Hypertrophic cardiomyopathy (HCM) is clinically defined by the presence of left ventricular hypertrophy not attributed to abnormal loading conditions. It is recognized as the most common genetic cardiac disease, occurring in 1 per 500 adults. Compatible with the largely heterogeneous genetic background, involving more than 400 different mutations in at least 10 different contractile proteins, and the influence of multiple modifying factors, the cardiac morphology, pathophysiological characteristics and clinical manifestations vary greatly, even in members of the same family. A significant proportion of patients remain asymptomatic, but others develop debilitating symptoms of dyspnea on exertion, angina, which may also be atypical, reduced exercise capacity and syncope or may present serious life threatening ventricular arrhythmias leading to sudden death. Most patients have dynamic left ventricular outflow tract (LVOT) obstruction (hypertrophic obstructive cardiomyopathy, HOCM), which is accepted as an important cause of significant symptoms in some patients. In general, treatment of patients with HCM aims at relieving symptoms, reducing the risk of sudden death and offering genetic counselling. For patients with significant obstruction the primary focus of treatment is the reduction of the pressure gradient. The first line of therapy is medical treatment with β-blockers, or disopyramide as first choice and verapamil as second choice. Cibenzoline, another antiarrhythmic drug, has also been used in some countries with reportedly good results. However, medical treatment fails to relieve symptoms in a considerable number of patients with LVOT obstruction and surgical treatment with septal myectomy/myotomy has been the traditional gold standard treatment for such patients, with excellent results in highly experienced centers.

Percutaneous transluminal septal myocardial ablation (PTSMA; the injection of alcohol in a septal perforator branch perfusing the basal septum) has emerged as an efficacious alternative treatment option in the past 15 years. This technique aims to reduce the hypertrophied septum through the production of a small myocardial infarction confined to the part of the septum that is involved in the pathophysiology of the gradient. During the past decade, the existence of a less invasive and broadly available therapeutic modality has invigorated interest in the determinants and implications of LVOT obstruction in HCM.

**Pathophysiology and Effect of Obstruction**

Ever since the first modern descriptions of HCM 50 years ago, the pathophysiology of LVOT obstruction, together with its clinical implications, has been an issue of controversy in the cardiovascular community. Imaging studies over the past 20 years have proven that dynamic LVOT obstruction is produced by contact between the anterior, and less commonly the posterior mitral valve leaflet, and the interventricular septum (IVS) during systole. The key event in this process is the systolic anterior motion (SAM) of the mitral valve leaflet towards the IVS, which is determined by the forceful left ventricular ejection and the morphological characteristics in HOCM: narrow LVOT due to the basal septal hypertrophy, anteriorly displaced mitral valve with elongated leaflets. The LVOT obstruction represents an increase in left ventricular...
lar afterload, because approximately half of the stroke volume remains to be ejected after the gradient appears. Apart from the stroke volume reduction, SAM is associated with mitral regurgitation and load-dependent diastolic dysfunction, and obstruction causes an increase in left ventricular pressure and coronary flow abnormalities. In the absence of SAM, midventricular obstruction can occur in some patients, because of either muscular apposition causing midventricular obstruction or anomalous insertion of the papillary muscle into the anterior mitral leaflet.14

The basal part of the IVS and the septal artery (arteries) that supply it comprise the recently described “first septal unit”15 and this part of the IVS is involved in the SAM–septal contact, which has to be abolished by the interventional treatment. The anterior two-thirds of the IVS are supplied by septal perforators originating from the left anterior descending (LAD) artery and the posterior one-third is supplied by septal perforators from the posterior descending artery; however, there is a high degree of collateralization between those branches. The target of PTSA is usually the first larger septal branch, but there is significant variety in its size, angiographic morphology, supplying territory and collateralization with other septal branches that needs to be always kept in mind.16,17

