**FOCUS:** Nonsurgical Septal Reduction

# CATHETER TREATMENT OF HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

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## ABSTRACT

Non-surgical septal reduction (NSSR) is a promising new therapy for the treatment of classical hypertrophic obstructive cardiomyopathy (HOCM). Patients should have symptoms related to a significant left ventricular outflow tract gradient. The procedure involves the selective injection of absolute alcohol into the hypertrophied basal septum via the epicardial coronary vessels. This results in localized infarction with septal thinning and the other changes that tend to reduce the LVOT gradient. The procedure is well tolerated with low mortality. The principal complication is the development of heart block, which demands pacemaker implantation in around 20% of patients.

Hemodynamic and functional improvement may take some time to become evident and improvement may continue for several months after the procedure. Emerging medium-term follow-up data suggest that the benefits are sustained with no late morbidity. The long-term outcome of the procedure is not known and its value has never been compared to other therapeutic options in randomized controlled trials. **(Heart Views. 2000;1(9): 334-340 )** © 2000 Hamad Medical Corporation.

**Keywords:** ? hypertrophic cardiomyopathy ? nonsurgical septal reduction ? percutaneous transluminal septal myocardial ablation ? Sigwart procedure ? alcohol septal ablation

## Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disease characterized by hypertrophy of the left ventricle (LV), with markedly variable genotype and phenotype. In a subset of patients, the site and extent of cardiac hypertrophy results in obstruction to left ventricular outflow tract (LVOT). This may be present at rest but, in others, significant obstruction occurs under conditions that tend to reduce ventricular pre-load (dehydration, sudden adoption of the upright posture and the Valsalva maneuvre) or increase ventricular contractility particularly exercise.

In the classic form of hypertrophic obstructive cardiomyopathy (HOCM), patients manifest asymmetric septal hypertrophy (ASH), systolic anterior motion (SAM) of the anterior leaflet of the mitral valve and, in most cases, mitral regurgitation (Figure1). The inward movement of the hypertrophied septum during systole further narrows the LV outflow tract resulting in high LVOT blood velocities that pull the mitral valve leaflet toward the interventricular septum (Venturi effect). The SAM of the mitral valve with valve-septal contact is, in many patients, the most important determinant of the severity of LV outflow obstruction and the cause of the mitral regurgitation.

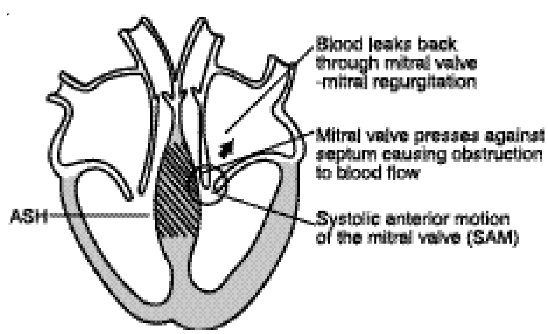


***Fig. 1*** *Schematic diagram of hypertrophic obstructive cardiomyopathy illustrating asymmetric septal hypertrophy (ASH), systolic anterior motion of the mitral valve leaflet (SAM) and obstruction of the left ventricular outflow tract. Mitral regurgitation may also be present.*

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A number of variants of obstructive HCM have been characterised:

? Mid-cavity obstructive hypertrophic cardiomyopathy – due to the systolic apposition of hypertrophied papillary muscle and LV wall at the level of the mid-LV, producing two distinct LV chambers.

? Complex obstructive HCM – consists of obstruction at the level of both the papillary muscle (mid-LV cavity) and the aortic valve leaflets.

? Obstructive HCM in the elderly – associated with calcification of the mitral valve annulus and anterior displacement of the mitral valve.

Although patients with these variants may manifest high LVOT gradients and limiting symptoms, current experience with non-surgical septal reduction is generally restricted to the classical form of HOCM.

