Alcohol Septal Ablation for the Treatment of Hypertrophic Obstructive Cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is an inherited myocardial disorder characterised by left ventricular hypertrophy. A subgroup of patients develops limiting symptoms in association with left ventricular outflow tract obstruction (LVOTO). Current international guidelines recommend that symptomatic patients are initially treated by alleviating exacerbating factors and negatively inotropic medication. Drug-refractory symptoms require a comprehensive evaluation of the mechanism of LVOTO and review by a multidisciplinary team to consider the relative merits of myectomy, alcohol septal ablation (ASA) and pacing. This article provides a brief overview of HCM and the pathophysiology of LVOTO, and reviews the use of ASA in patients with drug-refractory symptoms secondary to LVOTO.

Keywords

Hypertrophic cardiomyopathy, outflow tract obstruction, left ventricular outflow tract obstruction, alcohol septal ablation, myectomy

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Hypertrophic cardiomyopathy (HCM) is a genetic disorder of cardiac muscle with a heterogeneous clinical course.¹ The disease is clinically characterised by left ventricular hypertrophy (LVH), which is typically asymmetric, and a subgroup of patients have left ventricular outflow tract obstruction (LVOTO) caused by systolic anterior motion (SAM) of the mitral valve leaflet(s).^{2,3} LVOTO is often associated with limiting cardiovascular symptoms and a worse prognosis.^{4–8}

This article provides a brief overview of HCM and the pathophysiology of LVOTO, and reviews the use of alcohol septal ablation (ASA) for the treatment drug-refractory symptoms secondary to LVOTO.

Hypertrophic Cardiomyopathy Diagnostic Criteria

HCM is defined by the presence of LVH (left ventricular wall thickness ≥ 15 mm in a single myocardial segment) in the absence of systemic hypertension, congenital heart disease and valve lesions of sufficient severity to explain the observed degree of hypertrophy.^{1,9} In first-degree relatives who have inherited a disease-causing mutation, lesser degrees of LVH are sufficient to make the diagnosis.^{10,11} The diagnosis is reached by integrating clinical and imaging data from echocardiography and increasingly cardiac magnetic resonance (CMR) imaging.

Epidemiology

The prevalence of HCM ranges from 0.02 % to 0.23 %, depending on the characteristics of the study population and methodology used.^{12–20}

Aetiology

In adults, HCM is primarily inherited in an autosomal dominant manner and is caused by mutations in cardiac sarcomere protein genes.^{21–23} Mutations in these genes can be found in ~60 % of patients with HCM,^{21–23} and the majority involve cardiac myosin binding protein-C

(MYBPC3) and cardiac myosin heavy chain (MYH7).²⁴ There is a poor correlation between genotype and phenotype.^{25,26}

Metabolic diseases (e.g. Anderson-Fabry disease), syndromes (e.g. Noonan) and amyloid can mimic sarcomeric HCM.^{1,27} Phenocopies may be recognised by the presence of specific phenotypic 'red flags' (e.g. conduction disease in Anderson-Fabry disease), which help rational selection of diagnostic tests and ultimately disease-specific treatments (e.g. enzyme replacement therapy for Anderson-Fabry disease).²⁷

Left Ventricular Outflow Tract Obstruction

LVOTO at rest is encountered in ~30 % of patients with HCM, and is associated with limiting symptoms (dyspnoea, angina, syncope) and worse prognosis.^{4–8} Unlike symptom limitation from ischaemic heart disease and left ventricular systolic dysfunction, effort tolerance in obstructive HCM is often variable, and patients often describe both good and bad days; this may make assessments of functional class (for example using the New York Heart Association [NYHA] classification) challenging. Approximately a third of HCM patients report postprandial exacerbation of symptoms.²⁸

