Long term left atrium remodeling after successful reduction of the left ventricular outflow tract obstruction with surgical myectomy in patients with hypertrophic cardiomyopathy.

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DISCUSSION

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REFERENCES
HYPERTROPHIC CARDIOMYOPATHY

Classification

A cardiomyopathy is defined as a disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality.

![Classification diagram]

Figure 1. Summary of proposed classification system. ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy

In this context, familial refers to the occurrence, in more than a family member, of either the same disorder or a phenotype that is caused by the same genetic mutation and not to acquired cardiac or systemic disease in which the clinical phenotype is influenced by genetic polymorphism. Most familial cardiomyopathies are monogenic disorders. A monogenic cardiomyopathy can be sporadic when the causative mutation is de novo.
Non-familial cardiomyopathies are clinically defined by the presence of a cardiomyopathy in the index patient and the absence of disease in other family members (based on pedigree analysis and clinical evaluation). They are subdivided into idiopathic (no identifiable cause) and acquired cardiomyopathies in which ventricular dysfunction is a complication of the disorder rather than an intrinsic feature of the disease.¹

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1. Definition

Hypertrophic cardiomyopathy (HCM) is defined by the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading condition.¹
Epidemiology

A number of methodologically diverse studies in North America, Europe, Asia and Africa report a prevalence of unexplained increase in LV wall thickness in the range of 0.02–0.23% in adults. Many show an age-related prevalence, with much lower rates in patients diagnosed under the age of 25 years. While HCM is most frequently transmitted as an autosomal-dominant trait most studies report a small male preponderance. This finding remains unexplained but might reflect bias in screening strategies as well as genetic and hormonal modifiers. The prevalence of HCM in different racial groups is similar. ²

Diagnosis

The diagnosis of HCM rests on the detection of increased LV wall thickness by any imaging modality, but the disease phenotype also includes myocardial fibrosis, morphologic abnormalities of the mitral valve apparatus, abnormal coronary microcirculatory function and electrocardiographic abnormalities.²

Diagnostic criteria in adults:

In an adult, HCM is defined by a wall thickness ≥15 mm in one or more LV myocardial segments as measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging (CMR) or computed tomography (CT)) that is not explained solely by loading conditions. Genetic and non-genetic disorders can present with lesser degrees of wall thickening (13–14 mm); in these cases, the diagnosis of HCM requires evaluation of other features including family
history, non-cardiac symptoms and signs, electrocardiogram (ECG) abnormalities, laboratory tests and multi-modality cardiac imaging. The clinical diagnosis of HCM in first-degree relatives of patients with unequivocal disease (LVH ≥15 mm) is based on the presence of otherwise unexplained increased LV wall thickness ≥13 mm in one or more LV myocardial segments, as measured using any cardiac imaging technique (echocardiography, CMR or CT).

Left ventricle outflow obstruction and systolic anterior movement of mitral valve leaflet

Left ventricular outflow tract obstruction (LVOTO) does play a major role in the pathophysiology of a subgroup of patients with HCM. It may be present at rest, provokable (mild at rest but significant with provocation), or latent (not present at rest but evident with provocation). Although altered diastolic filling is evident in all patients with hypertrophic cardiomyopathy, it is the high contraction load imposed by the obstruction that significantly worsens ventricular filling and relaxation. Other mechanisms by which obstruction produces symptoms are limitation of cardiac output, increased myocardial oxygen demand, and decreased coronary perfusion pressure. In addition, obstruction is associated with distortion of the mitral valve apparatus, resulting in secondary mitral regurgitation, further elevating left atrial pressure, and contributing substantially to severe symptoms of dyspnea. The mechanism by which obstruction is produced is complex. It was initially thought that the obstruction was the result of the hypertrophied septum projecting into the LVOT, causing a Venturi effect that would “suck” the mitral valve leaflets into the left ventricular
outflow tract. Through intricate flow studies in the left ventricular cavity, it has been shown that obstruction can be secondary to an anterior displacement of the mitral valve apparatus coupled with accelerated flow around the septal hypertrophy, which produces a drag force to “push” the mitral leaflets into the outflow tract. Other morphological features that contribute to LVOTO include papillary muscle abnormalities (hypertrophy, anterior and internal displacement, direct insertion into the anterior mitral valve leaflet) and mitral leaflet abnormalities such as elongation or accessory tissue. Irrespective of the mechanism, we now know that obstruction plays a major role in this disease. The presence of obstruction portends a poorer prognosis as compared with non-obstructive hypertrophic cardiomyopathy. Evaluation of symptomatic patients who have mild or no resting gradients (<50 mm Hg) should always include provocative maneuvers to determine whether a severe obstruction can be provoked. The findings of obstruction, either at rest or during provocation, can then be used to target therapy.

**Natural History**

Based on more recent, balanced overviews of patients with HCM, the annual mortality for patients with HCM is estimated at 1% per year. Though the prognosis of HCM appears better than previously believed, many patients with HCM can suffer from a variety of symptoms. First, a subset of patients experiences sudden death in the absence of antecedent symptoms. Second, 20% of patients develop atrial fibrillation (AF), which exacerbates other
accompanying clinical symptoms and carries a risk of embolic stroke. Third, the patients can experience anginal chest pain because of microvascular ischemia from a (blood) supply and demand (excess myocardium) mismatch or, rarely, myocardial bridging.\textsuperscript{10} Finally the patients may suffer from progressive heart failure. This includes patients with preserved or reduced ejection fraction as well as those with or without outflow tract obstruction. Any patient with HCM may eventually progress to end-stage heart failure with reduced LV systolic function.\textsuperscript{11} The evolution to this dilated hypokinetic phenotype of HCM is believed to occur progressively as myocardial fibrosis and other adverse remodeling changes accumulate.\textsuperscript{12-13} The evolution of severe heart failure (New York Heart Association [NYHA] functional class III or class IV) occurs in 10–20\% of patients with HCM.\textsuperscript{14} While these symptoms can occur at any age, they are most frequently seen in middle-aged adults. The risk of heart failure is augmented by the presence and degree of outflow tract obstruction.\textsuperscript{15} Heart failure can occur in one-third of patients who have HCM without outflow obstruction, though it is less common.\textsuperscript{16} Further risk factors of heart failure include the presence of AF\textsuperscript{17} and diastolic dysfunction. Notably, LV wall thickness is not predictive of progressive symptoms of heart failure.\textsuperscript{18}

