Time to Significant Gradient Reduction Following Septal Balloon Occlusion Predicts the Magnitude of Final Gradient Response During Alcohol Septal Ablation in Patients With Hypertrophic Obstructive Cardiomyopathy

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Objectives The purpose of this study was to investigate whether a relationship exists between an acute reduction in resting left ventricular outflow tract (LVOT) gradient with balloon occlusion and the final invasive gradient response following alcohol septal ablation (ASA).

Background ASA is an alternative therapy to myectomy surgery to reduce the basal septal thickness and decrease the resting and/or provocable LVOT gradient in patients with hypertrophic cardiomyopathy. Patients have a variable gradient response to occlusion of the septal perforator artery before ethanol infusion for ASA.

Methods From November 1998 to November 2008, 120 patients (mean age 60 years [range 16 to 87 years], 50% women) with hypertrophic cardiomyopathy underwent ASA at our institution. The resting LVOT gradient (peak systolic left ventricle [LV] pressure – peak systolic aortic pressure) was measured continuously during the ASA procedure. The time to significant LVOT gradient decrease (defined as >50% decrease from baseline) was recorded following balloon occlusion of the dominant septal perforator coronary artery, which was found to perfuse the basal septum based on contrast echocardiographic studies.

Results The mean baseline resting LVOT gradient was 86 ± 43 mm Hg, and it decreased to 17 ± 11 mm Hg following ASA (−80.2%). The mean time to significant gradient reduction was 3.6 ± 2 min (range 25 s to 11 min). The time to significant LVOT gradient reduction strongly correlated with the final magnitude of gradient reduction following ASA (r = −0.81, p < 0.001).

Conclusions This study demonstrates a correlation between the time to significant LVOT gradient reduction following septal perforator balloon occlusion and the magnitude of final gradient response after ASA. (J Am Coll Cardiol Intv 2011;4:1030–4) © 2011 by the American College of Cardiology Foundation
Hypertrophic cardiomyopathy (HCM) is a complex inheritable cardiac disease that affects approximately 1 in 500 individuals in the general population (1–4). A significant proportion of patients with HCM have evidence of the resting and/or provocable obstruction of the left ventricular outflow tract (LVOT), which can result in severely limiting symptoms, including dyspnea, angina, syncope, and sudden death (5–8).

Some patients with significant LVOT gradients are unresponsive to medical therapy and may require surgical myectomy or alcohol septal ablation (ASA) to reduce basal septal thickness and decrease their LVOT obstruction (9,10). At our institution, we offer ASA as an alternative to myectomy therapy in older patients with refractory symptoms who do not have concomitant requirement for other surgical repair (e.g., mitral valve repair or replacement, or coronary artery bypass graft surgery), and for patients who prefer this less invasive approach. Although we determine whether the candidate septal perforator artery perfuses the systolic anterior motion (SAM)–septal contact point through the use of contrast echocardiography during the procedure, we have noted that balloon occlusion of the vessel can result in variable gradient reduction before ethanol infusion.

The purpose of this study was to investigate whether a relationship exists between the rate of acute reduction in resting LVOT gradient with balloon occlusion of the anatomically appropriate septal perforator and the final gradient response following ASA.

**Methods**

From November 1998 to November 2008, 120 patients with HCM underwent ASA at the Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada. The procedure was offered to patients referred to our HCM clinic with refractory symptoms despite being on maximally tolerated medical therapy (beta-blockers, calcium-channel blockers, and disopyramide) who were not candidates for surgical myectomy, due to either comorbidities or patient preference. All patients underwent comprehensive clinical, echocardiographic, and coronary angiographic evaluation at the Peter Munk Cardiac Centre. Coronary angiograms were screened pre–ethanol ablation to ensure that there was at least 1 anatomically appropriate septal perforator vessel of at least 1.5-mm diameter that perfused the proximal interventricular septum.

This study was approved by the University Health Network Research Ethics Board.

**Interventional procedure.** The ethanol ablation procedure took place in our cardiac catheterization laboratory with the assistance of a dedicated HCM echocardiographic team. Just before procedure initiation, resting LVOT gradient and septal thickness measurements were taken in the catheterization laboratory, at which point the patients had been off medical therapy for 24 to 48 h. Resting LVOT gradients were measured using the maximum outflow tract flow velocity using continuous-wave Doppler imaging and calculated using the modified Bernoulli equation.

