Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy
A Word of Balance

Paul Sorajja, MD

ABSTRACT

The management of drug-refractory symptoms of obstructive hypertrophic cardiomyopathy has long been debated and is primarily centered on the choice between surgical myectomy and alcohol septal ablation. Decision making in these patients requires consideration of procedural risk, expertise and efficacy, and the long-term impact on patients’ survival. Although there have been numerous reports on these procedures that may help guide decision making, these data continue to be self-reported and voluntary. Greater insight into the real-world experience for these therapies and how they should be applied in practice would be gained from mandatory reporting, akin to other multidisciplinary, transcatheter-based therapies. (J Am Coll Cardiol 2017;70:489–94) © 2017 by the American College of Cardiology Foundation.

Hypertrophic cardiomyopathy (HCM) is an inheritable cardiac disease with a prevalence of 1 in 500 persons, thus leading to millions of persons affected worldwide (1). Although most of these individuals have normal longevity and minimal morbidity, some patients have drug-refractory symptoms of left ventricular outflow tract (LVOT) obstruction. The management of patients with HCM and drug-refractory symptoms has long been debated, with the major focus of these discussions being the comparison of surgical myectomy and alcohol septal ablation.

These debates have fallen largely along 2 lines. On 1 side, surgical myectomy is put forth as the most effective and safe therapy for relief of LVOT obstruction, and alcohol ablation is described as less efficacious and associated with an increased risk of pacemaker dependency, as well as a scar that is potentially proarrhythmic in a vulnerable patient. On the other side of the argument, alcohol ablation is presented as less invasive and thus patient preferred; the favorable outcomes of surgical myectomy are noted to be mainly from experienced centers, and the low number of these centers limits accessibility for those patients who may be myectomy candidates. So, how do we reconcile these differences in opinion when counseling our patients? And what do we need to resolve this debate?

GOALS OF THERAPY

Relief of morbidity and improvement in survival comprise the mantra of modern medical practice, and these therapeutic goals remain at the center of any discussion of the management of our patients with HCM. Certainly, for some patients, the predominant focus is on symptom relief, but this alleviation still must be pursued and achieved while minimizing harm and impairment of longevity.

For any given patient, the risk of the procedural options is a major driver of the therapy chosen because the clinical factors that lead to the risk profile...
cannot be well controlled, but we can effectively alter therapeutic risk by choosing which therapy to pursue. These considerations are widely accepted and in use for the management of disease entities besides HCM when both surgical and nonsurgical therapeutic options are available (e.g., transcatheter aortic valve replacement [TAVR] and mitral valve repair). Similarly, these considerations also serve as talking points when discussing the most appropriate therapy, surgery or alcohol septal ablation, for the management of drug-refractory, obstructive HCM. The procedural risks are contemplated in the context of the potential benefit, in which different degrees of therapeutic effectiveness are tolerated for different degrees of risk. In other words, lower clinical efficacy may be more acceptable when one is trying to avoid a higher procedural risk.

**BASIS FOR CLINICAL PRACTICE**

The benefits and the potential risks of surgery and alcohol septal ablation are the basis for the current practice recommendations, as put forth in multiple societal guidelines (2,3) (Central Illustration).

It is well accepted that surgery, when performed in experienced centers, is associated with a success rate of >90% for relief of LVOT obstruction and has a low operative mortality rate. Studies of surgical myectomy, which may include concomitant mitral valve repair, also have demonstrated long-term survival to be highly favorable and even comparable to normal longevity (4–8). Notably, it is also recognized that outcomes of surgical myectomy performed outside of experienced centers are poor because of the technical expertise required for mastery of the procedure. In an analysis of 6,386 patients who had surgical myectomy at 1,049 U.S. hospitals between 2003 and 2011, the surgical mortality rate was 15.6% for patients in those centers in the lowest tertile of procedural volume, compared with 9.6% for the second tertile and 3.8% for the highest tertile (9). Surgical centers with the highest level of expertise have exceptional outcomes, with operative mortality rates <1%, as described in a report on the collective experience of ~3,700 patients at these institutions (10). Taken together, these data led to the guideline recommendation that the preferred treatment modality for drug-refractory symptoms of obstructive HCM is surgical myectomy performed in an experienced center.

