The Role of Mitral Valve in Hypertrophic Obstructive Cardiomyopathy: An Updated Review

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Abstract: Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease and the most common cause of sudden cardiac death in young population, especially in athletes under 35 years old. Mutations occur primarily in the β-myosin heavy chain gene and involve the cardiac myosin-binding protein C gene. In this review we would like to focus on the importance of the examination of mitral valve apparatus and the mitral valve abnormalities in patients with HCM. Abnormalities in mitral valve (elongated mitral leaflets, displacement of papillary muscles, and systolic anterior motion) may be the primary pathognomonic elements, even in the absence of hypertrophy. Echocardiography is the gold standard for the diagnosis of HCM. Magnetic resonance imaging emerges as one of the most important imaging modalities for precise diagnosis, assisting in risk stratification and treatment strategy. Mitral valve abnormalities take part fundamentally in the formation of systolic anterior motion of the mitral valve and, they have substantially been repaired surgically. Although myectomy addresses the septum reduction, obstruction relief should be maximally achieved with a potential combination of myectomy and mitral valve repair. (Curr Probl Cardiol 2021;46:100641.)

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, which is associated with sudden cardiac death (SCD) in young patients. It affects the left ventricle with predominantly left ventricular (LV) hypertrophy. The degree of the maximal wall thickness is considered an important risk factor of sudden cardiac deathSCD. HCM can lead to SCD, mainly due to ventricular arrhythmias. Among the other risk factors, left ventricular outflow tract obstruction (LVOTO) is the most common feature in HCM. Abnormalities of the mitral valve (MV) apparatus are features of HCM. These abnormalities include elongated leaflet length,[1-4] thick leaflets,[5] displacement of papillary muscle (PM),[6-9] and systolic anterior motion (SAM) of the MV,[10] not only from anterior leaflet but also, one of the rarest phenotypes, from the posterior mitral leaflet (PML).

Studies of HCM populations based on autopsy or after operative treatment with myectomy and/or excision of the MV have suggested that the MV apparatus may be abnormal, belongs to the HCM pathophysiology and may be the only feature of this heart disease by the time of diagnosis even without hypertrophy.[15]

Abnormal Mitral Valve Leaflets

In HCM, the anterior mitral leaflet (AML) averages 34 mm compared with healthy individuals with an average of 24 mm.[11,12] Sherrid et al.[13] termed this abnormality the "nightcap" MV because of its morphology at the moment of systolic coaptation (Fig 1). Elongated mitral leaflets extend into LV with a mean of 26 mm above the annulus vs 13 mm in healthy population.[14]

Elongation of MV leaflets has been observed in subjects with mutated genes related to HCM but who have not yet developed LV hypertrophy, suggesting that elongation can be a primary phenotypic expression.[15]

In the study from Maron et al.,[15] the AML and PML lengths were greater among HCM patients than control group. Interestingly, among HCM group, no relationship has been found between AML or PML length and either LV mass index or septum thickness. Another important result of the study demonstrated an association with mild hypertrophy and markedly elongated mitral leaflets ($\geq$30 mm in length), compared with patients with extreme LV hypertrophy. Furthermore, no differences

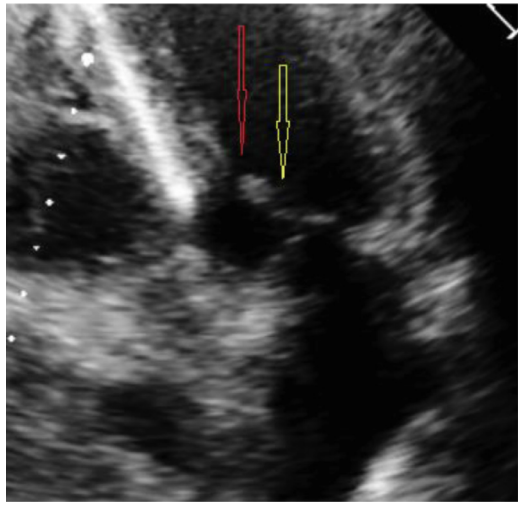

FIG 1. Apical 4 chamber view, TTE, systole. Yellow arrow: elongated mitral leaflets, red arrow: systolic anterior motion (SAM) can be appreciated. (Color version of figure is available online.)

were evident in either AML or PML leaflet length with respect to the presence or absence of late gadolinium enhancement.

