

**REVIEW**

# Contemporary management of obstructive hypertrophic cardiomyopathy: focus on technical advances in surgical myectomy

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**Abstract:** Hypertrophic cardiomyopathy (HCM) is a common genetic cardiac disease characterized by a diverse clinical presentation and natural history. Many affected individuals have mild or no symptoms and remain undiagnosed, others develop severe heart failure, and some die suddenly, often at a young age and in the absence of previous symptoms. Left ventricular outflow tract obstruction is the most frequent cause of heart failure. Abolition of outflow obstruction and alleviation of symptoms in drug-refractory patients requires invasive intervention. In the 1960s, surgical septal myectomy emerged as the primary strategy to relieve the obstruction. Since the 1990s, alcohol septal ablation has become a frequent alternative to myectomy, because it reduces the obstruction without requiring open-heart surgery. However, in recent years, the enthusiasm for septal ablation has decreased because of its arrhythmogenicity and incomplete abolition of obstruction. On the other hand, during the last 15 years, surgical myectomy has undergone important technical evolution and has become one of the safest open-heart procedures, with an operative mortality of <1% when performed by experienced surgeons at specialized centers. The operation substantially improves quality of life, prolongs survival and is considered by the international HCM guidelines the gold standard for invasive treatment of outflow obstruction.

**Keywords:** HCM, ventricular obstruction, surgical myectomy

**Rezumat:** Cardiomiopatia hipertrofică (CMH) este o boală cardiacă genetică și are atât o prezentare clinică cât și o istorie naturală diversă. Mulți dintre indivizii afectați sunt asimptomatici sau prezintă simptome ușoare, astfel rămânând nediagnosticsați, alții dezvoltă insuficiență cardiacă severă, iar unii mor subit, deseori la vârste tinere, în absența altor simptome. Cea mai frecventă cauză de insuficiență cardiacă este obstrucția tractului de ejeție al ventriculului stâng. Eliberarea obstrucției tractului de ejeție și ameliorarea simptomelor la pacienții ce nu răspund la terapia medicamentoasă necesită intervenții invazive. În 1960 miectomia septală chirurgicală a apărut ca primă strategie de a elibera obstrucția la acești pacienți. Din 1990 ablația septală cu alcool a devenit o alternativă frecventă la miectomia chirurgicală pentru că reducea obstrucția fără a necesita o intervenție chirurgicală. Totuși, în ultimii ani a scăzut entuziasmul pentru ablația septală din cauza potențialului său aritmogen și a eliminării incomplete a obstrucției. Pe de altă parte, în ultimii 15 ani miectomia septală a cunoscut o evoluție tehnică importantă și a devenit una din cele mai sigure proceduri de chirurgie cardiacă, având o mortalitate operatorie ≤1% atunci când este realizată în centre specializate, de către chirurghi experimentați. Intervenția îmbunătățește substanțial calitatea vieții, prelungește supraviețuirea și este considerată de către ghidurile internaționale pentru CMH "gold standard" pentru tratamentul invaziv al obstrucției tractului de ejeție al ventriculului stâng.

**Cuvinte cheie:** CMHO, obstrucție ventriculară, miectomie chirurgicală

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease and has been estimated to occur in 1 of every 500 persons, a prevalence based on large study populations of different ethnicity<sup>1</sup>. These data also imply that many thousands of Roma-

nians are affected by HCM. Such a high prevalence of the disease in the general population is in apparent contradiction with the clinical perception that HCM is relatively uncommon. This inconsistency between scientific evidence and clinical experience indicates that

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most affected individuals do not develop HCM-related symptoms and remain undiagnosed<sup>2</sup>. Indeed, the natural history of HCM is extremely heterogeneous. A large proportion of patients remain asymptomatic throughout life, while others develop important symptoms of heart failure, and some die suddenly often at a young age and in the absence of previous symptoms<sup>1-5</sup>. This strikingly diverse clinical course can be explained by the variety of morphologic expressions and pathophysiologic complexity of HCM, ranging from mild and localized to massive and extensive left ventricular (LV) hypertrophy<sup>6</sup>, and including diastolic dysfunction, LV outflow tract obstruction, mitral valve regurgitation, arrhythmias and myocardial ischemia<sup>7-10</sup>.

