Contemporary Septal Reduction Therapy in Drug-Refractory Hypertrophic Obstructive Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a complex and relatively common genetic cardiac disease that has been the subject of intense investigation for over 50 years. Most patients with HCM are asymptomatic, but some develop symptoms, often many years after the appearance of electrocardiographic or echocardiographic evidence of left ventricular hypertrophy. Symptoms due to the left ventricular outflow tract obstruction frequently worsen over time, requiring septal reduction therapy (SRT) despite optimal medical therapy. Percutaneous transluminal septal myocardial ablation (PTSMA) and surgical myectomy are collectively known as SRT. In this review, we will focus on the emerging concept and practical implication of SRT and the available evidence on either PTSMA or surgical myectomy in the literature.

Key Words: Heart failure; Hypertrophic cardiomyopathy; Septal reduction therapy

Hypertrophic cardiomyopathy (HCM) is a complex and relatively common genetic cardiac disease that has been the subject of intense investigation for over 50 years. The prevalence of HCM in the general adult population is reported to be approximately 0.2% (or 1:500). Most people with HCM are asymptomatic, but some develop symptoms, often many years after the appearance of electrocardiographic or echocardiographic evidence of left ventricular hypertrophy. Symptoms of HCM also display heterogeneity. Dyspnea is one of the most frequent symptoms of HCM and derives from left ventricular outflow tract obstruction (LVOTO), diastolic dysfunction with preserved ejection fraction, or systolic dysfunction. Atrial fibrillation can complicate and exacerbate this symptom, and can also cause thromboembolism, the risk of which is significantly higher in patients with HCM than in those without the condition. Chest pain is also a frequent symptom and derives from myocardial ischemia caused by microvascular dysfunction, increased LV wall stress and LVOTO. Syncope can be induced by several factors, such as fatal arrhythmia, LVOTO, and abnormal vascular reflexes. Unexplained syncope is associated with an increased risk of sudden cardiac death (SCD), as well as with younger age, ventricular wall thickness, non-sustained ventricular tachycardia, family history of SCD, left atrial diameter, and LVOTO. These factors are included in the HCM SCD risk prediction model, which is useful for deciding the indication for implantable cardioverter defibrillator (ICD). To relieve LVOTO-associated symptoms including dyspnea, chest pain, and syncope, septal reduction therapy (SRT) was established decades ago. This review focuses on the details of contemporary SRT.

What Is SRT?

Percutaneous transluminal septal myocardial ablation (PTSMA) and surgical myectomy are collectively known as SRT. SRT is the Class I recommendation for drug-refractory symptomatic hypertrophic obstructive cardiomyopathy (HOCM) with LV obstruction ≥30mmHg, either at rest or after provocation, which was documented in the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines for HCM in 2011 and in the European Society of Cardiology (ESC) guidelines for HCM in 2014.

Indication for SRT

Regarding the indication for SRT, the following 2 points should be considered in patient selection: presence of LVOTO and drug-refractory symptoms.

Presence or Absence of LVOTO If there is an instantaneous LVOT pressure gradient (LVOT PG) ≥30mmHg at rest on Doppler echocardiography, a diagnosis of LVOTO is made, and if it exceeds 50mmHg the patient is an indication for SRT. A latent LV obstruction refers to a case in which the peak LVOT PG is ≤30mmHg at rest, and ≥30mmHg under provocation. A provoked peak LVOT PG of ≥50mmHg is required for SRT. SRT is also indicated for patients with mid-ventricular obstruction (MVO), but the indication criteria have not been established.

Drug-Refractory Symptoms For patients without symptoms, even if the peak LVOT PG exceeds 50mmHg, SRT is not indicated. HOCM cannot be judged as refractory unless adequate drug therapy has been administered. In some studies, the prescription rate of β-blockers, which are the first-line therapy, is ≥60–70%, but the prescription rate...
of other drugs is ≤40–50%. If a patient is taking cibenzoline or disopyramide in addition to β-blockers and/or calcium antagonist without relief of symptoms, that may be diagnosed as being “drug-refractory”.

**Several Considerations Before SRT**

**LVOTO** The LVOT comprises the septum and anterior mitral leaflet. LVOTO is caused by a thickened septum and the corresponding systolic anterior motion (SAM) of the anterior mitral leaflet. When the PG through the LVOT is high, the consequent increase in wall tension of the LV muscles causes myocardial ischemia. In particular, when a high-grade PG (i.e., ≥50 mmHg) persists, myocardial fibrosis may develop and ventricular arrhythmias arising from fibrotic cardiac muscles might ultimately trigger SCD or the dilated phase of HCM.

