

Exercise Stress Echocardiography in Hypertrophic Cardiomyopathy: How, When and Why?

Ecoestresse Físico na Cardiomiopatia Hipertrófica: Como, Quando e Por Quê?

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Abstract

Historically, the role of exercise stress echocardiography in the management of hypertrophic cardiomyopathy has been neglected in clinical practice according to the analysis of the 2002 Guidelines of the American College of Cardiology/American Heart Association, which recommended caution use of this methodology in patients with hypertrophic cardiomyopathy due to the risk of both cardiac arrhythmia and hemodynamic collapse on exertion. Exercise stress testing in patients with hypertrophic cardiomyopathy is currently part of the routine assessment of symptomatic patients with or without a resting left ventricular outflow tract gradient < 50 mmHg. For this group, it is a safe and reliable method for measuring the left ventricular outflow tract gradient during exertion and a solid differentiator of patients with non-obstructive hypertrophic cardiomyopathy (absent gradient, both at rest and on exertion) from those with labile gradients (absent gradient at rest and present on exertion). Therefore, in the assessment of hypertrophic cardiomyopathy, exercise stress is equally useful for quantifying the degree of mitral regurgitation and left ventricular segmental contractility changes as well as assessing left ventricular diastolic function on exertion and is able to predict the future development of heart failure symptoms. The method is also important for determining different treatment strategies for each patient, from surgical myectomy or alcohol septal ablation for those with a labile gradient, limiting symptoms, and who refractory to drug treatment to heart transplantation for those without a gradient.

Hypertrophic cardiomyopathy – An update

Hypertrophic cardiomyopathy (HCM) is the most frequent monogenic cardiovascular disorder, being characterized by

its varied clinical presentation and natural history. In the last 15 years, our understanding has increased of its diagnostic characteristics, genetic factors, and clinical course. The management of the broad spectrum of contemporary HCM has immeasurably progressed after more than 50 years since its discovery by Donald Teare and Eugene Braunwald.¹ This progress in diagnosis and patient management is due to technological advances in genetic testing, cardiac imaging, the prevention of severe arrhythmias, and in surgical and other interventions.²

HCM is estimated to be present in 122 countries and affect about 20 million people. Epidemiological studies based on echocardiography findings have shown a prevalence of one case per 500 people in the general population. However, the prevalence is higher, reaching one case per 200 people, when clinical and genetic diagnoses are considered, including those in family members.³⁻⁵

It is noteworthy that 10% of patients are clinically identified, including 6% symptomatic and 4% asymptomatic; thus, 90% of cases are undiagnosed. Symptomatic patients not recognized as having HCM may not be adequately treated; moreover, the disease might not be detected in first-degree relatives.^{3,6}

HCM, an autosomal dominant disease with variable expressiveness and age-related incomplete penetrance, is usually caused by protein mutations in the cardiac sarcomere. Descendants of an affected person have a 50% chance of inheriting a mutation as well as at risk for clinically presenting the disease. Genetic counseling shows that the most frequently involved genes in 75% of genotyped cases are MYBPC3 and MYH7.⁷

Mutations occur in 11 or more genes that encode contractile sarcomere myofilaments. Genetic test panels show vast heterogeneity and diverse molecules with more than 2,000 sarcomere mutations, making it difficult to locate the mutation. The process starts with the primary gene mutation, followed by impaired protein expression and defective sarcomere function, and ends with post-translational modifications and mitotic factors.^{8,9}

Histopathological elements are the key points that link genotype to phenotype and clinical expression.¹⁰ The clinical phenotype occurs independently of the genetic mutation. Genetic testing screens the family and creates a new group, the genotype-positive relatives without signs and symptoms who need clinical follow-up.¹¹ Patients with the sarcomere protein mutation have a higher prevalence of a family history of HCM

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and sudden cardiac death (SCD) compared to those without the mutation.^{12,13} They also tend to have more severe hypertrophy, mitral valve (MV) morphological abnormalities, abnormal coronary microcirculation function, and myocardial fibrosis.¹⁴

Patients can be asymptomatic, have mild symptoms, or be severely symptomatic. The most common symptoms are dyspnea, precordial pain, fatigue, presyncope, and syncope.

