The Diagnosis of Left Ventricular Outflow Tract Obstruction in Hypertrophic Cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy is a prevalent genetic disease characterized by left ventricular hypertrophy, presenting dynamic obstruction of outflow tract with subaortic gradient happening at rest in 30% of the cases. It is attributed to the intricate interaction between the anterior mitral leaflet, the interventricular septum and altered flow vectors generated in left ventricle along with changes in outflow tract geometry. Mitral regurgitation in varying degrees is found with or without association with structural deformities of the valve apparatus. The exercise echocardiogram evidences latent obstruction easily induced by exercise in 60 to 75% of non-obstructive forms. The determination of the gradient under this condition must be considered in routine investigation of patients with mild or no obstruction at rest. The evaluation of hypertrophic cardiomyopathy incorporates methods based on the ultrasound image, which, along with MRI, allow recognizing ventricular obstruction generating mechanisms, thus facilitating the diagnosis and management of obstructive and latent obstructive forms.

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disease of complex nature. Its prevalence is estimated in one per each 500 individuals[1]. It is characterized by left ventricular hypertrophy (LVH) identified in the absence of chamber dilation and any other disease capable of producing a similar anomaly[2]. The dynamic obstruction of left ventricular (LV) outflow tract, developing subaortic systolic gradient, may be evidenced at rest or under provocation[3]. At a smaller rate, forms with midventricular obstruction are found with or without concomitant apical aneurysm and, exceptionally, obstructive impairment of right ventricle[2].

Keywords

Cardiomiopathy, hypertrophic/diagnosis; hypertrophy, left ventricular/diagnosis; echocardiography; Magnetic resonance.

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HCM is transmitted through autosomal dominant inheritance with incomplete penetrance. It is caused by over 1400 mutations in genes encoding sarcomeric proteins or, more rarely, in other proteins related to this structure, such as Z-discs and interleaved discs. The wide phenotypic variation is attributed to the action of environmental and genetic factors[2,4].

In the modern era, HCM was reported between 1957 and 1958 in England, by the pathologist Robert D. Teare[5] and surgeon Russell C. Brock[6], who identified the asymmetric hypertrophy of LV associated to myocardial cell disorganization and subvalvar aortic obstruction of muscular nature. The clinical bases of HCM were defined gradually from the 1960s in fundamental studies developed by Cohen et al.[7], which introduced the current nomenclature[7,8], as well as Braunwald et al.[9] and Wigle et al.[10], whose suggested designations, idiopathic hypertrophic subaortic stenosis and muscular subaortic stenosis, stressed the obstructive character of the disease.

Mechanisms

The left ventricular obstruction was preliminarily interpreted as being fixed, produced by septal hypertrophy and consequent change in the outflow tract's geometry. The dynamic character was suspected by maneuvers which, modifying the preload and afterload, changed the intensity of the murmur generated[9]. The presence of obstruction was subsequently demonstrated during hemodynamic study, by means of drop in ventricular pressure in the outflow tract[11]. At the time, the labile behavior of the obstruction was demonstrated in detailed analyses, through drug interventions with vasodilators or inotropic agents, which, producing reduction in left ventricle volume and peripheral vascular resistance, determined increase in subaortic gradient[9,11]. Notwithstanding this, the likelihood that the gradient was a mere artifact of the rapid ejection and cavity obliteration was still admitted[12].

Angiocardiography helped demonstrate the existence of mechanical obstruction of LV outflow tract triggered by affixation of the mitral valve on the basal septum, which was initially attributed to the vigorous systole[13]. However, the hypothesis that a true hemodynamic obstruction did not exist was still considered, given the labile character and the varying gradients in serial measurements, as well as the tendency to progressively disappear and the lack of correlation with symptom severity[8].

The introduction of echocardiography applied to the diagnosis of HCM between 1969 and 1973 not only allowed the examination of issues previously seen on invasive investigation, but it also contributed decisively to identify non-

obstructive forms and obstruction generating mechanisms. With M-mode echocardiography, it was possible to demonstrate that the flow impedance, rather than caused by muscular constriction, was due to the contact of the anterior leaflet of the mitral valve with the septum during mesosystole, which was longer in patients with more severe obstruction. Otherwise, the contact of the anterior leaflet of the mitral valve with the septum during mesosystole, which was more prolonged in higher obstruction, was a possible cause[14].

Preliminarily, the vision that the systolic anterior motion of the mitral valve (SAM) was the result of the Venturi effect prevailed, whereby the high flow velocity in the outflow tract would lead to suction of this structure towards the interventricular septum[15]. Through two-dimensional echocardiography, the SAM was revealed to begin before ejection, and slightly differentiated from the Venturi effect[16]. The obstruction is truly determined by the complex interaction between septum, mitral valve and flow vectors generated in ventricular cavity. The anterior direction and high systolic flow velocity on reaching the LV outflow tract originate vectors that run across the closed mitral valve and thereby push the anterior mitral leaflet against the septum[17].

