**Review Article**

**Low flow low gradient aortic stenosis: clinical pathways**

I. Sathyamurthy a,*, K. Jayanthi b

a Director and Interventional Cardiologist, Department of Cardiology, Apollo Main Hospitals, 21, Greams Lane, Off Greams Road, Chennai 600026, India

b Consultant Interventional Cardiologist, SRM Institutes for Medical Sciences, Vadapalani, Chennai, India

**Abstract**

Aortic stenosis patients with severe LV dysfunction and low cardiac output present with relatively low transvalvular gradients. It is difficult to distinguish them from aortic sclerosis and LV dysfunction with low cardiac output. The former condition is severe AS with LV dysfunction and latter is primarily a contractile dysfunction. Dobutamine stress echocardiogram is key to diagnosis.

AS with LV dysfunction associated with preserved contractile reserve benefit from valve replacement and those without contractile reserve needs critical evaluation on a case to case basis. Patients of AS with LV dysfunction with associated coronary artery disease need coronary angiograms to decide regarding need for valve replacement with bypass surgery.

A subset of AS patients have low flow, low mean gradients with preserved ejection fraction in whom one must evaluate global hemodynamic load to assess ventriculo-arterial impedance.

In this review an approach to the clinical pathways for assessment of low flow, low gradient aortic stenosis has been discussed.

Copyright © 2014, Cardiological Society of India. All rights reserved.

**1. Introduction**

There are four hemodynamic variants of severe valvular aortic stenosis (AS) 1) Asymptomatic severe AS with preserved left ventricular (LV) function 2) Symptomatic severe AS with either preserved LV function or LV dysfunction 3) Low flow (LF) low gradient (LG) aortic stenosis with severe LV dysfunction 4) LF, LG, AS with preserved LV function. The aim of the present review is to discuss the last two variants.

In this article an attempt has been made to simplify clinical pathways of patients with AS presenting with low stroke volume (SV), consequently low flow and low gradients across aortic valve. Low flow, low gradients occur in the setting of LV systolic dysfunction with low ejection fraction (EF) or small ventricular volumes, consequent to severe LVH with preserved EF. These patients can be classified into 5 categories (A–E) as shown in flowchart (Fig. 1).

The new entity of LF LG AS associated with preserved LVEF forms Group E (Fig. 1-E). Patients with LF LG AS with low EF can

* Corresponding author.
E-mail address: isathya@hotmail.com (I. Sathyamurthy).
http://dx.doi.org/10.1016/j.ihj.2014.10.423
0019-4832/Copyright © 2014, Cardiological Society of India. All rights reserved.
be further divided into those with associated coronary artery disease (CAD) – the Group D (Fig. 1-D) and those without CAD. Patients without associated CAD can be further divided into pseudo severe AS – Group C (Fig. 1-C) or true AS by Dobutamine stress echocardiography (DSE). Patients with true AS can be further subdivided into those with preserved contractile reserve (CR) – Group A (Fig. 1-A) and those without CR – Group B (Fig. 1-B).

These pathways help us evaluate whether it is true AS or pseudo severe AS and also useful for assessment of reversible causes of myocardial dysfunction like associated CAD needing aortic valve replacement (AVR) with additional coronary artery bypass graft (CABG) surgery, prediction of perioperative mortality and long term survival based on presence or absence of contractile reserve.

2. LF LG AS with severe LV dysfunction (Group A & B in Fig. 1)

American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for diagnosis of severe AS is shown in Table 1. LF LG AS is characterized by combination of severe aortic valve stenosis (calculated aortic valve area (AVA) <1 cm² or ≤0.6 cm²/m²), low transvalvular gradient (mean gradient <40 mm Hg) and low flow (stroke volume <35 ml/m²).

with this hemodynamic presentation it is difficult to distinguish true aortic valve stenosis where the primary culprit is severe aortic valve disease and LV dysfunction from pseudo severe AS where primary problem is myocardial dysfunction (due to other secondary causes like severe multivessel CAD or myocardial disease) in whom aortic valve disease severity is over estimated due to incomplete opening of rigid aortic valve leaflets, as a consequence of decreased force of opening by dysfunctional myocardium.

