




Pulmonary congestion during Exercise stress Echocardiography in Hypertrophic Cardiomyopathy

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Abstract

Background B-lines detected by lung ultrasound (LUS) during exercise stress echocardiography (ESE), indicating pulmonary congestion, have not been systematically evaluated in patients with hypertrophic cardiomyopathy (HCM).

Aim To assess the clinical, anatomical and functional correlates of pulmonary congestion elicited by exercise in HCM.

Methods We enrolled 128 HCM patients (age 52 ± 15 years, 72 males) consecutively referred for ESE (treadmill in 46, bicycle in 82 patients) in 10 quality-controlled centers from 7 countries (Belgium, Brazil, Bulgaria, Hungary, Italy, Serbia, Spain). ESE assessment at rest and peak stress included: mitral regurgitation (MR, score from 0 to 3); E/e' ; systolic pulmonary arterial pressure (SPAP) and end-diastolic volume (EDV). Change from rest to stress was calculated for each variable. Reduced preload reserve was defined by a decrease in EDV during exercise. B-lines at rest and at peak exercise were assessed by lung ultrasound with the 4-site simplified scan. B-lines positivity was considered if the sum of detected B-lines was ≥ 2 .

Results LUS was feasible in all subjects. B-lines were present in 13 patients at rest and in 38 during stress (10 vs 30%, $p < 0.0001$). When compared to patients without stress B-lines ($n = 90$), patients with B-lines ($n = 38$) had higher resting E/e' (14 ± 6 vs. 11 ± 4 , $p = 0.016$) and SPAP (33 ± 10 vs. 27 ± 7 mm Hg $p = 0.002$). At peak exercise, patients with B-lines had higher peak E/e' (17 ± 6 vs. 13 ± 5 $p = 0.003$) and stress SPAP (55 ± 18 vs. 40 ± 12 mm Hg $p < 0.0001$), reduced preload reserve (68 vs. 30%, $p = 0.001$) and an increase in MR (42 vs. 17%, $p = 0.013$) compared to patients without congestion. Among baseline parameters, the number of B-lines and SPAP were the only independent predictors of exercise pulmonary congestion.

Conclusions Two-thirds of HCM patients who develop pulmonary congestion on exercise had no evidence of B-lines at rest. Diastolic impairment and mitral regurgitation were key determinants of pulmonary congestion during ESE. These findings underscore the importance of evaluating hemodynamic stability by physiological stress in HCM, particularly in the presence of unexplained symptoms and functional limitation.

Keywords B-lines · Pulmonary congestion · Hypertrophic cardiomyopathy · Exercise stress echocardiography · Echocardiography

Abbreviations

CI cardiac index.
EDV end-diastolic volume.
EDV end-diastolic volume.
EF ejection fraction.
ESE exercise stress echocardiography LUS = lung ultrasound.

ESV end-systolic volume.
HCM hypertrophic cardiomyopathy.
HR heart rate.
LV left ventricle.
LVOT left ventricular outflow tract.
LVOTG left ventricular outflow tract gradient.
MR mitral regurgitation.
SBP systolic blood pressure.
SCD Sudden cardiac death risk.
SPAP systolic pulmonary arterial pressure.

Extended author information available on the last page of the article

SV stroke volume.
WMSI Wall motion score index.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic disorder of the myocardium with variable phenotypic expression (1). Exploration of new clinical markers related to cardiac pathophysiology through the prism of cardiac imaging may help to identify the functional heterogeneity and different phenotypes (2), which represent potential therapeutic targets in HCM (3). Current European guidelines assign IB class of recommendations to exercise stress echocardiography (ESE) in symptomatic HCM patients without resting left ventricular outflow tract (LVOT) obstruction, to detect hemodynamically important exercise-induced LVOT gradient (LVOTG) and mitral regurgitation (MR) (4). However, the information provided by ESE in HCM extends far beyond the evaluation of the LVOTG and MR (5, 6). B-lines can be assessed by lung ultrasound (LUS) during ESE and provide a unique way to evaluate semi-quantitatively extravascular lung water, a physiologic variable with well-established diagnostic and prognostic value in a range of cardiac diseases (7). B-lines at rest and during stress in HCM may help to identify the pulmonary congestion phenotype, which is an actionable therapeutic target for diuretic therapy. Proper use of diuretics is a challenging issue in HCM, as these agents may decrease preload and worsen dynamic obstruction if used inappropriately. Despite the growing evidence on the clinical significance of exercise-induced pulmonary congestion assessment by LUS, its clinical value has never been investigated in patients with HCM. Therefore, in this study we aimed to evaluate the feasibility of stress LUS in HCM and to assess the clinical, anatomical and functional correlates of pulmonary congestion during ESE in HCM.

