



Non-Surgical Myocardial Reduction in Hypertrophic Obstructive Cardiomyopathy

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Abstract

Background: Percutaneous transluminal septal ablation was recently introduced as an alternative to surgical treatment of hypertrophic obstructive cardiomyopathy. In this procedure, alcohol is injected into a proximal septal artery to create a localized myocardial infarction.

Objectives: To characterize the immediate and medium-term results following PTSMA.

Methods: Of 13 patients referred for PTSMA, 8 were found suitable for the procedure. Hemodynamic parameters were evaluated prior to and following the procedure, and clinical and echo-Doppler parameters at 2 weeks and 9 months later.

Results: The procedure was technically successful in all patients. Resting left ventricular outflow gradient at rest (by Doppler) fell from 82 ± 37 to 15 ± 8 mmHg ($P < 0.001$) 9 months later. Late post-procedural gradient after the Valsalva maneuver was 2 ± 24 mmHg. The degree of mitral regurgitation fell from 2.0 ± 0 to 1.5 ± 0.5 ($P < 0.05$). New York Heart Association class for dyspnea improved from 2.8 ± 0.5 to 1.8 ± 0.8 ($P < 0.01$) and Canadian Cardiovascular Society class for angina from 2.0 ± 1.3 to 1.3 ± 1.2 ($P = 0.08$). Complete right bundle branch block developed in six patients, temporary complete atrioventricular block in three, and persistent block requiring permanent pacing in one. No flow in the distal left anterior descending coronary artery (presumably due to spilling of alcohol) was seen in one (with development of a small antero-apical infarction) and ventricular fibrillation 2 hours post-procedure in one. None of the patients died.

Conclusion: PTSMA provided a substantial reduction in left ventricular outflow gradient associated with an improvement in symptomatology. Serious complications are not uncommon. Long-term follow-up is unknown.

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Hypertrophic cardiomyopathy is a relatively common genetic disorder of the sarcomeric proteins, with an estimated prevalence of 0.2–0.5% in the population [1,2]. The disease process is characterized by the presence of inappropriate and unexplained myocardial hypertrophy usually predominant in the interventricular septum [1–6]. A distinctive pathophysiologic feature of hypertrophic cardiomyopathy is left ventricular outflow tract obstruction, present in 25% of patients and often called hypertrophic obstructive cardiomyopathy [4–6]. Most authors now hold the view that there is a true mechanical impediment to left ventricular emptying caused by systolic approximation of the anterior leaflet of the mitral valve and the hypertrophic septum just below the aortic valve [7]. LVOT obstruction may be evident at rest or can be induced with a provocation maneuver, such as Valsalva, or after extrasystole. In addition to the hemodynamic burden caused by LVOT obstruction, other pathophysiologic features contribute to the disabling symptoms. These include LV diastolic and systolic dysfunction, mitral regurgitation, ischemia and arrhythmias [3–5].

Based on an understanding of this pathophysiology, several therapeutic options for patients with HOCM have been suggested including negative inotropic agents, dual-chamber pacing, mitral valve replacement, and surgical myotomy-myectomy of the interventricular septum [8,9]. These options aim mostly at relieving symptoms and reducing obstruction. None is curative and none has clearly been shown to improve prognosis. Recently, PTSMA was introduced as an alternative non-surgical procedure that may lessen the symptoms by reducing or abolishing the LVOT obstruction [10–17]. In this study we report on the acute and mid-term clinical and echocardiographic results in eight patients who underwent this procedure.

LVOT = left ventricular outflow tract obstruction

LV = left ventricular

HOCM = hypertrophic obstructive cardiomyopathy

PTSMA = percutaneous transluminal septal ablation

Methods

Patients

Between March 1998 and July 2000, 13 patients with symptomatic HOCM resistant to medical treatment were referred to our department for PTSMA therapy. Five of 13 patients referred for PTSMA were excluded following routine pre-procedural coronary arteriography: two had extensive coronary artery disease and were referred for coronary bypass. No appropriate large septal artery feeding the hypertrophic basal septal area was found in one patient. Another patient had a severe stenosis of the right coronary artery; his symptoms improved following coronary angioplasty and he declined PTSMA. Another patient refused the procedure. All eight patients included in the study group had evidence of LVOT obstruction at rest and all had limiting symptoms. Seven patients were receiving maximally tolerated pharmacotherapy. One patient refused all medication. One of the eight patients had failed to improve following implantation of a dual-chamber pacemaker. Another remained symptomatic after dilatation and stenting of a 90% stenosis of the left circumflex coronary artery. All patients gave informed consent.

