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Patterns of cardiac dysfunction coinciding with exertional breathlessness in hypertrophic cardiomyopathy

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ABSTRACT

Objective: The commonest cause of breathlessness in hypertrophic cardiomyopathy (HCM) is left ventricular outflow tract (LVOT) obstruction which improves with its removal. However, in the absence of outflow tract obstruction, as in dilated cardiomyopathy, patients may be limited by similar symptoms, thus suggesting a potential common mechanism for the two conditions. We aimed to assess cardiac function at the time of symptoms in a group of unselected patients with HCM to identify other patterns of cardiac dysfunction which coincide with their breathlessness.

Methods: We studied 37 HCM patients (aged 55 ± 15 years, 13 female) with septal thickness >15 mm and 17 controls (aged 58 ± 12 years, 12 female) using Doppler echocardiography, at rest and at peak dobutamine stress. Stress end points were symptoms, >20 mm Hg drop in systolic blood pressure, arrhythmia, or maximum dobutamine dosage of 40 μg/kg/min.

Results: At rest: LV systolic function was maintained (EF 68 ± 7 v 76 ± 12%, respectively), LVOT velocity raised ($p < 0.005$), lateral and septal long axis amplitude reduced ($p < 0.05$ and $p < 0.005$, respectively) and dyssynchronous and QRS duration was also broader ($p < 0.005$) in patients compared to controls. *At peak stress*: Overall LVOT velocities were higher in patients than controls (4.3 ± 1.7 v 1.7 ± 1.0 m/s, $p < 0.005$, respectively) due to systolic anterior movement of the mitral valve and mitral regurgitation developing. In the 15 patients who did not develop significant LVOT obstruction (velocity <4 m/s), LV ejection time increased and peak systolic amplitude did not increase. In the 10 patients with neither LVOT obstruction nor restrictive filling, QRS duration prolonged by 12 ms ($p < 0.05$), post-ejection shortening worsened and peak systolic amplitude fell ($p < 0.005$). Also, LV ejection time prolonged by 5 s/min ($p < 0.05$), filling time failed to increase as it did in controls ($p < 0.005$) and Tei index was higher than controls ($p < 0.01$).

Conclusion: Exertional breathlessness in HCM is associated with LV outflow tract obstruction and functional mitral regurgitation in almost two thirds of patients. The remaining one third have either resistant restrictive physiology or dyssynchronous cavity at fast heart rate. Despite similar exercise limiting breathlessness in the three groups, means of management should be quite different.

1. Introduction

Breathlessness is the commonest symptom in patients with hypertrophic cardiomyopathy (HCM) which in the majority has been shown to be related to left ventricular outflow tract obstruction (LVOT). While this pattern used to be a diagnostic feature of the syndrome, other phenotypic presentations are now well documented and clearly described, i.e. apical hypertrophy, which does not cause LVOT obstruction. Once the diagnosis of LVOT obstruction as the cause of resistant breathlessness to medical therapy is made, other management options are sought including surgical myectomy [1], non-surgical septal reduction by alcohol injection in the septal branches of the left anterior descending artery [2] or dual chamber pacing (DDD) [3,4]. All these procedures aim at removal of the LVOT obstruction with its consequences. Symptomatic response to these treatments varies, in keeping with the broad phenotypic spectrum of the disease. Indeed, patients in whom such procedures prove successful in abolishing or reducing the outflow tract obstruction may continue to complain of residual exercise-limiting symptoms. This suggests other mechanisms such as arrhythmia or stiff left ventricle and restrictive physiology with raised left atrial pressure, and hence pulmonary venous hypertension and breathlessness [5].

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We hypothesized that in the absence of LVOT obstruction exertional breathlessness could be caused by either restrictive LV physiology or cavity dyssynchrony, similar to what is seen in dilated cardiomyopathy. The aim of this study therefore was to assess cardiac electrical and mechanical function at the time of symptoms in a group of HCM patients, and determine potential mechanisms that explain their breathlessness, which should guide towards optimum management.