Within this large spectrum of HCM pathophysiologic abnormalities, LV outflow obstruction represents the most frequent cause of heart failure symptoms and poses difficult management decisions<sup>1,2,10</sup>. Therefore, proper patient management requires a clear understanding of the pathophysiology and natural history of the disease, as well as an up to date knowledge of the recent advances in the treatment of LV outflow obstruction. Purpose of the present review is to summarize the most recent approaches to the management of HCM patients with outflow obstruction and new technical advances in HCM surgery, which are also now available in Romania.

## **PATHOPHYSIOLOGY OF HEART FAILURE IN HCM**

Symptoms of heart failure usually manifest as exertional dyspnea and occur in about 50% of HCM patients evaluated at referral centers<sup>1,2,10</sup>. In >60% of such patients, symptoms are predominantly caused by obstruction to LV outflow, which is most commonly due to systolic anterior motion of the mitral valve against the hypertrophied ventricular septum and is often associated with mitral valve regurgitation<sup>2,10</sup> (Figure 1). In HCM, LV outflow obstruction is routinely assessed with echocardiography and defined as a peak instantaneous LV outflow gradient >30 mmHg<sup>2,10</sup>. Outflow obstruction is present at rest in about 25% of patients and develops in another 50% of patients using physiologic maneuvers, such as the Valsalva maneuver and exercise echocardiography<sup>11</sup>. In those patients with heart failure symptoms and without a significant LV outflow gradient either at rest or induced by the Valsalva maneuver, exercise echocardiography should be performed to identify a significant LV outflow obstruction, not elicited by the Valsalva maneuver, that may be responsible for symptoms during effort<sup>2,11-13</sup>.

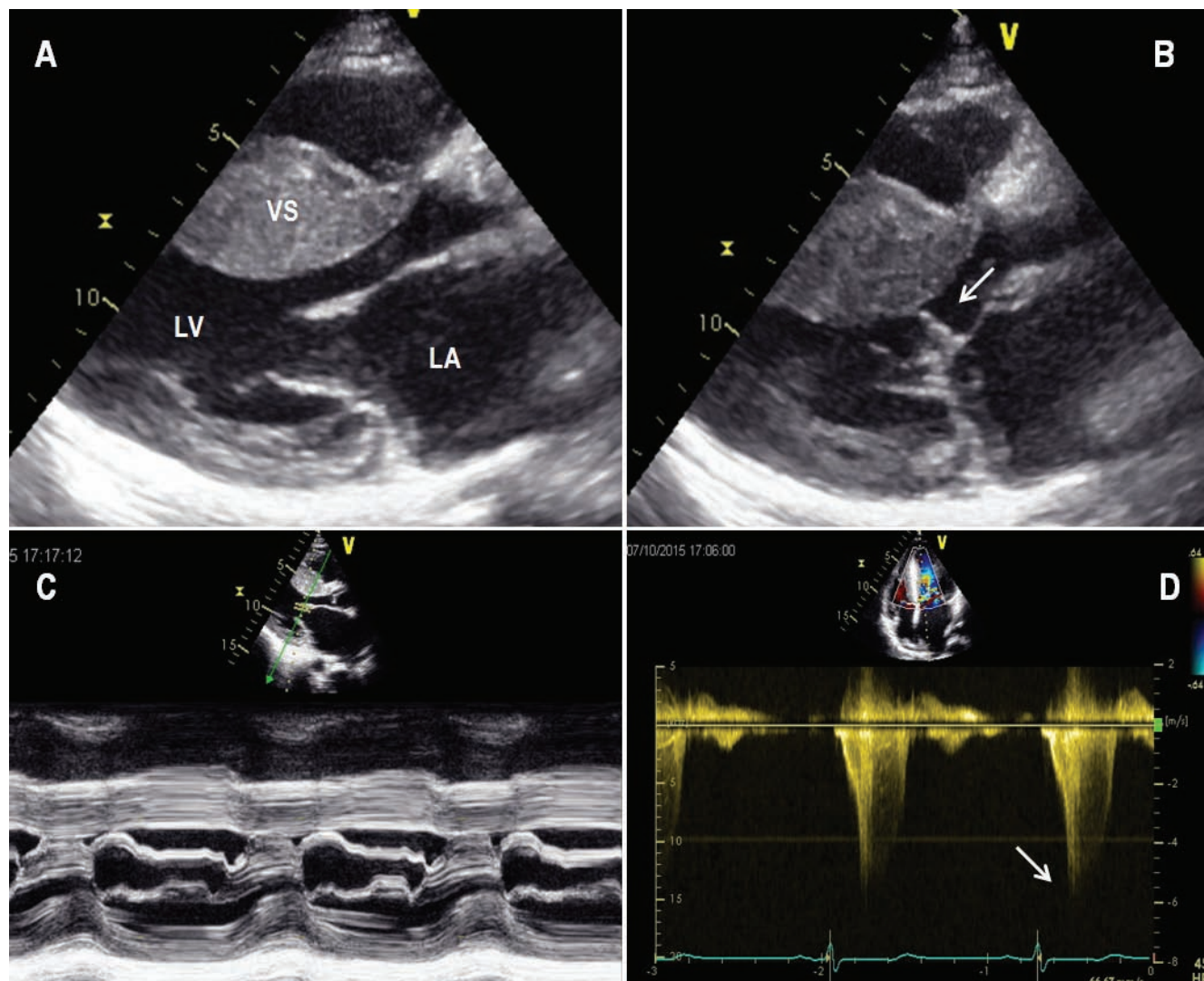
In the absence of LV outflow obstruction, symptoms of heart failure are due to diastolic dysfunction (with or without atrial fibrillation) in about 30% of HCM patients<sup>2,10</sup>. In patients with LV diastolic dysfunction who are in sinus rhythm, left atrial dysfunction may contribute to impaired LV filling and heart failure symptoms<sup>14</sup>. In about 5% of HCM patients, symptoms of heart failure are due to systolic dysfunction (ejection fraction <50%) with LV wall thinning and cavity dilatation<sup>2,10,15</sup>. This latter functional and morphologic evolution of the disease, generally described as the end-stage phase, is associated with the most advanced symptoms of heart failure within the HCM spectrum and may require heart transplantation<sup>15</sup>.

