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Long mitral valve leaflets determine left ventricular outflow tract obstruction during exercise in hypertrophic cardiomyopathy☆

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ABSTRACT

Background: Development of left ventricular outflow tract obstruction (LVOTO) in patients with hypertrophic cardiomyopathy (HCM) is important for explaining symptoms and designing management. LVOTO is mostly caused by a combination of septal hypertrophy and systolic anterior movement of the mitral valve (SAM). The aim of the present study was to determine predictors of exercise induced LVOTO in a group of HCM patients.
Methods: We performed supine exercise Doppler echocardiography, including measurements of LV morphology and function and anterior mitral leaflet length, in 51 mildly symptomatic HCM (septal thickness ≥ 15 mm) and compared them with 50 healthy controls. Measurements were made at 1) rest, 2) Valsalva maneuver, 3) peak exercise and 4) post exercise. LVOTO was diagnosed as a LVOT gradient of >30 mm Hg at rest, after Valsalva and after exercise or ≥50 mm Hg at peak exercise.
Results: All patients stopped exercise because of exhaustion. 35% of the patients had resting LVOTO and 48% during Valsalva. At peak exercise, only 37% had LVOTO, who increased to 64% post exercise. Patients who developed LVOTO at peak exercise were more prone to continue having it post exercise ($p < 0.001$), to have attenuated systolic blood pressure rise ($p = 0.011$) and to have long anterior mitral valve leaflets ($p < 0.001$). Backward multiple regression analysis showed the anterior mitral leaflet length as the strongest single independent predictor ($\beta = 0.36$, $p = 0.010$) for increased LVOT velocities, followed by basal septal thickness.
Conclusion: In patients with HCM, LV outflow tract obstruction seems to be relatively uncommon during exercise but rather occurring minutes after stopping exercise. Exercise LVOTO seems to be determined by long anterior mitral leaflets in addition to the well established septal hypertrophy.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited genetic cardiac disease characterized by increased left ventricular (LV) wall thickness and myocardial fiber disarray. In addition to the LV hypertrophy, which might take various shapes and forms, myocardial thickness may predominantly affect the basal septal region and cause LV outflow tract obstruction (LVOTO) which may cause symptoms e.g. breathlessness and syncope [1]. HCM patients also vary in their presentation from being clinically silent, for years, to having heart failure and even sudden cardiac death (SCD) as the first presentation, although rare. [1].

Thus, LVOTO is an important component for risk stratification in HCM [2], being related to the above symptoms and complications [3], but such relationships have been studied mainly at rest [3,4]. The mechanism behind LVOTO is primarily increased septal thickness and systolic anterior movement (SAM) of one or both mitral valve leaflets against the basal septal region with increased heart rate, which by the Venturi effect results in perpetual increase in OT velocities and pressure drop. This is contributed to by the anatomical location of myocardial hypertrophy, aortoseptal angulation, papillary muscle position, chordal anatomy and LV cavity size. Consequently, significant LVOTO attenuates the normal rise in systolic blood pressure and hence symptoms development. LVOTO has also been shown to be dynamic, occurring in 70% of patients post exercise [5,6], commonly due to long anterior mitral valve leaflets. Therefore, determining the exact cause for LVOTO as well as its relationship to symptoms is crucial for proposing optimum treatment strategies [7]. Thus, in view of the number of factors contributing to the development of LVOTO with its significant clinical consequences we sought to test the hypothesis that long anterior mitral leaflet is a predictor of dynamic LVOTO during exercise.

2. Methods

Subjects: We prospectively investigated 51 mildly symptomatic HCM patients (mean age 60 ± 13 year, 23 females) between 2007 and 2015 based on clinical evaluation and echocardiographic confirmation of wall thickness ≥ 15 mm [1]. Patients were compared with 50 healthy controls

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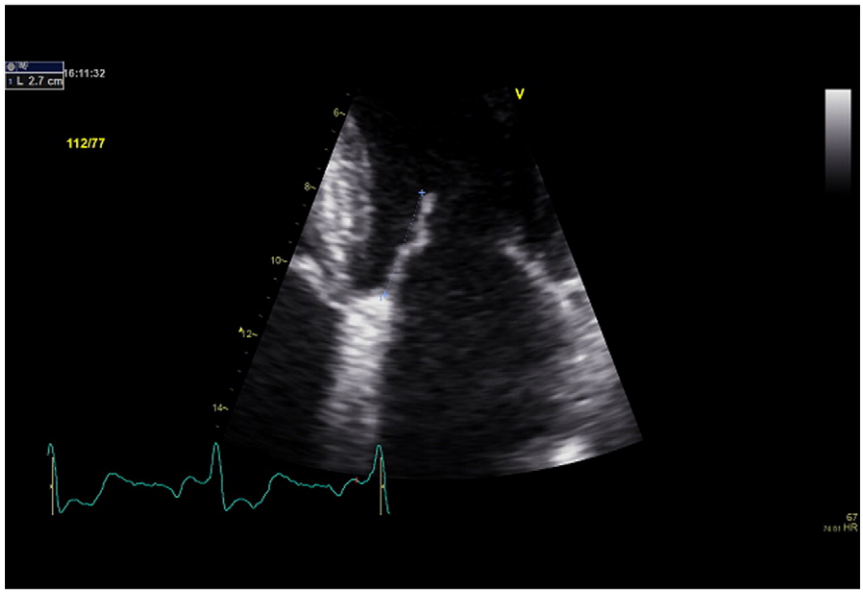

