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Percutaneous Septal Ablation in Hypertrophic Obstructive Cardiomyopathy

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Abstract
This article reviews etiology, pathogenesis, natural history, and current treatment options in hypertrophic obstructive cardiomyopathy with a special focus on percutaneous septal ablation which has evolved as an alternative to myectomy in patients with symptoms refractory to medical treatment. Literature data and the own series of 337 interventions planned and 312 procedures completed (in-hopital mortality and pacemaker implantation rates: 1.2% [4/312] and 7% [22/312]) are discussed. Overall satisfactory clinical results were seen in about 90% of the patients treated with septal ablation.

Key words: Hypertrophic obstructive cardiomyopathy, percutaneous septal ablation, myectomy, risk stratification, myectomy, HOCM, HCM, HNCM

Introduction

Hypertrophic cardiomyopathy (HCM) is a cardiac condition morphologically characterized by unexplained myocardial hypertrophy. The disease is considered to be rare, however, since a prevalence of 1/500-1000 has been reported, about 80000-160000 HCM german individuals are supposed to be affected, and a substantial proportion of these will be diagnosed and treated outside specialized institutions. It is therefore important that every physician interested in cardiology has a basic understanding of this disease.

Etiology, Pathogenesis, and Pathophysiology of HCM

In >50% of patients, HCM has a familiar background; in the remainder, a new mutation has to be suspected. Inheritance is monogenetic, autosomal-dominant, with a highly variable penetrance. Mutations have been found in 10 genes coding for sarcomeric proteins; the condition therefore has been characterized as a "sarcomeric disease", with impaired generation of contractile force on the intra-cellular level. Recently, however, this concept was challenged by the finding of mutations in non-sarcomeric proteins being also associated with a HCM phenotype [1, 19, 30, 31].

Histologically, the prominent findings in HCM are myocardial disarray, hypertrophy, and increased fibrosis. The coronary arteries are also involved showing wall thickening and frequently myocardial bridging; the leaflets of the mitral valve are often elongated. A summary of these abnormalities is given in Figure 1. One concept of the pathogenesis in HCM is that of a "de-

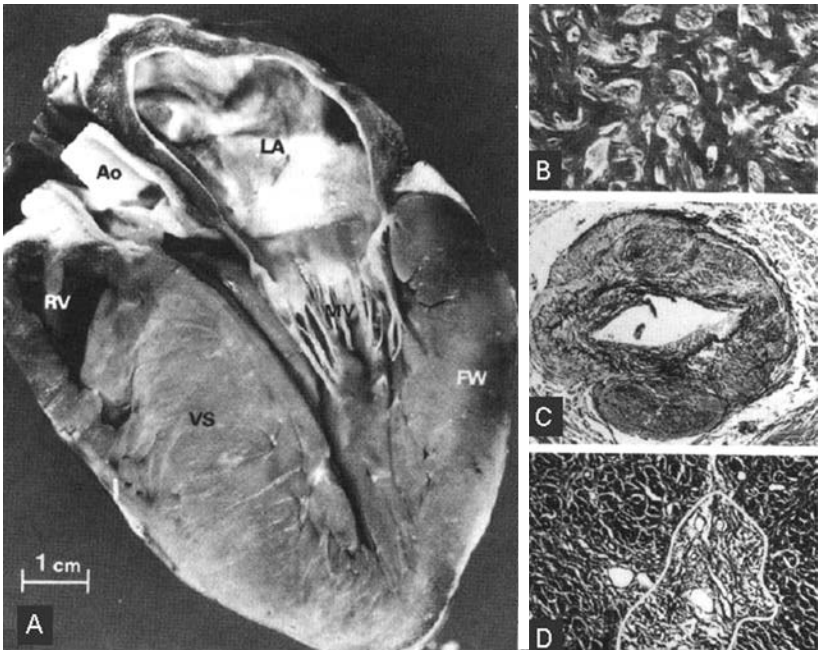

Fig. 1. Anatomic and histologic features in HCM with massive left ventricular hypertrophy (A), myocardial disarray (B), thickened coronary artery vessels (C), and areas of myocardial fibrosis (D).

