Alcohol Septal Ablation for Hypertrophic Cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy is the most common inheritable congenital heart disease. The gene mutation results in abnormal thickening of the myocardium. The symptoms of hypertrophic cardiomyopathy depend on the severity of hypertrophy. The diagnostic modalities include echocardiography and cardiac magnetic resonance imaging. Management focuses on decreasing risks of sudden death, stroke prevention, anti-arrhythmia treatment for atrial fibrillation and therapies for progressive heart failure. Septal reduction therapy should be considered for obstructive hypertrophic cardiomyopathy with refractory symptoms or left ventricle outflow tract pressure gradient ≥50 mmHg at rest or under physiological provocation. Septal reduction therapy includes surgical myectomy and alcohol septal ablation. Long-term survival is almost the same among these septal reduction therapies, but the risk of atrioventricular block is higher with alcohol septal ablation. Previously, surgical myectomy was the standard treatment and alcohol septal ablation was reserved for cases of advanced age, high surgical risk and with more comorbidities. However, more recent study has revealed better long-term survival, reduced heart failure symptoms and lower pacemaker implantation rate after alcohol septal ablation in a younger group, compared to an older group. Therefore, alcohol septal ablation could be considered as an alternative intervention for obstructive hypertrophic cardiomyopathy. The myocardial damage from alcohol ablation could be diminished by using intra-coronary myocardial contrast echocardiography for guidance. The target vessel could be precisely localized to a small branch from a septal artery, thus decreasing unnecessary myocardial damage. Being less invasive and achieving comparable outcome to surgical myectomy, alcohol septal ablation should be considered not only for patients with high surgical risk but also as a primary option.

Keywords: HOCM, alcohol septal ablation, septal reduction therapy

Introduction

Hypertrophic cardiomyopathy (HCM) is an inheritable disease which occurs in approximately 1 in 500 persons,[1] with almost the same incidence in Asian populations.[2] However, the true incidence is higher than estimated owing to the 50% penetrance of the sarcomere protein mutation carrier.[3] A recent study revised the prevalence up to 0.6% using advanced diagnostic

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modalities.[4] The genetic pathophysiology is defined by autosomal dominant mutation in the sarcomere or sarcomere-associated proteins. The 2 most common genes are beta myosin heavy chain 7 (MYH 7) and myosin-binding protein C3 (MYPBC3), carried by 70% of variant-positive patients.[5] These mutations result in abnormal thickening of the myocardium, especially the interventricular septum. Although an asymmetric pattern of hypertrophy is more common, concentric, apical, and other atypical distributions also arise.[6] The hypertrophy can also affect the papillary muscle and right ventricle.[6] The histology reveals a disarray of myocytes of various sizes and shapes due to abnormal intercellular connections.[7]

The clinical symptoms include chest pain, dyspnea, palpitations, fatigue or syncope, especially during exercise. The above symptoms depend on the severity and extent of the hypertrophy. Patients with HCM can develop left ventricle outflow tract (LVOT) obstruction, diastolic dysfunction, myocardial ischemia or mitral regurgitation (MR).[8] The diagnostic modalities include echocardiography, cardiac magnetic resonance imaging (MRI) and exercise testing. Echocardiography can evaluate left ventricle (LV) wall thickness, increased pressure gradient through the LVOT and septal anterior motion of the mitral leaflet with eccentric MR.[7] Cardiac MRI not only measures the severity and distribution of left ventricle hypertrophy (LVH), but can also be used to assess myocardial tissue characteristics to evaluate the risk of sudden cardiac death.[7] An exercise test can help to differentiate who should receive intervention therapy based on symptoms, increased LVOT pressure gradient or abnormal blood pressure response.[7]