Virtually from the initial observations of patients with HCM, it has been resolved that the level of the intraventricular pressure gradient measured at rest has only poor correlation with the severity of the patient’s symptoms.18 The existence and severity of the obstruction depend on the loading conditions of the left ventricle, may vary greatly with physiological or pharmacological provocations that alter left ventricular preload, afterload or contractility, and may change dramatically after meals or alcohol intake.19 Spontaneous variation of the measured gradients from day to day or during the same day has also been observed in some patients.18,19 Despite the recognized dynamic nature of the obstruction, conventional measurement of the gradient only in the resting state has created the perception that only one-quarter of patients have LVOT obstruction.2 Nevertheless, most patients without an obstruction at rest can generate a significant pressure gradient with provocation (eg, exercise).20 Those observations have shifted our understanding of LVOT obstruction in HCM, because it has been resolved that 25% of patients with HCM have LVOT obstruction at rest, and a total of 75% of patients have obstruction either at rest or with provocation.21 Furthermore, because many patients have symptoms only on exertion, it is obvious that identifying a latent obstruction by measuring the LVOT gradient after provocation is crucial.

The Valsalva maneuver in the catheterization laboratory or during the echocardiographic study is the simplest method of provocation, although exercise echocardiography imitates normal physiology and is more sensitive than the Valsalva.21 Gradient measurement after a fortuitous extrasystolic beat during the Doppler study or a deliberately produced one during cardiac catheterization can also expose latent obstruction.22 Afterload reduction with amyl nitrate or nitroglycerin can also be used, but positive inotropes (eg, dobutamine) are not recommended, however, as they may also yield false-positive results in healthy young people without HCM or in young athletes.2

The mere existence of obstruction measured only at rest has been correlated with clinical deterioration and increased mortality.2,3,22 Symptomatic patients have a worse prognosis compared with asymptomatic subjects, as have older patients compared with younger ones.3 Patients with obstruction at rest develop atrial fibrillation, a major determinant of clinical deterioration in HCM,24 in a higher proportion than patients without obstruction.25 Severe obstruction has also been correlated with sudden death risk and might be included in the list of clinical risk factors for sudden death (ventricular tachycardia, abnormal exercise blood pressure response, family history of premature death, unexplained syncope, severe left ventricular hypertrophy).26 In conclusion, it has become evident that obstruction in HCM not only influences symptomatic status but may also have prognostic significance.

### History of Alcohol Septal Ablation

The idea of a nonsurgical interventional treatment for HOCM grew with the advances of interventional cardiology in the 1980s. Early in that decade, it was observed that temporary balloon occlusion of the LAD artery caused left ventricular wall motion abnormalities.27 In particular, patients with HOCM developed nonobstructive physiology after myocardial infarction.28 On the other hand, electrophysiologists were trying a chemical septal branch ablation procedure for the treatment of ventricular arrhythmias in patients with coronary artery disease.29 Those observations inspired the original description of the technique of alcohol septal ablation in 1989 (G. Berghofcer, personal communication). In the early 1990s, it was reported that temporary balloon occlusion of the first septal branch led to a gradient reduction in some patients.29,30 The first procedure of alcohol-induced septal branch occlusion in humans was performed by Dr Sigwart in 1994.9 Several years later, echocardiographic guidance with echo-contrast-mediated identification of the target septal branch was introduced, which was clearly the most significant improvement of the original technique.31 Alcohol septal ablation has gained remarkable popularity and it is estimated that more patients have been treated with the interventional technique in the past decade than with surgical myectomy in the past 45 years.8 A benefit of this growing volume of data is that medium-term results were published in the early 2000s and long-term results have already appeared in the literature.32–38