Sudden cardiac death
Most contemporary series of adult patients with HCM report an annual incidence for cardiovascular death of 1–2\%, with SCD, heart failure and thromboembolism being the main causes of death.\textsuperscript{19} The most commonly recorded fatal arrhythmic event is spontaneous ventricular fibrillation (VF), but asystole, AV block and
pulseless electrical activity are described.\textsuperscript{20} Estimation of SCD risk is an integral part of clinical management. A large body of evidence suggests that, in adolescents and adults, the risk assessment should comprise of clinical and family history, 48-hour ambulatory ECG, TTE (or CMR in the case of poor echo windows) and a symptom-limited exercise test. Clinical features that are associated with an increased SCD risk shown: age, non-sustained ventricular tachycardia, maximum left ventricle wall thickness, family history of sudden cardiac death at young age, syncope, left atrial diameter, LVOT obstruction.\textsuperscript{2}

\textbf{Echocardiography}

Echocardiography is central to the diagnosis and monitoring of HCM. In most patients the distribution of left ventricular hypertrophy is characteristically asymmetric and particularly heterogeneous, encompassing most possible patterns of wall thickening, from extensive and diffuse to mild and segmental, and with no single morphologic expression considered typical or classic.\textsuperscript{21} As increased ventricular wall thickness can be found at any location (including the right ventricle), the presence, distribution and severity of hypertrophy should be documented using a standardized protocol for cross-sectional imaging from several projections.

\textit{Assessment of left ventricle wall thickness:}

In patients with known or suspected HCM it is essential that all LV segments from base to apex be examined, ensuring that the wall thickness is recorded at mitral, mid-LV and apical levels.\textsuperscript{2} Classical LV hypertrophy cut-off suggestive of
HCM in the general adult population is 15 mm. Usually the pattern of LV hypertrophy is asymmetrical, with the anterior septum involved in the majority of cases being also the site of the maximal LV hypertrophy in most patients. Accurate assessment of LV wall thickness can be challenging when hypertrophy is confined to one or two segments, particularly in the anterolateral wall or the LV apex.

**Assessment of LVOTO and SAM:**

Systolic anterior motion of the mitral valve nearly always results in failure of normal leaflet coaptation and mitral regurgitation, which is typically mid-to-late systolic and infero-laterally oriented; measurement of the velocity and timing of the mitral regurgitation jet helps to differentiate it from LV outflow tract turbulence. SAM-related mitral regurgitation is inherently dynamic in nature and its severity varies with the degree of LVOTO. The presence of a central or anteriorly directed jet of mitral regurgitation should raise suspicion of an intrinsic mitral valve abnormality and prompt further assessment with TOE if necessary. By convention, LVOTO is defined as an instantaneous peak Doppler LV outflow tract pressure gradient ≥30 mmHg at rest or during physiological provocation such as Valsalva manoeuvre, standing and exercise. A gradient of ≥50 mm Hg is usually considered to be the threshold at which LVOTO becomes haemodynamically important.

**Assessment of latent obstruction:**

It is well recognized that some patients without outflow obstruction at rest have
gradients that can be provoked by physiological and pharmacological interventions that diminish left ventricular end-diastolic volume or augment left ventricular contractility. Over 60% of symptomatic patients with apparently non-obstructive hypertrophic cardiomyopathy have obstruction during exercise. Left ventricular outflow tract obstruction in HCM is characteristically labile, its magnitude varying spontaneously or following heavy meals and ingestion of alcohol. In some cases, obstruction only appears during a haemodynamic challenge such as inhalation of amyl nitrite, Valsalva manoeuvre and infusion of positive inotropes. 2D and Doppler echocardiography during a Valsalva manoeuvre in the sitting and semi-supine position, and then on standing if no gradient is provoked, is recommended in all patients. Exercise stress echocardiography is recommended in symptomatic patients if bedside manoeuvres fail to induce LVOTO ≥50 mmHg. Pharmacological provocation with dobutamine is not recommended, as it is not physiological and can be poorly tolerated. Similarly, nitrates do not reproduce exercise-induced gradients and should be reserved for patients who cannot perform physiologically stressful procedures.
Assessment of left atrial dimension:

The left atrium is often enlarged and its size provides important prognostic information. The cause of LA enlargement is multifactorial, but the most common mechanisms are SAM-related mitral regurgitation and elevated LV filling pressures. Although most published studies use antero-posterior LA diameter, comparable findings using LA volume indexed to body surface area are reported. Given that LA diameter and volume are consistently shown to be independently associated with AF, patients with atrial enlargement should be monitored on a regular basis.25
Assessment of systolic function

Radial contractile function (EF or fractional shortening) is typically normal or increased in patients with HCM. However, EF is a poor measure of LV systolic performance when hypertrophy is present.\textsuperscript{26} Myocardial longitudinal velocities and deformation parameters (strain and strain rate), derived from Doppler myocardial imaging or speckle tracking techniques, are often reduced despite a normal EF and may be abnormal before the development of increased wall thickness in genetically affected relatives.\textsuperscript{27}

