

VIEWPOINT

Surgical Myectomy Versus Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy

Will There Ever Be a Randomized Trial?

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Dynamic left ventricular outflow tract obstruction is an important pathophysiologic feature of hypertrophic cardiomyopathy (HCM) and a predictor of clinical deterioration and cardiovascular mortality. Patients with marked obstruction and severe limiting symptoms refractory to maximum medical management are considered candidates for invasive septal reduction therapy, which includes surgical myectomy and alcohol septal ablation (ASA). Availability of both surgical myectomy and ASA has polarized the cardiovascular community concerning the most appropriate implementation of these two interventions. The ensuing controversy of whether myectomy and ASA are truly equivalent options has resulted in calls for a prospective randomized trial. However, upon analysis, such a myectomy versus ASA trial, adequately powered to compare the key issue of long-term outcome, poses a myriad of practical problems that seem virtually insurmountable. Therefore, it is appropriate to revisit this evolving debate at this time, identify the unique obstacles to a randomized study design, and achieve some clarity concerning the most realistic clinical strategies for symptomatic patients with HCM and outflow obstruction. (J Am Coll Cardiol 2007;50:831-4) © 2007 by the American College of Cardiology Foundation

An important and highly visible subgroup of patients with hypertrophic cardiomyopathy (HCM) develop symptoms of progressive heart failure associated with obstruction to left ventricular (LV) outflow (1-4). Since its initial clinical description in the 1960s, surgical septal myectomy has been the primary treatment option for reversing heart failure and restoring acceptable quality of life in obstructive patients with drug-refractory symptoms (1,4-8). However, over the last 5 to 7 years, the percutaneous alternative of alcohol septal ablation (ASA) has been actively promoted for patients with obstructive HCM (1,4,9,10).

The controversy of whether myectomy and ASA are truly equivalent options, in terms of efficacy and outcome, has received considerable attention within the cardiovascular community, frequently resulting in a call for definitive randomized trials (1,11). Therefore, it is appropriate to revisit this important evolving debate, particularly to identify unique obstacles to a randomized study design.

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Background

Mechanism of obstruction and treatment. Left ventricular outflow tract obstruction is present at rest in approximately 25% of HCM patients (4). In addition, >50% of patients without obstruction at rest can generate significant intraventricular gradients with exercise (12). Mechanical impedance to outflow in HCM typically occurs at the subaortic level, owing to mitral valve systolic anterior motion (SAM) and mid-systolic contact with ventricular septum, associated with mitral regurgitation due to incomplete leaflet coaptation (4). In patients in whom LV outflow tract obstruction is associated with heart failure symptoms, conventional pharmacologic treatment with beta-blocking agents, verapamil, or disopyramide might improve functional limitation (4). In those patients with severe limiting symptoms refractory to maximum medical management and marked outflow obstruction (peak instantaneous gradient ≥ 50 mm Hg at rest or with physiologic [exercise] provocation) invasive treatment options to relieve the subaortic gradient should be considered (i.e., myectomy or, selectively, ASA) (4,6-10).

Myectomy. Surgical septal myectomy has been an established treatment in HCM for almost 50 years (4-6). The classical technique involves resection of a discrete portion of hypertrophied muscle from the basal septum, via transaortic

**Abbreviations
and Acronyms**

ASA = alcohol septal ablation
CABG = coronary artery bypass graft surgery
HCM = hypertrophic cardiomyopathy
LV = left ventricular
PTCA = percutaneous transluminal coronary angioplasty
SAM = systolic anterior motion

approach. Some surgeons now prefer an extended muscular resection and might perform additional procedures such as mitral valve repair or plication (6). Over the last 10 years, surgical mortality related to isolated myectomy has approached zero at major North American centers (6-8). Myectomy permanently abolishes or markedly reduces LV outflow gradient (and mitral regurgitation), leading to substantial improvement in symptoms in the vast majority of patients (4-

8). Surgical relief of obstruction confers long-term survival equivalent to that of the general population (7,8) as well as improved quality of life.

ASA. Alcohol septal ablation has experienced rapidly increasing popularity since its recent introduction (4,9,10), largely because it is seemingly less invasive than surgery and more accessible outside HCM referral centers. Penetration of ASA into cardiologic practice has been so striking, compared with surgery, as to raise the possibility that a lowered threshold for selection of patients might be employed (6).

Alcohol septal ablation achieves relief of the subaortic gradient, which is mediated by a chemically induced myocardial infarction (13), leading to reduced septal thickness and outflow tract remodeling (9,10). Accordingly, ASA relieves heart failure-related symptoms in most patients, although approximately 20% might require repeated procedures (9,10,14-17). Procedural mortality for ASA is somewhat higher than for surgery at HCM referral institutions over the last decade (6).

After ASA, clinical observations have unavoidably been confined to approximately 2-year mean follow-up periods, precluding truly long-term outcome assessments (9,10,14-17). Consequently, a number of specific issues remain unresolved, predominantly related to the significance of ASA-intramycardial scars as potentially arrhythmogenic substrates (18-20).