Management

Management for clinically identified HCM patients covers three categories, namely decreasing sudden death risk, stroke prevention and anti-arrhythmia treatment for atrial fibrillation (AF) and therapies for progressive heart failure.[9] Several clinical markers, such as family history of HCM-related sudden death, unexplained syncope, apical aneurysm, multiple/repetitive non-sustained ventricular tachycardia, massive LVH ($\geq$30 mm), extensive late gadolinium enhancement, and ejection fraction < 50%, have been used for primary prevention of sudden death with implantable cardioverter-defibrillators.[9] AF occurs in 20% of HCM patients with the onset usually between 50 and 55 years of age.[10] Anti-arrhythmic drugs, catheter ablation or the maze procedure can reduce the frequency of symptomatic AF and progressive heart failure. Stroke prevention with anticoagulants is also an important issue due to the eight times greater ischemic stroke risk in the AF group, compared to HCM patients without AF.[11] Progressive heart failure treatment differs between obstructive and non-obstructive HCM. Non-obstructive HCM cases should undergo guideline directed medical therapy and further cardiac resynchronization therapy or cardiac transplant.[5] For obstructive HCM cases, atrioventricular nodal blocking agents and disopyramide are recommended for their negative inotropic properties to reduce resting gradient and symptoms.[9] Invasive treatment should be considered in patients with medical refractory symptoms or LVOT pressure gradient $\geq$50 mmHg at rest or under physiological provocation.[5] Different strategies for invasive treatment of LVOT obstruction include septal reduction therapy (SRT) and sequential DDD pacing.[12] Sequential DDD pacing studies reveal a significant reduction of LVOT pressure gradient, but the functional capacity improvement is limited.[12] Furthermore, LV or biventricular (BiV) pacing brings a much greater LVOT pressure gradient reduction, compared to conventional right ventricular pacing, with improvement of symptoms and functional capacity in obstructive HCM patients unsuitable for SRT.[12]

Septal reduction therapies for symptomatic obstructive HCM

SRT includes surgical myectomy (SM) and alcohol septal ablation (ASA). Transaortic extended SM is used for a broad range of symptomatic patients with obstructive HCM, with mortality under 1% and clinical success rate over 90 to 95%.[5] Long-term survival after SM is similar to an age-matched general population, and recurrent outflow tract obstruction is rare.[13] Accordingly, SM is the standard treatment for obstructive HCM. ASA was previously reserved for patients with high surgical risks or of advanced age. Excluding cases of high resting LVOT pressure gradient ($\geq$100 mmHg), extreme septal thickness ($\geq$30 mm) and some specific anatomical features of the LVOT (abnormally positioned papillary muscle, anomalous papillary muscle insertion directly into the mitral valve, accessory muscle bundles and abnormal chordal connection), long-term survival after ASA is almost the same as SM.[5] The major complication of ASA is atrioventricular block requiring a permanent pacemaker.[5] The risk of atrioventricular (AV) block is about 10% with ASA, compared to 5% with SM.[5] A recent study has revealed longer long-term survival, better New York Heart Association (NYHA) functional class, and lower pacemaker implantation rates in a younger group than in an older one after ASA.[14] Therefore, ASA could be considered as an alternative intervention for obstructive HCM. Other SRTs such as coil embolization, gelatin sponge and covered stent have been proposed for obstructive HCM. Although coronary stent graft implantation may be beneficial in obstructive HCM combined with coronary artery disease involving the left anterior descending artery,[15] the long-term LVOT pressure gradient shows no improvement owing to collateralization of the occluded septal branch from the right coronary artery.[16] In addition, in some cases, it is hard to restrict the alcohol to the irritating area due to a large target septal branch with high retrograde flow.[17] Small absorbent gelatin sponge particles were used for unsuccessful ASA with no LVOT pressure gradient at 2 years follow-up.[17] The case series reveals less infarct size, lower elevation of cardiac enzyme and no permanent AV block with coil embolization, compared to ASA, but the residual LVOT pressure gradient is higher in the coil embolization group than in the ASA group.[18] The current results from gelatin sponge and coil embolization reveal satisfactory safety outcomes with less elevation of cardiac enzyme and less pacemaker implantation, but hemodynamic success may be limited, with less reduction in LVOT pressure gradient.