**SAM and Lift/Drag** SAM is caused by 2 forces. The first is lift (Venturi effect) and the second, which is the stronger force, is drag [flow drag (pushing) mechanism]. Which mechanism is predominant? Previously, the main mechanism was considered to be the Venturi effect. However, it is now thought that the Venturi effect is not predominantly involved. Instead, the position of the mitral valve (MV) complex shifts in LV systole, which causes further drag on the anterior leaflet by the drag force. Finally, this shift results in LVOTO and is the main mechanism for SAM. As evidence, reports show that the flow velocity of the LVOT is within the normal range in many cases at the beginning of SAM.

**Effect on the MV** As abnormal forces are chronically applied to the MV complex, deformation or degeneration (e.g., elongation of cusps, chordal rupture, etc.) occurs over time and this occasionally causes organic mitral regurgitation. Furthermore, it can cause secondary hypertrophic degeneration of the leaflet.

**Anomaly of the Mitral Subvalvular Apparatus** HOCM may accompany some anomalies of the mitral subvalvular apparatus. This includes papillary muscle abnormality, in which the papillary muscles are attached directly to the MV or fibrous trigone, or chordae tendineae abnormality, in which the chords are attached to the septum, cusps, or annulus. When the MV cusps are pulled towards the septum because of these abnormalities, LVOTO can occur.

**Symptomatic Drug-Refractory HOCM: Which SRT Is Indicated?**

First, whether a patient is indicated for surgical myectomy or not should be considered. If patients have a comorbid disease that can be repaired at the same time with thoracotomy, surgical myectomy should be performed. Severe MV insufficiency, which is not actually caused by SAM, may be the most frequent comorbidity. We will describe cases in which surgical myectomy should be considered: (1) structural abnormalities in the LVOT or MV complex requiring surgical treatment, (2) HOCM complicated by organic aortic or mitral valve disease requiring surgical treatment, (3) HOCM excluding cases (1) and (2), especially in the young and young adults, (4) HOCM with a ventricular septal wall thickness ≥30 mm, and (5) PTSMA has failed to relieve heart failure symptoms (adapted from guidelines for catheter intervention for congenital heart disease and structural heart disease from Japanese Circulation Society (JCS) 2014). It is important to confirm the presence or absence of a structural abnormality of the MV complex before SRT by using various cardiac imaging modalities. Although not described in the above guidelines, there are cases that are unsuitable for PTSMA, in which it is impossible to select the septal branches that perfuse the target myocardium by the guidewire. However, even if the septal branches can be selected by the guidewire, PTSMA is still unsuitable if the over-the-wire (OTW) balloon cannot pass the septal branches. In such cases, surgical myectomy is also indicated. DDD pacing therapy is not SRT but is one of the invasive treatments in the latest guidelines and should be selected only if the patient is not suitable for the SRT.

**Importance of Age in Patient Selection for PTSMA or Surgical Myectomy**

It is generally agreed that if a patient is young (<40 years old), surgical myectomy should be the first-choice SRT for drug-refractory HOCM. However, the therapy of choice if the patient is middle-aged (≥40 years old) is unclear. A previous report indicated that surgical myectomy should be performed if the patient is <65 years old, and above this age, both therapies are indicated depending on the case. A recent report showed that PTSMA is acceptable even in patients ≤50 years old. Because not only age but also background factors and various examination findings (echocardiography, transesophageal echocardiography, cardiac computed tomography (CT), and cardiac magnetic resonance imaging) influence the result of SRT, the heart team, including cardiologists and cardiac surgeons, should discuss which therapies are effective for the patient.

**Overview of PTSMA**

PTSMA is a catheter-based therapy for the relief of drug-refractory symptoms in patients with HOCM. It was introduced by Sigwart in 1995 and then rapidly spread globally. However, 2 issues must be considered with regard to this procedure: (1) the outcome depends on the experience of the interventional cardiologists and (2) the long-term prognosis is uncertain.