Another study from Groarke et al.[16] demonstrated that HCM sarcomere mutation carriers have anterior MV leaflets that are disproportionately elongated relative to their LV cavity size. Ratio of ALL/LVEDVi

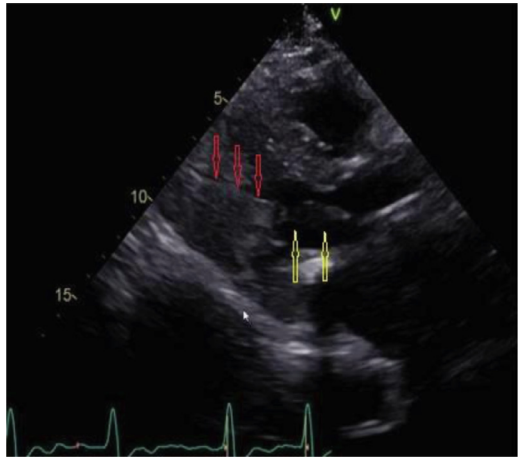

FIG 2. Parasternal long axis view, TTE. Anomalous papillary muscle (red arrow) inserts without chordae into the anterior leaflet and tents it anteriorly (yellow arrow). (Color version of figure is available online.)

and ALL/LVOT diameter were higher in subclinical subjects compared to controls. Absolute ALL and ALL indexed to BSA, LVEDVi, and LVOT diameter were significantly higher in overt HCM patients compared to control group. Control and subclinical HCM groups had similar AML thickness, but the group with overt HCM had significantly thicker AML. The subclinical group consisted of mutation carriers without LVH.

Displacement of Papillary Muscles

Anterior displacement of PMs in the LV was first described in 1974.[17] Anterior displacement leads to an anterior position of the coaptation plane of MV into LV cavity. This anatomic constellation predisposes to SAM.[18,19,20,21]

Two of the most frequent abnormalities of the PMs are an anterior and basilar displacement of the base of the anterolateral PM, as well as abnormal muscular connections between PM head and the anterolateral wall.[22] Magnetic resonance imaging (MRI) studies from Kwon et al.[23] have shown higher frequency of bifid PM and anterior displacement of the anterolateral PM. Furthermore, there was an evidence of closer proximity between the superior PM and the ventricular septum.

Another interesting finding based on MRI studies has been the direct insertion of a head of the anterolateral PM directly into the middle of the AML without chordae (Fig 2). This direct insertion may give rise to obstruction by apposition of the PM with the septum.[24-26]

Systolic Anterior Motion

LVOTO in patients with HCM is primarily due to SAM of the AML, which contacts with the interventricular septum (IVS) during systole. Furthermore, SAM can also appear without hypertrophy, in case of anomalous insertion of PM, elongation of mitral leaflets and quite rarely, due to SAM of PML. Therefore, obstruction to the LVOT happens because of structural abnormalities. Interestingly, LVOTO can also be provoked or altered by a change in the physiological conditions (dynamic LVOT

TABLE 1. SAM-grading and echocardiographic criteria (Pollick et al., 1982)

Grade 0	Nonexisting
Grade 1	Deviation > 5 mm (M-Mode)
Grade 2	Nonholosystolic contact to ventricular septum
Grade 3	Holosystolic contact to ventricular septum

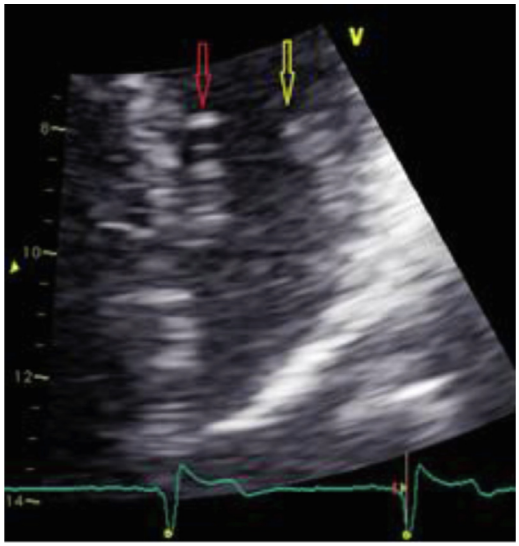

FIG 3. Apical 4 chamber view, TTE, end diastole. Red arrow: AML, yellow arrow: PML. (Color version of figure is available online.)