## Treatment Options in Classical HOCM

Many patients with HOCM eventually develop one or more of the following symptoms: dyspnea, chest pain, syncope, palpitations and fatigue. Symptoms are variable and not exclusively related to left ventricular outflow tract gradient with which there is a poor correlation. Other mechanisms include:

? Impaired myocardial function in the absence of obstruction

? Arrhythmia or conduction delay

? Impaired filling due diastolic dysfunction

Drug therapy with beta blockers or other negative inotropes can be effective but a number of patients are intolerant of these agents or remain symptomatic despite treatment. Right ventricular contraction immediately following atrial systole reduces LV outflow tract gradients without adversely affecting systemic arterial pressure. This observation provided the rationale for the evaluation of dual chamber (DDD) pacing for the treatment of HOCM. Randomised controlled trials (RCT) have demonstrated only very limited hemodynamic and clinical improvement with DDD pacing and the inability to predict response in an individual patient means that this is rarely used as routine therapy[1].

Patients with resistant symptoms have traditionally been considered as candidates for cardiac surgery. Left ventricular myectomy, performed in the septal area and sometimes combined with mitral valve replacement, eliminates or improves symptoms in most patients and significantly reduces LV outflow tract pressure gradients. The long-term efficacy of this procedure has been demonstrated in a number of reports though there is an associated procedural mortality of around 5% and considerable morbidity including complete heart block, ventricular septal defect formation, and cerebrovascular accident [2,3].

## Non-Surgical Septal Reduction

Percutaneous methods of septal reduction have been developed as an alternative to open surgical therapy. A number of terms have been used to describe these procedures including 'percutaneous transluminal septal myocardial ablation (PTSMA)', 'the Sigwart procedure', 'alcohol septal ablation' and 'transcoronary ablation of septal hypertrophy' (TASH)[4-6]. We prefer the more generic description 'non-surgical septal reduction' (NSSR) that encompasses a variety of techniques that can be employed in this setting.

Initial observations in this field had demonstrated that transient occlusion of a septal artery with an angioplasty balloon resulted in a reduction in the LVOT gradient. In 1994 Ulrich Sigwart introduced a small volume of absolute ethanol by selective injection into a septal vessel to create an area of localized myocardial infarction in the area of the left ventricular outflow tract [7]. This technique has been adopted by a number of groups world-wide and more than 100 procedures have now been performed. As with all new interventions there has been a process of rapid evolution in patient selection and operative technique. This paper describes our current approach and identifies aspects that are the subject of ongoing evaluation.

## Patient Selection and Initial Investigation

Patients should exhibit symptoms despite medical therapy or have proven intolerant of drug agents. Patients with previous surgical myectomy or DDD pacemaker implantation can be treated.

Echocardiography confirms the anatomical diagnosis. Magnetic resonance imaging provides comprehensive diagnostic information in almost all patients and may be an alternative when echocardiography is suboptimal.[8]. The patient should manifest classical HOCM with SAM as described in the introduction. Although we have performed a small number of procedures in patients with the mid-cavity obliteration variation of HOCM, experience in this clinical setting is limited.

Doppler examination can be used to measure the LVOT gradient at rest and under conditions of exercise or pharmacological stress. A resting gradient of >50mm Hg or a stress gradient of >100mm Hg are commonly used thresholds for intervention, although highly symptomatic patients with less significant findings may benefit from the procedure. Exercise testing is relatively safe in HOCM and for research purposes we document exercise capacity with measurement of maximal oxygen uptake.

Diagnostic cardiac catheterization provides important information. Left ventriculography can demonstrate LV outflow obstruction, SAM, and mitral regurgitation. Coronary angiography is performed to exclude co-existing significant coronary disease and to identify the probable anatomy of blood supply to the septum.

Although most cardiologists avoid trans-septal puncture we still measure the LV outflow tract pressure gradient with simultaneous recordings using a Brockenbrough catheter in the left ventricle (placed via a trans-septal approach) and a coronary angioplasty guide catheter in the ascending aorta. Other units use bilateral femoral artery puncture for retrograde cannulation of the LV cavity and aorta with separate catheters. It is best to deploy an end-hole catheter in the LV since the level of obstruction can be very localized. The pressure gradient may also be measured with a double lumen catheter or by withdrawing an end-hole catheter slowly from the apex of the LV to the ascending aorta (Figure 2). These methods do not allow continuous examination of changes in the gradient over the course of the procedure.

