Resting Aortic Valve Area at Normal Transaortic Flow Rate Reflects True Valve Area in Suspected Low-Gradient Severe Aortic Stenosis

Navtej S. Chahal, MBBS,* Maria Drakopoulou, MD,* Ana M. Gonzalez-Gonzalez, MD,* Ramasamy Manivarmane, MBBS,* Rajdeep Khattar, MBBS,* Roxy Senior, MD*yz

ABSTRACT

OBJECTIVES This study sought to assess the diagnostic impact of stress echocardiography (SE) in patients with suspected low-flow, low-gradient aortic stenosis but normal resting transvalvular flow rate.

BACKGROUND SE may help to distinguish between true severe aortic stenosis and pseudosevere aortic stenosis in patients with low aortic valve area (AVA) and mean gradient. However, if rest flow rate is normal, then SE may not confer any additional diagnostic value, irrespective of resting left ventricular ejection fraction (LVEF) and indexed stroke volume (SVi).

METHODS Sixty-seven patients with suspected low-flow, low-gradient aortic stenosis who underwent SE were retrospectively studied. Following stratification by rest LVEF, SVi, and flow rate—using cutoffs of 50%, 35 ml/m², and 200 ml/s, respectively—we tested for significant changes in AVA during SE.

RESULTS Mean age was 77 ± 9 years and 60% of patients were male. Mean values for rest variables were as follows: AVA: 0.77 ± 0.12 cm²; mean gradient: 27 ± 7 mm Hg; flow rate: 182 ± 37 ml/s; SVi: 32 ± 8 ml/m²; and LVEF: 45 ± 15%.

During SE, significant increases in AVA were observed regardless of resting LVEF and SVi state. In patients with rest flow rate ≤200 ml/s, AVA did not increase significantly during stress (rest AVA: 0.90 cm² vs. stress AVA: 0.97 cm²; p = 0.11), and positive predictive value for confirming underlying true severe aortic stenosis was 84%. In adjusted analyses, rest flow rate was the only parameter associated with severe AS (odds ratio: 1.05, 95% confidence interval: 1.0 to 1.1; p = 0.002).

CONCLUSIONS Rest AVA measured under normal flow rate conditions is likely to reflect the true severity of AS and unlikely to change significantly with SE. Flow normalization may only be required in patients with AVA <1 cm² and mean gradient <40 mm Hg when the rest flow rate is ≤200 ml/s. (J Am Coll Cardiol Img 2015;8:1133–9)

© 2015 by the American College of Cardiology Foundation.

The constellation of low cardiac output state, symptoms of aortic stenosis (AS), reduced aortic valve area (AVA), and transvalvular gradient on echocardiography represents the entity of low-flow, low-gradient aortic stenosis (LFLGAS) and challenges the clinician to discern between the presence of true severe aortic stenosis (TSAS) or pseudosevere aortic stenosis (PSAS). In the former, low transvalvular flow can result in a low gradient, potentially masking genuinely severe AS. In the latter, the diminished flow does not fully open moderately restricted leaflets, producing a spuriously low AVA (1,2).

Low-flow states can arise due to impairment of left ventricular ejection fraction (LVEF), or independently of LVEF, in the presence of restrictive...
physiology and/or reduced longitudinal function (3). LFLGAS is typically suspected in patients with a rest mean gradient (MG) <40 mm Hg, an AVA <1 cm², an LVEF <50%, and/or or indexed stroke volume (SVi) <35 ml/m² (4). To help differentiate between true stenosis and pseudosevere disease, stress echocardiography (SE) is performed to normalize flow, permitting AVA and trans-aortic gradient to be remeasured at this juncture (4-6).

