

Septal reduction therapy for hypertrophic obstructive cardiomyopathy¹

Amir-Ali Fassa, Ulrich Sigwart

Division of Cardiology, Geneva University Hospitals, Switzerland

Summary

Hypertrophic obstructive cardiomyopathy can cause symptoms such as dyspnoea, angina pectoris and syncope. First-line pharmacological therapy includes beta-blockers, verapamil and disopyramid. However, 5–10% of patients with left ventricular outflow tract gradient are unresponsive to medical treatment. Therapeutic options for patients with drug-resistant symptoms include surgical myectomy (SM) and alcohol septal ablation (ASA). The former has been performed for more than 50 years and involves surgical resection of the basal septum. The latter, which was proposed as an alternative to surgical therapy 15 years ago, is a catheter-based technique involving selective injection of ethanol in a septal coronary artery to induce a scar at the level of the basal septum. Both procedures are associated with excellent symptom relief and long-term survival. Complication rates are also comparable, although complete heart block requiring permanent pacemaker implantation tends to occur more frequently following ASA. Moreover, SM and ASA have never been compared by a randomised controlled trial. The choice of treatment should therefore be based on local availability and expertise as well as patient's preference and associated conditions, taking into account the benefits and limitations of both techniques.

Introduction

Hypertrophic cardiomyopathy is defined by myocardial hypertrophy in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident. It is the most prevalent heritable cardiovascular condition (approximately 1:500 in the general adult population), and is marked by phenotypic and genotypic heterogeneity [1]. Many individuals have familial disease with an autosomal dominant pattern of inheritance. Several hundred mutations in at least 27 genes that encode sarcomeric, calcium-handling and mitochondrial proteins have been identified [2]. The

majority of patients typically present an asymmetrical pattern of hypertrophy with a predilection for the interventricular septum. Approximately 25% of patients with hypertrophic cardiomyopathy have left ventricular outflow tract (LVOT) obstruction under resting conditions, which is an independent predictor of mortality (relative risk vs non-obstructed patients, 2.0) [3–5]. In addition, >50% of patients without obstruction at rest may generate significant gradients during exercise. The obstruction causes an increase in left ventricular systolic pressure leading to a complex interplay of abnormalities that include prolongation of ventricular relaxation, increased left ventricular diastolic pressure, myocardial ischaemia, decreased cardiac output and mitral regurgitation due to systolic anterior motion of the mitral valve [6]. While most patients with hypertrophic obstructive cardiomyopathy (HOCM) remain asymptomatic throughout life, LVOT obstruction may cause symptoms such as exertional dyspnoea, chest pain (either typical of angina or atypical in nature), fatigue and presyncope or syncope. Initial management for HOCM includes pharmacological agents (negative inotropes such as beta-blockers, verapamil and disopyramid). However, approximately 5–10% of patients remain symptomatic despite maximal medical therapy and are therefore candidates for septal reduction therapies (SRT), which include surgical myectomy (SM) and alcohol septal ablation (ASA). Dual chamber pacemaker implantation is another nonpharmacological treatment, although its indications have currently become rather limited [5] (table 1).

Correspondence:

Amir-Ali Fassa, MD
Interventional Cardiology Fellow
Division of Cardiology
Geneva University Hospitals
Rue Gabrielle-Perret-Gentil 4
CH-1211 Geneva 14
Switzerland
Amir-Ali.Fassa@hcuge.ch

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Table 1
Treatment modalities for relief of left ventricular outflow tract gradient in hypertrophic obstructive cardiomyopathy.

Pharmacological therapies	Beta-blockers Verapamil Disopyramide	
Nonpharmacological therapies	Septal reduction therapies	Surgical myectomy Alcohol septal ablation
	Dual chamber pacing	

