

Left ventricular outflow obstruction occurs immediately after exercise in patients with non-obstructive hypertrophic cardiomyopathy

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We evaluated the hemodynamic and geometric determinants of latent obstruction (LO, trans-left ventricular outflow tract (LVOT) gradient ≥ 30 mmHg with provocation) in patients with non-obstructive hypertrophic cardiomyopathy (HCM). A total of 35 patients with non-obstructive HCM underwent stepwise supine bicycle exercise echocardiography. Trans-LVOT pressure gradients, mitral geometric parameters, left ventricular ejection fractions (LVEF) and left ventricular end-systolic and diastolic dimensions (LVESD, LVEDD) were measured at each stage. The highest peak LVOT pressure gradient predominantly occurred immediately after exercise ($n = 32$, 91.3%) rather than during peak exercise ($n = 3$, 8.7%). Significant LO developed in nine patients (25%). No significant differences were found in resting echocardiographic parameters. Compared to the remaining patients, however, patients with LO had longer residual mitral leaflets (defined as residual portions of leaflets after coaptation; 4 ± 4 vs. 13 ± 4 mm, respectively; $p = 0.001$) and higher resting LVOT pressure gradients (7.4 ± 3.7 vs. 12.9 ± 5.8 mmHg, respectively; $p = 0.001$). Substantial decreases in mitral annular diameters from peak exercise to recovery after exercise were observed in the LO group, while mitral annular diameters increased after exercise in the non-LO group. In conclusion, the highest peak LVOT pressure gradient predominantly occurred immediately after exercise rather than during peak exercise, regardless of LO. Abrupt decrease of mitral annular diameter immediately after exercise, a longer residual mitral leaflet and a higher resting LVOT pressure gradient at rest might be related to LO.

Keywords

Latent obstruction; Non-obstructive hypertrophic cardiomyopathy

1. Introduction

Obstruction of the left ventricular outflow tract (LVOT) is an important pathophysiologic component of hypertrophic cardiomyopathy (HCM) [1]. Resting outflow gradients are independent determinants of progressive heart failure symptoms and cardiovascular mortality [2, 3]. Resting LVOT obstruction, however, has been classically reported to be present in only 20% to 25% of patients with HCM [4, 5]. Indeed, Maron *et al.* [1] showed that among HCM patients

who sought clinical evaluation, inducible LVOT obstruction was identified in as high as 70%. Also, Shah *et al.* [6] demonstrated that approximately two-thirds of 87 patients with symptomatic non-obstructive HCM had latent obstruction (LO). Recently, Vaglio *et al.* [7] documented that LO in HCM is an adverse prognostic indicator in patients with HCM. These findings suggest that all patients with non-obstructive HCM should be diagnosed using provocative maneuvers to identify LO. Despite LO having been shown to be associated with poorer prognosis in patients with non-obstructive HCM, hemodynamic and geometric determinants of LO are not fully understood. In addition, provocative methods to induce LO have not been standardized.

We evaluated the pathophysiology of exercise-induced LO in non-obstructive HCM with a single exercise protocol. In addition, we sought to identify the determinants of LO, including morphologic and hemodynamic parameters.

2. Materials and methods

2.1 Patients

Thirty-five patients with non-obstructive HCM (resting trans-LVOT gradient < 30 mmHg) were examined with stepwise supine bicycle exercise echocardiography after comprehensive resting echo-Doppler evaluations between January 2008 and May 2009. The diagnosis of HCM was based on the echocardiographic demonstration of a non-dilated, hypertrophied LV in the absence of other cardiac or systemic diseases that could cause LV hypertrophy. Patients were eligible for the study if they had non-obstructive HCM and structurally normal mitral valves. None of the patients had resting obstructive HCM, structural mitral valve or subvalvular lesions, or other cardiac disease, including organic valvular, pericardial, congenital, or infiltrative heart disease. If the patients had been prescribed beta-blocker, they requested to stop beta-blocker at least 3 days before the exercise echocardiography.

