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Alcohol septal ablation for hypertrophic obstructive cardiomyopathy

BY MICHAEL A. FIFER, MD

Hypertrophic cardiomyopathy (HCM) is a disease characterized by idiopathic hypertrophy of the left (and sometimes right) ventricle. Clinical manifestations include angina (even in the absence of coronary artery disease), heart failure (due in large part to diastolic dysfunction), and arrhythmias. While the disease is often inherited in an autosomal dominant pattern, there is wide variability in the age at which the phenotype becomes apparent.¹ The prevalence of the disorder is estimated to be 0.2%, so that 600,000 Americans are afflicted. There are several anatomic variants of HCM (Table 1). Of these, hypertrophic obstructive cardiomyopathy (HOCM), which is present in approximately ¼ of patients with HCM, is the variant that has been the subject of the most intense investigation. HOCM was previously termed idiopathic hypertrophic subaortic stenosis (IHSS), and is characterized by 4 closely related pathoanatomic features (Figure 1). Obstruction to left ventricular (LV) outflow is caused by bulging of the thickened septum into the left ventricular outflow tract (LVOT) during systole, with apposition of the anterior leaflet of the mitral valve, which moves abnormally in an anterior direction during systole. Mitral regurgitation is usually present, although the degree varies greatly among patients with HOCM.

Treatment of HOCM

Management of HOCM is directed at both symptoms and prognosis. For patients at high risk of sudden death, implantation of a cardioverter-defibrillator (ICD) should be considered.² The first-line of therapy for symptoms consists of medications with negative inotropic properties that diminish the extent of septal bulging into the LVOT; including β -blockers, calcium channel blockers (of which there has been the largest experience with verapamil), and disopyramide. In most patients, symptoms can be adequately controlled with these medications, used alone or in combination.

In patients with symptoms refractory to medical therapy, traditional management has consisted of a septal myectomy.³ In this approach, the surgeon visualizes the thickened septum through an incision in the aortic root and excises a rectangular segment from the basal septum towards the apex. In patients with a septal thickness < 15-18 mm, septal myectomy carries a risk of causing a ventricular septal defect. In these cases, an alternative strategy is resection of the mitral valve (the other structure implicated in obstruction), resulting of course in the requirement for mitral valve replacement. At high-volume surgical centers, surgery brings about a substantial reduction in LVOT gradient in $\geq 90\%$ of patients and amelioration of symptoms for ≥ 5 years in $\geq 70\%$ of patients.¹ Surgical mortality is $\leq 2\%$ in young, otherwise healthy patients, but is higher in elderly patients and in those requiring concomitant surgery such as coronary artery bypass grafting.³

Dual chamber pacing with a short AV delay was introduced as an innovative approach to the management of HOCM. The rationale for this strategy was that preexcitation of the apical portion of the LV before the septum would result in discoordinate contraction, a lower LVOT gradient, and improvement in symptoms. While marked beneficial effects of pacing were reported in uncontrolled series,⁴ these findings have not been reproduced in randomized controlled trials,^{5,6} although there is a suggestion that a small subset of patient benefits from pacing.⁶



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Table 1: Hypertrophic cardiomyopathy: anatomic variants

- Hypertrophic obstructive cardiomyopathy (idiopathic hypertrophic subaortic stenosis)
- Midventricular obstruction
- Apical HCM
- LV free wall hypertrophy
- Concentric LVH

Alcohol septal ablation

Transcatheter ablation of the septum with ethanol was first performed in 1994 at the Royal Brompton Hospital in London and reported by Sigwart in 1995.⁷ Knight et al. reported a series of 18 patients from that institution.⁸ The idea for alcohol septal ablation arose from the observation that balloon occlusion of the first major septal branch of the left anterior descending (LAD) coronary artery caused a reversible decrease in LVOT gradient. Refractory ventricular tachycardia had been successfully treated with intracoronary injection of ethanol.⁹ Investigation in a canine model had demonstrated transmural myocardial necrosis caused by the injection of ethanol.¹⁰ The first patient to undergo septal ablation had severe symptoms despite β -blockade and a resting gradient of only 25 mm Hg that increased markedly during Valsalva maneuver. Peak creatine kinase (CK) was 2500 U/liter. She was discharged 3 days after septal ablation, and was asymptomatic 10 months later. The results were similar for the other 2 patients in the initial report, both of whom had LVOT gradients that were low (< 30 mm Hg) at rest and much higher in response to provocative maneuvers.

