Progressive decrease of outflow gradient and septum thickness after percutaneous alcoholization of the interventricular septum in hypertrophic obstructive cardiomyopathy

Flavio Airoldi*, Carlo Di Mario*§, Antonio Catanoso*, Aniruddha Dharmadhikari*, Vaios Tzifos*, Angelo Anzuini*, Mauro Carlino*, Carlo Briguori*§, Matteo Montorfano*, Marco Vaghetti§, Salvatore Tolaro**, Antonio Colombo*§

*Interventional Cardiology Unit, Hospital San Raffaele, §Centro Cuore Columbus, Milan, **Centro Cuore Morgagni, Pedara (CT), Italy*

Key words:
Hypertrophic cardiomyopathy; Septal alcoholization; Intraventricular gradient.

Background. **The aim of this study was to evaluate the immediate- and mid-term results of percutaneous transluminal septal myocardial ablation (PTSMA) of the interventricular septum performed in 15 consecutive patients with hypertrophic obstructive cardiomyopathy between 1996 and 1999.**

Methods. **Prior to intervention, all patients (7 males, 8 females, mean age 62 – 11 years) complained of severe dyspnea (NYHA functional class III-IV) despite medical treatment with β-blockers and/or verapamil. Family history of hypertrophic cardiomyopathy was present in 2 cases. Dehydrated alcohol (4.8 – 1.5 ml/pt) was selectively infused into the first septal perforator artery through over-the-wire balloon catheters. In 5 patients a second or a third septal branch was treated because the intraventricular gradient persisted above 50 mmHg after the initial alcohol infusion.**

Results. **Alcohol infusion induced an average peak creatine phosphokinase level of 1524 – 427 IU/l. No iterating ventricular arrhythmias occurred during the procedure or in the 2-3 days of continuous ECG monitoring after the procedure. Two patients (13%) developed a complete atrioventricular block after the procedure, requiring permanent double-chamber pacing. Electrocardiographic changes included a > 2 mm ST segment elevation and transient right bundle branch block or left anterior/left posterior hemiblock in all patients. Peak basal intraventricular gradient decreased from 80 – 27 to 24 – 27 mmHg ($p < 0.01$) during cardiac catheterization and from 81 – 27 to 35 – 25 mmHg ($p < 0.01$) at the echocardiograpic control performed during the hospital stay. At follow-up (mean 5.1 – 3.6 months), all patients were in NYHA functional class I or II. Repeat echocardiography showed a further significant decrease in intraventricular gradient to 25 – 26 mmHg ($p < 0.01$) and a progressive decrease in intraventricular septum thickness (25 – 5 mm before treatment, 21 – 6 mm before hospital discharge, 17 – 3 mm at follow-up, $p < 0.01$).**

Conclusions. **PTSMA of the intraventricular septum effectively relieves symptoms in selected patients with hypertrophic obstructive cardiomyopathy. The immediate decrease in intraventricular gradient is followed by a further decline at follow-up with a progressive reduction in the intraventricular septum thickness.**

(Ital Heart J 2000; 1 (3): 200-206)

Received January 7, 2000; revision received March 1, 2000; accepted March 2, 2000.

Address:

Dr. Carlo Di Mario

Unit di Emodinamica e Cardiologia Interventistica Ospedale San Raffaele Via Olgettina, 60 20132 Milano E-mail: segreteria.emodinamica@hsr.it

Introduction

Patients with hypertrophic obstructive cardiomyopathy may have chest pain, dyspnea or syncope despite optimal medical treatment with β-blockers, verapamil or disopyramide. In some cases, symptoms may initially respond to medical therapy but later become refractory or side effects to these medications may develop and require reduction of dose to subtherapeutic levels[1-6]. In the past, surgical resection of the interventricular septum (IVS) was the only alternative therapy. More recently, dual-chamber pacing has been proposed but this treatment only induces a mild reduction of intraventricular gradient and no improvement in exercise capacity has been documented[7,8]. Percutaneous transluminal septal myocardial ablation (PTSMA) was first proposed by Ulrich Sigwart[9] in 1995 for the treatment of patients with severe symptoms and significant left ventricular outflow tract (LVOT) gradient.

