Current state of the roles of alcohol septal ablation and surgical myectomy in the treatment of hypertrophic obstructive cardiomyopathy

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Abstract: Hypertrophic cardiomyopathy is a genetically determined disorder resulting in left ventricular hypertrophy. In a majority of the estimated 20 million people affected worldwide, left ventricular outflow obstruction is present at rest or with provocation. The presence and degree of obstruction influence the symptomatic presentation, treatment strategies and prognosis of affected individuals. Pharmacologic therapy with beta-adrenergic blocking drugs and calcium channel blockers is the principal treatment strategy in symptomatic patients with left ventricular outflow obstruction but is ineffective in many patients. When symptoms of exertional shortness of breath, chest pain and/or syncope prove refractory to medical therapy and there is persisting left ventricular outflow obstruction, or when there is drug intolerance, septal reduction strategies (surgical myectomy and alcohol septal ablation) are quite effective. Selection of the optimal septal reduction strategy for a given patient has become controversial and is determined largely by the medical system providing treatment strategies for the patient. Regretably, there are no randomized trials comparing myectomy and ablation and none are anticipated. The comprehensive Hypertrophic Cardiomyopathy Guideline Statements published in 2011 and 2014 differ significantly with the earlier statement favoring surgical myectomy and the more recent statement giving equal class I status to the two septal reduction strategies in adult patients with drug-refractory symptoms. Recently published studies of long-term follow-up of patients after alcohol septal ablation in Europe, where surgical myectomy is rarely performed, confirm long-term safety and effectiveness with survival free of cardiac events exceeding 96% at 15 years. The lesser degree of discomfort and more rapid recovery associated with the minimally invasive catheter-based alcohol ablation procedure coupled with the recently published long-term safety data favor an increased use of this strategy in symptomatic adult patients with hypertrophic obstructive cardiomyopathy (HOCM).

Keywords: Hypertrophic cardiomyopathy (HCM); myectomy; alcohol septal ablation

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Introduction

Hypertrophic cardiomyopathy (HCM), the most common inherited heart disease, is characterized by the presence of left ventricular hypertrophy without loading conditions or other known causes of hypertrophy. HCM, which is inherited in an autosomal dominant Mendelian pattern, is caused by one of over 2,000 mutations of genes encoding sarcomeric proteins. Based on echocardiographic surveillance, HCM has been estimated to occur in one per 500 individuals in the general population worldwide but a higher prevalence of 1 case per 200 individuals is estimated when all gene positive persons are included (1). Because of the diverse genetic makeup of affected individuals and occurrence of spontaneous mutations, genetic testing is primarily reserved for assessment of gene positivity in family members of probans. Phenotypic expressions of a
given genotype are not predictable. Therefore, clinical manifestations and prognosis of gene (+) family members may vary substantially. It has been estimated that the vast majority of genotype (+)–phenotype (+) persons are asymptomatic or mildly symptomatic and have not been diagnosed with HCM. Dyspnea on exertion is the most common clinical presentation but sudden cardiac death as the first manifestation has been observed. HCM is the most common cause of sudden cardiac death in athletes and pre-participation screening is largely aimed at detecting HCM in young athletes (2). The presence of HCM disqualifies young athletes from participation in intense competitive sports in most environments. Heart failure characterized by the presence of exertional dyspnea and fatigue is the most common clinical complication in adult patients with HCM. In contrast to the patient with conventional congestive heart failure who has impaired ventricular emptying, reduced ejection fraction, volume overload, and peripheral edema, the vast majority of patients with HCM have preserved systolic ventricular function and rarely require acute hospitalization for diuresis. The availability of effective treatments in the HCM patient with heart failure account for the 20-fold lower mortality rate compared to the conventional heart failure patient (0.5% vs. 10% annual mortality) (3). Recognizing the presence of HCM may be difficult due to compensating life style changes to avoid symptoms and non-specific physical findings and electrocardiograms. Left ventricular outflow tract (LVOT) obstruction (LVOT pressure gradient ≥30 mmHg) at rest is present in one-third of individuals with HCM and in an additional one-third LVOT obstruction can be provoked by maneuvers that diminish left ventricular filling and volume (Valsalva maneuver, nitroglycerin, standing) or increase contractility (post-extra-systolic potentiation or exercise). The British pathologist Donald Teare’s landmark description of asymmetric septal hypertrophy ushered in the beginning of our current understanding of this disorder (4). Systematic characterization of the hypertrophic obstructive cardiomyopathy (HOCM) phenotype was first performed by Braunwald et al. (5) over 50 years ago using the newly developed technique of cardiac catheterization. Since that time echocardiographic imaging has been a powerful tool to further understanding of the pathophysiology, variable phenotypes and prognosis of HCM and to monitor therapy. Magnetic resonance imaging (MRI) provides a more detailed morphologic evaluation as well as improved risk stratification by identification of late gadolinium enhancement, a measure of myocardial fibrosis. Dynamic LVOT obstruction results from a combination of factors including narrowing of the LVOT due to septal hypertrophy, abnormal anterior location of the mitral valve apparatus and resultant turbulent flow in systole that drags the longer than normal mitral valve leaflets into the LVOT. The systolic anterior motion (SAM) of the anterior mitral valve leaflet results in SAM-septal contact, mechanical impedance to left ventricular outflow and a posteriorly directed jet of mitral regurgitation. There is a positive correlation between the amount of LVOT obstruction and the severity of mitral regurgitation. In symptomatic patients without a resting LVOT pressure gradient, provocation with Valsalva maneuver, nitroglycerin, or exercise echocardiography should be performed to determine the presence of inducible LVOT obstruction. The presence of LVOT obstruction adversely affects long term outcomes with respect to mortality and is a determinant of treatment strategies.