**Operative Method of PTSMA**

Because of the risk of developing complete atroventricular block, a temporary pacemaker lead should be inserted in patients without a permanent pacemaker or ICD in place. The LVOT PG is recorded simultaneously via a guiding catheter placed in the ascending aorta and a specially designed pigtail guiding catheter, with holes only in the distal part and not on the shaft, placed in the apex of the LV. The LVOT PG is then recorded both at rest and during provocative maneuvers, such as the Valsalva maneuver and after a premature ventricular contraction. After angiographic identification of the target septal branch that is presumed to be responsible for the blood supply to the hypertrophied septal area involved in obstruction, wiring of this vessel is performed with a 0.014-inch guidewire. After selecting the septal artery, a short (≤10 mm in length) OTW balloon catheter is advanced and inflated in the septal branch. The diameter of the balloon is usually between 1.25 and 2.0 mm. To avoid alcohol leakage in the left anterior descending artery (LAD), a slightly oversized balloon is used. A small amount of contrast media is injected through the guidewire lumen of the inflated balloon.
catheter; angiography is performed to reconfirm the correct selection of culprit branch and exclude the filling of any other coronary artery through septal collaterals. Additionally, a small amount of echocardiographic contrast is injected through the guidewire lumen under echocardiographic monitoring, which enables identification of the supply area of the septal branch to be ablated. After these confirmations, the absolute alcohol is injected slowly from the central lumen of the OTW balloon under continuous fluoroscopic, hemodynamic, and electrocardiographic observation. The quantity of injected alcohol should be determined by the septal thickness or septal artery diameter. The balloon remains inflated for 5–10 min post-ethanol injection to prevent reflux in the LAD and to enhance delivery at the target myocardium. After withdrawal of the balloon catheter, a final angiogram is obtained to document complete occlusion of the septal branch and normal flow in the LAD. At least 48–72 h of hemodynamic and arrhythmia monitoring in the coronary care unit is required. Depending on the rhythm, a decision is made on implantation of a permanent pacemaker or ICD.

**PTSMA Based on the SAM Mechanism**

The flow drag (pushing) mechanism is the main mechanism for SAM that causes LVOTO. Previously, selective alcohol septal ablation was the chosen method of minimizing scar area that could be arrhythmogenic or to prevent LV remodeling after PTSMA. However, extended myocardial ablation is sometimes required to decrease the drag force related to the maintenance of lower peak LVOT PG and to relieve heart failure symptoms over the long-term. Therefore, dedicated techniques are occasionally required to select the target septal artery and to completely ablate the target myocardium. When the septal arteries branch off from the LAD at a sharp angle, the reverse wire technique is useful for selecting such septal arteries (Figure 1A–C). Our data showed a larger volume of injected ethanol and a larger number of injected vessels were required in a good-responder group than in a poor-responder group in the long term. To diminish the drag force, a bigger ablation volume may be unavoidable, especially in HOCM patients with diffuse hypertrophied myocardium. As mentioned next, this concept is consistent with contemporary surgical myectomy. In addition, the optimization of outcomes for PTSMA is essential because residual LVOTO after PTSMA is associated with a higher likelihood of death, not just a higher likelihood of persistent symptoms.

**Outcomes of PTSMA**

There is no standard definition of procedural success in PTSMA, although a definition that reflects the results typically achieved by expertly performed surgical myectomy is reasonable (i.e., residual LVOT gradient at rest <10 mmHg). With this definition, PTSMA is successful in almost 80% of cases. Alam et al, in a systematic review in 2006, reported a significant improvement in NYHA functional class and an increase in exercise capacity after 1-year follow-up of PTSMA. Moreover, the long-term survival after PTSMA has been assessed. Jensen et al reported in 2003 that survival was similar between PTSMA-treated patients and the background population. A contemporary, large PTSMA registry in Europe, the Euro-ASA registry, reported that the 30-day mortality rate after PTSMA was 1%, and the 1-year, 5-year, and 10-year survival rates were 98%, 89%, and 77%, respectively. However, 12% of all patients required permanent pacemaker implantation because of periprocedural complete atrioventricular block, which was associated with a larger volume of alcohol injection. This registry concluded that PTSMA was effective for drug-refractory HOCM for relieving LVOTO and heart failure symptoms.