Further, this phenomenon sets off the generation of the systolic subaortic gradient resulting from the progressive reduction of the outflow tract surface area. Increasing acceleration of the flow is observed as the mitral leaflet is pushed against the septum by the rising gradient. A continuous feedback mechanism is established, wherein the reduction of the outflow tract produced by the SAM determines a gradual increase of the pressure gradient, which, in turn, imposes even greater degree of impedance to ejection in proportion to its increase. In spite of the obstruction, the antegrade flow persists throughout systole until the aortic valve closure, with prolonged ejection time proportional to the gradient. There is mesosystolic decrease of flow rate greater than 50% after contact of the mitral valve with the septum at gradients > 60 mmHg, with higher reduction in the outflow tract area[17]. In these cases, there is early interruption of longitudinal shortening during systole and mesosystolic closure of aortic valve with detrimental effect relating to the LV mechanical function[18].

The position of the mitral valve leaflets in relation to the outflow tract is fundamental for the obstruction to develop[16]. The anterior displacement of papillary muscles and mitral subvalvar apparatus change the outflow tract geometry, reducing the respective area, favoring the contact between the anterior leaflet and the septum[19]. Fibrous adherences between the septum and papillary muscles, free wall of the LV or mitral apparatus pull this structure anteriorly, contributing to a higher degree of obstruction[20]. Anomalies of papillary muscles identified by magnetic resonance imaging (MRI), include thickening, bifid character and anterior apical displacement, are common in HCM and are connected to the higher prevalence of SAM and higher gradients, regardless of septum thickness[21].

The SAM is more frequent and prolonged in patients with diffuse or extensive hypertrophy involving two to four segments of the LV[22]. Only 25 to 50% of those presenting this anomaly show gradient at rest[23]. In many of them, mild to moderate mitral regurgitation is developed. In non-obstructive forms, mitral movement tends to be absent or be incomplete. In 30% of the cases with obstruction, there are complex deformities involving the mitral valve, such as anterior and/or posterior leaflet lengthening, or even direct implantation in papillary muscles, which can obstruct the outflow tract[24]. In these cases, the mitral valve coaptation point may be displaced anteriorly and be placed along the leaflets, and not on their borders[16]. The anterior leaflet lengthening associated with low-diameter outflow tract is connected to gradient increase[24].

In approximately 30% of the patients with HCM, there is obstruction of LV outflow tract at rest, with a maximum systolic gradient ≥ 30 mmHg, criterion which is adopted for identifying the obstructive forms. Gradients below 30 mmHg, which rise above this level with provocative maneuvers, characterize cases with latent obstruction. Non-obstructive forms are characterized by gradient < 30 mmHg at rest and under provocation. We may conclude that the LV outflow tract's obstruction in HCM has a complex genesis and multiple factors[2]. Hence, correct identification of determining factors is germane for selecting patients and their management.

Diagnosis

The HCM diagnosis is performed routinely by clinical evaluation, and is confirmed using echocardiography or MRI. The molecular genetic study provides definitive identification of the disease in its clinical and preclinical stages, as well as family evaluation, but its application in risk stratification for sudden death is not fully ascertained[2,4].

The differential diagnosis is usually established through non-invasive research and includes athlete's physiologic hypertrophy and, in concentric forms, hypertensive heart disease and cardiac amyloidosis. The genotype determination is critical in the recognition of myocardial storage diseases, such as Fabry, Danon and gene mutations in AMP-activated protein kinase (AMPK), considered clinically indistinguishable phenocopies of HCM[2,4].

Clinical picture

Since the first descriptions of the disease, the potential relation between obstruction of LV outflow tract and cardiovascular symptoms, such as chest pain and dyspnea, on exertion or at rest, have been identified. The chronic obstruction, rather than a stimulus for hypertrophy, causes an increase in LV wall stress, conditioning myocardial ischemia and replacement fibrosis, factors usually implicated in diastolic dysfunction and arrhythmias[15,25]. Physical exercise produces increase of contractility and heart rate, effects which, along with the decrease of peripheral vascular resistance, trigger or determine worsening of obstruction and increase in LV filling pressure[26,27]. Syncope or presyncope may be the consequence of arrhythmias or autonomic disorder[28-30], but would derive from outflow tract obstruction when related to larger exertion or to swiftly assuming standing position[31].

