Subvalvular aortic stenosis: a review of current literature

Subodh R. Devabhaktuni1 | Eyas Chakfeh2 | Ali O. Malik2 | Joshua A. Pengson2 | Jibran Rana2 | Chowdhury H. Ahsan1

1Division of Cardiology, University of Nevada School of Medicine, Las Vegas
2Department of Internal Medicine, University of Nevada School of Medicine, Las Vegas

Correspondence
Subodh R. Devabhaktuni, MD, Indiana University School of Medicine, Krannert Institute of Cardiology, 1800 N. Capitol Avenue, E371, Indianapolis, IN 46202
Email: sdevabha@iu.edu

Subvalvular aortic stenosis (SAS) is one of the common adult congenital heart diseases, with a prevalence of 6.5%. It is usually diagnosed in the first decade of life. Echocardiography is the test of choice to diagnose SAS. Surgical correction is the best treatment modality, and the prognosis is usually excellent. In this review, we describe the pathophysiology, diagnosis, prognosis, and management of SAS with a focus on different pathophysiologic mechanisms, diagnostic approach, and prognosis of the disease by reviewing the current literature.

KEYWORDS
Review, Subaortic Stenosis, Subvalvular Aortic Stenosis

INTRODUCTION

Subvalvular aortic stenosis (SAS) is the second most common type of aortic stenosis, accounting for 14% of left ventricular outflow tract (LVOT) obstruction, with valvular aortic stenosis being the most common cause (70%). The prevalence of SAS is 6.5% of all the adult congenital heart diseases. It predominantly involves males, with a male-to-female ratio of 2:1. SAS is associated with defects such as VSD, AVSD, or conotruncal anomalies in 60% of cases and may develop after patch closure of a perimembranous or malaligned VSD or AVSD. SAS is considered an acquired disease. It is rarely diagnosed during infancy, but it often manifests in the first decade of life with features of progressive LVOT obstruction, left ventricular hypertrophy (LVH), and aortic regurgitation (AR). A familial form of this disease, Shone syndrome, has also been described.

ANATOMY AND PATHOPHYSIOLOGY

SAS encompasses a variety of anatomic lesions that can occur either alone or in combination. The following discrete entities have been described in literature (Figure 1):

1. Thin, crescent-shaped membrane just below the aortic valve: discrete SAS. This represents 75% to 85% of SAS cases.
2. Thick fibromuscular ridge.
3. Tunnel or tubular: long, narrow, fibromuscular channel along the LVOT.

Rarely, abnormal mitral valve chords can cause outflow tract obstruction mimicking SAS. SAS caused by a thin fibrous membrane is more focal. In contrast, a fibromuscular ridge causes more diffuse obstruction and often results in a tunnel-type lesion that is associated with a greater degree of stenosis.

Additionally, SAS due to a misaligned VSD with posterior deviation of the outlet septum into the LVOT has been described in literature. This is usually in association with coarctation or interruption of the aortic arch.

Possible theories explaining development of anatomic lesions

In 1979, Rosenquist et al described 22 heart specimens with SAS and found out that the mean mitral aortic separation in patients with SAS was more than twice that in normal hearts. Based on this particular finding, they speculated that an increase in mitral aortic separation could contribute to the etiology of SAS if this alters the angle at which blood is ejected from the left ventricle during a critical period of early heart development. This, in turn, could cause the embryonic cells near the crest of the ventricular septum to accumulate and eventually differentiate into a ridge or band of fibroelastic tissue.

Another explanation for it to be considered as an acquired lesion is that it is associated with abnormalities in the LVOT and also requires some preexistent morphologic substrate for development. Sigfusson et al. have demonstrated that steepened aortoseptal angle may be a risk factor for the development of SAS (see Supporting...
Information, Figure 1, in the online version of this article). Fluid modeling studies have shown that the steepened angle results in altered shear forces. Altered fluid shear stress has been shown to induce vascular endothelial-cell turnover in vitro and has been connected to the development of vascular obstruction in animal models.

There is a possible genetic component that has yet to be fully understood. Additionally, there is a possible association with other congenital cardiac defects, as prevalence of congenital cardiac defects has been reported to be as high as 6.5% in adult patients with SAS.

2.2 Progression and hemodynamics

The progressive nature of LVOT obstruction caused by SAS in children has been well documented in literature. However, discrete SAS progresses slowly in adulthood. In particular, patients with associated coronary heart disease are at risk for faster progression and should be monitored closely. Oliver et al. in their analysis of 134 adults diagnosed with SAS, found that the gradient across LVOT measured by Doppler echocardiography increased from a mean of 39 mmHg to 46 mmHg over an average follow-up of 4.8 years.

