Regression of Left Ventricular Hypertrophy After Nonsurgical Septal Reduction Therapy for Hypertrophic Obstructive Cardiomyopathy

Wojciech Mazur, MD; Sherif F. Nagueh, MD; Nasser M. Lakkis, MD; Katherine J. Middleton, RCT; Donna Killip, RN; Robert Roberts, MD; William H. Spencer III, MD

Background—Hypertrophic obstructive cardiomyopathy (HOCM) is characterized by left ventricular hypertrophy (LVH) in the absence of increased external load. Recently, nonsurgical septal reduction therapy (NSRT) with intracoronary ethanol has been introduced to treat severely symptomatic patients with outflow tract obstruction. Its long-term effects on LV mass, however, are unknown.

Methods and Results—The LV size, function, and outflow tract gradient of 26 HOCM patients (53±15 years old) who underwent NSRT were assessed by echocardiography at baseline and 1 and 2 years after the procedure. LVH was evaluated by wall thickness of individual myocardial segments, planimetric myocardial area, and mass. The outflow gradient decreased from 36±6 mm Hg before NSRT to 0±3 mm Hg at 2 years (P<0.001), with patients experiencing symptomatic improvement (P<0.05). LV end-diastolic and end-systolic dimensions increased significantly at both 1 and 2 years (P<0.001). All parameters of LVH showed evidence of regression. LV mass decreased (301±78 g at baseline, 223±5 g at 1 year, and 190±58 g at 2 years; P<0.01), with the 2-year reduction in mass related to infarct size and the acute reduction in outflow tract gradient (r=0.48, P<0.05 and r=0.63, P<0.01, respectively).

Conclusions—NSRT results in LV remodeling that is characterized by an increase in LV size and a decrease in the extent of LVH. (Circulation. 2001;103:1492-1496.)

Key Words: hypertrophy ▪ cardiomyopathy ▪ remodeling

Hypertrophic obstructive cardiomyopathy (HOCM) is a genetic disorder associated with significant morbidity and mortality, including heart failure and sudden death.1,2 Risk factors for sudden death include the presence of certain genetic mutations and the extent of left ventricular hypertrophy (LVH).3,4 Symptomatic patients with outflow tract (OT) obstruction are usually medically treated; in the few patients with persistent symptoms, surgical myectomy offers satisfactory control.5,6 Recently, nonsurgical septal reduction therapy (NSRT) has gained popularity as an alternative to surgery.7–10 Clinical evaluation from several centers suggests that NSRT is a safe and effective procedure for the relief of symptoms and OT obstruction. Given the strong association between LVH and sudden death, we thought that a complete data set regarding the long-term effects of NSRT on LVH would be particularly important and consequently evaluated the extent of LVH at 1 and 2 years after NSRT.

Methods

Patient Population

The Baylor College of Medicine Institutional Review Board approved the study protocol, and all patients provided written informed consent before participation. The first 26 consecutive patients with symptomatic HOCM and documented LVOT obstruction gradient (≥40 mm Hg at rest or ≥60 mm Hg on dobutamine provocation: mean dose 15±3 μg·kg⁻¹·min⁻¹) who underwent NSRT, as previously described,10 and completed a 2-year follow-up composed the study cohort. The group had a mean age of 53±15 years (9 of 26 women). All patients had a septal wall thickness ≥1.5 cm with a ≥1.3 ratio of septum to posterior wall thickness. All had dyspnea, 17 had angina, and 12 suffered from presyncope/syncope.

Patients completed an NYHA classification questionnaire as well as a Bruce protocol stress test at baseline and 1 and 2 years after the NSRT procedure. Creatine kinase (CK) levels were determined before and every 6 hours during the 24-hour period after NSRT.

Echocardiographic Studies

Echocardiograms were performed with an HP or Acuson ultrasound imaging system equipped with 2.5-, 3.5-, and 5-MHz transducers. Standard parasternal and apical views were obtained. Short-axis tomograms were acquired at 3 levels: mitral valve, papillary muscle, and apex.

Color-guided continuous-wave Doppler was applied in the apical views to determine the peak LVOT gradient, with care taken to avoid contamination with the mitral regurgitation jet.11 Studies were stored for later analysis.

Received December 31, 2000; revision received January 18, 2001; accepted January 18, 2001.
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Echocardiographic Analysis

Using a computerized reading station offline, a single observer blinded to the patients’ identity, clinical data, and study sequence performed all measurements at baseline and 1 and 2 years after NSRT.

LVH and major dimensions at end diastole and end systole, wall thickness, end-diastolic volume (EDV), and ejection fraction (EF) were measured according to American Society of Echocardiography recommendations. Left atrial volume was derived with the multiple-disks method.

