Myocardial Mechanics Explains the Time Course of Benefit for Septal Ethanol Ablation for Hypertrophic Cardiomyopathy

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We hypothesized that the time course of left ventricular (LV) outflow tract gradient reduction during septal ethanol ablation for patients with symptomatic hypertrophic obstructive cardiomyopathy is related to changes in myocardial mechanics. A total of 21 patients with hypertrophic obstructive cardiomyopathy undergoing septal ethanol ablation were analyzed. LV outflow tract gradient decreased with septal balloon occlusion, further decreased postethanol injection, and partially rebounded at discharge (5-6 days postprocedure). During balloon occlusion longitudinal and circumferential strain significantly decreased in all analyzed segments, significantly improved with alcohol injection only at sites distant to infarction, and normalized at all segments except infarcted ones at discharge. LV twist significantly improved with ethanol injection and remained high at discharge. Myocardial mechanics suggest that the decrease in LV outflow tract gradient during septal ethanol ablation coincides with global LV dysfunction despite only local ischemia during septal balloon occlusion. Global dysfunction is transient and the gradient rebounds when dysfunction is limited to the basal septum.

Hypertrophic obstructive cardiomyopathy (HOCM) may cause disabling symptoms and is associated with a worsened prognosis.[1] Invasive interventions are usually considered when pharmacotherapy either fails to control symptoms or is not tolerated.[2] These invasive options include dual-chamber permanent pacing, surgical myectomy, and septal ethanol ablation (SEA). SEA was introduced as an alternative to surgical myectomy in the 1990s.[3,4] The objective of SEA is to produce a localized infarction of the hypertrophied portion of the interventricular septum. This is achieved by cannulating and injecting ethanol into the proximal septal branch of the left anterior descending coronary artery that supplies the hypertrophied septum in order to cause occlusion of the vessel. Targeted infarction of the proximal septum leads to an acute decrease in the degree of systolic anterior motion, decreased anterior mitral leaflet-septal contact, and an acute reduction in left ventricular (LV) outflow tract (LVOT) obstruction.[5] As the pathogenesis of dynamic LVOT obstruction is complex, the mechanism of relief of the gradient with SEA is also complex and differs in the acute and chronic periods after ethanol injection.[5-9] Immediate basal septal dysfunction (hypokinesis or akinesis) has been described.[5,7] There is an early partial reappearance of the gradient that is almost always temporary,[5-8] with gradual reduction in the LVOT gradient over the succeeding weeks to 1 to 2 years after the procedure.[5] The clinical and functional improvement of patients usually mirrors the hemodynamic changes with the vast majority of patients continuing to improve through the first year and beyond.[5] This long-term benefit is thought to be the result of widening of the LVOT as a consequence of infarction, myocardial necrosis, and replacement fibrosis, which is apparent at 6 to 12 weeks with further widening developing at later follow-up.

To better understand the origin of the temporal changes in LVOT obstruction during and early after SEA, we analyzed regional and global LV mechanics using a novel 2-dimensional echocardiographic strain imaging modality in patients with HOCM undergoing SEA.

METHODS

Study Cohort

We studied consecutive patients with HOCM who underwent SEA at the Toronto General Hospital (Toronto, Ontario, Canada) from January 2004 to December 2006. The diagnosis of HOCM was based on the typical echocardiographic findings of septal hypertrophy ($\geq$15 mm) in the absence of any other cause that could account for the degree of hypertrophy detected.[4] To be eligible for SEA, patients had to have HOCM with unacceptable symptoms refractory to medications, an LVOT gradient of greater than or equal to 50 mm Hg at rest or after provocative maneuvers (inhalation of amyl nitrate or after a ventricular premature beat) as measured during echocardiographic Doppler examination or at cardiac catheterization, and a suitable septal perforator branch demonstrated by coronary angiography.[5] Patients were selected for SEA rather than surgical septal myectomy based on age, comorbidities, and patient preference in light of the documented effectiveness of this procedure.[3,5,6,9] In addition, to be included in this study, patients needed to have echocardiographic images obtained at the following time intervals: (1) baseline, (2) 5 minutes after balloon occlusion of the septal perforator branch, (3) after the injection of ethanol, and (4) 5 to 6

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days after the SEA procedure. Patients with poor quality 2-dimensional echocardiographic images that could not be adequately analyzed were excluded from this study.

Our control group consisted of 24 healthy age- and sex-matched participants. These individuals had no family history of hypertrophic cardiomyopathy (HCM) and they had normal clinical and echocardiographic examination results.

Interventional Procedure

Patients were admitted before the procedure and cardiac medications were withheld 24 to 48 hours before SEA. The procedure, as performed at our institution, has been described previously.[5] After target vessel selection, its suitability was assessed using myocardial contrast echocardiography with the intra-arterial injection of the echocontrast agent, Definity (Bristol-Meyers Squibb Medical Imaging, New York, NY), through the lumen of the target vessel and transthoracic echocardiographic imaging.[7,10-12] This was followed by slow 1- to 3-mL injection of ethanol. Hemodynamic and echocardiographic studies were performed to evaluate early effects.