Assessment of diastolic function

Patients with HCM often have diastolic dysfunction and the assessment of LV filling pressures is helpful in the evaluation of symptoms and disease staging. Doppler echocardiographic parameters are sensitive measures of diastolic function, but are influenced by loading conditions, heart rate and age, and there is no single echocardiographic parameter that can be used as a diagnostic hallmark of LV diastolic dysfunction. Therefore, a comprehensive evaluation of diastolic function—including Doppler myocardial imaging, pulmonary vein flow velocities, pulmonary artery systolic pressure and LA size—is recommended as part of the routine assessment of HCM.\textsuperscript{28} Patients with a restrictive LV filling pattern may be at higher risk for adverse outcome, even with a preserved ejection fraction.\textsuperscript{29–30}
Assessment of symptoms

Most people with HCM are asymptomatic and have a normal lifespan but some develop symptoms, often many years after the appearance of ECG or echocardiographic evidence of LVH. It is well known the association of symptoms with exertion, post-prandial period and alcohol assumption.\(^{31}\)

- **Heart failure**: HCM is an important cause of heart failure-related disability over a wide range of ages. In some patients heart failure is associated with diastolic dysfunction with preserved EF and small LV size; in others, symptoms are caused by systolic left ventricular dysfunction or LVOTO (with or without mitral insufficiency). Atrial fibrillation can complicate any of these scenarios and exacerbate symptoms.\(^{32}\)

- **Chest pain**: Many patients complain of chest pain at rest or on exertion. The causes of chest pain include myocardial ischaemia due to microvascular dysfunction, increased LV wall stress and LVOTO. Atherosclerotic coronary artery disease may also be responsible.\(^ {33}\)

- **Syncope**: Causes of syncope in HCM include hypovolaemia, complete heart block, sinus node dysfunction, sustained ventricular tachycardia, LVOTO, and abnormal vascular reflexes.\(^ {34}\) Occasionally atrial arrhythmias with fast ventricular response can precipitate syncope, particularly in individuals with preserved atrial function and high filling pressures.\(^ {35}\) Syncope after prolonged standing in a hot environment, or during the postprandial absorptive state, is suggestive of neurally mediated syncope, particularly when it is associated with nausea and vomiting. Syncope during exertion, or immediately following
palpitation or chest pain, suggests a cardiac mechanism. Provocable obstruction should be excluded when patients experience recurrent effort syncope in similar circumstances, for example when hurrying upstairs or straining.

- **Palpitations**: Many patients complain of palpitations, caused by symptomatic cardiac contractions and ventricular ectopy. A sustained episode of palpitation lasting for more than a few minutes is often caused by supraventricular arrhythmia.

**Atrial tachyarrhythmia**

Atrial fibrillation is the most common arrhythmia in patients with HCM. Predisposing factors include increased left atrial pressure and size, caused by diastolic dysfunction, LVOTO and mitral regurgitation. In a recent systematic review, the prevalence and annual incidence of AF were 22.5% and 3.1%, respectively. Clinical features most closely associated with paroxysmal or permanent AF include age and left atrial enlargement. Other possible predictors include LVOTO, P-wave duration > 140 ms on signal-averaged ECG, paroxysmal SVT, ST-T changes on baseline electrocardiography, premature ventricular contractions, late Gadolinium enhancement on CMR, and abnormal coronary flow reserve.

**Acute treatment**

New-onset AF is frequently associated with heart failure symptoms and so
should be treated promptly. Immediate direct current (DC) cardioversion is recommended in haemodynamically unstable patients. If patients have severe symptoms of angina or heart failure, intravenous β-blockers or amiodarone are recommended. In haemodynamically stable patients, oral β-blockers or nondihydropyridine calcium channel antagonists are recommended to slow the ventricular response to AF. If pre-excitation is present, non-dihydropyridine calcium channel antagonists and adenosine are contraindicated. Digoxin should be avoided in patients with LVOTO and normal EF. Similarly, Class IC antiarrhythmics, such as flecainide and propafenone, should be avoided as they may prolong QRS duration and the QT interval, and increase the ventricular rate due to conversion to atrial flutter and 1:1 ventricular conduction. When rate control is achieved, elective DC cardioversion should be considered after a minimum of 3 weeks effective anticoagulation with a vitamin K antagonist (VKA). If earlier DC cardioversion is contemplated, a TOE-based strategy should be followed.37-38

**Thromboembolism prophylaxis**

As patients with HCM tend to be younger than other high-risk groups and have not been included in clinical trials of thrombo-prophylaxis, use of the CHA2DS2-VASc score to calculate stroke risk is not recommended. Given the high incidence of stroke in patients with HCM and paroxysmal, persistent or permanent AF, it is recommended that all patients with AF should receive treatment with VKA.37-38 In general, lifelong therapy with oral anticoagulants is recommended, even when sinus rhythm is restored. There are no data on the use of new oral anticoagulants (NOAC) in patients with HCM, but they are recommended when adjusted-dose
VKA (INR 2.0–3.0) cannot be used due to a failure to maintain therapeutic anticoagulation or when patients experience side-effects of VKAs or are unable to attend- or undertake INR monitoring.39

**Ventricular rate control**

Ventricular rate control using b-blockers and non-dihydropyridine calcium channel antagonists, alone or in combination, is recommended in patients with paroxysmal, persistent or permanent AF. When adequate rate control cannot be achieved, AV node ablation and permanent pacing may be considered. In the absence of significant LVOTO, digoxin, alone or in combination with β-blockers, may be used to control heart rate response in patients with AF and an EF < 50%, although data on its efficacy in this context are lacking.37-38