2.2 Exercise echocardiography

Echocardiographic studies were performed at baseline according to the recommendations of the American Society of Echocardiography. Left ventricular outflow tract gradients were measured with continuous-wave Doppler interrogation directly parallel to the LVOT in the apical five-chamber view under direct visualization. Also, the data examined included left ventricular ejection fraction (LVEF), left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension (LVEDD), maximal septal wall thickness and mitral geometric parameters such as mitral annular diameter and mitral leaflet length (which was defined as the distance from the anterior mitral leaflet tip to the point of its attachment to the mitral annulus). Residual mitral leaflets were defined as residual portions of leaflets after coaptation (Fig. 1).

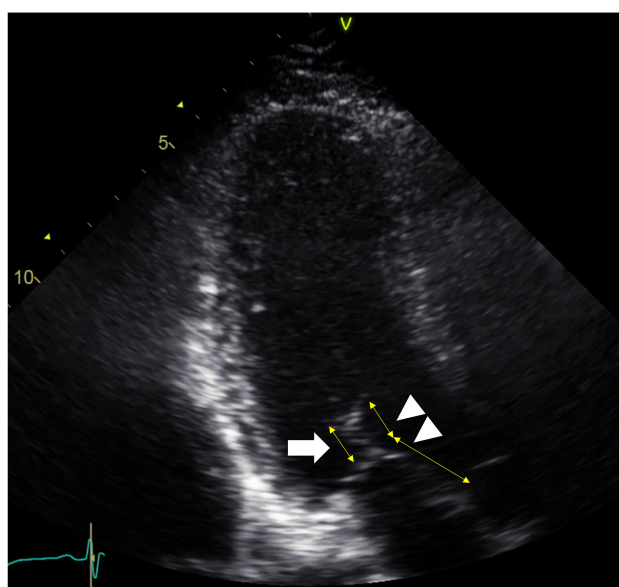


Fig. 1. Mitral leaflet length was defined as the distance from the anterior mitral leaflet tip to the point of its attachment to the mitral annulus (two white arrow heads). Residual mitral leaflet was defined as residual portions of leaflets after coaptation (white arrow).

After resting images were obtained, images were taken as the patients performed bicycle ergometry at two-minute workloads of 25, 50, 75, 100, 125, 150 and 175 watts. Images were also taken immediately post-exercise and after resting for one minute and three minutes. Images in three planes were viewed (apical five-chamber view, apical four-chamber view, and parasternal long view). Trans-LVOT pressure gradient, mitral geometric parameters, LVEF, LVESD, and LVEDD were measured at each stage.

LO was defined as a left ventricular outflow pressure gradient <30 mmHg at rest that increased to ≥ 30 mmHg with provocation [8].

Patients were divided into two groups according to the development of LO (LO group and non-LO group).

2.3 Statistical analysis

All analyses were performed using the SPSS statistical package version 25 (IBM Corp., Armonk, NY, USA). Differences between the LO group and the non-LO group were analyzed by Student's *t* tests or Mann-Whitney tests for continuous variables. Categorical variables, expressed as numbers or percentages, were analyzed using the chi-square test or Fisher's exact test. Comparisons of changes in the morphologic and hemodynamic parameters between groups at each stage were by two-way analysis of variance. *p* values < 0.05 were considered statistically significant.

3. Results

The mean age of subjects at initial evaluation was 49.4 ± 13.9 years. There were 24 men and 11 women in the study sample. All patients were clinically stable and in sinus rhythm. In 26 patients (75%), LO could not be induced in response to exercise provocation. Significant LO developed in a total of nine patients (25%). The correlations between baseline clinical and echocardiographic characteristics associated with a response to exercise are listed in Tables 1 and 2, respectively. Between the two groups, gender, medical therapy, resting hemodynamics, left ventricular dimensions, and ejection fractions were comparable. Compared to the remaining patients, however, patients who had LO in response to exercise provocation were characterized by a longer residual mitral leaflet (4 ± 4 mm vs. 13 ± 4 mm, $p = 0.001$) and a higher resting LVOT pressure gradient (7.4 ± 3.7 mmHg vs. 12.9 ± 5.8 mmHg, $p = 0.001$).