### Description of the Ablation Technique

The femoral approach is most convenient for PTSA. In patients without a permanent pacemaker or implantable cardioverter defibrillator (ICD), a temporary pacemaker should be placed transvenously in the right ventricular apex through a femoral venous sheath and kept in situ for 24–48 h. If temporary pacing is required for a longer time or ambulatory monitoring is not available post procedure, the jugular or subclavian venous route is preferred. In patients with an implanted pacing device, septal pacing is less reliable than right ventricular pacing and an increased pacing amplitude might be required. Constant recording of the LVOT gradient can be achieved by simultaneous measurement of the left ventricular and aortic pressures with 2 arterial catheters. A specially designed pigtail catheter, with holes only in its distal part and not on the shaft (Cordis, Miami, FL, USA), is inserted through a left femoral artery sheath and remains positioned in the apex of the left ventricle, and a coronary angioplasty guide catheter is positioned at the ostium of the left coronary artery, through a right femoral artery sheath. With this approach, transseptal puncture (and its related risk) can be avoided. Furthermore, the LVOT gradient can be recorded both at rest and during provocative maneuvers, such as Valsalva, and after an extrasystolic beat. Weight-adjusted
Before any alcohol injection, echocardiographic contrast echocardiography is indispensable to the procedure. Injection into the optimal septal branch will cause an obvious opacification of the septal area next to maximal flow acceleration that involves the point of contact between the mitral valve and the septum during systole. It is evident that myocardial contrast echocardiography can change the interventional strategy by dictating the need for a change in the target branch or even cessation of the procedure if the proper septal branch can not be identified (Figure 2). Once the correct target has been proven, however, 1–3 ml of absolute alcohol is then injected slowly in 1-ml increments through the central lumen of the balloon under constant fluoroscopy. The total amount of alcohol injected depends on the acute hemodynamic effect and the echocardiographically estimated size of the contrasted septal area. In fact, it is considered that the use of less alcohol is associated with less complications, and small or ultra low doses of alcohol can have equally effective hemodynamic results as larger doses.  

Balloon catheter dislodgement, kinking or severe difficulty in alcohol injection should prompt the termination of the procedure. In order to prevent complications, the balloon should not be deflated or removed earlier than 10 min after the last alcohol injection.  

A final coronary angiographic image is taken to show the occluded septal branch and exclude any damage to the coronary arteries.

The patient is subsequently transferred to the coronary care unit for hemodynamic and rhythm monitoring for at least 48 h.

Alcohol septal ablation is referred in the literature under different acronyms, which reflect substantial technical differences (Table 1). PTSMA, as described, is the most commonly performed technique, but in recent years, various efforts have been made to substitute alcohol with the use of coils, polyvinyl alcohol particles, used angioplasty wires, cyanoacrylate glue, gelatin particles, radiofrequency ablation, and cryoablation. None of these methods has prevailed, however, because the myocardial necrosis caused by alcohol plays a key role in the pathophysiology of septal reduction therapy.

**Indications and Patient Selection**

It has been emphasized that the patients who gain the most benefit from PTSMA are the ideal candidates for this interventional treatment. Such as patients with drug-refractory symptoms limiting daily activities (NYHA/CCS III or IV) and/or recurrent syncope on exertion, who also have significant obstruction >30 mmHg at rest and/or >60 mmHg with provocation. The typical morphology of the “first septal unit” comprises significant thickness of the asymmetrically hypertrophied septum (>15 mm) at the level of the LVOT obstruction, which is related to SAM of the mitral valve. In contrast, other types of left ventricular hypertrophy associated with HCM, but not involving the septum (eg, apical hypertrophy, hypertrophy limited to the free wall), are definite contraindications for interventional treatment.

Mitrail valve regurgitation associated with SAM of the mitral valve is expected to diminish after successful treatment. Echocardiographically manifested reduction of mitral insufficiency after acute gradient reduction following intravenous administration of disopyramide can confirm this consideration. In contrast, patients with abnormal mitral valve morphology/structure (eg, extremely long or flail leaflets, anomalous papillary muscle insertion) should be referred for
patients with concomitant coronary artery disease requiring revascularization should be individually managed. If percutaneous treatment of the coronary lesion(s) is feasible, it can be primarily performed and PTSMA should follow after confirmation of persistent symptoms at follow up. A combined all-in-one approach is warranted only if the target septal branch originates at the site of a coronary lesion in the LAD artery. In that case, 2 angioplasty guidewires are used and a coronary stent is placed in the coronary lesion after alcohol septal ablation is completed.