Methods

Study population

We enrolled 128 consecutive HCM patients from 10 different SE laboratories [Rome, Italy (n = 54); Belgrade, Serbia (n = 17); Szeged - Hodmezovasarhely, Hungary (n = 17); A Coruna, Spain (n = 14); Porto Alegre, Brazil (n = 12); Antwerp, Belgium (n = 6); Florence, Italy (n = 4); Benevento, Italy (n = 2); Passo Fundo, Brazil (n = 1); Pleven, Bulgaria (n = 1)] of the Stress echo 2020 multicenter study (8). Diagnosis of HCM was based on the contemporary guidelines cautiously excluding HCM phenocopies (4). All patients underwent symptom-limited dynamic echocardiographic

examination according to the referring physician's indications as part of the routine work-up. The inclusion criteria were: (1) Diagnosis of HCM; (2) age > 18 years; (3) no known coronary artery disease; (4) ability to perform ESE. The following exclusion criteria were used: (1) comorbidities known to generate B-lines of extracardiac origin (e.g. pulmonary fibrosis, lung cancer, pneumonia); (2) atrial fibrillation; (3) technically poor acoustic window precluding sufficient imaging of the left ventricle (LV); (4) resting ejection fraction (EF) < 40%, (5) HCM phenocopies of non-sarcomeric nature (Fabry, Danon and amyloidosis). The study was conducted in accordance with the Declaration of Helsinki. The study protocol and the informed consent were reviewed and approved by the institutional ethics committees as a part of the SE 2020 study. All subjects gave their informed consent for inclusion before they participated in the study. Sudden cardiac death risk (SCD) was determined according to the European Society of Cardiology's HCM Risk-SCD formula (4).

Exercise stress

Patients underwent ESE according to the recommended protocols with one of the following stresses: semi-supine bicycle (25 watts increments every 2 or 3 min); upright bicycle; treadmill exercise with modified Bruce protocol (9). Routinely used medications were administered as usual before and after the exam. Electrocardiogram and blood pressure were monitored continuously. Criteria for terminating the test were severe chest pain, diagnostic ST-segment shift, excessive blood pressure increase [systolic blood pressure (SBP) \geq 240 mmHg, diastolic blood pressure \geq 120 mmHg], symptomatic hypotension with a sudden drop in blood pressure (> 40 mmHg), limiting dyspnea, maximal predicted heart rate (HR), significant arrhythmias or limiting side effects (7, 8).

Hemodynamic measurements

All echocardiographic measurements were measured at rest and with stress by experienced cardiologists according to standard criteria of execution and interpretation recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging (9, 10, 11). Wall motion score index (WMSI) was calculated applying the four-point score system ranging from 1 (normal) to 4 (dyskinetic) in a 17-segment model of the left ventricle. LV volumes were evaluated by the biplane Simpson method. LVOTG was the maximum instantaneous gradient as measured by continuous-wave Doppler. LV force was defined by the following formula: LVOTG + SBP / end-systolic volume (ESV). LV contractile reserve was calculated

by dividing the stress by rest LV force values. Heart rate reserve was calculated as the peak/rest HR from 12-lead ECG (7). Stroke volume (SV) was calculated as end-diastolic volume (EDV)-ESV. Cardiac output was computed using the following formula: EDV-ESV x HR. Cardiac output and SV were normalized to body surface area to obtain SV index and cardiac index (CI). Preload reserve impairment was defined as peak stress EDV < rest EDV (12). MR was evaluated with semi-quantitative method and graded as: none or trivial (0), mild (1), moderate (2), and severe (3) (13). Pulse pressure was assessed by the difference between SBP and diastolic blood pressure. Abnormal blood pressure response was defined as the fall of SBP by > 20 mm Hg or a failure to increase the SBP by > 20 mm Hg during exercise (4). The ESE examinations were performed by cardiologists who were not involved in the patients' management and had passed the quality control procedures upstream to patient recruitment, with inter-observer variability < 10% in quantifying B-lines and < 10% in estimating LV area by planimetric method (7, 8, 14).

Lung ultrasound

The LUS acquisition was performed at rest and peak (or immediately after) stress with the 4-site simplified scan at the third intercostal space on the anterior and lateral hemithoraces, using the same probe employed for the cardiac scan. B-lines were defined as hyperechoic reverberation artifacts rising from the pleural line to the bottom of the screen moving synchronously with lung sliding without fading (7). After scanning the 4 chest sites, the cumulative B-line score was obtained by summing the number of detected B-lines at each site. B-lines were considered present if at least 2 B-lines could be detected.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation or median and IQR, according to the variable's distribution. Categorical variables were reported as frequency and percentage. Data distribution was assessed graphically. Student's independent t-test and Mann–Whitney U test were used to compare differences between continuous variables. Categorical variables were compared using Chi-squared test or Fisher's exact test. Spearman's correlation was used to assess the relationship between stress B-lines and functional parameters. Univariate and multivariate logistic regression analyses were performed to assess the baseline predictors of exercise B-lines. The multivariate analysis was performed on clinically relevant variables with forward stepwise method using likelihood ratio test. Statistical significance was set at $p < 0.05$. Statistical Package for the Social Sciences (IBM

SPSS Statistics, version 26) and MedCalc for Windows (version 7.6.0.0.) was employed for analysis.

