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, planimetered 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. Risk factors for sudden death include the presence of certain genetic mutations and the extent of left ventricular hypertrophy (LVH). Symptomatic patients with outflow tract (OT) obstruction are usually medically treated; in the few patients with persistent symptoms, surgical myectomy offers satisfactory control. Recently, nonsurgical septal reduction therapy (NSRT) has gained popularity as an alternative to surgery. 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, 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. Studies were stored for later analysis.

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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.

LV minor 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.12 Left atrial volume was derived with the multiple-disks method.13 LVH was assessed according to previously published criteria.12,14 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:14 anterior septum, anterior lateral, inferior lateral, and inferior septum. Subsequently, the total wall thickness score was calculated at both levels.14 Second, end-diastolic myocardial areas at the mitral, papillary muscle, and apical levels recorded in the parasternal short-axis views were planimetered. Third, LV mass and mass indexed to body surface area were calculated.12 The end-diastolic myocardial area at the papillary muscle level 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 myocardial area and mass at baseline and at 1 and 2 years (r=0.8, 0.86, and 0.89, respectively, all P<0.01).

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,10 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
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

| TABLE 1. Changes in Symptoms, Gradient, and Dimensions After NSRT |
|------------------|------------------|------------------|
|                  | Baseline         | 1 Year After NSRT | 2 Years After NSRT |
| NYHA class       | 3 (3–3)          | 1 (1–1)*          | 1 (1–1)*           |
| Angina class     | 2 (0–2)          | 0 (0–0)*          | 0 (0–0)*           |
| Exercise duration, seconds | 320 (219–598)   | 547 (330–721)*    | 548 (365–728)*     |
| Resting LVOT gradient, mm Hg | 36 (15–64)       | 0 (0–0)*          | 0 (0–0)*           |
| Provocable LVOT gradient, mm Hg | 81 (80–107)     | 25 (0–64)*        | 0 (0–31)*†         |
| Left atrium maximum volume, mL | 90±37           | 64±20*            | 60±16*             |
| LV end-diastolic dimension, mm | 36±5            | 44±6*             | 46±6*              |
| LV end-systolic dimension, mm | 20±6            | 27±6*             | 29±7*              |
| LV long axis, mm | 81 (76–85)       | 79 (75–85)        | 80 (78–85)         |
| LVEDV, mL        | 96±19            | 117±23*           | 124±26*            |
| LVEF, %          | 72.5±8           | 70.3±10           | 68±9*              |

Values are mean±SD or median (25th–75th percentile). *P<0.05 vs baseline; †P<0.05 vs 1 year.
thickening score at both levels continued to decrease (Figure 1B and 1C) up to 2 years after NSRT.

Similarly, the myocardial area at the mitral, papillary muscle, and apical levels was significantly smaller after NSRT ($P<0.01$).

LV mass also continued to decrease through the 2-year follow-up (Figure 1D); likewise, mass corrected for body surface area decreased significantly ($P<0.001$). This latter change was greater in year 1 than in year 2 (median values 38 versus 11 g/m$^2$; $P<0.05$). The incidence of complete heart block was distributed equally between patients having LVH regression $\geq20\%$ or $<20\%$.

**Determinants of LVH Regression**

Significant but weak correlations were present between the reduction in LV mass at 2 years and the infarct size as assessed by both CK ($r=0.48$, $P=0.05$) 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 ($r=0.72$, $R^2=0.52$, $P<0.001$).

**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>Septal thickness at infarct site, mm</td>
<td>20 (18–23)</td>
<td>12 (10–13)*</td>
<td>10 (8–11)*</td>
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<tr>
<td>Wall thickness at mitral valve level, mm</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Anterior septum (not at infarct)</td>
<td>21±4</td>
<td>15±4*</td>
<td>13±4*</td>
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<tr>
<td>Anterior lateral wall</td>
<td>21±3</td>
<td>17±3.5*</td>
<td>15±3†</td>
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<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>
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<tr>
<td>Wall thickness at papillary level, mm</td>
<td></td>
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<td></td>
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<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>
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<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>
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<tr>
<td>Myocardial area, cm$^2$</td>
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<tr>
<td>Mitral valve level</td>
<td>31±7.5</td>
<td>23.8±6.6*</td>
<td>21.3±6.4†</td>
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<tr>
<td>Papillary muscle level</td>
<td>32±6.6</td>
<td>24.6±5.6*</td>
<td>21±5.9†</td>
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<tr>
<td>Apical level</td>
<td>26 (22–32)</td>
<td>21.5 (17–25)*</td>
<td>18.5 (15–23)†</td>
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<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/m$^2$</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.

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