Technique

The zone of myocardial necrosis by ASA is the most important factor determining effectiveness and safety. Unnecessary myocardial damage causes more risk of AV block, but insufficient alcohol ablation results in recurrent symptoms and residual high LVOT pressure gradient. The most common target vessel for basal septum is the first septal artery, but excessive anatomic variation impedes direct alcohol injection which can induce additional right ventricle infarct.[20] How to determine the safe zone is answered by intracoronary myocardial contrast echocardiography. Under the guidance of intracoronary myocardial contrast, the margin of territory from the septal artery could be clarified and the target vessel could be precisely localized to a small septal branch. For example, there are two candidate septal branches from the first septal perforator of the left anterior descending artery (Figure 1A). An over-the-wire balloon catheter is inserted into a small septal branch from the first septal artery (Figure 1B). After intracoronary contrast is administered, the target vessel can be identified through the enhancement of basal septum by echocardiography (Figures 1C and 1D). The target is diminished from the first septal perforator to a small septal branch and alcohol ablation can be done safely. Current guidelines

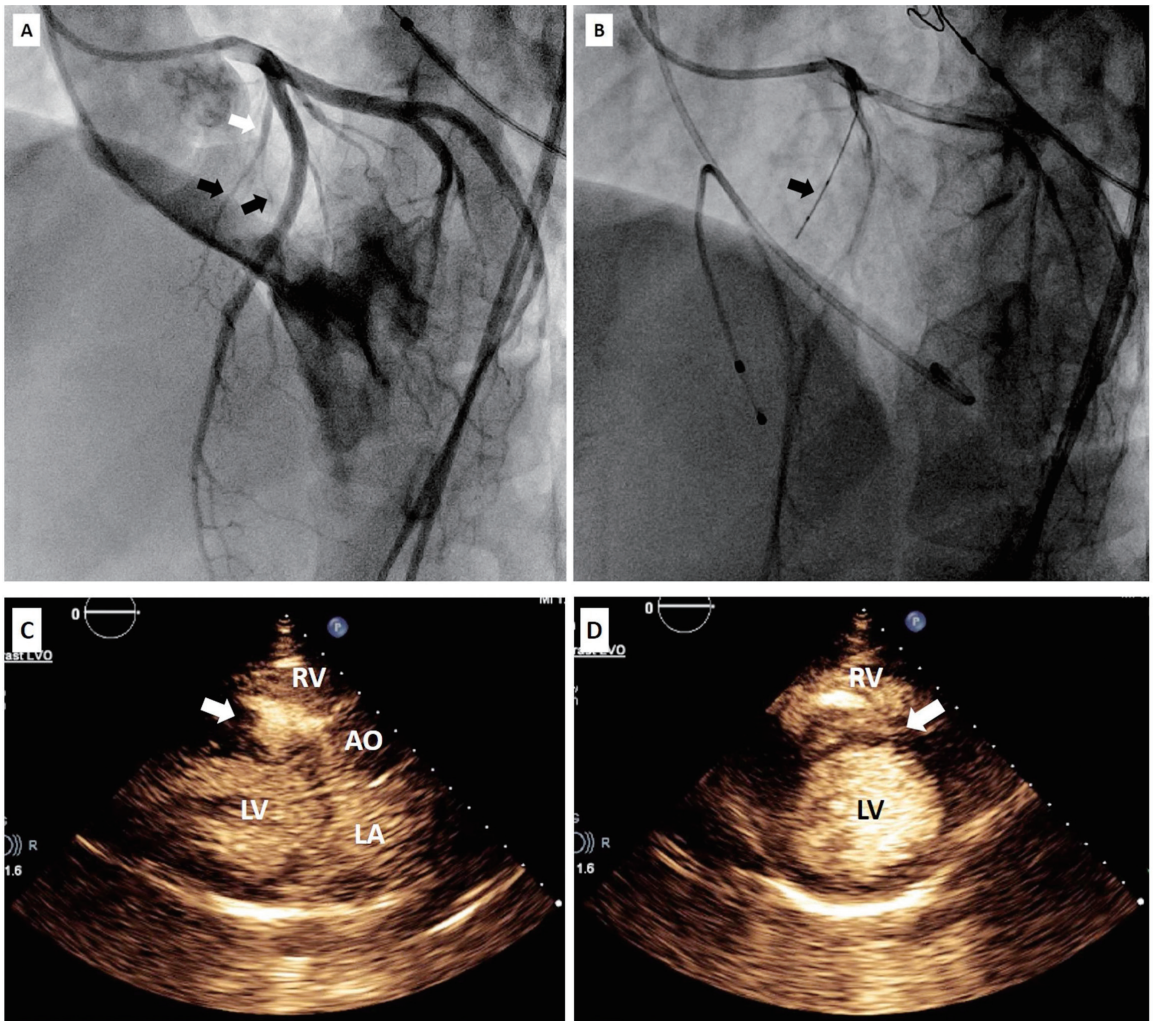

Figure 1. A: Coronary angiography reveals two septal branches (black arrow) from the first septal perforator (white arrow) on the left anterior oblique (LAO) 44°, in cranial (CRA) 19° view. **B:** An over-the-wire balloon is inserted into a septal branch (black arrow). **C:** After intracoronary contrast is administered, basal septal enhancement (white arrow) is observed by parasternal long axis view. **D:** Basal septal enhancement (white arrow) is observed by parasternal short axis view.
RV: right ventricle, LV: left ventricle, AO: ascending aorta, LA: left atrium.

recommend 1 to 3 mL of alcohol administered in the target septal perforator.[5,20] Some authors suggest the quantity of ethanol as 0.1 mL per 1 mm of septal thickness.[21] Low doses and high doses of alcohol have similar 30-day rates for mortality and major adverse events, but patients treated with a low dose of alcohol had a higher rate of repeated procedure.