To date, alcohol septal ablation is not acceptable for patients without significant symptoms who have satisfactory exercise capacity, even if they might have signs of com-

Table 1. Acronyms of Alcohol Septal Ablation

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Identification of target septal branch</th>
<th>Criterion of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSMA</td>
<td>Percutaneous transluminal septal myocardial ablation</td>
<td>Transthoracic myocardial contrast echocardiography</td>
<td>Alcohol depot in echocardiography</td>
</tr>
<tr>
<td>TASH</td>
<td>Transcoronary ablation of septal hypertrophy</td>
<td>Haemodynamic effect of temporary branch occlusion</td>
<td>Until gradient is abolished</td>
</tr>
<tr>
<td>NSRT</td>
<td>Nonsurgical septal reduction</td>
<td>Echocardiographic study with the use of angiographic contrast dye</td>
<td>Until gradient is abolished</td>
</tr>
<tr>
<td>NSMR</td>
<td>Nonsurgical myocardial reduction</td>
<td>Hemodynamic effect of temporary branch occlusion</td>
<td>Occlusion of several septal branches until gradient is abolished</td>
</tr>
</tbody>
</table>
pathophysiology of alcohol septal ablation

early after injection, alcohol causes a coagulation necrosis of the myocardium and the septal perforator arteries. the arteries are filled with necrotic debris and “fixed” blood, with neutrophilic infiltration at the margin of the necrotic tissue. tissue edema appears early in the process, whereas muscle replacement by scar formation develops only after several days.\(^4\)

the progression of the histological changes affects the hemodynamic response after ptasma, which shows 3 separate phases: perioperative, early postoperative and late postoperative.\(^5\) the first phase is characterized by akinesia of the ablated septum, caused by stunning, with significant lvot gradient decrease. in the second phase, the probable edematous expansion of the necrotic area of the septum causes an increase in the lvot gradient in approximately half of the patients, which is evident for approximately 7–10 days without any clinical worsening, however.\(^5\) in the following few months, thinning of the ablated septum because of scar formation will cause a further decrease of the obstruction and the concomitant mitral regurgitation.\(^5\) studies with spect and magnetic resonance imaging (mri) have shown that the necrotic area produced by ptasma is ≤10% of the left ventricular myocardium.\(^5,52\) furthermore, it has been clearly resolved by nuclear mri that the scar created by the transmurral infarction as a result of ptasma will shrink during the following months.\(^5,51\) in accordance, the lvot cross-sectional area gradually increases during the first months after ptasma.\(^5,52\) on the other hand, the remodeling process also affects the left ventricular free wall, with left ventricular mass decreasing disproportionally to the reduction caused by the ablated area only.\(^5\) a reduction in free wall thickness has also been described after myectomy, implying that the increased afterload in hocm may boost left ventricular hypertrophy, which can be subsequently lessened with effective reduction of the lvot gradient.\(^5\)

changes in coronary blood flow after ptasma have been investigated with various methods. invasive assessment of coronary flow reserve shows an immediate improvement after ptasma as a result of the reduced contraction load of the left ventricle.\(^5\) in accordance with this, an mri study has shown that the resting blood flow in the lad artery decreases at 1 month and 6 months after ptasma compared with baseline.\(^5\) this reduction is associated with a decrease in the lvot gradient and has no relation to the scarred tissue mass. myocardial flow reserve has been estimated with myocardial contrast echocardiography to be significantly improved after ptasma, although it does not reach the level of healthy controls.\(^5,60\)

acutely after ptasma, the systolic function of left ventricle is reduced. the end-systolic and end-diastolic volumes are increased and ejection fraction decreases.\(^41\) the diastolic function, however, improves significantly, with reductions of end-diastolic pressure, diastolic stiffness and tau. at 6 months, changes in the pressure–volume loops indicate...
preserved myocardial contractility, with improvement of the active and passive diastolic properties of the left ventricle. Echocardiographic indices of diastolic function remain improved at 1- and 2-year follow-up in patients with successful PTSMA, indicating a sustained favorable hemodynamic result. As a consequence, the left atrial pressure and volume decrease in the first 3 months after PTSMA, with a simultaneous increase in left atrial ejection fraction that correlates with the LVOT gradient reduction.