Methods

Patients. In this study the eligibility for treatment required the presence of disabling symptoms, severe asymmetric left ventricular hypertrophy (IVS/posterior wall thickness > 1.5) and outflow gradient 50 mmHg at rest or after Valsalva maneuver or dobutamine infusion. Fifteen consecutive patients met the indications for the procedure in the period between 1996 and 1999. The clinical characteristics of the patients are reported in table I. Repetitive persistent ventricular tachycardia requiring amiodarone treatment or implantable defibrillator was not present in any of the patients treated, including the 3 patients who experienced syncope.

Table I. Baseline clinical characteristics of the patients.

Age (years)	62 – 11 (range 45-82)
M/F	7/8
NYHA functional class	9 class III (60%)
	6 class IV (40%)
Previous DDD pacing	2 (%)
Previous myectomy-myotomy	0
Previous atrial fibrillation	2 (13%)
Previous syncope	3 (20%)
Family history of HCM	3 (20%)
Medications	
β-blockers	8
Verapamil	3
β-blockers and verapamil	4

HCM = hypertrophic cardiomyopathy.

Procedure. After the diagnostic angiogram, a 6 or 8F left extra back-up guiding catheter was advanced via the right femoral approach. A 6F multipurpose catheter, with a side-hole 3 mm proximal to the tip, was advanced to the apex of the left ventricle from the contralateral femoral artery and maintained in place to monitor the intraventricular gradient throughout the procedure. A 6F pacing electrode was advanced from the femoral vein to the right ventricular apex, pacing was tested and maintained stand-by during the entire procedure (Fig. 1A). The LVOT gradient was measured at rest in all patients and in 3 patients with basal gradient 50 mmHg the measurement was repeated after isoprenaline infusion (100-200 μg). After intravenous heparin administration of 70 IU/kg, a 0.014 180 or 300 cm long guide wire was advanced to the distal segment of the first large septal branch and an over-the-wire catheter was placed in the proximal part of the septal branch. Custom-made short balloons were used for the initial 5 cases. Standard 10 or 20 mm over-the-wire balloons were subsequently used. The balloon diameter was selected based on the size of the septal branch to be treated (range 2-3 mm) and low-pressure inflation (2-3 atm) was performed. The correct positioning of the balloon was confirmed by the absence of septal filling and by the patency of the left anterior descending artery following contrast injection into the left coronary artery (Fig. 1B). Contrast was also injected into the balloon catheter after removal of the wire to evaluate the supply area of the septal branch and confirm the absence of back-flow into the left anterior descending artery. Before starting alcohol infusion, Fentanest 0.30 mg and Diprivan 30 mg were administered intravenously and arterial saturation was monitored. Treatment of the supply area of the septal branch was performed with 98% dehydrated alcohol injected over 30-60 s through the balloon catheter into the septal branch keeping the balloon inflated. After completion of the infusion, the catheter was maintained in place for 10 min, the wire and balloon were removed and the angiogram was repeated (Figs. 1C and D). A second or a third septal branch was treated in 5 cases because of persistence of a LVOT gradient > 50 mmHg in basal condition or after isoprenaline, with incomplete distribution of alcohol in the basal IVS as assessed by intraprocedural transthoracic echocardiography. Post-interventional monitoring was carried out in the intensive care unit and included electrocardiographic monitoring and measurement determination of serial total creatine kinase (CK) and CK-MB fraction every 4 hours till they returned to baseline levels. ECG monitoring was maintained for 3-4 days.

