Hypertrophic cardiomyopathy is a primary myocardial disorder defined clinically by the presence of unexplained left ventricular hypertrophy.\(^1\) Its phenotypic prevalence in the general population has been estimated as 1:500, which renders it the most common genetic heart disease. It has been described as a highly heterogeneous genetically transmitted disease of the sarcomere that involves more than 400 different mutations in at least 10 different contractile proteins (http://genetics.med.harvard.edu/seidman/cg3/index.html). This genetic complexity leads to a wide diversity in cardiac morphology, pathophysiological features, and clinical manifestations, even in a single family.\(^2\) The clinical course and outcome may vary greatly, with many patients having hardly any or no discernible cardiovascular symptoms, whereas others have profound exercise limitation and recurrent arrhythmias.\(^4\) Approximately one third of the patients with hypertrophic cardiomyopathy have dynamic left ventricular outflow tract (LVOT) obstruction at rest, caused by contact between the anterior, or less commonly the posterior, mitral valve leaflet and the interventricular septum during systole (hypertrophic obstructive cardiomyopathy, HOCM).\(^5,8\) In some patients this obstruction may be associated with thickening and distortion of the mitral leaflets and occasionally obstruction may be caused by anomalous insertion of the papillary muscle into the mitral leaflet.\(^9\) Lately, it has been resolved that most patients with hypertrophic cardiomyopathy may have LVOT obstruction under provocation with the Valsalva manoeuvre or exercise (Figure 1).\(^10,11\)

Treatment of symptomatic patients with HOCM should effectively reduce symptoms, improve functional capacity and provide better quality of life.\(^1,12\) The pathophysiological target of any treatment is to reduce the extent of the outflow tract gradient and improve diastolic filling. The clinical significance of the outflow gradient has been an issue of debate for many years, but gradient is now accepted as an important cause of limiting symptoms in some patients.\(^8,12\) Medical therapy, with the administration of negatively inotropic drugs, e.g. beta blockers,\(^13-15\) verapamil,\(^14-16\) or disopyramide,\(^17-20\) is always the first line of treatment.\(^1,12\) However, a considerable number of patients with marked LVOT obstruction continue to have severe symptoms regardless of any medical therapy.\(^21\) Such patients have traditionally been referred for surgical myectomy/myotomy, which has been the gold standard treatment for decades. In highly experienced centres, the initially high postoperative mortality rates have been reduced to <1-2%.\(^22-26\) Surgery has provided

**Alcohol Septal Ablation in Hypertrophic Obstructive Cardiomyopathy**

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long-term symptomatic relief in a substantial proportion of patients.\textsuperscript{22,25}

Percutaneous transluminal septal myocardial ablation (PTSMA) by means of alcohol-induced occlusion of a septal branch has emerged as a novel interventional treatment option during the last decade.\textsuperscript{27} It is less invasive than surgery and aims directly to reduce the hypertrophied interventricular septum with consequent expansion of the LVOT and reduction of the LVOT gradient.\textsuperscript{28} This is achieved through a circumscribed infarction of the area supplied by the occluded septal branch.

Technique description

The idea that permanent ischaemic damage to the basal septum could be beneficial in HOCM came after preliminary studies had shown that temporary balloon occlusion of the first larger septal branch resulted in substantial resting outflow gradient reduction in some patients.\textsuperscript{27,29} After the description of a similar technique for treating ventricular arrhythmias,\textsuperscript{30} Sigwart was the first to report a successful non-surgical myocardial reduction after occlusion of the septal branch using 96% alcohol.\textsuperscript{27}

The original technique of PTSMA was based on the injection of alcohol in the first septal branch through the central lumen of an over-the-wire balloon catheter positioned and inflated inside the target septal branch. Subsequently, the technique was further refined, with the addition of several modifications, in order to improve the identification of the most appropriate target septal perforator branch.\textsuperscript{27,31,32} The main objective in performing PTSMA should be to achieve an optimal haemodynamic result with minimal complications.\textsuperscript{33} The generally accepted technique, which is performed by most groups across the world, is described in sufficient detail below.\textsuperscript{28,33}

