Predictors of Outcome After Alcohol Septal Ablation Therapy in Patients With Hypertrophic Obstructive Cardiomyopathy

Su Min Chang, MD; Nasser M. Lakkis, MD; Jennifer Franklin, RN; William H. Spencer III, MD; Sherif F. Nagueh, MD

Background—Alcohol septal ablation (ASA) therapy results in clinical and hemodynamic improvement in patients with hypertrophic obstructive cardiomyopathy. However, a subset remains symptomatic afterward, requiring additional procedures. We sought to examine the determinants of an unsatisfactory outcome, defined as unchanged symptoms with <50% reduction of baseline left ventricular outflow tract (LVOT) gradient.

Methods and Results—Of 173 consecutive hypertrophic obstructive cardiomyopathy patients who underwent ASA, 39 had an unsatisfactory outcome after the first procedure. Patients with an unsatisfactory outcome had a higher baseline LVOT gradient, fewer septal arteries injected with ethanol, lower peak creatine kinase (CK), smaller septal area opacified by contrast echocardiography, and higher residual gradient in the catheterization laboratory after ASA (all \( P < 0.05 \)). Symptoms, septal thickness, mitral regurgitation severity, and ventricular function were not determinants of outcome. On multiple logistic regression, LVOT gradient reduction after ASA in the catheterization laboratory to \( \geq 25 \) mm Hg (OR, 5.5; \( P = 0.01 \)) and peak CK <1300 U/L (OR, 2.5; \( P = 0.04 \)) were the independent predictors of an unsatisfactory outcome.

Conclusions—The residual LVOT gradient in the catheterization laboratory and peak CK leak after ASA are the independent predictors of ASA outcome. (Circulation. 2004;109:824-827.)

Key Words: ablation ▪ cardiomyopathy ▪ hypertrophy ▪ alcohol

Hypertrophic cardiomyopathy is a common genetic disorder that can lead to significant morbidity and mortality, particularly in patients with dynamic left ventricular outflow tract (LVOT) obstruction (hypertrophic obstructive cardiomyopathy [HOCM]). Patients with HOCM with severe dyspnea or angina despite adequate medical therapy are often referred for septal reduction therapy. Alcohol septal ablation (ASA) with ethanol has been shown in several studies to be an effective procedure in relieving obstruction and improving symptoms. Although ASA successfully relieves the dynamic gradient in most patients, a subgroup remains symptomatic, with significant residual LVOT obstruction requiring additional interventions. It is important to identify the determinants of ASA outcome for better selection of patients and potential modification of treatment plan in individual cases. The purpose of the present study was therefore to examine the clinical, echocardiographic, and procedural determinants of ASA outcome.

Methods

Patient Population

The database of 286 consecutive patients who underwent ASA for the first time at Baylor College of Medicine was reviewed. Patients with a septal thickness >1.6 cm, a septal-to–posterior wall thickness ratio \( \geq 1.3 \), and a rest LVOT gradient \( \geq 30 \) mm Hg were eligible if, despite medical therapy, their New York Heart Association (NYHA) class was \( \geq III \) or Canadian Cardiovascular Society angina class was \( \geq III \) with repeated syncopal episodes. Patients able to exercise underwent treadmill exercise testing with a Bruce protocol at baseline and follow-up. All patients were evaluated by echocardiography before and after ASA. Echocardiographic assessment included septal thickness, ejection fraction (EF), mitral regurgitation (MR) severity by color Doppler, and left ventricular (LV) filling pressures estimated noninvasively.

Patients with severe symptoms despite medical therapy who had systolic anterior motion of the mitral valve and a rest LVOT gradient \( < 30 \) mm Hg were provoked with dobutamine (mean dose, 10±3 \( \mu g/kg \) per min) and were considered candidates for ASA if their provoked gradient was \( \geq 60 \) mm Hg. Given the use of isoproterenol for decades in provoking dynamic LVOT obstruction in patients with HCM, and because most patients without HCM do not develop LVOT obstruction due to systolic anterior motion at a dobutamine dose of 20 \( \mu g/kg \) per min, we used a dobutamine stimulation protocol to provoke LVOT obstruction. Additional evidence supporting our selection of this protocol and the 60-mm Hg gradient cutoff has been confirmed in a follow-up study. Specifically, the improvement (symptoms, exercise duration, and regression of LV hypertrophy) observed in severely symptomatic HOCM patients and a...
dobutamine-induced gradient was similar to that observed in patients who qualified with a gradient at rest.

