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REVIEW

Controversies in cardiovascular medicine

Hypertrophic obstructive cardiomyopathy: alcohol septal ablation

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Alcohol septal ablation (ASA) was introduced in 1994 as an alternative to septal myectomy for patients with hypertrophic obstructive cardiomyopathy and symptoms refractory to medical therapy. This procedure alleviates symptoms by producing a targeted, limited infarction of the upper interventricular septum, resulting in an increase in left ventricular outflow tract (LVOT) diameter, a decrease in LVOT gradient, and regression of the component of LV hypertrophy that is due to pressure overload. Clinical success, with improvement in symptoms and reduction in gradient, is achieved in the great majority of patients with either resting or provocable LVOT obstruction. The principal morbidity of the procedure is complete heart block, resulting in some patients in the requirement for a permanent pacemaker. The introduction of myocardial contrast echocardiography as a component of the ASA procedure has contributed to the induction of smaller myocardial infarctions with lower dosages of alcohol and, in turn, fewer complications. Non-randomized comparisons of septal ablation and septal myectomy have shown similar mortality rates and post–procedure New York Heart Association class for the two procedures.

Keywords Alcohol septal ablation • Hypertrophic cardiomyopathy • Hypertrophic obstructive cardiomyopathy

Introduction

Hypertrophic cardiomyopathy (HCM) is a disease characterized by idiopathic hypertrophy of the left ventricle (LV). Clinical manifestations include diastolic dysfunction and dysrhythmias. Symptoms include dyspnoea, angina, lightheadedness, and syncope. Hypertrophic cardiomyopathy patients with LV outflow tract (LVOT) gradients under resting conditions or with provocation (as with Valsalva manoeuvre or exercise) are classified as having hypertrophic *obstructive* cardiomyopathy (H*O*CM). Obstruction results from a combination of interventricular septal hypertrophy, hyperdynamic LV contraction, and drag and Venturi forces, creating systolic anterior motion (SAM) of the anterior leaflet of the mitral valve (*Figure 1*). Left ventricular outflow tract obstruction at rest is observed in ~25% of the patients with HCM and is an independent predictor of poor prognosis.[1,2] In one report, the majority of patients with HCM had resting or provocable obstruction.[3]

Although symptoms are effectively alleviated in the majority of symptomatic HOCM patients by negative inotropic drugs, namely β-blockers, verapamil, and disopyramide, they are refractory to medical therapy in 5–10% of the patients.[4] Surgical septal myectomy has been performed for half a century, and abolishes the gradient and relieves symptoms in the great majority of patients.[5] Some patients, however, have absolute or relative contraindications to surgery in the form of concomitant medical conditions, advanced age, or previous cardiac surgery.[6,7] In experienced centres, surgical mortality is <2% in young, otherwise healthy patients, but is higher in older patients and in those requiring concomitant surgical procedures, such as coronary artery bypass grafting.[8] In 1994, Sigwart[9] introduced a catheter treatment that uses absolute alcohol to induce a relatively small, targeted myocardial infarction in the septum as an alternative to surgery.

Intracoronary injection of alcohol had been previously employed for therapy of refractory ventricular tachycardia.[10] Injection of ethanol had caused transmural myocardial necrosis in a canine model.[11] This technique was applied to HOCM after the observation, in patients with septal hypertrophy, that the LVOT gradient was transiently reduced during septal artery occlusion by a balloon catheter. The procedure has gone by a variety of names, including non-surgical myocardial reduction, transcoronary ablation of septal hypertrophy, percutaneous transluminal septal myocardial ablation, and alcohol septal ablation (ASA). Although initially confined to

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Europe and North America, this technique is now being performed worldwide.[12] In the absence of randomized controlled trials comparing ASA to medical therapy or septal myectomy, our current view of the procedure is based on registry data, meta-analyses, and personal experience.