The debate: bypass surgery versus angioplasty revisited?

Availability of both surgical myectomy and ASA has polarized the cardiovascular community regarding the most appropriate implementation of these 2 interventions (1,5,6,11,21). Institutions offering both treatments advocate myectomy as the gold standard for severely symptomatic patients with outflow obstruction and regard ASA as an important alternative for selected patients (1,5,6). Conversely, many interventional cardiologists consider ASA to be the primary treatment option (21). The resulting myectomy versus ASA controversy presently represents a crossroads in the evolving management strategy for obstructive HCM.

It has been repeatedly asserted that this debate can only be resolved with a prospective and randomized study sys-

tematically comparing the 2 techniques (1,11). Indeed, it is tempting to promote a myectomy versus ASA trial, drawing a historical parallel with prior controversy surrounding coronary artery bypass graft surgery (CABG) versus percutaneous transluminal coronary angioplasty (PTCA) (22-24). If randomized trials for the invasive management of atherosclerotic coronary artery disease were possible, then why not translate this experience to HCM? However, close inspection of the data suggests this is not a tenable argument.

Coronary artery disease. To compare long-term results of CABG versus PTCA, 13 randomized clinical trials were conducted, involving approximately 8,000 patients, with a long and challenging enrollment processes (22-24). Eventually, enrolled patients comprised $\leq 12\%$ of those originally screened (24). Such low rates were due largely to patient or physician preferences for either treatment strategy, as evidenced in the BARI (Bypass Angioplasty Revascularization Investigation) and EAST (Emory Angioplasty Versus Surgery Trial) studies (22,23), in which about 60% of eligible patients refused randomization.

HCM. Although HCM is the most common genetic heart disease, it is relatively uncommon within the general population. Given the estimated prevalence of 1:500, the number of HCM patients in the U.S. is approximately 500,000, including many who have not achieved clinical recognition (25). Of these, only a minority have an indication for invasive relief of obstruction (4). Thus, even with a multicenter study design, the number of patients available for pre-randomization screening would be relatively small and only a fraction of that in CABG versus PTCA trials.

Furthermore, owing to the substantial heterogeneity of the HCM disease spectrum, several clinical variables potentially represent exclusion criteria for either myectomy or ASA, constituting an obstacle to randomization. Of these, the most important is age. Most investigators would oppose randomization of children, adolescents, or young adults, given the long risk period ahead and lack of data regarding long-term outcome of ASA (4,6). Also, randomization would not be acceptable in the presence of compelling indications to surgical myectomy (such as correction of mitral valve apparatus abnormalities, CABG, or the MAZE procedure for atrial fibrillation) (6) or to percutaneous ASA (such as particularly advanced age or significant comorbidity) (4).

Is a randomized study feasible? Short-term issues such as acute complication rates, magnitude of gradient reduction, and early symptomatic benefit have been largely resolved for both myectomy and ASA by virtue of available observational data (4,9,10,13-17). Therefore, it would seem unjustified to conduct an expensive and difficult multicenter randomized trial only to confirm what is already known. Indeed, the major unanswered question in this debate concerns the comparison of long-term outcome for the 2 septal reduction therapies (6).

However, a randomized myectomy versus ASA trial, adequately powered to compare outcome as the primary end point, poses a myriad of practical obstacles, which seem