Indications for septal reduction therapies

The objective of SRT is relief of symptoms related to the LVOT gradient. Patient selection for SRT is based on careful individual evaluation of clinical and echocardiographic parameters [5]. According to the recommendations of the American College of Cardiology / European Society of Cardiology, SRT should be proposed to patients with heart failure symptoms who have substantial lifestyle limitation (New York Heart Association [NYHA] class III or IV) refractory to maximal drug therapy, in the presence of significant LVOT obstruction (defined as >50 mm Hg at rest or with provocation) (table 2). However, in current practice both procedures are often performed in patients with less severe symptoms (as illustrated by a mean baseline NYHA class of 3.0 for both SM and ASA in a recent meta-analysis comparing both SRT) [7]. Hence other proposed criteria include abnormal blood pressure response during exercise or recurrent syncope/presyncope in less symptomatic patients (NYHA or Canadian Cardiovascular Score [CCS] class II symptoms) who have a resting or provokable gradient >50 mm Hg (or >30 mm Hg at rest and >100 mm Hg with provocation) and also patients with NYHA or CCS class III or IV symptoms and a LVOT gradient >30 mm Hg at rest or >60 mm Hg with provocation [8, 9].

Table 2
Selection criteria for septal reduction therapies in patients with hypertrophic obstructive cardiomyopathy.

Symptoms refractory to adequate tolerated drug therapy	
NYHA or CCS class III or IV with:	LVOT gradient >30 mm Hg at rest or \geq 60 mm Hg under stress or LVOT gradient \geq 50 mm Hg at rest or under stress
NYHA or CCS class II in selected patients (see text):	LVOT gradient >50 mm Hg at rest or LVOT >30 mm Hg at rest and \geq 100 mm Hg under stress
Septal thickness >(15–)18 mm	
NYHA = New York Heart Association; CCS = Canadian Cardiovascular Society; LVOT = left ventricular outflow tract	

Surgical myectomy

SM was first performed by Cleland in 1958, and was later pioneered by Morrow, Kirklin and Bigelow [10, 11]. The procedure is performed through the aortic valve via aortotomy, and involves resection of the basal septum allowing relief of outflow obstruction and elimination of systolic anterior movement of the mitral valve and associated regurgitation [10, 12] (fig. 1). Classically, the intervention described by Morrow is achieved by creating two parallel longitudinal incisions in the basal septum which are extended distally, and then transversely connected, proximally below the aortic valve and distally just beyond the mitral-septal contact and subaortic obstruction. In recent years the procedure has evolved into more extensive septal myectomy combined with repair of possible mitral valve and submitral apparatus abnormalities (such as elongated or flexible leaflets, anomalous chordae, anterior displacement or fusion of the papillary muscles) [10, 12, 13]. Furthermore, guidance by intraoperative transoesophageal echocardiography is currently the mainstay, allowing direct monitoring of the efficacy of the resection and possible surgical revision [10].

Long-term improvement in symptoms is seen in a majority of patients, with reported rates of 78–94% of patients with NYHA class I or II functional capacity after a mean follow-up of 5–7 years [14–16]. Mean LVOT resting gradient decreases from >65 mm Hg at the time of operation to <5 mm Hg (mean follow-up of 3–5 years). In addition, long-term follow-up in series from three high-volume centres shows survival rates of 95–96% at 5 years and 83–90% at 8–10 years, which are not different from matched controls in the general population [14–16]. Although there is at present no evidence that SM improves long-term prognosis, it was recently reported in a retrospective study that SM appears to decrease the risk of appropriate discharge in patients with implantable cardioverter defibrillators [17].

Complete heart block (CHB) requiring permanent pacemaker implantation occurs in 1–10% of patients following SM [14–16, 18, 19]. This is due to the fact that the left bundle branch is frequently injured during the procedure (in 46–93% of patients with normal baseline ECG) [18, 19]. Consequently, patients with baseline right bundle branch block (RBBB) are at increased risk for CHB following SM [15, 18, 19]. Other rare complications such as ventricular septal defect (due to excessive removal of muscle) or aortic regurgitation (secondary to traction of the aortic valve to improve visualisation and access to the septum) have also been reported [14, 16, 20, 21].

Figure 1
Schematic diagram of a patient undergoing surgical myectomy. Before the operation there is severe hypertrophy of the basal septum, with systolic anterior motion of the mitral valve (A). This results in severe outflow tract obstruction as well as mitral regurgitation. During surgery (B), the portion of the basal septum that projects into the outflow tract is removed by a scalpel, resulting in abolition of the outflow tract obstruction (C). In addition, there is no longer systolic anterior motion of the mitral valve, and the mitral regurgitation is abolished. Reproduced with permission from [6]: Nishimura RA, Holmes DR Jr. Hypertrophic obstructive cardiomyopathy. *N Engl J Med.* 2004;350:1320–7. Copyright © 2004 Massachusetts Medical Society. All rights reserved.