## **MEDICAL TREATMENT OF HEART FAILURE ASSOCIATED WITH LV OUTFLOW OBSTRUCTION**

In patients with LV outflow obstruction and symptoms of heart failure, medical therapy with beta-blockers represents the first treatment option<sup>2</sup>. By their negative chronotropic and inotropic effects, these drugs reduce the heart rate, thereby increasing LV diastolic filling, and improve the myocardial oxygen supply-demand relationship<sup>16</sup>. Beta-blockers often alleviate heart failure symptoms and may reduce the LV outflow gradient during exercise. There is no definitive evidence that these medications reduce the outflow gradient at rest, or prolong survival<sup>2</sup>.

In HCM patients with outflow obstruction who do not tolerate beta-blockers, or whose symptoms are unresponsive to these drugs, verapamil or diltiazem may relieve heart failure by negative chronotropic and inotropic effects similar to those of beta-blockers<sup>2,17</sup>. However, calcium channel blockers, by reducing peripheral resistance and systemic arterial blood pressure may increase the LV gradient and worsen heart failure symptoms in HCM patients with outflow obstruction. Therefore, these medications should be used with caution and started at low doses<sup>1,2,4,5,10</sup>.

In patients with persisting heart failure symptoms and elevated systolic pulmonary pressure despite the use of beta-blockers and calcium-channel blockers, the addition of diuretics may be effective for symptomatic relief<sup>1,2,10</sup>. However, diuretics should be used at low dosages in obstructive HCM, because an important decrease in LV filling pressure and diastolic volume may increase the outflow gradient in a disease which is also characterized by diastolic dysfunction and a small end-diastolic cavity<sup>2,10</sup>.



**Figure 1.** Echocardiogram from a patient with severe symptomatic obstructive HCM. (A) Still frame obtained during diastole shows a marked increase in ventricular septal thickness. (B) Still frame obtained during systole shows systolic anterior motion of the mitral-valve apparatus that causes obstruction of the left ventricular outflow tract (arrow). (C) M-mode echocardiogram shows prolonged mitral-septal contact during systole. (D) Doppler echocardiographic recording in the outflow tract demonstrates a peak instantaneous 130 mmHg gradient (arrow). LA=left atrium; LV=left ventricle; VS=ventricular septum.

