50 to 50 mm Hg. Each pressure was applied only once during end-expiration held for 10 s. The maximal change in the RR interval over three beats, immediately after application of neck pressure, represented the reflex response for that applied pressure. The slope of the linear regression of the RR intervals versus applied neck pressures was taken as the carotid artery baroreflex sensitivity.

Responses to handgrip and phenylephrine. To assess whether the vasoconstrictor response to alpha-adrenergic stimulation is impaired in patients with HCM, we assessed the blood pressure response to the $alpha_1$ agonist phenylephrine in patients and control subjects. In brief, phenylephrine was injected into an antecubital vein. The dose of phenylephrine required to produce an increase in systolic blood pressure of ~30 mm Hg was divided by the patient's weight to give a weight-adjusted dose/response ratio.

To assess whether reflex responses to other pressor maneuvers were impaired in patients with HCM, the response of diastolic blood pressure to handgrip was assessed in patients and control subjects. Handgrip was maintained at 30% of the maximal voluntary contraction up to a maximum of 5 min, using a handgrip dynamometer, and blood pressure was measured each minute. The difference between baseline blood pressure and blood pressure immediately before release of handgrip was taken as the measure of response.

Data analysis. Results are expressed as the mean value ± SD. The data were normally distributed. Statistical analysis was performed using paired and unpaired *t* tests and the chi-square test where appropriate. A p value <0.05 was considered significant.

Table 2. Baroreflex Sensitivities in Patients With Hypertrophic Cardiomyopathy Versus Control Subjects

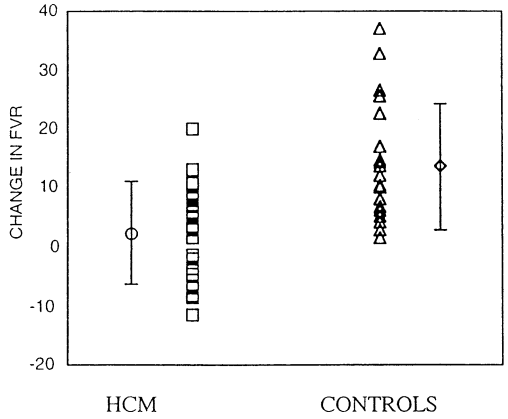
	Patients	Control Subjects	p Value
CPG (mm Hg)	2.1 ± 7.9	13.7 ± 10.7	0.0001
Integrated gain (ms/mm Hg)	14 ± 7	14 ± 6	NS
Carotid artery BRS (ms/mm Hg)	−3 ± 2	−4 ± 2	NS

Data presented are mean value ± SD. BRS = baroreflex sensitivity; CPG = cardiopulmonary gain at −15 mm Hg lower body negative pressure.

Results

Cardiopulmonary baroreceptor sensitivity. In the patient group, FVR increased from 39.7 ± 16.9 to 40.5 ± 16.3 U during −15 mm Hg LBNP, compared with an increase from 36 ± 12.0 to 47.7 ± 18.1 U during −15 mm Hg LBNP in the control group (p = 0.001) (Table 2 and Fig. 1). This related to a decrease in forearm blood flow from 2.53 ± 0.8 to 2.01 ± 0.6 ml/min during 15 mm Hg LBNP in the control group compared with a decrease from 2.46 ± 0.9 to 2.37 ± 1.08 ml/min during 15 mm Hg LBNP in the patient group (p = 0.01). Data from one patient were excluded owing to a decrease in systolic blood pressure >5 mm Hg during LBNP. In eight patients there was a paradoxic fall in FVR during LBNP, a response seen in none of the control subjects. Heart rate did not change during LBNP in either group (66.3 ± 9.3 beats/min at rest vs. 66.4 ± 10.3 beats/min during LBNP in patients compared with 65.4 ± 10.2 beats/min at rest vs. 68.5 ± 12.7 beats/min during LBNP in control subjects). Similarly, there were no changes in blood pressure during LBNP in either group (80.4 ± 11.7 mm Hg at rest vs. 82.7 ± 13.1 mm Hg at −15 mm Hg LBNP in patients compared with 84.8 ± 13.8 mm Hg at rest and 86.4 ± 14.5 mm Hg at −15 mm Hg LBNP in control subjects). The change in central venous

