Percutaneous Septal Reduction Therapy in a Patient with Severely Symptomatic Hypertrophic Obstructive Cardiomyopathy

An experience from a tertiary care center

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Introduction

Hypertrophic cardiomyopathy (HCM) is a heterogenous group of genetically-transmitted diseases characterized by abnormal hypertrophy and disarray of the cardiomyocytes. The hypertrophy is usually asymmetric affecting the basal septum, though other morphological variants such as apical or mid septal are also not uncommon. Although the global prevalence of HCM is reported to be around 0.16-0.29% (approximately 1 in 500) of the general adult population, the true prevalence is likely higher as many patients with HCM are asymptomatic and are diagnosed during family screening or late in adult life once symptoms begin. With increased awareness of the disease, improved cardiac imaging modalities and increased availability of genetic screening of families, the reported prevalence appears to be increasing and it is now estimated that around 0.6% of the population carry HCM-related genes. Patients usually present with symptoms late in adult life. The more severe forms may present in early childhood or in the teenage years. The symptoms include dyspnea related to the diastolic dysfunction or left ventricular outflow tract (LVOT) obstruction, angina-like chest pain due to
oxygen demand supply mismatch caused by the severe hypertrophy or lightheadedness, syncope or palpitations due to the LVOT obstruction or arrhythmias. LVOT obstruction at rest occurs in around a third of patients with HCM while another third has provokable obstruction. The remaining third have hypertrophy without obstruction.\(^1\)

Management of patients with HCM can be challenging and depends on the symptoms experienced by the patient. Pharmacological management with negative inotropic and negative chronotropic agents such as betablockers, calcium channel blockers and disopyramide helps alleviate symptoms by improving left ventricular diastolic filling and systolic stroke volume, but is only effective in 50\% of the cases.\(^5\) Additional interventional treatment strategies should be considered early during the course of the disease. Outcomes of randomized studies on dual-chamber electrosystolic stimulation with a dual chamber pacemaker have been disappointing.\(^6\) Implantable cardioverter-defibrillators should be considered for those at high risk for sudden cardiac death.

For patients with significant LVOT obstruction, septal reduction strategies in the form of surgical septal myectomy (SM) or alcohol septal ablation (ASA) should be considered. These alternative therapeutic modalities are supported by a large body of evidence confirming positive short- and long-term outcomes in symptomatic patients.\(^1\) The open-heart surgical approach was the only treatment option available until the early 90s. In this commentary we describe our experience with treating a severely symptomatic middle-aged lady with obstructive HCM, who did not respond to medical therapy and successfully underwent alcohol septal ablation at the Sultan Qaboos University Hospital, which also happens to be the first such experience in the Sultanate of Oman.

**An exemplary case from our service**
The patient was a 51-year-old active, obese lady (BMI 36.8 kg/m\(^2\)) with Sjögren’s syndrome, dyslipidemia, fatty liver, and obstructive sleep apnea, who in 2017 presented with worsening exertional dyspnea. She had been investigated previously and had an echocardiogram a few years earlier which was reported as good left ventricular function with concentric left ventricular
hypertrophy (LVH). A 12-lead electrocardiogram (ECG) revealed sinus rhythm with LVH and secondary repolarization abnormalities (Figure 1-A). A gated cardiac computed tomographic study showed normal coronary arteries. Investigations for a possible respiratory cause were unremarkable.

In view of the worsening dyspnea and possible pulmonary hypertension, she underwent a repeat echocardiogram. The echocardiogram revealed moderate asymmetrical septal hypertrophy (ASH) with an interventricular septal diastolic dimension (IVS$_d$) of 21 mm (normal <11 mm) and a posterior left ventricular wall diastolic dimension (PW$_d$) of 10 mm (normal <11 mm) (IVS/PW ratio of 2.1). Systolic anterior motion (SAM) of the anterior mitral valve leaflet was noted with a resting left ventricular mid-cavitary gradient of 42 mmHg that accentuated to 51 mmHg with the Valsalva maneuver. There was mild concomitant mitral regurgitation with a normal appearing mitral valve apparatus. There was no evidence of pulmonary hypertension. Her previous echocardiogram, from approximately 5 years earlier, was reviewed and confirmed the absence of ASH or SAM.