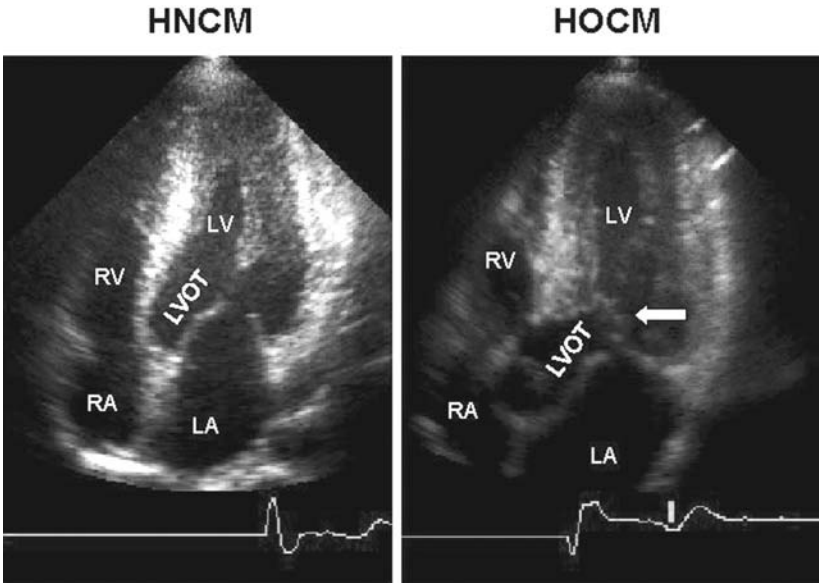

Fig. 2. Echocardiographic differentiation between non-obstructive (HNCM, left) and obstructive (HOCM) hypertrophic cardiomyopathy (arrow: SAM phenomenon).
LA: left atrium, RA: right atrium, LV: left ventricle, RV: right ventricle; LVOT: left ventricular outflow tract

fect healing" with the molecular dysfunction as the primary abnormality, and the hypertrophic process as the compensation. Left ventricular systolic function is indeed normal in the vast majority of patients. Myocardial fibrosis and hypertrophy, however, lead to increased myocardial stiffness and impairment of diastolic left ventricular function early in the disease process.

Independent from functional limitations, supraventricular and ventricular arrhythmias may occur. Again, fibrosis and disarray are considered as the arrhythmogenic subtrate; myocardial ischemia due to hypertrophy and thickened vessel walls may be a trigger [5, 19, 30, 31]. Sudden cardiac death due to ventricular tachyarhythmias is a feared complication of the disease, and sometimes its first manifestation. Among young (<35 years) athletes dying suddenly, HCM is considered to be responsible in about 30%. The dissociation between morphology, functional status, and arrhythmogenic risk is a major problem of HCM management.

A very important differential diagnosis is that between the non-obstructive (hypertrophic nonobstructive cardiomyopathy: HNCM) and the obstructive (HOCM) variant of the disease [31]. Dependent on the distribution of hypertrophy within the left ventricle, the septal curvature, the configuration of the mitral valve, and left ventricular loading conditions, about 20-30% of HCM patients develop a dynamic obstruction between a "high-pressure" (in the own series of nearly 1000 patients: up to 400 mm Hg) and a "low-pressure"compartment of the left ventricle. Typically this obstruction occurs between the subaortic septum and parts of the mitral valve ("SAM"-phenomenon), and is associated with mitral regurgitation. In a minority of cases it may be located in the midcavity region, or in the apex. Figure 2 shows typical echocardiographic examples of non-obstructive and obstructive HCM.

The hemodynamic significance of obstruction seems to depend on the size of the LV compartment that is working against increased afterload (subaortic>midcavity obstruction); apical gradients are considered to be insignificant. The pathphysiology of obstruction was heavily debated upon in past decades; the current concept combines a "trigger" (= vigorous ejection during early systole) with a "substrate" (= anatomy of the subaortic septum, the outflow tract, and the mitral valve). Not surprising, a substantial degree of variability has been decribed regarding gradient severity, and provocation (by physical exercise, pharmacological or physically induced preload reduction, or post-extrasystolic augmentation) is essential to distinguish between HNCM and HOCM both during echocardiographic and invasive hemodynamic studies [31].

Symptoms, Clinical Workup, and Natural History in HCM

Typical symptoms in HCM patients are dyspnea, angina, or dizziness on exertion. Palpitations or syncope occuring both with and without exercise are reported by 20-30%. Recurrent syncope and a family history of sudden cardiac death (at <45 years) are considered risk factors [5]. Overall, a very variable degree of limitation is characteristic. On the other hand, a severe phenotype does not necessarily preclude normal exercise capacity, or even athletic performance.