As a prerequisite in all patients without a permanent pacemaker, a temporary pacemaker should be placed transvenously in the right ventricular apex, because of the risk of atrioventricular conduction disturbances following alcohol injection. Once an aortic valve gradient has been excluded, a special pigtail catheter, with holes only in its distal part and not on the shaft (Cordis), is introduced and remains positioned in the LVOT. Figure 1. Left ventricular outflow tract (LVOT) gradient recording in the catheterisation laboratory during the Valsalva manoeuvre. The initial LVOT gradient at rest is below 30 mmHg and during Valsalva the LVOT obstruction increases: the left ventricular systolic pressure is increased while the aortic pressure decreases. In addition, the aortic pressure curve gradually turns to a “spike and dome” configuration (arrow), typical of significant LVOT obstruction. Ao – aortic pressure; LV – left ventricular pressure.
left ventricular apex, providing constant pressure recording. A coronary angioplasty guide catheter is then positioned at the ostium of the left coronary artery. Left Judkins catheters can normally be used in most patients, although special catheters for extra back-up are sometimes needed in cases of complex aortic root or coronary anatomy. The guide catheter serves also for pressure measurement in the ascending aorta and therefore the LVOT gradient is recorded constantly throughout the procedure, both at rest and during provocative manoeuvres (Valsalva manoeuvre, extrasystolic beat) (Figure 2a).

All patients receive intravenous weight-adjusted heparin and early analgesic medication (preferably with opiates) before the alcohol injection.

Baseline coronary angiography allows the identification of usually one or more target septal branches. The most often chosen target septal branch is the first septal branch, as it is expected to perfuse the basal part of the interventricular septum. After introduction of an angioplasty guidewire into the target septal branch (Figure 3a), an over-the-wire balloon catheter with a short balloon (<1 cm in length) is advanced and inflated in the proximal part of the septal branch. The Concerto® balloon catheter (OCCAM International BV), which is specially manufactured for PTSMA, is provided with a radiopaque marker at the proximal end of the balloon, thus allowing exact positioning in the septal branch and preventing balloon positioning in the left anterior descending artery (Figure 3b). It is available in diameters of 1.5 to 2.5 mm, which in practice include all possible septal branch diameters. Selection of a slightly oversized balloon compared to the septal branch diameter ensures tight sealing of the branch with inflation of the balloon at the nominal pressure. Injection of a small amount of angiographic contrast dye (1-2 ml) through the guidewire lumen of the inflated balloon catheter provides angiographic demonstration of the supply area of the septal branch and excludes the possibility of reflux into the left anterior descending artery (Figure 3c). In addition, any possible collateral vessels can be identified before the injection of alcohol.35

The first septal branch may have an unpredictably variable anatomy and perfusion bed, which can also involve other structures apart from the basal septum, such as the papillary muscle or the right ventricular free wall. For this reason, echocardiographic monitoring of the procedure was introduced, which aims to verify the correct target and avoid alcohol injection.

Figure 2. Haemodynamically recorded left ventricular outflow tract gradient at rest and post-extrasystole before (a) and after (b) percutaneous septal ablation. Ao – aortic pressure; LV – left ventricular pressure.
into an unsuitable area. Consequently, prior to any alcohol injection, 1-2 ml of an echocardiographic contrast agent is administered through the central lumen of the balloon catheter under real-time two-dimensional echocardiographic and colour Doppler monitoring. Among several agents that have been used worldwide, the one with the largest experience is Levo- 

tal area adjacent to Doppler maximal flow acceleration and involving the area of mitral valve contact during the systolic anterior motion of the mitral valve, without, on the other hand, opacification of any other cardiac structure (Figure 4). All standard echocardiographic views (apical 2- and 4-chamber, parasternal short- and long-axis, subcostal) are examined and compared with baseline stored echocardiograms. Once contrast echocardiography has convincingly shown that the chosen septal branch is optimal, 2 (4)
ml of >95% alcohol in 1 ml portions are slowly injected through the central lumen of the over-the-wire balloon catheter. Injection of alcohol is performed under ongoing fluoroscopy so that any possible balloon dislocation that would carry a risk of subsequent alcohol misplacement will be noticed immediately. Echocardiography is repeated after alcohol injection in order to identify the alcohol impregnation of the target septal area. The amount of injected alcohol depends principally on the echocardiographically estimated size of the contrasted septal area and less on the acute haemodynamic effect. This has gradually led to the use of lower alcohol doses over the years. It is estimated that 1 ml of alcohol should be enough for every 10 mm of echocardiographically measured septal thickness. In search of the minimum dose of alcohol that can produce an optimal haemodynamic result, alcohol injection of <2 ml seems to be equally effective as larger doses. Ultra low doses of ~1 ml have also been used with comparable results. This signifies the importance of correct and precise identification and targeting of the myocardial area that will be ablated.