Electrocardiographic changes precede echocardiographic changes and are present in up to 95% of cases with no characteristic pattern. The most common abnormalities are ST-segment and T-wave changes, followed by evidence of left ventricular hypertrophy (LVH).⁷

The diagnosis of HCM is based on a hypertrophic but not dilated left ventricle (LV) (< 15 mm), especially that identified on Doppler echocardiography or cardiac magnetic resonance (CMR).⁷

HCM can progress with complications such as the risk of SCD, arrhythmia, progressive heart failure (HF) and atrial fibrillation (AF).

Recent studies with large populations and longer follow-up periods reported annual mortality rates of 0.5–1.5% after the development of new therapies for each adverse complication of HCM, including implantable cardioverter defibrillators (ICD) to prevent SCD, heart transplantation for end-stage HF, surgical myectomy (or alcohol septal ablation) to alleviate HF symptoms, abolishing LV outflow tract obstruction (LVOT), and ablation procedures via a catheter to control AF.

Current and effective management has changed the natural history of the disease, preventing SCD and reversing HF, transforming contemporary HCM into a treatable disease.⁶

Great changes in the clinical profile of HCM depend on its refined stratification after the initial diagnosis, including patient orientation and the need for a family investigation.^{3,11}

Transthoracic doppler echocardiography

Transthoracic Doppler echocardiography is the diagnostic method of choice for HCM since assesses cardiac morphological and functional patterns in addition to providing data and prognostic information.

Hypertrophy frequently occurs in the anterior basal septum, posterior anterior wall, and posterior medial septum, affecting one or two segments in 10% of cases. Apical hypertrophy and the concentric form occur in 1% of cases.¹⁵

The LV is considered hypertrophic when its wall thickness is ≥ 15 mm. Wall thickness values of 12–14 mm can be considered in patients with a family history of HCM. A septum/posterior wall a ratio > 1.3 without LV enlargement is also used for diagnostic definition. A hypertrophic right ventricle (≥ 8 mm) occurs in one third of cases.^{9,16}

An MV evaluation is imperative. The MV systolic anterior movement (SAM) toward the HCM LVOT has 99% specificity for obstructive HCM of genetic etiology. MV regurgitation is often associated with obstructive HCM and related to SAM (Figures 1A and 1C).¹⁷

An increased left atrial volume > 118 mL denotes LV diastolic dysfunction, mitral regurgitation, and atrial myopathy and is a predictor of HF, SCD, and AF (Figure 1E).^{18,19}

The analysis of LV diastolic and systolic function is essential for patient management. Diastolic dysfunction involves decreased volume due to LVH.²⁰ The study of the E/e' line