Physical examination is usually normal in patients with HNCM; the characteristic finding in HOCM is the variable systolic murmur which accentuates with preload reduction (Valsalva maneuver) and diminshes with preload increase (squatting). The diagnosis can usually be made non-invasively by imaging techniques (echocardiography, cardiac MR, multislice CT); the examiner should be prepared to see highly variable hypertrophy patterns. A wall thickness of >30 mm has to be actively looked for since this seems to be another risk factor for sudden cardiac death [5, 19]. Provocative maneuvers are essential to differentiate HNCM and HOCM. Typical ECG changes are "giant negative T waves" in HNCM and "pseudo-infarction Q waves" in HOCM, however, all types of ECG changes may be present. Holter monitoring should be performed for

risk stratification (non-sustained VT's). Stress testing is useful to measure the degree of functional limitation, and to check the blood pressure response to exercise which is considered another risk factor for sudden cardiac death

Invasive studies are needed to exclude coexistent coronary artery disease, to visualize the anatomy of the septal perforator arteries if septal ablation is considered, and to perform endomyocardial biopsy if a myocardial storage disease is suspected. The level of suspicion for such a storage disease should be high in presence of a low-voltage ECG [1, 19]. A prevalence of storage diseases of up to 10% has been reported in "HCM" series. Diastolic LV performance and the outflow gradients can also be assessed invasively; in our patient cohort, matching with the respective echocardioraphic findings was reliable. The role of invasive electrophysiology studies for risk stratification is uncertain [1, 19].

Natural history in HCM is again highly variable. In most cases the diagnosis is made during adolescence and early adulthood, and symptoms are slowly progressive. Disease manifestation in childhood is considered prognostically ominous. Late manifestation, however, is typical in carriers of the myosin-binding protein C mutation. Prognosis is determined by arrhythmic events in younger patients, and typically independent from symptoms in this group, and by cardiac failure and stroke in elderly patients. In non-selected cohorts, the annual mortality rate is reported to be around 1%/year, in high-risk group this figure rises up to 5-6% [1, 5, 19, 30].

Therapeutic Options for Obstructive HCM

General Considerations and Risk Stratification

Whether or not obstruction or symptoms are present, HCM patients should not engage in competitive sports. A limitation with respect to moderate physical activities in asymptomatic patients, however, does not seem to be justified. Outflow obstruction may exacerbate with alcohol intake, and includes an increased risk for infective endocarditis, prophylaxis is thus recommended. HCM patients in atrial fibrillation are especially prone to thrombembolic stroke, oral anticoagulation is mandatory in these cases [1, 19, 30].

All HCM patients should be risk-stratified, since the implantation of an ICD reliably reduces arrhythmogenic cardiac events. Risk stratification is based on a "malignant" family history (- of sudden cardiac death at <45 years), recurrent syncope, non-sustained ventricular tachycardia on Holter monitoring, inadequate blood pressure rise with exercise, and excessive LVH (>30 mm). In individuals with two or more of these risk markers, ICD implantation should be considered [1, 5, 19, 30].

Medical Therapy:

Medical therapy with negative inotropic drugs (beta blockers, calcium anatgonists of the verapamil type, disopyramide) is the first line of treatment in order to reduce symptoms and improve quality of life [1, 19, 30, 31]. The influence on obstruction is moderate, mostly due to reduction of the "trigger" (- forceful LV contraction during early systole). Additional anti-fibrillatory effects may be present for beta blockers, while verapamil is supposed to have a positive effect on diastolic LV function. About 5-10% of pts. have a paradoxical response to verapamil, the initiation of verapamil treatment therefore should be monitored closely. Overall, in many pts. the effect of drug treatment vanishes over the years, and none of these strategies is really "evidence-based". Drugs that lead to a marked pre- or afterload reduction, or those with positive inotropic effects are contra-indicated in HOCM since they may produce drastic exacerbation of obstruction and hemodynamic collapse.

Surgical Therapy

Surgical myotomy/myectomy, developed in the late 50ies and 60ies, traditionally has been the treatment of choice for patients with drug-refractory symptoms and significant (>50 mm Hg at rest) outflow tract obstruction [1, 12, 19-25, 30, 31]. The procedure primarily aims at the "substrate" of obstruction, i e. the protruding septal myocardium, leaves a left bundle branch block on surface ECG in >50 % of the patients treated, and usually a clearly visible septal trough on imaging studies. If necessary, valvular correction/replacement or coronary bypass grafting can be combined with the reduction of septal myocardium. Acute clinical and hemodynamic success rates of >90% have been reported together with postoperative mortality rates that finally were reduced to <1-2% in experienced centers; the rate of pacemaker dependency is about 5%. A prognostic influence is suspected from long-term observations of post-myectomy patients; however, a randomized study against medical treatment does not exist [1, 19, 30].