## INVASIVE THERAPY OF LV OUTFLOW OBSTRUCTION

Two very different invasive interventions, surgical septal myectomy or catheter-based alcohol septal ablation, can be performed for the purpose of relieving heart failure in HCM patients with LV outflow obstruction and symptoms unresponsive to medical therapy<sup>1,2,5,10</sup>. Because of the documented long-term results and many decades of experience with surgical septal myectomy, the *American College/American Heart Association Guidelines* and the *European Society of Cardiology Guidelines* have selected septal myectomy as the gold standard treatment (i.e. Class I recommendation) for relief of

LV outflow obstruction and heart failure symptoms in HCM patients with marked gradients (>50 mmHg) at rest or with provocation and important symptoms unresponsive to medications<sup>2,12</sup>. Surgical myectomy remains the only option in patients who have outflow obstruction and associated abnormalities of the mitral valve apparatus that require surgical correction<sup>12</sup>. The Guidelines recommend the preferential use of alcohol septal ablation in elderly patients, or patients with significant comorbidities that would increase surgical risk<sup>2,12</sup>. Because HCM is an extremely heterogeneous disease and is relatively uncommon in the general cardiology practice, surgical myectomy and alcohol septal

ablation require specific operator and institutional experience. Therefore, in order to obtain successful outcomes with a low complication rates, it is imperative that these interventions are performed by operators and teams with a large expertise in the evaluation and treatment of patients with HCM<sup>2,12</sup>.

Despite these recommendations, the selection of patients for these two invasive interventions has varied substantially in different geographical areas. In the United States, surgical myectomy is generally performed by highly trained surgeons at HCM referral centers<sup>18,19</sup>. At the same centers, alcohol septal ablation is performed in a smaller and highly selected number of patients. On the other hand, a number of alcohol septal ablations are performed across the United States by interventional cardiologists at centers with more limited experience with HCM<sup>20</sup>. The decision of which procedure the patient should undergo is often influenced by the geographic location and HCM experience of the managing cardiologist.

In Europe, invasive treatment of LV outflow obstruction has become a sore point in the management of patients with HCM, because in many European countries surgical myectomy has been virtually eradicated and replaced by alcohol septal ablation, including some countries with previous important surgical myectomy programs, such as Germany and Switzerland<sup>21</sup>. Therefore, in most European countries, HCM candidates to invasive treatment of outflow obstruction are left with alcohol septal ablation as the only therapeutic option, independently of their age and clinical presentation<sup>18</sup>. However, during the last 10 years, some European surgical centers in Rotterdam (the Netherlands)<sup>22,23</sup>, and Bergamo and Monza (Italy)<sup>24,25</sup>, have developed major myectomy programs with results that are similar, in terms of operative mortality (<1%) and long-term clinical improvement and survival, to those of some of the most qualified centers in the United States, such as the Mayo Clinic and Cleveland Clinic<sup>18,19</sup>.

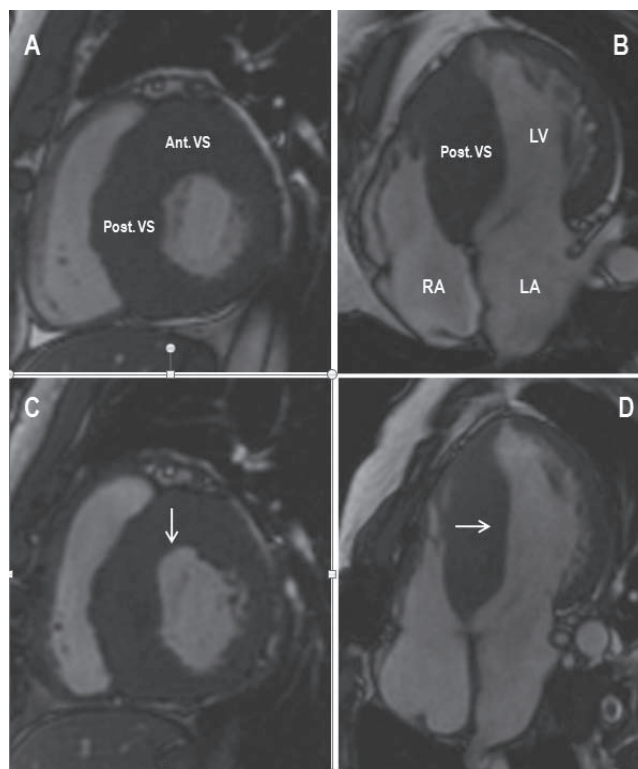
This resurgence of septal myectomy in Europe has been driven by the evidence of frequent failures of alcohol septal ablation in relieving the LV outflow gradient<sup>2,23,20</sup> and continuing concern with the potential consequences of the sizable myocardial infarction caused by alcohol ablation<sup>10,20</sup>. Indeed, the distribution of the septal perforator arteries in individual patients limits the possibility of this catheter-based procedure to target the site of outflow obstruction. Disaffectation with septal ablation has also increased as a result of the rapidly growing evidence that abnormalities of the mitral valve leaflets contribute importantly to LV

outflow obstruction in many (probably most) patients with HCM and cannot be resolved with septal alcohol ablation, but only by surgery<sup>23,25-29</sup>.

