

Acute and long-term results after transcatheter ablation of septal hypertrophy (TASH)

Catheter interventional treatment for hypertrophic obstructive cardiomyopathy

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Aims To evaluate acute and long-term symptomatic, haemodynamic (at rest and during exercise) and electrophysiological results of transcatheter ablation of septal hypertrophy (TASH), a catheter interventional treatment for hypertrophic obstructive cardiomyopathy.

Methods and Results Sixty-two transcatheter ablations of septal hypertrophy were performed by injection of 4.6 ± 2.6 ml 96% ethanol into septal branches in 50 patients with hypertrophic obstructive cardiomyopathy and severe symptoms. Serial left and right heart catheterization, transoesophageal echocardiography and electrophysiological investigations were repeated 2 weeks and 7 ± 1 months ($n=37$) after intervention. Transcatheter ablation of septal hypertrophy led to a reduction in septal thickness, sustained elimination of the outflow obstruction (51 ± 41 vs 6 ± 10 mmHg at rest, $P<0.001$; 134 ± 48 vs 28 ± 32 mmHg, $P<0.001$, post-extrasystolic), a decrease in left ventricular filling pressures at rest and during exercise and a pronounced clinical improvement. There was no evidence for

the creation of an arrhythmogenic substrate as assessed by serial programmed electrical stimulation in 39 patients. However, permanent high-grade atrioventricular block occurred in 17% of the patients. There were two early, but no late deaths during a mean follow-up time of 10.6 ± 5.6 months.

Conclusion Transcatheter ablation of septal hypertrophy is a promising new treatment for hypertrophic obstructive cardiomyopathy in patients with severe symptoms. It should now be compared with alternative treatment strategies in prospective randomized studies.

(*Eur Heart J* 1999; 20: 1342–1354)

Key Words: Therapy of hypertrophic obstructive cardiomyopathy, catheter interventional therapy, cardiac hypertrophy, effect of ethanol.

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Introduction

Hypertrophic obstructive cardiomyopathy is a frequently genetically transmitted cardiac disorder, characterized by a hypertrophied and non-dilated left ventricle not induced by other cardiac or systemic diseases. A reduction in intraventricular pressure gradient and improvement of symptoms are major objectives of all established therapeutic strategies such as beta-receptor

blockade, medication with verapamil and surgical myectomy^[1–11] as well as atrioventricular sequential pacing^[12–16].

In 1994, the concept of a catheter interventional treatment for hypertrophic obstructive cardiomyopathy was first described^[17,18]. It suggested selective septal branch injection of 96% ethanol in a PTCA technique to reduce septal thickness, left ventricular outflow obstruction, left ventricular filling pressures, and symptoms. The concept was based on (1) favourable acute haemodynamic results of transient septal branch occlusion^[17,18], (2) the results of chemical ablation of septal branches, used since 1988 to treat supraventricular and ventricular arrhythmias^[19–22], (3) the benefit of surgical

Revision submitted 8 January 1999, and accepted 15 January 1999.

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myectomy — the removal of a small amount of muscle from the basal septum^[1–5,8–11].

To date, the proposed technique has been applied by several groups^[23–29]. The objective of the present study was to evaluate the acute and long-term results of transcatheter ablation of septal hypertrophy in terms of symptoms, haemodynamics (at rest and during exercise) and electrophysiology in patients with hypertrophic obstructive cardiomyopathy and severe symptoms refractory to drug therapy.

Methods

Patients

The study group consists of 50 consecutive patients (28 females and 22 males) aged on average 62 ± 13 years (range 29–81 years). All patients had hypertrophic cardiomyopathy with subaortic obstruction based on typical clinical, echocardiographic and angiographic findings. Entry criteria included severe symptoms during daily activity, asymmetrical septal hypertrophy ≥ 15 mm, systolic anterior motion of the mitral valve and an intraventricular pressure gradient of ≥ 30 mmHg at rest ($n=30$) or after provocation by a single premature ventricular beat. The mean NYHA functional class was 3.0 ± 0.3 despite maximal tolerated doses of medical treatment with verapamil or beta-blockers in all patients and additional diuretics in 10 patients (at the time of hospitalization and more than 6 months before). Three patients were in NYHA functional class IV, 46 in class III and one in class II (with symptomatic intermittent arrhythmias). Besides dyspnoea, major complaints were chest pain (60%), palpitations (40%) and syncope (24%). Ventricular fibrillation occurred in one patient. Atrioventricular sequential pacing had failed to reduce symptoms in five patients. Concomitant systemic hypertension was known in two patients. The mean septal thickness was 22 ± 3.0 mm (range 15–30 mm). The invasively measured mean resting gradient was 55 ± 43 mmHg (range 0–140 mmHg), the mean post-extrasystolic gradient 140 ± 53 mmHg (range 30–250 mmHg) and the mean left ventricular end-diastolic pressure 18 ± 5 mmHg (range 9–35 mmHg). Systematic investigations of family members were not performed. However, genetic transmission of the disease was evident by virtue of the history or clinical and echocardiographic documentation in nine patients including one with an identical twin treated by atrioventricular sequential pacing because of severe symptoms related to hypertrophic obstructive cardiomyopathy. Detailed data are given in Table 1.

All patients received comprehensive information on the relative merits of further medical treatment, atrioventricular sequential pacing, surgical myectomy and the transcatheter ablation of septal hypertrophy procedure. The study was approved by the institutional review committee. Written informed consent was given by all patients before the intervention.

Table 1 Baseline Characteristics*

Number of patients	50
Age (years)	62 ± 13
Sex (female/male)	28/22
NYHA functional class	3.0 ± 0.3
IV/III/II	3/46/1 pts.
Syncope	12 pts.
FHCM	9 pts.
Preexisting DDD-pacemaker	5 pts.
IVS-thickness (mm)	22 ± 3
Left heart catheterization	50 pts.
LVOT-gradient	
Rest (mmHg)	55 ± 43
Post-ES (mmHg)	140 ± 53
Rest ≥ 30 (mmHg)	30 pts.
Post-ES ≥ 50 (mmHg)	47 pts.
LVEDP (mmHg)	18 ± 5
LVEF	0.70 ± 0.08
LVEDVI ($\text{ml} \cdot \text{m}^{-2}$)	87 ± 15
Right heart catheterization	36 pts.
Workload (watts)	67 ± 29
PAP (mmHg)	42 ± 7
VO_2max ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	13 ± 4
CI ($\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$)	5.8 ± 1.8
Electrophysiological testing	39 pts.
Inducible ventricular fibrillation	3 pts.

