

# Pitfalls in the diagnosis and management of aortic stenosis

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## ABSTRACT

**In many instances the diagnosis and management of aortic stenosis (AS) is straightforward. In others, however, the diagnosis and management of AS can be extraordinary difficult. Clinicians need to be aware of the pitfalls in diagnosis and management. Diagnosis and assessment of disease severity begins with a detailed history and physical examination. Echocardiography in experienced hands is the standard investigation of choice to confirm the diagnosis and to assess its severity. While the treatment of symptomatic severe AS is surgery, asymptomatic patients with severe aortic disease and concomitant disease, like hypertension, requires an individualised approach.** SAHeart 2009; 6:76-82

## INTRODUCTION

AS has become the most frequent valvular heart disease and the most frequent cardiovascular disease after hypertension and coronary artery disease in the Western world. The prevalence of AS in the population older than 65 years is between 2-7% and is expected to rise with an aging population.<sup>(1)</sup>

The most common form is primary calcific AS, a disease characterised by progressive leaflet calcification and fibrosis that results in left ventricular (LV) outflow obstruction with symptom onset in the sixth decade. Once thought to be purely an age-related or degenerative disease, it is now well accepted that this condition is an inflammatory disease similar to atherosclerosis. When this disease process involves bicuspid aortic valves, patients usually present one to two decades earlier. When the aortic valve is diseased (possibly calcified), but non-obstructive, the term aortic sclerosis is applied. We consider this unwise and prefer to use the term aortic valve disease with minimal or no gradient. Aortic sclerosis is a precursor of calcific AS with an average time of progression to severe AS of 8 years.<sup>(2)</sup> The rate of progression in any individual is unpredictable and labelling patients as "aortic sclerosis" creates a false sense of complacency and comfort. All patients with clinically detectable aortic valve disease require careful serial monitoring to detect disease progression.

It is important to remember that AS is not a disease confined to the elderly population. Congenital AS presents in the young and rheumatic AS is still encountered in developing countries. Rheumatic AS frequently coexists with aortic regurgitation and mitral valve disease and it is well recognised that clinical severity of aortic stenosis may be underestimated in the face of significant mitral stenosis.

This article will highlight some of the common pitfalls and address some of the controversies in the diagnosis and management of primary calcific AS.

## PITFALLS IN THE CLINICAL DIAGNOSIS OF AS

The diagnosis of AS begins with a detailed history and physical examination.

In primary calcific AS, there is usually a long latent asymptomatic period before symptoms develop usually in the sixth decade of life. History taking must determine whether patients are indeed symptomatic (the classic symptoms being angina, dyspnoea and syncope) or not, keeping in mind that many patients will often reduce their physical activity to compensate for "minor symptoms". Patients may also present with non-specific symptoms such as dizziness, fatigue or unsteadiness on exercise which

have the same significance as episodes of syncope or dyspnoea. It must be remembered that dyspnoea on exertion, orthopnoea and PND are usually late symptoms of AS.

The classical teaching is that severe AS causes a small, slow-rising pulse, a loud long ejection systolic murmur, a soft or absent second heart sound and systemic hypotension with a reduced pulse pressure. However, not all patients will have these signs. A combination of a right clavicular murmur and the following signs: a reduced carotid upstroke; reduced carotid volume; soft second heart sound; and a maximal murmur intensity at the right sternal edge, strongly predicts moderate or severe AS.<sup>(3,4)</sup>

The classic delayed rise of the pulse can be absent even with severe disease particularly in the elderly population with an inelastic arterial bed. Although hypotension and a low pulse pressure may be signs of AS, a normal blood pressure or even severe hypertension does not exclude AS. Between 22-40% of patients requiring aortic valve replacement have a systolic blood pressure of > 130mmHg.<sup>(5,6)</sup> Not all murmurs of AS will radiate to the neck. The murmur may best be heard at the apex (Gallavardin's phenomenon) and may be confused with mitral regurgitation. Listening carefully for post-ectopic accentuation of the murmur which occurs with AS, but not with mitral regurgitation, can be a helpful distinguishing feature. It is important to note that when LV dysfunction occurs, the murmur intensity may decrease or disappear completely despite severe valve obstruction or so-called occult AS. The clinician needs to look for other clues for the presence of AS including observing calcification of the aortic valve which is found in nearly all patients > 50 years with severe AS and LV hypertrophy on ECG which is seen in 85% of patients with significant AS.<sup>(7)</sup>

In the differential diagnosis of AS always consider hypertrophic obstructive cardiomyopathy and congenital sub/supravalvar aortic stenosis in younger patients. The murmur of hypertrophic cardiomyopathy softens on squatting and increases in intensity during the valsalva manoeuvre and when standing, which reduces transvalvular flow. Consider sub/supravalvar AS in a patient with suspected congenital valvar AS without an ejection systolic click.

