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. The prevalence of HCM in the general adult population is reported to be approximately 0.2% (or 1:500).1 Most people with HCM are asymptomatic,2 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).1 Most people with HCM are asymptomatic,2 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.

What Is SRT?
Percutaneous transluminal septal myocardial ablation (PTSMA) and surgical myectomy are collectively called SRT. SRT is the Class I recommendation for drug-refractory symptomatic hypertrophic obstructive cardiomyopathy (HOCM) with LV obstruction ≥30 mmHg, 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 2014.6,7

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) ≥30 mmHg at rest on Doppler echocardiography, a diagnosis of LVOTO is made, and if it exceeds 50 mmHg the patient is an indication for SRT. A latent LV obstruction refers to a case in which the peak LVOT PG is <30 mmHg at rest, and ≥30 mmHg under provocation. A provoked peak LVOT PG of ≥50 mmHg is required for SRT.6,7 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 50 mmHg, 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%.

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/Dray 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 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.

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 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 atrioventricular 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.
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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
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. 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 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. 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.
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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).

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 2cm 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).

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 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
missing an abnormal subvalvular apparatus, it must be identified preoperatively by imaging evaluations.

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 arrhythmias, 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.6

ICD Implantation Before SRT

When SRT is performed, it is important to consider whether prior ICD implantation is necessary. In HCM

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### Table. Major Comparative Studies of the Outcomes of PTSMA and Surgical Myectomy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Procedure</th>
<th>n</th>
<th>Age (years)</th>
<th>Follow-up period (years)</th>
<th>Pacemaker (%)</th>
<th>30-day mortality (%)</th>
<th>Sudden death (%)</th>
<th>Redo (%)</th>
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<tr>
<td>Liebregts et al</td>
<td>2015</td>
<td>Myectomy</td>
<td>2,791</td>
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<td>4.4</td>
<td>2.5</td>
<td>1.6</td>
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<tr>
<td></td>
<td></td>
<td>PTSMA</td>
<td>2,013</td>
<td>56</td>
<td>6.2</td>
<td>10.0</td>
<td>1.3</td>
<td>7.7</td>
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<tr>
<td>Singh et al</td>
<td>2016</td>
<td>Myectomy</td>
<td>1,019</td>
<td>44±12</td>
<td>4.5±4.4</td>
<td>1.6</td>
<td>1.9</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTSMA</td>
<td>805</td>
<td>49±14</td>
<td>2.9±2.0</td>
<td>1.0</td>
<td>1.9</td>
<td>9.9</td>
<td></td>
</tr>
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</table>

PTSMA, percutaneous transluminal septal myocardial ablation.
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, PTMSA 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 PTMSA is uncertain and there is a higher risk for complete atioventricular 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 inhospital 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**