Differentiation of true severe AS from pseudo severe AS is usually done by increasing flow across the stenotic aortic valve by pharmacologic means by infusing dobutamine. Effective orifice area (EOA) is the smallest cross sectional area of the aortic Jet (area of the vena contracta) measured by doppler.2,3 The EOA does not change in true AS even though gradient may increase whereas in pseudo severe AS the calculated EOA increases with no significant change in gradient. Various quantitative criteria like peak stress EOA <1.0 cm², gradient >30 mmHg and absolute increase in EOA <0.3 cm² are sufficient for diagnosing true AS. However it should be remembered that magnitude of flow augmented by dobutamine is highly variable in individual patients and depends upon multiple factors like contractile reserve, chronotropic response, drugs like betablockers.

To overcome this variability of flow response in individual patients, a new parameter, projected EOA (EOAproj) at normal transvalvular flow rate of 250 ml/s has been suggested. The EOA proj is calculated by using transvalvular flow at each stage of DSE, valve compliance which is derived as slope of regression line fitted to the EOA versus flow (Q) plot. The diagnostic significance of EOA proj is superior to other echo indices, as evidenced by the multicenter TOPAS study4 (true or pseudo severe aortic stenosis study) of low flow AS.

The effect on SV with dobutamine infusion helps indirectly to assess the contractile reserve in patients with true AS. When the SV increases by more than 20%, it confirms

**Table 1 – Guideline criteria for severe aortic STENOSIS.**

<table>
<thead>
<tr>
<th>Metric</th>
<th>ACC/AHA</th>
<th>ESC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve area (AVA)</td>
<td>&lt;1.0 cm², &lt;0.6 cm²/m² of body surface area</td>
<td>&lt;1.0 cm², &lt;0.6 cm²/m² of body surface area</td>
</tr>
<tr>
<td>Aortic mean pressure gradient (dpm)</td>
<td>&gt;40 mm Hg</td>
<td>≥50 mm Hg</td>
</tr>
<tr>
<td>Maximum aortic jet velocity</td>
<td>&gt;4 m/s</td>
<td></td>
</tr>
</tbody>
</table>
preserved CR. These patients with preserved CR constitute group A and those without CR constitute group B (Fig. 1).

Group A patients with preserved CR fare better with AVR than those in Group B. An operative mortality of 10% in group A and 30% in group B was reported by Monin et al with better long term survival in group A. There was significant improvement in symptoms and LV function following AVR in group A as reported by the same investigators.

In a well selected patient population with AVA ≤0.7 sq cm and mean gradient ≤30 mm Hg, 4 year survival was <15% if not operated as against 78% after AVR. Six year survival after AVR was 75% in patients with preserved CR as against survival of 35% at 2 years in those without CR in a series of 136 patients with EOA ≤1 sq cm, mean gradient ≤40 mm across AV reported by Monin et al.

Without AVR however, the outcomes were extremely poor in those without CR (Group B) managed conservatively with 2 year survival of only 15%. Though operative mortality is high in this subset of patients, 90% of those who survive perioperative period show functional improvement and in 60% of them improvement in LVEF upto 10% was observed in one series. An absence of CR should not be considered an absolute contraindication for AVR and case by case evaluation of LF LG AS without CR should be stressed upon as recommended by Current European Society of Cardiology (ESC) guidelines.

3. **Pseudo severe AS (Group C in Fig. 1)**

Pseudo severe AS is defined as AVA ≥1.2 sq. cm with mean transaortic gradient ≤30 mm Hg at peak dobutamine infusion. An example of a patient’s response to inotropic stimulation is shown in Table 2. In these cases LV dysfunction is due to myocardial fibrosis or intrinsic myocardial disease in the absence of any significant CAD. In these cases increase in cardiac output causes much greater increase in flow than gradient, resulting in large increase in AVA. Only 15% of cases of LF LG AS belonged to Pseudo severe AS group as shown in the Pooled data from 5 reported series. The documented mortality was 48–57% at 20 months follow up in these patients. Emilie et al compared AVR versus conservative management in 305 patients of LF LG AS and concluded that in patients with pseudo severe AS, five year survival with conservative management was better than true AS. Caution should be exercised as DSE sometimes may not distinguish Pseudo severe AS (Group C) from true AS without CR (Group B). Patients with pseudo severe AS, LV dysfunction is mainly due to intrinsic myocardial disease and they do not benefit from AVR.