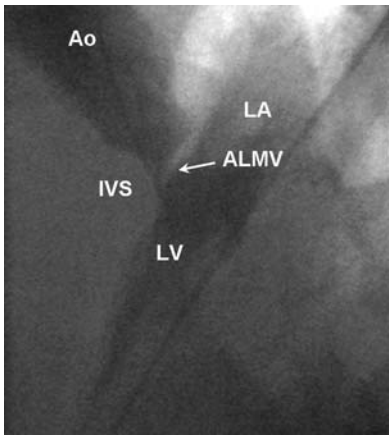

Figure 1 End–systolic frame from a left ventriculogram in left anterior oblique, cranially angulated projection in a patient with hypertrophic obstructive cardiomyopathy. There is systolic anterior motion of the anterior leaflet of the mitral valve (ALMV), which comes into apposition with the interventricular septum (IVS), associated with a left ventricular outflow tract gradient. Ao, aorta; LA, left atrium; LV, left ventricle.

The procedure

β-Blocker therapy should be discontinued and intravenous fluid boluses avoided in order to allow for optimal assessment of the LVOT gradient. Patients receive aspirin and heparin for this intracoronary procedure. Because the proximal septal branches of the left anterior descending (LAD) coronary artery supply the conduction system as well as the basal septum (*Figure 2*), transient (and, in some cases, sustained) atrioventricular (AV) block is a common effect of alcohol injection. All patients without permanent devices therefore receive a temporary right ventricular pacemaker. The use of a flexible screw–in pacemaker electrode may lower the incidence of pericardial tamponade resulting from cardiac perforation.[13]

Although operators at some centres monitor the LVOT gradient with echocardiography only, most prefer to rely on intraprocedural haemodynamic measurements, with either retrograde or (using the transseptal technique) anterograde catheterization of the LV. Studies have shown that the clinical success of ASA in patients with provocable obstruction is comparable to that in patients with obstruction at rest.[14,15] Candidacy of patients for ASA should be determined with exercise rather than pharmacological provocation, since drugs may produce intracavitary gradients of questionable pathophysiological significance. Since exercise is impractical in the midst of the ASA procedure, intraprocedural LVOT gradients are provoked instead by administration of a positive inotropic drug such as isoproterenol or dobutamine or a vasodilator such as nitroglycerin or amyl nitrite, by induction of extrasystoles with