**Rhythm control**

There are no randomized, controlled trials examining the effect of anti-arrhythmic drugs or radiofrequency ablation on long-term prevention of AF in patients with HCM. Disopyramide is used to treat LVOTO, but its effect on AF suppression in HCM is unknown.36 There are few data on catheter ablation for AF in patients with HCM but the technique should be considered in patients without severe left atrial enlargement, who have drug refractory symptoms or who are unable to take anti-arrhythmic drugs.40

**Management of symptoms in patients with LVOTO**

*General measures*
All patients with LVOTO should avoid dehydration and excess alcohol consumption; weight loss should be encouraged. Arterial and venous dilators, including nitrates and phosphodiesterase type 5 inhibitors, can exacerbate LVOTO and should be avoided if possible. Digoxin should be avoided in patients with LVOTO because of its positive inotropic effects.²

Drug therapy

By consensus, patients with symptomatic LVOTO are treated initially with non-vasodilating β-blockers titrated to maximum tolerated dose.⁴¹ If β-blockers alone are ineffective, disopyramide, titrated up to a maximum tolerated dose (usually 400 – 600 mg/day), may be added. This Class IA anti-arrhythmic drug can abolish basal LV outflow pressure gradients and improve exercise tolerance and functional capacity without pro-arrhythmic effects or an increased risk of sudden cardiac death.⁴² Verapamil (starting dose 40 mg three times daily to maximum 480 mg daily) can be used when β-blockers are contraindicated or ineffective, but close monitoring is required in patients with severe obstruction (≥100 mm Hg) or elevated pulmonary artery systolic pressures, as it can provoke pulmonary oedema. Short-term oral administration may increase exercise capacity, improve symptoms and normalize or improve LV diastolic filling without altering systolic function.⁴³ Low-dose loop or thiazide diuretics may be used cautiously to improve dyspnea associated with LVOTO, but it is important to avoid hypovolaemia.
Invasive treatment of LVOTO

Indication for surgery

Exertional dyspnea, chest pain, pre-syncope, syncope, fatigue, occasionally orthopnea and paroxysmal nocturnal dyspnea can be associated to LVOTO. Initially, such symptoms should be treated with medications including high-dose β-blockers, verapamil, disopyramide,44-46 and low-dose diuretics in the presence of congestive heart failure. Despite appropriate medication adjustment, however, symptom relief can be incomplete, transient and accompanied by intolerable drug-related adverse effects. In such patients, providing they have resting or provokable gradients of 50 mmHg or more, septal myectomy is the preferred treatment.44

A long-standing problem facing clinicians caring for patients with HCM is the scarcity of robust clinical evidence on which to base therapeutic decisions. For most interventions, there are no randomized controlled trial data. Rather, much of the literature consists of retrospective observational studies with historical controls. Against this background of uncertainty, one area in which there have been clear data and a firm consensus is that patients with obstructive HCM who have persistent symptoms, or exercise limitation, despite maximum medical therapy benefit symptomatically from procedures to reduce the outflow gradient. 44

In approximately 25% of patients with HCM, there is a dynamic obstruction of the left ventricular outflow tract caused by septal hypertrophy and systolic anterior motion of the mitral valve. Surgical septal myectomy effectively abolishes systolic anterior motion of the mitral valve and the concomitant mitral
regurgitation, improving left ventricular hemodynamics. Long-term experience from a number of centers convincingly shows that this approach is a proven one that provides lasting amelioration of symptoms.\(^{47}\) Moreover, surgical mortality in specialist centers is now \(< 1\% \text{ to } 2\%\). Despite this, the uptake of surgical myectomy is relatively low, with \(< 5\%\) of patients with HCM being treated in this way in most case series. In contrast, there has been a marked proliferation of percutaneous, catheter-based, alcohol septal ablation, which achieves remodeling in the left ventricular outflow tract by causing a localized myocardial infarction in the proximal septum.\(^{48-50}\)

Although significant controversy exists typically because individual centers strongly favor one or other technique and few offer significant experience of both, the general consensus is that operative risks, hemodynamic benefits, and initial symptomatic benefits are broadly comparable (in centers with appropriate expertise) with either technique. A critical difference is that long-term follow-up data are not yet available for alcohol septal ablation, and there are concerns that the intra-myocardial scar may provide a long-term arrhythmogenic substrate and that the extent of myocardial damage may exceed the target area and lead to further, undesirable, remodeling. Although this procedure is associated with an overall success rate of about 80\%, there is a high incidence of heart block necessitating pacemaker implantation, and the overall procedural complication rates could exceed those observed with myectomy.

Although ablation represents an important therapeutic tool, its role is still to define and the consensus panel of physicians experienced in the management of HCM has stated that surgical myectomy should be considered as the first option
and ablation as an alternative, particularly in those with serious comorbidity or advanced age.\textsuperscript{44}

Of note, there are alternatives to septal myectomy for HCM patients with drug-refractory symptoms. Dual-chamber pacemakers were the subject of intense scrutiny a decade ago. Although initial case reports and small series showed promise, the results of rigorous clinical trials and long-term follow-up suggested that these devices provided limited benefit.\textsuperscript{51,52} Currently, pacing is considered for symptomatic patients with concomitant advanced conduction system disease or excessive comorbidities that increase the risk of myectomy unacceptably.