Echocardiography. Before treatment, transthoracic echocardiograms were performed and evaluated according to the guidelines of the American Society of Echocardiography[10] using a Hewlett-Packard Sonos 2500 System. The LVOT gradient was assessed by continuous wave Doppler echocardiography using the Bernoulli equation ($p = 4V^2$). Regurgitation at the mitral valve was graded semiquantitatively (i.e. from 0 = absent to 4 = severe). In all cases, echocardiography was used at the end of the procedure to confirm the gradient reduction and the correct distribution of alcohol, visible as intensely bright echos, in the septum at the site of maximal flow acceleration pre-procedure. Echocardiography was also repeated before discharge.

Statistical analysis. Continuous variables are expressed as mean – SD. Paired data at various times were compared with Student s t test and a $p < 0.05$ was considered statistically significant.

Results

Baseline data. The mean LVOT gradient obtained with transthoracic echocardiography was 81 – 27 mmHg (range 50-147 mmHg). The mean instantaneous systolic pressure gradient between the intraventricular catheter placed in the apex and the guiding catheter difference in the LVOT as assessed by invasive catheterization was 80 – 27 mmHg (range 20-161 mmHg). The measurements were repeated after intravenous infusion

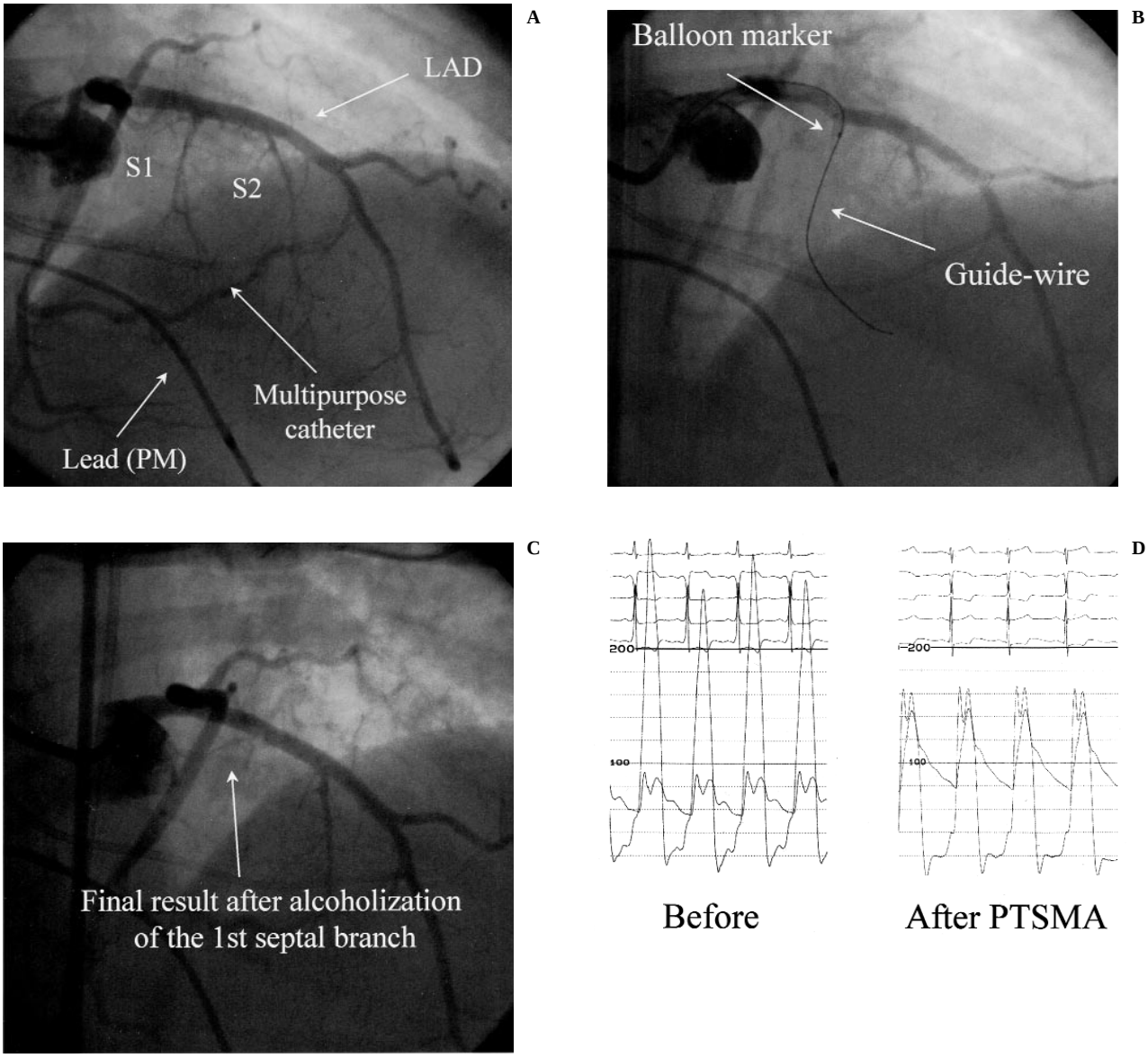

Figure 1. A: *right caudal view of the left coronary artery before percutaneous transluminal septal myocardial ablation (PTSMA). S1 and S2 indicate the first two large septal branches during systole with their typical milking aspect.* Arrows *indicate the left anterior descending artery (LAD), the 6F pacing electrode lead positioned in the right ventricular apex and the 6F multipurpose catheter advanced to the apex of the left ventricle. PM = pacemaker.