ALCOHOL SEPTAL ABLATION FOR OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

Coronary disease

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Hypertrophic cardiomyopathy (HCM) is a genetic condition characterised by the presence of otherwise unexplained left ventricular hypertrophy. The clinical spectrum of the disease is remarkably heterogeneous, ranging from individuals with normal life expectancy and minimal symptoms to those with lives severely restricted by breathlessness and chest pain and potentially lethal arrhythmias. Around 25% of patients with HCM have dynamic left ventricular outflow tract (LVOT) obstruction caused by both protrusion of the hypertrophied interventricular septum into the outflow tract and systolic anterior motion of the mitral valve. The presence of outflow tract obstruction is a powerful predictor of adverse prognosis.¹ While it is not yet clear whether therapeutic relief of obstruction improves prognosis (see below), there is good evidence that surgical procedures to reduce obstruction are effective in relieving symptoms in patients that have not responded to medical treatment (for example, β blockers, disopyramide). Traditionally, septal myectomy (resection of that portion of the septum responsible for obstruction) has been the surgical technique of choice.² Over the last decade alcohol septal ablation (ASA) has been developed as an alternative to open heart surgery. This percutaneous technique produces a reduction in outflow tract obstruction localised infarction of the septal myocardium by alcohol injection into the appropriate septal artery.³ Correct localisation of the infarction is provided by myocardial contrast echocardiography.⁴

INDICATIONS FOR ALCOHOL SEPTAL ABLATION

Prognosis

There is no definitive randomised data to suggest that either ASA or septal myectomy have an effect on prognosis. Recently, a retrospective analysis of 1337 patients with HCM showed that those symptomatic patients with obstruction that underwent septal myectomy had a better long-term prognosis than those that were medically treated.⁵ While these findings are of interest they should not be extrapolated to a recommendation that septal myectomy should be recommended for asymptomatic patients with LVOT obstruction—firstly because such patients were not included and secondly because of the inherent limitations of a retrospective, non-randomised study. At the present time, ASA and septal myectomy can only be recommended on symptomatic grounds.

Symptoms

Patients with HCM may experience cardiac symptoms as the consequence of one or more pathological processes. These include mitral regurgitation, congenital mitral valve abnormalities, left ventricular diastolic dysfunction, abnormalities of small coronary arteries, myocardial ischaemia, atrial fibrillation, abnormal peripheral vascular response, and LVOT obstruction. It is also important to recognise that the presence of a haemodynamically significant LVOT gradient may not always be associated with symptoms, and the co-existence of symptoms with LVOT obstruction does not necessarily imply causality. It therefore follows that all patients being considered for ASA or septal myectomy should undergo a careful clinical and echocardiographic assessment to determine the appropriateness of the procedure.

Key components of this assessment include the following:

- ▶ Is there potential for improving symptoms by improved medical therapy? Patients should be reviewed by a physician experienced in the management of HCM before ASA or septal myectomy to ensure that medical treatment is optimised and that a full risk assessment for sudden cardiac death is completed and family screening arranged if appropriate.
- ▶ Are there associated abnormalities of the mitral valve? Patients with HCM may have associated abnormalities of the mitral apparatus that contribute towards obstruction such as the direct insertion of the papillary muscle into the anterior mitral valve leaflet, leading to exaggerated anterior displacement of the papillary muscles and mid-cavity muscular obstruction.⁶ Such patients are best dealt with surgically. The frequency with which these abnormalities are encountered will vary with the referral population but in some surgical series nearly 20% had some mitral valve abnormalities.⁶ These cases must be distinguished from the far more common form of mitral regurgitation secondary to systolic anterior motion seen almost

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Figure 1 Transthoracic echocardiography in obstructive hypertrophic cardiomyopathy. (A) Parasternal long axis view showing pronounced septal hypertrophy and mitral valve/septal contact. (B) Continuous wave Doppler signal across the left ventricular outflow tract (LVOT), indicating significant obstruction.

universally in patients with significant LVOT obstruction. This can be expected to improve following relief of obstruction either with ASA or septal myectomy.

- Is there a significant outflow tract gradient? Symptomatic patients are suitable for ASA if they have evidence of significant (≥ 50 mm Hg) outflow tract obstruction at rest (fig 1). It must be recognised that the degree of dynamic outflow tract obstruction varies considerably with time and activity/arousal in any given patient and that some patients with little resting gradient may experience a pronounced increase in obstruction with relatively light exercise. Some centres have reported favourable results from ASA in patients with gradients only present after dobutamine provocation, but caution should be exercised with this approach as dobutamine stress can induce LVOT gradients in normal hearts.⁶

ALCOHOL SEPTAL ABLATION: THE PROCEDURE

A guiding catheter is introduced into the left main coronary artery and a 0.014 inch guidewire into the left anterior descending artery (LAD). The first septal artery is usually selected (fig 2A), and a short (~10 mm) “over the wire” (OTW) balloon introduced into the branch. The lumen of this device provides the route for delivery of angiographic contrast, echo contrast, and ultimately alcohol, selectively into the septal artery. As transient heart block is common at

the time of injection, a temporary pacing wire is routinely inserted, usually via the femoral vein.