2. Methods

We studied 37 HCM patients (Table 1), with clear echocardiographic evidence for LV hypertrophy (wall thickness ≥15 mm) irrespective of its distribution, concentric or asymmetrical, (mean age 55 ± 15 years and 13 female). Patients were in NYHA class II, and none had coronary artery disease on conventional angiography, atrial fibrillation, dilated LV, previous heart surgery, pacemaker, valve disease or pulmonary disease. Patients were compared with 17 normal controls, (mean age 58 ± 12 years, 12 female) who were consecutive individuals presenting with atypical chest discomfort and who proved to have normal cardiac function on echocardiography and no evidence for coronary artery disease on coronary angiography or ischemic myocardial dysfunction on myocardial perfusion scanning. None of the controls had systemic disease, diabetes, hypertension or cardiac risk factors. All participants provided written informed consent; the study was approved by the institutional ethics committee.

2.1. LV segmental function

Patients and controls underwent resting and stress transthoracic Doppler echocardiographic examination using the conventional dobutamine stress protocol. The echocardiograms were performed with the subject in the semi lateral supine position using a Hewlett Packard Sonos 5500 echocardiograph (Andover, MA) interfaced to a multi-frequency transducer. Two-dimensional guided M-mode echograms of the LV, left atrium, aortic root and mitral valve were recorded from the parasternal short and long axis views according to the recommendations of the American Society of Echocardiography (ASE) [6]. LV systolic and diastolic dimensions, septal and posterior wall thickness and left atrial diameter were all measured using leading edge methodology. LV long axis function was also studied from the apical four-chamber view with the M-mode cursor positioned at the lateral and septal angles of the mitral ring. Systolic long axis amplitude of motion was measured and defined as the extent of mitral annulus displacement [7–10] between the onset of QRS and end-ejection, at the time of aortic valve closure A2, the first high frequency component of the second heart sound on the phonocardiogram. Post-ejection shortening (PES), a sign of dyssynchrony [11–13] was measured as the amplitude of further inward long axis movement after A2. LV long axis myocardial velocities were recorded using Tissue Doppler Imaging (TDI) technique with the pulsed wave Doppler sample volume placed at the basal region of the lateral and septal segments, adjacent to the mitral ring. Care was taken to align the echo image so that the ring motion was parallel to the Doppler TDI cursor. A Doppler velocity range of −30 to 30 cm/s was selected using the lowest wall filter settings and the minimum optimal gain at a sampling rate of 100 Hz. From the TDI recordings lateral and septal segment systolic - s′ and early diastolic velocity - e′ velocities were measured.

2.2. LV global function measurements

LVOT velocities were recorded from the apical 5 chamber view using continuous wave Doppler and peak velocities were taken at mid systole rather than those in late-systole, which reflect mid-cavity obliteration. LV filling velocities were obtained from the apical 4 chamber view using pulsed wave Doppler with the sample volume positioned by the tips of the mitral valve leaflets, from which peak early diastolic 'E' wave and atrial systolic 'A wave' velocities were recorded. A number of time intervals in the cardiac cycle were measured. LV ejection time was taken from the onset of ejection to A2 or the aortic valve closure artefact on the pulsed Doppler recording. LV filling time was measured from the onset of the transmitral E wave to the end of the A wave. Summation LV filling pattern was diagnosed when E and A waves were superimposed; filling time was then measured as the total duration of the trans-mitral flow pulse. LV ejection time and filling time were presented as the product of the corresponding time interval multiplied by the heart rate and expressed in seconds per minute. Global markers of LV dyssynchrony were taken as: total isovolumic time (t-IVT) calculated as [60 − (total Filling + total ejection time)] [14] and Tei index calculated as t-IVT divided by ejection time [15,16]. Transmitral E/A and E/e′ were calculated to gauge raised left atrial pressure [17]. Restrictive LV filling was defined as E/A >2 and E wave deceleration time of <140 ms. Mitral regurgitation severity was assessed from colour Doppler mitral regurgitant jet area with respect to that of the left atrium. All records were acquired at rest and peak stress at a speed of 100 mm/s with an ECG (lead II) and a phonocardiogram superimposed.

