Role of Transcoronary Ablation of Septal Hypertrophy in Patients With Hypertrophic Cardiomyopathy, New York Heart Association Functional Class III or IV, and Outflow Obstruction Only Under Provocable Conditions

Frank H. Gietzen, MD; Christian J. Leuner, MD; Ludger Obergassel, MD; Claudia Strunk-Mueller, MD; Horst Kuhn, MD

Background—Transcoronary ablation of septal hypertrophy (TASH) for hypertrophic cardiomyopathy seems to be an effective alternative to surgical myectomy. It remains a point of debate whether an outflow obstruction at rest is a necessary criterion for interventional therapy.

Methods and Results—TASH was compared in 45 consecutive patients with no resting gradient and a provokable gradient of ≥30 mm Hg (group I) and in 84 consecutive patients with a resting gradient of ≥30 mm Hg (80±33 mm Hg) (group II). At baseline, all patients were in NYHA functional class (FC) III or IV, unresponsive to medical treatment. Patients in group I were older (63±12 versus 55±17 years, P=0.005) and had a lower postextrasystolic gradient (110±44 versus 171±40 mm Hg, P<0.001). The groups were similar with respect to NYHA FC (3.1±0.3 versus 3.1±0.3), basal septal thickness (22±4 versus 23±3 mm), maximal oxygen consumption (13.1±4.6 versus 14.5±5.0 mL/kg per minute), and pulmonary artery mean pressure at workload (42±9 versus 42±10 mm Hg) (P>0.05). Median follow-up was 7 months after TASH. The 2 groups showed a significant and similar improvement in provokable obstruction (to 24±24 and 56±51 mm Hg, respectively), basal septal thickness (to 12±3 and 12±4 mm, respectively), NYHA FC (to 1.7±0.6 and 1.5±0.6, respectively), maximal oxygen consumption (to 16.0±5.3 and 16.6±6.0 mL/kg per minute, respectively), and pulmonary artery mean pressure at workload (to 36±9 and 34±9 mm Hg, respectively) (P>0.05).

Conclusions—TASH seems to have beneficial clinical and hemodynamic effects in patients with either provokable or resting outflow obstruction. (Circulation. 2002;106:454-459.)

Key Words: cardiomyopathy ■ hypertrophy ■ catheter ablation ■ alcohol ■ hemodynamics

Patients with hypertrophic cardiomyopathy (HCM) and an outflow tract gradient (HOCM) who have severe symptoms of heart failure unresponsive to medical treatment are candidates for interventional therapy.1–4 The therapy most widely applied is surgical myectomy by removing a small amount of muscle from the basal interventricular septum.5–9 Surgery substantially reduces the subaortic outflow gradient in >90% of patients and results in persistent symptomatic improvement in ≈70% to 90%.1–2,4,7–10 In recent years, transcoronary ablation of septal hypertrophy (TASH) by selective transcatheter septal branch injection of ethanol has been shown to substantially reduce outflow obstruction in 80% to 90% and symptoms in 84% to 90% of patients.11–17 Therefore, TASH may be an effective alternative to surgery.18–21 It remains a point of debate whether in patients with severe symptoms a provokable outflow gradient is sufficient to justify interventional therapy.4,22–24

The purpose of the present study was to compare the results of TASH in consecutive patients with HCM, drug-refractory severe symptoms (NYHA functional class [FC] III or IV), and an outflow gradient under basal conditions and in patients with a similar clinical profile but an outflow gradient only under provocation.

Methods

Study Population

The study comprises 129 consecutive patients (56 males) with HCM who were treated by TASH at our institution between October 1995 and November 1999. The average age was 56±16 years. All patients had HCM with subaortic obstruction according to typical clinical, echocardiographic, and angiographic findings. Entry criteria included severe symptoms during daily activity or at rest, asymmetrical septal hypertrophy ≥15 mm, systolic anterior motion of the mitral valve, and an intraventricular pressure gradient of ≥30 mm Hg after provocation by a single premature ventricular beat or in basal conditions. Despite maximal tolerated doses of medical

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investigations

Clinical evaluation of the severity of symptoms, transthoracic echocardiography, and left and exercise right heart catheterization were performed before TASH and at a median follow-up of 7 months (range, 6 to 51) after the procedure. Exercise doppler echocardiography substituted the invasive strategy for reevaluation of the left ventricular outflow tract gradient in the last 32 consecutive patients. Patients’ self-perception of overall improvement was evaluated with a questionnaire that categorizes the subjective feeling of-well-being as improved, unchanged, or deteriorated.