In order to avoid alcohol spilling in the left anterior descending artery, the balloon catheter is deflated and removed at least ten minutes after the last alcohol injection. A final angiographic control excludes left coronary artery damage and verifies septal branch occlusion (Figure 3d), while final haemodynamic measurements confirm the immediate result of septal ablation (Figure 2b). Subsequently, the patient is transferred to the coronary care unit for haemodynamic and rhythm monitoring, which is required for at least 48 hours. The temporary pacemaker lead remains in place for at least 24 hours and usually can be removed if no conduction abnormalities appear during that time.

Apart from PTSMA, several other acronyms for alcohol septal ablation that have appeared in the literature correspond to different techniques. TASH (Transcoronary Ablation of Septal Hypertrophy) relies only on the haemodynamic response during balloon inflation and alcohol injection in the angiographically recognised target septal branch and the procedure does not involve echocardiographic guiding. NSRT (Nonsurgical Septal Reduction Therapy) employs echocardiographic guidance using angiographic contrast dye to delineate the septal area to be ablated and also involves dobutamine provocation for the baseline evaluation of patients. NSMR (Nonsurgical Myocardial Reduction) also relies on the haemodynamic result of temporary balloon inflation in the (usually more than one) septal branches that would be ablated.

### Indications and contraindications

The clinical indications for PTSMA refer to highly symptomatic patients, in classes ≥ New York Heart
Association (NYHA) III or Canadian Cardiovascular Society III despite optimal drug therapy, or with severe side effects that preclude optimal medication. The haemodynamic indication requires a significant obstruction either at rest or under provocation. The absolute gradient level criteria were originally set higher than is currently accepted as an indication (≥30 mmHg at rest or ≥60 mmHg under provocation). It should be emphasised that gradient provocation should only be tried with exercise or physiological manoeuvres such as Valsalva, or after an extrasystolic beat. Dobutamine infusion for gradient generation is clearly not recommended in symptomatic patients with HOCM. In individual patients with less severe symptoms interventional treatment can be considered if they have a high LVOT gradient (as above) and additional findings, such as recurrent exercise-induced syncope, abnormal blood pressure response at exercise, paroxysmal atrial fibrillation, and/or objectively verified reduction of exercise capacity. These considerations are supported by actual data that have shown a correlation between a resting gradient of more than 30 mmHg and both HOCM-related death and progressive heart failure. It is also particularly important to mention that a considerable number of patients may gradually get used to their lower than normally expected exercise capacity and tend to underestimate their symptoms, thus failing to receive optimal treatment. At the present time, however, interventional treatment is contraindicated in symptomatic patients with a low LVOT gradient or asymptomatic patients with preserved exercise tolerance.

Morphological indications for echocardiography-guided septal ablation include patients with subaortic as well as midventricular obstruction. The geometry of the left ventricular wall should suggest that lessening of the septal thickness would abolish obstruction. Patients with a history of previous, haemodynamically unsuccessful, surgical myectomy can also be treated. Existence of concomitant cardiac diseases indicating surgery — e.g. extensive coronary artery disease, valvular disease, and anatomical ailments of the mitral valve or papillary muscles responsible for gradient formation or mitral regurgitation — should not be treated interventionaly, but rather referred for surgical therapy. It must be noted, however, that a combined percutaneous treatment (PCI and PTSMA) can be performed in individual patients with single vessel disease amenable to balloon dilatation and stenting.

To ensure the safety and efficacy of the procedure, alcohol injection should not be attempted under certain circumstances. Such contraindications include the failure of myocardial contrast echocardiography to identify a target septal branch, the echocardiographic contrast opacification of any cardiac structure other than the target septal area, or insecure balloon positioning that bears the risk of alcohol reflux during injection. Furthermore, alcohol injection should be avoided if there is any suspicion of collateral flow that could lead to infarction far from the target septal area.

Based on the reported results, symptomatic HOCM patients have been classified by L. Faber according to the indication and the expected efficacy of PTSMA as ideal, possible and poor candidates (Table 1).