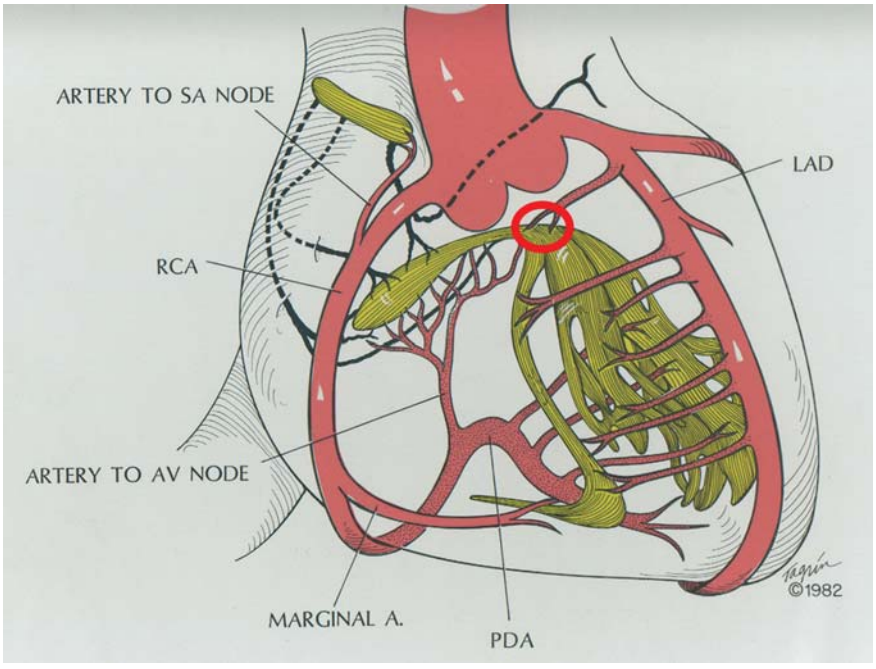

Figure 2 Schematic diagram of blood supply to cardiac conduction system. The first septal branch of the left anterior descending (LAD) coronary artery supplies a critical portion of the interventricular conduction system (red oval). AV, atrioventricular; marginal a., marginal artery; PDA, posterior descending artery; RCA, right coronary artery; SA, sinoatrial. Reproduced, with permission, from Harthorne JW, Pohost. GM, Electrical therapy of cardiac dysrhythmias. In Levine, HJ (ed) *Clinical Cardiovascular Physiology*, New York, Grune and Stratton: 1976. pp. 853–882.

programmed stimulation utilizing the temporary pacemaker, or by the Valsalva manoeuvre.[15]

Standard coronary angioplasty guiding catheters and guide wires are used, along with short, small-diameter over–the–wire angioplasty balloon catheters. Guidance by myocardial contrast echocardiography (MCE; *Figure 3*) has proved to be particularly useful and may influence the interventional strategy in 15–20% of the cases, by either changing the target vessel or prompting that the procedure be aborted. In addition, MCE allows higher success rates despite lower infarct sizes, in turn reducing complication rates.[16,17] Echo contrast or agitated X-ray contrast is injected via the inflated balloon catheter while transthoracic echocardiography is performed. This allows for the determination of whether the opacified myocardium is adjacent to the point at which the anterior leaflet of the mitral valve comes into contact with the septum and at which there is maximal flow acceleration. If the territory perfused by the contrast agent is not optimal, for example, if the right side of the interventricular septum is predominantly opacified, alcohol administration is withheld.[18] This technique also serves to delineate any retrograde leakage of contrast or involvement of the myocardium, such as the ventricular free wall or papillary muscles, remote from the target region.[17,19,20] Alternatively, ASA may be guided by the assessment of reduction in LVOT gradient during transient balloon occlusion of the septal branch.[9,21]

Alcohol is usually injected into the most proximal accessible septal branch of the LAD. Once the septal perforator is deemed suitable, 96% ethanol, 0.5–1.0 mL at a time to a total of 1–3 mL, is injected through the inflated balloon catheter after analgesia is given for control of chest pain. With greater operator experience and the use of MCE, there has been a trend towards using lower dosages of ethanol, without loss of efficacy.[21–23] There is considerable variability in the blood supply to the upper interventricular septum.[24] The target septal branch may occasionally originate from the left main coronary artery, an intermediate or diagonal branch,[17] or the posterior descending coronary artery.[25] The haemodynamic objective is a decrease in the gradient to <10 mmHg at rest in patients with resting gradients (*Figure 4*) or a decrease by >50% of a provocable gradient.[25] In some cases, alcohol is injected into subbranches of the septal artery, whereas, in others, injection into two or even three septal branches is required to reduce the gradient.

Length of stay varies considerably among centres performing ASA. Patients are observed in the cardiac intensive care unit for 24–72 h, with removal of the temporary pacemaker after 24–48 h in the absence of AV block. Patients may then be transferred to a monitored step-down unit for the remainder of the hospital stay.

Treatment efficacy

Septal ablation performed by skilled operators at high–volume centres results in a marked immediate decrease in LVOT gradient in the great majority (usually ≥80%) of patients.[26–31] Pooled results of published studies on ASA show acute reductions in the mean resting LVOT gradient from 65 to 17 mmHg and the mean post-extrasystolic gradient from 125 to 53 mmHg, with persistence of the reduction after 12 months (16 and 32 mmHg, respectively).[32] In addition, there is a significant improvement at 12 months in functional class [New York Heart Association (NYHA) class 2.9 to 1.2, Canadian Cardiovascular Society (CCS) class 1.9 to 0.4], peak oxygen consumption (17.8 to 23.6 mL/kg/min), and exercise capacity (86 to 123 W). At mean 4.6–year follow–up at one centre, there were progressive decreases in resting and provoked LVOT gradients; NYHA class had decreased from 2.8 to 1.2, CCS class had decreased from 2.1 to 1.0, and exercise time had increased from 4.8 to 8.2 min.[33] The benefit of ASA in older patients is similar to that in younger patients.[34,35]