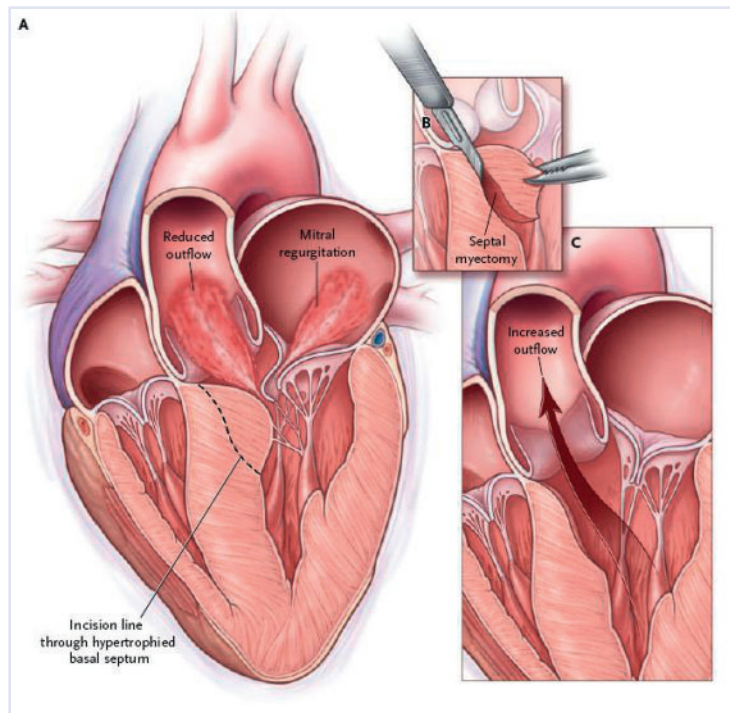
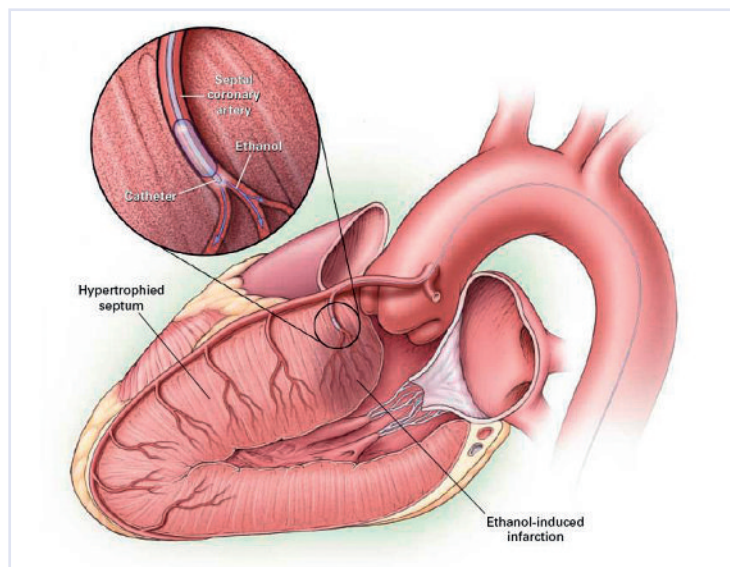


Figure 2
Schematic diagram of a patient undergoing alcohol septal ablation. Section of hypertrophied left ventricle. The inset shows a balloon occluding the septal coronary artery and alcohol-induced septal infarction. Reproduced with permission from [27]: Braunwald E. Hypertrophic cardiomyopathy – the benefits of a multidisciplinary approach. *N Engl J Med.* 2002;347:1306–7. Copyright © 2002 Massachusetts Medical Society. All rights reserved.



Perioperative death has significantly decreased over the past 50 years, with mortality rates lower than 1% reported in recent series from experienced centres [7, 14–16]. In patients undergoing additional concomitant procedures (such as coronary bypass grafting or valve replacement), which represent a proportion varying from 18 to 55% of SM operations, reported perioperative mortality is somewhat higher (3.7%) [14–16].