AV Sequential Stimulation

Dual-chamber pacemaker implantation was introduced as a less invasive alternative to myectomy in the early 90ies. Pacing from the RV apex may be understood as a combination of "trigger" reduction with a certain degree of "substrate" modification, i. e. a global negative inotropic effect and some outflow tract opening due to delayed activation of the basal septum. It also induces a left bundle branch block pattern; a gradient reduction of 50-90% has been reported [18]. Enthusiasm for this approach, however, was soon tempered since a considerable placebo effect became obvious in several randomized trials. At present, we consider AV sequential pacing a "niche indication" for

1) patients with left bundle branch block (- and thus a very high risk for complete AV block during septal ablation [see below]),
2) patients who need an ICD for risk reduction anyway, and
3) selected patients with isolated midcavity obstruction.

Septal Ablation

From 1995 onward, the therapeutic options for HOCM have dramatically changed by the introduction of percutaneous septal ablation [2, 29]. This procedure produces a circumscript septal infarction, leaves a septal lesion that often is undistiguishable from a myectomy trough, thus also aims at the "substrate" of obstruction, and reproduces the hemodynamic effect of a surgical myectomy. About 60% of the patients treated show a right bundle branch block on surface ECG, and have transient complete heart block during the procedure; the pacemaker rate should be <10% but is still >20% in some centers (- in patients with pre-existing left bundle branch block - see above: >60%). Hospital mortality figures are comparable to those in the best myectomy series (1-2 %). Several acronyms are in use (in alphabetical order: alcohol septal ablation (ASA), non-surgical myocardial reduction (NSMR), percutaneous transluminal septal myocardial ablation (PTSMA), or transcoronary ablation of septal hypertrophy (TASH), reflecting different procedural strategies [mainly with or without intra-procedural echocardiography; 2-4, 6-11, 13-17, 20-22, 26-28]. Overall, during the past decade septal ablation has gained wide acceptance as the non-surgical alternative of choice for patients with hypertrophic cardiomyopathy, significant outflow obstruction, and symptoms refractory to medical treatment.

Septal Ablation Procedure

A detailed description of the technique has been repeatedly published by our and other groups, differing in several technical aspects [3, 6-11, 13-17, 20-22, 26-28]. There is consensus that a temporary pacemaker lead is to be inserted in all patients. The LVOT gradient is constantly monitored by simultaneous pressure recordings from the left ventricular apex and the ascending aorta. An over-the-wire balloon catheter is introduced into the target septal branch presumed to be responsible for the blood supply to the septal area involved in obstruction. The balloon is inflated, and the effect on obstruction measured (Fig. 3). In contrast to other techniques who strongly rely on the effect of balloon-induced ischemia on gradient severity, in our practice the correct vessel selection is assured by way of injecting 1–2 ml of a non-toxic echocardiographic contrast agent (Levovist", Schering, Berlin, Germany; 350 mg/ml) through the central lumen of the balloon catheter under simultaneous transthoracic echocardiographic monitoring. This exactly shows the septal area that will be attacked, i. e. the future area of necrosis (Fig. 3). Opacification of any other cardiac structure