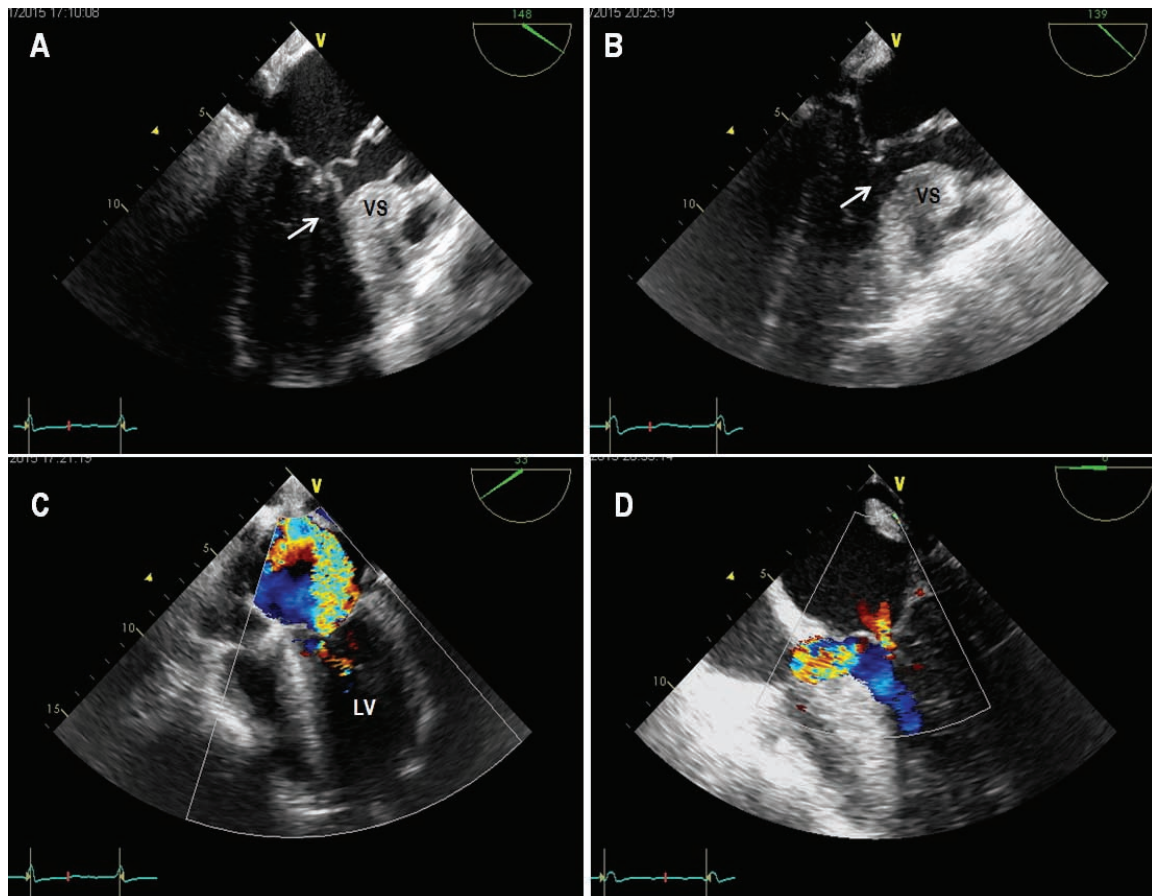
## TECHNICAL EVOLUTION OF SURGICAL MYECTOMY

A surgical myectomy for obstructive HCM was first performed in the late 1950s by Cleland and colleagues<sup>30</sup>. In the 1960s, the operation progressively evolved to a transaortic resection of a small amount of muscle from the proximal ventricular septum, a technique generally described as the Morrow classic myotomy and myectomy<sup>31</sup>.

