Current Status of Alcohol Septal Ablation for Patients with Hypertrophic Cardiomyopathy

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Since the early 1960s, surgical myotomy-myectomy has been the standard treatment for patients with drug-refractory symptoms due to hypertrophic cardiomyopathy and dynamic outflow tract obstruction. Comparable morphologic and functional results can be achieved by percutaneous septal ablation (PTSMA) by alcohol-induced septal branch occlusion. The circumscribed therapeutic myocardial infarction results in widening of the left ventricular outflow tract with consecutive gradient reduction. Follow-up studies show clinical and objective improvement as well as further gradient reduction due to left ventricular remodeling. In this article, an updated review of the latest results of PTSMA is provided.

Introduction

Hypertrophic cardiomyopathy is defined as a primary and genetic myocardial disease [1,2]. At present mutations in nine different genes encoding sarcomeric proteins have been identified as disease-causing. More than 25% of the patients have dynamic left ventricular outflow tract obstruction. Additionally, a variant degree of diastolic dysfunction is present. In addition to asymmetrical hypertrophy of the ventricular myocardium, primarily of the interventricular septum, morphologic changes of the papillary muscles and the mitral valves can also often be observed [3,4]. Typical symptoms are dyspnea, angina pectoris, stress-induced syncope, and an increased risk for sudden cardiac death in some patients. Hypertrophic obstructive cardiomyopathy (HOCM) is the most frequent cause of exertional syncope or sudden cardiac death in younger patients [5].

In recent years, the potential therapeutic options for symptomatic patients have been dramatically increased by the introduction of DDD pacemaker implantation and percutaneous septal ablation (PTSMA) by alcohol-induced septal branch occlusion.

Treatment Options

Treatment of symptomatic patients with HOCM aims to improve clinical disability. From the hemodynamic standpoint, this can be achieved by reduction of the outflow tract obstruction and improvement of diastolic filling. Drug therapy, with the administration of negatively inotropic substances such as β-blockers, calcium antagonists such as verapamil, or disopyramide, [3,6] is the treatment option of first choice. However, at least 10% of patients with marked outflow tract obstruction have severe symptoms that are unresponsive to medical therapy [7] or report severe side effects of effective dose of drugs. In this group, a more active approach may be considered to improve hemodynamic function and clinical status. The reported number of drug-refractory patients may be influenced by referral bias. In our own group, in which patients are referred for interventional treatment, about two thirds require an active treatment, either by alcohol ablation or surgical myectomy, whereas in one third of the patients, modification of medical treatment results in symptomatic improvement.

Since the early 1960s, widening of the outflow tract by myotomy-myectomy has been a well-established surgical treatment for symptomatic patients with HOCM [8–11]. In brief, the surgical results should be reported to allow assessment of PTSMA results. Primarily, it should be mentioned that the most cited surgical series include up to 30% patients with relatively mild symptoms (New York Heart Association [NYHA] class II or better). Surgery substantially reduces the outflow tract gradient in 90% of the patients. However, the surgical procedure is complicated by perioperative mortality, which could be reduced to 1% to 2% by growing surgical experience [8]. Older and highly symptomatic (NYHA class IV) patients had been identified as high-risk patients [8–10]. Perioperative complications include the occurrence of a ventricular septal defect (up to 3%), complete atrioventricular block (5%) with permanent pacemaker implantation, cerebral embolism (1%–2%), and postoperative left bundle-branch block (40%) [8]. Modifications of surgical technique are necessary in selected patients with anatomic abnormalities of the mitral valve and papillary muscles [11,12].

Percutaneous Transluminal Septal Myocardial Ablation

Because of the favorable hemodynamic and clinical results of surgical myotomy-myectomy and the growing experience of interventional cardiologists, a percutaneous approach of septal myocardial ablation by inducing a localized therapeutic infarction was considered and primarily described in the late 1980s (Berghoefer, Personal communication). Preliminary studies had shown that isolated hemodynamic estimation of the target septal branch by temporary balloon occlusion of the first larger septal branch resulted in a greater than 50% resting outflow tract gradient reduction in only 3 of 10 patients and had no effect in 4 patients [13]. Sigwart [14] was the first to report a successful percutaneous myocardial reduction after occlusion of the septal branch using 96% alcohol.