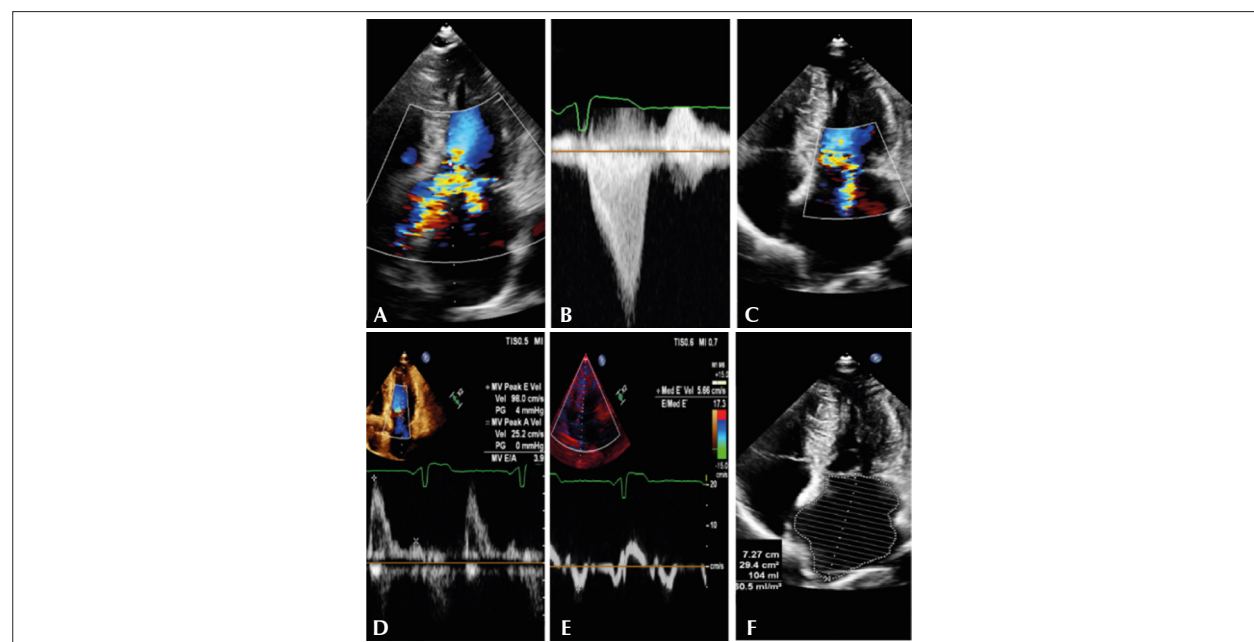


Figure 1 – Doppler echocardiography taken at rest of a 50-year-old man with hypertrophic cardiomyopathy complaining of dyspnea on mild exertion. His brother experienced sudden cardiac death. Our patient used losartan and a beta-blocker for six months. (A and B) Presence of left ventricular outflow tract gradient (55 mmHg). (A and C) With systolic anterior motion and mitral insufficiency. (D, E, and F) Diastolic dysfunction. (D) E/A ratio = 3.9. (E) E/e' ratio = 17.3. (F) LA volume = 60.5 mL/m².

ratio, the propagation velocity of the color M mode, and the peak E-wave velocity predicts exercise tolerance and whether filling pressures decrease after myectomy or alcohol septal ablation.^{21,22}

A tissue Doppler evaluation demonstrates decreased myocardial systolic velocity in obstructive and non-obstructive patients. Decreased mitral annular diastolic velocity (in the absence of LVH), the presence of sarcomere mutation, and tissue Doppler systolic velocity in a lateral annulus > 13 cm/s have 100% sensitivity and 99% specificity for the diagnosis of HCM (Figures 1D and 1E).²³⁻²⁵

Systolic function is usually normal in HCM. LV ejection fraction values should be evaluated using Simpson's method – and the results are often above those considered normal (Figures 2A and 2B).²⁶

Assessment of the left ventricular outflow tract gradient (LVOTG) is an important step in resting echocardiography for HCM patients that can be complemented by an examination under physical exertion. LVOTG is considered obstructive when > 30 mmHg (flow velocity: 2.7 m/s).²⁷ Labile or obstructive LVOTG is defined as an episode not observed during resting echocardiography but induced by exercise testing (Figure 1B). Obstructive LVOTG is characterized by the dagger-shaped sign, which translates a delayed peak of flow, causing subaortic obstruction due to MV SAM toward the interventricular septum in the middle of systole, producing a Venturi effect generated by vigorous ventricular contraction (Figure 1B).

An impedance mechanism in LVOT blood flow generates a pressure gradient between the ventricular cavity and the aorta. This is corroborated by septal thickening and bulging into the LV cavity. The apical displacement of the papillary muscles and the stretching of the anterior MV leaflet reduce the LVOT sectional area due to hydrodynamic forces (Venturi and drag forces), causing MV SAM and an early and rapid LV ejection.²⁷

In rare cases, obstruction occurs in the middle of the ventricular cavity due to papillary muscle and lateral wall hypertrophy without SAM and with apical hypertrophy, which may present hypertrophy in the right ventricular outflow tract. In a minority of cases, muscle apposition occurs in the LV middle cavity associated with apical aneurysm with or without thrombus or with anterior lateral papillary muscle insertion into the anterior MV leaflet.³

It is noteworthy that an LVOTG $\geq$ 50 mmHg at rest contraindicates exercise stress (ES). Patients presenting LVOTG < 50 mmHg at rest and LVOTG $\geq$ 50 mmHg on exertion, if symptomatic and refractory to medications, will be referred for surgical myectomy or alcohol septal ablation.²⁸

A global longitudinal strain (GLS) analysis determines regional, global, and LV function mechanisms. Abnormalities in the myocardium precede LVH in patients with sarcomere mutations; thus, GLS can provide an early diagnosis of this pathology.