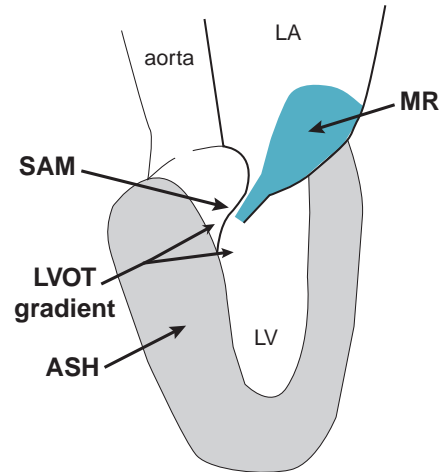
Since then, approximately 2000 alcohol septal ablation procedures have been performed. Cardiologists at two centers in Germany have each performed hundreds of alcohol septal ablation procedures,^{11,12} as has Dr. William H. Spencer III at Baylor College of Medicine in Houston and Medical University of South Carolina in Charleston.¹³

Patient selection

Alcohol septal ablation is appropriate for patients with HOCM who have symptoms that interfere importantly with lifestyle and are refractory to *optimal* medical therapy. While there is some suggestion that prognosis may be related to the presence of a resting LVOT gradient,¹⁴ there are no data to indicate that reducing or abolishing the gradient improves prognosis. We therefore do not offer the procedure to patients, even those with large gradients, if they have no or mild symptoms. Other inclusion criteria are listed in Table 2. HOCM must be differentiated from discrete subaortic stenosis, a rare condition.

The team

The judgment and experience of the septal ablation team are critical to the success of the procedure and the avoidance of complications. Deciding how much ethanol to inject – enough to relieve symptoms, but not so much as to cause complications – is particularly challenging. Other members of the team at the Massachusetts General Hospital (MGH) are interventional cardiologists Igor Palacios, MD and Ik-kyung Jang, MD, echocardiographers Michael Picard, MD and Danita Yoerger, MD, arrhythmia specialist Theofania Mela, MD, and cardiac surgeon Gus Vlahakes, MD.

Figure 1: Pathoanatomy of HOCM, showing asymmetric septal hypertrophy (ASH), systolic anterior motion (SAM) of the anterior leaflet of the mitral valve, left ventricular outflow tract (LVOT) gradient, and mitral regurgitation (MR)

The procedure

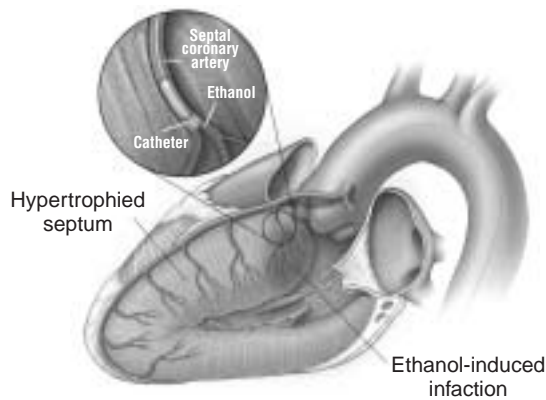
Since the proximal septal branches of the LAD supply the conduction system as well as the basal septum,¹⁵ AV block is a common complication of septal ablation. For this reason, a temporary pacemaker is placed prior to the procedure. If the resting LVOT gradient is < 30 mm Hg, we infuse dobutamine at a dosage of 5-30 $\mu\text{g}/\text{kg}/\text{min}$ to provoke a higher gradient.¹⁶ At other centers, the gradient is measured in postextrasystolic beats.¹⁷