After administration of conscious sedation, a right internal jugular or right femoral venous sheath was placed for insertion of a temporary pacemaker wire into the right ventricular apex in all patients unless a permanent pacemaker system was already present. The temporary pacemaker was set at 60 beats/min during the procedure and was kept in place for a minimum of 48 h after the procedure. Patients that become pacemaker-dependant at any point following the ablation procedure receive a dual-chamber permanent pacemaker implantation later during the admission. A 7-F femoral arterial sheath was inserted for the guide catheter system, and a 5-F radial sheath was inserted for pigtail catheter placement into the left ventricular cavity. Continuous invasive peak-to-peak gradients were measured across the LVOT by comparing the peak left ventricular and aortic pressures.

Initial angiographic assessment was performed to size the septal perforator and to localize the vessel origin. The targeted septal branch was usually the largest and most proximal septal branch arising from the left anterior descending artery (LAD). An over-the-wire 8-mm balloon with a diameter matching that of the target branch was advanced into the septal branch so that the proximal marker was placed just beyond the vessel ostium. Following balloon inflation, 1 ml of echocardiographic contrast agent either Levovist (Berlex Canada Inc., Lachine, Quebec, Canada) or Definity (Lantheus Medical Imaging Inc., North Billerica, Massachusetts) was injected into the index perforator vessel, while simultaneous echocardiographic assessment took place. The target vessel was considered suitable if there was appropriate contrast echocardiographic opacification of the interventricular septum at the site of the anterior mitral leaflet SAM–septal contact point, and if there was not opacification of other large nonseptal regions, such as the inferior wall or papillary muscles. Further details on the echocardiographic evaluation for ASA were previously published (11,12).

If the target vessel appeared to be perfusing the appropriate septal region, a final check of the adequacy of balloon seal was made by injection of dilute dye through the balloon to confirm the absence of spillage back into LAD. Before

**Abbreviations and Acronyms**

ASA = alcohol septal ablation  
HCM = hypertrophic cardiomyopathy  
LAD = left anterior descending artery  
LVOT = left ventricular outflow tract  
SAM = systolic anterior motion

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ethanol was infused through the over-the-wire balloon, we left the balloon inflated in the septal perforator until the LVOT gradient decreased by 50% from the baseline gradient, or the balloon was left inflated for 11 min without a significant (>50% from baseline) gradient response. Then, 95% Ethanol (0.1 ml per 1 mm of septal thickness, range 1.2 to 2.5 ml) was injected slowly through the over-the-wire balloon over 8 min. The balloon was left inflated for an additional 5 min following ethanol delivery to ensure that there was no spillage back into the LAD following balloon removal. Following balloon deflation and removal, invasive and echocardiographic measurements were made. If an adequate LVOT gradient reduction had not occurred, further interrogation of other suitable perforator vessels was performed, and additional ethanol was injected if appropriate. All patients were monitored in the coronary care unit following the procedure for at least 24 h. Creatine kinase activity was monitored at 8-h intervals over the first 24 h and daily thereafter for 3 days.

Statistical analysis. Data were expressed as mean ± SD or as frequencies (%). The significance of the association between time to significant gradient reduction and final procedural gradient response was tested through the use of the Spearman correlation test. The software used for statistical analysis was SPSS (version 16.0, SPSS Inc., Chicago, Illinois).

Results

Baseline patient characteristics are depicted in Table 1. The study population had a mean age of 60 ± 15 (16 to 87) years, with 50% women. Baseline symptoms in order of frequency included dyspnea (90%), angina (50%), and pre-syncope or syncope (38%). Medical therapy consisted of disopyramide (82%), beta-blockers (71%), a combination of these therapies (55%), and calcium-channel blockers (2%). Coronary artery disease was present in 17.5% of patients.

Echocardiographic and hemodynamic variables are summarized in Table 2. The average amount of ethanol injected during the ablation was 1.8 ± 0.5 ml (range 0.5 to 3.25 ml). Peak post-procedural creatine kinase elevation was 1,106 ± 538 IU/l (range 239 to 3,252 IU/l).

Delivery of ethanol for septal ablation occurred in 109 patients (91%). The 11 remaining patients (9%) did not have ethanol injected for the following reasons: inappropriate anatomical correlation between the septal artery and the SAM-septal contact point by contrast echocardiography (6 patients); technical failure with wiring or balloon advancement (2 patients); left main and LAD coronary dissection (1 patient); and no gradient response with balloon inflation (1 patient).