In HCM patients, GLS reduction identifies segmentary contractile function changes with or without preservation of the basal to apical gradient. In the absence of LVH obstruction, the GLS is higher, i.e., less negative, and predicts HF. This group, which corresponded to 10% of cases, is currently increasing in tertiary centers, with patients progressing to an ejection fraction < 50%, myocardial thinning, and ventricular cavity dilation.²⁹

Es: key element in the evaluation of hypertrophic cardiomyopathy

Safety

The safety of ES testing in patients with HCM is already well established. The incidence of serious complications such as death, cardiac arrest, and atrial or ventricular arrhythmias was reportedly only 0.04%.³⁰

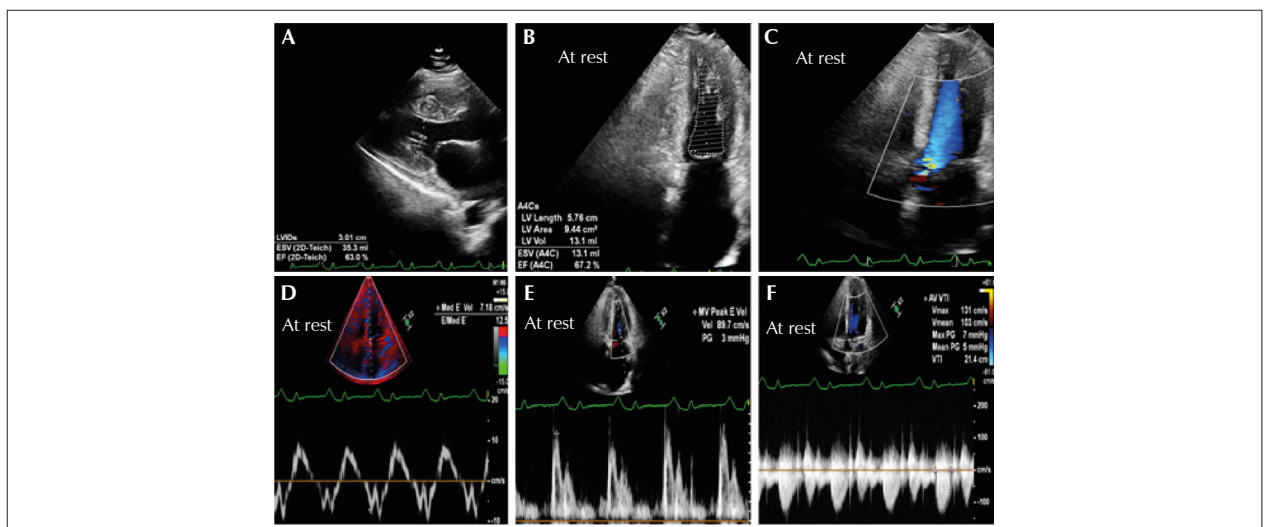


Figure 2 – Exercise stress test performed on an exercise bike by a 38-year-old man with hypertrophic cardiomyopathy. The patient complained of dyspnea on slight exertion. His cousin and aunt had experienced sudden cardiac death, while his mother had died of refractory heart failure. He had used a beta-blocker for four years. Resting data: (A and B) analysis of systolic function. (C and F) Left ventricular outflow tract gradient (7 mmHg). (D and E) Diastolic function. (D) E/e' ratio = 12.5.

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Complications occur when there is a history of presyncope or syncope, significant LVOTG, and decreased systemic blood pressure during the exertion phase.^{30,31} Thus, the test must be conducted by experienced professionals who observe the safety standards for the patient in places that have the ability to manage these possible complications.

A monitoring system including an automatic sphygmomanometer and a 12-lead electrocardiogram monitor is required. ES is currently indicated for patients with HF symptoms, who are at risk of SCD, and who are using an ICD.³²

Indications

The 2014 European Society of Cardiology guidelines for HCM recommend the initial LVOTG assessment of all HCM patients at rest using the Valsalva maneuver in the semi-supine, sitting, or upright positions. These guidelines recommend ES in patients with symptomatic HCM and a peak LVOTG < 50 mmHg.

They do not recommend dobutamine stress testing in patients with HCM⁷ since it is not a physiological test in terms of volume and heart condition status. Dobutamine increases cardiac contractility without increasing preload, resulting in a decreased LV end-systolic dimension in healthy people. These findings in HCM patients are not related to symptoms during exertion or exercise tolerance.³³ However, an ES test is recommended in HCM since it is physiological and provides personalized information, such as symptoms presented during exertion and exercise tolerance, that reproduces daily activities.