Results

Baseline characteristics

In a total of 128 HCM patients (age 50 ± 15 years, 85 men) LUS and echocardiographic examinations were performed applying bicycle in 82 (64%; semi-supine in 28 and upright in 54) and treadmill in 46 (36%) with LV imaging at peak stress or in the immediate post-exercise period. Most ($n = 120$, 94%) patients were in NYHA I-II functional class; 92 patients (72%) were on beta-blockers and 16 (13%) were on diuretic therapy. Eighteen patients (14%) had haemodynamically important LV outflow tract gradient (> 50 mm Hg) at baseline (Table 1). Twenty-three patients (18%) had moderate or severe MR at rest.

LUS and exercise test findings

No complications occurred during ESE. LUS was feasible in all subjects, with additional scanning and analysis time less than 1 min each for rest and peak stress. B-lines were detected in 13 patients at rest and in 38 during stress (12% vs. 31%, $p < 0.0001$). B-lines were present both at rest and at peak stress in 13 patients (12%). We divided the cohort into two groups according to the peak stress lung profiles: HCM patients with stress B-lines (congestive phenotype, with wet lungs: Group 1) and without stress B-lines (non-congestive phenotype, with dry lungs: Group 2). An example of LUS and ESE findings in a patient with B-lines is shown in Fig. 1. Exercise-time tended to be lower in patients with stress-induced B-lines (Group 1 = 8.7 ± 3.0 vs. Group 2 = 10.8 ± 3.8 min, $p = 0.056$). The reason for stopping the test was more frequently fatigue/exhaustion in patients with stress-induced B-lines (Group 1 = 54% vs. Group 2 = 32%, vs., $p = 0.129$). The second more frequent reason for prematurely stopping the test was dyspnea (Group 1 = 46% vs. Group 2 = 67%, $p = 0.159$).

B-lines and clinical, echocardiographic and ESE findings

HCM patients in Group 1 were older at first diagnosis and had higher SCD risk scores at the time of the evaluation compared to patients in Group 2. At rest, patients with stress-B-lines showed a trend to higher prevalence of history of syncope (Group 1 = 11% vs. Group 2 = 4%, $p = 0.236$) but similar NYHA class than patients without stress B-lines (Table 1). In our population, 79% of "wet" patients with

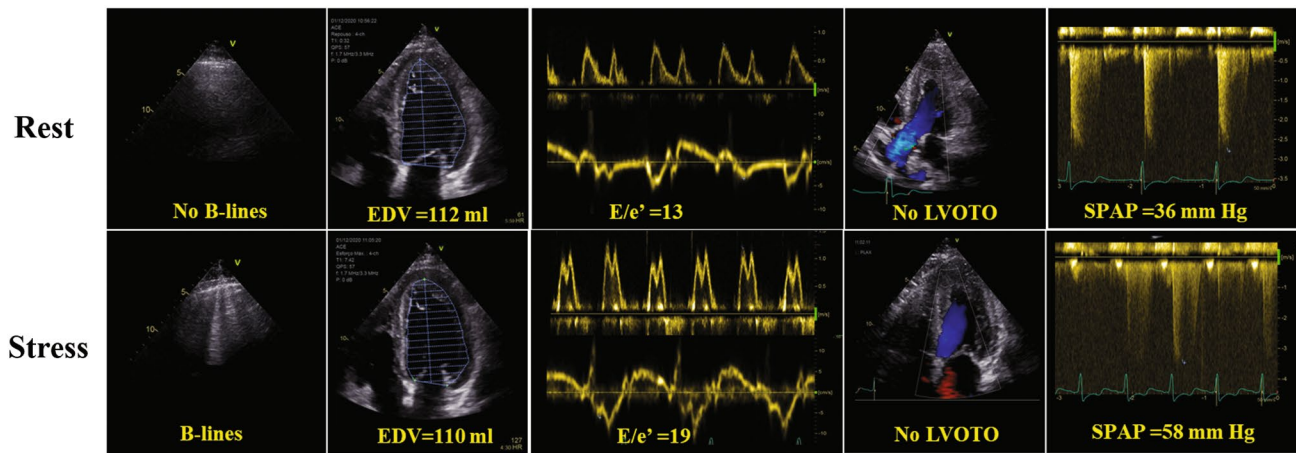


Fig. 1 Example of exercise B-lines in a non-obstructive HCM patient with exertional dyspnea and negative coronary angiography. During ESE B-lines were associated with reduced diastolic reserve mirrored by falling EDV, increasing E/e' and worsening pulmonary pressures.