Figure 1. Change in FVR evoked by application of −15 mm Hg LBNP. Overall, patients demonstrated less marked constriction than control subjects and, in some cases, paradoxical vasodilation.



pressure (rest compared with LBNP) was similar in both the patient and control groups (4 ± 4 vs. 4 ± 4 mm Hg, p = NS).

Although cardioactive medications were withdrawn for five half-lives before the study, the possibility of a beta-blocker withdrawal effect was considered. When three patients who had been taking beta-blockers (propranolol, 100 mg, and metoprolol, 50 mg) before enrollment in the study were removed from the analysis, there was still a significant difference between the change in FVR in the patients and that in control subjects (2.4 ± 8.2 vs. 13.7 ± 10.7 U, p = 0.001).

Relation of cardiopulmonary sensitivity to LV outflow tract gradient and echocardiographic data. When comparing patients with a significant LV outflow tract (mean Doppler gradient >20 mm Hg) and those without it, there was no significant difference in the change in FVR between the two groups (3.1 ± 7.4 vs. 1.2 ± 8.7 U, p = NS). When the patients were classified into those with a significant outflow tract gradient or complete or incomplete systolic anterior motion of the mitral valve leaflets, or both, and those remaining, again there was no significant difference between the two groups (3.1 ± 8.1 vs. 1.5 ± 8.2 U, p = NS).

Assessment was made of LV outflow tract gradients and LV end-diastolic measurements at rest and during application of −15 mm Hg LBNP in a subgroup of seven patients. Of the two patients with a significant rest LV outflow tract gradient (>20 mm Hg), the gradient increased in both patients (from 42 to 58 mm Hg and from 34 to 39 mm Hg). One of these patients exhibited normal forearm vasoconstriction and one exhibited forearm vasodilation during LBNP. Of the five patients without a significant outflow tract gradient (<20 mm Hg), none developed a significant outflow tract gradient during application of LBNP. There were no significant changes in LV end-diastolic dimensions during LBNP in any of the patients (46 ± 8 mm at rest vs. 44 ± 6 mm during LBNP, p = NS). Similarly, there were no changes when comparing systolic dimensions at rest (2.76 ± 0.92 cm) with those during LBNP (2.58 ± 0.58 cm) and fractional shortening at rest (45 ± 8%) with that during LBNP (43 ± 9%).

Relation of paradoxic forearm vasodilation during LBNP to clinical syncope or presyncope. Paradoxic vasodilation during LBNP was associated with a clinical history of syncope. Although paradoxic vasodilation occurred in five of seven patients with a history of syncope, vasoconstriction occurred in 17 of 22 patients without a history of syncope (chi-square 5.6, p = 0.02).

Relation of FVR to age and LV wall thickness. There was no correlation between a patient's percent change in FVR and either maximal LV wall thickness (r = 0.33) or age (r = 0.11).

Integrated and carotid artery baroreceptor sensitivities. Integrated and carotid artery baroreceptor sensitivities were similar in patients and control subjects (14 ± 7 vs. 14 ± 6 ms/mm Hg, p = NS and −3 ± 2 vs. −4 ± 2 ms/mm Hg, p = NS) (Table 2).

Responses to handgrip and phenylephrine. The increase in diastolic blood pressure during handgrip was similar in patients and control subjects (18 ± 8 vs. 22 ± 10 mm Hg, p = NS). The phenylephrine dose/response ratio was also similar (3.2 ± 2.0 vs. 3.9 ± 2.0 mm Hg/kg body weight per μg phenylephrine, p = NS).

