Hypertrophic cardiomyopathy is characterized by a slowly increasing asymmetric septal hypertrophy, which can lead to dynamic left ventricular outflow tract (LVOT) obstruction (1,2). As a consequence, progressive systolic and diastolic left ventricular (LV) dysfunction may develop (1–3), leading to dyspnea, angina, arrhythmias and even sudden cardiac death. Nonsurgical myocardial reduction (NSMR) of septal hypertrophy has recently been shown to decrease LVOT obstruction and to improve symptoms in patients with HOCM (4–8).

Nonsurgical myocardial reduction is accomplished by a septal infarction, which reduces or abolishes LVOT obstruction (9). In the majority of studies, ethanol has been used to induce septal infarction (4–10). However, the amount of ethanol injected (1 to 6 ml) and, thus, infarct size, as reflected by the increase in creatine kinase (CK), differ considerably among the studies published so far (4–9). The impact of large infarct sizes (6,11) on the long-term outcome of these patients has not been determined. However, it might provide a substrate for the development of life-threatening ventricular arrhythmias, similar to patients who have had a myocardial infarction. Furthermore, there is evidence that the early incidence of complications, such as complete heart block with necessary permanent pacemaker implantation (<10%), is influenced by the amount of ethanol injected during the procedure (6,7). Whether other factors, such as the speed of ethanol injection, are related to the incidence of complications has not been systematically investigated so far.

Therefore, we tried to keep the infarct sizes as small as possible by reducing the amount of ethanol injected per septal branch at the beginning of this study (10). After following pressure-guided criteria, as suggested by the initial clinical applications of the procedure (9,12), we report here on the short- and long-term results, as well as the complication rates, of a pressure-guided approach to NSMR aiming at the minimal required size of septal infarctions.

METHODS

Study group. Fifty patients (age 55 ± 14 years; 25 men and 25 women) with symptomatic HOCM (New York Heart Association [NYHA] functional class 2.8 ± 0.6) and an echocardiographically determined LVOT gradient...
All patients gave written, informed consent at least 24 h before the intervention, after the primary investigator (P.B.) provided the patients with detailed information on the different therapeutic options and the risk of the procedure. The patients’ histories included pulmonary edema (n = 17), syncope (n = 18), stroke (n = 1) and survival of sudden cardiac death (n = 1). Thirteen patients were treated with beta-blockers and 26 patients with verapamil before NSMR. Significant coronary artery disease was detected in four patients and treated by single-vessel stent implantation. Four to six months later, these patients were enrolled for NSMR after restenosis at the stent site, as well as progression of coronary artery disease, had been excluded.

Noninvasive evaluation. For assessment of quality of life, all patients answered a standardized questionnaire (SF-12) (13) before and 28 days, four to six months and 12 to 18 months after NSMR. The NYHA functional class was determined at the same time.

CARDIOPULMONARY EXERCISE TESTING. An incremental symptom-limited cardiopulmonary exercise test was performed in 32 of 50 patients, as described in detail previously (14). Eight patients who were in NYHA functional class IV did not tolerate cardiopulmonary exercise testing. In addition, seven patients underwent previous cardiac catheterization in another hospital within seven days before the intervention and were not eligible for exercise testing. Because the anaerobic threshold was not reached in another seven patients, the final analysis included only 25 of 50 patients. Cardiopulmonary exercise tests were performed before NSMR, 7 days, 4 to 6 months and 12 to 18 months after the procedure.

LEFT VENTRICULAR HYPERTROPHY. For determination of myocardial mass, an Imatron C-150 Scanner (Siemens, Germany), with an acquisition time of 100 ms at a spatial resolution of 0.7 mm², was used. After injecting 70 ml of nonionic contrast agent into the right cubital vein, 20 images were recorded during each cardiac cycle. Starting at the aortic valve, eight slices (3-mm thick) were acquired from the basis to the apex of the heart. Epicardial and endocardial borders were marked manually, and the myocardial area of each slice was determined. This area was divided into 12 segments, and the volume and myocardial mass (specific gravity 1.05 g/cm³) were calculated for each segment (15–17). Two septal segments of each of the first four slices (eight segments total) were taken to estimate septal mass. Correspondingly, two segments of the contralateral wall of the same four slices were taken to calculate the volume of eight lateral segments. Follow-up was obtained at seven days (n = 50), four to six months (n = 49) and 12 to 18 months (n = 25) after NSMR.