*Mean values \pm standard deviation; CI=cardiac index at maximal workload; IVS-thickness=interventricular septal thickness; FHCM=familial hypertrophic cardiomyopathy; LVOT-gradient=left ventricular outflow tract-gradient; LVEDP=left ventricular end-diastolic pressure; LVEF=left ventricular ejection fraction; LVEDVI=left ventricular end-diastolic volume index; NYHA=New York Heart Association; Rest=resting gradient; Post-ES=postextrasystolic gradient; PAP=pulmonary artery mean pressure at pretreatment workload; VO_2max =oxygen consumption at maximal workload

Investigations

Serial left heart catheterization, transthoracic and transoesophageal echocardiography, exercise right heart catheterization and electrophysiological testing were carried out before, as well as 2 weeks and 7 ± 1 months after, transcatheter ablation of septal hypertrophy. Clinical information was obtained over a total of 499 months after treatment. The mean follow-up time was 10.6 ± 5.6 months (range 0.5–25 months).

Transthoracic and transoesophageal echocardiography were performed on HP Sonos 1500 ultrasound and recorded on an S-VHS video to allow serial review and side-by-side comparison of the studies. For transthoracic echocardiography, a 3.5 MHz transducer was used. Multiplane transoesophageal echocardiography was performed with a 5 MHz probe. Basal ventricular septal thickness was derived from an integrated analysis of M-mode and two-dimensional echocardiograms. M-mode echocardiograms were derived from direct anatomical visualization of the two-dimensional images. Measurements were made according to the recommendations of the American Society of Echocardiography^[30]. The two-dimensional echocardiographic images were obtained in the parasternal long- and short-axis

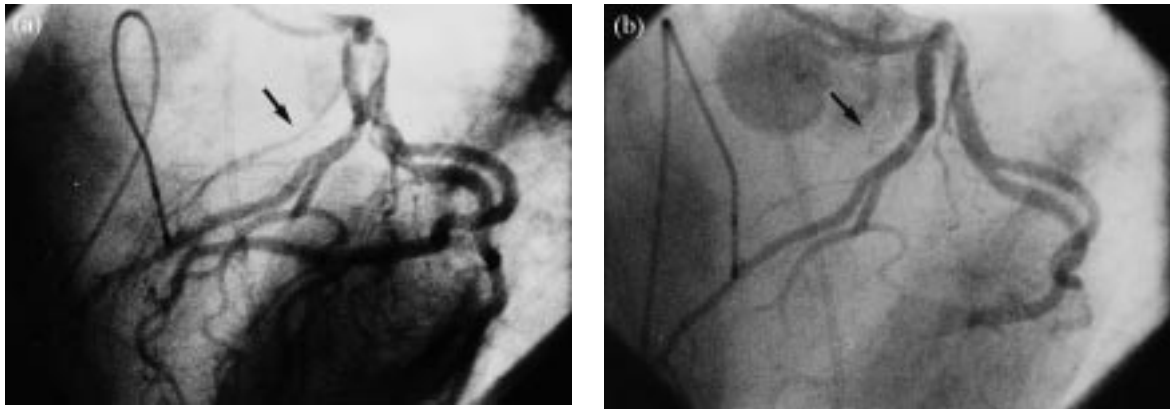


Figure 1 Transcoronary ablation of septal hypertrophy technique. (a) large first septal branch (black arrow) in the left anterior oblique projection with cranial angulation (b) occluded first septal branch (black arrow) after 96% ethanol (2 ml) was injected via the balloon catheter.

views and apical two- and four-chamber views using standard transducer positions. For transoesophageal acquisition, the probe was placed in the mid-oesophageal position, where an adequate four-chamber view could be obtained. Short-axis views were derived from a basal gastric position. Care was taken to achieve a similar probe position for the follow-up examinations. Systolic anterior motion of the mitral valve was defined as mild, moderate or severe according to the classification of Gilbert^[31].

Exercise right heart catheterization was performed with 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 with an Oxycon Oxyscreen (Jäger GmbH). Supine bicycle exercise was performed from an initial workload of 25 watts to maximum capacity, with stepwise increases of 25 watts every 3 min.

Electrophysiological studies included measurements of conduction intervals and programmed stimulation at two right ventricular sites with the use of three 5F quadripolar electrode catheters positioned in the high right atrium, in the region of the His bundle, and at the right ventricular apex and outflow tract. In addition to the intracardiac signals, leads I, II, and V₁ were recorded on a six-channel ink-writing recorder (modified Mingograph, Siemens-Elema). Programmed stimulation was performed with the Conduction System Analyser (Medtronic, 5328). The stimuli were 1.0 ms in duration and twice diastolic threshold (always less than 2 mA). The stimulation protocol included the introduction of single and double ventricular extrastimuli during sinus rhythm and paced ventricular rhythms at rates of 120, 140, 160 and 180 beats . min⁻¹, as well as the introduction of triple ventricular extrastimuli rhythms during paced ventricular rhythms at a rate of 120 beats . min⁻¹.

Transcoronary ablation of septal hypertrophy and left heart catheterization

By incorporating experience on chemical ablation of septal branches collected from rhythmological studies^[19–22], transcoronary ablation of septal hypertrophy extended the technique of transient septal branch occlusion^[18,28] to include a therapeutic selective injection of 96% ethanol (Fig. 1).

In hypertrophic obstructive cardiomyopathy, the septal target site for transcoronary ablation of septal hypertrophy was identical with the site of intraventricular obstruction, as defined by echocardiography, left ventricular angiography and — if necessary — stepwise intraventricular pressure recordings using a multi-purpose end-hole catheter. For the ablation procedure in patients with typical subaortic obstruction, the first septal branch technically applicable by standard ‘over the wire’ PTCA technique was chosen.

A 7 French PTCA-guiding catheter was placed in the ostium of the left coronary artery and a guidewire (0.014 inch) as well as a standard PTCA balloon catheter (diameter 1.5–2.5 mm) were inserted into the septal branch. After removal of the guidewire, the balloon was inflated by 300–800 kPa to prevent reflux of ethanol into the left anterior descending coronary artery and to avoid early washout of ethanol from the septal target site. 1–2 ml of radiographic contrast agent injected via the inflated PTCA catheter verified the correct position of the balloon. This was also verified by a $\geq 30\%$ ischaemia-induced decrease of the intraventricular pressure gradient. In patients without an acute reduction of the outflow tract gradient after balloon inflation, the second or third septal branch was tested during haemodynamic monitoring of the intraventricular pressure gradient. For definitive ablation of the septal hypertrophy, 96% ethanol was injected via the balloon-catheter into the most proximal septal branch demonstrating an acute decrease of obstruction. On average, 4.6 ± 2.6 ml were administered. In small septal vessels, 2 ml were

injected whereas in large septal branches up to 2×4 ml were injected. A two-session procedure (interval 8–12 days) was preferred if occlusion of more than one septal branch appeared to be necessary to meet the efficacy criteria of gradient reduction.