Discussion

Exercise hypotension is common in patients with HCM (1,2) and is associated with an increased risk of sudden death (3). It is due to an exaggerated fall in systemic vascular resistance, postulated to be related to profound activation of LV mechanoreceptors (1,2). To date, there has been no definite evidence of dysfunction of these receptors in patients with HCM.

This study has shown that patients with HCM have 1) either impaired forearm vasoconstriction or paradoxic vasodilation during application of subhypotensive LBNP, compared with age-matched control subjects; 2) a normal response both to handgrip and pressor response to alpha$_1$-adrenergic stimulation; and 3) integrated and carotid artery baroreceptor sensitivities similar to those of control subjects. These data, as will be discussed, suggest a dysfunction of cardiopulmonary (principally LV) mechanoreceptors during central blood volume unloading in patients with HCM. Mechanosensitive receptors located in the ventricles, atria and great veins (cardiopulmonary receptors), aortic arch and carotid sinus are normally tonically active. Carotid artery afferent fibers are carried in the glossopharyngeal nerve and cardiopulmonary and aortic arch afferent fibers in the vagus nerve to the brain stem. This tonic activity restrains sympathetic efferent activity and increases vagal afferent activity. Increased pressure further increases baroreceptor firing (causing vasodilation and bradycardia), and reduced pressure causes decreased firing, with the opposite effects (Fig. 2).

The rationale for the widespread use of subhypotensive LBNP to assess cardiopulmonary baroreceptor function is the belief that the attendant reduction in preload reduces tonic LV (and other cardiopulmonary) mechanoreceptor firing with a minimal influence on carotid artery and aortic arch mechanoreceptor firing. Although blood pressure does not fall during application of up to −20 mm Hg LBNP, changes in stroke volume may nevertheless alter the rate of change of pressure (dP/dt) and influence carotid artery baroreceptor function. Human studies suggest that cardiopulmonary baroreceptor inactivation is the principal cause of forearm vasoconstriction during subhypotensive LBNP (12,16), even though there may also be some carotid artery baroreflex inhibition. The observation of markedly impaired forearm vasoconstriction in heart transplant recipients suggests that LV mechanoreceptors are more important than other cardiopulmonary receptors in this response (17).

Reduced cardiopulmonary baroreceptor sensitivity in patients with HCM. Our data suggest that during subhypotensive central blood volume unloading induced by application of −15 mm Hg LBNP, there is reduced inactivation or increased paradoxic activation, or both, of cardiopulmonary baroreceptors in patients with HCM. Paradoxic vasodilator responses

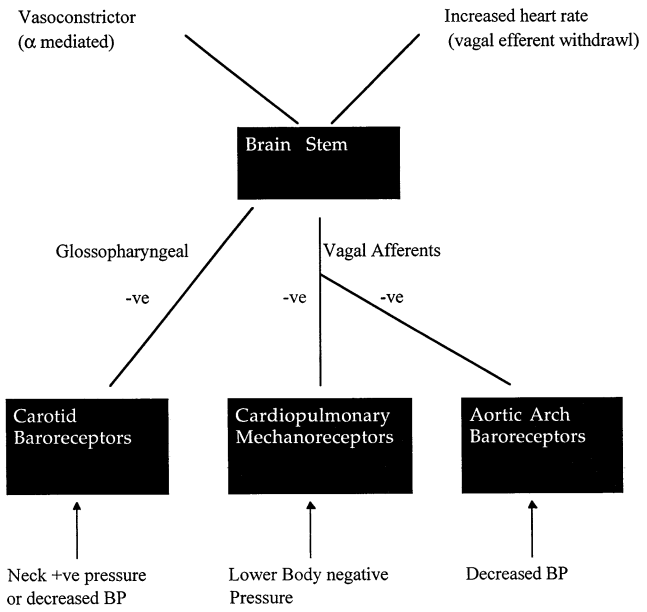


Figure 2. Diagram of the baroreflexes and mechanoreflexes investigated in this study. Cardiopulmonary baroreflexes are directly activated by a reduction in venous return (application of LBNP). Aortic baroreflexes are activated by a reduction in arterial blood pressure (BP). Afferent activity from both of these receptor groups traverses the vagus nerve to the brain stem. Afferent activity from the carotid artery baroreflexes (by application of positive [+ve] and negative [−ve] pressure to the neck) traverses the glossopharyngeal nerve to the brain stem. A normal response to these stimuli will produce an increase in both heart rate and vasoconstriction in an attempt to increase venous return.