Test performance

ES can be performed using a treadmill, a sitting ergometer (bicycle), or an ergometer (supine or semi-supine), but there is no specific recommended modality for HCM patients. The supine bicycle has the advantage of allowing image recording during peak stress and the disadvantages of reaching a lower degree of maximum stress and presenting less reproducibility of clinical symptoms.³⁴

The protocol should be chosen considering the preferences of the patient, executing physician, and institution. Fundamentally, the patient must be encouraged to reach 85% of the maximum heart rate or the onset of limiting symptoms. The test must be interrupted under the following conditions: systemic blood pressure (BP) > 250/120 mmHg; drop in BP > 10 mmHg compared to the pre-test BP; presence of sustained tachyarrhythmia or extensive hypokinesia; or onset of dyspnea and precordial pain.

When complaints of limitations in daily exercises are not reflected in the formal test, the patient's preexisting physical fitness level and motivation should be analyzed, and it is the physician's role to motivate the patient by demonstrating the safety of the equipment and the people involved in the test.³³

It is possible to assess LVOTG, mitral insufficiency (MI), SAM, and segmental changes during the test. The images are recorded immediately after physical exertion on an exercise bike using the Astrand protocol or on a treadmill using the Bruce protocol.

It is recommended that LVOTG be measured more than once. As it is dynamic, the test can be influenced by several situations, such as dehydration, use of diuretics or vasodilators, use of alcoholic beverages, and being performed after eating. Thus, the physician should not be satisfied with a single measurement.

Hemodynamic assessment

The ES test provides valuable information, such as electrocardiographic findings, exertion duration and tolerance, BP and heart rate behavior, magnitude of the gradients reached, and the correlation of symptoms with physical exertion.³⁵

The presence of diastolic dysfunction, dynamic LVOT obstruction associated with mitral regurgitation, and microvascular ischemia lead to different tolerances to ES in patients of different functional classes.

ES is a provocative test for quantifying LVOTG in symptomatic patients without a gradient or with low measurable gradients at rest (< 50 mmHg) and in asymptomatic patients with low gradients (< 50 mmHg).²⁶

Echocardiographic assessment

Left ventricular outflow tract gradient

The echocardiographic assessment is performed after treadmill exercise or during and after exercise on an exercise bicycle. The performance of ES in HCM patients aims to assess LVOTG,^{36,37} SAM, MI,³⁸ ventricular segmental contractility changes,^{39,40} and LV diastolic function.⁴¹

The MV SAM contributes to the LVOT dynamic obstruction mechanism. LVOT systolic Doppler flow gradually increases the velocity in the beginning of systole and accelerates in the middle of it (dagger-shaped). In contrast, MI occurs abruptly in early systole and rapidly increases velocity (> 6 m/s), persisting throughout systole (bell-shaped) (Figure 3).⁴²

LVOT obstruction at low exercise levels has been correlated with decreased functional capacity. LVOTG is a risk factor for sudden death or severe cardiovascular events, although consensus is lacking regarding labile LVOTG.^{7,43,44}

Shah et al. reported that approximately two thirds of HCM patients with precordial pain, dyspnea, and presyncope without LVOTG at rest had labile LVOTG.⁴⁵ This emphasizes the importance of quantifying LVOTG during ES in symptomatic patients even if it is not observed during echocardiography at rest.

Maron et al. reported that 37% of patients with HCM already had LVOTG (obstructive HCM) at rest, 33% had labile exertion-induced LVOTG not observed at rest, and 30% had true non-obstructive HCM with no LVOTG at rest or during exercise.⁴⁶

Echocardiographic findings at rest that cause LVOTG include basal interventricular septum hypertrophy, LVOTG narrowing (> 2 cm), and a markedly increased angle between the LV long axis and the ejection flow ($\geq 35^\circ$).⁴⁷⁻⁴⁹

Some studies reported decreased LVOTG during physical exertion in HCM patients. One study showed that 24% of HCM patients presented a paradoxical response of LVOTG