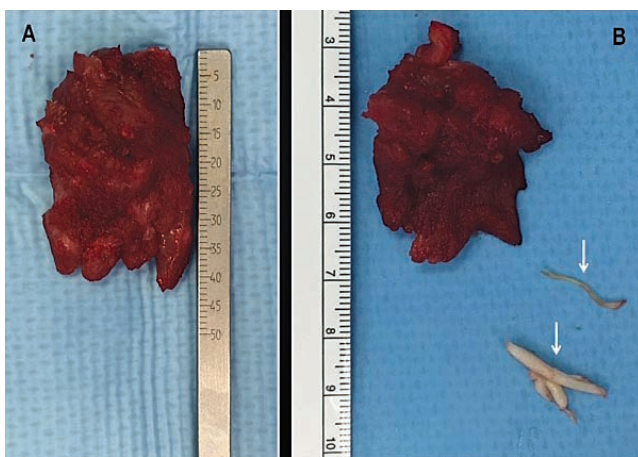
In the late 1970s, replacement of the mitral valve with a prosthesis was suggested as an alternative to septal myectomy for the purpose of abolishing the outflow gradient and improve symptoms<sup>32</sup>. However, the main disadvantage of this procedure is that outflow obstruction is merely replaced with the important



**Figure 2.** Comparison of preoperative and postoperative cardiovascular magnetic resonance (CMR) images shows the location and extent of the surgical myectomy. (A and B) Preoperative short axis and 4-chamber CMR images show marked hypertrophy of the anterior and posterior ventricular septum. (C and D) Postoperative short axis and 4-chamber CMR images show the area of the myectomy at the level of the anterior ventricular septum (arrow in C) and posterior ventricular septum (arrow in D). Ant.=anterior; LA=left atrium; LV=left ventricle; Post.=posterior; RA=right atrium; VS=ventricular septum.



**Figure 3.** Intraoperative transesophageal echocardiography in a patient with obstructive HCM undergoing surgical myectomy. (A) Before myectomy, transesophageal echocardiographic still frame obtained in systole shows a redundant posterior mitral leaflet, and an anterior mitral leaflet that comes into contact with the anterior ventricular septum, causing left ventricular outflow obstruction (arrow); and (B) transesophageal Color Doppler shows severe mitral valve regurgitation with a jet directed towards the lateral wall of the left atrium. (C) In the same patient, after myectomy, transesophageal echocardiographic still frame obtained in systole shows absence of mitral-septal contact and outflow obstruction (arrow); and (D) transesophageal Color Doppler shows only minimal mitral valve regurgitation. LV=left ventricle; VS=ventricular septum.



**Figure 4.** Specimen from an extended septal myectomy operation in two different patients. (A) The excised cardiac muscle specimen measures 4.5 cm in length and 3.0 cm in width, with a weight of 11 grams. (B) The excised cardiac muscle specimen measures 4.0 cm in length and 2.5 cm in width, with a weight of 5 grams. Two secondary chordae resected at the time of the myectomy are also shown (arrows). The cardiac muscle is excised via two incisions in the basal septum from 2 to 3 cm below the aortic valve and then extended distally to the base of the papillary muscles.