Ommen et al.\textsuperscript{53} report an observational study of 1,337 consecutive patients with HCM drawn from four U.S. and European specialist centers between 1983 and 2001 (Figure 3). These patients were retrospectively grouped into three categories: patients with surgically treated outflow tract obstruction, patients with medically treated outflow tract obstruction, and patients without obstruction. Survival after myectomy was not different from survival in the non-obstructive group but was better than survival in the non-operated obstructive group (for all-cause mortality, HCM-related mortality, and sudden cardiac death). The authors concluded that surgical myectomy appears to improve survival in patients with highly symptomatic obstructive HCM.
Figure 3: Survival in three subgroups of patients with hypertrophic cardiomyopathy: obstructive with surgical myectomy (n = 289), obstructive without surgical myectomy (n = 228), and nonobstructive (n = 820). Overall log-rank P <0.001; myectomy versus nonoperated obstructive hypertrophic cardiomyopathy P = 0.001; myectomy versus nonobstructive hypertrophic cardiomyopathy P = 0.8. © Ommen SR et al. (2005) J Am Coll Cardiol 46: 470–476.

**Septal myectomy**

The most commonly performed surgical procedure used to treat LVOTO is ventricular septal myectomy (Morrow procedure\textsuperscript{54}), in which a rectangular trough that extends distally to beyond the point of the mitral leaflet–septal contact is created in the basal septum below the aortic valve. This abolishes or reduces LV outflow tract gradients in over 90% of cases, reduces SAM-related mitral regurgitation, and improves exercise capacity and symptoms. Long-term symptomatic benefit is achieved in 70–80% of patients with a long-term survival comparable to that of the general population. The main surgical complications
are AV nodal block, ventricular septal defect and aortic regurgitation (AR), but these are uncommon in experienced centers using intraoperative TOE guidance. When there is co-existing mid-cavity obstruction, the standard myectomy can be extended distally into the mid-ventricle around the base of the papillary muscles, but data on the efficacy and long-term outcomes of this approach are limited.

Concomitant mitral valve surgery is required in 11–20% of patients undergoing myectomy. In patients with marked mitral leaflet elongation and/or moderate-to-severe mitral regurgitation, septal myectomy can be combined with one of several adjunctive procedures, including mitral valve replacement, posterior-superior realignment of the papillary muscles, partial excision and mobilization of papillary muscles, anterior mitral leaflet plication, and anterior leaflet extension using a glutaraldehyde-treated pericardial patch that stiffens the mid-portion of the leaflet. An elongated anterior mitral leaflet favours mitral valve repair instead of replacement. Surgical mortality for myectomy with mitral intervention is around 3–4%.

The learning curve for performing this procedure is considerable, however, and early surgical experience was associated with complications of complete heart block, ventricular septal defect, injury to the aortic or mitral valves, and incomplete relief of obstruction.

- History of surgical treatment

Surgical treatment of obstructive HCM began in the late 1950s. The first surgical procedures proposed for relief of left ventricular outflow tract obstruction
(LVOTO) involved a simple incision in the basal septal bulge, sometimes
deepened with the surgeon’s finger (myotomy), or excision of muscle
(myectomy).^{53-59}

Cleland described the first procedure for surgical treatment of LVOTO in 1960,
which comprised a limited transaortic septal myectomy.\textsuperscript{55} Since then, many
different surgical procedures have been described. Historically, access to the
septum has been obtained through the aorta, left ventricle, right ventricle or left
atrium; however, the transaortic approach remains the primary method used. A
decrease in left ventricular outflow gradient is accomplished by enlargement of
the outflow tract and interruption of the pathophysiological sequence of events
that are responsible for the outflow gradient (primarily systolic anterior motion
[SAM] of the anterior mitral leaflet). Complete relief of LVOTO by septal
myectomy also eliminates mitral value regurgitation caused by SAM. Any
residual mitral valve regurgitation after adequate septal myectomy is almost
always caused by intrinsic mitral valve abnormalities such as ruptured chordae,
leaflet prolapse or annular dilatation, and can be corrected by direct valve repair.
Replacement of the mitral valve, once proposed as an alternative to septal
myectomy, can eliminate the left ventricular outflow gradient and improve
symptoms. The chief disadvantage of this procedure is that outflow obstruction
is merely replaced with the risks of durability, infection, thromboembolism and
anticoagulation that are associated with prosthetic valves. Mitral valve
replacement is now reserved for patients with primary mitral valve pathology
(e.g. rheumatic valve disease) not amenable to repair.
- *Surgical technique*

Operations are guided by intraoperative transesophageal echocardiography (TOE) with particular attention paid to the septal anatomy and thickness, and mitral valve function. Access is gained through a median sternotomy and direct intracardiac pressures are measured simultaneously in the left ventricle and aorta. If the left ventricular outflow tract (LVOT) gradient is low (<30 mmHg) because of anesthesia, isoproterenol is administered or premature ventricular contractions are induced to determine the maximal gradient. Standard cardiopulmonary bypass with normothermia or mild hypothermia (32–34 °C) is used, and during aortic occlusion, the heart is protected by infusion (approximately 1,000 ml) of antegrade cold blood cardioplegia into the aortic root, followed by additional doses administered selectively into the left and right coronary ostia every 10–20 min. A transverse aortotomy is made, carried rightward toward the noncoronary sinus and down to the aortic annulus, and retracted with pledgeted sutures. Optimum visualization of the ventricular septum is facilitated by posterior displacement of the left ventricle with sponge forceps. In addition, a small rake retractor can be used to engage the distal septum so that it can be pulled cephalad toward the aortic annulus. The incision begins in the septum at the nadir of the right aortic sinus and continue leftward toward the mitral valve. Importantly, the incision should be continued apically beyond the point of mitral–septal contact (usually marked by a fibrous friction lesion). The resection is then extended in several ways, beginning with continued resection leftward toward the mitral valve annulus and apically to the bases of the papillary muscles. This wide incision beneath the valve improves exposure of
the important area toward the apex. Resection from the apical third of the septum to the right of the coronary cusp incision is then performed, effectively making a much wider trough at the apex than the base. All areas of papillary muscle fusion to the septum or ventricular free wall are divided, and anomalous chordal structures and fibrous attachments of the mitral leaflets to the ventricular septum are divided or excised. If desired, the resected area can be deepened with a rongeur. The adequacy and distal extent of resection are evaluated by direct inspection and digital palpitation. The most common reason for residual gradients is incomplete extension of the septectomy toward the apex of the heart. In general, the bases of the papillary muscles can be visualized while looking through the aortic root after the myectomy has been completed. The aortic and mitral valves are inspected to insure they have not been injured. After the patient is weaned from cardiopulmonary bypass, pressures are remeasured in the left ventricle and aorta and TOE evaluation is repeated. If myectomy has been successful, there will be little or no residual gradient, and little or no SAM of the mitral valve. In general, if the gradient were greater than 15–20 mmHg, a cardiopulmonary bypass would be resumed for re-resection. Transthoracic echocardiographic evaluation is routinely performed before hospital discharge.