LVOTO is caused by the SAM of the mitral valve. In systole, the anterior mitral valve leaflet moves into the left ventricular outflow tract (LVOT), which is already narrowed by the hypertrophied septum creating a physical barrier, which impedes the flow of blood from the ventricle to the aorta during systole (see *Figure 1*).^{2,3} Contact of the mitral valve leaflets to the septum is termed 'complete' SAM, and lesser forms of SAM where there is no contact are termed 'incomplete'. SAM of the mitral valve leaflets is often associated with varying degrees of mitral regurgitation since the two mitral valve leaflets are pulled apart during SAM, creating an orifice through which retrograde,

posteriorly-directed flow in the left atrium can occur. Consequently, conditions which increase LVOTO also increase the severity of mitral regurgitation.^{3,29} LVOTO is also promoted by coincident abnormalities of the mitral valve leaflets. The leaflets (particularly the anterior leaflet) are frequently elongated and displaced anteriorly, with abnormal attachments to the papillary muscles and chordae.^{30,31} Early investigators attributed SAM of the mitral valve to suction forces (Venturi effect) caused by accelerating blood flow in LVOT during systole, drawing the mitral valve leaflets anteriorly into the outflow tract. However, SAM of the mitral valve commences in early systole when the Venturi effect is minimal, and this is therefore unlikely to be the sole explanation for LVOTO.^{32,33} The mechanism underlying LVOTO is probably multi-factorial, involving the interaction of abnormalities of papillary muscles, chordae, mitral leaflets and LVH, which culminate in abnormal flow forces that push and/or pull the mitral valve towards the outflow septum.³³ Although LVOTO gradient is the most evident abnormality, the physiology of obstructive disease includes elevated left ventricular (LV) end-diastolic pressure, mitral regurgitation and a potential for abrupt changes in LVOTO magnitude (for example with postural change or sudden exertion); these abnormalities, as well as the increased LV afterload, may all contribute to symptoms.

A characteristic feature of LVOTO is that the severity of the obstruction is dynamic and subject to prevailing haemodynamic conditions. LVOTO is exacerbated by conditions causing reduced preload (e.g. Valsalva, squat to stand), reduced afterload (e.g. vasodilators) or positive inotropes.³ Notably, although LVOTO is most often seen in HCM, it may also occur in other conditions or physiological states and is not pathognomonic of HCM.^{34,35}

In a smaller subgroup of HCM patients, obstruction can develop at the mid-left ventricular cavity. Mid-cavity obstruction is caused by the systolic apposition of hypertrophied mid-ventricular segments and/or papillary muscles creating a characteristic hour-glass appearance with a distinct apical cavity.^{36,37} This form of obstruction is often associated with apical aneurysm formation.^{36,37} Mid-cavity obstruction can exist in isolation (see *Figure 2*) or in conjunction with LVOTO. Even though ASA has been used in the treatment of mid-cavity obstruction,^{38,39} this is not routine practice and further discussion is beyond the scope of this review.

Assessment of Left Ventricular Outflow Tract Obstruction

All patients with HCM should undergo a detailed transthoracic echocardiogram to examine:

- the severity and distribution of hypertrophy and in particular the septal wall thickness at the point of mitral-septal contact;
- intra-cavity gradients with continuous and pulsed-wave Doppler to determine the severity and level of obstruction (LVOTO, mid-cavity obstruction or both);
- the mitral valve apparatus for systolic anterior movement of the mitral valve, hypertrophied papillary muscles, abnormal chordal attachments and intrinsic mitral valve disease; and
- other cardiac pathology that may have an impact on treatment (e.g. aortic valve disease).

If the transthoracic echocardiogram fails to provide the necessary diagnostic information, a transoesophageal echocardiogram, CMR or an invasive haemodynamic study may be required.

Figure 1: Typical Echocardiographic Findings in Left Ventricular Outflow Tract Obstruction