Fig. 1. Measurement of anterior mitral leaflet length in apical four-chamber view.

(mean age 51 ± 13 year, 22 females) without any history of cardiovascular disease who were not on any medication. Patients and controls underwent Doppler echocardiographic examination (PL, SA and CB) using the same protocol and images was analyzed by one investigator (PL).

3. Methods

3.1. Resting echocardiograph

All subjects underwent conventional Doppler echocardiographic examination including detailed measurements of LV morphology and function according to the American and European recommendations [8,9]. For morphological cardiac assessment, measurements of interventricular septal thickness (IVSt) and posterior wall thickness (PWt) were made from the parasternal long-axis views and 2D measurements and total LV wall thickness was calculated (IVSt + PWt). Anterior septal to posterior wall thickness ratio (IVSt/PWt) was also calculated to assess the degree of asymmetrical hypertrophy. From the apical four- and two-chamber views, left atrial (LA) end systolic volumes (LAVI), LV end diastolic (EDVI) and end systolic (ESVI) volumes were measured and indexed (I) to body surface area (BSA). LV ejection fraction (LVEF) was estimated using Simpson's biplane model. From the pulsed wave Doppler recordings of LV filling, early (E) and late (A) diastolic velocities, E/A ratio and E wave deceleration time were measured in order to assess LV diastolic function. Peak systolic velocities across the LV outflow tract (LVOT) were measured using continuous wave Doppler velocities. LVOT velocities were measured at rest, after Valsalva maneuver (performed in 29 HCM patients), at peak exercise and 4 min after exercise (post exercise). Pulsed wave Doppler was also used to differentiate between mitral regurgitation and LVOT velocities with the onset of the former normally starting at the onset of the R wave and the latter starting >30 ms after the R wave of the superimposed ECG. LVOTO was also confirmed when showing a flow pattern with peak velocity at mid systole in contrast with late systolic ones that manifest intracavitary obliteration. From pulsed Doppler myocardial velocity recordings, the peak longitudinal early diastolic velocities (e′) were measured at LV lateral wall, from which the E/e′ ratio was calculated, to reflect the degree of rise of LA pressure. From apical four chamber view the anterior mitral leaflet (AML) length was measured, at end-diastole, between the leaflet tip and the point of its attachment to the mitral annulus from the apical four-chamber view, Fig. 1.

3.2. LV myocardial deformation analysis

Speckle tracking studies were performed from the B-mode apical four-chamber view to assess LV longitudinal deformation by strain rate measurements. The delineation was traced manually using a region of interest (ROI) and the software automatically defined LV longitudinal strain rate throughout the cardiac cycle. Care was taken to place the ROI within the myocardium, not entering LV blood pool or the pericardium [10]. Global LV longitudinal strain rate (GLSr) was measured at end

Table 1
Patient's demographic data.

	Controls (50)	HCM (51)	P-Value	HCM LVOTO exercise (≥50 mm Hg) [19]	HCM non-LVOTO exercise (<50 mm Hg) (32)	P-Value
Age, years	51 ± 13	60 ± 13	<0.001	56 ± 13	62 ± 12	ns
Female, n (%)	23(46)	22(44)	ns	4(27)	19(51)	ns
Systolic blood pressure, mm Hg	131 ± 15	138 ± 23	0.07	146 ± 23	138 ± 23	ns
Diastolic blood pressure, mm Hg	81 ± 9	80 ± 11	ns	79 ± 14	80 ± 10	ns
Height, cm	172 ± 10	172 ± 111	ns	177 ± 11	170 ± 9	0.02[a]
Weight, kg	75 ± 15	83 ± 16	0.02	88 ± 19	80 ± 14	ns
Heart rate, bpm	71 ± 13	71 ± 14	ns	73 ± 11	71 ± 15	ns
Betablockers, n (%)	–	48(92)		14(93)	33(89)	ns
ACE-inhibitors, n(%)	–	19(56)		4(27)	16(43)	ns

Ns = P > 0.1.
[a] = confirmed with non-parametric *t*-test, Mann–Whitney.