Factors associated with rate of progression of LVOT obstruction are not completely clear. It is thought that abnormal fluid dynamic forces at the LVOT level can cause septal shear stress, causing cellular growth factors to engineer regional cellular proliferation contributing to the worsening of LVOT obstruction. Why the rate of progression is different in children compared with adults is not completely understood at this time. Perhaps, the earlier in life the septal shear stress is increased above a threshold, the more intense the response and the more rapid the progression of the LVOT obstruction.

The primary hemodynamic effect on the left ventricle is increased afterload. The ventricle hypertrophies in an attempt to reduce wall stress. Also, SAS is associated with AR in 30% to 80% of the patients due to damage of the leaflets from high-velocity jets caused by the stenosis.

3 DIAGNOSIS

Most adult patients with SAS are asymptomatic. Some patients will not have symptoms until they pursue activities that cause physical stress, such as exercise or pregnancy. Symptoms may include pre-syncope, shortness of breath, or fatigue. As the obstruction worsens, some patients may develop chest pain or syncope during exertion. Others may develop palpitations; rarely, it can lead to congestive heart failure. The diagnosis of SAS starts with the auscultation of a systolic ejection murmur, which is loudest at the left mid-sternal border radiating to the upper sternal border. This leads to the suspicion for the presence of LVOT obstruction. Differential diagnosis of such a murmur includes aortic stenosis, supravalvular aortic stenosis, SAS, and hypertrophic obstructive cardiomyopathy (HOCM). More detailed physical examination can help to distinguish subaortic stenosis from the other causes of LVOT obstruction, as highlighted in Table 1. A concurrent diastolic murmur may indicate the presence of AR that can be associated with SAS.

| TABLE 1 | Physical examination findings to differentiate various causes of LVOT obstruction |
|-----------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                | Discrete Subvalvular | Valvular | Supravalvular | HOCM |                             |
| Carotid pulse  | Normal or pulsus parvus et tardus | Normal or pulsus parvus et tardus | Unequal | Brisk, jerky, systolic rebound |                             |
| Ejection click | No | Yes | No | Uncommon or none |                             |
| Murmur of aortic regurgitation | Sometimes | Common after age 40 years | Rare | No |                             |
| Valsalva effect on systolic murmur | Decreased | Decreased | Decreased | Increased |                             |
| Fourth heart sound (S4) | Uncommon | If severe | Uncommon | Common |                             |
| Presence of paradoxical splitting | No | Sometimes | No | Common |                             |
| Location on maximal thrill and murmur | Second RIS | Second RIS | First RIS, suprasternal notch | Fourth LIS |                             |

Abbreviations: HOCM, hypertrophic obstructive cardiomyopathy; LIS, left intercostal space; LVOT, left ventricular outflow tract; RIS, right intercostal space.
Echocardiography is the test of choice to diagnose SAS. It is used to characterize the anatomy of the subaortic lesion, to assess LVOT involvement and dimensions and function of the LV, as well as the integrity of the aortic and mitral valves. However, often it is difficult to assess the degree of obstruction of outflow in SAS on a 2-dimensional echocardiogram, and thus Doppler examination is indicated.

In a study by Oliver et al., Doppler examination has aided in the precise identification of the cardiac abnormality leading to LVOT obstruction, which leads to the correct assessment of the different anatomic patterns.2 It is used to estimate the gradient and the extent of obstruction across the LVOT. In addition, by using Doppler, it was possible to diagnose small subaortic membranes causing acceleration of the LVOT flow, but without a hemodynamically significant pressure gradient.2

Differentiating SAS from other causes of LVOT obstruction, especially HOCM, can prove difficult at times.19 This is because some patients with SAS develop asymmetrical septal hypertrophy and secondary dynamic subaortic obstruction.20

Severe septal hypertrophy and dynamic obstruction of the LVOT can mask the existence of a subaortic membrane, leading to a false diagnosis of HOCM.2 In such cases where conventional Doppler examination may be inconclusive, transesophageal echocardiography is more reliable for the accurate diagnosis of a subaortic membrane that is masked by the hypertrophied and prominent ventricular septum.2