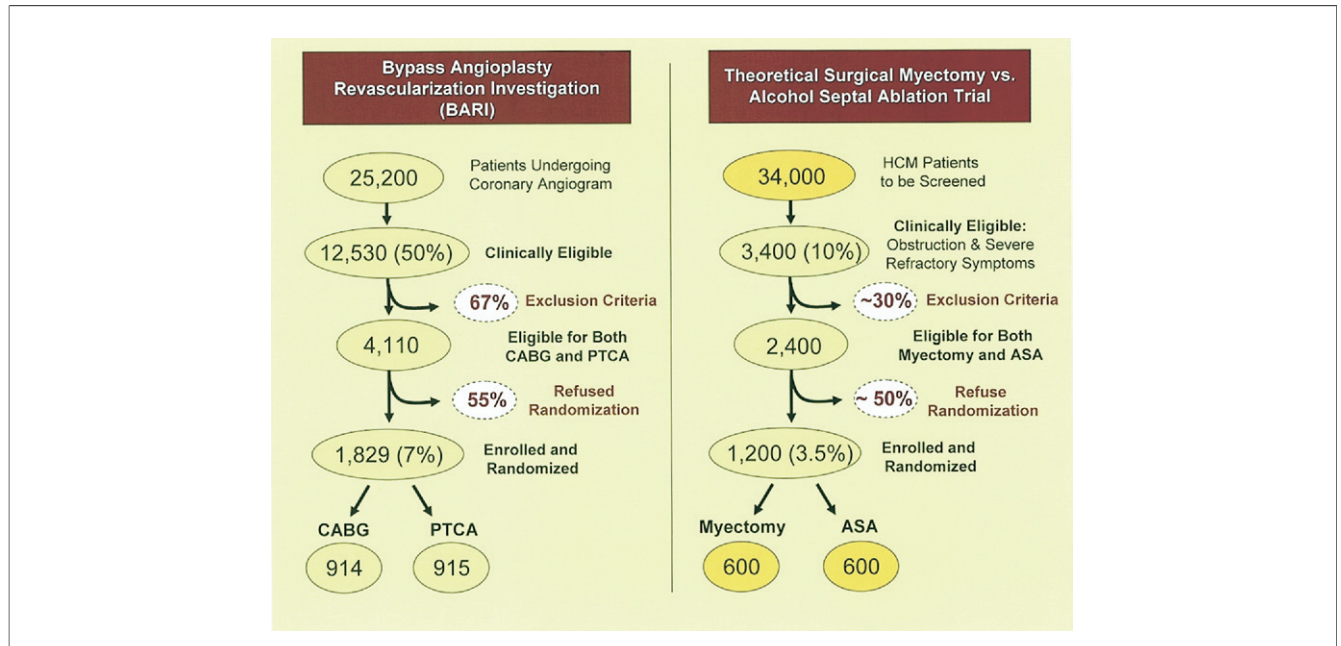


Figure 1 Estimates for a Theoretical Surgical Myectomy Versus ASA Trial

Flow diagrams comparing patient selection and recruitment in the BARI study (coronary artery bypass graft surgery [CABG] vs. percutaneous transluminal coronary angioplasty [PTCA]): a representative example of a coronary artery disease-related randomized trial (23) (**left**) and a hypothetical myectomy versus alcohol septal ablation (ASA) trial (**right**). HCM = hypertrophic cardiomyopathy.

virtually insurmountable. First, given the low event rates after either procedure, very large study cohorts would be required to detect differences in survival (or lack thereof). For example, assuming a 1% annual cardiovascular mortality rate over a 5-year follow-up (including procedural deaths, sudden cardiac or heart failure deaths, and surrogates such as appropriate implantable cardioverter-defibrillator interventions and heart transplantation) (2,7,8), approximately 1,200 patients with obstructive HCM and severe drug-refractory symptoms would be required to detect a doubling of annual mortality (to 2%) with a beta error rate of 10% at the 2-sided alpha level of 0.05, even assuming that none of the patients withdraw from the study or are lost to follow-up (26).

Enrolment of 1,200 suitable candidates (600 in each treatment arm) would require initial screening of as many as 34,000 consecutive patients with HCM (Fig. 1). Of these, $\leq 10\%$ (i.e., 3,400) (27) would initially qualify for invasive septal reduction, by virtue of marked LV outflow obstruction (usually present under resting conditions, but occasionally only with physiologic provocation) associated with severe heart failure (4,12). Of these 3,400 candidates, at least 30% would likely have 1 or more trial exclusion criteria on the basis of the aforementioned considerations for age and/or compelling indications for either myectomy or ASA (4,6). Of the remaining 2,400 patients, 50% would be expected to refuse randomization, on the basis of the prior experience with coronary intervention trials (22-24). There-

fore, the 1,200 patients available for randomization would ultimately represent only 3.5% of those initially screened.

Such an HCM population required for screening (i.e., 34,000) largely exceeds the size of the combined cohorts presently followed at major North American and European referral centers (2,3,8-10,15,16). Nevertheless, smaller sample sizes would fail to reach the desired statistical power, unless the follow-up period could be extended substantially (e.g., to 10 to 20 years)—an unrealistic consideration.

Conclusions and Future Perspectives

An adequately powered randomized trial comparing long-term benefits of myectomy and ASA in severely symptomatic patients with obstructive HCM is not feasible and unlikely to be undertaken at any time. Alternative strategies would include carefully conducted prospective, non-randomized studies assessing the long-term clinical outcome associated with both procedures, with particular regard to the risk of late sudden cardiac death. Such robust long-term observational data could be assembled through a standardized multicenter registry, possibly under the auspices and with the support of the National Heart, Lung, and Blood Institute. Similar successful registries have been created in the past for uncommon conditions, such as primary pulmonary hypertension. Indeed, although randomized study designs represent the indisputable gold standard for comparing competing treatment modalities,

well-conducted prospective observational studies can provide valid insights when randomization is not feasible (28).

Until that time when these issues have achieved greater clarity, it would seem most prudent to acknowledge the recommendations of the American College of Cardiology/European Society of Cardiology expert consensus panel on the management of HCM (4). Under these guidelines, surgical septal myectomy represents the primary treatment option for most severely symptomatic, drug-refractory patients with obstructive HCM. Alcohol septal ablation is an important treatment alternative for patients at increased operative risk, without access to expert surgical centers, or who refuse operation after both options have been discussed equitably (4).

Finally, it is highly desirable for both myectomy and ASA to be performed at referral centers with comprehensive clinical expertise in HCM, where both therapies are available. The choice between myectomy and ASA should be made by patients in concert with their cardiologist, on the basis of consensus guidelines; their individual clinical profile; and a full, unbiased, and evidence-based disclosure of the advantages and disadvantages of each septal reduction treatment.

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