We consider ASA to be successful if there is improvement by a least one NYHA or CCS class accompanied by a sustained reduction in the resting or provoked gradient by ≥50%. Reported predictors of procedural failure are total peak CK < 1300 U/L and immediate residual LVOT gradient ≥25 mmHg.[36] Repeat procedures (ASA or septal myectomy) despite initial success are required because of recurring gradient and symptoms in 9% of the patients.[32] Conversely, ASA has been performed successfully for residual or recurrent gradients and symptoms after septal myectomy.[36] The annual cardiac mortality rate after ASA was 0.7% in a large study.[37]

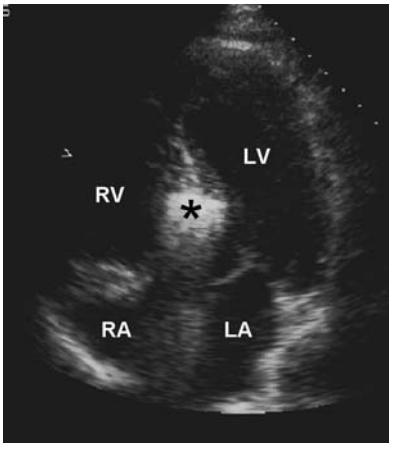

Figure 3 Four-chamber echocardiographic view of area of the upper septum opacified by alcohol injection (asterisk). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

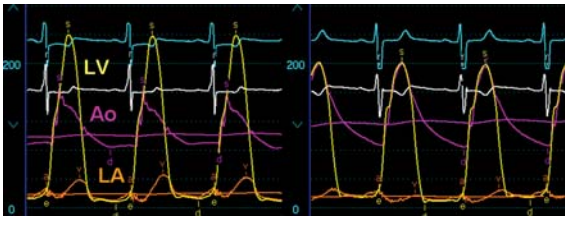

Figure 4 Left ventricular (LV), aortic (Ao), and left atrial (LA) pressures before (left panel) and immediately after (right panel) alcohol septal ablation.

Mechanisms of treatment efficacy

Alcohol septal ablation induces well–demarcated myocardial necrosis surrounding the septal branch.[27] Baggish *et al.*[38] found evidence of necrosis of the vascular endothelium as well (*Figure 5*). The haemodynamic response to the induced reduction in the septal myocardium is often triphasic.[39,40] Immediately after ASA, there is a marked reduction in the LVOT gradient. This initial relief is often followed during the following days by a rise in the LVOT gradient to ~50% of the pre-procedure level, possibly in relation to recovery from stunning or to oedema caused by the infarction. Finally, within the following weeks to months, there is a new decrease in LVOT gradient back to the immediate post-ablation level. Carasso *et al.*[41] have suggested that ASA induces changes in both septal and global myocardial mechanics, both of which contribute to the haemodynamic result. With the acute decrease in LV systolic pressure, there is also immediate improvement in coronary flow reserve.[42]

It is believed that long-term benefit results from the creation of localized septal infarction and scarring, which increase LVOT diameter as a result of septal thinning and 'therapeutic remodelling.'[16,43,44] Serial cardiac magnetic resonance imaging studies demonstrate an increase in area of the outflow tract over months, coinciding with the time course of amelioration of symptoms.[45] There is an increase in LV size, a decrease in LV mass,[44–46] and an alteration in septal activation that results in incoordination of contraction.[47] Regression of hypertrophy in areas remote from the basal septum after ASA indicates that myocardial hypertrophy is not entirely due to a genetic defect, but rather is in part afterload–dependent.[44,48]

After ASA, the degree of mitral regurgitation is lessened,[26,27,49] LV end–diastolic pressure falls,[26,27] and the left atrium is smaller.[26] Furthermore, changes in diastolic function resulting from ASA also seem to contribute to long-term improvement in haemodynamics[50] and exercise tolerance.[49] Improvement in diastolic function may be due to more favourable load–dependent relaxation, as well as a reduction in LV stiffness due to regression of hypertrophy[44,49,51–53] and decrease in interstitial collagen content. There is also normalization of the blood pressure response to exercise.[29] Although studies have demonstrated improvement in these parameters in most patients, there is considerable individual variability in the response to ASA.