Top left: Transthoracic echocardiogram parasternal long axis view shows asymmetric septal hypertrophy with a septal wall thickness of 18 mm. This provides the substrate for left ventricular outflow tract obstruction (LVOTO), particularly when the mitral valve leaflets are long. Top right: There is systolic anterior movement of the anterior mitral valve leaflet, which makes contact with the hypertrophied septum. Once the mitral-septal contact occurs a pressure gradient develops across the left ventricular outflow tract. The septal site where the mitral valve makes contact is often fibrosed and is echogenic (impact lesion). Middle left: Colour Doppler flow examination of the left ventricular outflow tract reveals aliasing arising adjacent to the mitral-septal contact point indicating increased velocities in the outflow tract. In cases of mid-cavity obstruction, aliasing originates in the mid-ventricle. Middle right: Colour Doppler flow examination of the mitral valve shows mild posteriorly directed mitral regurgitation. Severe mitral regurgitation and/or regurgitation, which is not posteriorly directed should raise suspicion of intrinsic mitral valve disease. Bottom left: M-mode examination of the mitral valve shows that during early systole the mitral valve moves anteriorly towards the septum in mid-late systole. Severe LVOTO tends to be associated with very early systolic mitral-septal contact with a large area of mitral-septal apposition. Bottom right: To determine the severity of obstruction, the left ventricular outflow tract is examined with continuous wave Doppler in the apical views. The Doppler envelope of LVOTO is characteristically 'dagger' shaped. Pulsed-wave Doppler examination can be used to confirm the level of obstruction; aliasing occurs with sampling on the aortic side of the mitral-septal contact point, whilst the flow pattern is normal apical to the mitral-septal contact.

An instantaneous Doppler LVOT gradient of ≥ 30 mmHg is considered significant, and such patients are classified as having the obstructive form of the disease. However, LVOTO is considered to be haemodynamically significant only when the LVOT gradient is ≥ 50 mmHg.³ There are few data to support these thresholds,³ which are largely empirically defined and reflect an understanding that when LVOTO is mild, therapeutic reduction of LVOTO is less likely to improve symptoms, and alternative causes of severe symptoms should be sought.

Figure 2: Isolated Mid-cavity Obstruction

In this invasive haemodynamic study synchronous blood pressure recordings are taken from a 7 Fr femoral sheath side-port and a 6 Fr end-hole pigtail catheter placed at the left ventricular (LV) apex (top left). Contrast injections show that there is an apical cavity with obliteration of the mid-ventricle during systole. There is a resting gradient of ~40 mmHg, which disappears when the pig-tail catheter is withdrawn basal to the point where the ventricle obliterates (top right). These findings are consistent with isolated mid-cavity obstruction.

Figure 3: Treatment Algorithm for Symptomatic Left Ventricular Outflow Tract Obstruction

LVOTO = left ventricular outflow tract obstruction.

Figure 4: Alcohol Septal Ablation

Alcohol septal ablation in a patient with left ventricular outflow tract obstruction (LVOTO) and drug-refractory symptoms. A haemodynamic study with synchronous blood pressure recordings from a 7 Fr femoral sheath side-port and a 6 Fr end-hole pigtail catheter placed in the left ventricular (LV) confirms the presence of LVOTO. As the pigtail catheter is withdrawn from the base (top left) to the subaortic position (top right) the gradient disappears. The first septal artery is wired and an over-the-wire balloon is positioned in the proximal third of the septal perforator. The balloon is inflated to isolate the septal from the rest of the coronary circulation and echocardiographic contrast is injected via the balloon lumen. A transthoracic echocardiogram shows that the contrast localises at a favourable position, adjacent to the mitral-septal contact. Additional views (not shown) illustrated that contrast did not localise at undesirable myocardial sites outside the target area. Angiographic contrast was then injected to ensure that there is no reflux into the left anterior descending (LAD) or collaterals that would allow infarction of distant myocardial segment. Alcohol is then injected slowly with close monitoring of the rhythm and appropriate analgesia. Since the patient had a defibrillator with anti-bradycardia pacing capabilities, a temporary pacing wire was not required. After 5–10 minutes the over-the-wire balloon is deflated and an angiogram at the end of the procedure shows that the septal artery is truncated.

Since LVOTO is dynamic, obstruction may not be apparent in the supine patient under resting conditions. Exercise, the Valsalva manoeuvre, postural changes or an isoprenaline infusion help demonstrate latent LVOTO.^{6,40–42} These additional tests are mandatory in the evaluation of patients with symptoms suggestive of obstruction, which is not demonstrable at rest.

