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.[1] 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.[2,3] 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.[4]

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 provocable 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

60 hypertrophy (LVH). A 12-lead electrocardiogram (ECG) revealed sinus rhythm with LVH and

61 secondary repolarization abnormalities (Figure 1-A). A gated cardiac computed tomographic

62 study showed normal coronary arteries. Investigations for a possible respiratory cause were

63 unremarkable.

64

65 In view of the worsening dyspnea and possible pulmonary hypertension, she underwent a repeat

66 echocardiogram. The echocardiogram revealed moderate asymmetrical septal hypertrophy

67 (ASH) with an interventricular septal diastolic dimension (IVS_d) of 21 mm (normal <11 mm)

68 and a posterior left ventricular wall diastolic dimension (PW_d) of 10 mm (normal <11 mm)

69 (IVS/PW ratio of 2.1). Systolic anterior motion (SAM) of the anterior mitral valve leaflet was

70 noted with a resting left ventricular mid-cavitary gradient of 42 mmHg that accentuated to 51

71 mmHg with the Valsalva maneuver. There was mild concomitant mitral regurgitation with a

72 normal appearing mitral valve apparatus. There was no evidence of pulmonary hypertension. Her

73 previous echocardiogram, from approximately 5 years earlier, was reviewed and confirmed the

74 absence of ASH or SAM.

75

76 The patient was started on oral bisoprolol up to a dose of 10 mg once daily, with a modest

77 symptomatic improvement. An exercise-stress echocardiogram was performed while on

78 maximum treatment. She was only able to exercise for 05:02 minutes on the standard Bruce

79 protocol attaining a total of 7 METs. Her blood pressure dropped from 146/68 mmHg to 135/37

80 mmHg at peak stress. The test was stopped due to severe dyspnea. No significant arrhythmias

81 were documented. However, the echocardiogram at peak exercise, recorded a significant gradient

82 of 80 mmHg across the mid-LV cavity with mild mitral regurgitation and normal pulmonary

83 artery pressure.

84

85 A detailed discussion was undertaken about her options for septal reduction therapy in view of

86 the failure of medical therapy and the worsening of symptoms and the presence of severe LVOT

87 obstruction at rest which was accentuated on provocation. The patient consented to alcohol septal

88 ablation. An initial coronary angiogram demonstrated angiographically normal coronary arteries

89 and delineated one dominant septal perforator (SP) branch in the proximal left anterior

90 descending (LAD) coronary artery. (Figure 2) The initial resting LV-aortic mean pressure

91 gradient was measured at 38 mmHg (Figure 3-A). The post-extra-systolic beat showed a

92 dramatic accentuation of the peak pressure gradient to 160 mmHg and the mean pressure

93 gradient to 100 mmHg indicating severe dynamic mid-cavity obstruction, which is the classic

94 Brockenbrough-Braunwald-Morrow sign of dynamic LVOT obstruction (Figure 3-B). Balloon

95 occlusion of the dominant SP for two minutes, resulted in a remarkable diminution of the LV

96 gradient down to 22 mmHg (Figure 3-C). A contrast-enhanced echocardiogram was performed

97 using agitated saline and iodinated contrast mixture as well as Definity® [LANTHEUS

98 MEDICAL IMAGING, Billerica, MA, USA] ultrasound contrast administered through a

99 microcatheter in the target SP branch revealed a very focal area of opacification in the septum, at

100 the point of anterior mitral valve leaflet-septal contact and the aliasing zone on color doppler

101 images [Figure 4 A&B].

102

103 A standard coronary guide wire was secured into the distal LAD and a stiffer support-type

104 coronary guide wire in the dominant SP branch. A coronary microcatheter was advanced into the

105 side branch. This was intended for local alcohol delivery. After excluding the SP from the LAD

106 with a 2.50x9 mm semi-compliant balloon, 100% ethanol was injected into the SP in 0.5 mL

107 aliquots to a total amount of 2 mL. The resting mean pressure gradient eventually decreased to

108 21 mmHg with no post-extra-systolic accentuation [Figure 3-D, 3-E and 3-F].

109

110 The procedure was well tolerated with no significant arrhythmias or heart blocks were

111 encountered. The patient's post-procedure ECG is shown in Figure 1-B. She experienced mild,

112 manageable chest pain and transient complete heart block that resolved with an otherwise

113 unremarkable hospital stay. The immediate post ablation transthoracic echocardiogram

114 demonstrated only a 5-mmHg gradient across the mid-LV cavity both at rest and post Valsalva.