The OTW balloon is positioned under fluoroscopic guidance to ensure that it is entirely within the septal branch and does not encroach on the lumen of the LAD (fig 2B). The OTW balloon is inflated and the guidewire removed. A small amount of angiographic contrast is injected through the OTW balloon to ensure that there is no spill back into the LAD (fig 2C). The balloon should not be placed too distally as this may result in a smaller (and solely right sided) septal infarct, with a consequent reduction in the effect on the outflow gradient.⁷

Echocardiographic localisation

An echocardiographic contrast agent (for example, Optison, Amersham Health, UK) is then injected through the OTW balloon, and the myocardium supplied by the septal artery is localised with transthoracic echocardiography (figs 3 and 4). The optimal location within the septum is the point of the anterior mitral valve leaflet and septal contact in the apical four chamber view. The right ventricular free wall and left ventricular apex may on occasion be supplied by proximal septal vessels. If these areas are demonstrated with echocardiographic contrast, ablation should not proceed. If present an alternative septal artery may be investigated. Echo guidance may influence the interventional strategy in 15–20% of cases, either by aborting the procedure, or changing the target vessel.⁴

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Figure 2 Coronary angiography during atrial septal ablation (ASA). (A) Angiography of the left coronary artery in the right anterior oblique cranial position at the start of the procedure. The left anterior descending artery (LAD) and first septal artery are indicated. (B) A 0.014 inch wire positioned in the septal artery. An “over the wire” (OTW) balloon is positioned within the vessel and inflated. Flow within the LAD remains unaffected. (C) Injection of contrast through the internal lumen of the OTW balloon following wire removal. There is no spill back into the LAD.

If echocardiographic localisation is supportive, ablation may proceed. The transvenous pacing wire is re-checked, and intravenous analgesia is administered, as the alcohol can cause intense but transient discomfort. Absolute alcohol (1–2 ml) is administered slowly through the lumen of the OTW balloon, with the balloon remaining inflated for five minutes. Generally, there is a trend towards the use of smaller volumes of alcohol with a recent randomised trial showing no difference in short-term outcome between patients treated with 1–2 ml as opposed to > 2 ml of alcohol.⁸ Following deflation, the balloon and wire are removed. A final coronary angiogram will usually demonstrate a biphasic flow pattern in the septal vessel. The echocardiographic gradient is reassessed and will usually be notably reduced, though this immediate measurement is likely to reflect a degree of myocardial stunning and may not accurately indicate the long-term outcome. The LVOT gradient will usually gradually increase in the first few days following the procedure, to then fall again over a period of weeks as remodelling of the septum occurs.⁹

Figure 4 Myocardial contrast echocardiography during ASA. Echocardiographic images in the parasternal long-axis view confirm the presence of increased echo signal situated correctly exclusively on the left side of the interventricular septum (circled).

Figure 3 Myocardial contrast echocardiography during ASA. Echocardiographic images in the apical four chamber view before (A) and after (B) injection of echo contrast through the lumen of the OTW balloon. Increased echo signal is seen in the correct position in the basal septum (circled).

CLINICAL AND HAEMODYNAMIC EFFECTS OF ASA

The short and medium term results of septal ablation are similar to that of septal myectomy in terms of symptomatic improvement and relief of outflow obstruction (fig 5), though inevitably the data come from relatively small case series (for example, Knight *et al*¹⁰). Recently, a systematic review of the results of ASA has been performed which provides the best summary of the current state of knowledge about ASA.¹¹ This review analysed 42 published studies involving 2959 patients between June 1996 and June 2005. At 12 months there was a sustained decrease in resting LVOT gradient (65.3 to 15.8 mm Hg, $p < 0.001$) with an associated reduction in basal septal diameter (20.9 to 13.9 mm, $p < 0.001$). This was associated with a significant improvement in symptoms with a decrease in New York Heart Association (NYHA) functional class (2.9 to 1.2, $p < 0.001$), an increase of 34% in mean exercise capacity on a treadmill ($p < 0.001$), and an increase of 33% in peak oxygen consumption ($p < 0.001$).

LV ejection fraction decreased slightly from 74.5% to 67.4% ($p < 0.001$) at one year. Left ventricular end-diastolic diameter increased from 44.5 mm to 45.8 mm ($p < 0.001$) and end-systolic diameter from 23.3 mm to 26 mm ($p < 0.001$).