* B: *after wire and balloon positioning and balloon inflation in the proximal tract of the first septal branch, its correct position is assessed by contrast injection into the guiding catheter.* C: *final result after alcohol injection and balloon and wire removal: the* arrow *indicates the vessel stump of the septal branch.* D: *peak-to-peak left ventricular outflow tract gradient treatment before and after PTSMA. The measurements are performed after isoprenaline administration (100 μg).*

of 100-200 μg of isoprenaline in 3 patients who had a baseline gradient 50 mmHg, and in all the 4 cases a significant increase was observed (from 30 – 13 to 113 – 17 mmHg, $p < 0.05$).

Immediate results. Only the first septal perforator artery was selectively infused in 10 cases while in 3 cases the first 2 septal branches and in 2 cases the first 3 septal branches were treated. The total volume of alcohol infused was 4.8 – 1.5 ml (range 3-8 ml) with mean infusion time of 46 – 20 s (range 30-60 s). An almost complete disappearance of the LVOT gradient was observed in 11 cases (< 30 mmHg resting gradient). A > 50% reduction occurred in 2 cases, while in 2 cases the gradient reduction was < 50%. The mean value of the LVOT gradient decreased from 80 – 27 to 24 – 27 mmHg ($p < 0.001$). In the 4 patients in whom isoprenaline infusion was used because a low (50 mmHg) basal gradient was present, the repeat measurements showed a significant reduction (from 113 – 17 to 33 – 8 mmHg, $p < 0.01$) (Fig. 2).

Basal and post-PTSMA LVOT gradients, amount of alcohol injected, number of septal vessels treated, maximum CPK increase and ECG changes are reported for each patient in table II.

Electrocardiographic changes. During the procedure, 6 patients developed short runs of non-sustained ventricular tachycardia. A temporary right bundle branch