115 There was now absence of SAM of the anterior mitral valve leaflet and only trivial mitral

116 regurgitation. Similar findings were documented on an echocardiographic study done 10 days

117 later, at which point the patient had already resumed her daily activities without any symptoms.

118 A stress echocardiogram was repeated 8 weeks after the intervention, off the bisoprolol. At this

119 time her exercise duration had increased significantly to 08:10 minutes attaining 10 METs with a

120   normal blood pressure response. Both the resting and immediate post exercise echocardiogram

121   revealed no mid-cavitary gradient. At 2-year follow up she is off-treatment and remains

122   asymptomatic with a good exercise tolerance.

123   The authors confirm that written consent for submission and publication of this work including

124   images and associated test has been obtained from the patient. The patient had no objection to

125   the publication, provided her identifying details were anonymized.

126

127

128   **Our reflections**

129   Alcohol septal ablation has been gaining favor worldwide as the procedure of choice in

130   managing patients with HCM and LVOT obstruction, who fail medical therapy. The first septal

131   ablation was performed by Urlich Sigwart in 1994. He described three patients with severe

132   dynamic subaortic obstruction.[7] All three patients responded to a trial of balloon occlusion of the

133   target SP branch, following which injection of absolute alcohol completely abolished the outflow

134   tract gradient within seconds of alcohol delivery, and remained eliminated even at 12 months of

135   follow-up. The procedure aims to induce a controlled chemical infarction of left ventricular

136   septal myocardium at the point of septed-mitral leaflet contact. It is not uncommon to see a

137   resurgence in gradient after days or weeks due to local myocardial edema. Once necrosis and

138   fibrosis set in, thinning and fibrotic retraction of the basal septum results in a more gradual

139   reduction in outflow gradient.[8] The effect is augmented by mild left ventricular dilatation and

140   regression of hypertrophy due to afterload reduction.

141

142   Clinical and echocardiographic outcomes after alcohol septal ablation (ASA) appear comparable

143   to septal myectomy (SM). Early observational studies comparing outcomes after ASA and SM,

144   showed a significant reduction in LV gradient and a marked improvement in functional status

145   without a significant difference in in-hospital mortality.[9] In a meta-analysis of twelve

146   observational studies, investigators from the Cleveland clinic showed no difference in short term

147   (3-month) and long term (5 year) mortality. ASA produced a significant improvement in NYHA

148   functional class, post-procedural reduction in septal thickness and LVOT gradient. There was no

149   difference in post-procedural LV ejection fraction and degree of mitral regurgitation. Patients

150 undergoing ASA very commonly developed RBBB after septal ablation and were more likely to

151 require permanent pacemaker implantation (OR 2.57, 95% CI 1.68-3.93, p<0.001 and had higher

152 residual gradients.[10] Another concern about ASA was the hypothetical risk of scar-related

153 ventricular arrhythmias and increased risk of sudden cardiac death. One systematic review

154 addressing this concern, reported similar rates of all-cause mortality and sudden cardiac death in

155 patients treated with ASA and SM. Furthermore, and when adjusted for baseline characteristics,

156 the odds ratio for treatment effect on all-cause mortality was 12.5% lower in the ASA-treated

157 patients [OR 0.28, 95% CI 0.16-0.46] compared to those who underwent SM [OR 0.32, 95% CI

158 0.11-0.97].[11]The annual risk of sudden cardiac death after ASA is reported to be 0.5% per year,

159 which is comparable to the general population.[12,13,14]

160

161 **Conclusion**

162 Alcohol septal ablation is a viable alternative to surgical myectomy in symptomatic patients with

163 hypertrophic obstructive cardiomyopathy. The procedure results in a significant improvement in

164 functional status and carries favorable short-term and long-term outcomes. Our experience has

165 shown a favorable immediate and long-term outcome for this condition in the first case treated

166 with ASA in Oman at the Sultan Qaboos University Hospital. Extant literature suggests that it is

167 relatively safe, less invasive and cheaper than open heart myomectomy which should be

168 performed by experienced surgeons in specialized centers capable of performing high risk

169 procedures. The successful outcome of this endeavor opens up a treatment option to patients in

170 Oman that was not previously readily available to them.

171

172 **Author Contributions**

173 All authors have contributed equally in writing the manuscript, verifying the scientific contents,

174 and preparing its final version after review for publication. All authors approved the final version

175 of the manuscript.