**Echocardiography** was performed on a Hewlett Packard Sonos 1500 ultrasound machine and recorded on S-VHS video to allow serial review and side-by-side comparison. Basal interventricular septal thickness was derived from an integrated analysis of M-mode and 2-dimensional echocardiograms. Measurements were made according to the recommendations of the American Society of Echocardiography. Magnitude of the peak instantaneous left ventricular outflow tract gradient under basal conditions and during exercise was estimated with continuous-wave Doppler.

Exercise right heart catheterization was performed using a 5F Swan-Ganz catheter and a calibrated Statham P23ID strain-gauge manometer. The catheter remained in the pulmonary artery for continuous monitoring of pulmonary artery pressures and to obtain blood samples for the calculation of cardiac output by the direct Fick method. Oxygen uptake was measured using a $V_{\text{max}}$ system 29c (SensorMedics).

Supine bicycle exercise was performed from a workload of 25 watts to maximum capacity with increases by 25 watts every 3 minutes.

Coronary angiography and biplane ventriculography (30-degree right anterior oblique and left lateral projections) were performed using standard techniques. Quantitative calculation of left ventricular ejection fraction was based on a single-plane 30-degree right anterior oblique view.

TASH was based on an “over-the-wire” percutaneous transluminal coronary angioplasty (PTCA) technique and has previously been described in detail. A PTCA guiding catheter (6F to 7F), a guidewire (0.014 inch), and a PTCA balloon catheter (1.5 to 2.5/20 mm) were used for the catheterization of a small septal branch supplying the area of obstruction. The target vessel was identified by
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<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Resting Gradient &lt;30 mm Hg</th>
<th>Resting Gradient ≥30 mm Hg</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol 96% injected, mL</td>
<td>2.8±1.5 (1.0–7.0)</td>
<td>3.7±2.5 (0.5–11.0)</td>
<td>0.038</td>
</tr>
<tr>
<td>Peak CK activity, U/L</td>
<td>404±210 (81–894)</td>
<td>648±391 (133–2166)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TASH procedures per patient</td>
<td>1.0±0.2 (1–2)</td>
<td>1.2±0.4 (1–2)</td>
<td>0.032</td>
</tr>
<tr>
<td>Septal vessels occluded per patient*</td>
<td>1.0±0.4 (0.5–2.0)</td>
<td>1.2±0.5 (0.5–3.0)</td>
<td>0.097</td>
</tr>
<tr>
<td>Total AV block after 2 weeks, n (%)</td>
<td>4 (9)</td>
<td>13 (16)</td>
<td>0.260</td>
</tr>
<tr>
<td>PM, implantation after 48 hours, n (%)</td>
<td>12 (27)</td>
<td>21 (25)</td>
<td>0.836</td>
</tr>
<tr>
<td>Total AV block after 48 hours, n (%)</td>
<td>13 (29)</td>
<td>25 (30)</td>
<td>0.918</td>
</tr>
</tbody>
</table>

Values are mean±SD (range) or n (%).
Peak CK activity indicates creatine phosphokinase activity within 24 hours from TASH; PM, implantation, implantation of a dual-chamber pacemaker.

P value is comparison between resting gradient<30 mm Hg and resting gradient≥30 mm Hg.

*Occlusion of only a small side branch of the septal target vessel was counted as occlusion of 0.5 septal vessels.

Statistics
Statistical analyses were performed using commercial software (SPSS Inc, release 6.0.1) with the Pearson χ² test for unordered categorical variables and the Mann-Whitney Wilcoxon test for ordered categorical variables. The Student’s t test for paired and independent samples was used for normally distributed continuous variables and the Mann-Whitney Wilcoxon test for not normally distributed continuous variables. P<0.05 (2-tailed) was considered statistically significant. Values are expressed as mean±SD.

Results
Baseline Characteristics
Group I patients with left ventricular outflow obstruction only under provokable conditions (n=45) were significantly older than group II patients with outflow obstruction at rest (n=84) (Table 1). The groups were similar with regard to sex, concomitant moderate hypertension, NYHA FC (class IV in 9% versus 10%, P=0.906), basal interventricular septal thickness, left ventricular end-diastolic pressure, left ventricular ejection fraction, incidence of prior syncope, and dual-chamber pacemaker therapy for HOCM. A significantly lower postextrasystolic gradient was measured invasively in group I. Even in this group, 67% of patients had a postextrasystolic gradient of ≥100 mm Hg and 87% of ≥50 mm Hg. Exercise right heart catheterization was performed in 44 of the patients in group I and in 80 of those in group II. The groups were similar with regard to exercise capacity, maximal oxygen consumption, cardiac index at peak exercise, and pulmonary artery mean pressure at workload.