**New Approach for PTSMA**

In 1998, myocardial contrast echocardiography (MCE) was introduced. With this technique, the perfusion area
useful for the prevention of SCD or other fatal events. Recently, surgical procedures have been indicated for more severe and complex lesions. In particular, septal myectomy is indicated in drug-refractory cases with a high degree of septal thickening and high LV PG (Figure 2A–C). For broad septal thickening, transapical extended myectomy, in addition to the conventional Morrow operation, is also effective. It is well known that HOCM causes MV degeneration caused by the anterior motion of the mitral leaflet. Furthermore, as anomalies of the mitral subvalvular apparatus often coexist, surgical repair is often required when considering the entire MV complex. Furthermore, ventricular aneurysm accompanying MVO tends to present a poor vital prognosis and requires resection.

Operative Method of Transaortic Septal Myectomy
The ascending aorta is opened and septal myectomy is performed via the aortic valve. First, the septum is opened with 2 longitudinal incisions. The first incision is directly beneath the right coronary ostium and the second is somewhat nearer to the left coronary cusp beneath the right/left commissure. As a result, their widths are half the LVOT- muscular septum. Its depth must be determined beforehand by measuring the thickness of the septum on preoperative echocardiography. Thereafter, a third incision of the septal branch can be shown on echocardiography after injection of contrast medium. MCE has improved the success rate of PTSMA. Recently, 3-dimensional MCE-guided PTSMA was reported. It has the potential to further improve the safety and effectiveness of PTSMA, as well as its accuracy and ability to quantify the expected extent of myocardial tissue affected by the ablation. CT-guided PTSMA is also emerging. CT angiography has the dual benefit of detailing the vascular anatomy and providing information on myocardial distribution. In contrast, coronary angiography cannot provide information about the areas supplied. CT-guided PTSMA enables identification of the appropriate vessel for alcohol delivery in the target myocardium and to track it back to its source, wherever that parent artery may be (e.g., left circumflex and right coronary artery).

Overview of Septal Myectomy
Septal myectomy was reported by Morrow in the 1960s. The original technique and its modifications are now widely used. The prognosis of septal myectomy is good; death during hospitalization occurs in less than 1% and the long-term prognosis is as good as in the general population. Compared with medical therapies, septal myectomy can improve the symptoms in the long term. Furthermore, it is

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Figure 2. (A) Transthoracic echocardiogram and (B) cardiac magnetic resonance image of a 36-year-old man with hypertrophic obstructive cardiomyopathy exhibiting a high degree of septal thickening (white arrows). (C) The patient’s 12-lead electrocardiogram demonstrates a left ventricular strain pattern, indicating left ventricular hypertrophy.
SRT in HCM

As there is almost no risk of bundle branch block in case of mid-ventricular or apical septal myectomy, more than the half of the septum can be resected (Figure 3A–E).

Surgical Repair of the MV Complex

As SAM is the cause in most cases of mitral regurgitation associated with HOCM, in theory, SAM will be ameliorated if the obstruction is eliminated. However, there are reports that when the MV leaflets are elongated because of long-standing overload, tendon transplantation or the shortening of anterior leaflets can be beneficial. Nevertheless, with middle-aged patients, valve replacement might be inevitable when at the time of the surgery the cusps are observed to have undergone hypertrophic degeneration. An abnormal subvalvular apparatus that is detrimental to MV function must be removed. Residual SAM could be a factor in worse prognosis because of the remaining PG. To prevent

Operative Method of Transapical Extended Septal Myectomy

When there is mid-ventricular hypertrophic myocardium or the root of the papillary muscles must be resected, the transapical approach is effective in terms of surgical field visibility, clear elimination of the PG, and safety. After performing transaortic septal myectomy, a 5-cm oblique incision is made from the apex towards 2 cm away from the LAD. As there is almost no risk of bundle branch block in case of mid-ventricular or apical septal myectomy, more than the half of the septum can be resected (Figure 3A–E).

Figure 3. Transaortic and transapical extended septal myectomy in the same patient. (A) Abnormal mitral valve chord(s) viewed through an apical incision. (B) Anterior mitral leaflet (AML) viewed from the same angle as in (A), after resection of the abnormal chord(s). (C) Ventricular septum viewed through an aortic incision: systolic anterior motion is causing the AML to contact the ventricular septum. There is white discoloration of the septum. Specimen images of resected abnormal mitral valve chord(s) (D) and 12 g of resected myocardium (E).
Table. Major Comparative Studies of the Outcomes of PTSMA and Surgical Myectomy

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<th>Author Year</th>
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<th>Age (years)</th>
<th>Follow-up period (years)</th>
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<th>30-day mortality (%)</th>
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<td>Singh et al 2016</td>
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<td>49±14</td>
<td>2.9±2.0</td>
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**Resection of an Apical Aneurysm**