Invasive procedures and NSMR by ethanol. All patients (n = 50) underwent coronary angiography before NSMR. In 40 of the 50 patients, invasive electrophysiologic testing was performed before and four to six months after NSMR to determine the patients’ susceptibility to ventricular arrhythmias before and after NSMR. As the majority of the patients did not have a history of ventricular arrhythmia or survival of sudden cardiac death, a single-site electrophysiologic test was chosen to prevent nonspecific ventricular fibrillation, which is known to occur with more aggressive protocols in patients with HOCM (8). Thus, programmed ventricular stimulation at a single site within the right ventricular apex, using a basal cycle length of 600, 500, 400 and 333 ms, with up to two premature beats, was analyzed to determine the induction of ventricular runs, ventricular tachycardia or ventricular fibrillation. Thereafter, the pacing catheter remained in the right ventricle for delivery of premature beats to determine the post-extrasystolic LVOT gradient and for back-up pacing in case of complete heart block after NSMR.

After exclusion of aortic valve stenosis, the LVOT gradient was continuously monitored. For measurement of LV pressure, a 6F pigtail catheter was advanced by using a retrograde approach and placed distally to the intraventricular obstruction in the LV. Aortic pressure was determined simultaneously by using a 7F guiding catheter with side holes (Judkins L4, Cordis). The systolic LVOT gradient was determined at rest and after a programmed premature beat. Hemodynamic variables, including LVOT gradient and LV end-diastolic pressure (LVEDP), were analyzed at baseline, during balloon occlusion of the target septal branch and 20 min after ethanol injection. Invasive hemodynamic measurements were repeated after four to six months (n = 49) and 12 to 18 months (n = 25).

In all patients, NSMR was guided exclusively by continuous monitoring of the LVOT gradient, as originally suggested by Sigwart (9). After intravenous delivery of 10,000 IU of heparin, a 0.014-in. (0.035-cm) guide wire was selectively placed in the presumed culprit septal branch, which was chosen only if it was of sufficient size (presumed diameter ≥1.5 mm) and length (≥2 cm). Thereafter, an over-the-wire angioplasty balloon (1.5 mm in diameter and 15 mm in length or 2.0 mm in diameter and 20 mm in length; Takumi, Schneider, Switzerland) was placed in the target septal branch. After balloon inflation (4 to 6 atm), correct placement was verified by injection of contrast agent into the left coronary artery and then into the septal branch.
distal to the balloon catheter, avoiding retrograde leakage along the balloon at the same time. Moreover, injection of contrast agent under fluoroscopic guidance in at least two projections allowed estimation of the extent of myocardium supplied by the septal branch, as well as detection of shunting from the septal branch to nontargeted myocardial regions, such as the lateral LV wall.

Subsequent ethanol injection was performed only if the LVOT gradient at rest decreased >30 mm Hg or >50 mm Hg after a programmed premature beat during occlusion of the septal branch, with or without injection of contrast agent. If these pressure-guided criteria were not met, the balloon was deflated and the procedure was repeated using a different septal branch (n = 11). If the pressure-guided criteria were fulfilled, 96% ethanol was injected into this septal branch. The first milliliter of ethanol was injected rapidly (mean injection time 7 ± 4 s), depending on the diameter of the balloon (1.5 up to 2.5 mm). The rest of the ethanol (0.5 to 1.0 ml) was slowly injected during 30 s. In four patients, the LVOT gradient was abolished completely after injection of 1 ml of ethanol, so that no further ethanol was administered. Otherwise, a total amount of 1.5 to 2.0 ml of ethanol was injected into a single septal branch, depending on the size of the vessel. The hemodynamic result was considered satisfactory if the LVOT gradient at rest or after a programmed premature beat was reduced by >50%. After ethanol injection and removal of the balloon, the LVOT gradient increased by >30 mm Hg in three patients. After choosing a more proximal position of the balloon in the same septal branch, re-injection of 1 ml of ethanol was followed by a satisfactory reduction in the LVOT gradient in all three patients. More recently, with shorter balloons becoming available for the NSMR procedure, occlusion of side branches was avoided. If the LVOT gradient after ethanol injection into a single septal branch was still >50% of the baseline value, a second or third septal branch was selected and injected (two branches in four patients and three branches in two patients).