However, if flow is normal at rest, then there may be little incremental value in performing SE at all. Transvalvular ejection flow, or flow rate, is the principal determinant of both AVA and transvalvular gradient (1). Rather than quantifying ejection flow, much of the research to-date, and consequently clinical practice, has focused on surrogate measures during rest and SE. Impaired LVEF has been assumed to be a prerequisite to the existence of a low-flow state, and in routine clinical practice, an LVEF <40% to 50% remains the principal “red flag” for suspecting LFLGAS (4,7-9). However, LVEF is poorly correlated with flow state. Cardiac output, stroke volume (SV), and flow rate can all be preserved in patients with reduced LVEF and a dilated heart (10). Conversely, in patients with preserved LVEF, but advanced hypertrophic remodeling/restrictive physiology, the consequent reduction in SV has been used to define “low-flow” in these patients (11).

Flow rate can be simply measured during rest and SE, by dividing the SV by the systolic ejection period (SEP), with a normal rate considered to be 200 ml/s (12). We hypothesized that transvalvular flow rate is superior to both SVi and LVEF in predicting the impact of flow correction on AVA in patients undergoing SE.

**METHODS**

**STUDY POPULATION.** From February 9, 2011 to November 20, 2014, echocardiographic data were retrospectively collected in 67 consecutive, symptomatic patients who were all candidates for valve intervention and who had been referred for SE to further assess severity of LFLGAS, which was defined as an AVA <1 cm², MG <40 mm Hg, and either LVEF <50% or SVi <35 ml/m². Of these, 18 patients (27%) and 49 (73%) underwent exercise and dobutamine SE, respectively.

Patients with other significant valve disease, prosthetic aortic valve, at least moderate aortic regurgitation, or who developed significant ischemia during stress imaging were excluded from the study. The study was approved by the local institutional review board.

**PROTOCOL.** The protocol included an echocardiogram at baseline followed by stress imaging. Exercise stress was performed either on a treadmill according to Bruce protocol or bicycle ergometer using the World Health Organization protocol. The test was interrupted when the patient developed symptoms of AS or when the patient reached the age-related maximum heart rate. Doppler echocardiographic data were collected at rest and peak- or post-exercise stress.

Dobutamine SE was performed according to a standard protocol. Dobutamine was infused at an initial dose of 5 µg/kg/min with 5-min increments up to a maximum dosage of 20 µg/kg/min depending on the severity of AS. Echocardiographic data were obtained at rest and intermediate dobutamine dose including pulse-wave Doppler-derived SV in the left ventricular (LV) outflow tract, mean and peak gradients by the simplified Bernoulli equation, AVA by the continuity equation, mean transvalvular flow rate, and LVEF determined by the modified biplane Simpson method. Flow rate was calculated by dividing SB by the SEP (ms). Twenty-four patients had suboptimal images for the assessment of LVEF and ultrasound contrast enhancement was used (Sonovue, Bracco, Milan, Italy). LV outflow tract diameter was assumed to have remained constant during the stress test protocol and was measured only at rest.

Patients with stress AVA remaining at <1 cm² and stress MG increasing to ≥40 mm Hg were classified as having TSAS (Figure 1A), with the remainder classified as having PSAS (Figure 1B), according to conventional criteria (4).

**STATISTICS.** Comparisons within groups were made using paired Student t test for continuous variables and McNemar test for categorical variables. To assess the impact of SE, paired Student t test was used to determine significant changes in AVA within groups and between groups using independent samples Student t test—following stratification by rest EF, SVi, and flow rate using cutoff values of 50%, 35 ml/m², and 200 ml/s, respectively. Positive predictive values (PPV) of normal rest flow rate and normal rest SVi for defining TSAS were calculated using conventional criteria as has already been mentioned; PPV was also calculated when only an increase in stress MG to ≥40 mm Hg was evident, irrespective of stress AVA.
Multiple logistic regression was used to identify independent, resting correlates of TSAS using a stepwise method, adjusting for relevant echocardiographic variables. Statistical significance was defined as $p < 0.05$, and all statistical analyses were performed using SPSS version 19 (IBM, Armonk, New York).

**RESULTS**

Analysis was performed in 67 patients who met the inclusion criteria and who successfully underwent both rest and SE. The mean age of our cohort was 77.6 years and 60% of the patients were male. Dobutamine stress was performed in the majority (73%).