Technique

Several modifications of the original ablation technique aim to improve the identification of the target septal perforator branch with optimization of the hemodynamic effect and reduction of complications [14,15••,16••]. All operators agree that a temporary pacemaker should be placed in the right ventricle because of the risk of trifascicular block during PTSMA. Ablation is performed by injection of 2 to 4 mL of absolute alcohol in the target septal branch. Identification of the septal branch by myocardial contrast echocardiography has become the standard technique [17,18]. Prior to alcohol injection, we administer 1 to 2 mL of echocardiographic contrast medium (Levovist; Schering, Berlin, Germany) through the central lumen of the balloon catheter under color Doppler and two-dimensional echocardiographic monitoring. Injection into the optimal septal branch leads to complete coverage of the echocardiography-contrast marked septal area on the one hand and the color Doppler estimated area of maximal flow acceleration as well as the area of systolic anterior movement–septal contact without opacification of any other cardiac structure on the other hand. To exclude contrast media (*ie*, alcohol) misplacements, several echocardiographic views are examined and compared with baseline echocardiograms. The amount of injected alcohol depends on the acute hemodynamic effect and the echocardiographically estimated size of the contrasted septal area. Furthermore, the reflux of alcohol into the left anterior descending coronary artery (LAD) should be excluded by injection of 1 to 2 mL of contrast dye through the central lumen of the inflated balloon catheter, which was placed in the estimated target vessel. This is of vital importance, to avoid LAD damage and infarction of the anterior wall. From the interventional standpoint, a slightly oversized balloon should be used and kept inflated 10 minutes after last alcohol injection. Actual reports confirmed that prolongation of balloon inflation periods after final alcohol injection excluded alcohol leakage down the LAD [19•].

Indication and Contraindication

Inclusion criteria for PTSMA include symptomatic patients with NYHA class III/Canadian Cardiovascular Society class III status or worse, despite drug therapy, or with important side effects from the medication. Patients with less severe symptoms were treated only if they had particularly high outflow tract gradients (50 mm Hg at rest or 100 mm Hg under stress) and documented high-risk factors for sudden cardiac death [3,6], or objective reduction of exercise capacity. It should be taken into consideration, however, that at present there are few data to suggest that a resting gradient greater than 30 mm Hg has an impact on the risk for sudden death [20]. Patients with exercise-induced syncope and recurrent episodes of atrial fibrillation with negative impact on clinical symptoms and potential embolic events should be considered to have a more active treatment.

Patients with previous but hemodynamically unsuccessful surgical myectomy or DDD pacemaker implantation can also be treated with ablation. Patients with concomitant cardiac diseases indicating surgery, such as extensive coronary artery disease, valvular disease, and morphologic changes of the mitral valve as well as papillary muscle responsible for gradient formation or mitral regurgitation, should not be treated interventionally. Furthermore, hypertrophic cardiomyopathy without resting or provocable outflow tract gradient is a clear contraindication for PTSMA. Alcohol should not be injected in the presence of echocardiographically failed identification of a target septal branch, when there is opacification of any cardiac structure other than the target septal area by echocardiographic contrast media, or when an unstable balloon position is creating a risk for alcohol reflux during injection.

In symptomatic patients with HOCM and coronary artery disease requiring revascularization, surgery—simultaneous myectomy and bypass—is the standard therapy. Because the surgical risk in this combined procedure is significantly increased, in individual cases involving a single vessel disease that is well suited to dilatation and stenting, combined percutaneous treatment (percutaneous transluminal coronary angioplasty and PTSMA) may be performed [21].

Results

Acute results and complications

At the present time, about 900 patients are known to have been treated worldwide. Left ventricular outflow tract gradient reduction can be achieved acutely in about 90% of the treated patients [14,15••,16••,19•,22,23•,24–28,29•].