The incidence of MVO is approximately 8–10%. As its cavity is greater than that of the LVOT, the PG is not as great as in LVOTO cases. However, symptomatic MVO shows greater myocardial hyperplasia and fibrosis than in cases of LVOTO. Further, in severe cases, a high-pressure chamber is created at the apex, causing ventricular aneurysms. At the entry to the aneurysm, viable myocardium becomes ischemic because of the luminal high pressure. This accelerates myocardial fibrosis in which ventricular arrhythmias may originate, thus, presenting a high risk for SCD. As an apical aneurysm associated with MVO has a poor prognosis, it can independently be a surgical indication regardless of a low LV PG. A fibrotic apical aneurysm should be resected and the cavity must be inspected. As the site where fibrosis starts is the substrate for ventricular arrhythmia, cryoablation should be performed all around the junction. To close the aneurysm, a patch or direct closure with a linear suture should be performed. Septal myectomy should also be performed if needed.

**Indication for Surgical Myectomy in MVO Cases**

Although surgery is not indicated in MVO with a low PG, according to the guidelines, treatment will be difficult in drug-refractory and severely symptomatic cases. Surgical treatment of these cases has been reported to have a good result. In the future, the surgical indication may be expanded with the accumulation of evidence.

**Comparison of PTSMA and Surgical Myectomy**

No randomized clinical trial has compared PTSMA and surgical myectomy because it would require 1,200 eligible patients that are willing to be randomized to PTSMA or myectomy, and this seems unfeasible. Liebregts et al performed a meta-analysis comparing the long-term outcomes of the 2 procedures, considering studies from 1963 to 2013 (patient numbers, 2013/2791; mean follow-up in years, 6.2±7.4; for PTSMA/surgical myectomy). The 30-day mortality rate was 1.3% for PTSMA and 2.5% for myectomy. The rate of new pacemaker implantation after the procedure was 10% for PTSMA and 4.4% for myectomy. The rate of reintervention was 7.7% for PTSMA and 1.6% for myectomy, and the values were significantly different. The annual all-cause mortality was 1.5% for PTSMA and 1.4% for myectomy. Moreover, there was no significant difference between procedures in NYHA functional class at late follow-up (Table).

**Do Case and Center Experiences Influence the Result of SRT?**

Generally, whether SRT is effective depends on operator and heart-team experience. SRT requires an experienced operator to improve the short- and long-term prognoses. In the 2011 ACCF/AHA guideline, an experienced operator is a person who has been involved in more than 20 PTSMA procedures in a facility with more than 50 PTSMA case experiences. The ESC 2014 guidelines and JCS 2014 guidelines for catheter intervention for congenital heart disease and structural heart disease have also stated operator experience in PTSMA. Likewise, it is recognized that outcomes of surgical myectomy performed outside of experienced centers are poor because of the lack of technical expertise required for mastering the procedure. In an analysis of 6,386 patients who had surgical myectomy at 1,049 US hospitals between 2003 and 2011, the surgical mortality rate was 15.6% for patients in centers in the lowest tertile of procedural volume, compared with 9.6% for the second tertile and 3.8% for the highest tertile. Surgical centers with the highest level of expertise have good outcomes, with operative mortality rates <1%, as described in a report on the collective experience of nearly 3,700 patients at these institutions.

**ICD Implantation Before SRT**

When SRT is performed, it is important to consider whether prior ICD implantation is necessary. In HCM...
patients, regardless of LVOTO, it is necessary to evaluate the risk for SCD. ICD implantation before SRT should be performed without hesitation if a patient requires an ICD.

Conclusions and Summary

Compared with surgical myectomy, PTSMA is a less invasive SRT, can lead to shorter hospital stays, and is widely available for drug-refractory HOCM, especially in elderly patients with several comorbidities. However, the long-term outcome after PTSMA is uncertain and there is a higher risk for complete atrioventricular block and a higher rate of repeat procedure to relieve recurrent symptoms. Surgical myectomy has a higher success rate and can maintain clinical efficacy in the long term and can improve long-term prognosis in experienced centers, but its in-hospital mortality rate is high, with a higher rate of repeat SRT in inexperienced centers. SRT should be performed by experienced operators and in experienced centers that have a better understanding of the mechanism of LV obstruction on a per-patient basis.

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Conflict of Interest

None.

References