The patient was started on oral bisoprolol up to a dose of 10 mg once daily, with a modest symptomatic improvement. An exercise-stress echocardiogram was performed while on maximum treatment. She was only able to exercise for 05:02 minutes on the standard Bruce protocol attaining a total of 7 METs. Her blood pressure dropped from 146/68 mmHg to 135/37 mmHg at peak stress. The test was stopped due to severe dyspnea. No significant arrhythmias were documented. However, the echocardiogram at peak exercise, recorded a significant gradient of 80 mmHg across the mid-LV cavity with mild mitral regurgitation and normal pulmonary artery pressure.

A detailed discussion was undertaken about her options for septal reduction therapy in view of the failure of medical therapy and the worsening of symptoms and the presence of severe LVOT obstruction at rest which was accentuated on provocation. The patient consented to alcohol septal ablation. An initial coronary angiogram demonstrated angiographically normal coronary arteries and delineated one dominant septal perforator (SP) branch in the proximal left anterior
descending (LAD) coronary artery. (Figure 2) The initial resting LV-aortic mean pressure gradient was measured at 38 mmHg (Figure 3-A). The post-extra-systolic beat showed a dramatic accentuation of the peak pressure gradient to 160 mmHg and the mean pressure gradient to 100 mmHg indicating severe dynamic mid-cavity obstruction, which is the classic Brockenbrough-Braunwald-Morrow sign of dynamic LVOT obstruction (Figure 3-B). Balloon occlusion of the dominant SP for two minutes, resulted in a remarkable diminution of the LV gradient down to 22 mmHg (Figure 3-C). A contrast-enhanced echocardiogram was performed using agitated saline and iodinated contrast mixture as well as Definity® [LANTHEUS MEDICAL IMAGING, Billerica, MA, USA] ultrasound contrast administered through a microcatheter in the target SP branch revealed a very focal area of opacification in the septum, at the point of anterior mitral valve leaflet-septal contact and the aliasing zone on color doppler images [Figure 4 A&B].

A standard coronary guide wire was secured into the distal LAD and a stiffer support-type coronary guide wire in the dominant SP branch. A coronary microcatheter was advanced into the side branch. This was intended for local alcohol delivery. After excluding the SP from the LAD with a 2.50x9 mm semi-compliant balloon, 100% ethanol was injected into the SP in 0.5 mL aliquots to a total amount of 2 mL. The resting mean pressure gradient eventually decreased to 21 mmHg with no post-extra-systolic accentuation [Figure 3-D, 3-E and 3-F].

The procedure was well tolerated with no significant arrhythmias or heart blocks were encountered. The patient’s post-procedure ECG is shown in Figure 1-B. She experienced mild, manageable chest pain and transient complete heart block that resolved with an otherwise unremarkable hospital stay. The immediate post ablation transthoracic echocardiogram demonstrated only a 5-mmHg gradient across the mid-LV cavity both at rest and post Valsalva. There was now absence of SAM of the anterior mitral valve leaflet and only trivial mitral regurgitation. Similar findings were documented on an echocardiographic study done 10 days later, at which point the patient had already resumed her daily activities without any symptoms. A stress echocardiogram was repeated 8 weeks after the intervention, off the bisoprolol. At this time her exercise duration had increased significantly to 08:10 minutes attaining 10 METs with a
normal blood pressure response. Both the resting and immediate post exercise echocardiogram revealed no mid-cavitary gradient. At 2-year follow up she is off-treatment and remains asymptomatic with a good exercise tolerance.

The authors confirm that written consent for submission and publication of this work including images and associated test has been obtained from the patient. The patient had no objection to the publication, provided her identifying details were anonymized.

Our reflections

Alcohol septal ablation has been gaining favor worldwide as the procedure of choice in managing patients with HCM and LVOT obstruction, who fail medical therapy. The first septal ablation was performed by Urlich Sigwart in 1994. He described three patients with severe dynamic subaortic obstruction. All three patients responded to a trial of balloon occlusion of the target SP branch, following which injection of absolute alcohol completely abolished the outflow tract gradient within seconds of alcohol delivery, and remained eliminated even at 12 months of follow-up. The procedure aims to induce a controlled chemical infarction of left ventricular septal myocardium at the point of septal-mitral leaflet contact. It is not uncommon to see a resurgence in gradient after days or weeks due to local myocardial edema. Once necrosis and fibrosis set in, thinning and fibrotic retraction of the basal septum results in a more gradual reduction in outflow gradient. The effect is augmented by mild left ventricular dilatation and regression of hypertrophy due to afterload reduction.