Our own experiences showed an acute reduction of left ventricular outflow tract gradients from 72 ± 36 mm Hg to 20 ± 22 mm Hg ($P < 0.00001$) at rest and from 148 ± 43 mm Hg to 62 ± 44 mm Hg post extrasystole ($P < 0.00001$). Younger patients, less than 40 years of age, showed lower gradient reduction than elderly patients [30]. Bigger septal

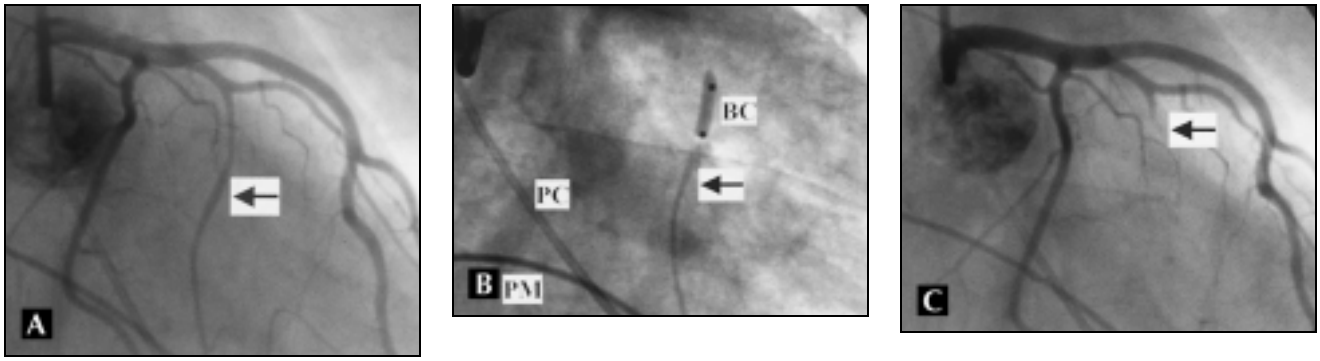

Figure 1. A, Left coronary angiography shows the target septal branch (*arrow*) atypically originating from the diagonal branch in RAO (right anterior oblique). **B**, Injection of dye through the central lumen of the inflated balloon (BC) determines the supply area of the septal branch *(arrow*) and excludes leakage into the diagonal branch. **C**, Final visualization of the vessel stump (*arrow*) after alcohol-induced septal branch occlusion.PC—pigtail catheter; PM—pacemaker lead.

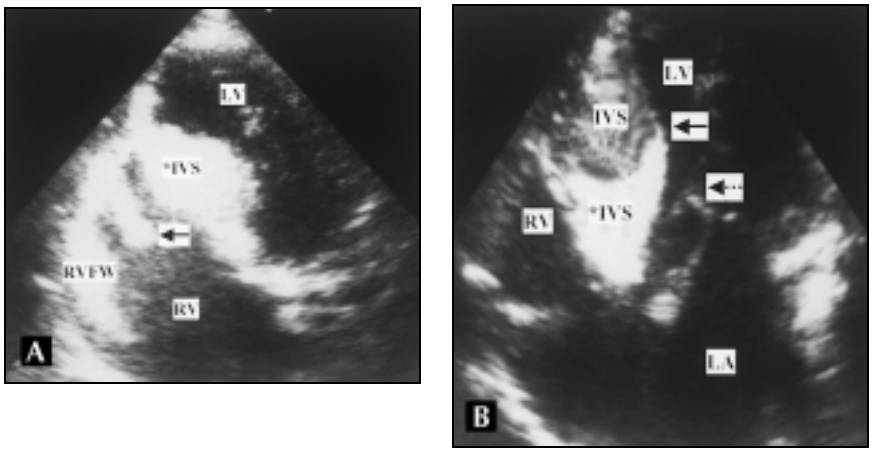

Figure 2. Angulated apical four-chamber view (*panel A*) with echo-contrast opacification of the intraventricular septum (*IVS), right ventricular free wall (RVFW), and papillary muscle (*arrow*). After change of the target vessel (*panel B*) optimal echo-contrast opacification of the subaortic septum (*IVS) with coverage (*dotted arrow*) of the systolic anterior movement-septum contact point and 1 cm below (*arrow*) LA—left atrium; LV—left ventricle; RV—right ventricle.