The transcatheter ablation of septal hypertrophy procedure was considered effective if a gradient reduction of $\geq 50\%$, with residual gradients of ≤ 30 mmHg at rest and ≤ 50 mmHg post-extrasystole, were persistently achieved 10 min and 2 weeks after one or two ablation sessions.

Pressure recordings were performed continuously between a pigtail catheter at the apex of the left ventricle and the PTCA-guiding catheter, placed in the ostium of the left coronary artery to record the left ventricular outflow gradient (peak to peak) at rest and after provocation by stimulated premature ventricular beats (fixed coupling interval 370 ms). For this purpose, a right ventricular stimulation catheter was inserted. This was intended to facilitate reproducible measurement of the post-extrasystolic gradient and served to treat high-grade atrioventricular block which frequently develops during ethanol ablation of septal branches^[21,22].

Coronary angiography and biplane ventriculography (30° right anterior oblique and left lateral projections) were performed using standard techniques. Quantitative calculation of the left ventricular ejection fraction and the left ventricular end-diastolic volume index was based on a single-plane 30° right anterior oblique view. The angiographic severity of mitral regurgitation was graded from I to IV (mild to severe) according to an accepted grading scheme (Sellers classification)^[32].

Post-procedure management included a transient right ventricular stimulation catheter and continuous ECG monitoring at the coronary care unit for up to 4 days after intervention. To avoid thrombus formation at the septal ablation site heparin was administered in the last seven cases by continuous intravenous infusion at a rate sufficient to raise the activated partial thromboplastin time to 1.5–2 times the patient's pre-heparin activated partial thromboplastin time. Medical treatment with verapamil or beta-blockers was continued during follow-up, as described in most series of surgical myectomy.

Statistics

The statistical calculations were performed using commercial software (SPSS Inc., TN, USA, release 6.0.1) with the Student's t-test for paired and independent samples. Correlations were determined with the Pearson correlation test. A *P*-value of <0.05 (two-tailed) was considered statistically significant. Values are expressed by the mean \pm SD.

Results

Left ventricular outflow obstruction and end-diastolic pressure

In 50 patients, 62 ablation sessions with occlusion of a total of 62 septal branches were performed. With two

exceptions, only a single septal branch (or super-selectively one or two of its small side branches) was occluded during the first transcatheter ablation of septal hypertrophy. Therefore, after an interval of 8–12 days a second procedure was required in 12 patients, with occlusion of a further septal branch ($n=10$) and/or a re-injection of ethanol into a reperfused septal branch ($n=5$).

Creatine phosphokinase activity was determined at hourly intervals during the first day after intervention. Peak values were 690 ± 465 U.l⁻¹ (range 134–2166 U.l⁻¹) and occurred after 5.9 ± 3.8 h (range 2–19 h).

Two weeks after the final intervention, resting gradients of ≤ 30 mmHg and post-extrasystolic gradients of ≤ 50 mmHg were measured in 40 out of 47 re-evaluated patients (Fig. 2). The average decrease in gradient in these 40 patients was 89% at rest (44 ± 38 vs 5 ± 6 mmHg, $P<0.001$) and 86% post-extrasystolic (125 ± 48 vs 17 ± 14 mmHg, $P<0.001$). Pre-defined efficacy criteria were finally achieved by occlusion of the anatomical first septal branch in 32 patients, of the second septal branch in seven patients and the third septal branch in one patient. In the remaining seven patients, the average decrease in gradient was 84% at rest (91 ± 33 vs 15 ± 21 mmHg, $P=0.002$) and 51% post-extrasystolic (184 ± 38 vs 90 ± 33 mmHg, $P=0.001$). Failure to reduce the resting gradient as well as the post-extrasystolic gradient by at least 50% was observed in none of these seven patients. One additional patient underwent successful mitral valve replacement and myectomy after failure of a single transcatheter ablation of septal hypertrophy procedure. On average, there was a significant reduction in the resting and in the post-extrasystolic gradient during transcatheter ablation of septal hypertrophy, which was persistent or even more pronounced at the follow-up examinations performed 2 weeks and 7 months after the final intervention. The reduction of outflow obstruction was accompanied by a significant decrease in left ventricular end-diastolic pressure. Detailed data are given in Table 2.

Identification of the septal target vessel was facilitated by a significant correlation of the ischaemia-induced gradient reduction before the ethanol injection and the long-term decrease in outflow obstruction after transcatheter ablation of septal hypertrophy ($r=0.8$, $P<0.001$).

Systolic left ventricular function

Left ventricular ejection fraction decreased from 0.7 ± 0.08 to 0.66 ± 0.09 ($P<0.001$) 2 weeks after the intervention but remained stable (0.67 ± 0.09) during the 7 months follow-up (Table 2). Furthermore, 7 months after intervention no significant differences were found between the subgroup of patients with one (0.68 ± 0.10) or two (0.66 ± 0.09) ablation procedures. With regard to regional left ventricular function, a small akinetic area of

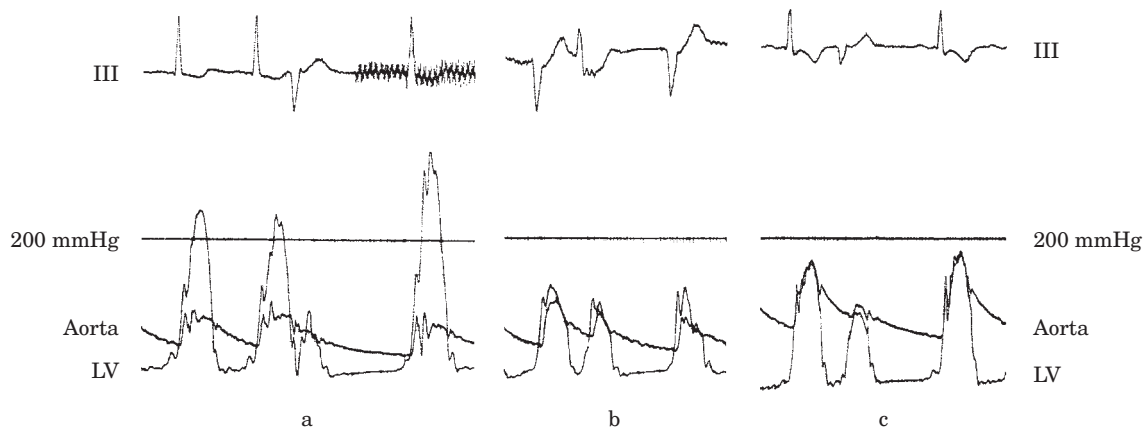


Figure 2 Effects of transcatheter ablation of septal hypertrophy on the intraventricular gradient. Compared with baseline (panel a), there is a pronounced reduction of the resting gradient (from 135 to 20 mmHg) and the post-extrasystolic gradient (from 220 to 40 mmHg) 10 min after ethanol injection. A total atrioventricular block develops and temporary VVI pacing is started (panel b). After 6 months, outflow obstruction is completely abolished during normal sinus rhythm (panel c).

the subaortic septum and a systolic widening of the outflow tract were documented (Fig. 3). This was accompanied by a slight increase in the left ventricular volume index from 87 ± 15 to 92 ± 21 ml \cdot m $^{-2}$ (ns) 7 months after intervention. In addition, there was a reduction or even complete disappearance of mitral regurgitation.

