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 provocative gradient of ≥30 mm Hg (group I) and in 84 consecutive patients with a resting gradient of ≥30 mm Hg (80 to 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 provocative 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 provocative 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 provocative 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 angiocardiographic findings. Entry criteria included severe symptoms during daily activity or at rest, asymmetric 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
TABLE 1. Baseline Characteristics*

<table>
<thead>
<tr>
<th></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>No. of patients</td>
<td>45</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>63±12 (27–81)</td>
<td>55±17 (21–83)</td>
<td>0.005</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>24 (53)</td>
<td>32 (38)</td>
<td>0.096</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>5 (11)</td>
<td>6 (7)</td>
<td>0.442</td>
</tr>
<tr>
<td>NYHA FC</td>
<td>3.1±0.3</td>
<td>3.1±0.3</td>
<td>0.906</td>
</tr>
<tr>
<td>Ill, No.</td>
<td>41</td>
<td>76</td>
<td>...</td>
</tr>
<tr>
<td>IV, No.</td>
<td>4</td>
<td>8</td>
<td>...</td>
</tr>
<tr>
<td>Syncope, No. (%)</td>
<td>12 (27)</td>
<td>28 (33)</td>
<td>0.435</td>
</tr>
<tr>
<td>Preexisting DDD-pacemaker, No.</td>
<td>6 (13)</td>
<td>7 (8)</td>
<td>0.369</td>
</tr>
<tr>
<td>IVS thickness, mm</td>
<td>22±4 (16–38)</td>
<td>23±3 (15–34)</td>
<td>0.224</td>
</tr>
<tr>
<td>Left heart catheterization, No.</td>
<td>45</td>
<td>84</td>
<td>...</td>
</tr>
<tr>
<td>LVOT gradient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest, mm Hg</td>
<td>14±9 (0–28)</td>
<td>83±34 (30–158)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-ES, mm Hg</td>
<td>110±44 (30–180)</td>
<td>171±40 (70–250)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>19±6 (8–33)</td>
<td>20±7 (9–38)</td>
<td>0.970</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.73±0.06 (0.60–0.87)</td>
<td>0.72±0.07 (0.60–0.90)</td>
<td>0.257</td>
</tr>
<tr>
<td>Right heart catheterization, No.</td>
<td>44</td>
<td>80</td>
<td>...</td>
</tr>
<tr>
<td>Workload, watts</td>
<td>64±28 (0–125)</td>
<td>68±31 (0–150)</td>
<td>0.540</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>42±10 (20–67)</td>
<td>42±9 (27–69)</td>
<td>0.874</td>
</tr>
<tr>
<td>VO2max, mL/kg per min</td>
<td>13.1±4.6 (5.3–24.3)</td>
<td>14.5±5.0 (3.9–26.6)</td>
<td>0.166</td>
</tr>
<tr>
<td>VO2max, % predicted</td>
<td>49±16 (20–92)</td>
<td>49±15 (17–84)</td>
<td>0.944</td>
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<tr>
<td>Cl, L/m² per min</td>
<td>5.2±1.6 (1.6–8.5)</td>
<td>5.7±1.7 (2.1–8.8)</td>
<td>0.206</td>
</tr>
</tbody>
</table>

*Mean values ±SD (range).

IVS thickness indicates interventricular septal thickness; LVOT, left ventricular outflow tract; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; Rest, resting gradient; Post-ES, postextrasystolic gradient; PAP, pulmonary artery mean pressure at pretreatment workload; VO2max, oxygen consumption at maximal workload; and CI, cardiac index at maximal workload.

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

treatment with verapamil or β-blockers in all patients and diuretics in 35 patients (for at least 3 months before hospitalization). 12 patients were in NYHA FC IV and 117 in NYHA FC III. Permanent atrioventricular sequential pacing had failed to reduce symptoms in 13 patients. The septal thickness was 22±4 mm, the invasively measured resting gradient was 59±43 mm Hg, the postextrasystolic gradient was 150±51 mm Hg, and the left ventricular end-diastolic pressure was 20±6 mm Hg.

The 129 study patients were divided into 2 groups. Group I included 45 patients with an intraventricular pressure gradient of <30 mm Hg at rest and ≥30 mm Hg after provocation by a single premature beat. These patients represent our study group with provokable outflow obstruction. Group II included 84 patients with a gradient of ≥30 mm Hg at rest and represents the study group with outflow obstruction under basal conditions (Table 1).

The institutional review committee approved the study. All patients gave written informed consent.