Echo-Doppler evaluation

After clinical evaluation all patients underwent complete echocardiographic study using an Accuson model ultrasound system. Using the guidelines recommended by the American Society of Echocardiography, the following parameters were measured: LV end-diastolic and end-systolic dimensions, septal and LV posterior wall thickness, and left atrial dimensions [18]. Mitral regurgitation detected by color Doppler was graded as follow: 0 = absent, 1 = trivial, 2 = mild, 3 = moderate, 4 = severe. LVOT gradient was recorded with continuous-wave Doppler from the apical view.

Hemodynamic evaluation

Cardiac catheterization was performed percutaneously from both groins. A temporary pacemaker lead was placed in the apex of the right ventricle in all patients except the one with a

permanent DDD pacemaker. A 5 or 6F right Amplatz or 7F Stefanadis catheter was introduced in one groin to LV inflow, and a 6 or 7F coronary guiding catheter in the other. Femoral artery pressure was monitored from the side arm of the femoral sheath for continuous measurement of the LV inflow-arterial gradient. Provocation of a mechanical ventricular ectopic beat was used to measure the post-extrasystolic gradient. All patients were heparinized (5,000 U). A 1.5–2.5 mm over-the-wire balloon catheter was introduced over a 0.014 wire into the first large septal artery. Following inflation of the balloon, 1–5 ml of absolute alcohol was injected slowly through the balloon lumen. Inflation was maintained for at least 5 minutes. The balloon was then deflated and withdrawn, followed by contrast injection in the left coronary ostium to confirm occlusion of the target septal artery. In three patients, contrast echocardiography was used to ascertain that the target septal branch indeed perfused the hypertrophic basal septum [16]. Morphine or midazolam to control pain was injected intravenously prior to alcoholization and thereafter as needed. Hemodynamic measurements were repeated 10 minutes following alcohol injection. All patients were kept in the Intermediate or Intensive Coronary Care Unit under constant electrocardiographic monitoring. Repeat clinical and echo-Doppler assessment was performed early and late after the procedure.

Statistical analysis

Values are presented as mean \pm 1SD. The paired *t*-test for continuous variables was used.

Results

The patients comprised six males and two females with a mean age of 49 ± 15 years (range 21–67 years). The procedure was technically successful in all patients: i.e., there was no flow in the target septal artery following alcohol injection [Figure 1]. Six patients required additional morphine or midazolam administration for pain relief. Maximal creatine kinase level post-