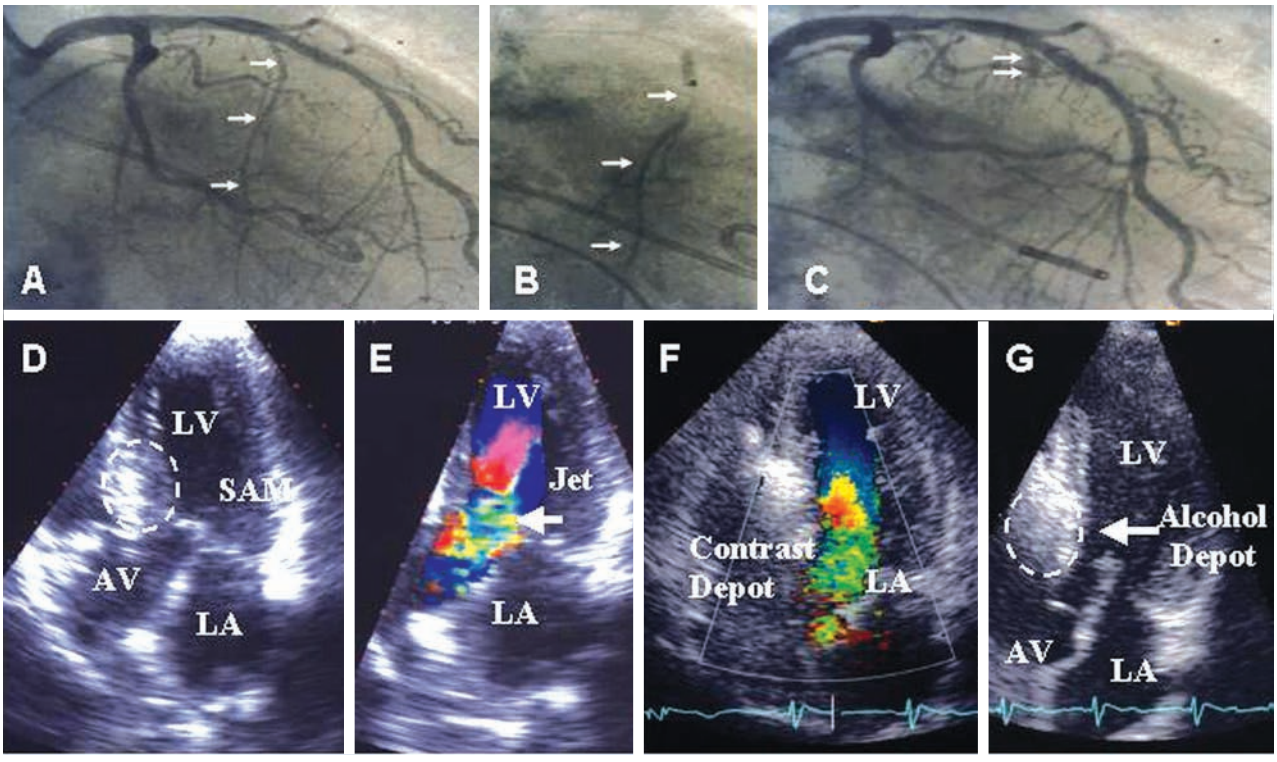

Fig. 3.
Upper panel: Left coronary angiography with the target septal branch (arrow) in RAO projection (A, arrows). Occlusion of the septal branch by balloon inflation and injection of dye through the central balloon lumen of the inflated balloon to visualize the supply area of the septal branch (B; arrow) and to exclude leakage into the LAD. Final visualization of the occluded septal branch (arrow) after alcohol injection (C).
Lower panel: Echocardiographic study during PTSMA. Baseline view, here with an angulated apical 4-chamber view (D), where the point of SAM-septal contact (dotted line: target area) and the obstructive jet (E) can be easily identified (arrow). Injection of echo-contrast agent (F) with satisfactory opacification of the target area (arrow). Visualisation after the alcohol injection (G)
LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle

has to be securely excluded. Currently, in about 10% the procedure has to be stopped based on echocardiographic findings (- usually contrast in areas distant from the septal target region), and a target vessel change is necessary for the same reason in 10-15 % [6-8, 15-17, 26, 27].

Only if the target region is correctly marked by the echo contrast agent, 1-3 ml of 96% alcohol (i. e. 1 ml per 1 cm of septal thicknesss) are slowly injected through the central lumen of the balloon catheter under analgesic medication. Ten minutes after the last alcohol injection the balloon is deflated and removed, ensuring that no alcohol backwash occurs into the left anterior descending artery. A final angiogram excludes LAD damage and verifies septal branch occlusion, and a final hemodynamic measurement is performed.

Patient Selection for Septal Ablation

Criteria for patient selection follow largely those established for septal myectomy. Septal ablation may be considered as an alternative to septal myectomy in [27]:

1) Patients with symptoms limiting daily activities (Functional class >II, exercise-induced syncope) despite adequate medical treatment, or if medical treatment is not tolerated. Patients in functional class II are accepted in our practice on an individual basis if objective measurement of exercise capacity point to a more severe limitation than subjectively perceived.

2) Patients with a substantial degree of outflow obstruction (pressure drop >30 mm Hg at rest or >100 mm Hg with provocation by a Valsalva maneuver, bicycle stress in selected cases, or post-extrasystolic augmentation)

3) Patients with a suitable left ventricular and coronary morphology, i. e. those with a "classical", subaortic obstruction produced by the protruding septum and the "SAM" of the mitral valve, and one or more septal perforator arteries that go to this septal area.