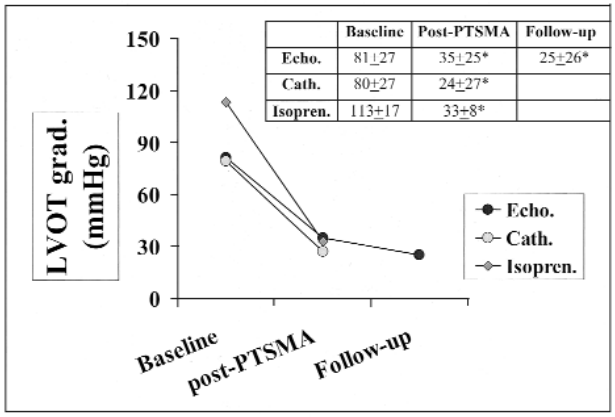

Figure 2. *Immediate- and long-term changes in left ventricular outflow tract (LVOT) gradient evaluated with catheterization (Cath) and echocardiography (Echo) both at baseline and after isoprenaline (Isopren) in 4 patients with rest gradient < 50 mmHg. PTSMA = percutaneous transluminal septal myocardial ablation. * p < 0.01 for comparison with basal levels.*

block or a temporary left anterior hemiblock were observed in 6 and in 4 patients respectively; a permanent right bundle branch block in 2 patients. Four patients developed a complete atrioventricular block; 2 recovered spontaneously within a few hours after the procedure while the other 2 required a permanent dual-chamber pacing. In one of these patients, the pacemaker was implanted 2 days after the procedure because of complete absence of recovery of atrioventricular conduction. The second patient developed a pre-syncopal episode 7 days after the procedure and ventricular escape rhythm was documented.

Clinical course. All patients, with the exception of this episode, were discharged after an uncomplicated hospital stay (5.2 – 3.1 days). The maximal increase in CPK was 1524 – 427 IU/l (range 798-2450 IU/l), with the mean MB fraction levels being 183 – 130 IU/l (range 90-376 IU/l). Low doses of β-blockers or verapamil were continued in all patients. The echocardiographic examination performed prior to discharge revealed a significant reduction of the septal thickness along with a significant decrease of the LVOT gradient and a reduction of mitral valve regurgitation. The diameters of the left ventricular cavity were unchanged (Table III).

Follow-up results. Clinical status assessment and echocardiographic measurements of LVOT gradients were repeated after a mean follow-up period of 5.1 – 3.6 months (range 1-17 months). No patients died or experienced a new syncopal episode. Eight patients were in NYHA functional class I and 7 patients were in NYHA functional class II. Long-term echocardiographic results are reported in table III. The LVOT gradient was < 50 mmHg in all cases except one in whom the gradient decreased from 146 to 92 mmHg. IVS thickness significantly decreased from 25 – 5 mm before procedure to 21 – 6 mm ($p < 0.05$) before discharge and to 17 – 3 mm ($p < 0.01$) at follow-up. A reduction in mitral regurgitation and a decrease in posterior wall thickness were also observed but they did not reach statistical significance (Table III).

Table II. Single values of left ventricular outflow tract (LVOT) gradients before and after percutaneous transluminal septal myocardial ablation (PTSMA), amount of alcohol injected, septal branches (SB) treated, peak of creatine phosphokinase (CPK), and major electrocardiographic changes.

Patient	LVOT gradient (mmHg)		Alcohol injected (ml)	SB treated	CPK peak (IU/l)	Conduction abnormalities
	Basal	Post-PTSMA				
1	80	20	7	2	1945	
2	116	99	4	2	864	
3	105	60	6	2	1520	
4	56	7	4	1	1360	
5	64	12	5	1	1645	Permanent RBBB
6	24 (124*)	5 (32*)	3	1	1208	Permanent grade III block
7	20 (96*)	10 (24*)	3	3	1204	
8	132	33	8	1	1610	
9	25 (102*)	10 (44*)	6	3	2079	Temporary grade III block Permanent RBBB
10	50 (132*)	10 (34*)	5	1	2096	Permanent grade III block
11	60	0	5	1	1650	
12	55	10	4	1	798	Temporary grade III block
13	161	54	5	1	1079	
14	89	11	4	1	2450	
15	102	20	4	1	1365	
Mean – SD	80 – 27	24 – 27	4.8 – 1.5		1524 – 427	

RBBB = right bundle branch block. * LVOT gradient after isoprenaline infusion (100-200 μg).