LVH was assessed according to previously published criteria. First, the wall thickness of each of the following myocardial segments was measured at both the mitral valve and the papillary muscle levels in the short-axis view: anterior septum, anterior septum basal segment that does not extend to the papillary muscle level, second, end-diastolic myocardial areas at the mitral valve and papillary muscle levels were significantly smaller than at baseline (6.1% (by SPECT), 6% developed an anterior septal scar of 6 mm at 2 years). Changes in LV Size and EF

Although the long-axis dimension was unchanged, LV end-diastolic dimensions (anteroposterior and mediolateral) increased significantly after NSRT (Table 1). Likewise, the minor-axis end-systolic dimensions increased (P<0.01), leading to significant increases in EDV (Figure 1A) and end-systolic volumes (P<0.01). LVEF was relatively unchanged; however, EF at year 2 was statistically lower (P<0.05).

Regression of LVH

Septal thickness at the infarction site decreased from 20 mm before to 12 mm at 1 year (P<0.01) and 10 mm at 2 years (P<0.01 versus baseline, P>0.05 versus 1 year), and all parameters of LVH showed evidence of regression. The anterior septum thickness (distal to infarction site), inferolateral wall, inferior septum, and anterolateral wall at both the mitral valve and papillary muscle levels were significantly less both 1 and 2 years after NSRT (Table 2). A number of segments became significantly thinner, and the total wall thickness score was calculated at both levels. The end-diastolic myocardial area at the mitral valve and papillary muscle levels was used to derive mass.

Because NSRT results in an infarction limited to the anterior septum basal segment that does not extend to the papillary muscle level, this approach would tend to underestimate the overall extent of regression in LVH. A good correlation was present between total thickness score, percent segmental wall thickness, end-diastolic volume (EDV), and ejection fraction (EF) were measured according to American Society of Echocardiography recommendations. Left atrial volume was derived with the multiple-disks method.

Reproducibility

For intraobserver variability (12 patients analyzed), the 95% interval of agreement was −5% to 7% for segmental wall thickness, −8% to 10% for total thickness score, −11% to 14% for myocardial area, and −12% to 14% for mass.

SPECT Myocardial Scintigraphy

Stress single photon emission CT (SPECT) imaging 6 weeks after NSRT was used to determine infarct size and was performed by previously reported methods, with images reconstructed and reoriented in standard views. Experienced nuclear cardiologists, blinded to all other data and using raw polar maps statistically compared with a corresponding normal data bank, determined the SPECT defect size.

Statistics

Repeated measures of ANOVA or ANOVA on ranks were applied to evaluate changes in clinical and echocardiographic parameters at the 3 time points. Bonferroni t or Student-Newman-Keuls tests were used for all paired comparisons. The relation between changes in mass, infarct size, and acute reduction in LVOT gradient was evaluated by simple linear regression analysis. The study had >80% power to detect a 20% change in LVH. Statistical significance was declared if P<0.05.

Results

The study cohort exhibited symptomatic and hemodynamic improvements after NSRT (Table 1). Angina class improved: only 1 patient had angina at 1 year, and none at 2 years (both P<0.001). None of the 12 patients with presyncope/syncope had any such events after NSRT (P<0.001), and only 4 of the 26 patients were on β-blockers 2 years after NSRT. Peak CK after NSRT averaged 2009 U/L (868 to 4230 U/L). Concomitantly with the ethanol-induced septal infarction, patients developed an anterior septal scar of 6±6.1% (by SPECT), and 7 developed permanent complete heart block (26.9%).

Changes in LV Size and EF

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Assessed by both CK (r = 0.48, P < 0.01) and SPECT imaging (r = 0.4, P = 0.05). This weak correlation was due to several large infarcts and big gradient reductions when we initially performed the procedure and to our later ability to reach successful hemodynamic results despite smaller infarcts by targeting ethanol delivery to the culprit septal segments using myocardial contrast echocardiography. The strongest relation was evident with the acute reduction of LVOT gradient at the time of the procedure (r = 0.63, P = 0.01; Figure 2).

On multiple regression analysis, CK leak and the acute reduction in gradient accounted for 52% of the variance in LV mass reduction (r = 0.72, R² = 0.52, P < 0.001).

**Discussion**

LVH assessed as wall thickness throughout the LV circumference was significantly reduced after NSRT in our study cohort, along with a preserved EF. These results are in keeping with an earlier study with M-mode looking at only the posterior wall basal segment that reported a decrease in wall thickness.15

**Implications for the Pathogenesis of HOCM**

LVH in HOCM is believed to be a compensatory process secondary to the decreased contractility induced by the mutation that leads to increased ventricular pressure and stress, which induces hypertrophy,16 which is further enhanced by obstruction.17 Results of the present study show the association of LVH regression with the elimination of obstruction, confirming the notion that hypertrophy may be a secondary phenomenon.