thickness and additional morphologic changes such as abnormal papillary muscles may be the reason for that finding. But, about 50% of the young patients with an insufficient acute result show improvement of gradient reduction at follow-up because of postinfarction remodeling and shrinkage of the ablated septal area. Patients with functional class IV disease showed acute results comparable with those in symptomatic patients [31].

In about 25% of our own patients, echocardiographic guidance had an important impact on the choice of the ablated area by identifying an atypically originating septal branch as target vessel (Fig. 1) or by avoiding alcohol misplacement after change of the vessel following echocardiographic contrast opacification of wrong septal areas or other cardiac structures such as papillary muscles or ventricular free walls (Fig. 2). Furthermore, a target septal area could not be identified in about 5%, in whom the procedure was stopped before alcohol was injected. Possible complications due to necrotization of these structures could thereby be avoided.

Furthermore, the induced scar can be reduced by the use of myocardial contrast echocardiography (MCE), thus avoiding unnecessary enlargement of the septal scar, with all of the associated potential negative consequences for left ventricular systolic and diastolic function. The optimization of ablated septal area could be shown by reduced rise in creatinine kinase after introduction of echocardiographic contrast guidance [16••]. Despite that, an outflow gradient reduction greater than 50% was achieved in 86% of the patients who underwent MCE compared with only 70% of the patients who did not have MCE ($P < 0.05$). As Ruzyllo *et al.* [19•] described, a gradient reduction of 50% compared with baseline values is needed to achieve an improvement of objective exercise measurements.

Before starting PTSMA, the typical complications related to acute induced myocardial infarction had to be taken into consideration: largely the occurrence of ventricular and supraventricular dysrhythmia and infranodal trifascicular blocks depending on the course and supply of the atrioventricular node. Furthermore, iatrogenic ventricular septal defects, cerebral embolisms, and papillary muscle rupture with consecutive acute mitral insufficiency, depending on the distribution pattern of the injected alcohol, had to be taken into account. But, echocardiographic monitoring helps to exclude most of the mentioned potential complications.

The most significant complications observed to date are hospital deaths, at a rate of up to 4% [23•]. Our own experience with PTSMA in 290 patients (Table 1) showed hospital mortality of 1.0%, which is at least comparable

Table 1. Published acute results of percuataneous septal ablation

Study	Patients, *n*	Success without complication, *n* (%)	Death, *n* (%)	Pacer, *n* (%)	Comments
Seggewiss *et al.* [21]	25	22 (88)	1 (4)	5 (20)	No echo-monitoring
Faber *et al.* [22]	91	89 (97)	2 (2.2)	10 (11)	Improvement of results by echo-monitoring
Gietzen *et al.* [23•]	50	NR	2 (4.0)	NR	12 re-interventions; no echo-monitoring
Nagueh *et al.* [33]	29	NR	0	10 (34)	4 patients with only provocable gradients at dobutamine infusion
Knight *et al.* [29•]	18	16 (89)	0	1 (5)*	1 patient with alcohol leakage down the left anterior descending artery
Kornacewicz-Jach *et al.* [32]	9	9 (100)	0	2 (22)	Echo-monitoring
Combined Bad Oeynhausen/ Schweinfurt results	290	261 (90)	3 (1.0)	16 (5.5)	DDD pacer rate with echo-monitoring 4.2%

NR—not reported.
* Six patients with pacemaker implantation before percutaneous septal ablation.

with the rate at experienced surgical centers. These deaths have occurred only in elderly patients and during the postinterventional period, which underlines the importance of careful hospital monitoring. Particular attention should be paid to a case report of a death occurring 10 days after the intervention as the result of an unexpected trifascicular block, which underlines the need for close arrhythmic monitoring for several days following the intervention.