Alcohol septal ablation

The first catheter-based septal reduction for HOCM was performed by the author (US) on June 16, 1994 at the Royal Brompton Hospital in London. In the first series of three patients reported, absolute alcohol was injected into a septal coronary artery to induce a myocardial infarction localised to the interventricular septum [22]. This resulted in a reduction of LVOT gradient and subsequent clinical improvement in all three patients. This procedure was performed after a preliminary study showing transient reduction in LVOT gradient during temporary septal artery balloon occlusion in patients with symptomatic HOCM, and also following clinical improvement observed in a patient with HOCM who had suffered an anterior myocardial infarction.

Since it was originally described there has been growing enthusiasm for ASA, and the number of procedures performed to date is probably more than 5000 [23]. Currently, ASA is performed in the catheterisation laboratory by experienced interventional cardiologists. Patients are conscious during the procedure, with mild sedation and analgesics commonly administered. Using a standard coronary angioplasty guiding catheter, a guide wire is placed in the first septal perforator, over which a balloon catheter is placed (fig. 2). Thereafter 1–3 ml ethanol is injected through the balloon catheter following inflation of the balloon in order to prevent backflow in the left anterior descending (LAD). Guidance by myocardial contrast echocardiography (MCE) for selection of the septal branch has become paramount for the success of the procedure [24–26]. This is achieved by performing transthoracic echocardiography while injecting an echocardiographic contrast agent through the balloon catheter placed in the septal branch, consequently delineating the zone that will become infarcted (fig. 3). MCE serves to determine whether the opacified myocardium is adjacent to mitral-septal contact and rule out any retrograde leakage or involvement of myocardium remote from the expected target region (such as the ventricular-free wall or papillary muscles). Ultimately, the interventional strategy is changed in 15–20% of cases on the basis of MCE, either by changing the target septal perforator or by aborting the procedure in the absence of suitable anatomy. Moreover, the use of MCE is associated with

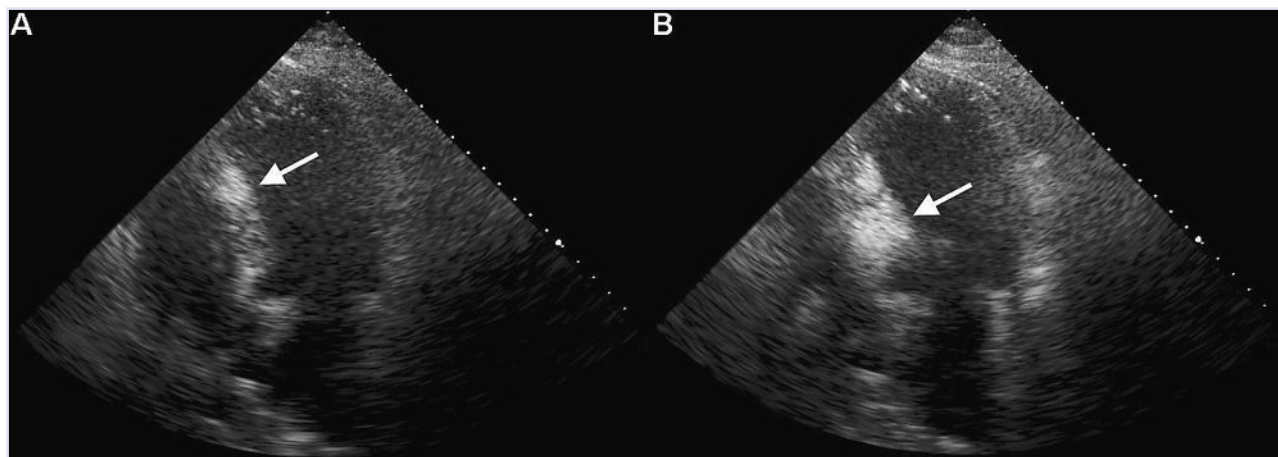
Figure 3

Myocardial contrast echocardiography.

A Apical four-chamber echocardiogram with injection of echocardiographic contrast via the occluded balloon catheter positioned in a septal perforator with opacification of the medium portion of the interventricular septum (arrow).