Exercise right heart catheterization

Exercise right heart catheterization was performed in 36 out of 50 patients. After 2 weeks, exercise tolerance increased from 67 ± 29 to 72 ± 27 watts (ns). Pulmonary arterial mean pressure decreased from 42 ± 7 to 33 ± 8 mmHg ($P < 0.001$) at identical pre-treatment workloads. The haemodynamic effects were confirmed by a re-examination after 7 months carried out in 32 consecutive patients to date. In these patients, exercise tolerance improved from 69 ± 29 to 88 ± 34 watts ($P < 0.001$) and pulmonary arterial mean pressure from 41 ± 7 to 34 ± 7 mmHg ($P < 0.001$). Maximal oxygen consumption ($n=24$) increased from 13 ± 4 to 16 ± 6 ml \cdot kg $^{-1}$ \cdot min $^{-1}$, i.e. from 49% to 58% ($P=0.012$) of predicted values. Cardiac index at peak exercise increased from 5.8 ± 1.6 to 6.8 ± 2.6 l \cdot min $^{-1}$ \cdot m $^{-2}$ ($P=0.048$) (Table 2).

Symptoms

During the procedure, the ethanol injection usually provoked moderate chest discomfort lasting for 30–60 s. At present a mean follow-up of 10.6 ± 5.6 months is available for 47 patients. Thirty-one patients reported marked improvement, 11 improvement and five stated that clinical symptoms were unchanged. None of the patients reported a further deterioration of symptoms

and no late deaths occurred. Therefore, the clinical success rate was 84% with subjective improvement in 42 out of 50 patients initially included in the study. Global NYHA functional class improved from 3.0 ± 0.3 to 1.9 ± 0.6 after 2 weeks ($P < 0.001$) and to 1.7 ± 0.6 after 10.6 ± 5.6 months ($P < 0.001$) (Table 2). Three patients remained in NYHA functional class III, whereas 26 patients improved to class II and 18 patients to class I (Fig. 4).

Transthoracic and transoesophageal echocardiography

Two weeks after transcatheter ablation of septal hypertrophy, subaortic septal thickness was reduced from 22 ± 3 mm to 14 ± 5 mm ($P < 0.001$) with very sharply delineated left-sided thinning in 33 out of 46 patients (Table 2). After 7 months, a further decline in septal thickness to 10 ± 3 mm (range 5–17 mm) occurred ($n=37$) (Table 2, Fig. 5). No mural thrombi were identified at the septal ablation site. A small akinetic or even dyskinetic subaortic septal area was found similar to that revealed by angiography. Subsequently, systolic anterior motion of the mitral valve and, if present, mitral regurgitation were reduced or abolished. Anterior mitral leaflet–septal contact was eliminated in all patients.

Ventricular arrhythmias and electrophysiological testing

During constant ECG monitoring in the coronary care unit, two patients developed spontaneous ventricular fibrillation within the first 48 h after the ablation procedure. Ventricular fibrillation was terminated by a

Table 2 Interventional and follow-up Data*

	Intervention			Follow-up 2 weeks			Follow-up 7 months					
	Pre	Post	P-value	n	Pre	Post	P-value	n	Pre	Post	P-value	n
Left heart catheterization												
LVOT-gradient												
Rest (mmHg)	55 ± 43	14 ± 21	<0.001	50	51 ± 41	6 ± 10	<0.001	47	45 ± 38	5 ± 7	<0.001	37
Post-ES (mmHg)	141 ± 53	42 ± 49	<0.001	49	134 ± 51	28 ± 32	<0.001	45	135 ± 50	25 ± 38	<0.001	37
LVEDP (mmHg)	18 ± 5	14 ± 5	<0.001	50	17 ± 5	12 ± 3	<0.001	45	17 ± 5	14 ± 3	<0.001	37
LVEF					0.70 ± 0.08	0.66 ± 0.09	<0.001	47	0.71 ± 0.09	0.67 ± 0.09	0.034	37
Right heart catheterization												
Workload (watts)					67 ± 29	72 ± 27	ns	36	69 ± 29	88 ± 34	<0.001	32
PAP (mmHg)					42 ± 7	33 ± 8	<0.001	36	41 ± 7	34 ± 7	<0.001	32
VO ₂ max (ml · kg ⁻¹ · min ⁻¹)					13 ± 4	14 ± 4	ns	29	13 ± 4	16 ± 6	0.012	24
CI (l · kg ⁻¹ · min ⁻¹)					5.8 ± 1.8	5.9 ± 1.9	ns	29	5.8 ± 1.6	6.8 ± 2.6	0.048	24
IVS-thickness (mm)					22 ± 3	14 ± 5	<0.001	46	22 ± 3	10 ± 3	<0.001	37
NYHA functional class					3.0 ± 0.3	1.9 ± 0.6	<0.001	47	3.0 ± 0.3	1.7 ± 0.6	<0.001	47

*Mean values ± standard deviation; CI=cardiac index at maximal workload; IVS-thickness=interventricular septal thickness; LVOT-gradient=left ventricular outflow tract – gradient; LVEDP=left ventricular end-diastolic pressure; LVEF=left ventricular ejection fraction; NYHA = New York Heart Association; Rest=resting gradient; Post-ES=postextrasystolic gradient; PAP=pulmonary artery mean pressure at pretreatment workload; VO₂max=oxygen consumption at maximal workload.