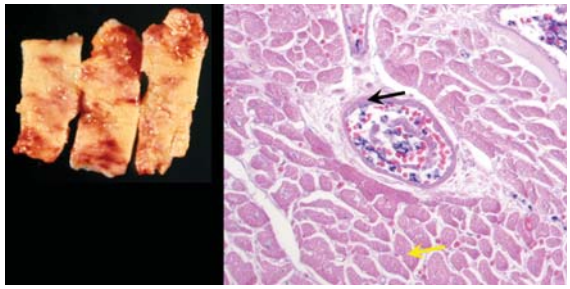

Figure 5 Gross and microscopic specimens of the interventricular septum from a patient who underwent septal myectomy after unsuccessful alcohol septal ablation. The myocardium is yellow, and thus necrotic (left panel). Both myocytes (yellow arrow) and vascular endothelial cells (black arrow) are devoid of nuclei, indicating necrosis (right panel). Adapted from Baggish *et al.*[38] with permission.

Adverse events

Early mortality (occurring ≤30 days after the procedure) is low, with a mean value of 1.5% reported,[32] similar to that for surgical myectomy. Causes of early mortality include LAD dissection, ventricular fibrillation, cardiac tamponade, cardiogenic shock, pulmonary embolism, and bradyarrhythmias in patients without functioning pacemakers. Spontaneous ventricular fibrillation in the immediate periprocedural period is not frequent (2.2%), and sustained ventricular tachycardia is unusual.[32,54] In patients with standard risk factors for sudden cardiac death, we consider the placement of an internal cardioverter–defibrillator (ICD) prior to ASA. The occasional patient with ventricular tachycardia after ASA may also be considered for ICD implantation.

The most frequent complication of ASA is complete AV block requiring permanent pacemaker implantation. The reason for this lies in the anatomical proximity of the septal perforators to the conduction system, in particular the right bundle branch.[55] Acute, self–terminating complete AV block during the procedure occurs in approximately half of the patients.[26,31,56–58] There is recovery of AV conduction, usually before the patient reaches the cardiac intensive care unit, in the great majority of patients.[56,57] Disappearance of procedural complete AV block has been reported as late as 13 days after the procedure.[56] Delayed complete AV block may also develop later in patients without previous procedural complete AV block[59] or as a recurrence after recovery from acute complete AV block. Depending on the definition used, delayed complete AV block occurs in 1–25% of the cases after a mean period of 36 h post-procedure and usually requires permanent pacemaker implantation due to persistence of the conduction defect.[57–59] Lawrenz *et al.*[58] obtained electrophysiological recordings at the end of ASA procedures and found that delayed AV block occurred in patients with impaired retrograde AV conduction. In one study, the use of MCE limited the infarct size and reduced the need for permanent pacemaker implantation from 17 to 7%.[26]

We and others implant a pacemaker if the block persists for >48–72 h. Ultimately, ~10% of the patients require permanent pacemaker implantation after ASA.[32] Predictors of subsequent permanent pacemaker implantation appear to be baseline left bundle branch block (LBBB), baseline first–degree AV block, procedural complete AV block, and post–procedure new first–degree AV block or intraventricular conduction defect.[36,57,58,60] Some authors suggest elective permanent pacemaker implantation prior to ASA in patients with pre–existing LBBB.[31]