Clinical and echocardiographic outcomes after alcohol septal ablation (ASA) appear comparable to septal myectomy (SM). Early observational studies comparing outcomes after ASA and SM, showed a significant reduction in LV gradient and a marked improvement in functional status without a significant difference in in-hospital mortality. In a meta-analysis of twelve observational studies, investigators from the Cleveland clinic showed no difference in short term (3-month) and long term (5 year) mortality. ASA produced a significant improvement in NYHA functional class, post-procedural reduction in septal thickness and LVOT gradient. There was no difference in post-procedural LV ejection fraction and degree of mitral regurgitation. Patients
undergoing ASA very commonly developed RBBB after septal ablation and were more likely to require permanent pacemaker implantation (OR 2.57, 95% CI 1.68-3.93, p<0.001 and had higher residual gradients.\textsuperscript{10} Another concern about ASA was the hypothetical risk of scar-related ventricular arrhythmias and increased risk of sudden cardiac death. One systematic review addressing this concern, reported similar rates of all-cause mortality and sudden cardiac death in patients treated with ASA and SM. Furthermore, and when adjusted for baseline characteristics, the odds ratio for treatment effect on all-cause mortality was 12.5% lower in the ASA-treated patients [OR 0.28, 95% CI 0.16-0.46] compared to those who underwent SM [OR 0.32, 95% CI 0.11-0.97].\textsuperscript{11} The annual risk of sudden cardiac death after ASA is reported to be 0.5% per year, which is comparable to the general population.\textsuperscript{12,13,14}

**Conclusion**

Alcohol septal ablation is a viable alternative to surgical myectomy in symptomatic patients with hypertrophic obstructive cardiomyopathy. The procedure results in a significant improvement in functional status and carries favorable short-term and long-term outcomes. Our experience has shown a favorable immediate and long-term outcome for this condition in the first case treated with ASA in Oman at the Sultan Qaboos University Hospital. Extant literature suggests that it is relatively safe, less invasive and cheaper than open heart myomectomy which should be performed by experienced surgeons in specialized centers capable of performing high risk procedures. The successful outcome of this endeavor opens up a treatment option to patients in Oman that was not previously readily available to them.

**Author Contributions**

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Figure (1): Patient’s electrocardiogram. (A) Baseline standard 12-lead electrocardiogram showing normal sinus rhythm and voltage criteria for left ventricular hypertrophy. There are secondary repolarization abnormalities seen in the lateral leads. (B) Standard 12-lead electrocardiogram after alcohol septal ablation. The tracing shows complete right bundle branch with ST elevation in V1-V2 consistent with a septal infarction. Atrio-ventricular conduction time is normal.
Figure (2): Selective coronary angiogram of the left coronary system in the cranial projection laying out the course of the left anterior descending coronary artery. Note the dominant septal perforator branch (yellow arrows) arising from the proximal segment, which was the target for balloon occlusion and subsequently alcohol injection.
Figure (3): Hemodynamics obtained at the time of the first left heart catheterization. (A) A gradual pull-back is performed using an end-hole catheter. This shows a significant pressure gradient between the LV apex and left ventricular outflow tract, but no gradient between the outflow tract and the aorta (B) The classic Brockenbrough-Braunwald-Morrow sign with a marked post-systolic accentuation of the peak to peak pressure gradient to 160 mmHg and mean gradient to 100 mmHg (C) Septal ischemia resulting from balloon-occlusion of the septal perforator branch caused a remarkable reduction of the LV-to-aortic pressure gradient to 22 mmHg. (D) A significant 100 mmHg gradient was measured between the LV and aorta using simultaneous pressure tracings from both chambers (E) After injection of a total of 2 mL of 100% ethanol into the target septal perforator, there was a marked reduction in the resting pressure gradient to only 21 mmHg and as shown in (F) Complete elimination of post-extra-systolic accentuation after alcohol injection.
Figure (4): Still frames obtained from the apical four chamber transthoracic echocardiogram done during the alcohol septal ablation with (A) agitated saline and iodinated contrast mixture (B) Definity® ultrasound contrast agent injected through a microcatheter in the targeted septal perforator branch. The target area for alcohol ablation appears to be quite localized as shown in the focal area of opacification in the mid interventricular septum [asterisk] without right ventricular extension or involvement of the papillary muscle.