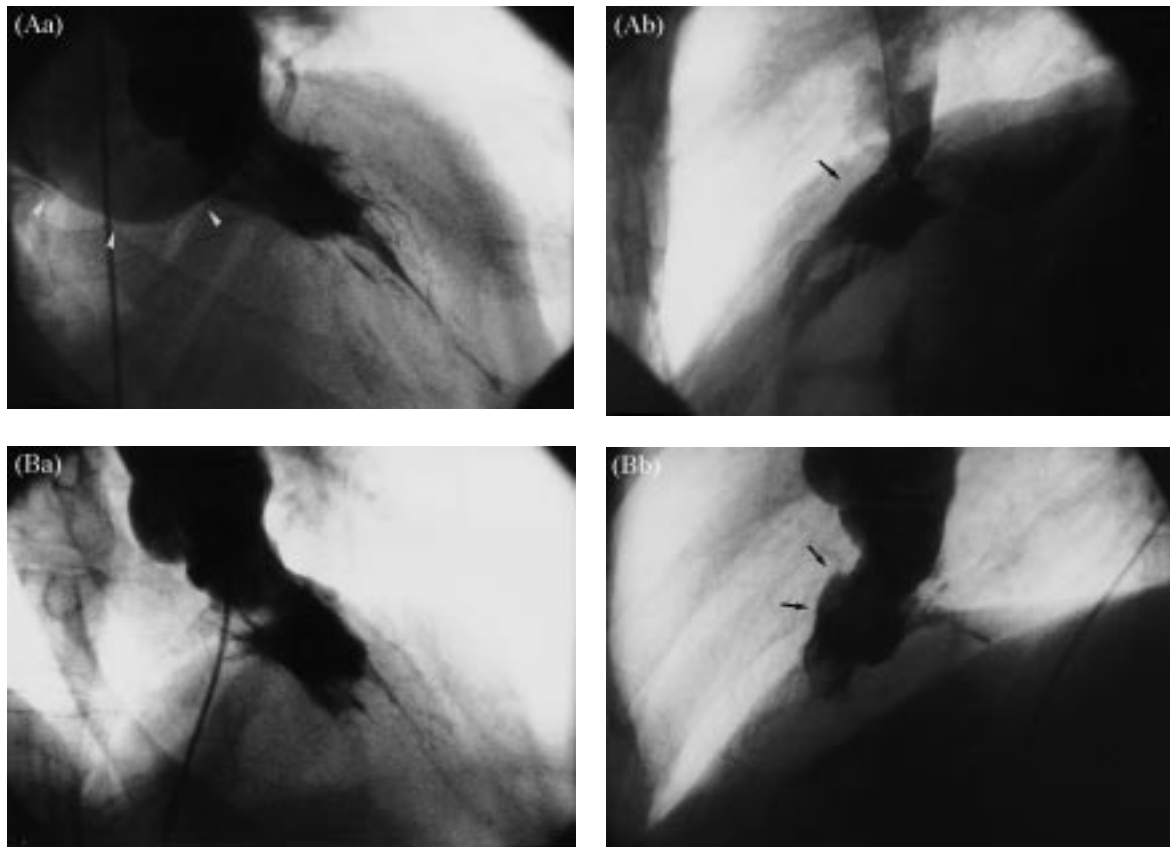


Figure 3 Left ventriculography (end-systole) in the 30° RAO projection (a) and the 90° LAO projection (b). Before (panel A) and 6 months after (panel B) transcatheter ablation of septal hypertrophy (same patient as in Fig. 1). The left ventricular outflow obstruction is abolished as a result of dyskinetic contractions of a small septal area (black arrows) without impairment of global left ventricular function even 6 months after the ablation procedure (b). This is accompanied by a reduction or even complete disappearance of mitral regurgitation (white arrowheads) (a).

single direct current defibrillation shock. After 48 h, no sustained ventricular arrhythmias or syncope occurred in any of the 50 patients treated.

To evaluate modification of ventricular vulnerability by transcatheter ablation of septal hypertrophy, programmed electrical stimulation was performed in 39 patients before and 2 weeks after the intervention. Twenty-two patients participated in a third investigation after 7 months, but in the remaining 17 patients (also asymptomatic) informed consent was not given.

In two patients, not inducible at baseline, ventricular fibrillation ($n=1$) or a sustained monomorphic ventricular tachycardia ($n=1$) was induced 2 weeks after intervention. Both were asymptomatic during follow-up without antiarrhythmic treatment and refused a third programmed stimulation after 7 months.

In three patients, ventricular fibrillation induced twice before the intervention was no longer inducible two weeks after transcatheter ablation of septal hypertrophy. They were asymptomatic during follow-up without antiarrhythmic treatment, and a third programmed stimulation was refused ($n=2$) or documented as non-inducible ($n=1$) after 7 months.

ECG changes and conduction disorders

Ethanol injection into small septal branches induced isolated ST-segment elevations and subsequent T-wave inversions in leads V_1 and V_2 . Occlusion of large septal branches, also supplying inferior parts of the septum, were additionally accompanied by ST-segment elevations, T inversions and Q waves in leads II, III and aVF. A persistent right bundle branch block occurred in 26 out of 45 patients (58%) with previously normal intraventricular conduction. A persistent left bundle branch block was observed in three patients (7%).

The most frequent side effect of transcatheter ablation of septal hypertrophy was the provocation of high-grade atrioventricular block^[21,22,25,26–29]. During the ethanol injection a third-degree atrioventricular block occurred in 32 of 50 patients (64%). This decreased over time and affected 20 of 50 patients (40%) after 48 h, eight of 48 (17%) after 2 weeks and five out of 37 (14%) after 7 months. Permanent pacing was initiated in the 20 patients with high-grade atrioventricular block that persisted for 48 h. One of these patients had a pre-existing DDD-pacemaker. The remaining 19 of 50

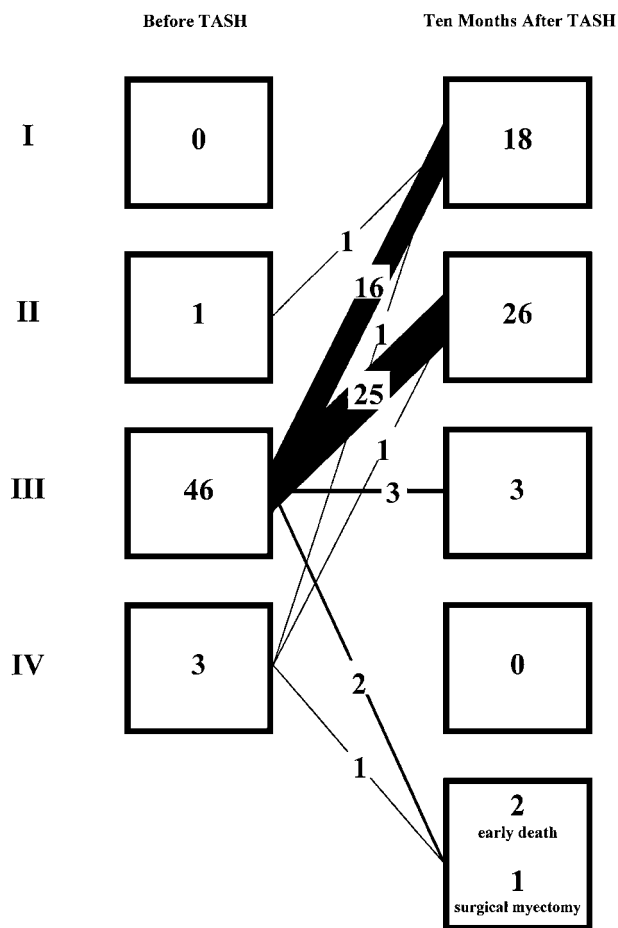


Figure 4 Changes in NYHA functional class 10 months after transcatheter aortic septal hypertrophy. NYHA functional class improved from 3.0 ± 0.3 to 1.7 ± 0.6 ($P < 0.001$).

patients (38%) therefore received an atrioventricular sequential pacemaker system in addition to transcatheter aortic septal hypertrophy. The risk of a persistent total atrioventricular block seems to be correlated to the relief of intraventricular obstruction ($r = 0.33$, $P = 0.05$).