### Treatment of HOCM

The primary goals in the treatment of HOCM are prevention of sudden cardiac death (Table 1) and relief of symptoms. Strategies for sudden death prevention include life style changes and implantation of cardioverter-defibrillator devices in high risk patients (6-10). In symptomatic patients with HOCM, pharmacologic therapy is the centerpiece of treatment and is aimed at reducing LVOT obstruction, and the attendant mitral regurgitation, elevated left atrial pressure and development of pulmonary hypertension. There is no clear role for pharmacologic therapy in asymptomatic patients and, although drug

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<td><strong>Sudden death prevention</strong></td>
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<td>Changes in lifestyle</td>
</tr>
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<td>Implantable cardioverter—defibrillator in high risk patients</td>
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<td><strong>Relief from symptoms</strong></td>
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<tr>
<td>Changes in lifestyle</td>
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<tr>
<td>Pharmacologic therapy</td>
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<tr>
<td>Septal reduction</td>
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<td>Surgical myectomy</td>
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<td>Alcohol septal ablation</td>
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HOCM, hypertrophic obstructive cardiomyopathy.
therapy aimed at reducing LVOT obstruction can result in symptom relief, there is no evidence that it fundamentally modifies the natural history of HOCM. Tailoring medical therapy in patients with HOCM should include avoidance of medications known to increase dynamic LVOT obstruction such as vasodilators, diuretics and digitalis. Beta-adrenergic blocking agents are the mainstay of drug therapy in HOCM. They reduce LVOT obstruction by negative inotropic properties, prolong diastole and improve left ventricular filling by negative chronotropic affects and blunt the adrenergically mediated tachycardia associated with exercise (6,10). Calcium-channel blockers (verapamil and diltiazem) may be added to or replace beta-blockers. Calcium-channel blockers should be used with caution in patients with severe LVOT obstruction, high pulmonary wedge pressure and/or low systemic blood pressure because of rare worsening of obstruction due to vasodilation. Disopyramide which has negative inotropic properties may be administered alone or with other agents but has significant proarrhythmic and anticholinergic side effects. It is remarkable that a clinical role for newer pharmacologic agents in the treatment of HOCM has not been established in over three decades.

In patients with HOCM whose symptoms and LVOT obstruction prove refractory to optimal medical therapy, more invasive options including dual-chamber pacing and septal reduction have been evaluated. Although, dual-chamber pacing appeared promising in initial use, randomized controlled cross-over trials uncovered a significant placebo effect with improvements in symptoms in a minority of patients. Currently, septal reduction therapy is the treatment of choice in drug-refractory HOCM. Pacing is reserved for drug-refractory patients who are poor candidates for septal reduction (6,10,11).