In patients who received ethanol injection, the mean maximum resting LVOT gradient was 86 ± 43 mm Hg, and it decreased to 17 ± 11 mm Hg following ASA (−80.2%) (Table 2). Data on time to significant LVOT gradient reduction were available for 97 patients (89%). Time required for balloon inflation to result in a significant LVOT gradient decrease ranged from 25 s to 11 min (mean 3.6 ± 2 min). The time to significant decrease in resting LVOT gradient following balloon occlusion was highly correlated with the overall magnitude of final LVOT gradient reduction following ethanol ablation (r = −0.81; p < 0.001) (Fig. 1).

Discussion

ASA is a safe procedure to treat appropriately selected patients with HCM whose symptoms are refractory to optimal medical therapy. In this report, we describe that a novel measurement (the length of time to significant LVOT gradient reduction) following balloon occlusion in patients undergoing ASA predicts final resting invasive LVOT gradient reduction. In this cohort, there exists an inverse relationship between the time to significant gradient reduction and final gradient response.

Sigwart et al. (13) first demonstrated in 1982 that brief occlusion of the septal artery with a balloon catheter causes transient reductions in the outflow pressure gradient. Before contrast echocardiographic techniques were widely used and available, balloon occlusion alone was the standard technique to evaluate the anatomical suitability of the target septal branch (14,15). The procedure has undergone significant technical refinements; the most notable of which is the introduction of myocardial contrast echocardiographic localization of the target area.

<table>
<thead>
<tr>
<th>Table 1. Baseline Patient Characteristics</th>
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<td>Age, yrs</td>
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<tr>
<td>Female</td>
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<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Dyspnea</td>
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<tr>
<td>Angina</td>
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<td>Syncope/pre-syncope</td>
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<td>Medications</td>
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<td>Beta-blocker</td>
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<td>Disopyramide</td>
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Values are mean ± SD or %.

<table>
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<tr>
<th>Table 2. Echocardiographic and Hemodynamic Parameters</th>
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<tr>
<td>Basal septal wall thickness, mm</td>
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<tr>
<td>Left atrial size, mm</td>
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<tr>
<td>Resting echo gradient, mm Hg</td>
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<tr>
<td>LV end-systolic dimension, mm</td>
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<td>LV end-diastolic dimension, mm</td>
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<td>Mean gradient pre-ASA, mm Hg</td>
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<td>Mean gradient post-ASA, mm Hg</td>
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<td>Mean time to significant decrease in resting gradient with balloon inflation, min</td>
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Values are mean ± SD. ASA = alcohol septal ablation; LV = left ventricular.
The use of myocardial contrast echocardiography to evaluate the area at risk is considered a key aspect for the localization of the ablation, which ideally should be centered at the point of contact with the anterior mitral leaflet (16,17). Echocardiographic evaluation of the change in myocardial mechanics and the septal strain after balloon occlusion and ASA was found to have an important role in the understanding of the time course of the gradient reduction (18). Moreover, the reduction in septal strain after ASA can serve as an early determinant for the outcome. Immediate decrease in ventricular septal strain after ablation correlates to the decrease in LVOT gradient long term (19). This suggests that the lower the septal strain, the better the long-term gradient reduction.

In this study, we have further refined this technique by demonstrating that patients who get a rapid gradient response following balloon occlusion are more likely to have a more significant final resting reduction. The fact that gradient reduction happens more rapidly in those patients with a larger post-procedural response may reflect more precise anatomical ablation of the appropriate SAM-septal contact point. Thus, although contrast echo is able to reliably identify patients who are likely to respond, this additional measurement predicted which patients would have the best post-procedural gradient outcomes. Importantly, patients who took a very long time to manifest a gradient reduction did not have a large magnitude of final LVOT gradient response. This raises a question regarding the efficacy of ethanol delivery to patients who have little or no significant responsiveness after a significant amount of time has passed following balloon inflation.

**Study limitations.** Several limitations must be considered in this report. First, this report has the limitations inherent to the analysis of retrospective nonrandomized data. We must also acknowledge the small sample size in this report. Some patients did not have data on time to gradient reduction following balloon inflation, which may have influenced the final results.

**Conclusions**

Through modern techniques, focal ASA is an attractive alternative to myectomy surgery in older patients with significant comorbidities and a favorable coronary anatomy. This study demonstrates a significant correlation between septal perforator balloon occlusion and the magnitude of final gradient response during ASA. Our findings suggest that patients who have a rapid gradient reduction during balloon occlusion are more likely to have a larger final gradient response following ethanol ablation.

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**REFERENCES**


Key Words: alcohol septal ablation ■ hypertrophic cardiomyopathy ■ invasive management.