Using standard coronary angioplasty guiding catheters, guidewires, and balloon catheters, the most proximal septal branch that can be catheterized is entered, and the angioplasty balloon inflated (Figure 2). In a minority of cases, septal branches arise from a diagonal or intermediate branch or from the left main coronary artery itself. Because this is an intracoronary interventional procedure, high-level anticoagulation is maintained. Balloon inflation itself often lowers the LVOT gradient, but not in some cases, despite correct catheter placement, probably due to immediate recruitment of collateral blood supply to the septal segment. X-ray contrast is injected through the balloon catheter to confirm filling of the septal branch and absence of backflow into the LAD itself. Correct catheter placement is also confirmed by myocardial contrast echocardiography (see below). Dehydrated ethanol, usually 1 ml at a time, is then injected slowly through the balloon

Table 2: Patient selection criteria for alcohol septal ablation

- Symptoms interfering substantially with lifestyle despite optimal medical therapy
- Septal thickness ≥ 16 mm
- LVOT gradient ≥ 30 mm Hg at rest or ≥ 50 mm Hg with provocation (as with dobutamine)
- Accessible septal branch(es)
- Absence of significant intrinsic abnormality of mitral valve (or papillary muscles) and of other conditions for which cardiac surgery is indicated

Figure 2: Schematic illustration of alcohol septal ablation procedure



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catheter, causing a carefully targeted myocardial infarction. Patients receive narcotics and experience mild to moderate chest pain, usually burning in quality. The gradient can usually be reduced by >50% (Figure 3). In some cases, ethanol is injected selectively into septal subbranches, while in others, it is injected into 2 or 3 septal branches. After delivery of ethanol, distal flow in the affected septal branch is slow or absent (“no reflow” phenomenon, Figure 4).

Failure to deliver ethanol to the septum may result from the presence of very small septal branches or of coronary atherosclerosis. An alternate strategy for septal ablation is the placement of a covered stent to block the septal branch.¹⁸ In our experience with this approach, initial success was reversed 6 months later by recruitment of collateral blood supply from the right coronary artery to the septum.¹⁹

Myocardial contrast echocardiography

Myocardial contrast echocardiography (MCE) has been introduced into the alcohol septal ablation procedure to localize the septal branch supplying the critical septal segment, ie, the point of mitral valve contact and maximal flow acceleration.^{20,21} Myocardial contrast may be achieved with microbubbles, X-ray contrast, or an echocardiographic contrast agent such as Optison[®] (Figure 5). MCE may identify inappropriate sites for injection of ethanol, such as a septal branch supplying myocardium too close to the apex, papillary muscle, inferoposterior LV, or right ventricle.²² Incorporation of this technique reduces the number of septal branches into which ethanol is

Figure 3: Left ventricular and systemic arterial pressure in the first patient treated at MGH before (A) and after (B) alcohol septal ablation, demonstrating abolition of a large LVOT gradient.

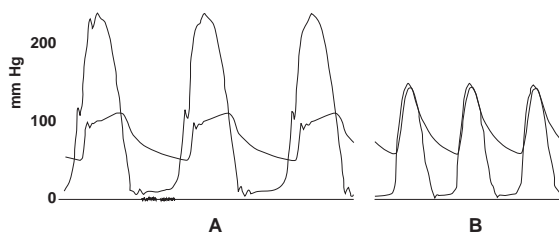
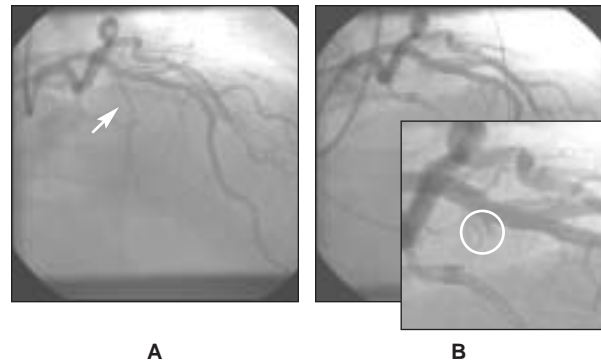


Figure 4: “No reflow” phenomenon. Target septal branch before (A, arrow) and after (B, inset, circle) alcohol septal ablation.



injected and may both improve success rate and lower enzyme release and the need for pacing.^{12,20} Alternatively, ethanol injection has been guided by the acute reduction in LVOT gradient during balloon occlusion of the septal branch.