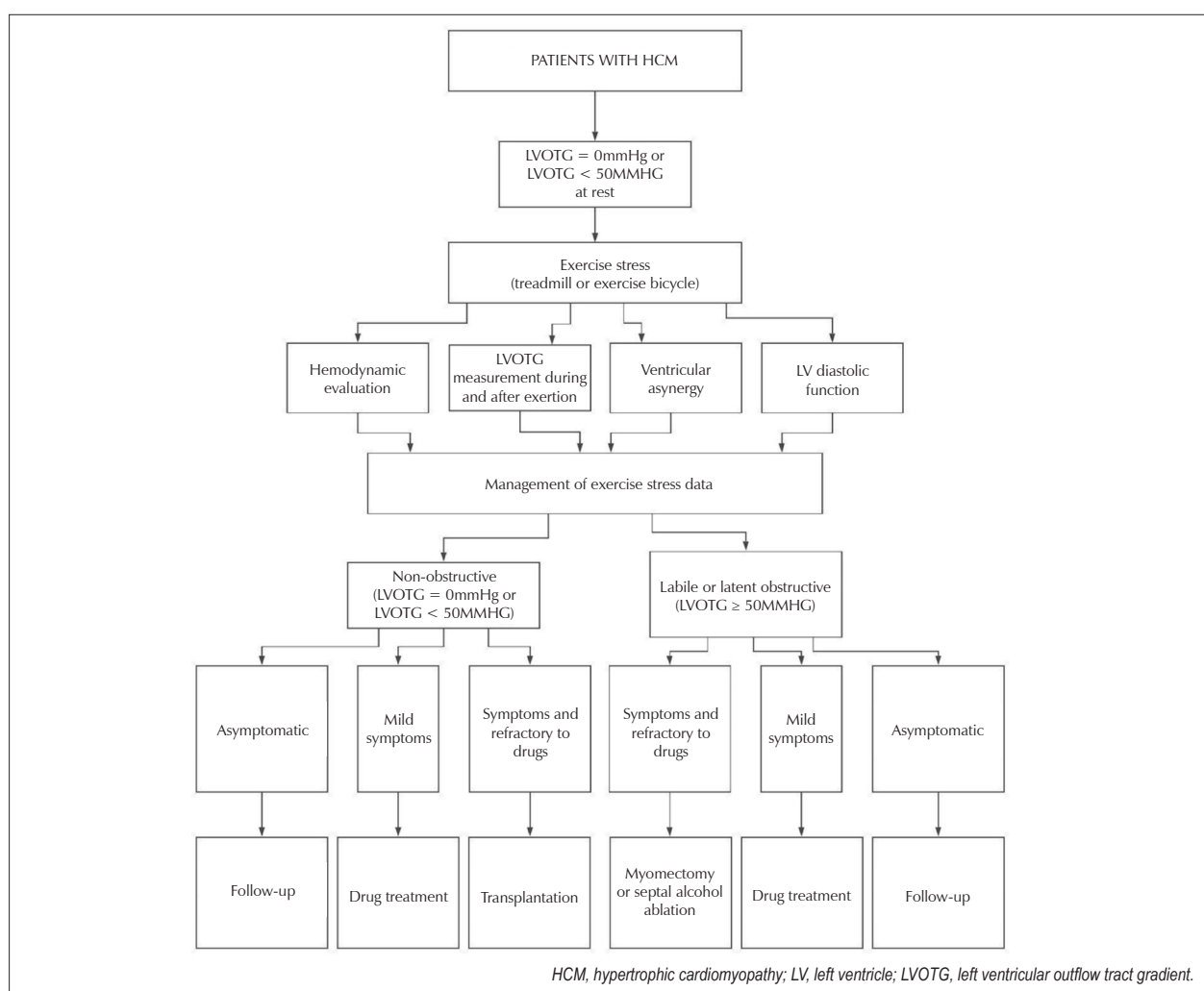


Figure 3 – Flow chart of the use of exercise stress testing in patients with hypertrophic cardiomyopathy without a gradient (left ventricular outflow tract gradient = 0 mmHg) or with a left ventricular outflow tract gradient (< 50 mmHg).

being relieved by physical exertion and a low incidence of cardiovascular events.⁵⁰ It is difficult to observe this phenomenon after ES using a treadmill, as the LVOTG often reappears after the test. To be better understood, LVOTG must be assessed during exercise on an exercise bicycle.