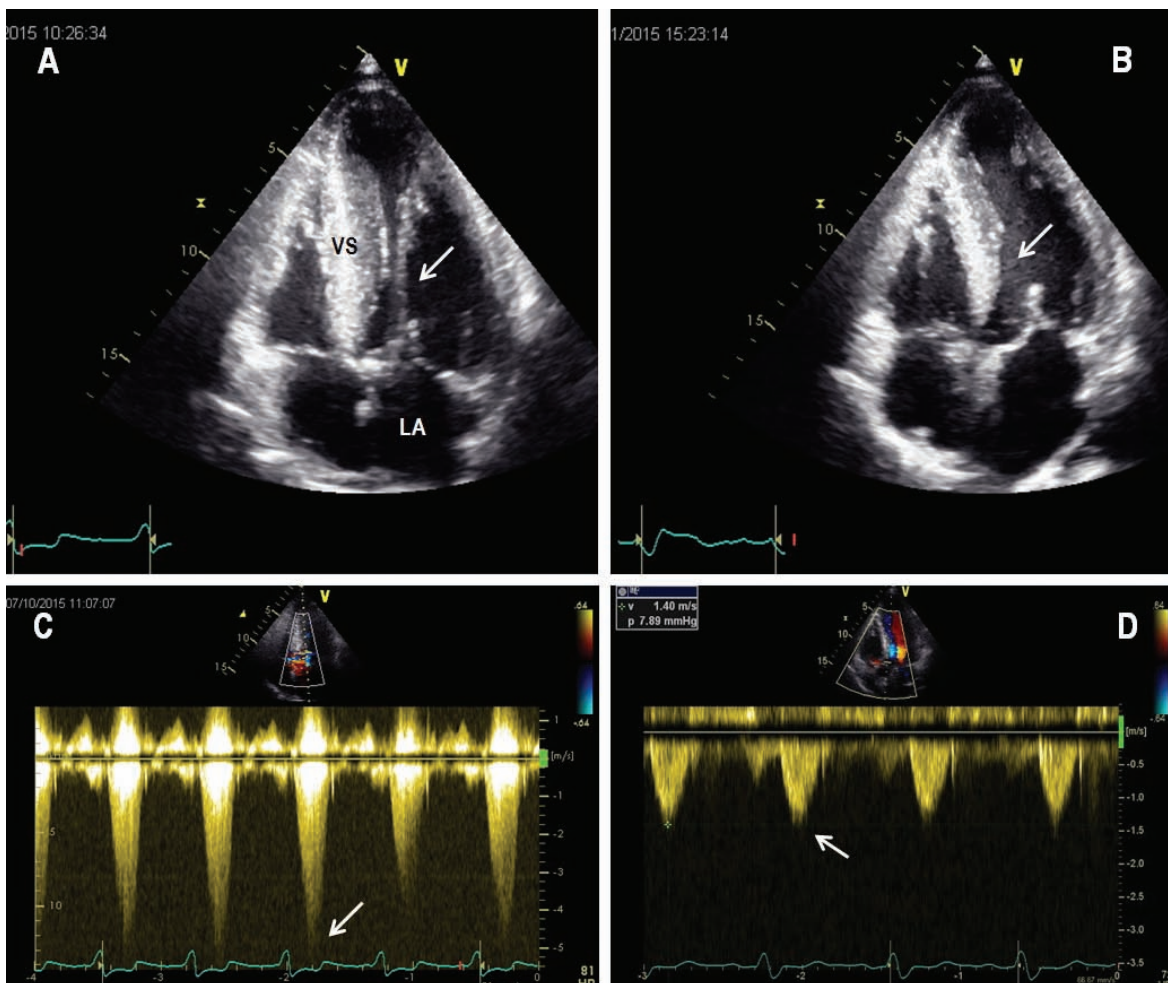
risks of limited durability, infection, thromboembolism and anticoagulation that are associated with prosthetic valves. Therefore, mitral valve replacement is now reserved for highly selected HCM patients with primary mitral valve abnormalities not amenable to repair<sup>2</sup>.

Over the past three decades, surgical myectomy has evolved from the classic Morrow operation to a more extended septal myectomy, which is guided by preoperative cardiovascular magnetic resonance and intraoperative transesophageal echocardiography<sup>2,18,19,33</sup> (Figures 2 and 3). Under the guidance of these imaging techniques that permit detailed visualization of septal anatomy and mitral valve function, the muscle incision is extended apically well past the 1.5 to 2.5 cm length of the original Morrow myectomy and beyond the area of mitral-septal contact<sup>18,19,24,25</sup> (Figure 4). Extending the myectomy beyond the point of mitral-septal contact is of crucial importance to obtain relief of the outflow gradient, because failure to achieve this sur-

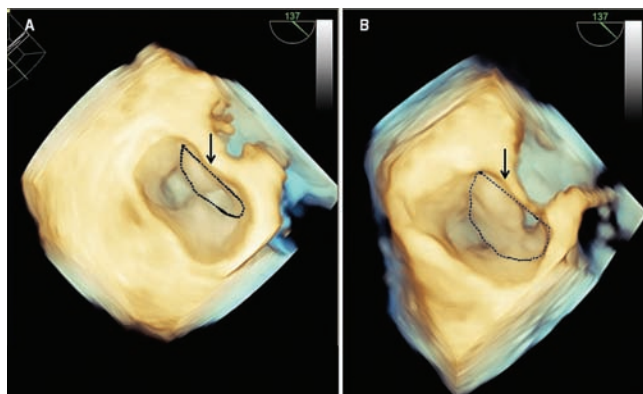
gical target is routinely associated with a persistent postoperative gradient<sup>33</sup>.