B After repositioning the balloon catheter in another septal branch, the target area of the basal septum is opacified with the echocardiographic contrast (arrow).

Courtesy of Professor René Lerch, University Hospital of Geneva, Switzerland.



higher rates of acute and mid-term success and a lower rate of CHB requiring pacemaker implantation [28–30].

Pooled results of studies on ASA show acute reductions in mean resting LVOT gradient from 65 to 17 mm Hg and mean provoked gradient from 125 to 53 mm Hg, with persistence of the reduction after 12 months (16 and 32 mm Hg, respectively) [31]. Furthermore, there is significant improvement of functional class, with mean NYHA Class reduction from 2.8–3.0 at baseline to 1.2–1.5 on long-term follow-up and persistence of the benefit for up to 8 years [30, 32]. This is also confirmed by objective increases in exercise capacity and peak oxygen consumption [7, 30–34].

Procedure success is achieved in 83–89% of cases [31, 33, 34]. Repeat ASA due to initial failure or recurring gradient and symptoms after primary success are performed in 2–14% of patients [7, 30, 31, 34]. Long-term follow-up after ASA shows survival rates of 92–97% at 5 years and 89% at 8 years [30, 32, 33].

The most common complication of ASA is CHB requiring permanent pacemaker implantation. Although CHB frequently occurs during the procedure (in up to 70% of cases), atrioventricular conduction recovers in the majority of patients within the first three days [29, 35–38]. Delayed CHB may also appear later during hospitalisation in patients without previous procedural CHB or as a recurrence after recovery from acute CHB [36, 38]. Ultimately, 7–20% of patients require permanent pacemaker implantation after ASA, although the rate has significantly decreased since the broad use of MCE and injection of lower doses of ethanol [30–34, 39]. Furthermore, in contrast to SM, the right bundle branch is frequently injured during ASA (new RBBB in

approximately 50% of patients). Hence patients with baseline left bundle branch block (LBBB) are at high risk of developing CHB, and some authors suggest elective permanent pacemaker implantation prior to ASA in these patients [18, 36–38, 40].

Other adverse events include coronary dissection (LAD or left main), sustained ventricular arrhythmias, stroke, pulmonary embolism and pericardial effusion, which can all be fatal. Reported periprocedural mortality rate is 0.6–1.8%, with a decreasing trend over recent years [30, 31, 33, 34, 39].

In addition, concern has been raised about creation of an arrhythmogenic substrate by ASA [10, 23]. However, there is currently no evidence to support an increase in incidence of ventricular arrhythmias or sudden death following ASA, as assessed by analysis of implantable cardioverter-defibrillator intervention rate or by serial electrophysiological studies before and after the procedure [41, 42].

Alternative percutaneous therapies

As an alternative to ethanol, some authors have proposed percutaneous septal reduction with coils, polyvinyl alcohol foam particles, absorbable gelatin sponge, glue, covered stents or angioplasty wires [43–48]. Although these techniques have only been described in case reports or small series, some of them may reduce the incidence of CHB compared to alcohol. Furthermore, reduction of septum by radiofrequency catheter ablation and cryoablation is also currently under investigation [49, 50].

A bite or a burn?

To date, there have been no randomised controlled trials comparing ASA to SM. Such a comparison would require recruitment of a very large number of patients and does not appear feasible at present [51]. Nonetheless, retrospective series comparing both SRT have been published, along with a meta-analysis summarising these results [7]. Comparison between ASA and SM showed that LVOT gradient during follow-up was slightly higher after ASA. However, this did not translate into any significant difference with regard to improvement of functional capacity and peak oxygen consumption. In addition, periprocedural mortality was also comparable with both techniques. Significant differences included the more frequent need for a repeat procedure (5.5% for ASA vs 0.6% for SM) and the higher rate of CHB leading to permanent pacemaker implantation following ASA (18.4% for ASA vs 3.9% for SM, $p = 0.04$). Finally, long-term survival in other series shows similar results following both procedures at 5–10 years, as mentioned above [14–16, 30, 33, 34].