Patients with co-existing, significant coronary artery disease in one vessel only may be treated percutaneously first; ablation should be delayed until documentation of a good long-term result of PCI. In cases with multiple (>1) vessel disease, we prefer a surgical approach. In atypical obstruction or midcavity obstruction, the decision must be individualized; results are less favourable than in subaortic obstruction. Patients without obstruction, without symptoms, or pediatric patients are not candidates for septal ablation.

A routine pre-interventional workup includes exercise testing (spiroergometry and pulmonary artery catheterization) and risk assessment with respect to the need for implantation of an automatic defibrillator; in patients who receive an ICD, pacing is tried first to reduce outflow obstruction (see above). A diagnostic left heart catheterization and coronary angiogram is performed to exclude significant coronary heart disease or another pathology that would require cardiac surgery.

Current Results of Septal Ablation

1. Short term results

Across all reported series including the learning curve of the individual group of investigators, septal ablation has a peri-procedural mortality of 1-4%, at present 1-2% [2, 4, 6-9, 11. 14-17, 20-22, 26]. This holds true both for several single-center series and for the one existing multicenter registry [16]. The injected ethanol doses gradually decreased over the years (from >5 to 1-3 ml), leading to smaller infarctions and less AV conduction problems. However, the rate of pacemaker implantation still varies considerably (between <5 up to 20%). Following a local remodeling process, the morphologic and hemodynamic treatment result should be judged no earlier than after 3-6 months. At that time point, gradients usually are reduced by 80-90%, associated with an increase in exercise capacity by 20% and an improvement of diastolic LV function markers [2, 4, 6, 9, 11, 26].

In our institution, between January 1996 and December 2002 PTSMA was attempted in 337 patients (selected from 760 patients evaluated and treated in our HCM clinic). The baseline characteristics of this patient cohort are displayed in Table 1. Out of these 337 patients, 312 (92%) received an average dose of 2.8 ± 1.2 ml ethanol. Doses of >5 ml were no longer used from 1997 onward. In 25 patients the intervention was aborted without ethanol injection, mostly for safety reasons / due to contrast echocardiographic findings. The resting gradient acutely dropped from 60 ± 33 to 19 ± 22 mm Hg, the maximum provokable gradient

Table 1. Baseline data in 337 pts. with HOCM prior to septal ablation therapy.

Clinical data	
Age (years)	54 ± 15 (13 - 86)
Familial HCM (n)	86 (28 %)
Documented supraventricular tachyarrhythia (n)	80 (24 %)
History of syncope (n)	99 (30 %)
Prior myectomy (n)	10 (3 %)
Prior DDD pacemaker as treatment for HOCM (n)	16 (5%)
NYHA functional class	2.9 ± 0.5 (2 - 4)
Prior acute pulmonary edema or left heart failure (n)	36 (12 %)
Medical therapy (at inclusion)	
Beta blockers (n)	112 (36 %)
Verapamil (n)	185 (59 %)
Echocardiography	
- Left atrial diameter (mm)	49 ± 7 (33 - 83)
- LV enddiastolic diameter (mm)	45 ± 6 (30 - 62)
- Septal thickness (mm)	20 ± 4 (14 - 37)
- LV posterior wall thickness (mm)	14 ± 2 (8 - 22)
- Resting outflow gradient (mm Hg)	60 ± 33 (0 - 182)
- Provoked outflow gradient (mm Hg)	120 ± 44 (80 - 272)

Table 2. Short-term (3 months) follow-up results of septal ablation in 312 pts. after septal ablation.

	baseline	follow-up	p value
NYHA functional class	2.9 ± 0.5	1.5 ± 0.6	<0.0001
Exercise capacity (watts)	94 ± 51	115 ± 43	<0.01
Peak VO2 (ml/kg/min)	18 ± 4	21 ± 6	<0.01
Left atrial diameter (mm)	49 ± 7	46 ± 7	<0.01
LV enddiastolic diameter (mm)	45 ± 6	46 ± 6	0.02
Septal thickness (mm)	20 ± 4	17 ± 4	<0.01
Resting outflow gradient (mm Hg)	60 ± 33	13 ± 18	<0.0001
Provoked outflow gradient (mm Hg)	120 ± 44	38 ± 35	<0.0001

Table 3. Long-term follow-up data in 178 patients after septal ablation therapy.