4. **LF LG AS associated with CAD (Group D in Fig. 1)**

In these cases severe AS is associated with coronary artery diameter stenosis ≥50% in one or more coronaries contributing to LV dysfunction. Majority of patients in this subgroup have comorbidities like diabetes, hypertension, dyslipidemia, smoking or prior history of acute coronary syndrome. Echocardiography reveals regional wall motion abnormalities, without any significant LV wall thinning. Position Emission Tomography scans may be needed to assess the viability in large akinetic areas. Surgical management with AVR plus CABG offers good long term survival and improvement in LV function if significant areas of viable myocardium and good target vessels for revascularization are present though with a high perioperative risk.

DSE is preferably avoided in this subset of patients with CAD as dobutamine can precipitate angina, arrhythmias and produce inconclusive results. In a large series of 217 consecutive patients reported by Frank Levy, DSE was done only in 38% of cases.

It is ideal to do invasive coronary angiography to detect and assess severity of CAD in these patients. As ostial left main or right coronary ostial stenosis can be missed due to densely calcific aortic valves, it is preferable to avoid multi detector CT coronary angiography in these cases.

Overall 5 year survival was less in patients with associated CAD compared to those without CAD as reported by Connelly et al in a series of 52 patients. Another study by Frank levy in 217 consecutive patients found that 5 year survival was 37% in those with associated multivessel CAD and 55% without multivessel CAD. Surgical treatment with AVR plus CABG improved LVEF significantly with Perioperative mortality of 16% in their study.

Some of the predictors of high surgical risk are higher Euro scores, very low mean gradients, low LVEF, preoperative atrial fibrillation, preoperative functional class and cardio pulmonary bypass time. Perioperative mortality of 25% was observed in patients with Euro score >10 as against 12% for those with Euro score <10. Improvement in functional class by more than one NYHA class post operatively was noted in 88% of patients in the series reported by connolly et al and 76% in the series by Levy et al.

5. **LF LG severe AS with preserved LV function (Group E in Fig. 1)**

Normal LVEF does not mean normal SV or normal systolic function. Ejection fraction is usually calculated by Simpson’s equation and is applicable when LV shape is elliptical. But in severe AS there is concentric hypertrophy of LV with >50% increase in relative wall thickness, a phenomenon known as increased concentric remodeling (ICR). This ICR alters LV geometry and shape resulting in decreased LV filling and low SV secondary to impaired diastolic function and decreased LV end diastolic volume. When SV is low it results in low flow situation leading to low mean gradients across aortic valve.
What is normal EF with normal LV geometry may be abnormal for altered geometry due to concentric LV remodeling. Inaccurate measurements of LV outflow tract (LVOT) diameter can alter the calculation of SV and AVA. Underestimation of LVOT area can occur if the shape of LVOT is eccentric to the aortic annulus and inconsistent measurement of the severity of AS can be noted in about 30% of cases. This inconsistency in the measurement of AVA by transthoracic echocardiogram can be offset by using planimetry with transoesophageal echocardiography or Magnetic Resonance Imaging but at an added cost to the patient.

Tissue Doppler imaging clearly demonstrates impaired long axis shortening and changes in LV geometry in severe AS with reduced contractility. LVEF may remain normal in these cases by use of preload reserve. One third of patients with asymptomatic severe AS and preserved LVEF were found to have an impaired systolic function in the SEAS substudy. A condition similar to LF LG AS was seen in these patients with low SV and transaortic gradients. The major concern in these cases is that underestimation of AVA can lead to underutilization of valve replacement.

Hachicha et al described ventriculo-arterial impedance (Zva), an index of global hemodynamic load and related this to the onset of symptoms and adverse events.

\[
\text{Ventriculo} - \text{Arterial impedance(Zva)} = \frac{\text{systolic arterial pressure} + \text{mean net transaortic gradient}}{\text{Stroke volume/BSA}^{2}}
\]

Height \( -2.04 \) can be substituted instead of BSA if SV is indexed to height in this formula. A value of Zva \( \geq 4.5 \text{ mm Hg/ml m}^{-2} \) may be useful to identify patients who are at risk of deterioration of myocardial function as per previously reported studies.