Surgical septal myectomy, the resection of muscle from the basal septum, was pioneered by Morrow and has proved safe and effective (12) with immediate- and long-term relief of LVOT obstruction and secondary mitral regurgitation. More extensive myectomy as well as surgical approaches to mitral valve and papillary muscle abnormalities have been advocated and have enhanced the benefit of surgical treatment in more complex patients with HOCM (13-16). By eliminating LVOT obstruction, significantly reducing or abolishing mitral regurgitation, and normalizing left ventricular and left atrial pressure, surgical myectomy relieves heart failure symptoms in a high percentage of patients. In patients with concomitant problems such as atrial fibrillation, obstructive coronary or valvular heart disease, surgical solutions to these problems can be undertaken. The risk of in-hospital mortality in centers of excellence has decreased significantly to <1% for isolated myectomy procedures (17,18). However, reports from the US Nationwide Inpatient Database (19,20) have revealed that most centers which performed surgical myectomy had very small numbers of procedures (median 1.0 per year) and that low volume was associated with higher mortality, longer length of stay and higher costs. There was an approximate 4-fold increase in mortality comparing the high- to low-volume tertile but the best mortality results reported by the high-volume tertile were almost 10-fold higher than those of North American HCM centers of excellence. This information strongly supports having a few highly focused specialized HCM centers (21). A recent report from the relatively new Tufts HCM Center of 507 surgical myectomies (mean age 54±14 years) with 0.8% 30-day mortality, long-term survival of 94% at 5 years and 91% at 10 years equaling the age—and gender—matched general US population supports this thesis (22). In 19 patients (3.8%) in the Tufts experience there was failure to respond symptomatically. Massive hypertrophy (septal thickness ≥3.0 cm) was 5-fold more common in non-responders (23). Surgical septal myectomy is an invasive procedure requiring sternotomy and cardiopulmonary bypass and the possibility of a second cardiopulmonary bypass run if needed to correct echocardiographically determined residual mitral regurgitation or LVOT obstruction. The requirement for superb surgical skills available in only in a few centers has resulted in reduced utilization particularly in Europe where alcohol ablation became the dominant septal reduction strategy (24). There are a few strong international myectomy programs in Italy, Israel, Belgium, the Netherlands and China but a need for more septal myectomy surgeons and more septal myectomy centers in Europe has been expressed (24-26). The most recent HCM guideline statement recommends 10 myectomies per operator/year as reasonable experience (10), a goal that can be met by a comparatively few centers particularly in Europe.

Alcohol septal ablation is a minimally invasive catheter-based technique for achieving septal reduction first reported by Sigwart in 1995 (27). Using angiographic and echocardiographic imaging during contrast media injections into septal perforating arteries, the arterial supply of the SAM-septal contact area of the basal septum is identified. Injection of a small amount of alcohol through an inflated balloon catheter leads to an iatrogenic myocardial infarction,
paradoxical septal motion, immediate abolishment of SAM, and reduction of LVOT obstruction (see Figure 1) with further decreases as septal thinning occurs. Long-term benefits include reductions in mitral regurgitation and in left ventricular end-diastolic pressure, reduced left atrial pressure and size, regression of LV hypertrophy and relief of pulmonary hypertension (28-32). Septal ablation leads to improvement in heart failure symptoms.