AR can be present in >50% of patients with SAS.2 There are no published guidelines particularly addressing the hemodynamic effect of AR on SAS. We believe that, similar to valvular aortic stenosis, when severe AR accompanies SAS, measures of SAS severity remain accurate, including maximum velocity and mean gradient.21 However, because of the high transaortic volume flow rate, maximum velocity and mean gradient will be higher than expected for a given valve area. As per the recent update of the American Society of Echocardiography guidelines on aortic stenosis, reporting accurate quantitative data for the severity of both stenosis and regurgitation is helpful for clinical decision-making.21

Cardiac catheterization is sometimes performed to further clarify the mechanism and extent of subaortic obstruction. This provides hemodynamic data such as the gradient across the valve, measurement of cardiac output, and estimates of the degree of AR. However, cardiac catheterization is not typically indicated in the diagnosis of SAS, but it can be utilized for preoperative hemodynamic evaluation and for preoperative workup before surgical repair to rule out significant coronary artery disease.

Cardiac magnetic resonance imaging (CMR) and cardiac computed tomography (see Supporting Information, Figure 2, in the online version of this article) are the up-and-coming imaging modalities being used to diagnose different etiologies of LVOT. CMR can be used to clarify anatomy and quantify flow velocity. This can be done using T1-weighted images with 3- to 5-mm slice thickness; but the images are usually inferior to those of transesophageal echocardiography.23 Another limitation of CMR is that the spin dephasing artifact usually obscures the area of interest. This, along with the fact that the SAS membrane is often thin, makes it difficult to visualize. Cardiac computed tomography, on the other hand, is typically used in a role that complements transthoracic echocardiography.22 To date, it has not replaced echocardiography in standard practice because of its limitations: it is more complicated, more expensive, and exposes patients to radiation and iodinated contrast.22

4 | PROGNOSIS

Survival after SAS surgery has been shown to be excellent (Figure 2A). However, the LVOT gradient still increases slowly over time. In most patients, follow-up can be done at 2- to 4-year intervals due to the slow nature of the progression of the LVOT obstruction.24 Two groups that have been found to have a higher rate of progression are females (Figure 2B) and patients age > 30 years at time of diagnosis; thus, these patient groups should be monitored more frequently, but there is no set time for echocardiography follow-up.

FIGURE 2 Kaplan–Meier plots. (A) Survival and intervention-free survival for patients with DSS and expected survival for the normal age-matched Dutch population. (B) By sex.2 Abbreviations: DSS, discrete subvalvular aortic stenosis
intervals. Eventually, most patients will require reoperation for recurrent SAS at some point in their lifetime.

Reoperation for recurrent discrete subaortic stenosis is common; the reoperation rate is reported between 6% and 30%. Most of the reports discussing the risk of reoperation in patients undergoing relief of subaortic obstruction have focused on anatomic subtypes. Two high-risk subgroups for recurrence and reoperation were clearly identified: first was the group of patients with tunnel SAS, and the other was the group with multilevel LVOT obstruction. It was suggested that patients with a residual left ventricle-aortic gradient >30 mmHg at the end of bypass should undergo reoperation with a more aggressive subaortic resection during the same operating session. Table 2 highlights the predictors of reoperation.

The risk of reoperation may be due to inadequate resection at the first operation, yet recurrent obstruction may appear despite the adequacy of surgical excision. One theory suggests that there is a dynamic component that may play a role in residual obstructive LVOT stenosis despite adequate resection. This occurs from regrowth of the tissue from the region of the septum to the initial fibromuscular obstruction. Another theory suggests that the formation of scar tissue in the subvalvular area during the healing process leads to a fixed size of the LVOT, resulting in localized hypertrophy and fibrosis of the LVOT. This may trigger fibromuscular recurrence even though initially it was a discrete membrane.

### TABLE 2  Independent predictors for increased reoperation rate

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>2.0</td>
</tr>
<tr>
<td>Peak instantaneous LVOT gradient progression over time</td>
<td>2.0</td>
</tr>
<tr>
<td>Difference between preoperative and postoperative peak instantaneous LVOT gradients</td>
<td>2.0</td>
</tr>
<tr>
<td>Preoperative peak instantaneous LVOT gradient ≥80 mmHg</td>
<td>2.0</td>
</tr>
<tr>
<td>Age &gt; 30 years at diagnosis</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Abbreviations: LVOT, left ventricular outflow tract.

Myectomy is another intervention that can be done to help alleviate LVOT obstruction in SAS. However, even after undergoing myectomy, there is still a high chance of recurrence, with reoperation rates between 10% and 20% within 10 years. In addition, myectomy is associated with an increased risk of complete heart block. Therefore, given the combination of no long-term benefit and the risk of heart block, myectomy should not be performed routinely, and it only should be performed if marked LVH is present.