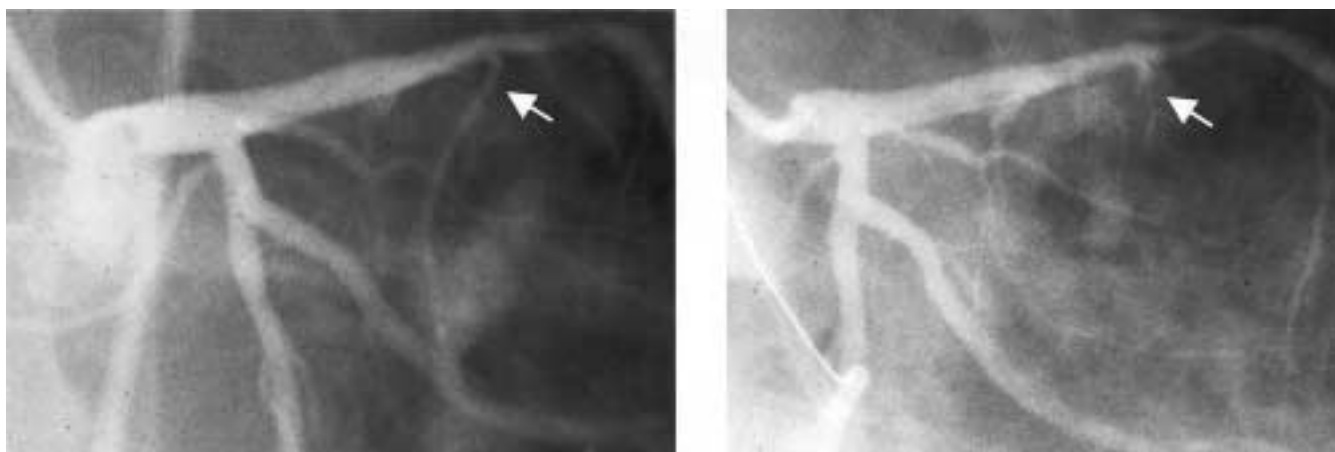


Figure 1. Left coronary angiography before [left] and immediately after alcoholization [right] of the second septal branch. In this patient contrast echocardiography indicated that the second (larger) septal branch fed the basal septal area to be infarcted. Right arrow points to occluded septal branch.

procedure was $1,838 \pm 674$ U/L. Mean hospital stay was 6.6 ± 3.1 days (range 4–13 days).

Early hemodynamic changes

Mean LVOT gradient at rest fell from 37 ± 38 (range 0–100) to 5 ± 10 mmHg (range 0–30) ($P < 0.05$). A $>50\%$ immediate post-procedural reduction of LVOT gradient was noted in all seven patients with a resting gradient. Mean LVOT gradient following a premature beat fell from 105 ± 30 (range 60–151) to 9 ± 12 mmHg (range 0–34) ($P < 0.001$).

Echo-Doppler changes [Table 1]

Early assessment was performed after 13 ± 12 days (range 5–33 days): mean resting LVOT gradient fell from 82 ± 37 mmHg pre-procedure (range 42–140) to 17 ± 16 mmHg (range 0–50) ($P < 0.05$). Late examination was performed 9 ± 10 months post-procedure (range 4–31 months, ≥ 6 months post-procedure in 4 of 8 subjects): mean LVOT was 15 ± 8 mmHg (range 9–30) ($P < 0.01$ vs. pre-procedure). Mean gradient during the Valsalva maneuver at the late echo assessment was 27 ± 24 mmHg (range 13–70 mmHg). Changes in heart measurements between the pre-alcoholization and late echo examination are detailed in Table 1. The degree of mitral regurgitation fell from 2 ± 0 to 1.5 ± 0.5 ($P < 0.05$). We noted a trend toward thinning of the basal septum: 1.61 ± 0.29 at baseline vs 1.53 ± 0.36 at late follow up ($P = 0.07$). Global left ventricular ejection fraction was not measured.

Functional capacity and therapy

NYHA class for dyspnea fell from 2.8 ± 0.5 to 1.8 ± 0.8 between the pre- and late clinical assessment ($P < 0.01$). Canadian Cardiovascular Society class for angina fell from 2.0 ± 1.3 to 1.3 ± 1.2 ($P = 0.08$). Most patients continued to take medication aimed at reducing the LVOT gradient, albeit at a lower dosage for some. Repeat PTSMA was required in one patient because of unsatisfactory primary results, namely insufficient gradient reduction and no clinical improvement. Marked clinical and hemodynamic improvement resulted from alcoholization of the second septal branch.