The most frequent complications are peri- and postinterventional trifascicular blocks at a rate of 60%; the majority of cases of these blocks are only transitory. After the introduction of MCE, the number of permanent pacemaker implantations due to permanent trifascicular block was reduced to less than 5%, a nearly postoperative range [8]. Besides trifascicular blocks, all groups reported on the occurrence of bundle-branch blocks in about 50% of patients, predominantly involving the right bundle branch in contrast to many patients after surgical myectomy who show left bundle branch block.

In contrast to patients with myocardial infarction due to coronary artery disease, the incidence of significant ventricular dysrhythmia during and after ablation is rare. The reason for that may be revealed by the findings of pathologic examinations, in which there is a marked distinction between the myocardial necrosis induced by the ablation and the noninfarcted myocardium in contrast to patients with myocardial infarction due to coronary artery disease [32]. Also, the QT interval decreases to less than pre-interventional values during follow-up, possibly contributing to the lack of occurrence of ventricular dysrhythmia following induced infarction [15••].

Another reported complication is iatrogenic reflux of alcohol into the LAD, with transitory vessel occlusion and anterolateral ischemia [19•,25]. This can be avoided by the use of a slightly oversized balloon and angiography of the LAD after each injection of alcohol, which should be slowly administered in fractions of 1 mL and septal branch balloon occlusion for 10 minutes after last alcohol injection. Ruzyllo *et al.* [19•] could avoid alcohol leakage after prolongation of septal branch balloon occlusion after having seen this dangerous phenomenon in the three of the first 12 patients with final septal branch balloon occlusion for only 5 minutes. Balloon-induced dissections of the LAD can be avoided by positioning of the balloon in the septal branch. Other reported complications included occurrence of a peri-interventional ventricular septal defect at day 11, a cerebral embolism with persisting neurologic deficit, LAD dissections due to the guidewire requiring emergency stent implantation and a large myocardial infarction, acute mitral regurgitation probably due to necrosis of a papillary muscle, and large right and left ventricular free wall infarctions due to unexpected alcohol run-off into these areas. These complications underline the importance of echocardiographic monitoring of the procedure, which may well have avoided many of them. Furthermore, the need of re-interventions with occlusion of several septal branches was reduced, thus avoiding unnecessary enlargement of the septal scar, with all of the associated potential negative consequences for left ventricular systolic or diastolic function and increased risk of sudden death. Echocardiographic monitoring also permits the interventional treatment of combined subaortic and mid-ventricular obstruction as well as a pronounced midventricular obstruction following the reduction of its afterload after successful subaortic myectomy [33].

Follow-up studies

Clinical and hemodynamic follow-up studies up to 4 years have shown no increased risk of sudden death or arrhythmic complications[15••,16••,19•,25,34–36]. Furthermore, septal perforation has not been reported during follow-up.

The most important finding is an impressive symptomatic improvement during short- and mid-term follow-up after outflow tract gradient reduction that is reported by all groups. Mean functional class improved from NYHA 2.8 ± 0.5 to 1.4 ± 0.6 after 3 months and to 1.2 ± 0.9 after 2 years (compared with baseline; $P < 0.0001$ each) in a consecutive series of 107 patients at our institution.

Our own objective measurements showed an increase of exercise capacity from 88 ± 57 to 110 ± 40 Watts after 3 months ($P < 0.0001$) with an ongoing effect evident after 2 years (122 ± 43 Watts). These observations are similar to those reported from other groups, with a follow-up period up to 3 years in the original London series [25,34]. Ruzyllo *et al*. [19•] show that a gradient reduction greater than 50% compared with baseline is needed to achieve an objective improvement. Spiro-ergometry data of a subgroup of our own patients show a significant increase of oxygen consumption (Fig. 3) [37].