Treatment of Symptomatic Left Ventricular Outflow Tract Obstruction

Currently, there is no evidence that asymptomatic patients with LVOTO benefit from treatment to reduce the severity of obstruction; treatment is reserved for patients with LVOTO and drug-refractory symptoms.^{43,44} A contemporary treatment algorithm for symptomatic patients with LVOTO is summarised in *Figure 3*. The first-line treatment for symptoms associated with LVOTO is correction of exacerbating factors (e.g. vasodilating antihypertensives, anaemia) followed by pharmacological therapy with β -blockers, verapamil and disopyramide, which modulate the dynamic physiology of obstruction through their negative inotropic and chronotropic effects.^{43–46} In patients with drug-refractory symptoms or unacceptable side effects, invasive treatments should be considered by a multidisciplinary team following a comprehensive evaluation of the mechanism of obstruction:

- Surgical myectomy involves excision of the hypertrophied septum at the point of mitral contact through an aortotomy under cardiopulmonary bypass.⁴⁷ Surgical myectomy is a technically demanding operation, but with improved peri-operative care and surgical techniques the current peri-operative mortality is low in high volume centres. In addition to the general complications of open heart surgery, specific peri-operative complications of myectomy include ventricular septal defects, aortic regurgitation and complete heart block requiring pacemaker implantation.^{48,49}
- Mitral valve repair/replacement may be required as an adjunct to myectomy.^{50–52} Mitral valve replacement in isolation also abolishes SAM and LVOTO, but is considered only when there are other indications for valve replacement such as intrinsic mitral valve disease.^{53,54}
- Alcohol septal ablation aims to reproduce the effects of myectomy via a minimally invasive percutaneous approach.^{55,56} Ethanol is injected via the septal perforator branches of the left anterior descending artery to the hypertrophied septum to induce a myocardial infarction and necrosis. Scar formation causes remodelling of the LVOT with relief of obstruction. ASA is discussed in more detail below.
- Atrioventricular (AV) sequential pacing from the right ventricular apex using dual-chamber pacemakers with short AV delay reduces LVOTO by causing septal dyssynchrony and modifying preload.⁵⁷ Placebo-controlled trials showed an improvement in symptoms but with a less consistent reduction in LVOTO.^{58–62}

ASA is currently the most frequently used invasive therapy, and while it is efficacious, relatively safe and minimally invasive, outcomes from randomised trials comparing different invasive techniques are not yet available. Several experienced opinions still regard surgical treatment as the 'gold standard'.^{43,44} Currently, patients must be counselled that choices between ASA, surgery and pacing are made on the basis of considerations other than proven differences in outcome.

In general, ASA may be unsuitable in the presence of co-existing mid-cavity obstruction and/or intrinsic mitral valve disease; in such cases a surgical approach should be considered. Septal reduction either by ASA or myectomy when the septal wall thickness is <15 mm at the site of mitral contact is also challenging, and alternatives such as mitral valve repair/replacement or AV sequential pacing should be considered. AV sequential pacing can also be useful in selected patients where aggressive pharmacological treatment

with a β -blocker, verapamil and disopyramide is contemplated, and in patients too frail to tolerate more invasive treatment. In others, pacing may be considered as an initial therapeutic trial before progression to more invasive treatment. This may include individuals with conventional indicators for device therapy (including pacing and defibrillator treatment) and patients at high risk of developing heart block following invasive treatment. Patient preference is also a key factor in decision-making.

Alcohol Septal Ablation – Procedural Aspects

The essential components of this percutaneous procedure include the identification of an appropriate septal perforator artery, its isolation from the rest of the coronary circulation and the selective injection of alcohol into this artery. The first septal artery is usually selected and a short over-the-wire balloon inflated within the artery. The balloon's lumen allows selective delivery of angiographic contrast, echo contrast and ultimately, alcohol into the septal artery. Angiographic contrast ensures that the septal artery is isolated from the left anterior descending (LAD) by the inflated balloon, and echo contrast confirms that the myocardial volume subtended by the selected septal artery is an appropriate target for ablation.^{63–65} The proximal septal vessels may also supply the right ventricular free wall, LV apex and papillary muscles, and several echocardiographic views are needed to ensure contrast enhancement is confined to the target area; the appropriate target lies adjacent to the point of mitral-septal contact. If echo contrast does not localise to the target area, other septal arteries should be selectively assessed. A temporary pacing wire is inserted prior to the injection of alcohol in case significant bradyarrhythmias follow conduction system damage. Right bundle branch block is observed in approximately 50 % of cases.⁶⁶ Adequate analgesia is provided and the alcohol is slowly injected to chemically ablate and infarct the target myocardium.⁶⁷ Approximately 0.1 ml of ethanol (concentration >95 %) per 1 mm of thickness of the target myocardium is injected slowly (1 ml/minute).⁶⁴ The balloon remains inflated for 5–10 minutes post-ethanol injection to prevent reflux in the anterior descending and to enhance delivery at the target myocardium. LVOTO is often reduced or abolished at the end of the procedure; this acute effect reflects septal stunning, and the LVOT gradient may again increase in the days following the procedure, to fall again over a period of weeks as septal remodelling occurs and a small scar develops in place of the ablated myocardium. The femoral or radial approach can be used.⁶⁸ Important procedural steps are shown in *Figure 4*.