### Short-term results

Alcohol septal ablation is generally well tolerated by patients. Most feel a slight chest discomfort at the time of alcohol injection, which may persist for several hours in some cases.

It is generally agreed upon by most reports that about 90% of the treated patients have an acute LVOT gradient reduction. Younger patients seem to have less gradient reduction than older patients, probably because they have greater septal thickness and additional structur-
al deformities, such as abnormal papillary muscles, that might make some contribution to the gradient formation. Even so, patients with an insufficient acute result may have further gradient reduction at follow up due to post-infarction remodelling and shrinkage of the ablated septal area. Unlike the immediate result of surgical myectomy, a remodelling process has been described in some patients after PTSMA, which lasts up to 12 months and results in further thinning of the septum with ongoing gradient reduction. It is therefore prudent to allow for that time course before the treatment is deemed ineffective and any decision about repeat intervention is made. Furthermore, this remodelling process seems to extend to the entire left ventricular myocardium, leading to regression of left ventricular hypertrophy. Indeed, total left ventricular mass decreases after septal ablation and this reduction exceeds that of septal mass, as has been shown by using contrast-enhanced magnetic resonance imaging. As in surgical myectomy, these findings can be regarded as a result of the elimination (or at least reduction) of the pressure overload.

Patients show significant symptomatic improvement after treatment (Figure 6). NYHA class is significantly lower after 3 months, with ongoing improvement during the first year. Exercise capacity and peak oxygen consumption are improved accordingly.

The symptomatic improvement is based on changes in cardiac physiology observed at follow up. Parallel to the LVOT reduction, the systolic anterior motion of the mitral valve and the resulting mitral regurgitation are constantly reduced. On the other hand, the systolic pulmonary artery pressure has been shown to decrease after successful alcohol septal ablation. The observed reduction of left atrial dimensions could suggest an expected lower long-term incidence of atrial fibrillation. This is in accordance with the sustained improvement of left ventricular diastolic function during follow up. Myocardial blood flow improves and myocardial perfusion is enhanced, which could explain in part the reduction of anginal symptoms.

Most complications of the procedure may occur in the catheterisation laboratory or during the early post-interventional period. Earlier series have shown in-hospital death as the most significant complication observed to date, with an earlier rate of up to 4% that has now fallen to around 1.5%. Growing experience has led to a reduction in mortality and complication rates. Reports of delayed occurrence of complete heart block up to 10 days after the intervention need special mention, as they emphasise the need for close arrhythmic monitoring for several days following the intervention.

After the introduction of myocardial contrast echocardiography, the need for permanent pacemaker implantation due to permanent heart block was reduced to less than 5%, a rate that is comparable to post-myectomy results. Furthermore, the development of complete heart block after septal ablation can be predicted using a score that has been introduced by Faber et al. This score is based on the ass-

Figure 5. Haemodynamic improvement after alcohol septal ablation. Chart shows the reduction in left ventricular outflow tract (LVOT) gradient reported in published studies with short-term follow up (1-48 months). Each study is represented by a line of a different colour.

Figure 6. Symptomatic improvement after alcohol septal ablation. Chart shows the New York Heart Association (NYHA) class reduction reported in published studies. Each study is represented by a line of a different colour.
Importance of echocardiographic guidance

Since its original appraisal, echocardiographic guidance with myocardial contrast echocardiography has become an indispensable part of the procedure. It has been clearly demonstrated that echocardiographic guidance had a crucial impact on the selection of the ablated area in a significant proportion of patients. Echocardiographic contrast also enables the identification of an atypically originating septal branch as target vessel. Most importantly, alcohol misplacement can be avoided by changing the target vessel after echo-contrast visualisation of wrong septal areas or other cardiac structures, such as papillary muscles or ventricular free walls, thus preventing a catastrophic remote infarction. As the anatomy and the perfusion bed of the septal branches are highly unpredictable, the choice of the first larger septal branch for alcohol septal ablation without any myocardial echocardiographic contrast validation could lead to failure to reach the target area, or even more serious complications.

It is expected that advances in cardiac imaging in the future may provide non-invasive estimation of the underlying histological substrate of the septal myocardium before treatment, thus allowing better patient selection. Predominance of fibrotic over muscle tissue in the basal septum may be a reason for a less significant haemodynamic result after PTSMA. Thus, detection of unfavourable histology, together with elongation of the mitral leaflets, may be helpful in the future to exclude patients from PTSMA on the grounds that their haemodynamic result is likely to be less pronounced.