Postprocedure care

Patients are managed after the procedure (as are patients after spontaneous myocardial infarction) in a monitored setting. At the MGH, we observe patients for ≥ 1 day in intensive care and for the remainder of a minimum 3-day hospital stay in a telemetry unit. Peak creatine kinase often exceeds 1000 U/liter (Figure 6). Conduction defects are common. Temporary pacemakers are routinely left in place for up to 2 days. We restrict activity for 2-4 weeks after discharge. Patients return in 3 months for clinical assessment and a follow-up echocardiogram.

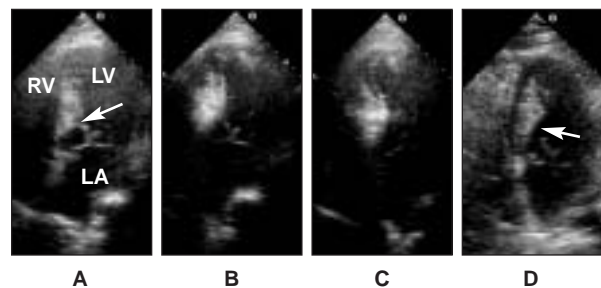
Pathology

Pathologic examination reveals sharply demarcated myocardial necrosis surrounding the septal branch.¹¹ We have found evidence of necrosis of the vascular endothelium as well (Figure 7).

Complications

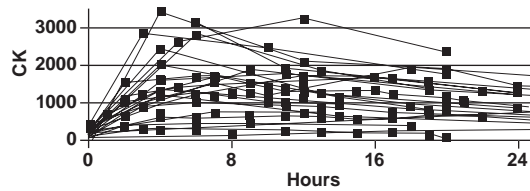
Third degree AV block occurs during the procedure in 60%-70% of patients.^{11,20,23} Following the procedure, right bundle branch block (RBBB) is present in approximately one-

Figure 5: (A) Point of SAM-septal contact (arrow) before alcohol septal ablation. (B) Myocardial contrast echo, delineating territory of instrumented septal branch. (C) Infusion of ethanol into myocardial segment. (D) Septal thinning (arrow) 3 months after ablation.



Courtesy of Danita M. Yoerger, MD.

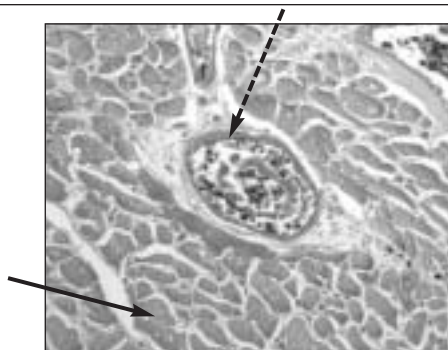
Figure 6: CK curves associated with the first 33 alcohol septal ablation procedures at the MGH



half of patients.^{11,20,23,24} A corollary is that patients with pre-existing left bundle branch block (LBBB) usually require permanent pacing after ablation. Another corollary is that patients who undergo sequential septal ablation and septal myectomy (which frequently causes LBBB) are likely as well to require permanent pacing.²⁵ While the rate of permanent pacemaker placement has varied from 17% to 38%,^{11,20,24,25} one group has reported a reduction in the rate to <10% since the introduction of MCE.^{12,20} In the MGH experience, persistent or recurrent AV block requiring placement of a permanent pacemaker occurs in 40% of patients who have 3rd degree AV block during the procedure (Figure 8) and only rarely in patients who do not have complete heart block during the procedure.²³