In approximately one third of the patients, there is emergence or exacerbation of symptoms after meals, attributed to arterial vasodilatation, decreased afterload and compensatory increase in heart rate. These changes directly or indirectly lead to worsening of the outflow tract obstruction and elevation of filling pressure, similarly to that observed on exertion[32]. The severity of symptoms presents great daily variation. The increase in ambient temperature, the lower

fluid intake and the use of alcoholic beverages may, due to modifications in heart rate and load conditions, determine the elevation of subaortic gradient[3].

On examination, the obstructive forms are characterized by propulsive and sustained apical impulse with double systolic peak and bisferiens arterial pulse. Fourth heart sound, occasionally palpable, is auscultated. Medium frequency systolic murmur, "crescendo-decrescendo", of variable intensity, is heard at the left sternal border, as well as in aortic and mitral areas, but does not radiate to the sternal notch, neck and axilla. Maneuvers that decrease the pre-and/or afterload, such as Valsalva and standing position, may exacerbate the murmur. On the contrary, the passive elevation of the lower limbs and handgrip reduces its intensity, mitral regurgitation systolic murmur with radiation to the axilla may be observed[8].

Longitudinal analyzes show that the obstruction of the left ventricular outflow tract with peak systolic gradient at rest ≥ 30 mmHg increases the likelihood of death related to the disease[25], particularly in those presenting mild or absent symptoms[33]. The risk of progression to functional class III or IV NYHA and death by heart failure or stroke is greater in the non-obstructive forms, mainly after 40 years old[25]. The latent obstruction is also implied in the development of disabling symptoms and evolution to heart failure[27,34].

Association was demonstrated between the severity of obstruction and predisposition to sudden death, which was also related to the presence of other risk factors[35]. However, the dynamic character of the obstruction makes the detection of independent risk predictor difficult, in addition to the fact that its isolated presence does not stand and indication for implantation of automatic defibrillator[2].

Echocardiogram

The HCM echocardiographic diagnosis centers on the identification of LVH with maximum wall thickness ≥15 mm in the absence of other causes. In family members affected by the disease, measures ≥ 12 mm should be valuated[4]. HCM mutation carriers may present borderline wall thickness or even normal ones[2]. Hypertrophy presents variable degree, extension and location[22]. There is no typical morphological pattern, although asymmetric forms prevail, presenting septum/posterior wall of the LV > 1.3, and anterior and posterior septum impairment, extending or not to the free wall[15,22]. With smaller frequency, there are cases of concentric or isolated hypertrophy of the LV posterior septum, anterior lateral wall or apex[22].

Continous wave Doppler echocardiography identifies the dynamic outflow tract obstruction by recording a typical curve, resulting from the contact of the anterior leaflet of the mitral valve with the basal portions of the interventricular septum during systole[17](Figure 1). The contact may also be related to the posterior leaflet. In many cases, there is variable mitral regurgitation jet directed posteriorly, resulting in SAM with coaptation failure. The presence of anterior or central jet denotes mitral valve structural abnormalities[15].

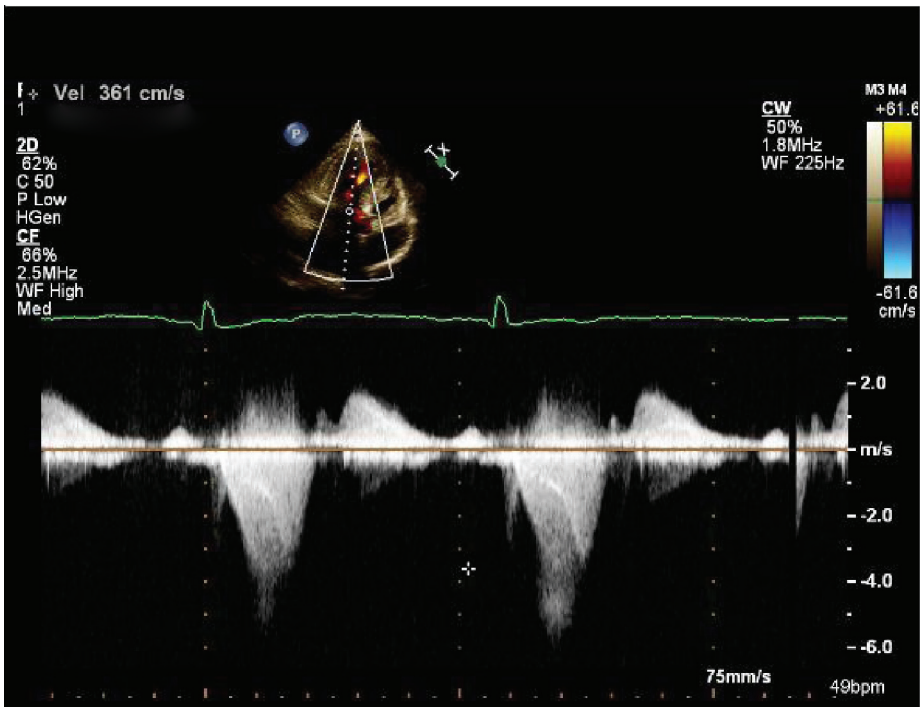


Figure 1 – *Continuous Doppler of obstructive hypertrophic cardiomyopathy: systolic gradient in left ventricle outflow tract = 48 mmHg at rest. Differentiation between mitral regurgitation (1st beat) and systolic gradient (2nd beat) by the most medial/anterior transducer orientation.*