Average serum creatine kinase (CK) peaked at 964 U/l. Repeat ASA was necessary in 6.6% of patients and 1.9% went on to septal myectomy. Procedural failure (defined as persistent symptoms post ASA) occurred in 11% of patients. Chang *et al*¹² have further examined predictors of an unsatisfactory outcome following ASA in 173 patients and identified a residual gradient of ≥ 25 mm Hg in the catheterisation laboratory and infarct size of <1300 U/l peak CK as independent predictors of poor symptomatic outcome. While the magnitude of serum marker rise is not identifiable

prospectively, some operators will inject more alcohol into the same or different septal arteries if there is a persisting immediate gradient. Alternatively, an expectant approach could be adopted, with the option of a second procedure after a clinical and echocardiographic evaluation at 3–6 months.

EFFECTS OF ASA ON THE CONDUCTING SYSTEM

New right bundle branch block (RBBB) developed in 46% of patients and first degree atrioventricular (AV) block in 53% following ASA in the systematic review.¹¹ Permanent complete heart block requiring permanent pacemaker was required in 10.5% of the patients treated. Heart block can occur several days following ASA and means that patients without pre-existing pacemakers or implantable cardioverter-defibrillators (ICD) need to have inpatient monitoring for approximately five days after septal ablation. The need for permanent pacemaker implantation has been shown to be higher in female patients, when more than one septal artery is treated, with more rapid bolus injection of the alcohol, and in those with pre-existing conducting system disease (especially left bundle branch block (LBBB)).¹³ This is because ASA causes transmural infarction in the basal mid septum close to, and often involving, the right bundle, unlike septal myectomy that targets the epicardial part of the basal anterior septum close to the left bundle. Thus patients with pre-existing RBBB are at higher risk of requiring permanent pacing after septal myectomy and those with pre-existing LBBB are at high risk of permanent pacing after ASA.¹⁴ Prophylactic permanent pacing or, if appropriate, ICD should certainly be considered before ASA in higher risk patients (for example, a female with LBBB with residual symptoms following failed septal myectomy).

COMPLICATIONS OF ASA

Serious complications were relatively uncommon in the systematic review.¹¹ Early (30 day) mortality was 1.5% with a late mortality of 0.5%. Ventricular fibrillation in the immediate perioperative period occurred in 2.2%, LAD dissection in 1.8%, and pericardial effusion in 0.6%. As this systematic review includes the early trials at the beginning of the learning curve for the technique, some of which only included sick patients that were deemed unsuitable for surgery, these data may reflect a slight overestimation of the risks and underestimation of the benefits that are currently obtained by experienced operators.

CARDIAC MAGNETIC RESONANCE STUDIES

Cardiac magnetic resonance (CMR) imaging has provided some useful insights into the results of ASA. A study of 24 patients⁷ reassuringly showed no evidence of remote infarction. The mean size of septal infarction was 20 (SD 9) g, corresponding to around 10% of the total left ventricular mass and 30% of the septal mass. Interestingly, a small number of patients had a predominantly right-sided infarction that consequently produced a less favourable result. At six-month follow-up¹⁵ there was further reduction in septal mass and interestingly also a reduction in remote non-septal mass from 114 (41) g to 111 (27) g ($p < 0.001$) that correlated with the extent of LVOT gradient reduction. This suggests that at least some of the myocardial hypertrophy in HCM may be afterload dependent and that ASA may have a beneficial effect in terms of favourable left ventricular remodelling.

Figure 5 Immediate haemodynamic effects of ASA. Simultaneous pressure recordings from the left ventricular cavity and aorta before (A) and after (B) ASA. Before ASA there is a large LVOT gradient which is enhanced following an extrasystole. After ASA there is abolition of the gradient at rest and after an extrasystole.

COMPARISONS BETWEEN ASA AND SEPTAL MYECTOMY

There are no randomised trials comparing ASA and septal myectomy. Four studies have been published comparing non-randomised groups of patients undergoing standard septal myectomy and ASA.^{16–19} With the exception of one report, where patients were age- and gradient-matched,¹⁸ the cohorts of patients undergoing ASA tended to be older and have more co-morbidity. Four reports did not show any difference in terms of serious adverse events, but one¹⁹ showed three late cardiac deaths after ASA compared with one after septal myectomy. More patients required permanent pacing following ASA than septal myectomy, with < 5% of patients requiring pacing following septal myectomy. Following ASA, a small number of patients (< 10%) required a second procedure (either repeat ASA or myectomy) because of an unsatisfactory result. Overall, patients experienced similar effects in terms of gradient reduction and symptom relief following either procedure.