From the hemodynamic standpoint, the most important finding is the continuing and increasing reduction of the left ventricular outflow tract gradients (Fig. 4) [24,35]. Compared with the acute results, 56% of our patients revealed a further reduction in their resting and provocable gradients after 3 months. Compared with the 3-month follow-up, 43% of the patients had a further gradient reduction after 1 year. These changes result in complete reduction of gradients in 40% of the patients after 3 months and 62% of the patients after 1 year ($P < 0.01$). This should be viewed as an expression of post-interventional remodeling following an induced septal infarction, analogous to the remodeling following acute myocardial infarction. These findings also underline our strategy to induce septal necrosis by alcohol ablation which, although sufficiently large, should be as small as possible.

Remodeling after PTSMA results in reduction of both the ventricular septal thickness and the left ventricular posterior wall thickness (Table 2). As in surgical myectomy [38], these findings must be interpreted as a result of the elimination (or at least reduction) of the pressure overload. Negative effects of the induced septal infarction, especially left ventricular enlargement, have not been described. Our studies found a decrease of left atrial diameter and mitral regurgitation. Furthermore, some groups report reduction of both left ventricular end-diastolic pressure and mean pulmonary arterial pressure [22,23•,25]. Preliminary studies have shown a reduction of described risk factors for sudden cardiac death, such as exertional syncope, abnormal blood pressure response, and exercise induced ischemia, after successful PTSMA.

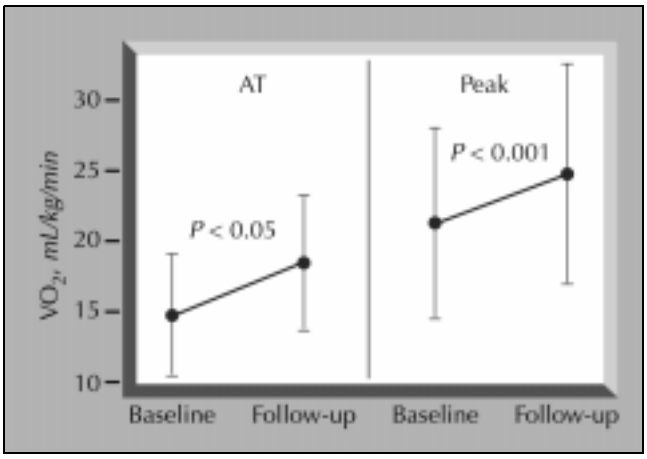

Figure 3. Results of spiroergometry show increase of oxygen consumption (VO_2) at the anaerobic threshold (AT) and peak VO_2 in 25 consecutive patients 1 year after successful percutaneous septal ablation.

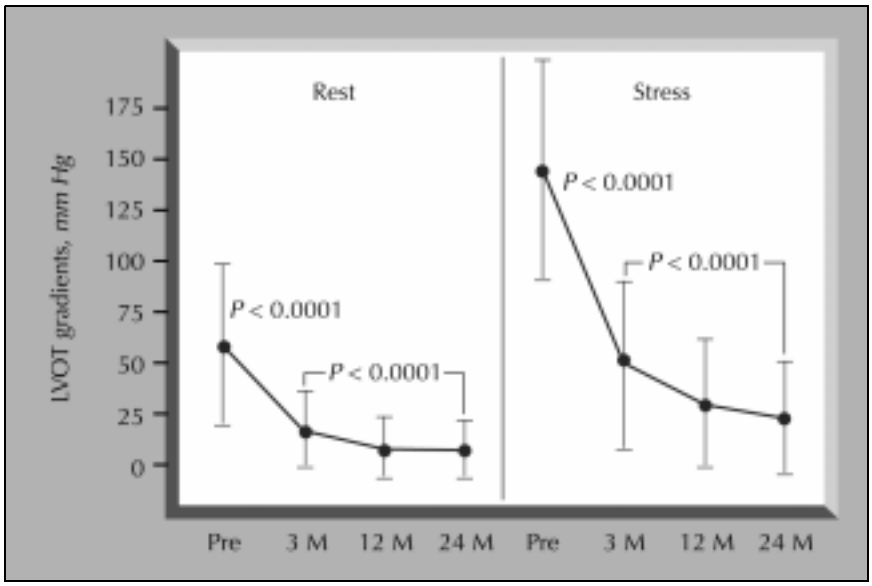

Figure 4. Ongoing reduction of left ventricular outflow tract gradients (LVOTG) at rest and stress. M—months.