The gradient estimated by Doppler echocardiogram shows a strong correlation with that one measured simultaneously by hemodynamic study[36]. Spontaneous change of gradient at rest of ± 32 mmHg was observed in consecutive measurements, with continuous Doppler, along five days[37]. Marked gradient labile character was evidenced in serial invasive measurements performed during a 48-hour period[38] and in multiple measurements during the same procedure. The assessment of gradient at rest should not be restricted to an isolated measurement. The precise dynamic nature of the obstruction should be properly valued, especially in the clinical evaluation of symptomatic patients, owing to its therapeutic implications.

Most patients do not present dynamic obstruction of the LV outflow tract at rest, but it tends to develop after provocative maneuvers capable of modifying the pre-and/or afterload or determine increased contractility. The assessment under provocation is indicated in symptomatic patients with reduced or absent gradient at rest. It should be practiced preferably under physiological exercise or, alternatively, through the Valsalva maneuver, or else under amyl nitrite administration. The isoproterenol infusion during cardiac catheterization is reserved for doubtful cases[2]. The use of dobutamine is discouraged due to lowly-specific response, capable of inducing obstruction in normal individuals or those with other heart diseases[2,27]. The application of Valsalva maneuver and other pharmacological provocative measures is controversial, since it does not reproduce the physiological conditions in which the obstruction typically develops[2]. The characteristic symptoms of the disease are more frequently induced by posture abnormalities and increase in contraction during exercise than with vasodilatation or hypovolemia[39].

The Valsalva maneuver increases or induces SAM (Figures 2A and B), but it underestimates the presence or magnitude of the exercise-induced gradient with sensitivity of only 40% for identifying the obstruction[27]. However, it is more sensitive than measurements in standing position[40]. In a series of patients submitted to percutaneous alcohol septal ablation, but, even though its application is arguable for recording purposes[41], the Valsalva maneuver and the exercise were found to produce similar degrees of elevation of the gradient in outflow tract[42]. In another series, the obstruction was triggered by the standing position in 21.6% of the cases and by moderate exercise in 34.5%[43].

The exercise echocardiogram is considered the most physiological and effective modality for evaluation of the obstructive component of HCM, particularly in cases with latent obstruction[2]. Studies demonstrate, by means of distinct methodologies, that 60 to 75% of the patients with baseline gradient ≤ 30 or 50 mmHg present ventricular obstruction easily induced by exercise[26,27,44]. History of syncope or presyncope, complete or incomplete SAM at rest, and the degree and extent of LVH evaluated by Wigle score[15] were considered independent predictors of higher elevation of the gradient during exercise[27]. A lower number of patients with obstruction triggered this way develops concomitant mitral regurgitation, which would mean that the subaortic gradient would be the most important factor determining the reduction of functional capacity[27].

Current guideline considers exercise echocardiography a class IIa, level of evidence B, indication for the detection and quantification of LV outflow tract dynamic obstruction in patients with a resting peak instantaneous gradients ≤ 50 mmHg, specially in symptomatic forms[2].

In studies using exercise echocardiography in HCM have initially grounded the determination of gradient in outflow tract in a single measurement, at the the peak of exercise[26] or immediately after it, in supine[27,44]. Consecutive measurements under baseline conditions in supine and orthostatic position, and after, at the peak of the exercise and on the recovery phase in orthostatism showed a continuous elevation of the gradient[45]. In a later study, the peak of exercise gradient was demonstrated to present correlation with that on the supine recovery phase, and that the early development of obstruction was associated to higher reduction of function capacity[46]. In other set of cases, although elevation of gradient in 76% of the patients in standing position has been observed, a higher increment was found in exertion, in measurements made in supine recovery phase[40].