Finally, although concern has been raised about creation of an arrhythmogenic substrate by ASA,[61,62] there is currently no evidence that indicates an increase in incidence of ventricular arrhythmias during follow–up, as assessed by analysis of implantable cardioverter-defibrillator intervention rates.[63,64] Similarly, sudden death after ASA occurs uncommonly.[21,65] A meta–analysis

comparing ASA to septal myectomy has shown no difference between the two procedures in the incidence of ventricular tachyarrhythmias.[66]

Comparison to septal myectomy

No randomized controlled trial comparing ASA to surgical myectomy has been performed. Although it would be useful to conduct such a trial in patients whose anatomy is conducive to both procedures,[67] some have calculated that it would be impossible to enrol enough patients to compare the effects of the two procedures on survival.[68] Evidence from non-randomized trials also indicates that ASA is similar to myectomy with respect to haemodynamic and functional improvement (*Table 1*).[69–72] In one of these studies, because patients were assigned to therapy according to the institutional preference, it was possible to match patients for age and LVOT gradient.[69] At 1–year follow–up, severity of symptoms, maximal oxygen consumption, gradient, septal thickness, and degree of mitral regurgitation were similar for the two interventions. Patients with higher mortality rates after ASA reported by Ten Cate *et al.*[73] (*Table 1*) had received higher doses (mean 3.5 mL) of ethanol than are used in the current practice.

Meta-analyses of comparative studies of ASA and septal myectomy have shown no difference in mortality or post–procedure NYHA class between the two procedures.[66,74] A report comparing meta-analyses of 19 ASA and 8 myectomy studies demonstrated lower all-cause mortality and sudden cardiac death rates after ASA after adjustment for baseline characteristics, with no difference in NYHA class.[75] All of these studies showed a higher residual gradient and a higher incidence of permanent pacemaker implantation after ASA. The general consensus is that in centres with appropriate expertise, operative risks, haemodynamic benefits, and initial symptomatic benefits are broadly comparable with either technique.[76]

Patient selection

Patient selection for either form of septal reduction therapy, myectomy or ASA, is based on a careful individual evaluation of symptoms, associated co-morbidities, and echocardiographic and angiographic parameters.[7,25,77] The primary indication for the procedures consists of symptoms that interfere substantially with lifestyle and which are refractory to optimal medical therapy. Most candidates are in NYHA heart failure or CCS angina class III or IV. Selected patients with advanced NYHA or CCS class II symptoms (e.g. those with syncope or severe pre-syncope) may also be considered for the procedures. Candidates have an LVOT gradient of $\geq$30–50 mmHg at rest or $\geq$50–60 mmHg with exercise. Septal wall thickness $<$16 mm is considered a contraindication to either myectomy or ASA because of the concern that the risk of septal perforation with creation of a ventricular septal defect may be higher in the absence of marked hypertrophy.

Patients with septal anatomy unfavourable for delivery of alcohol and those requiring surgery for a co-morbid condition such as intrinsic mitral valve disease are triaged to septal myectomy. Mitral regurgitation caused by SAM is invariably associated with a posteriorly directed jet; if regurgitation is not posteriorly directed, the mitral apparatus should be examined echocardiographically with particular care. Surgery is often preferred in younger patients and in those with severe hypertrophy of the septum (e.g.

Table 1 Studies comparing efficacy and safely of septal ablation and septal myectomy