Alcohol septal ablation emerged more than 20 years ago as an alternative to surgical myectomy for the treatment of symptomatic obstructive HCM (11). Alcohol septal ablation has advantages that characteristically accompany catheter-based procedures, such as being relatively less invasive, potentially more widely available, and associated with a short hospital stay. The procedural mortality rate for alcohol septal ablation is reported to be 1% to 2% and is less dependent on operator experience than is surgical myectomy (9). Nonetheless, 3 main issues are frequently noted when concerns are raised regarding the use of alcohol septal ablation for the treatment of obstructive HCM: 1) efficacy of the procedure; 2) potential impact of the iatrogenic myocardial infarction on long-term survival; and 3) performance of the procedure in centers without multidisciplinary expertise in HCM.

For alcohol septal ablation, the clinical effectiveness can be comparable to that of surgical myectomy when there is careful patient selection, 1 or more appropriate septal perforator arteries, and proper technical performance. There is no standard definition of procedural success with alcohol septal ablation, although a definition that reflects the results typically achieved by expertly performed surgical myectomy, as the gold standard of therapy, is reasonable (i.e., residual LVOT gradient at rest <10 mm Hg). With this definition, alcohol septal ablation is successful in ~80% of cases (12). Thus the procedure is effective in most patients, but there also will be a subset of patients with incomplete relief of LVOT obstruction, even when the procedure is performed by operators in a center with a high level of HCM expertise.

Relief of LVOT obstruction in the majority of patients is a noteworthy achievement for alcohol septal ablation, especially for patients who are at high surgical risk or those who cannot have surgical treatment, yet the results should still be considered inferior when there is the option for surgical myectomy. When considering the comparable efficacy of alcohol septal ablation, it is not surprising that there is a higher rate of recurrent symptoms in younger patients, who may tolerate incomplete relief of LVOT poorly (13). Optimization of outcomes with alcohol septal ablation is essential because residual LVOT obstruction after ablation is associated with a higher likelihood of death, not just a higher likelihood of persistent symptoms (13,14). The issue of outcome optimization also is important because there is a learning curve for the procedure, even though alcohol septal ablation shares techniques with conventional percutaneous coronary intervention (15). Pacemaker dependency is well recognized as a potential complication of alcohol septal ablation, although other possible complications (e.g., coronary
Creation of a targeted iatrogenic myocardial infarction is central to the effectiveness of alcohol septal ablation. By using echocardiographic contrast and meticulous techniques for alcohol injection, the size of the myocardial infarction typically is 5% to 10% of the left ventricular mass (16). The injected alcohol is directly cytotoxic and thrombotic, leading to immediate hemodynamic effects, with the potential for further ventricular remodeling that is usually complete within 3 to 6 months (17).

Because of the iatrogenic myocardial infarction, the potential for proarrhythmia has been a concern for alcohol septal ablation since the first description of the procedure (18). The link between the iatrogenic infarction and ventricular arrhythmias in patients who have undergone alcohol septal ablation seems logical, especially because the extent of delayed, gadolinium hyperenhancement on cardiac magnetic resonance imaging is known to be directly related to increased risk of sudden cardiac death in patients with HCM without prior septal ablation (19). In fact, a study by ten Cate et al. (20) reported sudden cardiac death (or ventricular arrhythmia requiring resuscitation or defibrillation) in 18 of 91 treated patients who had been followed up over a median period of 5.4 ± 2.5 years.

Impairment in long-term survival after alcohol septal ablation, however, has not been evident in other analyses. In a study of 177 patients treated with alcohol septal ablation, the 8-year survival rate (median follow-up, 5.7 years) was 79%, and comparable to that of surgical patients, as well as the expected survival for a matched U.S. general population (13). The favorable outcome likely reflects careful patient selection and technical performance and possibly a smaller infarction from a lower dose of alcohol used.