Table 2. Echocardiographic 2-year follow-up results in 107 consecutive patients with hypertrophic obstructive cardiomyopathy and percutaneous septal ablation

	Baseline, *mm*	Follow-up, *mm*	*P* value
Septal thickness	23.0 ± 5.0	13.4 ± 3.2	< 0.0001
Left ventricular posterior wall thickness	13.9 ± 2.5	11.4 ± 2.0	< 0.001
Left atrial dimension	47.0 ± 7.5	45.5 ± 7.2	< 0.05
Left ventricular enddiastolic dimension	46.8 ± 4.9	48.5 ± 5.2	< 0.05

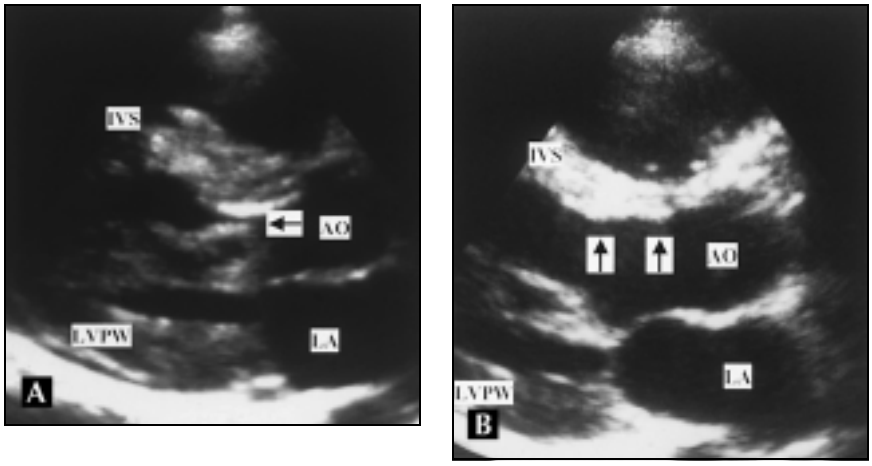

Figure 5. Parasternal long axis view at systole before (*panel A*) and 1 year after (*panel B*) percutaneous septal ablation (PTSMA). *Panel A* shows complete systolic anterior movement-septal contact (*arrow*) at the friction area of the septum (IVS). One year after PTSMA thinning of the subaortic septum (IVS) and left ventricular posterior wall (LVPW) are observed. AO—aorta; LA—left atrium.

Conclusions

Although it has been shown that mitral regurgitation and systolic movement of the mitral valve could be reduced after successful septal ablation, it should be kept in mind that the cause of mitral regurgitation should be carefully evaluated before PTSMA as well as the type and distribution of septal hypertrophy. Especially in younger patients, abnormalities of the mitral valve and papillary muscles responsible for gradient formation and mitral regurgitation should be ruled out to avoid unnecessary scarring of the septum. On the other hand, echocardiographically guided PTSMA provides the opportunity to treat patients with HCM and mid-ventricular obstruction, an unfavorable anatomy for surgical myectomy [33].

In summary, PTSMA is a promising treatment option in symptomatic patients refractory to medical treatment. Intraprocedure echocardiographic monitoring results in optimization of the ablated septal area with reduction of peri-interventional complications and improvement of acute and mid-term hemodynamic results. However, possible complications and limited long-term effects mandate careful patient selection. To avoid overuse of the technique, we would underline the importance of restricting PTSMA to a few centers with large interventional and echocardiographic experience and knowledge of this uncommon disease.

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Acute and short-term follow-up results of PTSMA pointed out the importance of necessary improvement of indentification of the target septal branch in order to optimize the amount of ablated septal area and reduce the rate of postinterventional trifascicular blocks with need of permanent pacemaker implantation.

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