Table 1
LV measurements: patients vs controls.

	Controls $n = 17$	HCM $n = 37$
Age	58 ± 12	55 ± 15
Left atrial diameter (cm)	3.8 ± 0.4	4.1 ± 0.9
LV end systolic diameter (cm)	3.3 ± 0.5	2.7 ± 0.8◦◦
LV end diastolic diameter (cm)	5.0 ± 0.4	4.2 ± 0.7◦◦◦
Septal thickness (cm)	1.0 ± 0.25	2.5 ± 0.58◦◦◦
Posterior wall thickness (cm)	0.7 ± 0.12	1.75 ± 0.42◦◦◦
Ejection fraction (%)	68 ± 7	76 ± 12

Values are mean ± SD.
HCM v controls $\circ p < 0.05$, $\circ\circ p < 0.01$, $\circ\circ\circ p < 0.005$.

2.3. Dobutamine stress protocol

Dobutamine was administered via an infusion pump (IVAC 770 syringe driver), starting at a dose of 5 μg/kg/min and increasing every 3 min by a similar amount to a maximum dose of 40 μg/kg/min. Systolic and diastolic blood pressures were measured automatically at the end of each stage of stress using a blood pressure Dinamap monitor (Criticon, Tampa, Fl., USA). Likewise, 12 lead ECG and oxygen saturation were recorded at the end of each stress stage. Patients on β blockers were asked not to take them 48 h before the test. Pre-determined stress end points for patients and controls were: reaching 85% predicted target heart rate (200 minus age in years) or the maximum dobutamine dose (corresponding to stage 8 of the dobutamine protocol), development of breathlessness, ST segment shift ≥2 mm, T-wave inversion, and/or a 20 mm Hg drop in systolic blood pressure. All clinical and Doppler echocardiographic measurements were made at rest and peak dobutamine stress.

2.4. Electrocardiogram

A standard 12-lead electrocardiogram (ECG) was recorded at rest and at the end of each stage of dobutamine stress using a Hewlett-Packard Pagewriter Xli (Andover, MA, USA), with a built in analysis software. Heart rate and all ECG intervals were measured automatically and registered on a printed chart at a speed of 25 mm/s. The frequency response of the machine was 0.05 to 150 Hz with the baseline filter (0.4 Hz) inactivated. The ST segment shift was measured manually, 80 ms after the J point in the lead showing the most change.

3. Statistics

Statistical analysis was performed using SPSS (SPSS Inc, Chicago, IL, USA). Results are presented as mean ± SD. Resting and stress values between groups were compared using unpaired Student's *t*-test and within groups using the paired *t*-test. A *p*-value < 0.05 was considered statistically significant. Correlations were calculated using linear regression analysis. The 95% confidence intervals were determined using Fisher's r-to-Z transformation.

4. Results

4.1. Clinical findings (Table 2)

4.1.1. At rest

There was no difference in heart rate between patients and controls but QRS was broader in patients ($p < 0.001$). Patients were not hypertensive with a mean blood pressure of 132/74 mm Hg.

4.1.2. At peak stress

All controls reached the end of the stress protocol (40 μg/kg/min dobutamine) which was terminated prematurely in patients (20–30 μg/kg/min dobutamine) because of breathlessness in all. No patient developed significant arrhythmia but 12 developed 1.5 mm ST shift. Although the heart rate increased equally in patients and controls (by +42 vs. +43 bpm, $p < 0.001$ from baseline) QRS duration increased by 7 ms in patients ($p < 0.01$) and fell by 4 ms in controls (p = NS). Systolic blood pressure dropped by ≥20 mm Hg in 5 patients (14%), but mean arterial pressure was unchanged (93 ± 13 vs. 95 ± 17 mm Hg).

4.2. Ventricular function (Tables 1 & 2)

4.2.1. At rest

Patients had normal LV cavity size with maintained ejection fraction, an inclusion criterion. Peak LVOT velocity was higher in patients than