Follow - up time (months)	60 ± 14	(36 - 84)
NYHA functional class at last follow-up	1.6 ± 0.7	(1 - 4)
Subjective improvement		147 (86 %)
Persisting class III or IV symptoms		17 (10 %)
Residual outflow gradient		
At rest (mm Hg)	6± 13	0 - 86
Provoked (mm Hg)	27 ± 30	0 - 146
Provoked outflow gradient >60 mm Hg		12 (7 %)
Tachyarrhythmic events		
ICD (secondary prophylaxis)		2 (1.2%)
ICD (primary prophylaxis)		1 (0.6%)
Sustained AF / refractory AF		24 (14%) / 6 (4%)
Bradyarrhythmic events		
Late AV block III (DDD -PM)		1 (0.6%)
Late AV block < III (DDD -PM)		2 (1.2 %)
Left ventricular failure		1 (0.6 %)
Infective endocarditis		2 (1.2 %)
Stroke (non-fatal)		6 (4 %)
Late death		9 (5 %): stroke: n = 2; SCD: n = 3, others: n = 4

AF: atrial fibrillation, DDD-PM: AV sequential pacemaker; SCD: sudden cardiac death

was reduced from 120 ± 44 to 64 ± 47 mm Hg. However, at the end of the intervention, in 119 pts. a significant provocable outflow obstruction (> 100 mm Hg) was still present. Mean CK peak was 542 ± 264 U/l with an MB fraction of 63 ± 35 U/l (normal values: < 80 and < 15 U/l, resp.). Transient AV conduction problems occured in 168 pts. (54 %); permanent AV sequential pacing was required in 22 pts (7%).

Peri-interventional mortality was 1.3 % (4 deaths). During the 3 months of follow-up there was one additional death in a pt. with coexistent coronary artery disease who developed an acute posterior infarction 4 weeks after intervention. Postmortem examination revealed plaque rupture in a mildly sclerotic right coronary artery. There were no further cardiac complications.

After 3 months self-reported exercise capacity had improved in 279 pts. (91 %); 164 pts. (54%) reported to be free of symptoms. Average NYHA functional class improved from 2.9 ± 0.5 to 1.5 ± 0.6 along with a significant increase in objective exercise capacity. In 252 pts. (83 %), gradient reduction was >50% relative to baseline values, 121 pts. (40%) were free from outflow obstruction both at rest and with provocation. Septal thickness and left atrial diameter were reduced, while there was a slight increase in enddiastolic LV diameter . LV dilatation exceeding the individual normal value or a global deterioration of systolic LV function was not observed. Tables 1 and 2 give an overview on baseline characteristics and short-time evolution of the own series.

2. Long-term results

To our best knowledge, the only publication on long-term effects of septal ablation comes from our own group ([9], Fig. 4). The main findings of this study