Abbreviations: E: early mitral inflow velocity; e' : early diastolic mitral annular velocity; EDV: end-diastolic volume; LVOTO: left ventricular outflow tract obstruction; SPAP: systolic pulmonary arterial pressure

Table 1 Baseline characteristics of the 128 HCM patients according to stress B-lines presence

	All patients (n = 128)	HCM patients with stress B-lines (n = 38)	HCM patients without stress B-lines (n = 90)	p value
Age (years)	50.3 ± 15.4	53.0 ± 17.3	49.2 ± 14.5	0.200
Age at first diagnosis (years)	42.8 ± 15.6	48.4 ± 17.8	40.9 ± 14.5	0.031
Male gender	85 (66%)	24 (63%)	61 (68%)	0.613
Body surface area (m ²)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.401
SCD risk (%)	2.9 ± 2.1	4.1 ± 3.2	2.6 ± 1.5	0.039
Syncope	8 (6%)	4 (11%)	4 (4%)	0.236
Coronary artery disease	4 (3%)	1 (3%)	3 (3%)	0.835
NYHA I-II	120 (94%)	35 (92%)	85 (94%)	0.694
Beta-blockers	92 (72%)	29 (76%)	63 (70%)	0.468
Diuretics	16 (13%)	7 (18%)	9 (10%)	0.188
LV max wall thickness (mm)	20.2 ± 5.4	21.6 ± 5.8	19.7 ± 4.8	0.095
LVOT gradient ≥30 mm Hg	26 (21%)	11 (29%)	15 (17%)	0.122
LVOT gradient ≥50 mm Hg	18 (14%)	7 (18%)	11 (12%)	0.423

Data are expressed as mean value ± SD, median value with the corresponding first and third quartile or number (%) of patients.

Abbreviations: HCM: hypertrophic cardiomyopathy; LV: left ventricular; LVOT: left ventricular outflow tract; NYHA: New York Heart Association; SCD: sudden cardiac death

stress B-lines were off diuretic therapy, and 12% of “dry” patients without B-lines were on diuretic therapy. At rest, patients who developed stress B-lines had higher rest E/e' and SPAP, with similar MR grade and EDV (Fig. 2). At peak stress, patients in Group 1 showed more elevated stress E/e' , SPAP, greater MR and smaller EDV compared to Group 2 patients (Table 2; Fig. 3). Another important finding was that patients in Group 1 showed twice more often a reduced preload response and an increase in MR in response to exercise (Table 2). Patients in Group 1 also showed lower baseline diastolic blood pressure, higher resting pulse pressure, more abnormal blood pressure response during exercise (47 vs 16%, $p < 0.001$) and lower stress SV index and CI (Table 3).

The individual number of stress B-lines showed moderate positive correlation with peak exercise E/e' ($r_s = 0.394$ $p < 0.001$) and SPAP ($r_s = 0.326$ $p = 0.001$) and inverse relationship with peak exercise SV index ($r_s = -0.359$ $p < 0.001$) and CI ($r_s = -0.344$ $p < 0.001$). Multivariate logistic regression analysis revealed that among baseline parameters the number of B-lines and SPAP were independent predictors of B-lines with exercise (Table 4).