Maneuvers designed to detect provoked obstruction are indicated when the gradient at baseline is less than 30 – 50mm Hg. The stimulation of ventricular premature beats may reveal a gradient in the post extra-systolic cycles. Ectopics can be induced with manipulation of the ventricular catheter or using a single paced beat from a temporary wire. The most reliable method of gradient provocation is to use a slow infusion of isoprenolol at an initial rate of 1µg/min. The rate is then increased until the heart rate reaches 100 – 110 beats per minute or the LV outflow pressure gradient exceeds 50mm Hg. Operators should note that there is often a delayed heart rate response with a lag time of up to a minute and close observation and careful monitoring of the infusion is essential.

As the pressure amplitude increases between the ascending aorta and femoral artery during isoprenolol infusion, particularly in young patients, a significant "systolic pressure gradient" often develops. This may give rise to an exaggerated estimation of the provoked LV outflow obstruction if pressures are recorded from the femoral sheath.

## Performance of the Non-Surgical Septal Reduction Procedure

### *Preparation*

The procedure is performed under local anesthetic with light pre-medication (temazepam 10 – 20mg)). An intravenous cannula should be placed in a peripheral vein. The right groin is

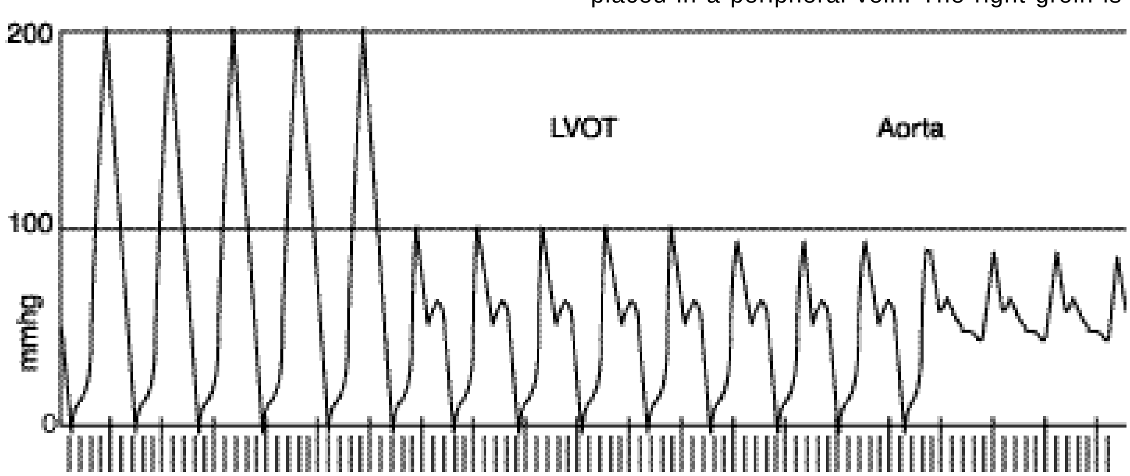


***Fig. 2*** *Pressure recording from a catheter pullback from the left ventricular cavity (LV), through the LV outflow tract (LVOT) and into the aorta. The level of obstruction is seen to lie in the LVOT.*

prepared in the usual manner and venous and arterial sheaths placed. The first venous sheath is used to introduce a temporary pacing electrode to the apex of the right ventricle. This is essential, as heart block (usually transient) is very common following alcohol injection. In our unit a second venous sheath is used for the trans-septal puncture equipment. An alternative strategy is to perform an arterial puncture (perhaps at the left groin) and use this to position an end-hole catheter at the apex of the LV.

The third and final sheath is placed in the femoral artery and is used to introduce the left coronary guide catheter. This can be selected from routine stock and sized for optimal access to the left coronary system. We favor the Judkins left short tip but patient anatomy and local preference will influence the choice. After the trans-septal puncture has been performed, systemic anti-coagulation is induced with a bolus of heparin (7,500 – 10,000 units as dictated by body weight) and diagnostic evaluation of the LVOT gradient performed (see below).

### *Identification of the Target Vessel*

Angiography images are acquired to identify the anatomy of blood supply to the septum. The vessel pattern is variable and can be confusing. Multiple angiographic projections may be required to distinguish septal and diagonal vessels (Figure 3).