176

177 **Acknowledgements**

178 Authors would like to acknowledge the cardiology unit in the department of medicine, the

179 nursing personnel and the cardiovascular technologists in the cardiac catheterization laboratory

180 and echocardiography laboratory for their valuable clinical input.

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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 in the lateral leads. (B) Standard 12-lead
electrocardiogram after alcohol septal ablation. The tracing shows complete right bundle branch
with ST elevation in V_1-V_2 consistent with a septal infarction. Atrio-ventricular conduction time
is normal.
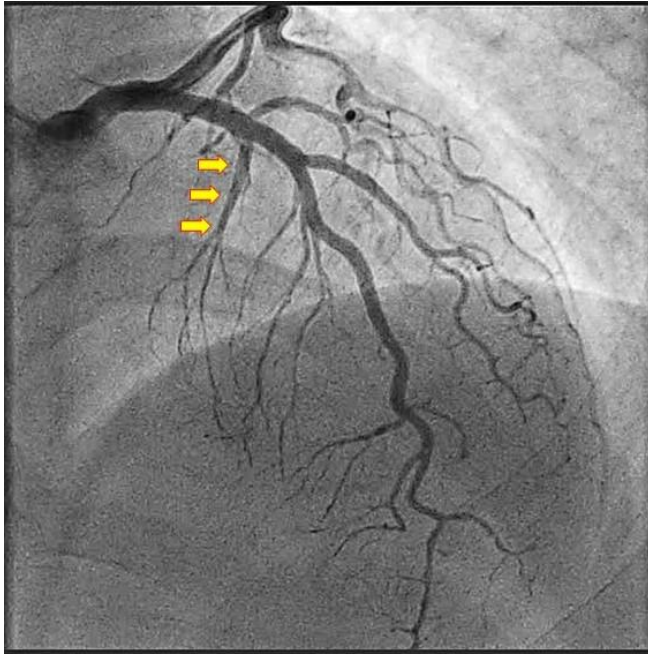
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239 **Figure (2):** Selective coronary angiogram of the left coronary system in the cranial projection
240 laying out the course of the left anterior descending coronary artery. Note the dominant septal
241 perforator branch (yellow arrows) arising from the proximal segment, which was the target for
242 balloon occlusion and subsequently alcohol injection.

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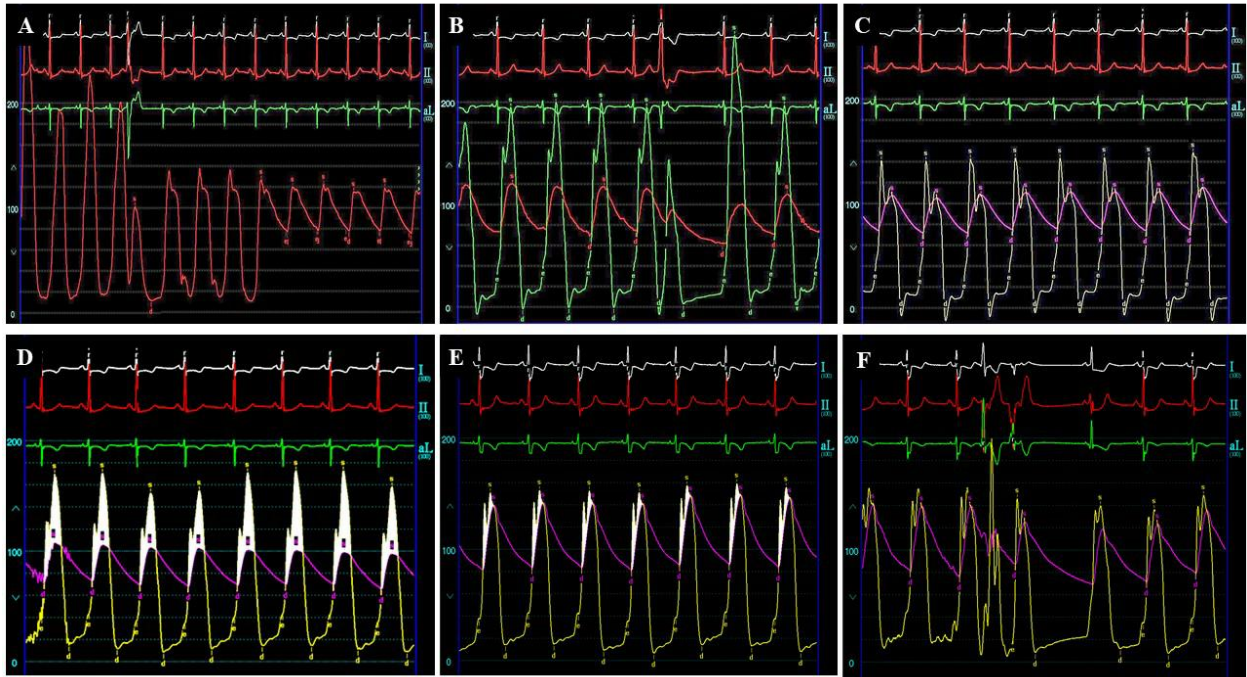
Figure (3): Hemodynamics obtained at the time of the first left heart catheterization. (A) A gradual pull-back is performed using an end-hole catheter. This shows a significant pressure gradient between the LV apex and left ventricular outflow tract, but no gradient between the outflow tract and the 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.