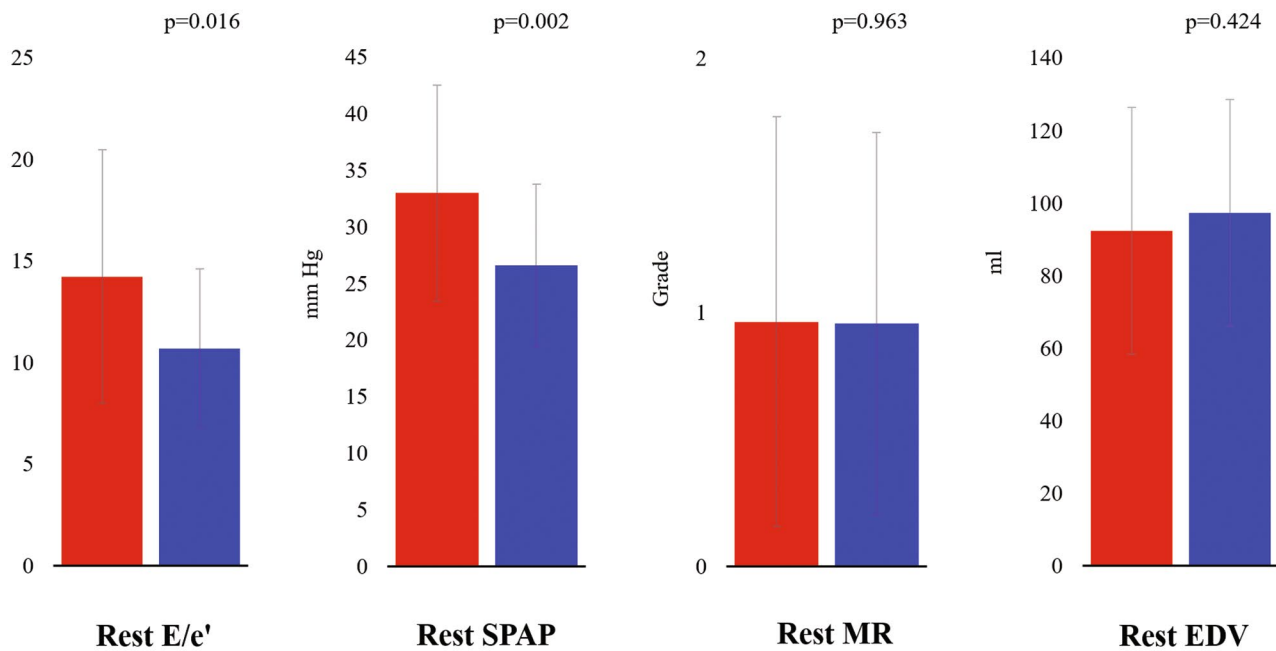


Fig. 2 Stress B-lines and resting echocardiographic findings. From left to right: rest E/e'; rest SPAP; rest MR; rest EDV. Abbreviations as in Fig. 1. Red bar: Group 1 (with stress B-lines); Blue bar: Group 2 (without stress B-lines)

Discussion

In the present study, LUS during ESE was feasible and simple in HCM, with 100% success rate for B-lines and only a minimal increase in imaging time. B-lines were found in about 10% of HCM patients at rest and in about 30% during ESE. HCM patients presenting B-lines at stress were diagnosed with HCM later in life and had higher SCD risk scores. They showed higher pulse pressure at rest, with similar heart rate and cardiac output compared to patients without stress B-lines, suggestive of a stiff aorta which may contribute to abnormal ventricular arterial interactions during stress eventually favouring myocardial fibrosis and dysfunction (15, 16). Stress B-lines were associated with worse diastolic function, greater SPAP and larger increment in MR during stress. Patients with pulmonary congestion at peak exercise had lower CI reserve at comparable heart rates, compared to those without B-lines, and more often had abnormal blood pressure response to exercise. Therefore, stress B-lines are relatively frequent findings in HCM patients, represent multiple mechanisms, are associated with signs of greater clinical and functional severity, and reflect hemodynamic vulnerability during exercise, mirrored by a reduced CI reserve and prevalent abnormal blood pressure response. Notably, the development of stress B-lines could not be reliably foreseen by the baseline echocardiographic features of our patients: the best predictor was SPAP > 28 mm Hg, with a positive predictive value of only 48%, 95% CI 32–65%.

Therefore, given its ease of implementation and utility, the systematic performance of lung scanning appears a valuable adjunct to ESE in HCM patients, even in the presence of baseline evidence of increased pulmonary pressures. Albeit stress echocardiography is included in current guidelines for the management of HCM, mostly it is considered only a tool to evaluate peak LVOT gradients. However, ESE is a powerful multi-purpose tool with far-reaching clinical implications also in non-obstructive patients and provides much broader information for clinical practice.

Pathophysiology of pulmonary congestion in HCM

The pathophysiology of heart failure and congestion in HCM is not yet completely understood (17). Left ventricular hypertrophy, ischemia and fibrosis lead to a stiff, non-compliant left chamber that restrains diastolic filling and elevates intracavitary end-diastolic pressures (1, 18). When the left ventricle fails, blood accumulates in the left atrium and left atrial pressure and pulmonary capillary pressure similarly rises (19). When pulmonary capillary pressure elevates above a threshold, the imbalance in the Starling forces across the pulmonary capillary endothelial barrier results in an increased accumulation of extravascular lung water (20). Distinct factors beyond diastolic dysfunction that contribute to backward HF in HCM include LVOT obstruction, structural or functional mitral valve alterations, increased large artery stiffness or less commonly, abnormal systolic function (21). Notably, baseline LVOTG was not

Table 2 Rest and peak stress ultrasound findings according to stress B-lines presence in HCM (n = 128)