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The amount of ethanol 96% injected, the peak creatine kinase activity values, and the proportion of reintervention (4% versus 18%, P=0.032) was significantly lower in group I (Table 2). However, in both groups, the number of septal vessels occluded per patient was similar. No significant difference was identified for the risk of a TASH-related persistent total atrioventricular block 2 weeks after intervention and the proportion of pacemakers implanted for atrioventricular conduction disturbances 48 hours after TASH.

Complications
The procedure-related in-hospital mortality was 0% in group I and 4.8% in group II (P=0.137); 4 patients with basal obstruction and severe comorbidity died during the first 2 weeks after TASH (Figure). Three of these patients were treated with this new technique before September 1997. Causes of death were sudden total atrioventricular block (n=1), progressive right heart failure (n=1), penetration of a pacing lead with acute pericardial effusion (n=1), and ventricular fibrillation (n=1). Other major complications (0% in group I, 6.0% in group II, P=0.095) were ischemic stroke (n=1), recurrent successfully terminated ventricular fibrillation (n=1), severe but reversible spasm of the left coronary artery (n=2), and successful myectomy with mitral valve replacement after failure of TASH (n=1).

Late Death
At a median follow-up of 7 months (mean, 10±8 months; range, 6 to 51 months) and a total of 95 patient years, late cardiac mortality was 0% in patients with provokable as well...
as in patients with resting obstruction. Three patients in group I (6.7%) and 2 in group II (2.4%) died from noncardiac causes (carcinoma in 2, pulmonary embolism, liver cirrhosis, and suicide), reflecting the high number of patients enrolled despite severe comorbidity (Figure).

Effect of TASH
A median of 7 months (mean, 10±8 months; range, 6 to 51 months) after TASH, clinical evaluation (100% complete follow-up in all patients remaining alive [n=120] excluding 1 patient with myectomy [n=119]) was obtained in 42 patients (100%) with provocable obstruction and in 77 patients (100%) with resting obstruction. The groups were not significantly different with regard to the magnitude of the improvement in NYHA FC and the reported overall subjective improvement of symptoms (Table 3). In group I, 39 patients (93%) improved to class I (n=17) or II (n=22), whereas 3 patients remained in class III (Figure, A). In group II, 72

TABLE 3. Effects of TASH at a Median Follow-Up of 7 Months

<table>
<thead>
<tr>
<th></th>
<th>Resting Gradient &lt;30 mm Hg</th>
<th></th>
<th>Resting Gradient ≥30 mm Hg</th>
<th></th>
<th>P Value</th>
<th>P Value</th>
<th>Δ</th>
<th></th>
<th>P Value</th>
<th>P Value</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Δ</td>
<td>P Value</td>
<td>Pre</td>
<td>Post</td>
<td>Δ</td>
<td>P Value</td>
<td>Pre</td>
<td>Post</td>
<td>Δ</td>
</tr>
<tr>
<td>Clinical evaluation</td>
<td>42 patients</td>
<td>72 patients</td>
<td>93%</td>
<td>0.784</td>
<td>3.1±0.3</td>
<td>1.7±0.6</td>
<td>-1.4±0.6</td>
<td>&lt;0.001</td>
<td>3.1±0.2</td>
<td>1.5±0.6</td>
<td>-1.5±0.6</td>
</tr>
<tr>
<td>Subjective improvement</td>
<td>38 patients</td>
<td>66 patients</td>
<td>93%</td>
<td>0.784</td>
<td>13±9</td>
<td>8±8</td>
<td>-41±60%</td>
<td>0.004</td>
<td>81±33</td>
<td>16±20</td>
<td>-78±29%</td>
</tr>
<tr>
<td>LVOT gradient</td>
<td>111±44</td>
<td>171±40</td>
<td>56±51</td>
<td>0.001</td>
<td>20±5</td>
<td>14±4</td>
<td>-28±24%</td>
<td>&lt;0.001</td>
<td>19±7</td>
<td>14±6</td>
<td>-21±31%</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>0.73±0.07</td>
<td>0.71±0.08</td>
<td>0.70±0.09</td>
<td>0.013</td>
<td>22±4</td>
<td>12±3</td>
<td>-43±19%</td>
<td>&lt;0.001</td>
<td>23±4</td>
<td>12±4</td>
<td>-47±18%</td>
</tr>
<tr>
<td>IVS thickness, mm</td>
<td>33 patients</td>
<td>58 patients</td>
<td>33 patients</td>
<td>58 patients</td>
<td>13.3±4.6</td>
<td>16.0±5.3</td>
<td>29±43%</td>
<td>0.013</td>
<td>14.8±4.5</td>
<td>16.6±6.0</td>
<td>13±25%</td>
</tr>
<tr>
<td>VO2max, mL/kg per min</td>
<td>50±17</td>
<td>60±18</td>
<td>29±43%</td>
<td>0.011</td>
<td>5.6±1.6</td>
<td>6.0±2.3</td>
<td>11±34%</td>
<td>0.340</td>
<td>5.9±1.6</td>
<td>6.5±1.7</td>
<td>15±31%</td>
</tr>
</tbody>
</table>