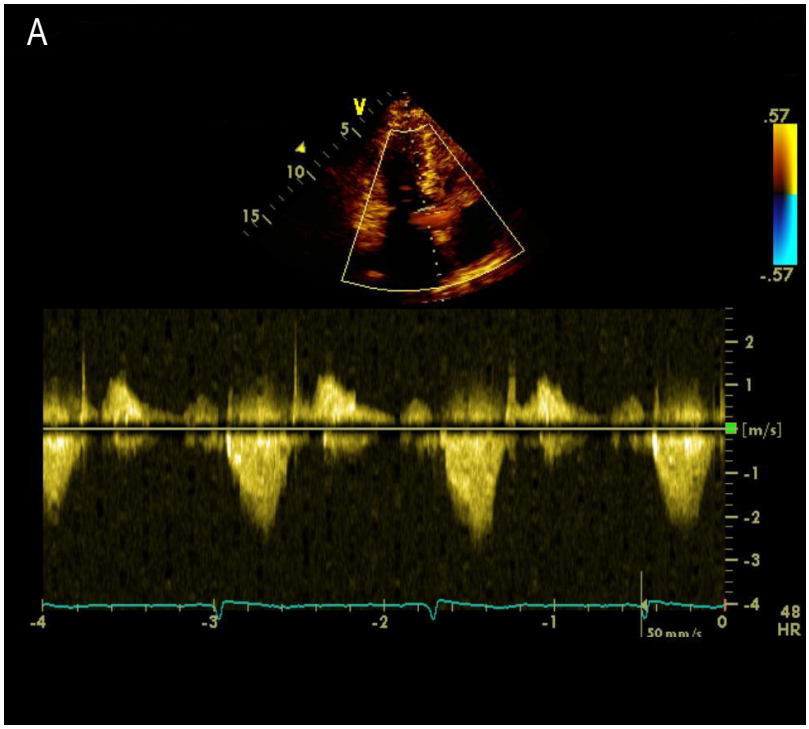
The record of the gradient at the peak of exercise while standing is believed to guarantee higher reliability compared to the usual activities involved in the onset of symptoms. Technical difficulties in obtaining the images can be minimized by greater operator's training and positioning of the patient's left arm on the head[40], or through the use of transducers with continuous hands-free recording[47].

Although there are restrictions on the performance of exercise testing in obstructive and non-obstructive forms of HMC[48,49], it is considered a safe procedure with low severe complication rates[50-52]. In recent studies, which jointly evaluated 1,747 patients with the disease, through stress echocardiogram, nonsustained ventricular tachycardia was detected in 1.2%[51] and 1.9%[52] of the cases, and ventricular fibrillation in only 0.2%[51] or there was no mention to complications[27,44].

The assimilation of exercise echocardiography in the routine evaluation of HCM, especially in symptomatic patients with absent or reduced gradient at rest, has decisive therapeutic implications, capable of changing paradigms. The excelent long term survival in obstructive forms after myectomy would indirectly prove the interaction between obstruction and prognosis[3]. The invasive, percutaneous or surgical treatment is indicated to patients who present limiting symptoms and gradient at rest or under provocation ≥ 50 mmHg[2]. The percutaneous alcohol septal ablation demonstrates comparable beneficial effects in cases with obstruction at rest or only under provocation[53]. A recent study shows that latent obstructive forms submitted to myectomy present symptomatic improvement and survival similar to normal population.

Tissue doppler

Tissue Doppler echocardiography shows minimal changes in left ventricular function by real time quantification of axial and longitudinal displacement of the myocardium. In HCM with normal ejection fraction, there was reduction in systolic myocardial velocity (S'), even in segments not presenting hypertrophy[55]. The early diastolic velocity (E') is diminished and



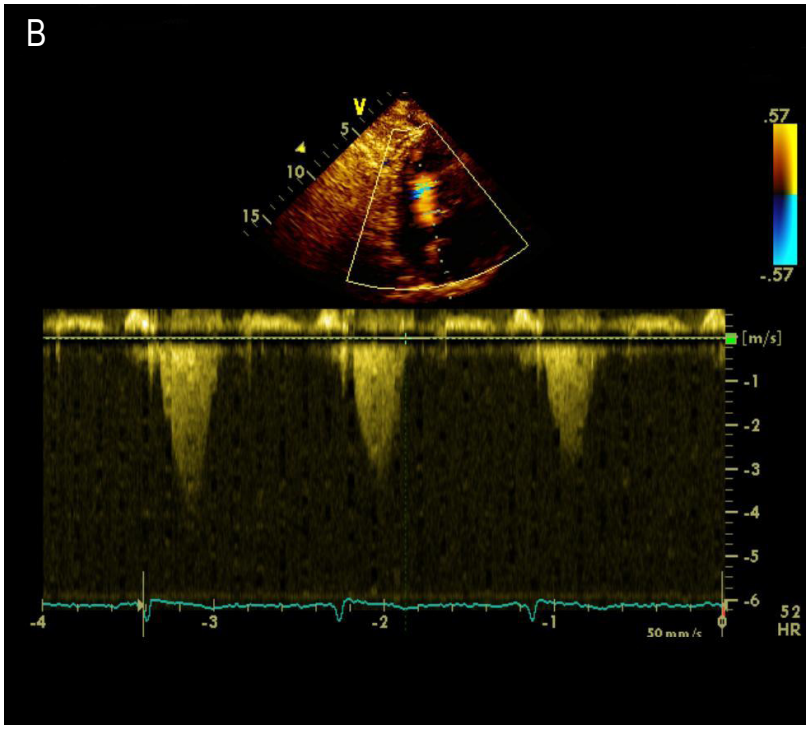


Figure 2 – *A) Latent obstructive hypertrophic cardiomyopathy: resting systolic gradient = 25 mmHg. B) Elevation of the gradient to 50 mmHg with Valsalva maneuver.*