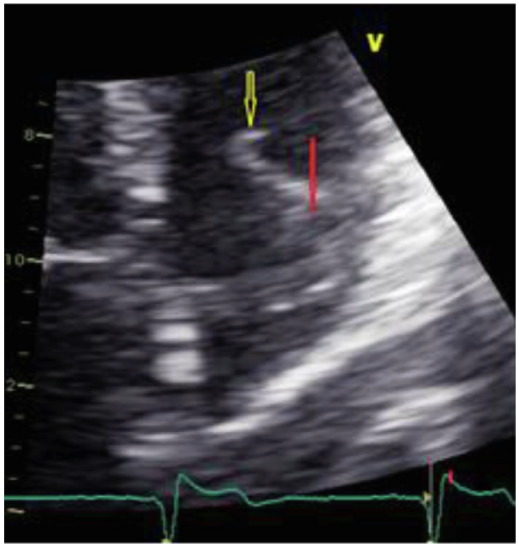

FIG 4. Apical 4 chamber view, TTE, early systole. Red arrow: AML, yellow arrow: PML. Elongated leaflets, coaptation of AML on the basis of PML. (Color version of figure is available online.)

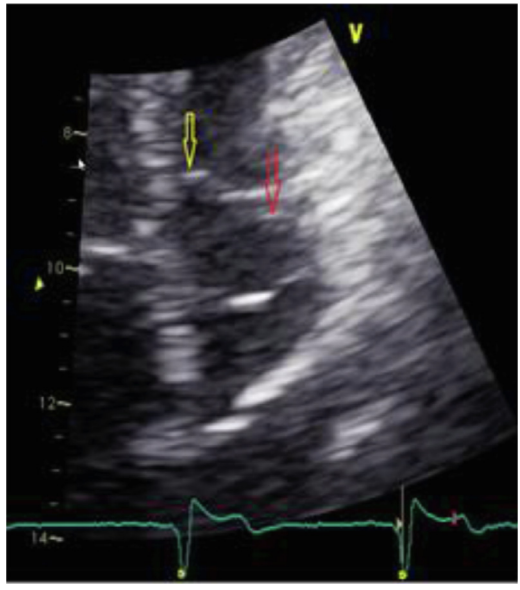

FIG 5. Apical 4 chamber view, TTE, mid systole. Red arrow: AML. Yellow arrow: SAM of PML, contact of PML to ventricular septum. (Color version of figure is available online.)

obstruction). The diagnosis of LVOTO is important to eliminate the factors that can potentially intensify the obstruction.

Concerning LVOTO, the movement of the anterior leaflet toward the IVS, and less often the PML during the Systole, the so-called SAM

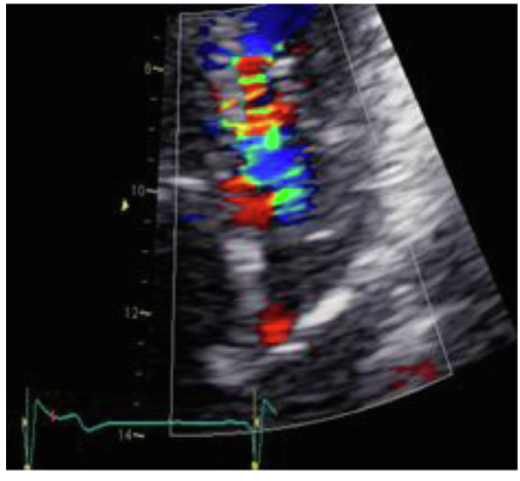

FIG 6. Apical 4 chamber view, TTE, mid systole, color-Doppler. Flow acceleration in LVOT due to SAM of PML can be appreciated.

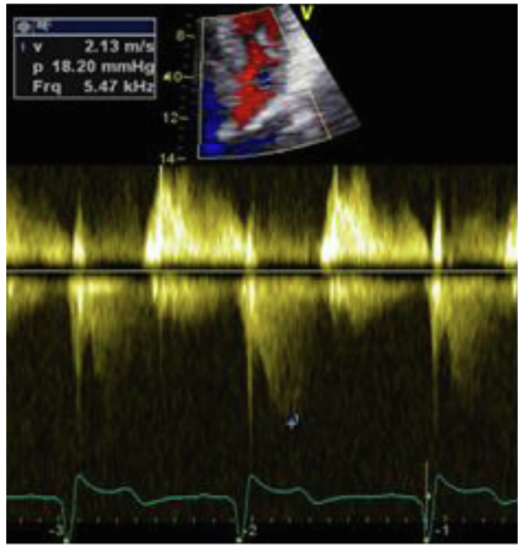

Fig 7. Apical 4 chamber view, TTE, early systole, continuous wave Doppler. LVOTO with a peak gradient of 18 mm Hg without Valsalva maneuver. A typical dagger-shaped CW-signal can be appreciated.