Procedures to decrease LVOTG, such as septal myectomy and alcohol and percutaneous septal ablation, are a Class I indication for symptomatic patients with LVOTG at rest who are refractory to drug therapy.⁷

Such procedures are also indicated as a Class I recommendation for symptomatic cases with a maximum LVOTG peak ≥ 50 mmHg during ES, even if the gradient is not observed at rest.⁷ ES is also useful for determining the postoperative effectiveness of these therapeutic procedures.^{51,52}

Mitral insufficiency

MI in HCM patients is caused by MV SAM or mitral complex abnormalities (valvular cusp, tendinous cords, and papillary

muscles). LVOT obstruction during exertion reportedly causes variable mitral regurgitation.⁵³ In HCM, exercise plays a key role in dynamic LVOT obstruction due to a hyperdynamic LV with a small cavity and MV SAM. SAM is possibly associated with MI. Complications due to morphological abnormalities of the tissues that form the mitral complex, in some cases, are not associated with LVOTG values or MI severity.

MI should be evaluated while LVOTG is being quantified during ES.⁵⁴ Since there is some difficulty distinguishing MI signals from LVSV blood flow signals, special care is required during measurement. These signs can be identified according to the MI velocity curve, which shows a marked increase in early systole with the slope reflecting the rate of increased LV pressure and the LVOT velocity gradually increasing during early systole with an abrupt change. As obstruction worsens, the velocity increases in middle to late systole associated with SAM.

MI signs have a long duration on cardiac auscultation and continue beyond the second heart sound until MV opening.

The flow velocity of mitral regurgitation is always greater than that of LVOT. LVOTG is overestimated when an MI sign is confused with LVOT blood flow.⁵⁵ Therefore, extreme caution is required during assessment (Figures 1A and 1B).

Changes in LV segmental contractility

Peteiro et al. subjected HCM patients to ES and found changes in LV segmental contractility in 7.9% of cases. They reported that these LV changes were independent predictive factors for sudden death and serious events such as heart transplantation.⁵⁶

Reant et al. investigated 115 HCM patients and demonstrated that, although LVEF was maintained during Doppler echocardiography at rest, some presented decreased GLS during exercise and an increased risk of severe events.⁵⁷ They suggested that any findings demonstrating latent ischemia could predict a poor prognosis.

Regardless of LV wall motion abnormality detection, clinical symptoms and test findings suggestive of myocardial ischemia, such as chest pain, abnormal Q waves, and ST-T changes, are frequently observed in HCM patients.⁵⁸ This is due to hypertrophy of the coronary arteriolar sinuses and intimal layers; decreased vasodilator reserve; stenosis due to compression of the intramyocardial coronary vessels, particularly of the septal branches triggered by the myocardium during contraction; decreased coronary artery flow caused by impaired LV relaxation; increased intraventricular pressure triggered by LVOTG; and decreased capillary density caused by hypertrophy and restricted subendocardial perfusion of the myocardium. These findings suggest that the presence of myocardial ischemia during the evaluation of wall movement in ES is associated with prognosis.⁵⁹

The evaluation of epicardial coronary artery disease using anatomical tests such as coronary computed tomography angiography demonstrated that ES presents a 50% false positive rate for myocardial ischemia.⁶⁰

LV diastolic function

LV diastolic function should be analyzed individually on exertion in patients with HCM. Parameters verified at rest, LVOTG behavior, and changes in the segmental contractility of LV walls directly influence filling pressures and LV compliance. In symptomatic patients without LVOTG at rest or on exertion, diastolic dysfunction surprisingly shows a preserved systolic function in the initial phase of HF onset (Figures 4D and 4E).⁵¹

Echocardiographic results management

The clinical course of HCM is diverse and unpredictable; thus, identifying markers that can anticipate outcomes is currently a priority.

ES can dictate decisions in specific cases. Patients without obstruction (LVOTG = 0 or < 50 mmHg) at rest who develop significant symptoms and gradients (LVOTG > 50 mmHg) during the exercise test are referred for myectomy or alcoholic septal ablation. These procedures should prevent the development of HF, improve quality of life, and increase survival. These interventions are indicated for patients with significant gradients (LVOTG > 50 mmHg) at rest⁶¹ as well as symptomatic patients with physiologically provocative gradients.