	All patients (n = 128)	HCM patients with stress B-lines (n = 38)	HCM patients without stress B-lines (n = 90)	p value
Lung ultrasound				
B lines score	rest	0 (0;0)	0 (0;0)	<0.0001
	stress	0 (0;2)	4 (2;7)	<0.0001
Echocardiographic parameters				
LA diameter (mm)	rest	40.7 ± 6.0	41.9	± 6.6
LA volume (ml)	rest	69.0 ± 28.1	79.4	± 38.5
	stress	69.6 ± 26.1	78.7	± 27.6
Δ		-0.8 ± 17.0	-3.8	± 19.7
LAVi (ml/m ²)	rest	36.9 ± 14.8	41.2	± 18.9
	stress	37.1 ± 13.7	40.8	± 13.6
Δ		-0.6 ± 8.7	-1.9	± 9.6
LV EDV (ml)	rest	95.8 ± 32.0	92.2	± 34.0
	stress	97.2 ± 32.0	83.7	± 29.4
Δ		1.3 ± 18.6	-4.8	± 18.8
Reduced preload response		56 (44%)	26 (68%)	± ±
LV EDVi (ml/m ²)	rest	51.0 ± 17.2	48.4	± 17.7
	stress	51.8 ± 17.5	43.4	± 14.1
Δ		0.8 ± 10.5	-2.6	± 10.8
LV ESV (ml)	rest	33.3 ± 14.5	31.4	± 14.1
	stress	30.6 ± 16.7	27.8	± 13.3
Δ		-2.7 ± 13.4	-2.0	± 14.2
LV EF (%)	rest	65.4 ± 7.8	65.9	± 8.0
	stress	69.3 ± 10.9	69.0	± 7.9
LVOT gradient (mm Hg)	rest	21.5 ± 27.7	25.7	± 33.8
	stress	43.1 ± 47.3	56.5	± 61.4
Δ		21.6 ± 30.7	30.7	± 42.7
LV Force (mm Hg/ml)	rest	5.2 ± 2.6	6.0	± 3.2
	stress	8.6 ± 5.1	10.8	± 6.9

Table 2 (continued)

	All patients (n = 128)	HCM patients with stress B-lines (n = 38)	HCM patients without stress B-lines (n = 90)	p value	
LVCR	1.7 ± 0.7	1.8	1.7 ± 0.6	0.591	
MR (grade)	rest	1.0 ± 0.8	1.0	0.8 ± 0.8	0.963
	stress	1.2 ± 0.9	1.5	1.1 ± 0.8	0.057
	Δ	0.2 ± 0.6	0.6	0.1 ± 0.5	0.008
	any change	33 (26%)	16 (42%)	17 (19%)	0.013
SPAP (mm Hg)	rest	27.8 ± 8.0	33.0	26.6 ± 7.2	0.002
	stress	43.2 ± 15.1	55.2	40.2 ± 12.6	<0.0001
TAPSE (mm)	rest	15.4 ± 12.9	23.4	13.5 ± 11.0	0.035
	stress	23.9 ± 4.5	24.2	23.8 ± 4.3	0.714
	Δ	29.8 ± 5.5	30.0	29.7 ± 5.6	0.865
	rest	5.8 ± 4.9	5.6	5.9 ± 4.8	0.854
E/e'	rest	11.5 ± 4.7	14.2	10.7 ± 3.9	0.016
	stress	13.5 ± 5.7	16.5	12.6 ± 5.4	0.003
	Δ	1.8 ± 4.8	2.1	1.7 ± 4.7	0.795
	rest	1.0 ± 0.1	1.0	1.0 ± 0.1	0.389
WMSI	stress	1.0 ± 0.0	1.0	1.0 ± 0.0	0.450
	Δ	0.0 ± 0.1	0.0	0.0 ± 0.1	0.199
	rest	-16.9 ± 4.7	-17.1	-16.8 ± 4.7	0.887

Data are expressed as mean value ± SD, median value with the corresponding first and third quartile or number (%) of patients.

Abbreviations: E: early mitral inflow velocity; e': early diastolic mitral annular velocity; EDV: end-diastolic volume; EDVi: end-diastolic volume index; EF: ejection fraction; ESV: end-systolic volume; GLS: global longitudinal strain; HCM: hypertrophic cardiomyopathy; LA: left atrial; LAVi: left atrial volume index; LV: left ventricular; LVCR: left ventricular contractile reserve; LVOT: left ventricular outflow tract; MR: mitral regurgitation; SPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; WMSI: Wall motion score index