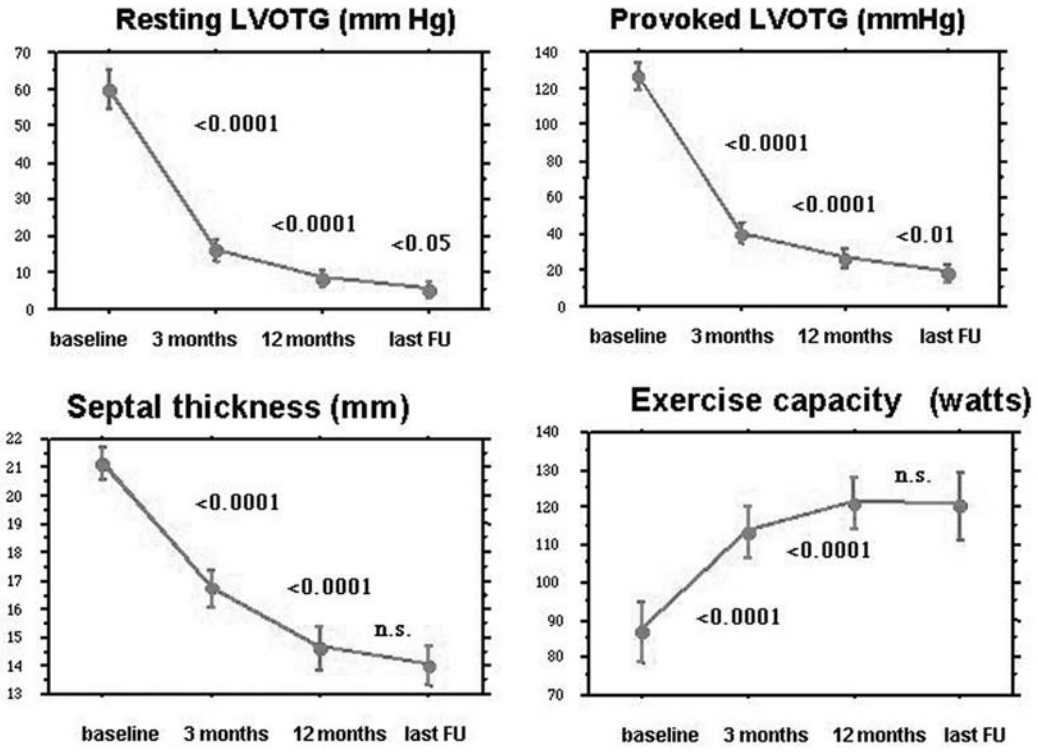

Fig. 4. Evolution of septal thickness, outfow gradient at rest and with provocation, and exercise capacity during long-term follow-up after septal ablation

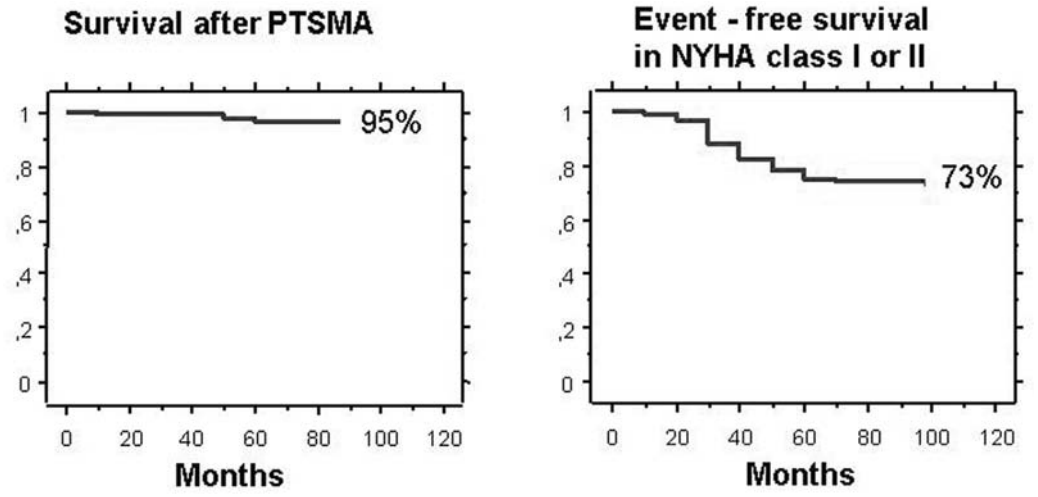

Fig. 5. Survival (left) and event-free survival in NYHA class I or II (right) after septal ablation

were for one that reduction of septal thickness and outflow gradient seems to continue over a 12-months period, presumably due to ongoing fibrosis and shrinking of the PTSMA-induced scar. The highest net gain in outflow tract diameter due to septal reduction occured between 3- and 12-months follow-up. Secondly, progressive LV dilatation was not observed, thus the remodeling process seems to remain limited to the region of intervention. Not only septal hypertrophy decreased as a consequence of the therapeutic infarction, but also left ventricular posterior wall thickness due to relief of the pressure overload, which in turn indicates that the hypertrophic process in HOCM may not be completely independent of LV afterload.

Since that publication, we repeatedly updated our "long-term cohort" of those 178 patients that were treated 1996-1998. Hemodynamic and clinical effects were maintained over a follow-up period of actually 60±14 months [36-84]. Overall survival was 94%; event-free survival in NYHA class II or lower 73% (Fig. 5). The most frequent clinical problem was atrial fibrillation (in 14 %). Overall survival and event free survival in our series were comparable to the reported post-surgical results. Since both treatment options predominantly target the outflow gradient, it can be speculated that effective gradient reduction may be the reason for this positive outcome.

Conclusion

In experienced institutions, about 90% of the patients with severely symptomatic HOCM of the subaortic type can be treated effectively with septal ablation, making this procedure an attractive alternative to the

„gold standard“ of surgical myectomy. The procedure
a) requires a careful patient selection,
b) should be part of a comprehensive program for HCM patients which offers all other options (medical treatment, myectomy, pacemaker- and ICD implantation)
c) results in a significant and long-standing clinical and hemodynamic benefit,
d) appears to have an acceptable safety profile.

Further long-term observations in large patient groups are necessary to define the role of septal ablation in comparison to surgical myectomy

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