In contrast, heart transplantation is indicated when patients without significant obstruction demonstrate no gradient increase in ES (LVOTG < 50 mmHg) at rest but present drug-refractory HF symptoms.⁶² Predictors of HF progression in patients without LVOT obstruction include left atrial enlargement and extensive fibrosis on CMR (> 15%).⁶³

Physical exercise reportedly causes a significant gradient in mildly symptomatic HCM patients. These patients progress to New York Heart Association HF functional class III/IV in a short period of time.⁶⁴

A decreased BP during exercise in patients with labile HCM indicates an increased risk of sudden death or serious

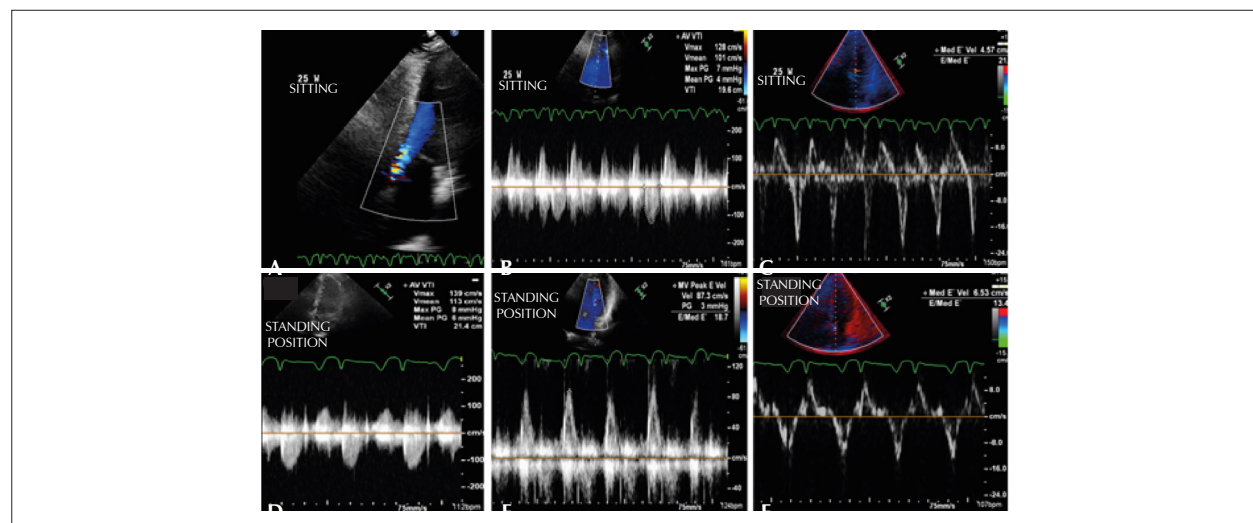


Figure 4 – Exercise stress on an exercise bike during and after exertion of the case shown in Figure 2: (A, B) left ventricular outflow tract gradient analysis on exertion (7 mmHg); (C, D) E/e' ratio = 21.7 on exertion; left ventricular outflow tract gradient analysis after exercise (8 mmHg); E/e' ratio = 18.7 and 13.4 during recovery.

cardiac events. Exercise-related syncope and/or ventricular arrhythmias may indicate the need for ICD implantation⁶⁵ for primary or secondary prophylaxis of SCD since it can reduce mortality from this complication.⁶⁶

With the exception of disopyramide, drugs used to control HCM symptoms have little or no effect on LVOTG at rest. Since the 1960s, it has been known that exercise-induced gradients are reduced by beta-blocker use. Thus, there is evidence that physically active patients with labile gradients should be treated early with beta-blockers to reduce high LV filling pressures during exertion.⁶⁷

Final considerations

ES is currently a reliable echographic method in the clinical evaluation of HCM patients with the power to predict the future development of progressive HF symptoms and differentiate patients with non-obstructive HCM from those with labile gradients. Consequently, ES indicates specific treatment strategies for each patient: surgical myectomy or alcohol septal ablation for those with a labile gradient and limiting symptoms who are refractory to drug treatment versus cardiac transplantation for those without a gradient.

This review demonstrated the role of ES in HCM to predict prognosis and guide decision-making in selected patients with this complex genetic disease.

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Authors' contributions

Research conception and design: KON Leal, IS Tavares, LFG Gonçalves, DP Oliveira, EJ Ferreira, M Aquino, and ACS Sousa; data collection: KON Leal, IS Tavares, UMMC Burgos, JO Belem, and M Aquino; data analysis and interpretation: KON Leal, IS Tavares, UMMC Burgos, and JO Belem; manuscript writing: JO Belem; critical review of the manuscript for important intellectual content: KON Leal, IS Tavares, LFG Gonçalves, DP Oliveira, EJ Ferreira, and ACS Sousa.

Conflict of interest

The authors have declared that they have no conflict of interest.

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