Authors	Institution	*n*	How triaged	Efficacy	Safety
Nagueh *et al.*[69]	Baylor (ablation), Mayo Clinic (myectomy)	41 ablation, 41 myectomy	Institutional preference	No difference in NYHA class, exercise capacity, or gradient	Death: 2% ablation vs. 0% myectomy; PPM: 22% ablation vs. 2% myectomy
Qin *et al.*[70]	Cleveland Clinic	25 ablation, 26 myectomy	Age, co-morbid conditions, need for concomitant surgery	No difference in NYHA class; >50% gradient reduction in 76% ablation vs. 100% myectomy	No deaths; PPM in 24% ablation vs. 8% myectomy
Firoozi *et al.*[71]	St George's Hospital	20 ablation, 24 myectomy	Age, patient and physician choice	No difference in NYHA class or gradient; exercise capacity better after myectomy	Death: 5% ablation vs. 4% myectomy; PPM: 15% ablation vs. 4% myectomy
Ralph–Edwards *et al.*[72]	Toronto General Hospital	54 ablation, 48 myectomy	Age, patient and physician choice	NYHA I or II in 41% ablation vs. 72% myectomy	Late death in 11% ablation vs. 0% myectomy
Sorajja *et al.*[13]	Mayo Clinic	123 ablation, 123 myectomy	Patient choice, co-morbid conditions	No difference in survival free of severe symptoms	No difference in mortality; PPM: 23% ablation vs. 2% myectomy
Ten Cate *et al.*[73]	Thoraxcenter	91 ablation, 40 myectomy	Patient choice, co-morbid conditions, need for concomitant surgery	Not reported	Higher rate of cardiac death or aborted sudden death after ablation

NYHA, New York Heart Association functional class; PPM, permanent pacemaker. Adapted from Fifer[78] with permission.

Table 2 Indications for alcohol septal ablation

Symptoms that interfere substantially with lifestyle despite optimal medical therapy
Septal thickness ≥16 mm
Left ventricular outflow tract gradient ≥30–50 mmHg at rest or ≥50–60 mmHg with exercise
Adequately sized and accessible septal branch(es) supplying the target myocardial segment
Absence of important intrinsic abnormality of mitral valve and of other conditions for which cardiac surgery is indicated
Absolute or relative contraindication to cardiac surgery or patient preference for septal ablation when both options are reasonable and patient has been fully informed regarding benefits and risk of both procedures

≥30 mm). Alcohol septal ablation is usually selected for elderly patients and those with co-morbid conditions that increase the risk of surgery. For many patients, both procedures are reasonable options; the principle of patient autonomy dictates that these patients should be offered the choice of the two procedures after a frank and thorough discussion of the relative benefits and risks.[78] Selection criteria for ASA are summarized in *Table 2*.

Future directions

Since the original description in 1994, the procedure has undergone several modifications and improvements that have led to optimization of the results and minimization of complications, most importantly the use of MCE and reduction in the dosage of alcohol. Veselka *et al.*[79] have suggested that the use of MCE with low mechanical index will result in less bubble destruction and, as a result, more accurate delineation of the territory supplied by the septal branch. The use of intracardiac echocardiography has been introduced as a means of providing continuous intraprocedural imaging of the treated segment of the septum.[80,81] Facilitation of septal artery cannulation by magnetic navigation has also been reported.[82] Other novelties include the use of polyvinyl alcohol foam particles, microspheres, absorbable gelatin sponges, or septal coils as alternatives to alcohol; these techniques may further reduce the incidence of complete heart block.[83–87] Finally, reduction in septal mass by radiofrequency catheter ablation and cryoablation are under investigation.[88,89]

Conclusion

Although surgical myectomy has set the standard of therapy for drug-resistant HOCM, ASA is an alternative that may be considered for many patients. Data indicate that medium–term functional and haemodynamic success of ASA is high and similar to that of surgery, with the advantage that it may be performed in patients for whom surgery may be considered unsuitable. Longer–term follow–up is needed to permit judgement of the durability of the benefit of ASA. Benefits of ASA in comparison to myectomy include shorter hospital stay, less pain, and avoidance of complications associated with surgery and cardiopulmonary bypass. Nevertheless, ASA has an important learning curve, with potentially serious complications, the most frequent of which is complete AV block requiring permanent pacemaker implantation in ~10% of the patients. Although these rates are declining with continuing experience, the advent of imaging techniques such as MCE, and the use of lower alcohol dosages, the procedure should be performed only by experienced operators and on carefully selected patients. There are no data that indicate that the indication for performing either ASA or septal myectomy should be extended to patients with HOCM and no or mild symptoms.

Conflict of interest: none declared.

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