Changes in heart rate and blood pressure differed significantly at each stage, and there were no differences between the two groups (Table 3). The mean LVEF, LVESD, and LVEDD did not differ significantly at each stage or between groups. However, mitral annular diameter decreased from peak exercise to post-exercise only in the LO group, while there were no changes in the non-LO group (-7.0 ± 2.1 mm vs. 0.5 ± 2.0 mm, $p = 0.001$) (Fig. 2).

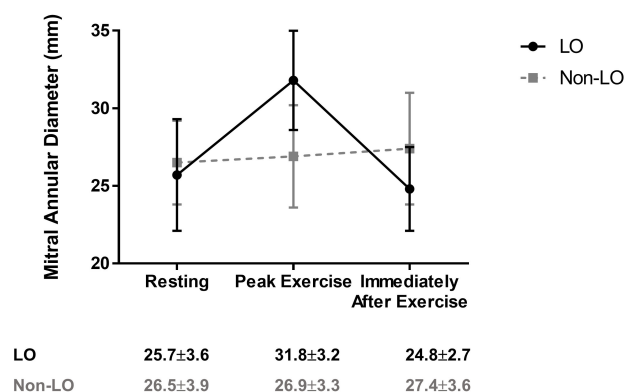


Fig. 2. Change in mitral annular diameter during exercise in both groups.

Table 1. Baseline clinical characteristics of the study cohort.

	Non-LO (n = 26)	LO (n = 9)	p value
Age (years)	46 ± 19	51 ± 12	0.346
Male (n, %)	73.1% (n = 19)	55.6% (n = 5)	0.329
Hypertension (n, %)	53.8% (n = 14)	44.4% (n = 4)	0.711
DM (n, %)	3.8% (n = 1)	11.1% (n = 1)	0.454
Smoking history (n, %)	50.0% (n = 13)	33.3% (n = 3)	0.460
Dyslipidemia (n, %)	23.1% (n = 6)	22.2% (n = 2)	0.958
Systolic blood pressure (mmHg)	126.6 ± 17.2	124.6 ± 17.8	0.857
Diastolic blood pressure (mmHg)	77.3 ± 12.2	73.4 ± 9.5	0.183
Medication (n, %)			
Beta-blocker	42.3% (n = 11)	22.2% (n = 2)	0.282
Calcium channel blocker	30.8% (n = 8)	22.2% (n = 2)	0.625
ACE inhibitor/ARB	50.0% (n = 13)	33.3% (n = 3)	0.460

Values are presented as n (%) or mean ± SD; LO, Latent Obstruction; DM, Diabetes Mellitus; ACE, Angiotensin-Converting Enzyme; ARB, Angiotensin Receptor Blocker.

Table 2. Baseline echocardiographic characteristics of the study cohort.

	Non-LO (n = 26)	LO (n = 9)	p value
LVEF (%)	68.2 ± 6.6	72.8 ± 4.8	0.064
E/E'	12.6 ± 4.7	11.8 ± 4.5	0.366
LA volume index	30.6 ± 12.5	30.0 ± 9.5	0.439
RVSP (mmHg)	12.5 ± 7.5	23.3 ± 8.1	0.651
Mitral leaflet length (cm)	2.6 ± 0.3	2.8 ± 0.4	0.185
LVOT PG (mmHg)	7.4 ± 3.7	12.9 ± 5.8	0.001
Maximal septal wall thickness (mm)	15.7 ± 4.3	13.6 ± 3.3	0.184
Residual mitral leaflet length (mm)	4 ± 4	13 ± 4	0.001

Values are presented as n (%) or mean ± SD.

LO, Latent Obstruction; LVEF, Left Ventricular Ejection fraction; LA, Left Atrial; RVP, Right Ventricular Systolic Pressure; LVOT PG, Left Ventricular Outflow Tract Pressure Gradient.

Fig. 3 illustrates the change in gradient profile at each stage for individual patients. The highest peak LVOT pressure gradient predominantly occurred immediately after exercise (n = 32, 91.3%) rather than during peak exercise (n = 3, 8.7%). Three patients complained of significant ongoing problems (presyncope, syncope, and chest discomfort) immediately after exercise. When these patients were compared to the remaining patients with echocardiographic parameters, sudden large LVOT gradients developed from peak exercise to immediately after exercise.