Normal LVEF does not mean normal SV. Hachicha et al showed that one third of patients with severe AS had reduced SV Index (SV/BSA < 35 ml/m²) despite preserved LVEF. This results in low flow situation which in turn results in low transvalvular gradients. In their study of 512 consecutive patients with echocardiographically determined low gradient severe AS (AVA \( \leq 0.6 \text{ cm}^{2}/\text{m}^{2} \)) and LVEF \( \geq 50\% \), Hachicha et al found normal flow (NF) having SV index \( \geq 35 \text{ ml} \) in 65% of cases and paradoxically low flow (PLF) having SV Index \( \leq 35 \text{ ml} \) in 35% of cases. During 5 year follow up, patients with PLF had a reduced survival compared to those with NF.

Guidelines24,25 regarding diagnostic and therapeutic recommendations for LF LG AS is shown in Table 5. Further prospective studies are needed to determine the prognosis and most appropriate timing of AVR in these asymptomatic paradoxically LF LG AS patients with preserved LV function.

### Table 3 – Low flow low gradient AS-DSE.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Incidence</th>
<th>Stress method</th>
<th>Follow up</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>deFilipi et al (1995)</td>
<td>5/18 (28%)</td>
<td>Echo</td>
<td>12</td>
<td>20%</td>
</tr>
<tr>
<td>Schwammenthal et al (2001)</td>
<td>8/24 (30%)</td>
<td>Echo</td>
<td>11</td>
<td>25%</td>
</tr>
<tr>
<td>Nishimura et al (2002)</td>
<td>7/32 (22%)</td>
<td>Cath</td>
<td>32</td>
<td>57–100%</td>
</tr>
<tr>
<td>Monin et al (2003)</td>
<td>7/136 (5%)</td>
<td>Echo</td>
<td>19</td>
<td>50%</td>
</tr>
<tr>
<td>Zuppiroli et al (2003)</td>
<td>10/48 (25%)</td>
<td>Echo</td>
<td>24</td>
<td>70%</td>
</tr>
<tr>
<td>Pooled</td>
<td>37/258 (15%)</td>
<td>–</td>
<td>20</td>
<td>48–57%</td>
</tr>
</tbody>
</table>

### Table 4 – Management according to DSE testing.

- **Whole Cohort** N=305
  - **Surgery within 6 months** N=198
    - True – Severe AS: Group IA N=126 (64%)
    - Pseudo AS: Group IB N=9 (4%)
    - No contractile reserve: Group II N=63 (32%)
  - **Conservative management** n=107
    - True – Severe AS: Group IA N=43 (40%)
    - Pseudo AS: Group IB N=29 (27%)
    - No contractile reserve: Group II N=34 (33%)

Class of recommendation Level of evidence Reference

Dobutamine stress echocardiography for evaluation cardiac catheterization for hemodynamic measurements with dobutamine infusion
AVR should be considered in symptomatic patients with low flow, low gradient (<40 mmHg) AS with normal EF only after careful confirmation of severe AS
AVR should be considered in symptomatic patients with severe AS, low flow, low gradient with reduced EF and evidence of flow reserve
AVR may be considered in symptomatic patients with severe AS, low flow, low gradient and LV dysfunction without flow reserve

6. Conclusions

Classical LF LG AS is diagnosed when AVA < 0.6 sq cm/m², mean gradient < 30 mmHg and LVEF ≤ 35%. It intriguess cardiologists and poses challenge in assessment of severity and appropriate management. They comprise 10% of all patients of AS. DSE is the key to proper diagnosis. An increased flow in the presence of constant AVA with dobutamine infusion indicates presence of true AS. Contractile reserve is considered present in these cases if SV increases by 20%. The operative mortality is higher with absent CR at 30% compared to 10% when CR is preserved. AVR is associated with improved survival compared to medical treatment even in those with absent CR in some patients. Proper evaluation and case by case decision is an absolute requirement in these cases. Patients with pseudo severe AS need conservative management. If there are large areas of viable myocardium with good distal target vessels in those with associated CAD seem to benefit from AVR plus CABG surgery. LF LG AS with preserved LV function is a new entity and one third of them may need AVR even if they are asymptomatic. Diligent evaluation to plan individually tailored therapy is the key to success in the management of LF LG AS.

Conflicts of interest

All authors have none to declare.

Acknowledgments

We sincerely thank Dr. V. Daya Sagar Rao, Senior consultant cardiologist, KIMS hospital, Hyderabad who inspired us to write this article, for his advices from time to time and also for correcting and editing this article to make it simple for the readers.

References

11. deFilippi CR, Willett DL, Brickner ME, et al. Usefulness of dobutamine echocardiography in distinguishing severe from