Fibrous or muscular structures connecting the papillary muscles to the ventricular septum or LV free wall are present in almost all patients with obstructive HCM. These abnormalities limit the mobility of the papillary muscles and, by displacing the leaflets into the outflow tract, contribute to systolic anterior motion of the mitral valve against the septum<sup>18,19,25,33</sup>. Therefore, careful inspection of the subvalvular mitral apparatus and mobilization of the papillary muscles from their attachments to the septum and ventricular free wall has become an integral part of the extended surgical myectomy. When present, these fibrous or muscular structures are systematically excised and/or dissected free (up to the base of the papillary muscle) in order to increase papillary muscle mobility. Anomalous

attachments of the papillary muscle directly into the anterior mitral leaflet are less common but must be resected when the papillary muscle is attached to the body of the leaflet<sup>24,25,33</sup> (Figure 5). Anomalous chordal structures or fibrous attachments of the mitral leaflets to the ventricular septum or free wall can also be found in patients with HCM and, whenever present, have to be excised or divided<sup>25,33</sup>. Cardiovascular magnetic resonance has proved useful in the identification of these multiple abnormalities of the subvalvular mitral apparatus and has gained an important role in the preoperative evaluation of HCM candidates to surgical myectomy<sup>34</sup>. Most recently, intraoperative transesophageal 3-D echocardiography has been used to obtain detailed reconstruction of the pre and postoperative morphology and function of the mitral valve leaflets in candidates to ventricular septal myectomy and associ-



**Figure 5.** (A) Preoperative echocardiogram from a patient with obstructive HCM shows an abnormal papillary muscle directly attached to the anterior mitral leaflet, in the absence of chordae, which comes into close proximity of the ventricular septum during systole (arrow). (B) Postoperative echocardiogram. The abnormal papillary muscle has been resected and the area of the septal myectomy (arrow) is clearly visible. There is normal coaptation of the mitral valve leaflets in systole, without systolic motion of the valve against the ventricular septum. (C) Preoperative Doppler echocardiographic recording in the LV outflow tract shows a peak instantaneous 100 mm Hg gradient (arrow). (D) Postoperative Doppler echocardiographic recording in the LV outflow tract demonstrates absence of a significant intra-ventricular gradient (8 mm Hg) (arrow). LA=left atrium; VS=ventricular septum.



**Figure 6.** Preoperative and postoperative 3D echocardiographic images of the mitral valve obtained at the time of mitral leaflet coaptation in a patient with obstructive HCM undergoing septal myectomy. (A) Preoperatively, the anterior mitral leaflet (delimited by the dotted area) represents only a minority of the mitral valve surface. (B) Postoperatively, the anterior mitral leaflet (delimited by the dotted area) represents the majority of the mitral valve surface.

ated mitral valve repair<sup>35</sup> (Figure 6). Indeed, the proper use of different imaging modalities is of critical importance for planning the surgical intervention, as well as monitoring the procedure during the operation, and assessing the results<sup>36</sup>.

In recent years, it has become evident that a wide range of mitral valve abnormalities (most of them secondary to LV remodeling) are present in patients with obstructive HCM, such as elongated or calcified mitral valve leaflets and fibrotic and/or retracted secondary chordae, and play an important role in the pathophysiology of the systolic anterior motion of the mitral valve and outflow obstruction<sup>25-29</sup>. A variety of surgical approaches have been devised to correct these mitral valve abnormalities, including transaortic extension or plication of the anterior mitral leaflet<sup>22,27,28</sup> and, more recently, resection of fibrotic and retracted secondary chordae of the anterior leaflet<sup>25</sup>.

At referral centers for HCM surgery, these advances in the myectomy operation have become a routine component of the surgical procedure and, together with modern myocardial preservation and other surgical techniques, have reduced operative mortality to <1% and improved long-term clinical results and survival<sup>10</sup>. Indeed, recent studies show that patients with obstructive HCM and severe preoperative heart failure symptoms who undergo the myectomy operation at experienced HCM surgical centers have a long-term outcome substantially more favorable than that of patients with outflow obstruction and no or mild symptoms at initial evaluation, and similar to that of HCM patients without outflow obstruction<sup>10,18,19,37,38</sup>.

## FINAL CONSIDERATIONS

Our review of the current management of patients with obstructive HCM underscores the complexity of this disease and the indisputable evidence that LV outflow obstruction leads to severe heart failure symptoms and reduced survival. From the late 1990s, in most European countries percutaneous septal ablation has replaced the myectomy operation as the intervention of choice to abolish the outflow obstruction. However, it has become increasingly evident that, in many HCM patients, septal ablation is incapable of abolishing the pathophysiologic mechanisms responsible for the outflow gradient, and that surgical myectomy is required to guarantee satisfactory results. This clinical evidence has generated an active surgical response and, in recent years, the number of centers of excellence for surgical management of patients with HCM has increased in European countries. Romania is on the way to become one of these countries. Because of this increasing access to surgical myectomy, many more patients with obstructive HCM and severe heart failure symptoms can now aspire to a substantially improved quality of life and an extended life span.

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