Long-term results

Long-term results from the first patients who were treated with PTSMA are now available and show that this treatment is both safe and effective. The impressive ongoing symptomatic improvement is accompanied by an increase of exercise capacity in objective measurements. Echocardiographic measurements during follow-up present continuing and growing reduction of the LVOT gradients. After a mean follow-up of 58 ± 14 months most patients showed complete elimination of the outflow tract gradient. This should be appraised as an expression of post-interventional remodelling following an induced septal infarction. These findings emphasise the sense of efficacy in our strategy at inducing septal necrosis by alcohol injection: the amount of scarred tissue should be limited to the extent that can offer haemodynamic benefit. In fact, injection of much lower alcohol doses than in the early years (<2 ml or even <1 ml), has shown comparable results to those of the earlier strategy of aiming at total abolition of the gradient during the procedure.

Indeed, the generation of an intra-myocardial scar has been a main issue of concern regarding the long-term outcome of patients after septal ablation, due to anxiety about a potentially higher risk of malignant ventricular arrhythmias. Ventricular arrhythmias have been reported as an in-hospital complication, possibly due to ischaemia, but they have rarely been described during follow-up. In fact, no increased risk of malignant arrhythmias after the procedure has been shown in patients with an already implanted ICD because of an estimated high risk of sudden death. Furthermore, a decrease in the occurrence of syncope has been reported after alcohol septal ablation.
plausible that, contrary to what happens in patients with myocardial infarction due to coronary artery disease, the incidence of significant ventricular arrhythmias after alcohol septal ablation is rare. As the existence of severe LVOT obstruction itself is an independent risk factor for sudden cardiac death and appropriate ICD discharges, the reduction of LVOT gradient and left ventricular hypertrophy after PTSMA may be beneficial. Moreover, it seems that necrosis produced by alcohol has entirely different morphologic characteristics than necrosis after coronary ischemia, which might also be extended to differences in electrophysiological behaviour.

Long-term follow up of the first 100 patients treated has shown an excellent 96% survival at 8 years, while survival without severe symptoms, atrial fibrillation, stroke or ICD implantation was 74%. Recently published data from a larger cohort of 347 patients has shown 94% survival after 5 years and 87% after 10 years, which is comparable to the results of large myectomy studies.

Perspective

Surgical and percutaneous treatments for septal reduction in HOCM have not been compared in randomised trials. It is doubtful, however, that such a trial can ever be performed. Non-randomised comparison between alcohol septal ablation and myectomy has shown that both therapeutic modalities offer a significant reduction of LVOT obstruction and symptomatic improvement. It is prudent, therefore, to take account of the benefits and drawbacks of each therapeutic method when deciding on treatment for LVOT obstruction. This decision has to take into consideration clinical, morphological, and technical aspects, as well as the merit of each treatment modality for the individual patient. Although successful combined percutaneous treatment of coexistent HOCM and coronary artery disease has been reported, it should be considered that surgery primarily incorporates the ability to deal with HOCM and coexistent cardiac diseases, such as coronary artery disease and valvular disease. In patients with HOCM and mitral regurgitation the presence or not of pathological findings on the mitral valve apparatus should determine the preferred treatment option. In view of the emerging long-term results, surgery and percutaneous septal ablation should be regarded as alternative treatment options in HOCM, in terms of safety and efficacy. The individual decision in each patient should realise the intention to achieve optimal results. This also means that the individual experience of the centre should be taken into consideration when dealing with such a heterogeneous disease. Furthermore, it is essential that symptomatic treatment of patients with HOCM should be part of an integrated treatment approach that includes the assessment and management of risk factors for sudden death, as well as adjustment of treatment to lifestyle parameters and quality of life requirements.

References


46. Lakkis NM, Naguch SF, Kleiman NS, et al. Echocardiography-guided ethanol septal reduction for hypertrophic ob-
Alcohol Septal Ablation

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(Hellenic Journal of Cardiology) HJC • 521


100. Olivotto I, Ommen SR, Maron MS, Cecchi F, Maron BJ. Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Will there ever be a randomized trial? J Am Coll Cardiol. 2007; 50: 831-834.