**Alcohol Septal Ablation**

The Baylor College of Medicine Institutional Review Board approved the study, and informed consent was obtained from the patients. ASA technique has been previously published. On the day of the procedure, an ECG was performed and blood was collected for the assay of creatine kinase (CK) level. A temporary pacemaker was placed in all patients except those who already had a permanent pacemaker. Echocardiographic (2D and Doppler) examination was performed at baseline and during the procedure. A 7F guiding catheter was engaged in the ostium of the left main coronary artery, a 1.5- to 3-mm balloon catheter was advanced over a 0.014-inch wire into the target septal perforator artery. Myocardial contrast echocardiography (MCE) was used through the catheter of patients with successful and unsuccessful outcome after ASA were compared by unpaired Student’s t and χ² tests, respectively. Logistic regression analysis was used for the prediction of outcome. P<0.05 was considered significant.

**Definitions**

Unsatisfactory outcome was defined by advanced dyspnea or angina, no improvement in exercise duration, and <50% reduction of baseline LVOT gradient. A successful outcome was defined as improvement in dyspnea and angina exercise duration and >50% gradient reduction.

**Predictors of Outcome**

Baseline variables considered in the analysis were age, gender, NYHA class, Canadian Cardiovascular Society class, exercise duration, LVOT gradient at rest and with provocation, septal thickness, EF, MR severity, and LV filling pressures. In addition, volume of ethanol injected, method of ethanol administration as bolus or slow injection (over 30 to 60 seconds), number of septal arteries occluded, MCE use, septal area opacified by MCE, pacemaker requirement, and peak CK level were examined.

**Statistical Analysis**

Continuous variables and categorical variables between the 2 groups of patients with successful and unsuccessful outcome after ASA were compared by unpaired Student’s t and χ² tests, respectively. Logistic regression analysis was used for the prediction of outcome. P<0.05 was considered significant.

**Results**

**Patient Population**

Two hundred eight-six patients underwent first-time ASA. Of these, 39 patients had an unsuccessful procedure (mean follow-up, 10.5±5 months) and 134 patients had a successful outcome at ≥1 year after ASA (113 without 1-year follow-up). The 39 patients with an unsatisfactory outcome included 28 patients who underwent repeat ASA, 6 who received surgical myectomy, and 5 who did not agree to additional procedures.

In the 28 patients with repeat ASA, other septal arteries were readily accessed and identified by MCE as supplying the culprit septal segments. Repeat ASA resulted in symptomatic improvement and >50% gradient reduction. In the 6 patients who underwent surgical myectomy, the target septal vessels were either already occluded by previous ASA or not accessible because of technical factors (angulation at take-off or inability to engage with the available balloon).

**Clinical, Echocardiographic, and Procedural Characteristics**

Patients with an unsatisfactory outcome had a higher LVOT gradient, fewer septal arteries injected with ethanol, lower peak CK, and smaller septal area opacified by MCE, and more were female than were male (all P<0.05, Table 1).

Only 1 patient qualified by a provokable gradient (versus 24 in the successful group, P<0.05). The gradient (by Doppler
TABLE 2. Clinical and Echocardiographic Outcome on
Follow-Up After ASA

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=39)</th>
<th>Group II (n=134)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class</td>
<td>2.3±0.7</td>
<td>1.1±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Canadian Cardiovascular</td>
<td>1.7±0.73</td>
<td>1.07±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Society angina class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise duration, s</td>
<td>311.5±202</td>
<td>447±207</td>
<td>0.003</td>
</tr>
<tr>
<td>LVOT gradient, mm Hg</td>
<td>56.5±35.1</td>
<td>8.3±1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF, %</td>
<td>70±7</td>
<td>68±6.5</td>
<td>0.51</td>
</tr>
<tr>
<td>MR grade</td>
<td>2.1±0.7</td>
<td>0.5±0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>LV pre-A pressure, mm Hg</td>
<td>18±4</td>
<td>13±3</td>
<td>0.01</td>
</tr>
<tr>
<td>Residual septal thickness, cm</td>
<td>1.65±0.36</td>
<td>1.35±0.36</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Values are mean±SD.

using the modified Bernoulli equation) reduction in the catheterization laboratory was significantly different between the 2 groups (P<0.01). In addition, both peak CK and the ratio of peak CK to septal thickness were significantly higher in patients with a successful outcome. Other characteristics (Table 1) were similar between the 2 groups.