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 septum 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 Vmax system 29c (SensorMedics). Supine bicycle exercise was performed from a workload of 23 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
Medical therapy with verapamil or reduce the risk of thrombus formation at the septal ablation site. Heparin was administered by continuous intravenous infusion to activity was determined at hourly intervals during the first 24 hours. Creatine phosphokinase ventricular stimulation catheter and continuous ECG monitoring in under provocable conditions (n = 45). 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.

**Transcoronary Ablation of Septal Hypertrophy**

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 provable 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 provokable 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>Resting Gradient ≥30 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Clinical evaluation</td>
<td>42 patients</td>
<td>72 patients</td>
</tr>
<tr>
<td>NYHA-FC</td>
<td>3.1±0.3</td>
<td>1.7±0.6</td>
</tr>
<tr>
<td>Subjective improvement</td>
<td>93%</td>
<td>93%</td>
</tr>
<tr>
<td>Hemodynamic at rest</td>
<td>38 patients</td>
<td>66 patients</td>
</tr>
<tr>
<td>LVOT gradient</td>
<td>Rest, mm Hg</td>
<td>13±9</td>
</tr>
<tr>
<td>Provocation, mm Hg</td>
<td>111±44</td>
<td>24±24</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>20±5</td>
<td>14±4</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.73±0.07</td>
<td>0.70±0.07</td>
</tr>
<tr>
<td>IVS thickness, mm</td>
<td>22±4</td>
<td>12±3</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>33 patients</td>
<td>58 patients</td>
</tr>
<tr>
<td>Workload, watts</td>
<td>66±29</td>
<td>85±27</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>42±10</td>
<td>36±9</td>
</tr>
<tr>
<td>VO2max, mL/kg per min</td>
<td>13.3±4.6</td>
<td>16.0±5.3</td>
</tr>
<tr>
<td>VO2max, % predicted</td>
<td>50±17</td>
<td>60±18</td>
</tr>
<tr>
<td>CI, L/m² per min</td>
<td>5.6±1.6</td>
<td>6.0±2.3</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 (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 on 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.11–17 Therefore, TASH may be an effective alternative to surgical myectomy for patients with the obstructive form of HCM and drug-refractory severe symptoms.18

Patients with provoked obstruction only under provocable conditions.4,22–24 In 1995, Cecchi et al25 described the clinical course and outcome of HCM in an unselected regional population and compared 40 patients with basal outflow obstruction of ≥30 mm Hg with 162 patients who had gradients of <30 mm Hg. Follow-up was up to 15 years. Cox regression analysis showed no relation between the presence of basal outflow obstruction and cardiovascular death (P=0.19). In 1996, Robbins and Stinson26 reported on 31 of 158 patients (20%) who were referred to surgery with resting gradients <20 mm Hg. Actuarial survival curves and the extent of functional benefit in these patients did not differ significantly from those in patients with higher gradients at rest. These considerations, and the increasing number of patients treated by catheter intervention, justify a reevaluation of the selection criteria used for interventional therapy in general and TASH in particular. The present study compares the effects of TASH in patients with HCM, drug-refractory NYHA FC III or IV symptoms, and resting obstruction and in patients with a similar clinical profile but an outflow gradient only under provocation.

At baseline, patients with provokable obstruction were significantly older, but with regard to symptoms and exercise hemodynamics, they were similar to the group of patients with resting obstruction. Identical selection criteria used for TASH in patients with and without resting obstruction (NYHA FC III or IV unresponsive to medical treatment including diuretics) avoided less severe symptoms in patients with provokable obstruction.

In patients with provokable obstruction, a lower amount of ethanol and fewer reinterventions led to a smaller ablation area indicated by lower creatine phosphokinase values.14

Compared with patients with basal obstruction, this was accompanied by a tendency to a lower rate of persistent total atrioventricular block and by fewer complications. But also in patients with basal obstruction, a reduction in the amount of ethanol contributed to a decrease in complications. Until December 2001, our overall experience increased to 333 patients treated by TASH with an in-hospital mortality of 1.8% (0.4% excluding patients with severe comorbidity) (Kuhn et al, unpublished data, 2002). Also, the arrhythmogenic risk of TASH might depend on lesion size and the amount of ethanol injected.30,32 However, the potential long-term consequences of the myocardial scar produced by septal ablation remain to be determined at a longer follow-up.13

Our results support the use of similar treatment strategies for patients with provokable outflow obstruction and patients with gradients under basal conditions.31 In both subsets, 93% of the patients reported a subjective improvement that was accompanied by a significant decrease in NYHA FC. This confirms similar observations made for myotomy-myectomy since the first description by Morrow et al3 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 provocable 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 experience 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.

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References
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