It should be remembered that these comparisons were all made at a time when the surgical procedure was well established and the interventional technique was not. This may lead to an exaggeration of the complications of ASA. For example, in one study,¹⁸ seven of the nine patients that required permanent pacing were treated before the use of myocardial contrast echocardiography and before modification of the ethanol injection technique towards a slower method of delivery—both now standard and essential parts of the ASA technique.

CONCERNS ABOUT ASA

Two major concerns have surfaced about the use of ASA. Firstly there is the issue of the risk of long-term arrhythmias. Commentators⁶ have felt that the intramyocardial scar produced by ASA is inherently more likely to lead to ventricular arrhythmias over long-term follow-up than the predominantly epicardial scar produced by septal myectomy. To date there is no evidence of this. Small studies have shown that ASA does not alter ICD intervention rates in high risk patients over three years and long-term follow up of our cohort of patients has not shown evidence of significant arrhythmias on repeat Holter monitoring (unpublished data).

The second concern centres on the numbers of ASA procedures that have been performed. In the last few years, approximately 3500 septal ablations have been performed worldwide—more than all the septal myectomies in the last 45 years. While some of this may reflect septal ablation's greater acceptability to patients, there is a concern about proper patient selection. It cannot be overstated that ASA is a procedure that can only be justified on symptomatic grounds in patients with significant LVOT obstruction.

FUTURE DIRECTIONS

The key to optimising results and minimising complications during ASA is to induce the minimum effective amount of myocardial necrosis in exactly the right location. As experience of the procedure grows and as echocardiographic images continue to improve, more accurate myocardial contrast echo will inevitably improve results and lessen the need for permanent pacing. There have been reports of the use of intracardiac echo, which could have potential as a promising imaging modality for ASA although difficulties may occur in the recognition of echo contrast using this

Alcohol septal ablation for obstructive HCM: key points

- ▶ Alcohol septal ablation (ASA) is only indicated in patients with hypertrophic cardiomyopathy who have significant left ventricular outflow tract obstruction and whose symptoms are not controlled by optimal medical treatment
- ▶ Not all such patients are suitable for ASA because of co-existing mitral valve abnormalities or unfavourable coronary anatomy
- ▶ ASA has a similar procedural mortality to septal myectomy
- ▶ ASA produces similar medium term gradient reduction and symptom relief to septal myectomy
- ▶ Around 10% of patients undergoing ASA will develop permanent heart block requiring pacemaker implantation. The risk is higher for female patients and those with pre-existing left bundle branch block
- ▶ Further studies are required to examine the long-term effects of ASA

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technique. One group²⁰ has reported successful haemodynamic results following septal ablation using polyvinyl alcohol foam particles rather than absolute alcohol to induce infarction—none of the 18 patients treated this way developed heart block.

PERSPECTIVE

The data that are now available to us suggest that ASA is an effective and safe procedure for reducing outflow tract obstruction and relieving symptoms in patients with obstructive HCM and symptoms unresponsive to optimal medical treatment. The results compare well with the more established procedure of septal myectomy. While there is a greater need for permanent pacing following ASA and a small number of patients may require a second procedure or crossover to myectomy, patients undergoing ASA are freed from the morbidity associated with open heart surgery. Patients with disabling symptoms and co-morbidities that make them unattractive surgical candidates now have an interventional option available to them. It seems clear that both septal myectomy and ASA have a place in the treatment of obstructive HCM, but too often the debate seems polarised between adherents of one or other technique. On the one hand, the wealth of experience and favourable long-term results of septal myectomy does not necessarily make it a better treatment option, just a more established one. The availability of a valid surgical option should not inhibit the development of less invasive techniques. On the other, it is clear that not all patients will obtain a good result from ASA, either because of associated abnormalities of the mitral valve or unfavourable coronary anatomy. These patients will continue to require surgical intervention.

Thus for a number of patients the options are already clear—for example, a 65-year-old man with LVOT obstruction and moderately severe chronic obstructive pulmonary disease should clearly be treated by ASA, and a 24-year-old woman with pre-existing LBBB and congenital mitral valve anomalies should undergo surgery. For the remainder of patients, potentially treatable by both techniques, a large randomised comparison of ASA and septal myectomy would be of great value. This would be a considerable task as the numbers of patients requiring either intervention is small, and the results would have to be interpreted in light of the

inevitably large proportion of patients that would refuse randomisation and opt for ASA before considering the possibility of septal myectomy. It is also vital that patients that have been treated with ASA are followed-up as carefully as possible over the long-term, preferably in established registries, to ensure that arrhythmic problems do not become a cause for concern. For the time being the optimal management of these patients must include a full work up by a team with experience of managing HCM and a full explanation of the treatment options—including a clear exposition of the continuing areas of uncertainty.

Additional references appear on the *Heart* website—<http://www.heartjnl.com/supplemental>

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