Table III. Immediate- and long-term echocardiographic changes after percutaneous transluminal septal myocardial ablation (PTSMA).

	Baseline	Post-PTSMA (first day after the procedure)	Follow-up (5.1 – 3.6 months)
IVS thickness (mm)	25 – 5	21 – 6*	17 – 3**
PW thickness (mm)	15 – 3	14 – 2	14 – 1
Left atrial diameter (mm)	47 – 6	45 – 5	45 – 6
LVEDD (mm)	43 – 4	41 – 3	43 – 4
LVESD (mm)	25 – 6	22 – 4	22 – 4
Mitral regurgitation (1-4)	2.6 – 1.1	1.8 – 0.4	1.5 – 0.6

IVS = interventricular septum; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; PW = posterior wall. * $p < 0.05$; ** $p < 0.01$ vs basal and vs post-PTSMA respectively.

Discussion

Patients with severe symptomatic LVOT gradient represent only a small subgroup of all patients with hypertrophic cardiomyopathy but if they are unresponsive to medical treatment it is imperative to offer them an effective alternative. The traditional therapeutic strategy in this clinical setting is surgery, which reduces the LVOT gradient by left ventricular septal myectomy. Mitral valve replacement has been proposed as adjunctive or alternative therapy to myotomy-myectomy. Although both interventions reduce the LVOT gradient in the vast majority of patients (90%), they are associated with a mortality rate which is not negligible and varies from 1.6 to 10% even in centers with vast experience[11-13]. Complications include the development of ventricular septal defects, cerebral embolism and complete atrioventricular block[11-13]. As an alternative to surgery, dual-chamber permanent pacing has been proposed[7,8] but, after the initial enthusiasm, recent studies have brought a note of caution to the efficacy of this technique in such patients. Betocchi et al.[14] and Nishimura et al.[15] have shown that prolonged dual-chamber pacing may worsen left ventricular diastolic function and that the reduction in LVOT gradient is negligible in most cases. Moreover, a recent randomized case-control study indicates that exercise tolerance is equal with the pacemaker on or off, suggesting that the often transient symptomatic improvement is due to an important placebo effect[16,17].

Although our center was the first to perform and report PTSMA in Italy[18], the stringent indication used explains the limited number of procedures performed in a highly selected population of patients with severe symptoms despite full medical treatment with β-blockers and/or verapamil, and the echocardiographic demonstration of a severe intraventricular gradient (> 50 mmHg) at rest or after provocative tests.

Since the upper half or two thirds of the IVS receives blood supply from the first-second septal perforator, a selective and limited necrosis of this area reduces the septal muscular mass and thus the extent of the outflow tract obstruction.

PTSMA is still an experimental technique and needs to be performed in a highly selected population in centers with large experience in percutaneous coronary interventions. In our experience the tachyarrhythmic events recorded during alcohol infusion were self-limiting and none of them required adjunctive treatment. Most of the bundle branch blocks and atrioventricular blocks reverted spontaneously since they were probably related to ischemia or tissue edema around the necrotic area. Two cases of complete atrioventricular block required permanent pacing; the incidence of this event in our series (13%) was similar to that reported by other authors (7-33%)[19-21]. The late recurrence (after 7 days) of atrioventricular block suggests prolonged monitoring and hospital stay at least in those patients with transient atrioventricular conduction disturbances after the procedure. The efficacy of PTSMA in reducing the LVOT gradient was immediately evident, but a further decrease was observed at follow-up as well as a concomitant progressive reduction of the IVS thickness likely due to edema regression and fibrosis. A reduction in mitral valve regurgitation was also observed and probably related to the decrease in systolic anterior motion of the mitral valve secondary to a reduction in the myocardial septum mass and contractility as reported in other experiences[22,23]. A small but significant reduction in posterior wall thickness at follow-up has been described by Faber et al.[23] and was considered a consequence of the relief of the pressure overload. In our experience, we noted similar changes even though the decrease was not statistically significant probably because of the small sample population. The CPK rise varies among the different experiences from 679 – 374 to 2200 – 520 IU/l[19-21]. In our patients the CPK rise was on the upper side of the reported experiences, equal to 1524 – 427 IU/l. Since the amount of myocardial necrosis depends on the amount of alcohol injected as well as the number of vessels treated, the high average of alcohol used (4.8 – 1.5 ml) and the treatment of multiple septal branches in 5 cases explain this finding. Because of the progressive decrease in intraventricular gradient, the aggressive strategy of this study might not have been necessary in all patients. A larger myocardial sep-