4. Discussion

The term latent obstruction (LO) has been used to describe gradients that only appear with provocation [9]. Although many mechanisms have been proposed to explain the pathophysiology of exercise-induced LO in non-obstructive HCM, the precise mechanism of its onset and cessation remain undefined. Various physical and pharmacologic maneuvers (e.g., catecholamine-stimulating drugs such as dobutamine and isoproterenol, Valsalva maneuvers, amyl nitrite inhalation, and premature ventricular contractions) have

Table 3. Heart rate and blood pressure during exercise echocardiography.

	Non-LO (n = 26)	LO (n = 9)	p value
Baseline			
HR	64.0 ± 9.9	69.1 ± 9.5	0.838
SBP	126.8 ± 16.2	121.1 ± 12.4	0.500
DBP	78.0 ± 10.7	72.4 ± 8.4	0.173
Peak exercise			
HR	126.6 ± 21.1	128.7 ± 28.8	0.516
SBP	181.3 ± 28.5	172.4 ± 23.2	0.157
DBP	91.4 ± 15.3	82.7 ± 13.2	0.707
Immediately post-exercise			
HR	106.7 ± 17.8	113.1 ± 22.5	0.293
SBP	168.2 ± 27.1	160.2 ± 27.4	0.691
DBP	75.3 ± 11.2	74.2 ± 15.3	0.112

Values are presented as mean ± SD.

LO, Latent Obstruction; HR, Heart Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

been used for the induction of pressure gradients in both cardiac catheterization and echocardiography laboratories. The problem with these methods is that they do not reliably reproduce the physiological circumstances in which LO is likely to occur [8, 10]. Recently, it has been proposed that exercise is the only provocative method that is truly physiologic and is therefore the most analogous to conditions under which HCM patients develop symptoms [1, 6].

We studied a selected group of patients with non-obstructive HCM using Doppler echocardiography both to evaluate the pathophysiology of exercise-induced LO and to identify the determinants of LO, which include morphologic and hemodynamic parameters. The results of this study showed that (1) patients with LO had a longer residual mitral leaflet and a higher resting LVOT pressure gradient than the remaining patients at baseline, (2) sudden decrease in mitral annular diameter from the peak exercise phase to the phase immediately after exercise was dominant in the LO group,

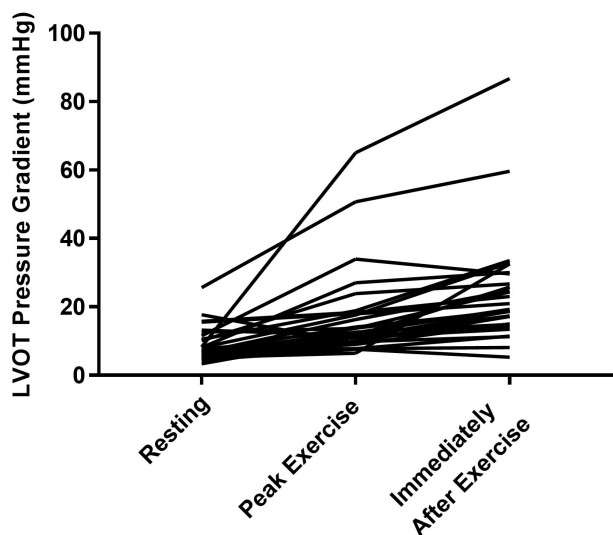


Fig. 3. Change in left ventricular outflow tract (LVOT) pressure gradient. The highest peak LVOT pressure gradient occurred immediately after exercise rather than during peak exercise.

and (3) the highest peak LVOT pressure gradient predominantly occurred immediately after exercise rather than during peak exercise.