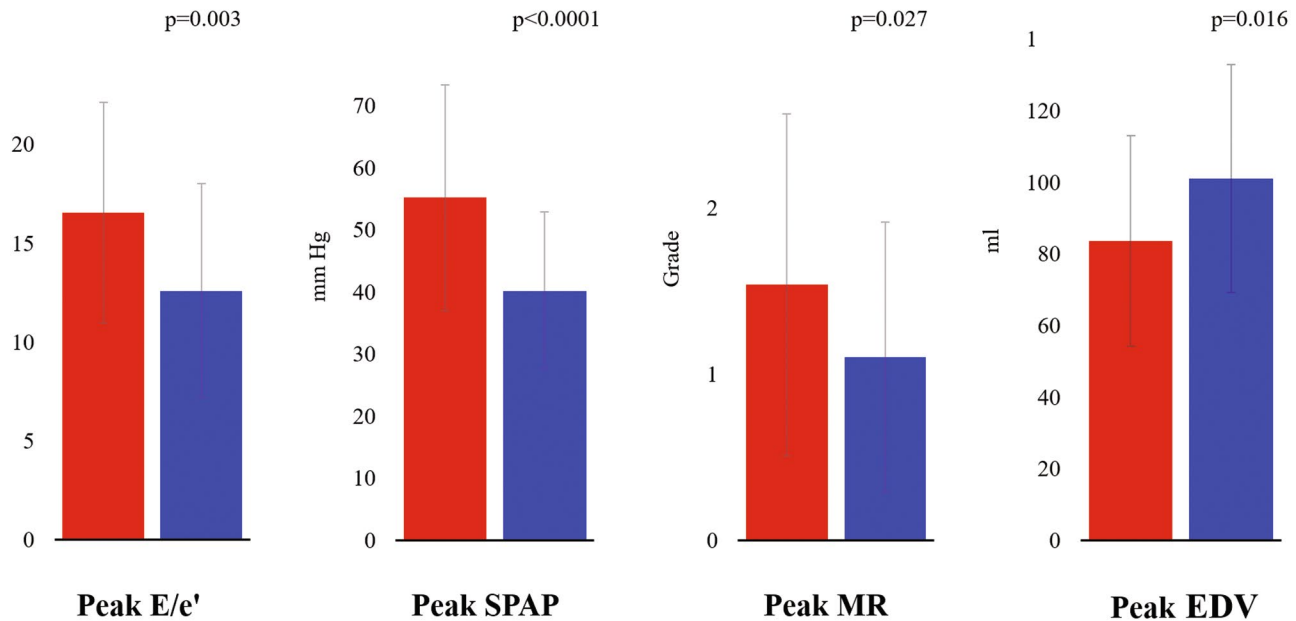


Fig. 3 Stress B-lines and stress echocardiographic findings. From left to right: peak E/e'; peak SPAP; peak MR; peak EDV. Abbreviations as in Fig. 2. Red bar: Group 1 (with stress B-lines); Blue bar: Group 2 (without stress B-lines)

a predictor of exercise pulmonary congestion. There was a trend of showing a higher gradients in the group of patients with stress B-lines but it was not significant. Although initially counterintuitive, this finding is consistent with clinical practice: only a minority of HCM patients with obstruction, even when severe, benefit from diuretics and many may worsen their symptoms due to preload reduction. Other factors seem to play a greater role than gradients, including the degree of MR at rest or during exercise and diastolic dysfunction.

Comparison with previous studies

Numerous investigations have shown the excellent feasibility, diagnostic and prognostic usefulness of B-lines assessment during stress echocardiography in different cardiovascular diseases (7, 22, 23). However, our report is the first in the literature focusing on HCM. We adopted the simplified 4-site scan technique which proved to be the best trade-off between accuracy and simplicity both at rest and especially after stress when imaging time is short and there are many parameters to scan (7). Prior studies have demonstrated that the number of stress B-lines is tightly related to E/e' and MR development during ESE in patients with HF, consistent with our findings in HCM (7, 23). In addition, we observed that in HCM stress B-lines were associated with lower EDV and CI reserve during stress. The findings of our study are in line with those of Lele et al., who evaluated 79 HCM outpatients in a hemodynamic study with

radionuclide ventriculography and expiratory gas analysis during symptom-limited exercise stress. They found that the ability to increase left ventricular EDV is a principal factor in stroke volume and cardiac output augmentation during dynamic exercise in HCM (24). The advantage of ESE is that it provides a one-stop shop view of all these interconnected variables, including pulmonary congestion, preload reserve, dynamic intraventricular gradients and MR, both at rest and during stress.

Clinical implications

Aggressive diuretic therapy can worsen symptoms related to LVOT obstruction by causing exaggerated decrease in preload and should be avoided in HCM. Conversely, with the clinical evidence of congestion, cautious use of low-dose diuretics can provide symptom relief and can be reasonable to apply also in patients with LVOT obstruction (3, 4). Clinical signs of pulmonary congestion such as pulmonary crackles on chest auscultation have substantial intra- and interobserver variability and are only loosely related to lung water accumulation (25). B-lines are also obtainable with pocket size instruments after a limited training and may guide an effective decongestion therapy with symptomatic and prognostic benefit, as it has been shown by randomized trials based on resting lung ultrasound in other clinical settings such as heart failure (26).