There were no significant differences in the demographic or baseline echocardiographic parameters between dobutamine and exercise stress groups, except that the former group had significantly more patients with reduced LVEF at rest (41% vs. 59%; $p < 0.001$) and SE (49% vs. 62%; $p = 0.03$).

Table 1 summarizes echo parameters measured at rest and stress. The average rest AVA was $0.77 \pm 0.12$ cm$^2$ and average MG was $27 \pm 7$ mm Hg. At rest echocardiography, 55% had impaired LVEF ($<50\%$), 70% had reduced SVi ($<35$ ml/m$^2$), and 72% had reduced flow rate ($<200$ ml/s). During stress, AVA remained $<1$ cm$^2$ in 73% and MG increased to $\geq 40$ mm Hg in 40%. TSAS (stress AVA $<1$ cm$^2$ and stress MG $\geq 40$ mm Hg) was evident in 36% of patients ($n = 24$).

The impact on AVA following stress and augmentation of flow/EF state within groups using paired Student $t$ test are shown in Table 2. Irrespective of LVEF or SVi at rest, significant increases in AVA were observed with stress. However, when

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Stress</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVA, cm$^2$</td>
<td>$0.77 \pm 0.12$</td>
<td>$0.89 \pm 0.22$</td>
<td>0.001</td>
</tr>
<tr>
<td>$&lt;1$</td>
<td>67 (100)</td>
<td>49 (73)</td>
<td>$-$</td>
</tr>
<tr>
<td>MG, mm Hg</td>
<td>$27 \pm 7$</td>
<td>$37 \pm 11$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>$\geq 40$</td>
<td>0 (0)</td>
<td>27 (40)</td>
<td>$-$</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>$45 \pm 15$</td>
<td>$52 \pm 16$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>$&lt;50$</td>
<td>37 (55)</td>
<td>22 (33)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>SVi, ml/m$^2$</td>
<td>$32 \pm 8$</td>
<td>$39 \pm 15$</td>
<td>0.002</td>
</tr>
<tr>
<td>$&lt;35$</td>
<td>47 (70)</td>
<td>15 (22)</td>
<td>0.001</td>
</tr>
<tr>
<td>Flow rate, ml/s</td>
<td>$182 \pm 37$</td>
<td>$239 \pm 73$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>$&lt;200$</td>
<td>48 (72)</td>
<td>14 (21)</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

Values are mean $\pm$ SD or n (%). Dashes indicate the $p$ values were not calculated.

AVA = aortic valve area; LVEF = left ventricular ejection fraction; MG = mean gradient; SVi = indexed stroke volume.
TABLE 2 Change in AVA During Stress, Stratified by Resting LVEF, SVi, and Flow Rate State

<table>
<thead>
<tr>
<th>LVEF &lt;50%</th>
<th>Rest AVA, cm²</th>
<th>Stress AVA, cm²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>0.75 ± 0.14</td>
<td>0.87 ± 0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF ≥50%</td>
<td>30 ± 0.79</td>
<td>0.93 ± 0.23</td>
<td>0.007</td>
</tr>
<tr>
<td>SVi &lt;35 ml/m²</td>
<td>47</td>
<td>0.74 ± 0.12</td>
<td>0.86 ± 0.23</td>
</tr>
<tr>
<td>SVi ≥35 ml/m²</td>
<td>20</td>
<td>0.83 ± 0.10</td>
<td>0.98 ± 0.21</td>
</tr>
<tr>
<td>Q &lt;200 ml/s</td>
<td>48</td>
<td>0.74 ± 0.12</td>
<td>0.89 ± 0.25</td>
</tr>
<tr>
<td>Q ≥200 ml/s</td>
<td>19</td>
<td>0.85 ± 0.09</td>
<td>0.89 ± 0.12</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Q = flow rate; other abbreviations as in Table 1.