were associated with a clinical history of syncope. There was no relation between impaired cardiopulmonary baroreceptor sensitivity and rest LV outflow tract gradient. We observed that −15 mm Hg LBNP did not provoke LV outflow tract gradients in patients without rest gradients, and furthermore did not significantly reduce LV diastolic dimension. These observations suggest that dynamic LV outflow tract gradients are unlikely to be an important mechanism of the abnormal FVR seen in most patients.

Our data suggest that the site of the abnormality of the cardiopulmonary baroreceptor reflex is probably in the afferent limb of the cardiac baroreflex (due to either a primary abnormality of the baroreceptors or local ventricular wall stresses). The observation of normal integrated and carotid artery baroreceptor function in patients with HCM suggests it is unlikely that the central processing of these baroreflex signals is abnormal. The normal response to handgrip implies that central command and skeletal metaboreceptor reflex arcs are intact. The normal pressor response to phenylephrine in patients with HCM implies that there is no impairment of peripheral responsiveness to alpha-adrenergic stimulation. Taken together, these data suggest that arterial baroreflex mechanisms, central processing and the efferent limb of the cardiac baroreflex are probably intact. Gilligan et al. (6) have previously reported a reduced Valsalva ratio and reduced heart rate variability during deep breathing in patients with HCM. The mechanism of this paradoxic activation of LV mechanoreceptors is conjecture. Myocyte disarray, which is associated with abnormal desmosome disposition (18), may result in marked focal abnormalities of LV wall stress, resulting in activation of these receptors. The possibility of a primary abnormality of the receptors cannot be excluded.

It is possible that abnormal local LV wall stresses, during both exercise and central hypovolemia, may be responsible for LV mechanoreceptor activation. This might be due to abnormal cardiac morphology. The development or exacerbation of LV outflow tract gradients during LBNP might be contributory in some cases, but our data suggest this is not an important mechanism. We have reported that similar abnormal reflex responses occur during exercise and during central hypovolemia in patients with vasovagal syncope (10,19,20). This raises the possibility of similar mechanisms of baroreflex dysfunction in the two conditions.

Significance of the findings. Comparable findings have been reported in patients with hypertensive LV hypertrophy, in whom similar mechanisms may be invoked (21). We and other investigators have also observed paradoxic vasodilation during central blood volume unloading in patients with severe heart failure (22–26). The mechanism in such patients may be different, and we have proposed that abolition of pericardial constraint and a diastolic–ventricular interaction may be important factors (27). None of the patients in the present study had LV systolic dysfunction, and their exercise capacity was only mildly limited.

We have previously reported exercise hypotension in approximately one-third of patients with HCM in association with paradoxic forearm vasodilation (1,2). Abnormal exercise blood pressure responses are associated with an increased risk of sudden death (3), and we and other investigators have proposed that hemodynamic collapse in the setting of an electrically unstable and perhaps ischemically compromised LV may be an important cause of sudden death (1,2,28,29).

However, ~50% of sudden deaths in patients with HCM are not related to exercise (30). Although primary arrhythmias may be responsible in at least some cases, our data suggest a substrate for hypotension in settings other than exercise. Indeed, a recent study demonstrated episodes of hypotension occurring during everyday life, both during and unrelated to exercise in patients with HCM (31). Central hypovolemia may provoke paradoxic cardiopulmonary baroreceptor activation with a consequent paradoxic fall in systemic vascular resistance and hypotension. This may provide a rationale for the observation of a high rate of positive tilt-table tests in patients with HCM (4). The association between abnormal forearm vascular responses during LBNP and a clinical history of syncope (itself a marker of increased risk of sudden death) is consistent with such a mechanism. Hypotension during central volume unloading might provide an additional or alternate trigger for malignant arrhythmias in some patients with HCM, although this is speculative.