Figure 1 A 65-year-old female had disabling symptoms of shortness of breath and fatigue attributed to HOCM in spite of maximal tolerated medical therapy. Echocardiogram revealed basal septal thickness of 2.2 cm, a narrow LVOT, SAM-septal contact in systole (A) and LVOT turbulence (B). Invasive evaluation revealed an 80–90 mmHg resting LVOT pressure gradient which increased to 120 mmHg with initiation of a Valsalva maneuver with decrease in systolic blood pressure to 85 mmHg and decrease in pulse pressure (C). A large septal branch was evident (D). This septal artery was entered with a 2.5×6 mm over the wire balloon catheter which was occlusive (E). Injection of agitated contrast media through the inflated balloon catheter caused brightening of the left side of the basal septum on echocardiography without brightening of other cardiac structures. Following injection of 2 cc of alcohol the septal artery was occluded (F). Increased brightening following alcohol injection was confined to the left side of the basal septum and SAM disappeared (G). A small inducible LVOT gradient appeared to be present by echocardiography (H), but catheter measurement revealed no LVOT pressure gradient at rest, with Valsalva maneuver (I), or following administration of 100 micrograms of nitroglycerin intravenously. Troponin—I was 34 ng/mL the following morning. The patient subsequently returned to an active lifestyle with no exercise limitation and no symptoms. This favorable hemodynamic and symptomatic response is common in patients with HOCM, basal septal hypertrophy and LVOT obstruction due to SAM-septal contact.
and exercise capacity measurable by higher peak oxygen consumption. As with surgical myectomy, patients after septal ablation have been shown to have long-term survival similar to age and sex matched members of the general population (29). Alcohol septal ablation has the advantage of being less invasive than surgical myectomy, requires less hospitalization and has a shorter recovery period. The less invasive procedure with earlier return to active life style has resulted in an increase in use of alcohol septal ablation worldwide and a reduction in surgical myectomy (24-26).

The primary limitation of septal ablation is the effect on the conduction system. Right bundle branch block occurs in about 60% of patients making need for permanent pacing very high in patients with left bundle branch block. In patients with normal baseline electrocardiogram, rates for permanent pacing as high as 20% have been reported (29). Among 31 consecutive patients undergoing alcohol septal ablation, Reinhard and colleagues (33) reported that 55% of patients experienced atrioventricular (AV) block during the procedure, with persisting AV block in 23% at 14 hours, 18% at 3 days, 7% at 1 week and only one patient (3%) required a permanent pacemaker. These investigators recommended waiting for ≥7 days of persistent AV block before pacemaker implantation. In contrast surgical myectomy results in left bundle branch block in about 50% of patients.

**Comparison of myectomy and septal ablation**

The older myectomy procedure, first performed in 1958, has been shown to be safe and to convey excellent long-term symptom relief and survival when performed by experienced operators in centers of excellence. Unlike minimally invasive percutaneous coronary angioplasty and trans-catheter aortic valve replacement procedures which were compared to surgery in randomized trials, no randomized trial of ablation and myectomy has been performed and none is expected. Until recently, the comparatively short follow-up and small sample size of ablation-treated patients and the specter of an alcohol induced septal scar in an arrhythmogenic milieu led to concerns regarding increased risk of sudden cardiac death following septal ablation. This is reflected in the 2011 ACCF/AHA Guideline statement (6) where myectomy is the preferred septal reduction strategy (class IIa) with ablation recommended when surgery is contraindicated or high risk (class IIa) or ablation is considered as an alternative to myectomy in a well-informed patient (class IIb). The 2011 Guideline further stated that alcohol ablation should not be done in patients less than 21 years of age (class III) and discouraged in those younger than 40 or with septal thickness ≥30 mm. There were some reports of adverse outcomes (19,20,33-35). The US Nationwide Inpatient Database 2003–2011 surveying over 1,000 hospitals reported that the median number of alcohol ablations was 0.7 per year per institution with slowly increasing rates of ASA. There was a lower incidence of death and acute renal failure in the higher-volume centers (20). The EURO-ASA registry which evaluated acute and long-term data of 1,000 patients treated with alcohol ablation in 10 tertiary centers from 7 European countries confirmed the safety, and durable relief of LVOT obstruction and symptoms in patients with HOCM (36) including younger patients ≤50 years of age (37,38), those with mild class II symptoms (39), and mild septal hypertrophy ≤16 mm (40) and reported that institution experience (41) and the degree of relief of LVOT obstruction (42) are important determinants of long-term outcome. These favorable results confirm and extend the earlier observational studies (28,29) and multicenter registries (43-45) of patients treated with alcohol ablation.