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**CENTRAL ILLUSTRATION**

Clinical Factors for Choice of Surgical Myectomy Versus Alcohol Septal Ablation

<table>
<thead>
<tr>
<th>Surgical myectomy management</th>
<th>Alcohol septal ablation management</th>
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<tbody>
<tr>
<td><strong>Pros:</strong></td>
<td><strong>Pros:</strong></td>
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<tr>
<td>High clinical efficacy</td>
<td>More widely available</td>
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<tr>
<td>High success rate at experienced centers (&gt;90%)</td>
<td>Less invasive; associated with a short hospital stay</td>
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<tr>
<td>Low operative risk in selected patients</td>
<td>Successful in ~80% of cases</td>
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<tr>
<td>Demonstrated long-term survival</td>
<td>Favorable long-term survival in some studies</td>
</tr>
<tr>
<td><strong>Cons:</strong></td>
<td><strong>Cons:</strong></td>
</tr>
<tr>
<td>High surgical mortality at inexperienced centers</td>
<td>Risk of pacemaker dependency</td>
</tr>
<tr>
<td>Risk of potential scar in vulnerable patients</td>
<td>Higher rates of residual/recurrent symptoms and need for possible repeat intervention</td>
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Greater insight into the real-world experience for these therapies and how they should be applied in practice would be gained from mandatory registry participation. Having standardized definitions for procedural success in a registry would help align management goals.

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Factors to consider for patients with drug-refractory symptoms of obstructive hypertrophic cardiomyopathy who are eligible for both surgical myectomy and alcohol septal ablation on the basis of clinical and anatomic features.
(1.8 ± 0.5 ml) compared with the amount used (3.5 ± 1.5 ml for the whole cohort; 4.5 ± 1.2 ml in the first 25 patients treated) by ten Cate et al. (20). Favorable long-term outcomes over a mean follow-up of 7.6 years also were reported by Vriesendorp et al. (21), who found survival rates among 321 patients treated with alcohol septal ablation to be comparable to those in both myectomy-treated patients (n = 253) and patients with nonobstructive HCM (n = 349). The annual incidence of sudden cardiac death for the ablation-treated patients was low at 1.0% per year, although higher than the rate observed with myectomy (0.8% per year) (21,22). Similar, encouraging outcomes also have been reported in other studies, including multicenter registries and meta-analyses comparing alcohol septal ablation and surgery (23,24).

Although these data are supportive, there are still several important considerations. The number of patients with available long-term data remains limited and may or may not be representative of the collective experience with the procedure thus far. As an example, the total number of patients reported worldwide with at least 3-year follow-up, as described by Liebregts et al. (24), is only 2,013, whereas a sampling of alcohol septal ablation procedures performed over an 8-year period in the U.S. alone was 4,862 (9). The appropriate discharge of implantable cardioverter-defibrillators is considered a surrogate of sudden cardiac death, and the description of such events after alcohol septal ablation has been noted to be incomplete. Moreover, when contemplating indications for alcohol septal ablation for young patients, the follow-up duration for these studies is considerably short (i.e., ~3 to 6 years). As a matter of perspective, TAVR is a lifesaving, catheter-based therapy that is widely available for the treatment of aortic stenosis. However, the minimum follow-up duration for TAVR trials in low-risk patients is 10 years (PARTNER 3 [The Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis; NCT02675114]; and Medtronic Transcatheter Aortic Valve Replacement in Low Risk Patients [NCT02701283]).

With or without certainty about the long-term effects of alcohol septal ablation, there remain the known higher rates of pacemaker therapy, residual symptoms, and need for repeat intervention. The outcomes of surgical myectomy are worse following alcohol septal ablation, and this incremental risk needs to be considered when choosing the first therapy for drug-refractory symptoms (25). Lower clinical efficacy and some, however small, degree of uncertainty for long-term survival weigh in the management of all patients with HCM, but especially for young patients, who have the low-risk, durable option of surgical myectomy. In this context, the 2011 American College of Cardiology Foundation/American Heart Association guidelines on HCM set lower age boundaries for the use of alcohol septal ablation with a Class III recommendation for those patients <21 years of age and discouragement of the procedure for patients <40 years of age when myectomy is viable (2). Few further, favorable data on the long-term outcomes of alcohol septal ablation have since been published, and there continues to be hesitancy for expanding the indications to young patients who could otherwise be treated with surgery (26,27).