related to the magnitude of LVH[55]. There is negative correlation between systolic and early diastolic velocities and the gradient of the outflow tract, which is also associated to the elevation of the E/E' ratio, which estimates the LV filling pressure[56,57]. A higher degree of LVH in presence of obstruction ≥ 30 mmHg would be a determining factor for significant elevation of the E/E' ratio[58]. In obstructive and non-obstructive forms, the functional capacity presents negative correlation with lateral E', lateral E/E' and left atrium volume index, but it is not related to the gradient or outflow tract and the LV maximum wall thickness[59].

Strain/strain-rate and speckle-tracking

The introduction of strain/strain-rate facilitated the overcoming of limitations inherent to tissue Doppler imaging, as it allowed to assess of LV wall motion and its effects on systolic and diastolic function. While estimating the LV deformation frame to frame, two-dimensional strain or speckle-tracking analyzes parameters of myocardial contraction independent of angle, presenting advantage over the strain derived from tissue Doppler imaging. The analysis of speckle-tracking strain in patients with the disease undergoing exercise shows that the dynamic obstruction of the outflow tract determines delay in untwisting of the LV, an effect related to the increased filling pressure and maximal oxygen consumption[60]. Untwisting rate from peak systolic twist to mitral valve opening was negatively correlated with the E/A ratio, showing a possible relation of this mechanism to the development of diastolic disfunction[61]. However, a recent study demonstrated that the alcohol septal ablation, although determining reduction in the gradient and myocardial mass, did not produce longitudinal two-dimension strain improvement in the 36-month follow-up, which would minimize the influence of obstruction and the degree of hypertrophy on the LV global systolic function[62].

Three-dimensional echocardiography

The real-time three-dimensional echocardiography allows detailed evaluation of the morphological changes undergone by the LV in HCM, with performance comparable to MRI and notably better than two-dimension echocardiography[63]. The qualitative and quantitative analysis of the LV outflow tract reveals asymmetric and eccentric form, with reduced transversal area relating to normal individuals[64]. Correlation is found between the subaortic gradient, the maximum velocity and the lowest area measured of the outflow tract[65]. The real-time geometric analysis demonstrates that SAM is asymmetric and dominantly medial, resulting in lateralization and narrowing of the outflow tract[66]. Sequential dynamic geometric abnormalities of the mitral apparatus, relating to the interaction between the coaptation point in mesosystole, papillary muscles and basal septum, have significantly contributed to generate subaortic gradient[67].