Complications

Complications were evident in all eight patients. Complete right bundle branch block developed in six of seven patients (excluding the patient with pre-procedure pacing) and persisted on discharge in five. Complete heart block developed immediately following alcoholization in four patients. The block was transient in three, lasting from 1 hour to 4 days, but persisted in the fourth patient who underwent implantation of a dual-chamber pacemaker 5 days after the procedure. In one patient, prominent QRS enlargement with extensive and marked ST-segment elevation in V1–V5, I1 and aVL were seen following alcohol injection and withdrawal of the balloon. Upon injection

Table 1. Echocardiographic parameters

	Pre-	Early	Late	P
LVDD (cm)	4.8 ± 0.2	4.8 ± 0.4	4.8 ± 0.4	NS
LVSD (cm)	2.7 ± 0.3	3.0 ± 0.5	2.9 ± 0.4	NS
IVS (cm)	1.61 ± 0.29	1.56 ± 0.33	1.53 ± 0.36	0.07
LVPW (cm)	1.13 ± 0.19	1.13 ± 0.15	1.15 ± 0.17	NS
Left atrium (cm)	4.4 ± 0.6	4.4 ± 0.4	4.5 ± 0.4	NS
Mitral regurgitation	2.0 ± 0	2.0 ± 0	1.5 ± 0.5	0.03
LVOT gradient-rest				
Mean (mmHg)	82 ± 37	17 ± 16	15 ± 8	0.001
Range (mmHg)	42–140	0–50	9–30	

LVDD = left ventricular end-diastolic dimension, LVES = left ventricular end-systolic dimension, IVS = interventricular septal thickness, LVPW = left ventricular posterior wall thickness. Mitral regurgitation: see Methods for estimation of severity of mitral regurgitation.

of contrast medium in the left coronary ostium, occlusion of the distal LAD with TIMI 0 flow was noted. Maximum creatine kinase rose to 2,793 U/L. On repeat echo study, LVOT gradient was 10 mmHg at rest and 13 mmHg during the Valsalva maneuver, indicating a satisfactory hemodynamic result. Yet, hypokinesia of the mid- and apical septum with thinning of the basal septum was noted, indicating that in addition to causing the planned basal septal infarction, distal LAD occlusion was associated with an anterior infarction. We assume that the distal LAD occluded as a result of alcohol spilling from the septal artery following balloon deflation. Another patient who had been treated by dual-chamber pacemaker prior to pacing developed ventricular tachycardia followed by ventricular fibrillation 2 hours after the procedure. He was promptly defibrillated. He was discharged after 8 days and did well subsequently. Another patient who developed recurrent paroxysmal atrial fibrillation is presently doing well with propafenone therapy.

Discussion

To the best of our knowledge, this is the first report on PTSMA from Israel. Our early experience with PTSMA parallels other reported studies [10–17]. Investigations performed early and late after the procedure generally showed a reduction in resting and provoked LVOT gradient, an improvement in functional capacity, a reduction in the severity of mitral regurgitation, and a trend towards a thinning of the interventricular septum. Because PTSMA is a new procedure with little information on its long-term effects, we limited PTSMA to patients who felt markedly limited by symptoms despite appropriate medical therapy. Other groups have extended the indication for PTSMA to patients with less severe symptoms, high outflow gradients and documented risk factors for sudden cardiac death [16]. This view is controversial [19]. The rationale for treating patients with marked gradient but few symptoms is the hope that reducing the LVOT gradient will prevent or delay left ventricular hypertrophy progression [9]. The technical aspects of the procedure have been well described [10–15]. We found that

NYHA = New York Heart Association

LAD = left anterior descending coronary artery

insertion and stabilization of the guide wire in the distal septal artery may be difficult when there is a >90 angulation between LAD and the septal branch. Insertion of the balloon into a fairly small target septal branch (<2.0 mm) may also be difficult, especially in the presence of a sharp angulation between LAD and the septal branch. Using a more supportive wire and/or a smaller sized balloon allowed introduction of the balloon in the target artery. Yet, use of a small balloon relative to the septal artery diameter may predispose to spilling of alcohol into the LAD following deflation of the balloon [16]. Early bifurcation of the septal branch into smaller branches is another technical problem that we encountered in two patients. In one, we had to withdraw the distal half of the balloon into the LAD so that the tip of the balloon was proximal to the bifurcation of the septal artery. This maneuver might predispose to alcohol spilling into the LAD [15]. In the second patient with early bifurcation, we chose to inject alcohol in only one of the small bifurcation branches (the more basal one). We did not inject into the second bifurcation branch because the early hemodynamic results were satisfactory. This patient did well subsequently, indicating that obliteration of small septal branches may be sufficient in some patients to markedly reduce the LVOT gradient. Small branches may not allow introduction of even the smallest balloon available (1.5 mm). In one patient, we had to repeat the procedure because of lack of improvement following the initial procedure. Seggewiss et al. [12] claim that occlusion of two to three septal branches may be necessary to obtain optimal hemodynamic and clinical results. Increasing the number of septal branches to be occluded will probably increase the incidence of complications [12,16]. Since the correlation between very early hemodynamic results and late echo results is not perfect, it might be safer to obliterate only one septal branch at a time, even if early results are unsatisfactory [13]. Contrast echocardiography may help detect the branch feeding the hypertrophied basal septum [14].