- *Abnormal mitral apparatus*

Some symptomatic patients with obstructive HCM have associated anomalies of the mitral sub-valvular apparatus, which, if unrecognized and untreated, can lead to incomplete or temporary relief of obstruction only.60 These anomalies include direct papillary muscle insertion into the anterior mitral leaflet, extensive fusion of papillary muscle(s) to the ventricular septum or left ventricular free wall,
abnormal chordae tendineae that attach to the ventricular septum or free wall ('false cords'), and accessory papillary muscles, all of which can tether the mitral leaflets towards the septum and contribute to LVOTO. Obstructive HCM associated with anomalous papillary muscles or chordae could be treated successfully without mitral valve replacement by surgical relief of the anomalies and an extended septal myectomy.

In selected patients with obstructive HCM and severe mitral regurgitation caused by primary valvular disease (e.g. prolapse or myxoma, or ruptured chordae), mitral valve repair, in addition to myectomy, is the most appropriate treatment. Occasionally, intrinsic mitral valve disease is severe enough to preclude repair (e.g. rheumatic mitral stenosis and regurgitation) and mitral valve replacement is, therefore, prudent.

- Long term results

Septal myectomy has been established as a proven approach for reversing the consequences of heart failure. This technique provides permanent amelioration of obstruction (and relief of mitral regurgitation) at rest, and restores functional capacity and an acceptable quality of life at any age, exceeding that achievable with chronic administration of cardioactive drugs. These benefits can be demonstrated both subjectively by patient history, and objectively by increased treadmill time, maximum workload, peak oxygen consumption, and improved myocardial oxygen demand, metabolism and coronary flow.

Gradient reduction results from basal septal thinning with resultant enlargement
of the LVOT area (and redirection of forward flow with loss of the drag and Venturi effects on the mitral valve).\textsuperscript{61-63} As a consequence, SAM of the mitral valve and mitral–septal contact are abolished.\textsuperscript{62} Mitral regurgitation is usually eliminated without the need for additional mitral valve surgery, left ventricular systolic wall stress and left ventricular end-diastolic pressures are normalized.\textsuperscript{44,61} Heart failure resulting from obstructive HCM can, therefore, be regarded as surgically correctable.

When considering HCM-related mortality after septal myectomy, long-term survival was 99%, 98% and 95%, at 1, 5 and 10 years, respectively.\textsuperscript{53}

Myectomy was also associated with reduced long-term risk for sudden cardiac death. Nonetheless, surgical myectomy does not eliminate the need to assess each patient’s risk for sudden cardiac death and to consider implantable cardioverter-defibrillator (ICD) placement in those with a clinically significant risk burden (i.e. positive family history of sudden cardiac death, ‘massive’ left ventricular hypertrophy, non-sustained ventricular tachycardia etc.).
PURPOSE OF THE STUDY

To measure the long term effects of a successful left ventricular septal myectomy on LA remodeling in patients with obstructive HCM.

To describe the possible influence of the septal myectomy on the prevalence of atrial arrhythmias in this group of patients.

METHODS

Population

The study population consists of 133 consecutive patients with obstructive HCM evaluated at The Heart Hospital (University College London Hospital) who underwent a successful septal myectomy were included in this retrospective study.

Preoperative, operative, and postoperative data were obtained from the Heart Hospital HCM database and from medical record review; data were de-identified before analysis.

Criteria of inclusion

Patients aged >18 years who underwent septal myectomy for refractory symptoms (NYHA functional class IIb-IV) despite optimal medical therapy at our institution from October 2003 to August 2013, were eligible for inclusion in the study. According to 2014 ESC Guidelines, the diagnosis of HCM was based on the presence of a wall thickness ≥15 mm in one or more LV myocardial segments as
measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging (CMR) or computed tomography (CT)) that is not explained solely by loading conditions. The clinical diagnosis of HCM in first-degree relatives of patients with unequivocal disease is based on the presence of otherwise unexplained increased LV wall thickness ≥13 mm in one or more LV myocardial segments, as measured using any cardiac imaging technique (echocardiography, CMR or CT). By convention we defined HCM as significantly obstructive in patients who satisfied one of the following criteria based on echocardiography: (1) rest LVOT peak gradient > 30 mmHg or (2) provoked (Valsalva maneuver or exercise) LVOT peak gradient > 50 mmHg. Labile LVOT obstruction was defined as the presence of provoked LVOT obstruction (peak gradient > 50 mmHg) in the absence of rest LVOT obstruction (peak gradient ≤ 30 mm Hg). The diagnosis of AF was based on electrocardiogram (ECG) or Holter monitoring at the visit, or by a documented history of AF.