In-hospital mortality at high-volume centers is 0%-3%.¹¹⁻¹³ Deaths are due to coronary dissection,¹³ pulmonary embolism,²⁰ and heart block.¹¹ Fatal ventricular fibrillation 9 days after the procedure has been reported.²⁰ The arrhythmia occurred in association with the use of β adrenergic agents for chronic obstructive pulmonary disease. In our experience and that of others,^{8,11} in-hospital sustained ventricular tachyarrhythmias occur in 3%-11% of cases. A theoretical concern of performing alcohol septal ablation – late occurrence of tachyarrhythmias due to superimposition of a myocardial infarction on a cardiomyopathic substrate – has not generally materialized as a problem in clinical practice. At the MGH, 1 patient had rapid VT 6 days after septal ablation (and 3 days after hospital discharge). He had undergone ICD implantation 5 years previously because of clinical features that

Figure 7: Pathology of alcohol septal ablation, showing absence of nuclei, indicating necrosis, in myocytes (solid arrow) and vascular endothelial cells (dotted arrow) from a patient who underwent septal myectomy after unsuccessful alcohol septal ablation.



Courtesy of Rex Neal Smith, MD.

Figure 8: Reappearance of 3rd degree AV block, with temporary pacing, 2 days after septal ablation in a patient who had complete heart block during the procedure



placed him at high risk of sudden death. In patients with such clinical features, we recommend ICD implantation before alcohol septal ablation, or after ablation, but prior to hospital discharge.

Other potential complications of the procedure are infarction of the anterior wall, papillary muscle, or right ventricle due to errant alcohol injection;⁸ ventricular septal rupture;¹² and cardiac tamponade resulting from right ventricular perforation by the temporary pacemaker wire in association with high-level anticoagulation.²⁰

Results

Our MGH team has performed 45 alcohol septal ablations in 43 patients. In a sizable subset of patients, we have noted a triphasic response to alcohol septal ablation, with an immediate reduction in LVOT gradient, followed by the early reappearance of the gradient before hospital discharge and an ultimate fall in the gradient by 3 months after the procedure.²⁶ This sequence suggests that myocardial stunning may be responsible in large part for the immediate reduction in gradient. After recovery from stunning, ultimate gradient reduction is associated with remodeling of the septum with an increase in LVOT area.²⁷ Improvement in symptoms occurs over the same 3-month period. We consider septal ablation to be successful if symptoms improve by ≥ 1 NYHA or CCS class and gradient is reduced by $\geq 50\%$ three months after the procedure. Using these criteria, success is achieved in >80% of patients.^{11,13,20,28} Unsuccessful procedures may be explained by the inability to deliver ethanol to the target tissue, failure of the LVOT gradient to decrease despite ethanol delivery, or failure of symptoms to improve despite lowering of the gradient. Experience from other centers, as well as from the MGH, suggests that if the procedure is effective at 3 months, the results are sustained, or in some cases improved upon, at 3-4 years.

Medium-term effects of alcohol septal ablation are listed in Table 3. In response to the reduction in LVOT gradient, there may be regression of hypertrophy throughout the LV (as after aortic valve replacement for aortic stenosis). It is likely that the concomitant improvement in LV diastolic function contributes significantly to amelioration of symptoms.

Two studies have examined the results of alcohol septal ablation in patients with low (<30 mm Hg) resting LVOT gradients.^{29,30} At one center, ablation was performed

Table 3: Results of alcohol septal ablation**Immediate**

- Chest pain
- Complete heart block in 60%-70% of patients
- Nonsustained VT common, sustained VT/VF uncommon
- LVOT gradient reduction, usually by > 50%
- "No reflow" phenomenon
- Localized upper septal akinesis

Early

- ST elevation in leads V₁₋₂
- Peak CK often > 1000 U/liter
- Conduction defects, most commonly RBBB
- Complete heart block in 10%-30% of patients