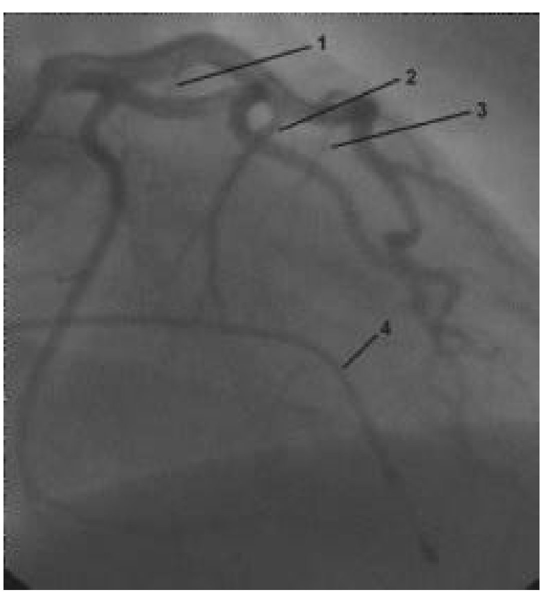


*Fig. 3 Selective coronary injection of the left coronary system in a right anterior angiographic projection. Potential target septal vessels are identified (1, 2, 3). A temporary pacing wire has been placed in the apex of the right ventricle (4).*

The ideal target vessel is a proximal septal of 1.0 – 2.0mm diameter. If more than one potential target is identified then additional techniques (described below) are required to identify the most suitable vessel. These methods, using intra-coronary echo contrast agents, are also of value in the very rare circumstances when the blood supply to the proximal septum is derived from the circumflex or an intermediate coronary trunk.[9]

An angioplasty guide wire is introduced into the selected septal vessel. A flexible, low trauma wire is the first choice though sometimes a stiffer shaft (intermediate or standard) may be needed to ensure balloon access to a septal arising at an acute angle from the main left anterior descending (LAD) vessel. An over the wire (OTW) angioplasty balloon catheter is advanced over the wire and positioned in the proximal part of the septal vessel. Any semi- compliant, OTW balloon system is acceptable but it is best if the balloon is of short length (maximum 10mm). Longer devices mean that the alcohol is delivered into a more distal portion of the target vessel, limiting its myocardial distribution, particularly if the balloon tip lies distal to a branch in the septal vessel. If the septal has an early bifurcation, each distal branch can be approached as if it were an individual vessel.

The balloon diameter should be sized to ensure complete occlusion of the septal at low or nominal inflation pressure. A two-marker balloon allows more precise positioning. The entire length of the balloon must be within the septal to eliminate the possibility of LAD barotrauma or the balloon 'melon-pipping' back into the LAD vessel (Figure 4). Sometimes balloon occlusion of the vessel

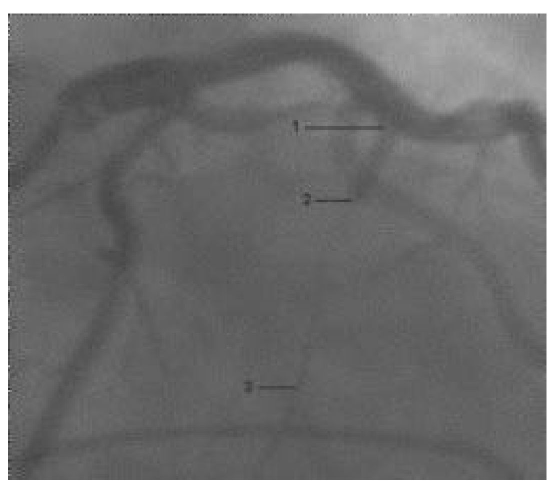

*Fig. 4 An over the wire angioplasty balloon is inflated in the proximal portion of the septal vessel. The margins of the balloon are illustrated (1,2). An angioplasty guide wire marks the course of the septal vessel (3).*