Among 177 patients at the Mayo Clinic treated with alcohol ablation and compared to myectomy-treated patients, 8-year survival was 79%, comparable to surgically treated patients and to the expected survival for matched US general population (29). In a more recent study using 2:1 propensity matching, 344 patients who underwent myectomy were compared to 167 matched patients who underwent septal ablation (46). There were no significant differences in procedural complications, survival or functional status achieved but more ablation patients required permanent pacemaker insertion (17.4% vs. 3.9%, P<0.001) and reintervention. Several meta-analyses have been reported comparing ablation and myectomy (47-49). The largest (50) and most recent included twenty-two ablation cohorts (N=4,213; follow-up =6.6 years) and 23 myectomy cohorts (N=4,240; follow-up =6.8 years). Ablation-treated patients were almost a decade older (54 vs. 45, P<0.001). Septal myectomy was associated with higher periopetural mortality and stroke rate and ablation treated patients had more need for permanent pacing (10% vs. 5%, P<0.001) and repeat septal reduction (11% vs. 1.5%, P<0.001). There was no difference with regard to long-term all-cause mortality, cardiovascular mortality or sudden cardiac death. Leonard and colleagues reported that despite greater septal thickness younger patients (<45 years of age) obtained equally good relief of LVOT obstruction.
and symptom relief with fewer complications (51). In a large single center study of 952 patients who underwent ablation and were followed 6.0±5 years, the mean age was 55.7±15 years (range, 14.9 to 85.1 years). In-hospital mortality occurred in two patients (0.2%) (52). A total of 94% reported improved symptoms and the estimated survival free of cardiac events at 15 years was 96.5%. There were only 4 sudden cardiac deaths among 952 patients during the 6-year follow-up. In a European registry, 26 patients who underwent alcohol ablation had septal thickness ≥30 mm (median, 32 mm) with equal efficiency compared to patients without massive septal hypertrophy. These studies suggest that alcohol septal ablation and myectomy result in similar relief of symptoms and long-term survival in adult patients and that septal ablation may be effective in selected patients with massive hypertrophy. Registries, meta-analyses and the excellent long-term outcomes recently reported in a single center observation (52) provide reassurance that alcohol septal ablation does not increase the risk of late sudden cardiac death. These findings support the 2014 European Guideline Statement granting equipoise between the selection of septal ablation or myectomy in the adult patient with drug-refractory HOCM (10).

**Performance of alcohol septal ablation in 2019**

The goal in the performance of septal ablation is to use echocardiogram guidance to identify the septal artery that supplies the portion of the basal septum that contacts the anterior mitral leaflet during systole and to deliver alcohol (approximately 1 cc per 1 cm septal thickness). In the largest single center experience reported, a target septal branch could not be identified in 62 of 1,014 (6.1%) patients and the procedure was aborted without alcohol injection (52). These operators confined the procedure to injection of a single septal branch, a strategy that resulted in a 39.6% rate of complete heart block during the procedure, a 10.5% permanent pacemaker insertion rate, a reduction in LVOT pressure gradient from 64 to 34 mmHg (P<0.001), and a need for repeat ablation in 17% of patients. This procedural strategy resulted in an excellent 15-year survival free of cardiac events. Many operators attempt to achieve a LVOT pressure gradient ≤20 mmHg, a strategy that frequently requires injection of alcohol in more than one septal branch.

The use of cardiac magnetic resonance (CMR) imaging to study the results of myectomy and alcohol ablation has provided important insights into the different effects of these two techniques (53). CMR showed that myectomy removed muscle tissue (6±4 grams by weight) from the LV aspect of the basal anterior septum whereas the muscle necrosis induced by alcohol was substantially larger (16±7 grams) affecting different locations causing transmural inferior septal necrosis in 75% of patients. In 25% of patients necrosis was confined to the right side of the septum sparing the anterior basal septum with resulting significant residual LVOT obstruction on follow-up. This variability in treatment affect with alcohol ablation is a significant limitation. In treatment of 350 patients with alcohol septal ablation, the author has attempted to avoid this limitation by preferentially selecting septal branches arising from diagonal and ramus intermedius coronary arteries. Septal branches arising from diagonal or ramus intermedius arteries are more likely to supply the left side of the septum, the ablation target.

**Conclusions**

In selected patients with drug-refractory symptoms attributed to HOCM, alcohol septal ablation is a safe and effective treatment strategy. Procedure related mortality is equal or less than with surgical myectomy, morbidity is substantially reduced and long-term symptom relief and survival are similar. Permanent pacing and second ablation procedures are required in a significant minority of patients. A continued growth in the use of this septal reduction technique in high volume HOCM centers of excellence is expected.

**Acknowledgments**

None.

**Footnote**

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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