Post-interventional monitoring was done at an intensive care unit for 12 to 24 h. Creatine kinase was determined every 4 h. The temporary pacemaker was left in place for 24 to 96 h only if complete heart block was present after NSMR. Otherwise, it was removed 30 min after the procedure.

Statistical analysis. All data are presented as the mean value ± SD and were analyzed using SPSS statistical software. Repeated measurements of continuous variables were compared by one-way analysis of variance (ANOVA).

Subsequent Bonferroni correction was used to adjust for multiple testing. For repeated determinations of quality-of-life scores, nonparametric one-way ANOVA (Kruskal-Wallis) was used. If the result was statistically significant (p < 0.05), comparison between time points was done using the Mann-Whitney U test. A p value <0.05 was considered statistically significant. Correlations between peak CK levels and the volume of ethanol injected and between peak CK levels and LVOT reduction were evaluated using Pearson’s correlation coefficient.

RESULTS

Infarct size and complications of the procedure. A mean of 1.2 ± 0.4 septal branches were ablated by injection of 1.9 ± 0.7 ml of ethanol in 50 patients. The mean peak rise in CK was 413 ± 193 U/l (range 179 to 1,019). A single septal branch was injected by only 1.7 ± 0.5 ml of ethanol (mean CK 367 ± 158 U/l) in 44 patients (88%). In 39 patients (78%), balloon occlusion of the septal branch, initially approached for anatomic reasons, provided a sufficient reduction in the LVOT gradient to meet the pressure-guided criteria, and the septal branch was subsequently injected with ethanol. For all 50 patients, there was a close correlation (r = 0.74, p < 0.001) between the volume of ethanol injected and the peak CK level, whereas no relationship (r = −0.03) existed between the peak CK level and the reduction in the LVOT gradient.

Transient complete heart block after ethanol injection occurred in 18 (36%) of 50 patients. In all of these patients, complete heart block resolved within 12 h. However, recurrent transient complete heart block was observed in 5 (10%) of 50 patients within seven days after the procedure, necessitating implantation of a permanent DDD-pacemaker for safety reasons. No other periprocedural complications occurred, and no patient died during the hospital stay. The patients remained in the hospital for at least seven days after the procedure (mean 7.5 ± 0.7 days). One patient with concomitant coronary artery disease who underwent stent implantation three months before NSMR died of an acute myocardial infarction five months after the procedure. No major cardiac event was observed in any of the other 49 patients during the follow-up period up to 40 months.

Short- and long-term hemodynamic results. In 50 patients, the mean rest LVOT gradient significantly decreased from 80 ± 33 to 45 ± 32 mm Hg (p < 0.001) during balloon inflation of the target septal branch. Subsequent ethanol injection was followed by an immediate further reduction in the rest LVOT gradient to 18 ± 13 mm Hg, associated with a decrease in the post-extrasystolic gradient from 154 ± 40 to 53 ± 40 mm Hg (p < 0.001) (Fig. 1). Invasive hemodynamic measurements at four to six months (n = 49) and 12 to 18 months of follow-up (n = 25) showed a sustained decrease in the rest and post-extrasystolic LVOT gradient (Fig. 1). Although LVEDP did not change significantly immediately after NSMR (23 ± 7 to 20 ± 10 mm Hg), there was a highly significant reduction in LVEDP four to six months (13 ± 7 mm Hg, n = 49, p < 0.001) and 12 to 18 months (12 ± 8 mm Hg, n = 25, p < 0.001) after the procedure.

Left ventricular hypertrophy. To quantify LV hypertrophy (LVH) after NSMR, LV mass was determined by electron beam computed tomography (15–17). As expected,
septal mass decreased within seven days after NSMR (28.7 ± 3.4 to 24.9 ± 3.4 g, n = 50, p < 0.001), whereas no change in the mass of the contralateral wall could be detected at that time (Fig. 2). After four to six months, however, a significant decrease in the contralateral wall mass, from 21.3 ± 2.3 to 16.9 ± 2.2 g (n = 49, p < 0.001) and contralateral wall mass (21.4 ± 2.8 to 14.4 ± 2.5 g, n = 25, p < 0.001). The mass of all 64 LV segments analyzed decreased by 17% after four to six months (n = 49, p < 0.001) and by 28% after 12 to 18 months (n = 25, p < 0.001) (Fig. 2).