**Implications for Treatment**

In our study cohort, NSRT essentially eliminated the LVOT gradient and was associated with marked reduction in symptoms and improved exercise tolerance. These long-term beneficial results are similar to those achieved with surgery.5,6 NSRT also resulted in regression of LVH, which may be another beneficial effect, given that the frequency of sudden death in HOCM patients increases with increased LVH.4 Regression of LVH may also contribute to symptomatic improvement and is probably related to the fact that the

### TABLE 2. Changes in LVH After NSRT

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 Year After NSRT</th>
<th>2 Years After NSRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Septal thickness at infarct site, mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior septum (not at infarct)</td>
<td>21±4</td>
<td>15±4∗</td>
<td>13±4†</td>
</tr>
<tr>
<td>Anterior lateral wall</td>
<td>21±3</td>
<td>17±3.5∗</td>
<td>15±3†</td>
</tr>
<tr>
<td>Inferior lateral wall</td>
<td>14.4±2.2</td>
<td>12.6±1.9∗</td>
<td>11±1.4†</td>
</tr>
<tr>
<td>Inferior septum</td>
<td>15.3±3</td>
<td>12.9±2.7∗</td>
<td>11.6±1.7†</td>
</tr>
<tr>
<td>Total wall thickness score</td>
<td>72.4±10.5</td>
<td>57.5±11∗</td>
<td>51.5±9∗†</td>
</tr>
<tr>
<td><strong>Wall thickness at papillary level, mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior septum</td>
<td>20±4</td>
<td>15±4∗</td>
<td>13±3†</td>
</tr>
<tr>
<td>Anterior lateral wall</td>
<td>19.8±3</td>
<td>16±2.7∗</td>
<td>14.7±2.6∗</td>
</tr>
<tr>
<td>Inferior lateral wall</td>
<td>16.4±3.2</td>
<td>13.8±2.6∗</td>
<td>12.5±1.8†</td>
</tr>
<tr>
<td>Inferior septum</td>
<td>16 (14–17.3)</td>
<td>13.5 (12–16)∗</td>
<td>11.5 (11–14)†</td>
</tr>
<tr>
<td>Total wall thickness score</td>
<td>73±11</td>
<td>59±8.8∗</td>
<td>53±8.7†</td>
</tr>
<tr>
<td><strong>Myocardial area, cm²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve level</td>
<td>31±7.5</td>
<td>23.8±6.6∗</td>
<td>21.3±6.6†</td>
</tr>
<tr>
<td>Papillary muscle level</td>
<td>32±6.6</td>
<td>24.6±5.6∗</td>
<td>21±5.9†</td>
</tr>
<tr>
<td>Apical level</td>
<td>26 (22–32)</td>
<td>21.5 (17–25)∗</td>
<td>18.5 (15–23)†</td>
</tr>
<tr>
<td>Total area</td>
<td>90.8±18.8</td>
<td>69.4±15.8∗</td>
<td>60.4±15†</td>
</tr>
<tr>
<td>Mass, g</td>
<td>301±78</td>
<td>223±52∗</td>
<td>190±58†</td>
</tr>
<tr>
<td>Mass index, g/m²</td>
<td>151±32</td>
<td>112±21∗</td>
<td>95±24†</td>
</tr>
</tbody>
</table>

Values are mean±SD or median (25th–75th percentile).∗P < 0.05 vs baseline; †P < 0.05 vs 1 year.
increasing hypertrophy in patients with obstruction contributes to a decrease in LV compliance and impaired exercise tolerance. The resultant septal infarction of NSRT, however, may predispose patients to ventricular dysrhythmias and potentially offset the benefit of LVH regression. Clearly, more prospective data are needed, because the number of patients followed up, despite no occurrence of sudden death over 2 years, is too small to determine the impact of NSRT on ventricular dysrhythmias. Also, when counseling HOCM patients regarding this procedure, serious complications of NSRT noted by others and ourselves should be considered. Side effects observed in our later experience, but not in the present group, include left anterior descending coronary artery dissection (6 patients, 3.2%), death (3 patients, 1.6%), and sustained ventricular tachycardia (1 patient, 0.5%, not on β-blockers).

Although complete heart block developed in 7 patients (27%), including 4 with CK >2500 U/L, after we modified our technique, the incidence of heart block in the subsequent 162 HOCM patients decreased to 8.6%. Our modifications included injecting ethanol at a slower rate (1 to 1.5 mL/min instead of bolus) and using intracoronary myocardial contrast echocardiography to help target ethanol to the culprit septal segments. This latter incidence (8.6%) of complete heart block after NSRT is close to the 5% to 7% rate reported after surgery.

Acknowledgments
This study was supported in part by grants from the T.L.L. Temple Foundation, Lufkin, Tex, and the Dunn Foundation and The Methodist Hospital Foundation, Houston, Tex. Dr Nagueh is supported by a Scientist Development grant (0030235N) from the American Heart Association—National Center, Dallas, Tex. We thank Maria Frias and Debbie Graustein for their invaluable assistance.

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_Circulation_. 2001;103:1492-1496
doi: 10.1161/01.CIR.103.11.1492

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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