Study limitations. The patients and control subjects were not exactly matched according to gender. There was a relative excess of men in the control group. However, there was no difference in cardiopulmonary, integrated or carotid artery gains between male and female control subjects; we therefore do not believe this bias is a significant limitation of the study.

Because central venous pressure fell equally in the patients with HCM and the control subjects, we have concluded that there was no evidence of exaggerated central hypovolemia in patients. However, because pressure is only an indirect reflection of volume, we cannot be certain of volume changes.

Although cardioactive drugs were withdrawn at least five half-lives before entry to the study, we accept that in the case of beta-blockers, beta-receptor upregulation may be present at this stage. However, excluding these patients from the analysis did not significantly alter the results.

Conclusions. The present study suggests that LV (and perhaps other cardiopulmonary) mechanoreceptors behave abnormally during central blood volume unloading in patients with HCM. This supports our previous suggestion that LV mechanoreceptors may be implicated in exercise hypotension in such patients (1,2). Hypotension occurring as a result of such mechanisms, during exercise or postural stress, may trigger a fatal arrhythmia. Consistent with this was our recent observation, in a prospective study, of an association between abnormal blood pressure responses during exercise and an increased risk of sudden death (3).

References

1. Frenneaux MP, Counihan PJ, Caforio AC, Chikamori T, McKenna WJ. Abnormal blood pressure responses during exercise in hypertrophic cardiomyopathy. Circulation 1990;82:1995–2002.
2. Counihan PJ, Frenneaux MP, Webb DJ, McKenna WJ. Abnormal vascular responses to supine exercise in hypertrophic cardiomyopathy. Circulation 1991;84:686–96.
3. Sadoul N, Prasad K, Eliot P, Bannerjee S, Frenneaux MP, McKenna WJ. Assessment of blood pressure responses during exercise as a risk marker of sudden death in hypertrophic cardiomyopathy. Circulation 1997;96:2987–91.
4. Gilligan DM, Nihoyannopoulos P, Chan WL, Oakley CM. Investigation of a haemodynamic basis for syncope in hypertrophic cardiomyopathy. Circulation 1992;85:2140–8.
5. Almquist A, Goldenberg J, Milstein S, et al. Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. N Engl J Med 1989;320:346–51.
6. Gilligan DM, Chan WL, Sbarouni E, Nihoyannopoulos P, Oakley CM. Autonomic function in hypertrophic cardiomyopathy. Br Heart J 1993;69:525–9.
7. Counihan PJ, Fei L, Bashir Y, Farrell TG, Haywood GA, McKenna WJ. Assessment of heart rate variability in hypertrophic cardiomyopathy: association with clinical and prognostic features. Circulation 1993;88(Pt 1):1682–90.
8. Tanabe T, Iwamoto T, Fusegawa Y, Yoshioka K, Shiina Y. Alterations of sympathovagal balance in patients with hypertrophic and dilated cardiomyopathies assessed by spectral analysis of RR interval variability. Eur Heart J 1995;16:799–807.
9. Fei L, Slade AK, Prasad K, Malik M, McKenna WJ, Camm AJ. Is there increased sympathetic activity in patients with hypertrophic cardiomyopathy? J Am Coll Cardiol 1995;26:472–80.
10. Thomson H, Wright K, Frenneaux M. Baroreceptor sensitivity in patients with vasovagal syncope. Circulation 1997;95:395–400.