Table 3 Rest and stress hemodynamic findings according to stress B-lines presence in HCM (n = 128)

	All patients (n = 128)	HCM patients with stress B-lines (n = 38)	HCM patients without stress B-lines (n = 90)	p value
Hemodynamic and exercise parameters				
SBP (mmHg)				
rest	125.1 ± 15.4	128.4 ± 15.6	123.7 ± 15.1	0.110
stress	160.3 ± 25.9	155.3 ± 28.9	162.4 ± 24.3	0.159
Δ	35.2 ± 27.4	26.9 ± 30.6	38.7 ± 25.4	0.025
DBP (mmHg)				
rest	78.0 ± 9.5	73.6 ± 6.8	79.0 ± 9.7	0.025
stress	85.8 ± 14.4	82.7 ± 13.1	86.5 ± 14.7	0.314
Δ	7.8 ± 13.7	9.1 ± 14.9	7.5 ± 13.4	0.640
Pulse pressure (mmHg)				
rest	46.5 ± 13.9	52.7 ± 15.5	45.0 ± 13.2	0.029
stress	74.7 ± 27.6	70.8 ± 26.3	75.5 ± 28.0	0.506
Δ	28.2 ± 28.3	18.1 ± 26.1	30.5 ± 28.4	0.085
h (beats/min)				
rest	67.6 ± 14.6	66.2 ± 10.0	68.2 ± 16.2	0.485
stress	126.1 ± 25.4	122.1 ± 25.5	127.8 ± 25.3	0.252
Δ	58.5 ± 24.7	55.9 ± 25.7	59.6 ± 24.4	0.445
HHR				
rest	1.9 ± 0.4	1.9 ± 0.5	1.9 ± 0.4	0.576
SV index (ml/m²)				
rest	33.3 ± 11.4	32.0 ± 12.3	33.8 ± 11.1	0.444
stress	35.5 ± 13.0	29.1 ± 10.6	37.3 ± 13.1	0.005
Δ	2.2 ± 9.7	-1.7 ± 7.4	3.3 ± 10.0	0.023
Cardiac index (ml/min x m⁻²)				
rest	2212 ± 835	2070 ± 732	2271 ± 871	0.220
stress	4485 ± 1797	3474 ± 1381	4778 ± 1803	0.001
Δ	2275 ± 1465	1530 ± 1179	2492 ± 1475	0.003
ABPR	32 (25%)	18 (47%)	14 (16%)	< 0.001

Data are expressed as mean value ± SD or number (%) of patients

Abbreviations: ABPR: abnormal blood pressure response; DBP: diastolic blood pressure; HCM: hypertrophic cardiomyopathy; HR: heart rate; HRR: heart rate reserve; SBP: systolic blood pressure SV: stroke volume

Table 4 Baseline predictors of pulmonary congestion during exercise stress echocardiography in HCM (n = 128)

	Univariate analysis			Multivariate analysis			p value
	OR	95% CI	p value	OR	95% CI	p value	
Age at first diagnosis (years)	1.031	1.002	1.062				
SCD risk (%)	1.407	1.093	1.812				
B lines number rest	4.304	1.691	10.956	4.282	1.120	16.364	0.033
DBP (mmHg)	0.932	0.876	0.993				
Pulse pressure (mmHg)	1.040	1.003	1.078				
LA volume (ml)	1.016	1.001	1.031				
E/e' rest	1.154	1.049	1.271				
LV Force rest (mm Hg/ml)	1.183	1.019	1.373				
SPAP rest (mm Hg)	1.093	1.027	1.163	1.070	1.000	1.144	0.048

OR: odds ratio; C.I.: confidence interval

Abbreviations as in Tables 1, 2 and 3

Study limitations

We combined data from bicycle and treadmill ESE which have different hemodynamic effect and could have influence on cardiac volume changes and stress B-lines in some extent. Dynamic gradients are more obvious in orthostatic position, and treadmill increases EDV of the left ventricle more than semi-supine exercise in healthy subjects (11). Semi-supine exercise increases pulmonary artery wedge pressure more than upright exercise (27). Supine bicycle increases blood pressure more and heart rate less than treadmill, but the double product is similar (28). The observational study design did not interfere with the individual choice of the referring physician, which is a matter of personal experience, awareness of the individual patient indications and local practice. Data were obtained from different laboratories without core lab reading, but all readers underwent quality control prior to patient recruitment (8) and had established experience as referral centers for HCM. Transthoracic 2-dimensional echocardiography has recognized limitations in estimating absolute LV volumes in HCM but it remains the recommended first-line technique (29, 30). In the present study relative volumetric changes of EDV from rest to stress provided more information than absolute values. In assessing relative changes, most sources of inaccuracy average out and each patient acts as his or her own control during stress.

Conclusions

LUS is feasible and easily accessible at rest and during ESE in HCM. Pulmonary congestion occurs in about 1 of 10 HCM patients at rest and in 1 of 3 during ESE. Diastolic impairment (mirrored by increased left ventricular filling pressures with reduced EDV reserve) and worsening of MR are main determinants of pulmonary congestion during exercise in HCM. The combination of ESE and LUS provides a dynamic assessment of the HCM pathophysiology and has the capability to recognize the pulmonary congestive phenotype, possibly useful for effective and personalized diuretic treatment, as it has been shown in heart failure patients without HCM. ESE with LUS may open a new diagnostic window for earlier and more precise detection of pulmonary congestion and diastolic dysfunction in HCM.

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