Cardiopulmonary exercise capacity. Exercise capacity increased early (7 days) after NSMR, but showed a pronounced further increase after four to six months (n = 25) and 12 to 18 months (n = 25) (Fig. 3). Furthermore, there was a parallel increase in peak oxygen consumption. The anaerobic threshold, however, did not change after seven days, but significantly increased four to six months and 12 to 18 months after NSMR (Fig. 3).

Quality of life. Improvement of quality of life was demonstrated by a decrease in the score, from 31 ± 8 to 26 ± 8 points after 28 days and to 25 ± 9 points after four to six months (p < 0.01) post-NSMR. Concomitantly, the NYHA functional class decreased from 2.8 ± 0.6 to 2.0 ± 0.6 after 28 days and to 1.9 ± 0.7 after four to six months (p < 0.001) post-NSMR. Two years after NSMR (n = 25), the score data (25 ± 7 points) and functional class (1.7 ± 0.7) confirmed the sustained improvement in quality of life (Fig. 4).

Electrophysiologic studies. To assess the patients’ susceptibility to ventricular arrhythmias, electrophysiologic testing was performed in 39 patients before and four to six months after NSMR. The incidence of inducible ventricular tachycardia or ventricular fibrillation (2/39→3/39) and ventricular beats or runs (6/39→2/39), as well as clinical events (survival of sudden cardiac death: 1/39→1/39), did not change after NSMR. As expected, more than half of the patients (4/39→22/39) had complete right bundle branch block after the procedure, with prolongation of the QRS duration from 96 ± 12 to 125 ± 43 ms (p < 0.05).

DISCUSSION

Nonsurgical myocardial reduction by ethanol ablation has recently been shown to decrease LVOT obstruction and to improve symptoms in patients with HOCM (4–8). The anatomic substrate for the LVOT obstruction is a relative, distinct narrowing between the thickened septum and the mitral valve leaflet (18). Because septal muscle contraction might also contribute to LVOT obstruction, large infarct sizes have been induced in the first series of patients with HOCM treated by NSMR (4,6,9). Infarct size, as estimated by the rise in CK after NSMR, was substantially lower (peak CK 413 ± 193 U/l) in our study than in the reports by other groups (4–8), with a range of peak CK from 676 ± 347 (7) to 1,964 ± 796 U/l (6).
Impact of smaller infarct size on hemodynamic variables and clinical improvement. The main result of the present study was that rather small but correctly localized infarctions were sufficient to reduce the LVOT gradient to a similar extent as that described by the groups of investigators inducing larger infarct sizes (4–8). Considering the studies published so far with invasive determination of LVOT gradients (4,5,7,8), the reduction in the LVOT gradient at rest (62 mm Hg) and the remaining pressure gradient after NSMR (18 ± 6 mm Hg) observed in our study was comparable to the data reported by other groups (42 respectively 19 ± 21 mm Hg [5]; 57 respectively 17 ± 18 mm Hg [7]; 43 respectively 8 ± 5 mm Hg [4]; 45 respectively 12 ± 3 mm Hg [8]). In another study using Doppler measurements (6), the reduction in the pressure gradient was 37 mm Hg and remaining rest gradient was 12 ± 12 mm Hg.

Furthermore, long-term invasive hemodynamic follow-up of 12 to 18 months showed a sustained reduction in the intraventricular pressure gradient in our patients (Fig. 1), which was accompanied by a significant clinical improvement (Fig. 3). With regard to NYHA functional class improvement after NSMR, the published data range from 1.7 ± 0.6 (8) to 0.9 ± 0.6 (6). Improvement in functional class after NSMR appeared to be somewhat less pronounced in our study (1.9 ± 0.7 after four to six months and 1.7 ± 0.7 after 12 to 18 months). As functional class is a subjective measure, the differences in assessment and patient population may influence the results. The clinical improvement of our patients was also confirmed by the increase in cardiopulmonary exercise capacity, as well as the increase in maximal oxygen consumption and anaerobic threshold (Fig. 4).