11. WHO/ISFC Task Force. Report of the 1995 WHO/ISFC Task Force on the definition and classification of cardiomyopathy. Circulation 1996;93:841–2.
12. Eckberg D, Sleight P. Human Baroreflexes in Health and Disease. Oxford: Oxford Medical Publishing, 1992:194–6.
13. Hokanson DE, Sumner DS, Strandness E. An electrically calibrated plethysmograph for direct measurement of limb blood flow. IEEE Trans Biomed Eng 1975;22:21–5.
14. Smyth HS, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man: a quantiative method of assessing baroreflex sensitivity. Circ Res 1969;24:109–21.
15. Eckberg D, Cavanaugh MS, Mark AI. A simplified neck suction device for activation of carotid baroreceptors. J Lab Clin Med 1975;85:167–73.
16. Abboud FM, Eckberg DL, Johannsen UJ, Mark AL. Carotid and cardiopulmonary baroreceptor control of splanchnic and forearm vascular resistance during venous pooling in man. J Physiol 1979;286:173–84.
17. Mohanty P, Thames M, Arrowood J, Soweres J, McNemara C, Szentpetery S. Impairment of cardiopulmonary baroreflex after cardiac transplantation in humans. Circulation 1987;75:914–21.
18. Sepp R, Severs N, Gourdie R. Altered patterns of cardiac intercellular distribution in hypertrophic cardiomyopathy. Heart 1996;76:412–7.
19. Thomson H, Lele S, Atherton J, Wright K, Stafford W, Frenneaux M. Abnormal forearm vascular responses during dynamic leg exercise in patients with vasovagal syncope. Circulation 1995;92:2204–9.
20. Thomson H, Atherton J, Khafagi F, Frenneaux M. Failure of reflex venoconstriction using exercise in patients with vasovagal syncope. Circulation 1996;93:953–9.
21. Giannttasio C, Cattaneo BM, Seravalle G, Grassi G, Mancia G. Left ventricular hypertrophy and the 'cardiogenic reflex' in man. J Hypertension 1991;9 Suppl 2:S43–50.
22. Atherton J, Thomson H, Moore T, et al. Diastolic ventricular interaction: a possible mechanism for abnormal vascular responses during volume unloading in heart. Circulation. In press.
23. Creager MA, Hirsch AT, Dzau VJ, Nabel EG, Cutler SS, Colucci WS. Baroreceptor regulation of regional blood flow in congestive heart failure. Am J Physiol 1990;258:H1409–14.
24. Ferguson DW, Abhoud FM, Mark AL. Selective impairment of baroreflex-mediated vasoconstrictor responses in patients with ventricular dysfunction. Circulation 1984;69:451–60.
25. Golsmith SR, Francis GS, Levine TB, Coln JN. Regional blood flow response to orthostasis in patients with congestive heart failure. J Am Coll Cardiol 1983;1:1391–5.
26. Nishian K, Kawashima S, Iwasaki T. Paradoxical forearm vasodilatation and haemodynamic improvement during cardiopulmonary baroreceptor unloading in patients with congestive heart failure. Clin Sci 1993;84:271–80.
27. Atherton JJ, Moore TD, Lele SS, et al. Diastolic ventricular interaction in chronic heart failure. Lancet 1997;349:1720–4.
28. McKenna WJ, Camm AJ. Sudden death in hypertrophic cardiomyopathy: assessment of patients at high risk. Circulation 1989;80:1489–92.
29. Thomson H, Lele S, Frenneaux M. Sudden death in hypertrophic cardiomyopathy. Eur J Pacing Electrophysiol 1994;3:190–5.
30. Maron BJ, Roberts WC, Epstein SE. Sudden death in hypertrophic cardiomyopathy: a profile of 78 patients. Circulation 1982;65:1388–94.
31. Prasad K, Sneddon J, Gould M, McKenna W. Episodic hypotension during daily activity in hypertrophic cardiomyopathy and propensity to sudden death: utility of beat to beat blood pressure monitoring [abstract]. Heart 1997;77 Suppl 1:168.