There is some evidence suggesting that patients with obstructive HCMP have elongated mitral leaflets [11]. It has been reported that patients with obstructive HCMP with systolic anterior motion (SAM) demonstrated abnormal coaptation such that the posterior leaflet coapted with a mid portion of the anterior leaflet, leaving a distal residual anterior leaflet in the left ventricle during systole. Shah *et al.* [12] has reported that residual leaflet length correlates well with total leaflet length and the degree of SAM in turn correlates well with residual leaflet length in obstructive HCMP. Henein *et al.* [13] found that longer anterior mitral valve leaflets were predictor of exercise-induced LVOT obstruction. An important new finding of our study is that patients with exercise-induced LO in non-obstructive HCMP tend to have longer residual mitral leaflets than the remaining patients although anterior mitral leaflet lengths were not different. Mitral leaflet elongation, especially the residual leaflet length and leaflet mobility, may play an important role in promoting LO as a determinant in non-obstructive HCMP.

The abrupt decrease in mitral annular diameter immediately after cessation of exercise was significant in the LO group. Shah *et al.* [12] have shown a greater reduction in size of the mitral annulus in early systole in obstructive HCMP with SAM than in normal subjects. The ability of this phenomenon to explain the pathophysiology of LO, however, is limited because the movement of the mitral valve apparatus toward the ventricular septum due to the pressure gradient in LVOT can induce these findings. Change in mitral annular diameter in LO group of our study may also be secondary change related to systolic anterior motion of mitral valve.

This study showed that LO in non-obstructive HCMP is related to post-exercise hemodynamics rather than to peak-exercise hemodynamics. The response of the LVOT pressure gradient to exercise has shown considerable heterogeneity in studies. Shwammenthal *et al.* [10] reported that outflow gradients increase during exercise. The results of Klue *et al.* [14], however, are in agreement with ours to the extent that significant LVOT pressure gradients developed at the post-exercise stage. Our findings are also in accordance with results from Braunwald *et al.* [15], assessing pressure gradients with cardiac catheterization during exercise. The further increase in the pressure gradient shortly after the cessation of exercise is assumed to be due to a further decrease in the outflow tract area resulting from the combination of a sudden reduction in venous return to the heart coupled with a persistently low peripheral resistance and the continuation of sympathetic stimuli to the heart. These findings suggest that, in terms of pathophysiology, LO in non-obstructive HCMP might be related to post-exercise hemodynamics rather than to peak-exercise hemodynamics.

We found that significant LO developed in 25% of the present study cohort. LO in HCMP may importantly affect clinical decision making in that patients with severely symptomatic LO with physiological provocation are potential candidates for invasive treatments such as surgical reduction therapy (myomectomy and alcohol septal ablation) or alternatively mitral valve repair to normalize LV pressures and improve symptoms [6, 13, 16–18].

There are several limitations to our study. First, the number of patients with LO was limited and this could have affected our results. Second, although we requested study patient to stop medications at least 3 days before the exercise echocardiography, the use of beta-blockers before exercise might have affected the results. There was a higher proportion of beta-blocker use in the non-LO group, although this difference was not statistically significant. Third, some patients did not achieve appropriate workload levels due to leg pain or fatigue. If a patient cannot reach 85% of their maximal age-predicted target heart rate for whatever reason, the test's capacity for detecting significant LO may be reduced. Fourth, supine bicycle exercise may affect the study results. Compared to standing position, increased venous return and increased preload may attenuate LVOT obstruction during provocation in HCMP. Fifth, Valsalva maneuver was not included in this study protocol. Although Valsalva maneuver has frequently been recommended in echocardiographic examination of HCMP, it cannot not reliably reproduce the physiological circumstances. In previous study using exercise echocardiography in patients with patients with HCMP, LVOT obstruction during Valsalva maneuver could not predict exercise-induced LVOT obstruction [13].

In conclusion, we performed exercise echocardiography to evaluate the pathophysiology and determinants of exercise-induced LO in patients with non-obstructive HCMP. Decrease in mitral annular diameter immediately af-

ter exercise, a longer residual mitral leaflet and a higher resting LVOT pressure gradient at rest might be related to LO.

Author contributions

SJR designed the research study. SJR and WHK performed the research. EYC provided help and advice on the methodology. JYK and WHK analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All patients gave written informed consent and the Institutional Review Boards at our center approved this study (approval number: 3-2021-0088). The protocol for this study was in accordance with the Declaration of Helsinki.

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Conflict of interest

The authors declare no conflict of interest.

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