Mean values±SD.
Δ indicates proportional changes from preintervention values to postintervention values.
P value is comparison between preintervention values and postintervention values; P value Δ is comparison between Δ resting gradient<30 mm Hg and Δ resting gradient≥30 mm Hg.
Abbreviations as in Table 1.
patients (94%) improved to class I (n=41) or II (n=31), whereas 5 patients remained in class III (Figure, B).

A median of 7 months after TASH (mean, 7±3 months; range, 6 to 26 months) after TASH, hemodynamics at rest (87% complete follow-up) were evaluated invasively (n=72) or by exercise Doppler echocardiography (n=32) in 38 patients (90%) with provokable obstruction and in 66 patients (86%) with resting obstruction. The groups were not significantly different with regard to the proportional reduction of the provokable gradient, the left ventricular end-diastolic pressure, and the left ventricular ejection fraction (Table 3). In groups I and II, a similar and significant decrease of the provokable gradient and the left ventricular end-diastolic pressure was found. The left ventricular ejection fraction did not change significantly from the preinterventional values. By echocardiography the proportional reduction of the mean basal interventricular septal thickness was similar and significant in both groups.

A median of 7 months after TASH (mean, 7±3 months; range, 6 to 26 months), exercise right heart catheterization (76% complete follow-up) was performed in 33 patients (79%) with provokable obstruction and in 58 patients (75%) with resting obstruction. The groups were not significantly different with regard to the proportional improvement in exercise capacity, maximal oxygen consumption, pulmonary artery mean pressure at workload, and cardiac index at peak exercise (Table 3). In groups I and II, a significant improvement in exercise capacity, maximal oxygen consumption, and pulmonary artery mean pressure at workload was identified. In addition, group II showed a significant increase in cardiac index at peak exercise.

Patients with (76%) and without (24%) reevaluation of exercise right heart catheterization (because of severe comorbidity, age, or lack of informed consent) reported a similar and significant improvement in NYHA FC (−1.5±0.6 versus −1.4±0.7, P=0.384).

Discussion

On the basis of the results of recent studies, TASH leads to a reduction in basal interventricular septal thickness, a substantial and sustained decrease in outflow obstruction, a decrease in left ventricular filling pressures at rest and during exercise, and a marked clinical improvement.13–17 Therefore, TASH may be an effective alternative to surgical myectomy accompanied by a significant decrease in NYHA FC. This confirms similar observations made for myotomy-myectomy5–7,9 since the first description by Morrow et al5 of an effective surgical therapy in 13 patients without resting obstruction. Moreover, this indicates the special impact of provokable obstruction on the genesis of symptoms during exercise in HCM. Indeed, the relief of provokable obstruction during exercise (and the associated mitral regurgitation) seems to be of critical importance for the improvement in dyspnea on exertion. This is validated by objective substantiation of the perceived decrease in severe symptoms, because exercise right heart catheterization showed a significant improvement in exercise capacity, pulmonary artery mean pressure at workload, and maximal oxygen consumption in obstructed as well as in provokable obstructed patients without any significant difference in treatment efficacy between the groups.

Patients were accepted for intervention because of severe symptoms with a substantial subgroup in NYHA FC IV (9.3%) despite intensive medical treatment, including diuretics. Therefore, the results of our study should not be used as a justification to perform TASH in patients with provokable outflow obstruction and mild symptoms.
Conclusions

Previous surgical experience4–7,9 and our present results with TASH suggest that similar treatment strategies are justified in severely symptomatic patients with HCM and provokable left ventricular outflow obstruction as in patients with outflow obstruction under basal conditions.

Acknowledgment

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References

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