patients were stratified according to resting flow rate state, a significant increase in AVA was only evident among those with reduced flow rate at rest; in patients with normal flow rate at rest, there was no evidence of a significant increase in AVA during stress. Flow rate increased significantly both in low flow group from 165 ml/s to 228 ml/s (p < 0.001) and in normal flow group from 226 ml/s to 269 ml/s (p < 0.001). In patients with TSAS, a resting flow rate of 226 ± 21 ml/s corresponded to an AVA of 0.85 ± 0.1 cm² and a MG of 51 ± 4 mm Hg. Analysis comparing change in AVA from rest to stress, according to resting flow/function between groups, was performed using the Student t test for independent samples. Again this showed significant change in AVA during stress between those patients with rest flow rate <200 ml/s compared with those with normal rest flow rate (change in AVA 0.16 cm² vs. 0.04 cm², respectively; p = 0.025). However, when stratified by LVEF or SVi, no significant differences in AVA change was observed (p = 0.67 and p = 0.70, respectively), suggesting a similar magnitude of AVA increase was evident, irrespective of resting LVEF or SVi.

Table 3 shows the predictive value of normal resting flow rate, compared to SVi, in confirming the presence of TSAS. Of 19 patients with normal rest flow rate, 16 (84%) met the conventional criteria of TSAS during SE (Table 3, Figure 1A). Of the 3 patients that were classified as not having TSAS according to these criteria, 2 achieved MG ≥40 mm Hg during stress, with their stress AVA remaining <1.1 cm²; these patients could clinically be considered to have severe AS. Thus, at a normal resting flow rate, all but 1 patient demonstrated hemodynamic features of severe AS, improving the PPV to 95% (Table 3). However, patients with normal SVI at rest had a PPV of 55% for defining TSAS using conventional criteria (Table 3), increasing to 70% when only an increase in stress MG to ≥40 mm Hg was evident (Table 3).

Receiver-operating characteristic curve analysis of rest flow rate for predicting TSAS gave an area under the curve of 0.84 and a flow rate of 199 ml/s for optimal accuracy in predicting TSAS, which can be approximated to 200 ml/s for routine clinical practice.

A logistic regression analysis of resting function parameters (LVEF, SVi, and flow rate) is presented in Table 4, with only flow rate being independently associated with presence of TSAS (p = 0.002). The majority (73%) underwent dobutamine stress testing. PPV for predicting severe AS in patients with normal flow rate were similar between the groups, 12 of 14 (86%) for dobutamine versus 4 of 5 (80%) for exercise, although the number in the latter group is small.

DISCUSSION

We have demonstrated that in patients with suspected low-flow, low-gradient TSAS, the AVA does not change significantly during SE if rest flow rate is normal, irrespective of rest LVEF or SVi. Moreover, flow rate was the only resting parameter of systolic function independently associated with the presence of TSAS. A normal rest flow rate in suspected severe AS carries an 84% PPV of defining underlying TSAS.
Flow Rate and Low-Gradient Severe AS

(JACC: Cardiovascular Imaging, Vol. 8, No. 10, 2015)

OCTOBER 2015:1133-9

Chahal et al.

Flow Rate and Low-Gradient Severe AS

(stress AVA < 1 cm² and MG > 40 mm Hg) and this increases to 95% if stress MG ≥40 mm Hg at an AVA < 1.1 cm² is considered as severe AS, which is clinically acceptable in symptomatic patients. By contrast, PPV of normal SVi was 55% increasing to 70% when a stress MG ≥40 mm Hg alone was used to define severe AS. Our data confirmed that a low-flow state, defined either by flow rate or SVi, is a poor discriminator of severity of AS.

The findings of this study suggest that in patients with normal resting flow rate, the corresponding AVA is likely to be representative of the true hemodynamic severity of the stenosis, and further flow "correction" is unlikely to yield further clinically measurable changes and hence potentially obviating the need for performing SE. However, in those with reduced flow rate at rest, stress testing is still indicated as a significant change in AVA; hence potential for PSAS still exists.