For patients with maintained or restored atrioventricular conduction ($n = 39$), prolongation of the PQ interval from 187 ± 37 to 198 ± 53 ms ($P = 0.026$) was evident 2 weeks after intervention. AH intervals increased from 92 ± 24 ms to 102 ± 29 ms (ns) and HV intervals lengthened from 55 ± 10 ms to 67 ± 22 ms ($P = 0.016$) ($n = 26$). In patients with a loss of 1:1 atrioventricular conduction, the level of block was localized distal to the His bundle.

Complications

In one patient with pulmonary oedema, diabetes mellitus and moderate mitral stenosis, acute renal failure developed and haemodialysis was necessary for

3 days. In addition, endocarditis was diagnosed after an ischaemic stroke (documented by computed tomography with aphasia and hemiparesis showing partial restitution) had developed. Mural thrombi at the septal ablation site were ruled out by transoesophageal echocardiography.

The procedure-related early mortality was 4%, i.e. two patients died during the first 4 days after the intervention. The fatal events were provoked by the potential of transcatheter aortic septal hypertrophy-induced atrioventricular conduction disturbances and occurred in patients with severe comorbidity. One patient with recurrent syncope and two episodes of resuscitation during the previous year, received antiarrhythmic treatment and could not be resuscitated from sudden total atrioventricular block on the fourth day after a first ineffective transcatheter aortic septal hypertrophy. The second patient in NYHA functional class IV and terminal right heart failure due to severe pulmonary disease, had primary effective transcatheter aortic septal hypertrophy, but demonstrated an unusual intolerance of DDD pacing. A pacing-related irreversible low output syndrome developed immediately after loss of 1:1 atrioventricular conduction the second day after the intervention. After ineffective resuscitation (including cardiac compression) the post-mortem examination revealed a thrombus attached to the septal ablation site and a thrombus dislodged to the right middle cerebral artery. To avoid thrombus formation in the following cases, heparin was administered by continuous intravenous infusion at a rate sufficient to raise the activated partial thromboplastin time to 1.5–2 times the patient's pre-heparin activated partial thromboplastin time.

Pathoanatomical observations

Both patients had post-mortem pathoanatomical examinations. The size and the structure of the subaortic septal ablation site were identical to the findings in a third patient who died unrelated to the transcatheter aortic septal hypertrophy procedure (pulmonary thromboembolism due to immobilization because of vertebral body fracture and intensive pain) after a 4-week interval. A well-defined area of circular necrosis around the occluded first septal branch was found. The ablation area extended — nearly transseptally — from the anterior to the inferior parts of the subaortic septum with small finger-like protrusions to the posterior papillary muscle.

The histological picture of the ablated myocardium was characterized by homogeneous necrosis with persistent contracted fibres encircled by a sharply demarcated scar. This differs from an ischaemic infarction, in that separation of myocardial cells by granulation tissue extending through the necrosis could not be demonstrated, even after a 4-week interval (Fig. 6).

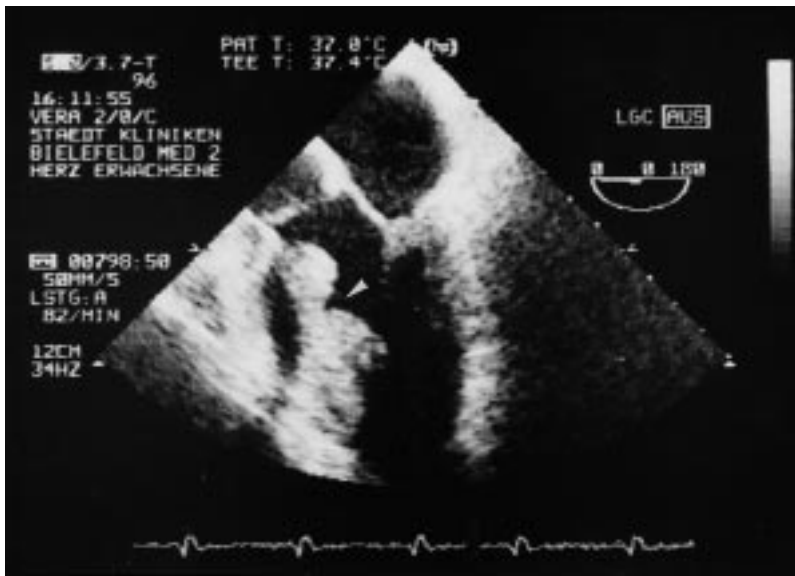


Figure 5 Transoesophageal echocardiogram 6 months after transcatheter ablation of septal hypertrophy (same patient as in Fig. 1). A sharply demarcated left sided thinning reduces septal thickness to 10 mm (white arrowhead). Systolic anterior movement of the anterior mitral leaflet is no longer evident.