Electrophysiological Changes After Alcohol Septal Ablation

Despite the fact that only a small artery is occluded, PTSMA induces significant ECG changes. New anterior ST elevation and new Q waves may appear immediately after the procedure in some patients and QRS duration may be prolonged. The appearance of a new right bundle branch block is the commonest change occurring in approximately half of the patients treated. The right ventricular bundle branch is contained in the part of the basal septum that is ablated, thus is

Figure 3. Collateralization between septal branches. (a) Left coronary angiography shows the target septal branch (white arrow). Injection of angiographic contrast dye through the central lumen of the inflated balloon catheter can determine the supply area of the septal branch and exclude leakage into the left anterior descending artery. The red arrow shows the collateral retrograde flow to a distal septal branch. Injection of alcohol at this point would probably cause spillage into the distal left anterior descending artery, generating a remote infarction. Instead, a second angioplasty guidewire is inserted in the second septal branch and a monorail balloon is inflated in this branch, thus obviating any misplacement of alcohol (b).
often prone to injury during PTSMA. Conduction abnormalities may appear as 1-degree atrioventricular block in approximately 50% or as complete heart block requiring a permanent pacemaker in 10% of patients. Clinical Outcome

Ever since the first patients were treated, numerous reports have shown success in ≥90% of those treated with the echocardiography-guided technique, with effective reduction of both resting and provokable LVOT gradients.9,11,30,31,46,48,55,66–74

Diminished LVOT obstruction is related to symptomatic relief and improved exercise capacity.43–73

During follow-up there is a sustained and constant hemodynamic improvement, with further reduction after the first year of the LVOT gradient, which is almost eliminated in most patients after several years.35 Relief of obstruction is permanent and does not reappear after successful treatment. Regular echocardiographic evaluation has shown an ongoing left ventricular remodeling process, with reduction of both septal and posterior wall thicknesses. Increases left ventricular dimensions, however, do not exceed normal limits, alleviating initial concerns about possible negative effects. The SAM with mitral regurgitation is also reduced with time,32 and pulmonary artery pressure decreases after successful percutaneous septal ablation.31,79 Consistent with the hemodynamic improvement, there is also an increasing improvement in clinical status during follow-up, as regards functional class, symptomatic relief and reduction of syncopal episodes.32,33

Increased exercise capacity and peak oxygen consumption provide objective confirmation of the clinical benefit.32–73

In a pooled analysis of 42 studies published between 1996 and 2005 involving 2,959 patients, the mean procedure-related (in-hospital) mortality was 1.5%.67 A noteworthy 6.6% of patients have needed redo procedures, and 2.0% were ultimately referred for myectomy. Results of longer follow-up, however, confirm the safety and efficacy of alcohol septal ablation (Table 2).32–38

In a cohort of the first 100 patients treated the overall survival was 96% at 8 years, and 74% of patients remained free of severe symptoms, atrial fibrillation, stroke or ICD implantation.32 A larger cohort of 347 patients, also treated with the echocardiography-guided technique, has shown 94% survival after 5 years and 87% after 10 years.34 It should also be mentioned that long-term results from a cohort of 55 high-risk patients, not eligible for surgical treatment, has shown a rather impressive 76% survival at 10 years, with only 1 patient dying of confirmed cardiac cause.37 Long-term mortality in this cohort was associated only with old age at the time of treatment. Reported data from a series of patients treated with percutaneous septal ablation in a highly esteemed myectomy center has shown 88% survival at 4 years, which was comparable to the outcome of an age-and gender-matched, but probably less sick, group of patients who underwent surgical myectomy.33