Outcome at Follow-Up

Patients with an unsatisfactory outcome had higher congestive heart failure class, LV filling pressures, and residual gradient; shorter exercise duration; thicker basal septum; and a more advanced grade of MR after ASA (Table 2). However, the need for a postprocedural permanent pacemaker was not significantly different between the 2 groups (P=0.52). The overall incidence of heart block in this cohort, which included patients from our early experience, was 16%, and its predictors were the number of occluded septal arteries (>2), bolus injection of ethanol, female gender, and left bundle-branch block.

Predictors of ASA Outcome

Septal thickness, EF, MR severity, LV filling pressures, and age were not among the predictors of outcome. On the other hand, female gender (P=0.015), number of septal arteries injected with ethanol (P=0.05), peak CK <1300 (P=0.006), ratio of peak CK to septal thickness <612 U/L per cm, rest gradient >60 mm Hg (P=0.006), septal area opacified by MCE (P<0.05), and gradient reduction in the catheterization laboratory after ASA (P<0.01) were all significant predictors of an unsatisfactory outcome. On multiple logistic regression analysis, LVOT gradient reduction after ASA in the catheterization laboratory to ≥25 mm Hg (OR, 5.5; CI, 2.5 to 20; P=0.01) and peak CK <1300 U/L (OR, 2.5; CI, 1.8 to 10; P=0.04) were the only independent predictors of an unsatisfactory outcome.

Discussion

Previous reports have confirmed the persistent improvement in symptoms, along with LVOT gradient reduction and LV remodeling, in the intermediate-term follow-up of ASA therapy.8,9 In the present study, we present the clinical, echocardiographic, and procedural determinants of ASA outcome.

Although an unsatisfactory response was initially observed in 23% of patients, repeat ASA was effective in improving symptoms and decreasing LVOT obstruction in most of this cohort, with an overall success rate of 94%. Postprocedural pacing was not different between the 2 groups, highlighting the therapeutic effectiveness of ASA alone in producing a satisfactory result. Furthermore, when compared with the group with unsuccessful outcome, ASA resulted in significant improvement in group II without a higher likelihood of advanced atrioventricular block.

Predictors of Outcome

We examined the impact of several baseline variables on the results of ASA. Age, NYHA class, angina class, exercise duration, EF, septal thickness, MR severity, and LV filling pressures did not influence the outcome. Therefore, age, symptomatic status, advanced septal hypertrophy, MR, and diastolic dysfunction should not be considered deterrents for recommending ASA to severely symptomatic HOCM patients with outflow tract obstruction.

Although rest LVOT gradient was higher in patients with unsuccessful outcome, this parameter was not a predictor on multiple regression analysis. The univariate association of rest gradient and outcome is likely attributable to the need for a larger infarct in certain cases with a large culprit septal area to achieve successful results. This line of reasoning is supported by the lack of such an association once infarct size was entered in the multiple regression model.

Unlike baseline factors, several procedural characteristics, particularly infarct size and gradient reduction in the catheterization laboratory, were related to ASA outcome. Interestingly, these 2 variables were the independent predictors of regression of LV hypertrophy at 2 years after ASA.9

Infarct Size

Ethanol-targeted delivery is needed to avoid inducing infarction in areas other than the culprit septal segments and to reduce the rate of complications, including heart block. Nevertheless, the present study supports the importance of not only a critical site but also a critical mass of septal necrosis for an effective ASA, particularly when baseline septal thickness is taken into consideration. This conclusion is supported by consistent observations among several parameters of infarct size, namely peak CK, ratio of peak CK to septal thickness, and septal area opacified by MCE.

Short-Term Results

During ASA, an acute gradient reduction is observed in the catheterization laboratory.2–5 The response varies and is related to septal stunning or infarction and the change in LV ejection dynamics.10 The longer-term reduction in gradient is determined, in addition, by progressive septal thinning and LV remodeling.10 Therefore, it is not necessary to aim for a complete abolition of the gradient immediately after ASA.

Notwithstanding, the present study shows that patients with a residual gradient ≥25 mm Hg in the catheterization laboratory after ASA end up with higher gradients and persistent symptoms at later follow-up. Ethanol injection into other arteries supplying the culprit septal segments is a reasonable
approach in patients with a NYHA class IV, who cannot tolerate a high residual gradient and increased filling pressures (because of diastolic dysfunction and MR). Other patients (NYHA ≤III) should be counseled about the potential need for a repeat procedure.

Limitations
It is difficult to assess and quantify operators’ experience, which can play a major role in ASA success. However, patients who underwent ASA early on (in the first 2 years) were not more likely to have a suboptimal result compared with patients whose procedure was performed later. Although we analyzed data from a large series of consecutive patients, it included only 39 subjects with an unsatisfactory outcome. Future studies are needed to validate our initial observations.

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References

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