phenomenon with subsequent contact of ventricular septum in midsystole is the reason for the obstruction. In the study of Sherrid et al. has been shown, that the SAM phenomenon is the result of a drag phenomenon in the sense of thrust effect of the AML due to LVH, particularly of septum. Blood flow in the LVOT occurs already at low blood flow speeds and not through the original blamed venturi effect, which increases blood speed in the LVOT, which is required to pull the mitral leaflet to the LVOT. The combination of SAM phenomenon and pre-existing septal hypertrophy gives rise to flow acceleration and subsequently to a pressure difference (gradient) in the LVOT.[27]

Echocardiography is considered as the gold standard for the diagnosis of HCM. SAM can be visualized with M-Mode or in 2-D display. The color Doppler mode assists for the quantification of mitral regurgitation (MR). MR jet in this case is posteriorly directed. The grading of the SAM phenomenon can be on a scale of 0-3 (Table 1).[28]

SAM of PML

Although less common, SAM of PML has already been described. This kind of SAM can be diagnosed with 2-D echocardiography with apical views (Figs3-7).

During end diastole, the edge of the AML coapts with the basis of the PML. Because of flow acceleration and Venturi effect, PML will be dragged toward LV outflow tract, resulting in obstruction. Although secondary MR may appear, it is the result of leaflet malcoaptation. In the SAM of PML, the unbalanced traction force plays a major role. Another variant of SAM of PML is the elongation of the middle portion of the leaflet, which comes into apposition with the IVS during systole.[29]

Discussion

In case of HCM, sarcomere mutations are related with abnormalities of the MV, which predispose to SAM. These abnormalities may be early phenotypic consequences of sarcomere mutations in the absence of hypertrophy.

Elongation of MV leaflets is independent of other HCM pathological features, therefore being considered as a primary phenotypic expression. This abnormality plays a key role in the dynamic obstruction of LVOT. Apart from echocardiography, MRI belongs also to diagnostic armamentarium and continues to emerge as one of the most important method for precise cardiac imaging.

Based on epidemiological studies, there are no data regarding the prevalence of MV abnormalities in HCM with or without hypertrophy. However, based on meta-analysis studies which investigated the outcome of surgical myectomy, 58% of patients underwent MV repair and 42% had MV replacement. Furthermore, several valve abnormalities, which were overlapped to each other, were degenerative in 31%, myxomatous in 20%, restrictive chordal 19%, restrictive leaflet in 70%, and long leaflet in 56%. Patients undergoing MV repair had higher prevalence of long leaflets and degenerative MV pathology.[30]

Considering therapeutic approaches of HCM, medical treatment includes beta-blocker, verapamil in case of side effect due to beta-blocker or noncardiac contraindication of beta-blocker and additional disopyramide in case of persistent LVOT gradient, persistent symptoms, and absence of contraindication to disopyramide. In patients with refractory symptoms and an already existing pacemaker, DDD pacemaker upgrade with short atrioventricular delay is an option. Furthermore, patients may

need a more invasive management and may have to undergo myectomy or alcohol septal ablation (ASA).[31]

In patients with systolic gradients ≥50 mm Hg who are not possible to control their symptoms with pharmacotherapy or who have side effects, septal myectomy is recommended. At this stage a very careful examination of MV apparatus is essential. Preoperative echocardiography and MRI can discover the mitral abnormalities in patients with HCM. This is very important as can directly lead to a judgment for surgical septal myectomy rather than ASA, because ablation only addresses the septal thickening. In case of distinctive and pronounced MV abnormalities, ASA alone perhaps may be not sufficient and surgical MV repair in association with septal myectomy is probably the preferred approach.[32] Finally, taking however into account that ASA has exceptionally good results, the final judgment call belongs to the patient after providing him precise information and clarification of both septal ablation and myectomy, ideally in expert HCM centers.

Conclusion and Future Aspects

In case of HCM, absence only of hypertrophy is perhaps not an evidence of a benign or a mild form of this cardiomyopathy. Careful examination of MV apparatus in rest and under Valsalva maneuver should always take place. Anatomic abnormalities, such as elongation of mitral leaflets, displacement of PM and SAM of AML or PML may be the only phenotypic expression of the same genetic background by the time of diagnosis and in the absence of hypertrophy can lead to LVOTO.

Future research would be useful to address how genotype affects the presentations of these particular phenotypes, prevalence of MV abnormalities with or without hypertrophy and to whether or not MV abnormalities should play any role in sudden death risk stratification.

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