A PATH FORWARD

Evolution is inherent in the practice of medicine, and the development of catheter-based technology is important because such approaches can help to minimize therapeutic risk, improve patients’ satisfaction, and expedite care. For the broad adoption of novel therapy, the science underpinning the technology must be rigorous. For this development, a surgical reference standard is almost always used, and such a standard has considerable relevance in the practice of HCM. Comparative studies on septal reduction therapy in HCM with long-term survival have emerged over the last several years, but they remain largely limited to single centers or small registries that are subject to selection bias. The practice guidelines reflect the observational nature of these data because the recommendations are predominantly formed on the basis of expert consensus (Level of Evidence: C) and there is no Class I indication for either surgical myectomy or alcohol ablation. These limitations are unfortunate given the known complexities of the diagnosis and management of HCM and my professional experiences and those of many others, who have personally witnessed the significant clinical benefits of these procedures in many patients with HCM. Alcohol septal ablation and surgical myectomy are both highly effective therapies. However, the data limitations continue to foster the ongoing controversy regarding the most appropriate therapy for drug-refractory symptoms of obstructive HCM.

With surgical and catheter-based options available, the field of HCM has lagged behind other cardiovascular specialty areas in terms of outcome surveillance and quality assurance. For example, TAVR, for the treatment of aortic stenosis, and transcatheter repair with MitraClip (Abbott Vascular, Santa Clara, California), for the treatment of mitral regurgitation, both emerged long after alcohol septal ablation became
widely used. For national coverage determinations, the performance of TAVR and MitraClip procedures mandates the use of multidisciplinary teams, participation in a national registry (i.e., The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry), and comprehensive reporting of procedural and 1-year outcomes. With the support of the American College of Cardiology and The Society of Thoracic Surgeons, these requirements have been remarkably embraced by hundreds of institutions and thousands of operators and thereby have facilitated insight into commercial practice patterns, clinical outcomes, health care economics, and areas in need of further study while fostering collaboration across surgical and medical specialties (28,29). National registry participation also exists for multiple other cardiovascular areas, such as percutaneous coronary intervention, implantable cardioverter-defibrillator therapy, and cardiac surgery, but not HCM.

Certainly, there are shortcomings in existing registries. These limitations include the following: reliance on site reporting; incomplete adjudication of data and events; and the economic costs of initiation, data entry, and housing of records. Examination of administrative claims data has been used as an alternative to a national registry. However, such analyses often do not contain patient-level data that are clinically relevant, especially when considering the complex nature of HCM and the elements that are needed (e.g., risk factors for sudden cardiac death, LVOT gradients, definitions for acute procedure success, among others) (30). Ideally, a randomized clinical trial comparing therapies would be most insightful, but the challenging logistics for such an investigation have already been described (31). Mandatory participation in a national registry for payment coverage, with outcome monitoring and public reporting, would encourage optimization of therapy for our patients. Having standardized definitions for procedural success in the registry would help align management goals. Requirements for multidisciplinary collaboration would help to overcome concerns that alcohol septal ablation is being offered to patients without full consideration of the therapeutic options. Opportunities for data entry for novel therapies, such as MitraClip for treatment of HCM, could be performed to understand their emerging role better (32).

The alteration of current practice patterns, which have been established over decades, certainly would have its challenges. However, the precedent for the benefit of such registries has been well established, and the number of patients with HCM who require therapy for drug-refractory symptoms is large. The establishment of a mandatory, national registry for septal reduction therapy would help to promote standards of care, help further define centers of expertise, and facilitate public reporting. These needs are elementary to the shared decision-making process that should be used and would help us move past controversies on the most appropriate management for patients with HCM.

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