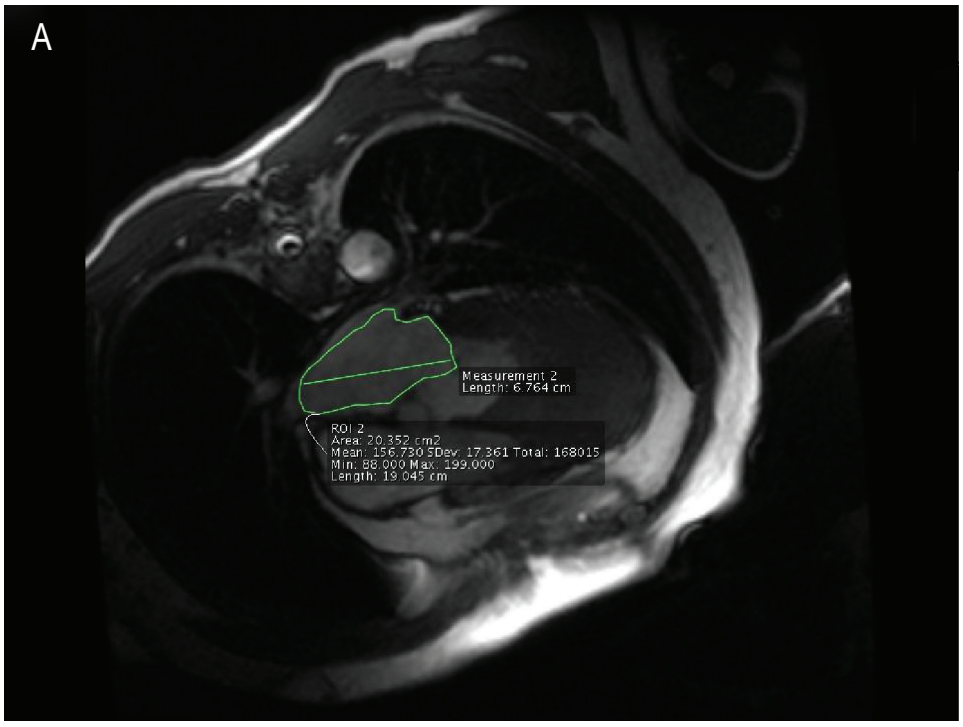
Magnetic resonance imaging

MRI allowed to redefine the phenotype of HCM by adding accurate information about the structure, morphology and function of the cardiac chambers through three-dimensional images of high spatial and temporal resolution in any plan[68, 69] (Figures 3 A and B). It quantifies accurately than echocardiography the LV global and segmental systolic functions[69]. Furthermore, it allows to detect hypertrophy restricted to the anterior lateral wall and apex, in addition to apical trabeculations and aneurysms[69]. It demonstrates that the hypertrophy may occur in less than 50% of the LV and be restricted to one or two segments. A greater degree of thickening happens on the basal anterior free wall of the LV adjacent to the anterior septum. Hypertrophic segments alternate with normal ones in a pattern not detected in other heart diseases. The number of hypertrophic segments is greater in hypertrophic obstructive forms than in non-obstructive ones[70]. The LV mass is related to maximum wall thickness and gradient at rest. The LV index mass is normal in 20% of patients with the phenotype and shows a sensitivity greater than the maximum wall thickness as a predictor of prognosis[71].

The LV outflow tract area is determined by MRI through planimetry. The adoption of 2.7 cm^2 as the cutoff point identifies obstruction in 100% of cases compared to Doppler[72]. The MRI demonstrates contact between the septum and the anterior mitral leaflet in multiple and distinct axis. Three-dimensional cutoffs are useful for analyzing the relationship between the septum and obstruction, as well as the consequences of the outflow tract narrowing on the flow acceleration, turbulence degree, SAM and mitral regurgitation. The maximum gradient is determined through measurements taken along the most narrowed segment of the outflow tract[69]. Distortion factors may interfere with the measurements of these parameters[72]. The angle formed between LV and the aortic root, more acute in HCM, is considered a predictor of gradient regardless of the thickness basal septum[73].

MRI with gadolinium detects and quantifies fibrosis areas with delayed enhancement (DE) of focal or diffuse character in 60-80% of patients with HCM, representing 0-40% of the LV myocardial mass[74-78] (Figure 4). The DE is associated with the record of nonsustained ventricular tachycardia in Holter in multivariate analyses[75,78], as well as the left ventricular reshaping and evolution of terminal dilated forms[74]. The association with the obstruction was not found in a study in which the prevalence of obstructive forms was similar between those with and without DE[76]. Longitudinal analyses showed relation between DE, sudden death and increased mortality, but it is still not proved[76-78]. Further investigations are necessary for the DE to be recognized as an independent prognosis predictor and a factor predisposing to sudden death[2].

MRI is indicated in the investigation of HCM when echocardiography is inconclusive or additional information about LVH, anatomy of the mitral valve and papillary muscles or fibrosis presence is needed[2]. MRI also contributes to the therapeutic planning and evaluation of results. In alcohol septal ablation, it identifies the transmural nature and the lowest and posterior location of the necrosis area, usually around 10%. In myectomy, it shows that the resection is restricted to the basal septum, ensuring greater gradient reduction[79]. In cases with severe obstruction and LV wall thickness slightly increased or normal, MRI detects structural anomalies of the mitral valve and/or papillary muscles responsible for the obstruction and which may be surgically corrected[21].