[22] Temporary transvenous pacemaker can be a standby for patients with high risk of complete AV block, especially with pre-existing left bundle branch block. Small balloon occlusion can be used when searching for the target vessel of basal septum if intracoronary myocardial contrast echocardiography is unavailable. Regional ischemia from temporarily occluded septal perforator results in a reduction of the intraventricular pressure gradient, followed by increased gradient after release of the occlusion of the septal branch.[23] We summarize the tips and tricks of ASA in Table 1.

Table 1. Alcohol septal ablation tips and tricks modified from Veselka[21]

Patient selection	Obstructive HCM with drug refractory symptoms.
Anatomical consideration	Septum thickness 15~30 mm, absence of abnormally positioned papillary muscle.
Pressure gradient	LVOT pressure gradient 50~100 mmHg at rest.
Pre-existing left bundle branch block	ASA is associated with a risk of right bundle branch block which might result in complete heart block in patients with pre-existing left bundle branch block.
Have a plan	Myocardial contrast echocardiography to localize small branches of septal perforators.
Intracoronary myocardial contrast echocardiography unavailable	Small balloon occlusion to search the target vessel from septal perforators results in reducing intraventricular pressure gradient.
Alcohol injection	0.1 mL of alcohol (concentration > 95%) per 1 mm of septum thickness injected slowly (1 ml/minute).
Hemodynamic and clinical improvement	Reduction of LVOT pressure gradient is 75% and final NYHA class is approximately 1.5 less than the original.
Institutional experience	An institutional experience of > 50 ASA procedures is associated with better outcomes.

HCM: hypertrophic cardiomyopathy, LVOT: left ventricular outflow tract, AV: atrioventricular, ASA: alcohol septal ablation, NYHA: New York Heart Association

Conclusion

Improvement of symptomatic obstructive HCM is expected in 90% of patients, with a mean reduction of LVOT pressure gradient by 75% and final NYHA class reduction of approximately 1.5 after ASA.[21] Complications could be minimized by intra-coronary myocardial contrast echocardiography. Despite adoption for an older cohort with significantly more comorbidities, ASA has outcomes comparable to SM, with low procedural mortality, excellent long-term survival and improvement in symptoms. Therefore, ASA should be considered not only for patients with high surgical risk but also as a primary option.

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