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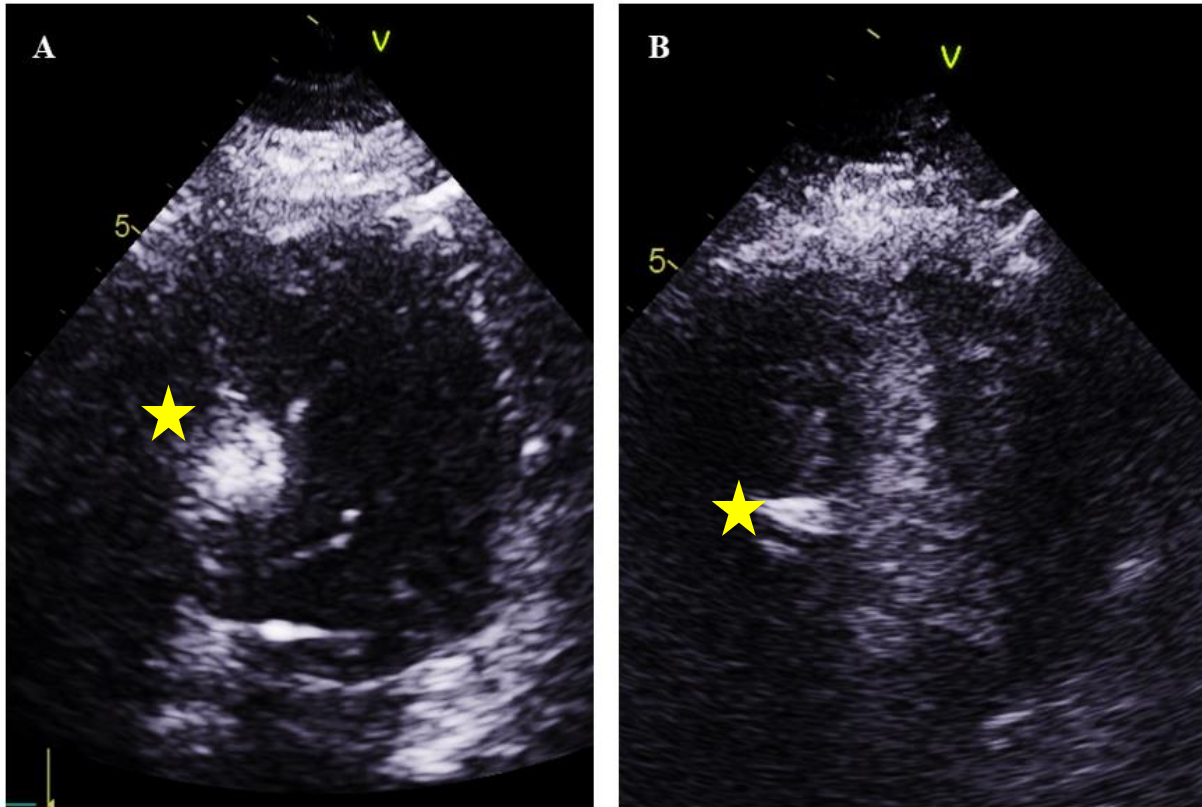
Figure (4): Still frames obtained from the apical four chamber transthoracic echocardiogram done during the alcohol septal ablation with (A) agitated saline and iodinated contrast mixture (B) Definity® ultrasound contrast agent injected through a microcatheter in the targeted septal perforator branch. 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.