We studied patients with both preserved and impaired LVEF at rest with reduced AVA and low mean transvalvular gradients. We observed that in patients with normal range resting LVEF or SVi, a significant increase in AVA was still achievable with stress. In multivariate analysis, rest flow rate was the only functional parameter independently associated with TSAS.

Our clinical findings closely reproduce experimental studies performed by Voelker et al. (12) who observed flow augmentation from low, initial resting flow rates (100 to 200 ml/s) increased the valve area from 5% to 29% depending on underlying stenosis severity. However at physiological flow rates, flow augmentation (200 to 300 ml/s) did not alter valve area in severe AS.

We have observed a high prevalence of PSAS in our cohort, with several likely explanations. First, although endorsed by recent American College of Cardiology/American Heart Association guidelines (4), there remains incongruity in the cutoffs for gradient and AVA values for defining severe AS. This paper acknowledged that a MG ≥40 mm Hg corresponds to a valve area of <0.8 cm². One study found that 30% of patients with severe AS by AVA had nonsevere AS by MG (13). Indeed, in our patients with TSAS, a rest AVA of 0.85 cm² corresponded to MG of 31 mm Hg, whereas a mean AVA of <0.8 cm² corresponded to a stress MG of 40 mm Hg. Second, vortices in the ascending aorta may result in underestimation of effective orifice area using Doppler at low flow rates, potentially causing overdiagnosis of PSAS. However, changes in AVA were found to be real rather than due to artifact in an experimental model using fixed and compliant orifices interrogated with particle imaging velocimetry (14). Finally, there may be patients without contractile reserve in this group whose status of AS may be undetermined. This is likely to be small because flow rate increased significantly both in the low and normal rest flow group during stress.

**IMPORTANCE OF DEFINING EJECTION FLOW, LIMITATIONS OF STROKE VOLUME AND LVEF.** There has been considerable interest in defining a “low-flow state” in patients with suspected severe AS but in whom the recorded pressure drop across the valve is low. Low-flow states were thought to essentially exist only in those patients with impairment of LVEF to at least <40%, and the role of dobutamine challenge to uncover fixed valve stenosis and underestimated transvalvular gradients was established in the literature (5). More recently, SV measured in the LV outflow tract has been used to define flow, and particularly in the so-called paradoxical low-flow states, whereby the LVEF is preserved but cardiac output is reduced due, usually, to restrictive physiology/hypertrophic concentric remodeling.

Flow refers to the volume of blood passing through a defined region over a period of time. With reference to AS states, ejection flow is most germane as this truly determines aortic valve opening as well as transvalvular gradient (1). Ejection flow, or flow rate, denotes the volume of blood that is ejected during systole and is calculated by dividing SV by the SE. The importance of flow rate has been acknowledged recently when classifying the hemodynamic response to dobutamine by calculating a projected AVA to a standardized flow rate (15). Although SV does reflect a temporal component of flow, namely a heartbeat, and is a reasonable measure of systolic function in most circumstances, it is less helpful as a measure of flow when assessing AS severity. The duration of each heartbeat is determined by the length of both systole and diastole. In severe AS, maximum obstruction occurs later in systole, which is best appreciated by the rounded shape of the continuous-wave spectral Doppler velocity profile. Consequently, the ejection period is lengthened and for the same heart rate, a patient with moderate stenosis will have a higher flow rate than a patient with severe AS will, but they will have similar SV. Thus, EF is not only determined by underlying systolic function, it also intrinsically reflects the severity of outflow tract obstruction—being reduced in severe stenosis due to prolongation of ejection time. In severe AS, flow rate can be significantly diminished but SV may remain in the normal range, potentially confounding interpretation of discordant valve area and gradient data.
Flow rate is more closely correlated with cardiac output, which will both vary with changes in heart rate. However, SV will plateau and then diminish with increasing heart rate (16); this phenomenon should be taken into consideration when calculating SV increase during SE as a measure of contractile reserve. Also, the optimal cutoff values for low SV also remain to be defined and will vary according to the technique used (volumetric vs. Doppler) and demographic variables such as age, sex, and ethnicity (17).