Occlusion of the distal LAD is a feared complication of PTSMA and was noted in one of our patients. The angiographic pattern suggested a no-flow phenomenon. The clinical picture was fairly dramatic, and we noted evidence of a small antero-apical infarction. Occlusion of the LAD distal to branching of the septal branch was seen in 3 of 25 patients studied by Ruzylo and co-workers [15], who attributed it to alcohol spilling from the septal branch into the LAD following deflation of the balloon. It has been suggested that longer inflations (10 minutes) and injection of smaller amounts of alcohol could avoid this serious complication [15]. The use of a slightly oversized balloon has also been recommended, with angiography of the LAD after each injection of alcohol, which should be administered slowly in fractions of 1 ml [16]. Evidence of damage to the conduction system of the heart was seen in all seven patients who did not already have a paced rhythm prior to the procedure. Implantation of a permanent pacemaker was required in one patient because of persistent complete heart block. Permanent complete heart block was not mentioned in

the initial report of Knight et al. [11], but was found to be a common complication of PTSMA in subsequent reports [12–15]. To date there has been no report of late (post-discharge) heart block. The long-term effect of conduction defects occurring in the context of HOCM and a septal infarction has not been determined and long-term follow-up of these patients is required. Ventricular fibrillation occurred 2 hours after the procedure in one patient. He was successfully defibrillated. The development of ventricular tachycardia/fibrillation after PTSMA is not unexpected but has been reported to occur rarely in the first 48 hours after the procedure [11–13]. Patients undergoing PTSMA require monitoring in an intensive care unit, similar to the care of any patient with acute myocardial infarction. Post-discharge ventricular fibrillation after PSTMA has not been reported so far but patients should be followed carefully for late appearance of ventricular tachyarrhythmias. In-hospital death rates have varied between 0 and 4% [11–15]. Other reported complications of the procedure are endocarditis and mural thrombus with embolic stroke [13]. Serious complications following discharge have been few.

The influence of PTSMA on the long-term prognosis of HOCM is presently unknown. It is hoped that the reduction of the LVOT gradient will be permanent and will reduce the stimulus for progression of LVH, ischemia and fibrosis [16,19]. Reduction of LVH may cause a prolonged improvement in symptomatology and possibly a better survival. Concern has been raised concerning the potential deleterious effects of PTSMA on long-term survival [9]. Thinning of the septum might induce septal rupture, although no such case has been documented. The possibility that PTSMA might aggravate LV dysfunction has been raised [9]. PTSMA-induced conduction defects might lead to late complete heart block, ventricular arrhythmias and sudden death [9]. Clearly, long-term follow-up studies are required. Eventually, only randomized studies comparing regular medical therapy with PSTMA associated with medical therapy will clarify the indications for PTSMA in the treatment of HCOM. As noted in our patients, the influence of PTSMA on symptomatology has been generally favorable. All reported studies indicate that PTSMA is associated with amelioration of dyspnea and angina and increased exercise capacity. The influence of PTSMA on syncope has not been reported. While these and our reports are encouraging, the long-term effect of PTSMA is still unknown and the possibility of a placebo effect cannot be discounted.

Conclusion

PTSMA provided a substantial reduction in left ventricular outflow gradient associated with an improvement in symptomatology. Serious complications are not uncommon. Long-term follow-up is unknown.

LVH = left ventricular hypertrophy

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