**Surgery**

The decision to perform surgery was made after consensus of a heart team consisting of a cardiothoracic surgeon, an interventional cardiologist, and a cardiologist specialized in HCM care. The surgical technique has been described previously. In brief, after induction of the anesthesia the surgeon opens the ascending aorta by an oblique incision, myectomy is performed to the left of an imaginary line through the nadir of the right coronary cusp in the beginning with a locally designed electrocautery device, later by excision with scissors and a rongeur or surgical knife. The surgical results are assessed with transesophageal
echocardiography immediately after weaning from cardiopulmonary bypass and at a systolic blood pressure of > 100 mm Hg.

Patients who underwent surgical myectomy in association with other procedures (i.e. mitral valve surgery) were excluded from the analysis.

*Echocardiography assessment*

Using the recommendations from the European Society of Echocardiography, 2D and Doppler echocardiographic measurements were performed. Every patient underwent a complete echo study performed by Cardiac Physiologist of the Diagnostic Testing Unit (DTU).

Left atrial antero-posterior diameter was measured in parasternal long axis, perpendicularly to the LA walls. The measurement of the LA diameter was in end-systole, from leading edge of the posterior aortic wall to the leading edge of the posterior LA wall. It could be measured in 2D, or in M-mode if the ultrasound beam was perpendicular to the LA walls.

LVOT gradient was measured using continuous wave Doppler in either the apical 4-chamber or apical 3-chamber view to determine the peak gradient at rest or under provocation.

Assessment of Systolic anterior motion and mitral valve regurgitation was performed using 2D, color and Doppler in both the parasternal long axis view and apical 4- 5- and 3-chamber.
Follow up

Baseline measurement were obtained pre surgery (T0), first follow up post procedure (T1) and at last follow up (T2).

LA dimensions, the presence of SAM and MR were obtained by transthoracic echocardiogram at each time interval.

Patients were excluded if preoperative and postoperative echocardiograms were not available for review. Survival status was determined by review of electronic medical records, patient correspondence, and cause of death were adjudicated by review of medical examiner record when possible.

Statistic methods

Statistical analysis was performed using the SPSS software. Continuous variables were expressed as mean±SD, and categorical variables as percentages. Numerical values were compared using the Mann-Whitney U test or student’s t test, and categorical values using the χ² test.
RESULTS

Table 1 shows the baseline characteristics of the 133 patients affected by obstructive hypertrophic cardiomyopathy who underwent surgical septal myectomy. Patients who had a mitral valve surgery were excluded.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>133</td>
</tr>
<tr>
<td>Male</td>
<td>69%</td>
</tr>
<tr>
<td>Age at myectomy</td>
<td>47 ±13 years</td>
</tr>
<tr>
<td>NYHA Functional Class</td>
<td>IIb-IV</td>
</tr>
<tr>
<td>LA diameter</td>
<td>47±7 mm</td>
</tr>
<tr>
<td>Complete SAM</td>
<td>74%</td>
</tr>
<tr>
<td>Moderate or severe MR</td>
<td>37%</td>
</tr>
<tr>
<td>Mean LVOT gradient</td>
<td>97±33 mmHg</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>14 (10.5%)</td>
</tr>
<tr>
<td>Persistent/permanent atrial fibrillation</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Beta-blocker/calcium-channel antagonists</td>
<td>92%</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>52%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>12%</td>
</tr>
</tbody>
</table>

Table 1: Clinical and echocardiographic characteristics at baseline of the study population

The mean age of the population at myectomy was 47 ±13 years (85 males, 69%). All patients were severely symptomatic (NYHA functional class IIb-IV) despite optimal medical treatment. At baseline, LA diameter was 47±7 mm; complete SAM was detected in 74% while moderate or severe MR was detected in 37% of patients. Mean LVOT gradient at baseline was 97±33 mmHg.
Before surgery, 117 (10.5%) patients were in sinus rhythm and their mean age at myectomy was 46±14 years (minimum 18, maximum 76); 14 (1.5%) patients had a history of paroxysmal atrial fibrillation (mean age at myectomy 53±8 years, minimum 41, maximum 68); 2 patients had persistent/permanent atrial fibrillation (mean age at myectomy 63 years, minimum 62, maximum 65). The difference of age at myectomy between the three groups was statistically significant (p=0.034), being the patients in AF significantly older than those in SR. Figure 1

![Figure 1: at the base-line (AF pre)](image)

1. Patients in sinus Rhythm
2. Patients with paroxysmal atrial fibrillation
3. Patients with persistent/Permanent atrial fibrillation

Regarding the medical therapy at baseline: 92% of patients were on beta-blocker/calcium-channel antagonists, 52% on disopyramide and 12% on
amiodarone.

**After myectomy**

First follow up post procedure (T1) was at a mean time of 1.7± 1.6 months and last follow up (T2) after surgery was at a mean time of 5.1±2.8 years (T2).

As expected, septal myectomy resulted in a significant and persistent reduction of LVOT gradient (14±17 mmHg at T2, p<0.001), reduction of complete SAM (2%, p<0.001 at T2) and reduction of severity of MR (1%, p<0.001), with an important clinical improvement in all patients (NYHA Class I-II). Regarding the medical therapy at the last follow up, 84% of patients were on beta-blocker or calcium-channel antagonists (p=0.04), 1% on disopyramide (p<0.001) and 10% on amiodarone (p=NS).

After surgery, at post operative follow up (T1) there was a significant decrease of LA diameter (45.2±7 mm, p=0.001). At T2 the LA diameter was 45.3±6 mm. Pair sample analysis of the difference of the LA size T0-T1 and T0-T2 showed long-term reduction (-1.8 mm, p=0.001, -1.72 mm, p=0.001) with no significant difference between early and long-term effects (T1-T2 -0.12, p =0.07). *Figure 2*

*Figure 2 Mean left atrial diameter at baseline and during first (LA post, T1) and last follow-up (LA last, T2)*
In the post-operative period (T1), 86 patients were in sinus rhythm and their mean age at myectomy was of 43±13 years (minimum 18, maximum 73); 45 patients had paroxysmal atrial fibrillation (mean age at myectomy 55±11 years, minimum 25, maximum 76); 2 patients remained in persistent/permanent atrial fibrillation (mean age 63, minimum 62, maximum 65). The difference of age at myectomy between the three groups was statistically significant (p=0.001).