Acute Complications of Alcohol Septal Ablation

Since its inception in 1995,⁶⁵ ASA has evolved and the routine use of echo contrast to select the target septal artery has made the procedure safer and more effective.^{63–65} In addition to complications arising from the injection of alcohol, ASA is also associated with the complications of percutaneous coronary intervention and temporary wire insertion:

- Vascular injury and haemorrhage.
- Coronary dissection from guide catheter, wire and over-the-wire balloon manipulation.^{69,70}
- Myocardial infarction from alcohol escaping from the septal branch into the LAD⁵⁶ or via septal collaterals.⁷¹
- Cerebrovascular accidents.
- Cardiac tamponade from temporary wire insertion.⁷²
- Sustained ventricular arrhythmias.⁷³
- Complete heart block requiring pacemaker implantation (~11 %).⁷⁴

Table 1: Meta-analyses Examining Mortality Following Septal Reduction Therapy

Meta-analysis	Inclusion Criteria	Number of Included Studies	Number of Patients	In-hospital Mortality	
Zeng et al. (2006) ⁷⁹	Case control studies comparing ASA with SM in adult patients	3	ASA: 86 SM: 91	2.3 % 1.1 %	p=NA
Alam et al. (2009) ⁸⁰	Case control studies comparing ASA with SM in adult patients	5	ASA: 183 SM: 168	1.6 % 0.6 %	p=0.2
				30 Day All-cause Mortality (RD)	Long-term All-cause Mortality (RD)
Agarwal et al. (2010) ⁸¹	Cohort and case control studies comparing ASA with SM in adult patients	9	ASA: 380 SM: 326	0.01 (0.01–0.03) p=0.35	0.02 (–0.05–0.09) p=0.55
				Annual Rate of All-cause Mortality	Annual Rate of Sudden Cardiac Death
Leonardi et al. (2010) ⁷⁴	Reports/studies with ≥5 ASA patients or ≥100 SM patients	19 ASA studies 8 SM studies	2,207 1,887#	1.8 (1.2–2.6) p=0.36 2.1 (1.7–2.7)	0.3 (0.2–0.6) p=0.37 0.4 (0.3–0.6)

ASA = alcohol septal ablation; NA = not available; RD = Risk difference; SCD = sudden cardiac death; SM = septal myectomy. # SM patients had longer follow-up periods than ASA patients. SM patients were also younger (mean age 44 versus 55 years), but had similar left ventricular outflow tract obstruction, New York Heart Association class and septal maximal wall thickness (MWT).

Table 2: Meta-analyses Examining Symptoms, Gradients and Need for Pacing After Alcohol Septal Ablation and Myectomy

Meta-analysis	NYHA Post-procedure Alcohol Septal Ablation Versus Septal Myectomy	Post-procedure LVOTg, mmHg Alcohol Septal Ablation Versus Septal Myectomy	Post-procedure Pacing Alcohol Septal Ablation Versus Septal Myectomy
Zeng et al. (2006) ⁷⁹	1.47 versus 1.36; p=NS	15.7 versus 9.4; p <0.05	20.9 % versus 4.4 %; p=NA
Alam et al. (2009) ⁸⁰	1.5 versus 1.3; p=0.20	18.2 ± 6.7 versus 10.8 ± 6.3; p<0.001	18.4 % versus 3.3 %; p=0.04
Agarwal et al. (2010) ⁸¹	0.30 (95 % CI -0.03, 0.63)*; p=NS	-0.09 (95 % CI -0.3, 0.1)*; p=NS	OR: 2.6 (95 % CI 1.7, 3.9); p=NS
Leonardi et al. (2010) ⁷⁴	1.5 (1.3, 1.7) versus 1.6 (1.5, 1.7)**; p=NS	22 (15, 23) versus 3 (2, 6)**; p<0.05	11 (8, 15) versus 5 (3, 9)**; p<0.05

*Standardised mean differences; ** median (interquartile range [IQR]); CI = confidence interval; LVOTg = left ventricular outflow tract gradient; NA = not available; NS = not significant; OR = odds ratio.