Impact of smaller infarct sizes on LVH. Another important issue addressed by serial studies using electron beam computed tomography was the effect of NSMR on the development of LVH. Ultrafast computed tomography has a high accuracy and reproducibility (i.e., low intraobserver and interobserver variabilities) with regard to the assessment of LV mass (17). As expected, there was a decrease in the septal mass due to the ethanol ablation seven days after NSMR, whereas the contralateral wall and the total LV mass were not different at that time (Fig. 2). As already described by other groups using echocardiography (6,7), the
contralateral wall and total LV mass significantly decreased after four to six months and 12 to 18 months, indicating that NSMR was followed by a sustained regression in LVH. Thus, similar to the reduction in pressure-induced LVH after aortic valve replacement (19), LVH decreased after NSMR. Apparently, these beneficial effects on LVH were present in our patients with rather small infarctions after NSMR.

Impact of smaller infarct size on complications and ventricular arrhythmias. The incidence of temporary (36%) and permanent complete heart block (0%), as well as permanent pacemaker implantation (10%), was rather low in our first group of 50 patients, compared with studies of patients with larger infarctions with a higher incidence of temporary (range 52% to 70%) (5,7,8) and permanent complete heart block (range 4% to 33%) (6–8), as well as subsequent pacemaker implantation (range 11% to 38%) (5–8). Furthermore, the susceptibility to ventricular arrhythmias did not change in the follow-up period of four to six months, as estimated from electrophysiologic testing and clinical events, which is in agreement with a previous study (8). Although we observed one death five months after NSMR, it was not related to the procedure, because the patient had concomitant coronary artery disease and died of an acute myocardial infarction. Therefore, the overall incidence of complications was acceptable, particularly with regard to the clinical improvement of our patients. From the invasive long-term hemodynamic measurements, as well as the subjective and objective measures of clinical improvement, we infer that small infarct sizes appear to be as effective as large infarct sizes for NSMR, but might be associated with a lower incidence of complications in the treatment of patients with HOCM.

Identification of the culprit septal branch. As the infarct size induced by ethanol injection is likely to be dependent on the amount of ethanol injected (4,5,20), we restricted it to a maximum of 2 ml per septal branch when we started this study in September 1996 (10). Indeed, the present study demonstrates a close correlation between the amount of ethanol injected and the maximal rise in CK levels as an estimate of infarct size, similar to the observations by other groups (5,7). However, there was no evidence that higher

Figure 3. Cardiopulmonary exercise testing before and after nonsurgical myocardial reduction. Peak VO$_2 = $ peak oxygen consumption; AT = anaerobic threshold. *p < 0.001 compared with baseline. n.s. = statistically nonsignificant.
CK levels were associated with a greater reduction in the intraventricular pressure gradient, not even in those patients with ethanol injection into more than one septal branch. To minimize the amount of ethanol required and, correspondingly, the size of the septal infarction, identification of the culprit septal branch appears to be of crucial importance. There is an ongoing discussion with regard to the best available technique to identify the culprit septal branch (6,7,21). Recently, intraprocedural myocardial contrast echocardiography has been suggested to define the extent and localization of the induced septal necrosis more precisely than pressure guidance (6,7). Despite similar use of intraprocedural myocardial contrast echocardiography, large infarctions (mean CK 1,964 ± 796 U/l) associated with a high rate of complete heart block after the procedure have been reported in one of these studies (6). The main difference between these two studies (6,7), however, was the amount of ethanol injected and the number of septal branches ablated. Therefore, these two factors seem to be more important than the use of myocardial contrast echocardiography. Other arguments to use intraprocedural contrast echocardiography appear reasonable at first glance, such as the identification of a septal branch supplying the lateral LV wall or a papillary muscle. Whether the incidence of such complications is actually reduced by echocardiographic guidance has never been demonstrated. Using pressure-guided criteria and the injection of low amounts of ethanol, we have never experienced procedural or clinical complications, indicating lateral wall or papillary muscle injections in >70 patients up to now. In addition, careful fluoroscopic examination of the passage of the contrast agent selectively injected into the septal branch might also help to avoid subsequent misinjection of ethanol.

Conclusions. Our study supports the assumption that restricting the amount of ethanol injected is more important, to reduce infarct size and complications of the procedure, than the technique used for the identification of the culprit septal branch. More than one septal branch was injected in only six patients showing several small septal branches. This might also reflect overlapping regions supplying the target myocardium responsible for the LVOT obstruction, rather than misidentification of the culprit septal branch. From these observations, we conclude that the anatomy and accessibility of the septal branches supplying the target area of NSMR is another important factor influencing the results of the procedure, which seem to be independent of the technique (21) used for the identification of the culprit septal branch.

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