tal scar and a possible higher incidence of atrioventricular block must be weighed against the need of a second procedure of PTSMA in case of insufficient gradient reduction and symptom relief.

The use of intraprocedural myocardial contrast echocardiography has been proposed to identify the culprit septal branch and reduce the amount of alcohol required[23,24]. The promising preliminary results obtained with this strategy suggest that the adjunctional use of such a technique may reduce the incidence of periprocedural complications and therefore provide better clinical results.

The efficacy of PTSMA has been demonstrated not only by a significant reduction in the LVOT gradient but also by good clinical outcome during follow-up. The improvement of the clinical status observed in patients treated with PTSMA cannot be explained by the reduction of the LVOT gradient only and many other mechanisms such as ventricular remodeling and changes in diastolic function have been described. Kuhn et al.[25] reported a reduction of subaortic septal thickness leading to an increase in the outflow tract area as assessed by transesophageal echocardiography. Improvements in left ventricular relaxation and compliance have been described as markers of the changes in left ventricular diastolic function[22]. A significant increase in overall exercise capacity has also been noted after PTSMA as a consequence of the amelioration of systolic function[19]. Even though PTSMA is able to reduce the LVOT gradient and to improve the clinical status of the patients, the influence of PTSMA on the long-term clinical prognosis of patients with hypertrophic cardiomyopathy has not been established. A randomized prospective evaluation to compare the long-term results of this percutaneous treatment versus medical therapy does not seem ethically acceptable in severely disabled patients. Yet, a prospective register can be addressed to evaluate the long-term results of PTSMA procedures, compared with the historical series[26,27] of patients with hypertrophic cardiomyopathy treated with medical therapy. It should be noticed however that because of case selection, the large series of patients with hypertrophic cardiomyopathy reported in the medical literature with malignant ventricular arrhythmias, repetitive syncope, and poor prognosis because of sudden death, seem to have different characteristics than most of the candidates for PTSMA and to be, on average, younger, often asymptomatic or mildly symptomatic, with documented or inducible repetitive arrhythmias.

Study limitations. We report a single center prospective experience in highly selected patients. A larger population and a longer follow-up are needed to assess the potential late phenomena such as life-threatening ventricular arrhythmias or progression to left ventricular dilation or systolic dysfunction. A limitation must be noted in our follow-up: an objective demonstration of an increase in exercise capacity has been described by other authors[21] while in our study the symptomatic improvement has not been confirmed by objective evaluation and therefore a potential role of a placebo effect of PTSMA cannot be excluded. Finally, in our experience, echocontrast assessment has not been employed to evaluate the territory of perfusion of the septal branch before alcohol injection and therefore we were not able to assess the potential immediate- and mid-term benefits of such adjunctive strategy.

In conclusion, PTSMA of the IVS may be proposed as an alternative treatment to surgical myotomy-myectomy in selected patients with symptomatic hypertrophic obstructive cardiomyopathy refractory to medical therapy. It achieves a persistent relief of dyspnea with immediate decrease of the intraventricular gradient followed by a further decline at follow-up due to the progressive reduction of the IVS thickness.

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