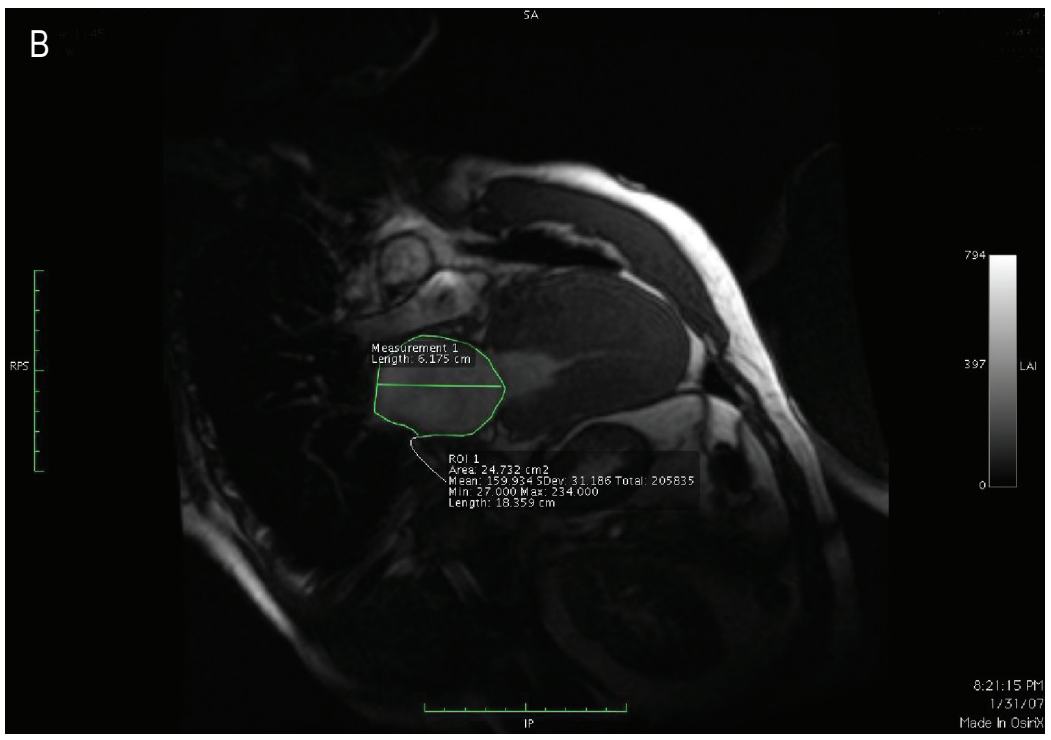


Figure 3 – *MRI of hypertrophic obstructive cardiomyopathy highlighting left atrial volume and left ventricular hypertrophy. A) 4-chamber view, B) 2-chamber view.*

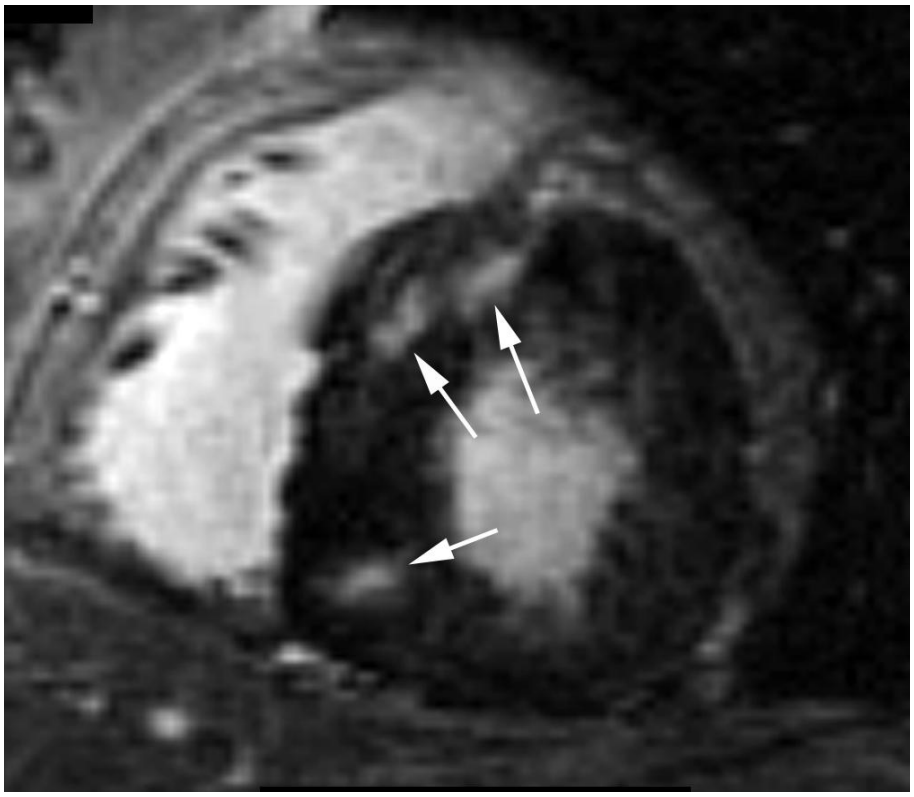


Figure 4 – *Magnetic resonance imaging with gadolinium of obstructive hypertrophic cardiomyopathy: delayed enhancement with diffuse pattern.*

Conclusion

We conclude that, in HCM, the obstruction of LV outflow tract, a prevalent characteristic with complex genesis, may influence clinical outcome patterns and mortality rates. Although it is detectable in the routine evaluation, it requires detailed, static and dynamic investigation by imaging methods in order to improve the diagnosis and management of obstructive and latent obstructive forms.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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