Complications

Complication rates have decreased during the past decade, probably because of the increasing experience of the operators. Procedure-associated mortality, reported to range from 0% to 4%,67 is clearly less in the latest cohort compared with the early cohort of patients treated by several groups.34,36 In fact, in the Leopoldina Hospital Registry, a series of >650 patients have been treated without any hospital deaths. Conduction abnormalities remain the most frequent adverse reaction, but they are mostly temporary, necessitating the use of a temporary pacemaker for the procedure and obligating careful rhythm monitoring throughout the hospital stay.30 The need for permanent pacing has been shown to be related to several predicting factors, such as female sex, bolus alcohol injection, occlusion of more than 1 septal branch, preexisting left bundle branch block and first degree atrioventricular block.77 A scoring system, based on the assessment of the ECG (ie, QRS duration, PQ duration, atrioventricular block occurrence and persistence or recovery, heart rate) as well as hemodynamic variables (baseline gradient) and myocardial enzyme kinetics (time-point of peak alanine aminotransferase), has also been proposed for the prediction of permanent pacemaker dependency after the intervention.76 Nonetheless, less than 10% of patients will eventually need a permanent pacemaker.79

Damage to the coronary arteries with the guidewire or balloon inflation is a rare complication and can be avoided with increasing experience and use of proper equipment.35 Alcohol leakage to the LAD artery is also uncommon, but can be disastrous for the patient.41,80 The use of a slightly oversized balloon catheter, with slow and watchful injection of alcohol and deflation of the balloon at least 10 min after the last alcohol injection will effectively prevent retrograde alcohol flow to the LAD artery,71 and meticulous angiographic demonstration of the target septal branch before alcohol injection will reveal the existence of collateralization between septal branches (Figure 3).32

The myocardial scar caused by percutaneous septal ablation has aroused concern of a potentially increased risk for malignant ventricular arrhythmias.53,81,82 This theoretical consideration has not been supported so far by either the long follow-up data or by analysis of data from patients who already had an ICD implanted at the time of intervention. Ventricular arrhythmias have been reported in the early post-procedural phase, possibly as an effect of ischemia.67,83–85 With the exception of 1 study,96 long-term follow-up data have described ventricular arrhythmias as a rare event.32–35

In contrast, no increased risk of malignant arrhythmias after the procedure has been shown in patients who already had an ICD implanted because of a previously estimated high risk of sudden death.87,88 In fact, it seems that a less successful hemodynamic outcome may be associated with a higher arrhythmic risk, with the risk of arrhythmia increasing as the post-interventional gradient increases.89

The advent of myocardial contrast echocardiography during percutaneous septal ablation has been shown to improve the hemodynamic result and decrease the complication risk.31,73 Use of the proper contrast agent enables better imaging quality, thus ensuring the safety of the procedure, which could be also applied to treat patients with midventricular obstruction or who had undergone a previously unsuccessful surgical attempt.90,91 The precise identification of the target septal region has permitted injection of less alcohol without compromising the hemodynamic result.74,75,92

Although it is evident that complications decrease with increasing experience, the upper range of reported complications is unacceptably high.67 Proper training and institutional organization should ensure the safety of alcohol septal ablation, and a deep understanding and extensive experience in clinical assessment and treatment of HOCM patients should be a prerequisite for institutions that offer alcohol septal ablation.
Conclusions and Perspective

In the past decade it can be shown that septal ablation in symptomatic patients with HOCM resulted in ongoing relief of clinical symptoms in more than 90% of the patients. Hospital mortality can be reduced to nearly 0% in experienced centers with knowledge of the special problems and complexities that can emerge in the postinterventional period. Therefore, the need for permanent pacemaker implantation in less than 10% of patients treated is in fact the most significant complication.

In the future, only randomized trials will show whether septal ablation or myectomy is the gold standard for symptomatic relief in HCM patients with significant obstruction.

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Circulation Journal Vol.75, January 2011

35
Septal Ablation in HCM