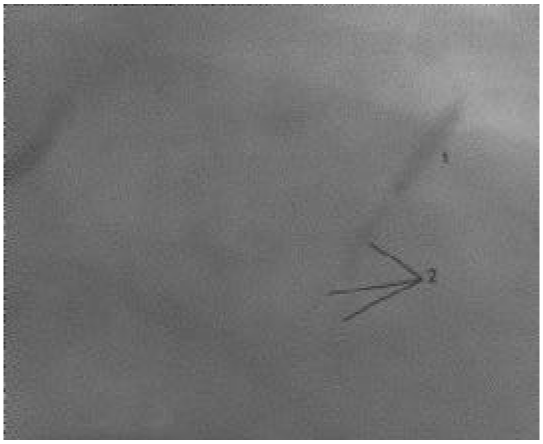

***Fig. 5*** *The angioplasty balloon is inflated in the proximal portion of the septal vessel. An injection of radiographic contrast has been made through the central lumen of the over the wire balloon. The contrast distribution in the septal vessel and its branches is clearly seen (2).*

reduces the resting gradient. This is a very favourable sign that an appropriate target septal vessel has been identified but the positive and negative predictive value of this observation is limited and does not obviate the desirability of a contrast echo study (see below).

With the balloon inflated, two injections of radiographic contrast are performed. In the first of these, a standard selective left coronary injection through the guide catheter demonstrates that the target septal vessel is sealed to the antegrade flow of dye and hence, by presumption, any subsequent retrograde leak of alcohol. In the second injection, contrast is introduced through the central lumen of the OTW balloon into the target vessel (Figure 5). This is to ensure that there is no major collateralization that takes dye (thus ensuring localized injection of alcohol) to the LAD or other major epicardial vessel. The ideal image seen at this stage is a septal myocardial blush.

Additional anatomical confirmation is provided with a myocardial echo contrast study. Transthoracic images in the parasternal long axis or apical four chamber views are used with recording for immediate play-back analysis. An echo contrast agent is injected through the central lumen of the OTW balloon. Suitable agents include Levovist‘ manufactured by Schering or Optison‘ though the latter has a very short dwell time in the myocardium. Echovist has been associated with arrhythmic induction in this setting and thus should be avoided. The region of myocardial distribution is then visible as a bright area on the echo images. The ideal target region is the hypertrophied muscle at the point where the SAM of the mitral valve touches the septum. If the septal vessel selected is too distal then contrast illuminates the septal muscle in mid cavity or near the apex. Contrast appearance in the left or right ventricular free walls identifies that the target vessel is a diagonal branch rather than a septal.

### *Alcohol injection*

After final angiographic confirmation of balloon positioning and septal occlusion, a small volume of absolute alcohol is injected through the OTW system. The dose depends on the size of the septal and the extent of the myocardial run-off. There has been a trend towards the use of reduced alcohol doses and typical injection volumes now lie in the range of 0.5 – 1.5ml. We favor the use of a single bolus injection rather than a slow infusion. We believe that this will promote dispersion in the perfusion bed without the risk of selective distribution caused by small vessel thrombus and occlusion in the early phase of the injection.

The patient will experience immediate pain and should be warned to expect this symptom. If required, diamorphine can be administered before the injection but we do not do this as a routine as the pain eases after 30 – 45 seconds and is rarely severe. ST segment changes and ventricular ectopic activity are routine. Transient heart block is common but the heart rate is supported by the temporary pacemaker, which is set to initiate capture if the native rate falls below 40 beats per minute. The balloon is kept inflated for 5 – 7 minutes after alcohol injection. Accordingly, the guide wire can be re-introduced into the distal septal artery though this is not essential. Deflation of the balloon and withdrawal into the guide catheter should be performed in a rapid and positive fashion to limit the possibility of any residual alcohol entering the LAD circulation.

It is possible to repeat this process with a second, third or even fourth septal vessel. Multiple vessel injection was our norm in the early series and may still be indicated in cases when the septal territory is supplied by a leash of small vessels or two proximal septal perforators. Other groups have adopted a policy of a single vessel injection with the option to perform a subsequent staged procedure on a second vessel if the patient does not demonstrate a good clinical response at medium term follow-up.

### *Repeat Diagnostic Evaluation*

A coronary angiogram usually, but not always, reveals occlusion of the target septal with no re-flow appearance. A repeat resting or stress echo gradient study can be performed, often with gratifying results though as discussed below, myocardial remodelling and hence the full benefits of the intervention may take many months to become apparent.