The limitation of LVEF as a surrogate of transaortic flow is evident in routine clinical practice. Flow rate and SV can be normal despite significant impairment in LV systolic dysfunction; for example, in a patient with a dilated LV, an end-diastolic volume of 200 ml and end-systolic volume of 130 ml yields an SV of 70 ml, a cardiac output of almost 5 l/min (assuming a heart rate of 70 beats/min) and flow rate of 200 ml/s (assuming an ejection time of 350 ms but with an EF of only 35%). Conversely, in patients with normal LVEF but concentric LV remodeling and small volumes, both SV and flow rate may be attenuated.

WHAT IS A NORMAL FLOW RATE? As mentioned earlier, recognizing that flow heterogeneity exists in patients undergoing dobutamine SE and the importance of true flow, the concept of a standardized flow rate of 250 ml/s was proposed, allowing projected AVA to be determined (15). The value of 250 ml/s chosen was an arbitrary one, based on data reported from previous studies of patients with AS. However, flow at this rate would be associated with a supranormal cardiac output ~6.1 l/min, at a heart rate of 70 beats/min and SEP of 350 ms. In our cohort of patients with suspected severe AS, only 1 patient had a rest flow rate of >250 ml/s, who ultimately had nonsevere stenosis with stress AVA increasing to >1 cm².

We chose a cutoff for normal flow rate of 200 ml/min as used in experimental studies (12), which for a heart rate of 70 beats/min and a SEP of 350 ms corresponds to a normal cardiac output of 4.9 l/min. Moreover, a receiver-operating characteristic curve analysis of rest flow rate for predicting TSAS gave a flow rate of 199 ml/s for optimal accuracy in predicting TSAS, which can be approximated to 200 ml/s for routine clinical practice.

STUDY LIMITATIONS. This study has a retrospective design, with relatively small number of patients. Thus, further studies in larger and prospectively determined cohorts are required with follow-up for hard events to confirm the utility of resting flow rate in helping to classify AS severity.

CONCLUSIONS

Resting flow rate, but not SVi or LVEF, can predict changes in AVA during SE and is more closely correlated with underlying AS severity. Resting AVA measured under normal flow rate conditions is likely to reflect the true severity of AS—and is unlikely to change significantly with SE—thus the need for SE maybe obviated.

CLINICAL IMPLICATIONS. We propose that flow rate should be measured routinely during rest echocardiography in all patients with suspected LFLG severe AS, which could obviate the need for SE in patients with normal flow rate. In our study, these patients had a mean AVA of 0.85 cm² and MG of 31 mm Hg at rest at a mean flow rate of 228 ml/s, and they can be considered to have severe AS (13). Thus, carefully measured parameters demonstrating an MG ≥30 mm Hg at a normal flow rate, with AVA <1 cm² should provide reassurance that the underlying obstruction is severe. This algorithm, however, would need to be tested in a prospectively designed, interventional study.

REPRINT REQUESTS AND CORRESPONDENCE: Prof. Roxy Senior, Royal Brompton Hospital and National Heart and Lung Institute, Imperial College, London, United Kingdom. E-mail: roxysenior@cardiac-research.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The entity of LFLGAS is well recognized and commonly encountered in clinical practice. At present, SE is the only diagnostic technique recommended to help distinguish between true and pseudosevere forms of AS. However, this may not be necessary if resting flow is normal, as the resting AVA is likely to be representative of the underlying stenosis severity. Therefore, accurate quantification of rest flow is of paramount importance. Flow rate incorporates both SV and ejection time and compared with SVi alone is a better measure of flow, particularly in patients with AS.

TRANSLATIONAL OUTLOOK: Prospective, observational, and interventional studies are required to assess whether in patients with LFLGAS resting flow rate alone is enough to exclude pseudosevere stenosis.
REFERENCES


KEY WORDS: aortic stenosis, flow rate, stress echocardiography