Despite these potential complications, ASA remains a relatively safe procedure with in-hospital death rates of around 1 %.^{69,75}

Post-operative Care

Patients should have a temporary pacing wire *in situ* with cardiac monitoring for 24–48 hours after the procedure, as they are at risk of arrhythmias. High-grade AV block resolves in the majority of cases within three days.⁷⁶ On discharge, patients should be advised to report arrhythmic symptoms as rarely new onset bradyarrhythmias develop late after the procedure.⁷⁷ Cardiac biomarkers peak at 12 hours post-ASA and correlate with the size of myocardial injury.⁷⁸ In the absence of new conduction abnormalities, pharmacotherapy for symptomatic LVOTO should continue until a clinical review in 3–6 months, and can then be tapered if symptoms have improved.

Long and Medium-term Outcomes – Alcohol Septal Ablation Versus Myectomy

Mortality associated with ASA and surgical myectomy has been examined and compared in four meta-analyses.^{74,79–81} Even though the meta-analyses included individual studies with very different inclusion criteria, they have consistently shown that the two procedures have similar survival outcomes (see Table 1). Both septal reduction therapies achieve similar improvements in symptoms, which is the principal aim of invasive therapy. However, myectomy is associated with a greater reduction in gradients and reduced need for post-procedural anti-bradycardia pacing (see Table 2).^{74,79–81} Concerns over the long term arrhythmogenic potential of the myocardial scar induced by alcohol septal ablation⁶⁷ are not supported by observational data of implantable cardioverter defibrillator (ICD) recipients undergoing the procedure⁸² or mortality data from the meta-analyses.^{74,79–81}

Procedural Failure

ASA is effective at reducing symptoms in more than 85 % of patients.⁶⁹ In cases of procedural failure, defined by the persistence of both symptoms and LVOTO (rest or latent), further intervention with any of the modalities may be considered following a repeat assessment of the mechanisms responsible for symptoms. As changes in LV morphology following ASA may be delayed, it is prudent to delay decisions regarding further intervention for 3–6 months.⁸³

Significant symptoms may persist in about 10–20 % of patients despite LVOTO abolition, illustrating the importance of the complexity of the disease and appropriate patient selection. It is therefore important to counsel patients that LVOTO reduction does not cure HCM and ongoing care will be required to monitor and treat their disease.

Alternative Percutaneous Septal Reduction Therapies

Alternative approaches to reduce hypertrophy at the point of mitral-septal contact by means other than alcohol have been investigated:

- Microcoils, polyvinyl alcohol foam and cyanoacrylate glue delivered in the target septal artery obstruct the vessel with infarction of the subtended myocardium.^{84–87}
- Direct endocavitary radiofrequency or cryotherapy ventricular ablation.^{88,89} This approach has the advantage of overcoming unfavourable septal anatomy.

Experience with these alternatives is limited and long-term safety data are not available.

Care Beyond Left Ventricular Outflow Tract Obstruction

LVOTO should not overshadow other aspects of management; patients in whom LVOTO is successfully abolished are still subject to other HCM-related risks and outcomes. HCM should be evaluated in units with relevant expertise to address family screening and genetic testing, the risk of sudden cardiac death, atrial arrhythmias and prevention of stroke.

Conclusion

LVOTO is associated with significant morbidity and mortality. In patients with LVOTO and drug-refractory symptoms, invasive treatment should be considered following a multidisciplinary team review. The choice of invasive therapy depends not only on disease-specific characteristics but also patient preference. Contrast echocardiography-guided ASA is a safe and effective modality, which will improve symptoms in the majority of patients. ■

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