Echocardiographic Studies

Baseline transthoracic echocardiographic images were obtained from the patients with HOCM on admission and from the control subjects. Two-dimensional echocardiographic Doppler and Doppler tissue imaging parameters were measured, as previously described,[13-16] by a cardiologist blinded to patients' clinical findings. Ejection fraction was estimated using the modified Simpson's rule from orthogonal long-axis views.[13] The mean left atrial pressure was estimated using the following formula: left atrial pressure = $(1.24 \times E/Ea) + 1.9$, where E is the early diastolic mitral inflow velocity and Ea is the early diastolic lateral wall annular velocity.[16]

Evaluation of Strain, Strain Rate, and Rotation

Echocardiographic studies for the evaluation of strain, strain rate, and rotation were performed on the control subjects. Serial echocardiographic studies were performed at the following time intervals on the patients with HOCM undergoing SEA: (1) baseline (preprocedural), (2) 5 minutes after balloon occlusion of the septal perforator, (3) after the injection of ethanol, and (4) 5 to 6 days after the SEA procedure (before hospital discharge). Circumferential strain and strain rate, as well as radial and rotation velocities and angles were measured at 3 parasternal short-axis planes (base, mid, and apex) in the septal and lateral walls. Longitudinal septal and lateral wall strains and strain rates were measured from the apical 4-chamber view, at the base, mid, and apex. The measurements were performed offline using velocity vector imaging (VVI) software (Siemens Medical Systems, Mountain View, Calif) from archived studies.[17] VVI quantifies myocardial motion from B-mode clips by automatically tracking user-defined points to define the inward and outward motion of the myocardial subendocardial regions using an advanced speckle-tracking program. Strain was defined as the instantaneous local trace lengthening or shortening, and strain rate was defined as the rate of lengthening/shortening.[16,18,19] In the long-axis images the software calculates longitudinal velocity, strain, and strain rate. In the short-axis images the software calculates circumferential strain and strain rate, as well as radial and rotational velocities and angles relative to the ventricular centroid (center of LV cavity) on each frame for the index short-axis image. Positive radial strain (thickening) is not calculated by VVI.

Myocardial contrast echocardiography identified the basal inferoseptal and basal anteroseptal segments as the infarct site. We analyzed myocardial mechanics in relation to distance from the infarct site. LV wall segments were categorized into 3 types: (1) infarct site, (2) LV segments near the infarct site (near segments), and (3) LV segments distant from the infarct site (distant segments). Segments that were adjacent to and in direct contact with the infarct site were labeled as near segments (6 LV wall segments). Distant segments were defined as segments without direct contact with the infarct site (10 LV wall segments).

Rotation and Twist Calculations

Averaged short-axis myocardial rotation angles were used to calculate LV twist. Instantaneous apical rotation angles were subtracted from basal rotation angles to generate twist-time curves. Peak twist was defined as the maximum of the twist curve.

Interobserver and Intraobserver Variability and Validation

Two-dimensional strain evaluations were performed offline by a single observer (S. C.). Ten randomly selected studies were reanalyzed by the same observer and another observer (H. Y.) for the assessment of interobserver and intraobserver variability. Interobserver and intraobserver variability was assessed by the correlation coefficient of observations and the 2SD of their mean percent difference.

Statistical Analysis

Summary statistics are presented as the mean ± SD (where appropriate). Continuous data were compared using the Wilcoxon rank sum test. Strain and twist measurements at the different stages of SEA were compared using repeated measures analysis of variance with Tukey's post hoc test. The relationship between local and global longitudinal strain with the LVOT gradient was assessed using Pearson's correlation coefficient. Finally, the relationship between infarct site strain and the LVOT gradient was assessed using curve-fitting quadratic regression analysis. All the analyses were done with software (SPSS, Version 12.0, SPSS Inc., Chicago, IL). Statistical significance was defined by a P value of less than .05.

Ethics

This study was approved by our research ethics board.

RESULTS

Preprocedural Clinical and Echocardiographic Characteristics

SEA was performed in 32 patients between January 2004 and December 2006. Our study cohort consisted of 21 patients who had complete preprocedure, intraprocedure, and postprocedure echocardiographic studies analyzable with VVI. The 11 excluded patients were similar in age, sex, New York Heart Association (NYHA) clinical status, degree of septal hypertrophy, and LVOT obstruction. The control group consisted of 24 participants (12 women) with a mean age of 55 ± 12 years ($P > .1$ compared with the patients with HOCM). Table 1 summarizes the clinical characteristics of these patients.

Dyspnea and chest pain were the most common preprocedure symptoms, with most patients having NYHA class III symptoms. However, three of the patients were young (<45 years), had milder symptoms (NYHA class II) under full drug therapy whose quality of life was unsatisfactory. The majority of patients were treated by a combination of beta-blockers and/or disopyramide. Baseline 2-dimensional echocardiographic Doppler studies (Table 2) demonstrated asymmetric septal hypertrophy, varying levels of LVOT obstruction, and normal LV systolic function. Diastolic filling parameters showed a relatively decreased ratio of the mitral inflow early diastolic