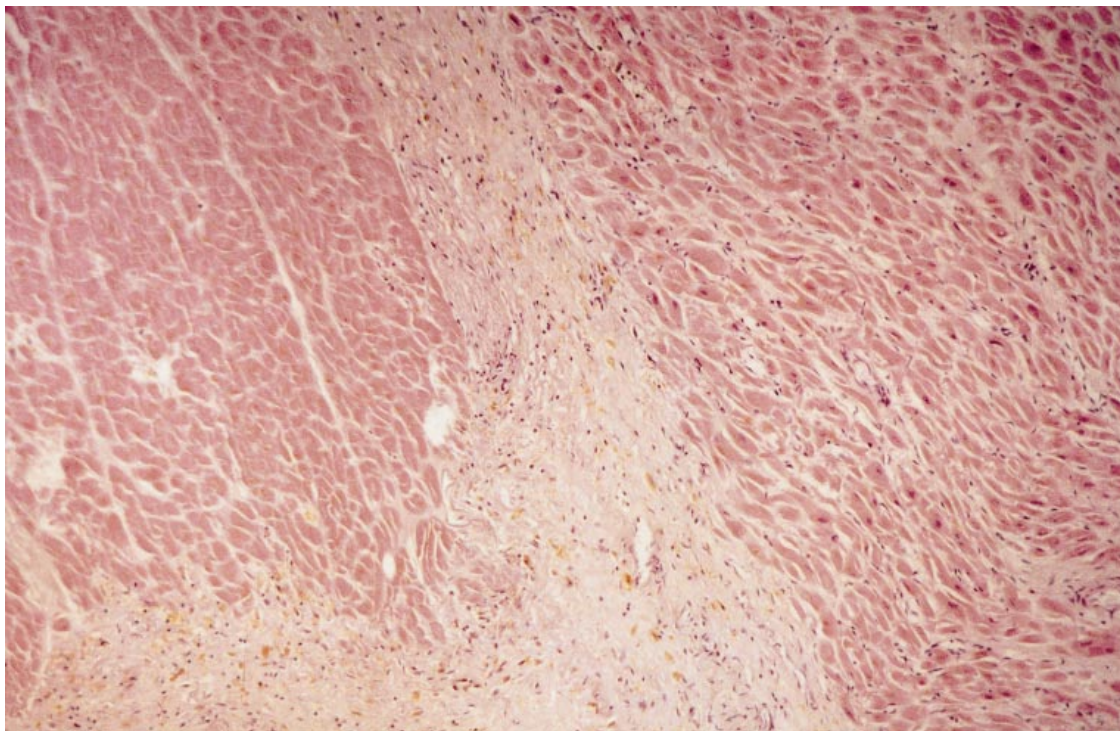


Figure 6 Ablated myocardium with homogeneous necrosis (left side of the figure), demarcated by fibrosis. Unaltered myocardium not affected by the injected ethanol on right side of the figure. Four weeks after the ablation procedure, there is no granulation tissue extending through the necrosis as one would expect in a typical ischaemic infarction (hematoxylin and eosin, $\times 125$, and reproduced here at 15 cm).

Discussion

Left ventricular outflow obstruction and symptoms

Patients with hypertrophic cardiomyopathy who present with an outflow gradient and suffer severe symptoms of heart failure that are unresponsive to medical treatment are candidates for interventional therapy. The strategy that is most widely applied and well documented in such patients is surgical myectomy, the removal of a small amount of muscle from the basal septum. Surgery abolishes or substantially reduces the subaortic outflow gradient in more than 90% of patients, and results in persistent symptomatic improvement in about 70–80%^[1–3,5,8,10]. The operative mortality has declined to less than 3% in recent years. However, despite extensive surgical experience, mortality rates remained up to 42% in patients in NYHA functional class IV^[9].

Based on the results of the present study, transcatheter ablation of septal hypertrophy using selective septal branch injection of ethanol, substantially reduced outflow obstruction in 80% and symptoms in 84% of patients. Transcatheter ablation of septal hypertrophy therefore appears to be an effective alternative to surgery. As with surgical myectomy, the positive effects were stable over time, and no recurrences in resting gradient and symptoms were observed at the follow-up examinations.

Left ventricular filling pressure

Beside a reduction in gradients, transcatheter ablation of septal hypertrophy led to a decrease in left ventricular end-diastolic pressure. Mechanisms responsible for the different behaviour of filling pressures after septal necrosis in hypertrophic obstructive cardiomyopathy and after myocardial infarction in coronary artery disease are not yet clarified. However, it might be suggested that ablation of septal hypertrophy removes myocardial tissue with impaired relaxation and abnormal passive stiffness^[4].

A decrease in afterload and oxygen demand, as well as a reduction in functional mitral regurgitation that accompany gradient reduction, might be further mechanisms involved.

The haemodynamic benefits of transcatheter ablation of septal hypertrophy could also be demonstrated by serial exercise right heart catheterization. Seven months after the intervention, significant improvements in pulmonary artery mean pressure, maximal oxygen consumption, maximal cardiac index and general workload were measured. During follow-up, a continuous increase in exercise tolerance was observed, that was not significant after 2 weeks, but highly significant after 7 months. This continuous increase is based on an ongoing reduction in gradients and septal thickness (from 22 ± 3 mm to 14 ± 5 mm after 2 weeks with a further decline to 10 ± 3 mm after 7 months) as

well as on an ongoing improvement in global physical condition after a period of bed rest early after the intervention. Medical treatment with verapamil or beta-blockers was unchanged during follow-up. The improvements in exercise haemodynamics compare favourable with the results of surgical myectomy^[33], whereas equivalent results for atrioventricular sequential pacing are not yet documented^[12–16].

Technical aspects and systolic function

The best predictor of acute and persistent elimination of intraventricular obstruction was the occlusion of the most proximal septal branch, demonstrating an ischaemia-induced reduction in gradient immediately after balloon inflation or injection of contrast agent.

There was a significant correlation of this ischaemia-induced gradient reduction before the ethanol injection and the long-term decrease in outflow obstruction after transcatheter ablation of septal hypertrophy ($r=0.8$, $P<0.001$). Hence, for the identification of the septal target vessel, we prefer this functional approach, which restricts the application of ethanol to a myocardial area that definitely contributes to the outflow obstruction. The functional approach might be a more precise identifier of the septal target vessel than the indirect anatomical approach of myocardial contrast echocardiography^[29]. However, for definitive conclusions, the different approaches should be compared in a randomized fashion.

To avoid unnecessarily large areas of ablation with potential induction of left ventricular dysfunction, the application of 96% ethanol should be restricted to a maximum of 4 ml during a single ablation session and a two-session procedure is recommended for the few patients who require injection of ethanol into several septal branches. This is supported by an ongoing decrease in septal thickness and residual gradients by processes of shrinkage in the chronic stage of necrosis, that sometimes renders additional ablation procedures unnecessary. Moreover, to preserve left ventricular function (and to avoid the risk of septal perforation) in patients with a very large first septal branch, a super-selective transcatheter ablation of septal hypertrophy with occlusion of only one or two small side branches of the first septal perforator artery should be chosen.

Altogether, the precautions described sometimes led to an area of ablation that might be inappropriately limited for the pre-existing septal hypertrophy, outflow tract narrowing and intraventricular obstruction.

In these patients, a stepwise extension of subaortic septal necrosis with a more complete reduction of septal thickness and elimination of gradients can be safely achieved by re-injection into a reperfused septal branch (indicating incomplete ablation of the myocardial area supplied) or by occlusion of a further septal branch without deterioration of global left ventricular function, as documented by biplane ventriculography 7 months after intervention.