AR was found in >50% of patients with SAS, but only 20% are considered to be hemodynamically significant. If present, the degree of AR can progress in patients who did not have any repair procedure for SAS. Studies have shown that there is a direct relationship between the severity of SAS and AR. But it has been shown that there is no significant progression of AR. A study by van der Linde et al. showed that in most patients, AR did not progress over time. They also found that 10% of patients who did not have AR before surgery developed mild aortic insufficiency relatively immediately in the postoperative period. Another 10% of patients progressed from mild to moderate AR, and progression to severe AR was found to be very rare (Figure 3). An LVOT gradient ≥80 mmHg was found to be a significant risk factor for developing AR postoperatively (see Supporting Information, Figure 3, in the online version of this article).

Hence, it is recommended to operate before the LVOT gradient reaches 80 mmHg. Furthermore, given the possible recurrence and the presence of mild AR, lifelong regular follow-up with echocardiography is required. A summary of long-term outcomes after an SAS operation, see Supporting Information, Table 1, in the online version of this article.

### 5 TREATMENT

Definitive therapy for SAS consists of surgical correction of the obstruction, which may involve simple membrane removal, extensive ring resection with or without myectomy, or a Konno procedure.
The timing of the surgery varies. Recommendations range from early operation to longer periods of observation, depending on patient characteristics. Ezon et al. reported that ≥2 studies recommended surgery at diagnosis, regardless of the severity of the obstruction.33 Brauner et al. suggested that early surgery prevents AR.34 However, prevention of AR alone is not a criterion for surgery. According to 2008 American Heart Association (AHA) guidelines, unoperated adults with mean gradient <30 mmHg and without significant LVH are recommended to be followed up annually, because some of these patients will eventually require surgery. In patients with equivocal indications for intervention, stress testing to determine exercise capability, symptoms, electrocardiographic changes or arrhythmias, or increase in LVOT gradient, is reasonable (the 2008 AHA/American College of Cardiology [ACC] guidelines are found in Supporting Information, Table 2, in the online version of this article).34

Currently, there are no established medical therapies to reverse or stop the progression of SAS, including balloon dilation. Thus, the appropriate intervention for patients with significant obstruction is surgical intervention. In those with significant muscular or tunnel-like obstruction, surgical resection of the subvalvular membrane or fibrous crescent, with or without septal myectomy, is preferred.35 For patients with diffusely narrow LVOTs, the Konno procedure and its modifications may be necessary (details of the Konno procedure can be found in Supporting Information, Figure 4, in the online version of this article).36 Postoperative complications of heart block, mitral valve injury, iatrogenic ventricular septal defect, as well as incomplete relief and/or recurrence of obstruction and infective endocarditis (IE), have been reported. In recent years, enucleation of the fibrous ridge by blunt dissection with myectomy in selected patients has shown promising results.35 In the study by Suri et al., there was a postoperative decline, but ejection fraction stabilized with time after the Konno procedure on the follow-up echocardiograms.37 Sharma et al. demonstrated that the recovery of ventricular function after the Konno procedure is similar to that seen after aortic valve replacement alone, in contrast to initial studies.38 Pulmonary valve regurgitation can occur as a complication of this procedure and may require pulmonary valve replacement in a minority of patients. In the long-term follow-up of the patients who underwent the procedure, New York Heart Association status remained class 1 after initial improvement. Mean follow-up period was 8.2 ± 5.7 years.37

IE prophylaxis before dental procedures is not recommended as per the 2008 ACC/AHA guidelines unless the patient had prior history of IE or repair with patch or residual defect. IE prophylaxis is recommended only in the initial 6 months after patch repair.34

6 | CONCLUSION

SAS is the second most common type of aortic stenosis, accounting for 6.5% of adult congenital disease. It is considered an acquired disease, with different rates of progression among adults and children. Most adult patients with SAS are asymptomatic. Symptoms may include pre-syncpe, shortness of breath, or fatigue with physical stress, such as exercise or pregnancy. Surgical correction is the treatment of choice, and the prognosis is usually excellent, with varied recurrence rates depending on the presence of certain risk factors.

Conflicts of interest

The authors declare no potential conflicts of interest.

ORCID

Subodh R. Devabhaktuni © http://orcid.org/0000-0002-0060-3907

REFERENCES


SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.