Medium-term

- Sustained reduction in NYHA/CCS class^{11-13,28}
- Sustained increase in exercise capacity^{11-13,28}
- Normalization of blood pressure response to exercise²⁸
- Fixed septal perfusion defect³²
- Thinning of septum with increase in LVOT area²⁷
- Sustained and sometimes progressive decrease in LVOT gradient¹¹⁻¹³
- Reduction in degree of mitral regurgitation^{11,20,33}
- Regression of hypertrophy at sites remote from septum^{12,22,34}
- Increase in LV size^{22,34}
- Small decrease in LV ejection fraction^{11,22,34}
- Decrease in LVEDP^{11,20}
- Improvement in LV diastolic function^{33,35,36}
- Reduction in left atrial size^{20,34}
- Reductions in myocyte size, collagen content, and myocardial TNF- α level³⁶

in 29 patients whose gradients were > 60 mm Hg during infusion of dobutamine.²⁹ The great majority of patients experienced reductions in symptoms, provoked gradient, and septal thickness. At the other center, ablation was done if the gradient was \geq 30 mm Hg in a postextrasystolic beat,³⁰ and patients with resting and provoked gradients were compared. Benefits of the procedure, as judged by symptoms, VO₂max, and septal thickness, were similar in the 2 groups of patients. These studies provide retrospective support for Sigwart's performance of septal ablation in his first 3 patients, all of whom had low resting gradients.⁷

Comparing alcohol septal ablation to septal myectomy

Investigators have compared the results of alcohol septal ablation to those of septal myectomy in 2 non-randomized studies.^{25,31} In 1 of these studies, from The Cleveland Clinic (an institution performing relatively large volumes of both procedures), patients were triaged according to clinical factors, so that the groups are not comparable.²⁵ In particular, the 25 patients undergoing septal ablation were older and had a higher prevalence of comorbid conditions than did the 26 patients undergoing myectomy. At 3-month follow-up, gradient reduction was more complete in the surgical cohort, whereas the 2 groups had similar reductions in symptoms, septal thickness, and degree of mitral regurgitation. There were no deaths in either group.

In the other study, from 2 hospitals that each favored 1 of the procedures, patients were triaged according to institutional preference.³¹ In this study, it was possible to match patients for age and LVOT gradient. The first 41 patients with resting LVOT gradient \geq 40 mm Hg undergoing septal ablation at Baylor College of Medicine were matched to patients managed with septal myectomy at Mayo Clinic. At 1 year follow-up, severity of symptoms, VO₂max, gradient, septal thickness, and degree of mitral regurgitation were similar for the 2 therapies. There was 1 death in the series that occurred during septal ablation as a result of coronary dissection (see above).

Conclusions

Longer-term follow-up will allow judgment regarding the durability of the medium-term improvement in symptoms observed in the great majority of patients after septal ablation. Multicenter participation in a randomized comparison of septal ablation and septal myectomy is not likely to materialize. If inclusion criteria for septal ablation are strictly applied (as they should be), few hospitals performing the procedure are likely to maintain a reasonable minimum case volume. Operators performing ablations at a lower rate may have lower success and higher complication rates. Performance of septal ablation should accordingly be confined to regional referral centers. If alcohol septal ablation is performed under this condition, it is likely that it will become the therapy of choice for HOCM patients who remain symptomatic despite optimal medical therapy and have the appropriate anatomic features.

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Michael A. Fifer, MD is the Director of the Coronary Care Unit at Massachusetts General Hospital and Associate Professor of Medicine at Harvard Medical School. He is a graduate of Harvard College and Harvard Medical School. He completed medical internship and residency at Massachusetts General Hospital and cardiology fellowship at Brigham and Women's Hospital. He was a recipient of a Clinician Scientist Award from the American Heart Association. He served in the Writing Group for the American College of Cardiology Expert Consensus Document on Use of Bedside Right Heart Catheterization in Patients with Cardiac Disease. Boston Magazine recently named him a Top Doctor. Dr. Fifer's research interests are centered on the application of invasive hemodynamics to the understanding of the pathophysiology of heart failure, cardiomyopathy, and valvular heart disease.

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