However, because the risk of a persistent total atrioventricular block seems to be correlated to the relief of intraventricular obstruction ($r=0.33$ $P=0.05$), further investigations regarding the correlation of gradient reduction and improvement of symptoms are necessary to decide if catheter interventional treatment for hypertrophic obstructive cardiomyopathy should always lead to complete elimination of obstruction, as with surgical myectomy. This information cannot be derived from the present data, because complete elimination of gradients was achieved, with the exception of only seven patients who also demonstrated an average decrease in gradient of 84% at rest and 51% post-extrasystolic.

Ventricular arrhythmias and electrophysiological testing

One of the potential risks of transcatheter ablation of septal hypertrophy is the induction of an arrhythmogenic substrate and a subsequent increase in the rate of syncope, sudden death or sustained ventricular tachycardia^[22]. However, the observed event-free survival of 100% after 10.6 ± 5.6 months and the results of programmed stimulation after 2 weeks and 7 months are encouraging.

The induction rate of sustained monomorphic ventricular tachycardia was much lower for ethanol-induced necrosis (2.6%) as its cause was ischaemic myocardial infarction due to coronary artery disease (20–34%)^[34]. Moreover, despite a debate regarding the specificity of programmed stimulation in hypertrophic obstructive cardiomyopathy, the decrease in inducible ventricular fibrillation from 7.8% to 2.6% of the patients (ns) and the histological findings (with less pronounced infiltration of connective tissue into the necrotic myocardium) may indicate that induction of an arrhythmogenic substrate is less probable in ethanol-induced necrosis than in ischaemic myocardial infarction. Nevertheless, besides the possible induction of left ventricular dysfunction, the question of long-term rhythmological consequences remains to be determined.

ECG changes and conduction disorders

Persistent right bundle branch block was induced in 58% of the patients. In this respect, there are clear differences from surgical myectomy (which leads to left bundle branch block in 31–47%)^[35] as well as from pacing therapy in hypertrophic obstructive cardiomyopathy, which regards right ventricular pre-excitation as part of its therapeutic mechanism. Haemodynamic effects of right bundle branch block after transcatheter ablation of septal hypertrophy remain to be determined.

Another aspect concerns the induction of atrioventricular conduction disturbances^[21,22,25–29]. Based on the results of rhythmological studies^[36], dual-chamber pacemakers were implanted in 19 of the 50 patients

(38%) because of a persistent high-degree atrioventricular block after 48 h. This decision was made in order to ensure that patient care was as safe as possible. We consider that this was justified in an initial series of transcatheter ablation of septal hypertrophy patients since implantation of a dual-chamber pacemaker in hypertrophic obstructive cardiomyopathy not only treats the side effects of catheter intervention but also enables adjunct pacing therapy to be administered if necessary^[12–14].

To date, the advanced experience regarding a time-dependent decrease of atrioventricular conduction disturbances (17% after 2 weeks) and the persistent positive haemodynamic effects of the transcatheter ablation of septal hypertrophy procedure encourage a more conservative approach with pacemaker implantation only in patients with high-grade atrioventricular block persisting up to 96 h. This would result in a 50% decrease in pacemaker indications. Moreover, the risk of a permanent high-grade atrioventricular block seems to be correlated to the operator's experience and to the degree of gradient reduction intended. Six of our initial 30 patients (20%) developed a permanent high-grade atrioventricular block, whereas only two of the subsequent 20 patients (10%) were affected. Comparable results, reflecting a learning curve, were reported by Faber *et al.*^[29]. Therefore, with growing experience, a further decrease in pacemaker-implantation rates might be possible.

In spite of this, modifications to the ablation technique, resulting in a lower incidence of atrioventricular conduction disturbances, should be a major objective of further investigations. Reliable preservation of atrioventricular conduction might minimize the procedure-related early mortality and morbidity that was provoked (in patients with severe co-morbidity) by the potential of transcatheter ablation of septal hypertrophy-induced total atrioventricular block. In addition, it would further reduce the risk of infection and thrombosis by avoiding a 4-day period on a temporary pacemaker, as well as the risk of concomitant medical treatment with beta-blockers, verapamil or amiodarone.

However, to reduce the risk of late sudden atrioventricular block at this point, drugs that impair atrioventricular conduction should not be given on a routine basis. The now well documented positive effects of transcatheter ablation of septal hypertrophy on symptoms and haemodynamics has changed our therapeutic strategy to discontinue medical treatment after effective catheter intervention.

Limitations of the study

In order to keep the haemodynamic effects of adjunct atrioventricular sequential pacing as small as possible, invasive determination of the pressure gradients was carried out in all but three cases during spontaneous contractions not induced by the pacemaker. Right heart catheterization was performed in the non-pacemaker

dependent state in 31 of 37 patients investigated. In view of a persistent reduction of the outflow gradient even after pacemaker inactivation^[13,37], it cannot be ruled out with certainty that in some patients the obstruction was additionally affected by previous atrioventricular sequential pacing. However, with regard to gradient reduction, left ventricular ejection fraction, improvement of NYHA functional class, exercise tolerance and pulmonary artery mean pressure at workload, no significant differences were observed between the subgroups of patients with and without a pacemaker.

Initially, we restricted the transcatheter ablation of septal hypertrophy procedure to patients with severe co-morbidity. Therefore, and because an NYHA functional class III or IV is much more common in older than in younger patients, the average age of the study population (62 ± 13 years) was higher, as in many other studies dealing with patients in hypertrophic obstructive cardiomyopathy. However, with regard to gradient reduction, improvement of NYHA functional class, exercise tolerance and pulmonary artery mean pressure at workload, no significant differences were observed between the subgroup of patients above 62 years of age ($n=25$) and the subgroup of patients 62 years of age or younger ($n=22$).

In view of the multimorbidity and the age of individual patients, examinations which were desirable had to be dispensed with in some cases. This applies in particular to exercise right heart catheterization and electrophysiological investigations.

Conclusion

Transcatheter ablation of septal hypertrophy appears to be a promising new treatment option in patients with hypertrophic obstructive cardiomyopathy^[38], as has also been described by others^[23,25,26–29] and in two editorials by Braunwald^[39,40]. However, in 17% of the patients, permanent high grade atrioventricular block occurred and contributed to procedure-related early mortality of 4%. Keeping this in mind, transcatheter ablation of septal hypertrophy should be performed only in patients with severe symptoms refractory to drug therapy (NYHA functional class III or life-threatening arrhythmias), as an alternative to surgery. Furthermore, the long-term effect of transcatheter ablation of septal hypertrophy on global left ventricular function and prognosis, as well as its relative merits compared to atrioventricular sequential pacing, remains to be determined. Surgical myectomy remains the first choice of treatment if additional operative procedures, such as coronary artery bypass graft surgery, mitral valve replacement or aortic valve replacement, are being considered.

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