### *Efficacy and Complications*

Like all new surgical and interventional procedures NSSR has undergone a period of rapid evolution and refinement. Coinciding with this a number of operators and centres have gained their initial experience with the technique. As a result it may be expected that the outcomes from these earliest cases may be less successful compared to experienced operators. Certainly, the use of myocardial contrast echocardiography has allowed more precise targeting of the alcohol injection and the trend towards the delivery of small alcohol volumes into fewer septal vessels has reduced the immediate procedure related complications particularly complete heart block.

Follow-up data has been published describing the short-term results in around 200 patients and medium term data in less than 100 cases. The longest reported follow-up period is to a mean of 30 months in 25 patients[10]. All outcome data were recently reviewed by Knight[4] who observed that the mortality rate was low (2%) both at the initial procedure and in subsequent follow-up. It must be remembered that early cases were often performed in patients with significant co-morbidity and involved more aggressive dose regimes. The current procedural mortality rate is probably well below this value.

The main complication of the procedure is the induction of permanent atrioventricular conduction block necessitating permanent pacemaker implantation. The presence of trifasicular or complete heart block persisting at 48 hours post-procedure is an indication for implantation of dual chamber pacing device. To date this has occurred in around 20% of cases though with better myocardial targeting we expect that this may fall to a value of 10%.

Some observers have been concerned that the induction of septal infarction may result in a range of adverse effects[11]. To date there have been no reports of late ventricular arrhythmia or induced ventricular septal defect. Another concern relates to the impact of the procedure on ventricular function, both systolic and diastolic. The natural history of HOCM can involve progressive impairment of ventricular function and this may be hastened or exacerbated by the infarction of healthy muscle. Fortunately, follow-up studies have not demonstrated any trend in increased ventricular cavity dimensions or reduced systolic performance, though the current observation period is too short and involves too few patients to draw any firm conclusions in this respect.

There is little doubt that NSSR is effective in the reduction of LVOT obstruction. Echocardiographic studies have observed that the procedure results in thinning of the basal septum with reduced SAM and mitral regurgitation. Left atrial size may also be reduced. Serial follow-up has revealed that the magnitude of the gradient continues to fall as the myocardium remodels with scar formation. The benefits of the procedure may take up to 3 months to become apparent and may continue to improve over the first post-operative year. In the German series with 2-3 year follow-up, the stress LVOT gradient was reduced from a pre-procedure mean of 147mm Hg to a mean of 12mm Hg at final assessment. All patients experienced greater than 50% reduction in gradient and there was complete elimination in over 70% of subjects[12].

The technique also results in an improvement of left ventricular diastolic function with improved relaxation and compliance[13]. In addition, there is consistent alteration of septal activation with secondary inco-ordination of contraction, similar to that seen with dual chamber pacing[13]. These factors could play a significant role in gradient reduction and subjective functional improvement.

The assessment of symptomatic benefit is complicated by the potential for a placebo effect. Nevertheless, follow-up reports suggest a substantial and sustained improvement of greater than 1 New York Heart Association functional class. Objective tests of functional capacity have also shown increases of around 40% in exercise performance at medium term follow-up.

### *Future Directions for NSSR Therapy in HOCM*

Developments in technique, principally the use of myocardial contrast echocardiography have refined the procedure and hold the prospect of reduced complication rates. Questions concerning the selection of a single or multiple target vessels, the total alcohol dose, and its rate of administration may be subject to further evaluation. We suspect that there will be an increase in the use of single vessel procedures with the option of repeat intervention if medium term maturation of the infarct area fails to bring the desired clinical benefit.

The elegance, simplicity, and apparent efficacy of this procedure have led to its rapid dissemination in the cardiology community. Maron has observed that the number of NSSR procedures performed over the last few years is ten times that predicted by the historic activity of the best surgical units offering the surgical myectomy procedure[6]. NSSR is a promising therapeutic option for the management of a selected group of patients with symptomatic HOCM resistant to medical therapy. The procedure may be best performed in specialist centres with a developed interest in the management of HOCM. All cases should be documented for inclusion in collaborative registries and other research ventures. Its long-term efficacy is yet to be evaluated and its value, compared to intensive medical therapy or traditional surgery, has not been assessed in prospective randomized trials. Such studies are now indicated but may be difficult to complete given the very disparate nature of the treatments under consideration.

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