However, effective comparison of both techniques based on non-randomised observational data should be interpreted with caution, since it is subject to the following limitations:

- SM has been performed for more than 50 years, during which it has undergone major technical progress resulting in improvement of outcomes. On the other hand, the results of ASA reported in the current literature frequently reflect very early experience with this technique, often including procedures performed during the steep portion of operators' learning curve and before the advent of major improvements such as MCE or use of low

doses of ethanol [52]. For instance, as reported recently, requirement of permanent pacemaker implantation following CHB has markedly decreased over time (28% for the earlier patients vs 6.5% for the most recent ones) [30]. Additionally, as mentioned earlier, acute and mid-term procedural success has significantly increased since the use of MCE has become routine, consequently reducing the need for subsequent repeat procedures.

- ASA has become widely available and is currently performed in many centres around the world, with generally comparable results [53–58]. In contrast, SM is rarely performed nowadays, and the excellent results mentioned above are reported mainly from three North American high-volume referral centres [14–16]. It is unknown whether SM performed in smaller centres is associated with similar outcomes.
- Patients included in the SM series are consistently younger than those reported in the ASA series (mean age 45–50 vs 53–64 years respectively) [14–16, 30, 31, 33, 34, 39]. This may be another reason for the higher rates of permanent pacemaker requirement in patients undergoing ASA, as they probably have a more vulnerable conduction system in relation to more advanced age. More importantly, this underscores the differences in patient selection for both procedures in clinical practice, with patients undergoing ASA probably more ill than those treated with SM, as age is obviously a surrogate of comorbid conditions and poorer subsequent outcome. Nevertheless, in spite of the age difference, long-term survival is comparable with both techniques. Furthermore, many patients deemed to be high-risk surgical candidates undergo ASA with excellent results [34, 59].

- Current SM series exclude patients undergoing concomitant surgery. However, these patients represent a significant proportion of SM patients (up to 55%) and are obviously at higher risk than those undergoing isolated SM [14–16]. Inclusion of these patients in the surgical series would certainly give a more comprehensive and balanced view of the current management of HOCM in clinical practice, and improve efforts to define the role of both treatment modalities.

Thus, in the absence of balanced data from randomised trials, and despite ongoing polarised debates between supporters of the two techniques within the cardio-

Table 3
Pros and cons of alcohol septal ablation and surgical myectomy.

	Alcohol septal ablation	Surgical myectomy
Advantages	Less invasive Less painful Avoidance of sternotomy Shorter hospital stay and recovery time Lower cost Wider availability Possible in high-risk patients Lower risk of stroke in older patients Ability to treat CAD requiring PCI	Ability to treat concomitant conditions (mitral valve disease, CAD requiring CABG, myocardial bridges) Lower incidence of CHB
Disadvantages	Requires suitable coronary anatomy Higher incidence of CHB High rate of RBBB	Open heart surgery with cardiopulmonary bypass Longer hospital stay Higher cost Limited availability of expertise High rate of LBBB

CAD = coronary artery disease; PCI = percutaneous coronary intervention; CHB = complete heart block; RBBB = right bundle branch block; CABG = coronary artery bypass grafting; LBBB = left bundle branch block.

vascular community, the current general consensus is that the operative risks, haemodynamic benefits, symptomatic improvements and long-term survival are broadly comparable in patients who are eligible for both procedures at centres with appropriate expertise [10, 23, 53, 60, 61]. Consequently, the choice should be based on local availability and expertise as well as patient's preference and associated conditions, taking into account the strengths and limitations of ASA and SM [52, 62] (table 3). Patients with concomitant surgical problems such as mitral valve abnormalities (most notably anomalous papillary muscles), or coronary artery disease not amenable to percutaneous coronary intervention, should certainly undergo surgery. This also applies to those who do not have a favourable coronary distribution allowing ASA. On the other hand, elderly patients with significant comorbidities who are deemed at high risk for SM should be treated with ASA. Furthermore, concomitant coronary artery disease can usually be treated either during the same procedure or as a staged intervention. In current practice, ASA is more frequently performed than SM [63]. This is probably due to the broader availability of the technique as well as the preference of patients more inclined to a less invasive procedure [62].

Conclusion

ASA and SM for drug-resistant symptomatic HOCM are both associated with excellent functional improvement and long-term survival. In the absence of randomised controlled trials comparing both SRT, choice of treatment should be based on individual patient assessment and local expertise.

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