At the last follow up (T2), 91 patients were in sinus rhythm and their mean age at myectomy was 45±14 years (minimum 18, maximum 76); 26 patients had paroxysmal atrial fibrillation (mean age at myectomy 51±13 years, minimum 18, maximum 68); 16 patients were in persistent/permanent atrial fibrillation (mean age 53±10 years, minimum 36, maximum 63). The difference of age at myectomy between the three groups was statistically significant (p=0.024).

*Figure 3*
Figure 3: in the last follow-up (AF last)
1. Sinus Rhythm
2. Paroxysmal atrial fibrillation
3. Persistent/Permanent atrial fibrillation

Age at myectomy and atrial fibrillation burden at last follow up

At the last follow up (T2, 5.1±2.8 years), 91 (68%) patients were in sinus rhythm, 26 (20%) patients had paroxysmal atrial fibrillation, 16 (12%) patients had persistent/permanent atrial fibrillation.

Among the 60 patients who were under 45 years at myectomy, 48 (80%) were in sinus rhythm at the last follow up, 8 (13.3%) had paroxysmal atrial fibrillation and 4 (6.7%) had persistent/permanent atrial fibrillation.

Among the 73 patients who were older than 45 years at the time of myectomy, 43 (58.9%) was in sinus rhythm at last follow-up; 18 (24.7%) had paroxysmal atrial fibrillation and 12 (16.4%) had persistent/permanent AF at the last follow-
up. The burden of AF accordingly to age at myectomy (older or younger than 45) was significantly different (p 0.05).

Before the myectomy, there was no significant difference in terms of LA diameter between patients <45 years (mean LA diameter 46.9 mm) and >45 years (mean LA diameter 47.21 mm, p=0.8), yet, in the last follow-up after surgical myectomy (T2), those >45 years had bigger LA diameters (mean LA diameter 46.75 mm) than those younger (mean LA diameter 43.62 mm, p<0.05).

**DISCUSSION**

The LVOT obstruction in patients affected by hypertrophic cardiomyopathy has been considered for a long time only a determinant of symptoms, such as dyspnea, angina and exertional syncope. More recently, it has been demonstrated that resting dynamic obstruction is a powerful predictor of heart failure and sudden cardiac death. Therefore, correct management of LVOT obstruction is essential. Patients with LVOT obstruction who are not treated or treated too late tend to develop left atrial dilatation and atrial fibrillation, which are adverse prognostic elements in the long-term outcome.

Septal myectomy is currently considered the best treatment for severely symptomatic patients despite maximal medical treatment. Good long-term outcome data support its efficacy and safety. It is well established that septal myectomy produces a significant reduction in LVOT gradient with subsequent improvement in mitral regurgitation due to SAM and cardiovascular symptoms. LVOT obstruction is strongly correlated with worsening LV diastolic function and increasing LA size.
The fact that, in patients who have undergone a successful surgical myectomy, two of the most important factors for prognosis are atrial dilatation and atrial fibrillation, suggests that a late surgical timing could be not beneficial.  

In our study it has been observed that LA diameter reduction follows after successful reduction of LVOT obstruction with surgical myectomy in patients with HCM. Reassuringly, this positive atrial remodeling appeared to be sustained at long-term follow up in this group of patients. 

We based our conclusion on a conventional and easy to obtain measurement: the antero-posterior LA diameter, which is a component of any clinical echocardiographic study. As previously demonstrated by Nistri and coll., LA diameter is a simple but powerful predictor of long-term disease progression and outcome in patients with hypertrophic cardiomyopathy. 

The significant reduction of LA antero-posterior diameter observed in our data may reflect the interruption of the vicious cycle secondary to the LVOT obstruction. 

The information derived by the left atrium are crucial in order to understand the clinical phenotype of our patient. A left atrium enlargement is a marker of both diastolic dysfunction and mitral regurgitation in patients with HCM and can be also one of the determinants of the risk to experience AF, with its complications in terms of thromboembolism and heart failure. 

In our data, in accordance with the literature, we observed that the more the patients got older, the more they experienced atrial fibrillation. This trend appeared not to be influenced by the myectomy. Yet, our data suggested that there might be an increased benefit on left atrial reversal remodeling if surgical myectomy is performed before the age of 45. In fact, at the base-line, before the
surgical procedure, there was no significant difference in terms of LA diameter between the group of patients older than 45 years old than those younger. On the contrary, after successful myectomy, the mean LA diameter in patients who had undergone the procedure earlier the age of 45, had a significant smaller LA diameter than those undergoing myectomy later. Furthermore, the burden of AF at last follow-up appeared to be critically related to the age at myectomy in our population with significantly lower prevalence of AF in patients younger than 45 at myectomy.

We have not collected information about presence and extension of fibrosis in the left atria. Atrial fibrosis could be related to both the severity of the ventricular hypertrophy and the diastolic dysfunction before myectomy but the relationship with AF susceptibility still needs to be fully understood.

CONCLUSION

Patients with hypertrophic obstructive cardiomyopathy who are not treated or treated too late tend to develop left atrial dilatation and atrial fibrillation, which are adverse prognostic elements in the long-term outcome. The surgical septal myectomy significantly reduces the left atrial diameter in the first months after surgery and the benefit is maintained during follow-up. Our data suggested that there might be an increased benefit on left atrial reversal remodeling if surgical myectomy is performed before the age of 45.
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