In summary, the clinical signs of AS may be unreliable and there should be a low threshold for requesting a diagnostic echocardiogram in a patient where the diagnosis is suspected.

### **PITFALLS IN THE ASSESSMENT OF DISEASE SEVERITY BY ECHOCARDIOGRAPHY**

All patients with a clinical diagnosis of AS should have an echocardiogram to confirm the diagnosis and to assess disease severity.

Echocardiography provides anatomic imaging of the possible underlying aetiology, level of obstruction, degree of valve calcification, aortic root anatomy and the left ventricle's response to the disease. The maximal transvalvular aortic jet velocity, mean transvalvular gradient and aortic valve area using the continuity equation can be measured and calculated.

AS can be graded as mild, moderate or severe.<sup>(8)</sup>

<b>Mild AS</b>	2.6-3.0 m.s <sup>-1</sup>	AVA > 1.5cm <sup>2</sup>	Mean gradient < 25mmHg
<b>Moderate AS</b>	3.0-4.0 m.s <sup>-1</sup>	AVA = 1.0-1.5cm <sup>2</sup>	Mean gradient = 25-40mmHg
<b>Severe AS</b>	> 4.0 m.s <sup>-1</sup>	AVA <= 1.0cm <sup>2</sup> AVA index <0.6cm <sup>2</sup> /m <sup>2</sup>	Mean gradient > 40mmHg

Accurate echocardiographic quantification of AS severity is a technically demanding procedure. The echocardiographer must ensure that the transducer and continuous wave doppler profile is obtained parallel with the aortic jet. Any deviation from a parallel intercept angle will result in underestimation of jet velocity. Several acoustic windows with optimal patient positioning and the use of the non-imaging continuous wave doppler transducer (stand-alone probe) are often needed. Although aortic jet velocity is the most reproducible measurement one has to be careful about assessing the severity of AS using velocities or gradients alone. Gradient is influenced by stroke volume, systolic ejection time, heart rate, preload, afterload and contractility. As a result gradient can often vary from one time to another. Aortic valve area calculation factors in some of these variables and is less influenced by variable haemodynamic states, but is less reproducible and is more prone to errors in measurement.<sup>(9)</sup>

Aortic valve area determined by echocardiography is calculated using the continuity equation.

$$CSA_{(LVOT)} \times VTI_{(LVOT)} / VTI_{(AS)}$$

$$CSA_{(LVOT)} = \pi (D/2)^2$$

*D* = LVOT tract diameter. *VTI* = velocity time integral. *CSA* = cross sectional area

LV outflow tract diameter is measured in midsystole just proximal to and parallel with the plane of the aortic valve from the inner edge of the septal echo to the leading edge of the base of the anterior mitral leaflet. Small errors in outflow tract diameter may lead to large errors in calculated cross-sectional area as the diameter is squared in the equation to calculate CSA. Multiple readings need to be taken.<sup>(9)</sup>

Co-existing moderate to severe aortic regurgitation may result in a falsely high transvalvar pressure gradient (due to a high transvalvar flow rate), but valve area calculations are still accurate because transvalvar stroke volume in the continuity equation still represents transvalvar stroke volume. Conversely, LV systolic dysfunction with severe AS can result in falsely low transvalvar pressure gradient because of a low transvalvar flow rate. Although calculation of valve area is less flow-dependent than pressure gradients, valve area can fall in parallel with flow rate and thus the valve area can be reduced even when the stenosis is not severe in patients with LV systolic dysfunction.<sup>(9)</sup>

There is a wide variation in the correlation of symptoms with the severity of AS defined by velocity, gradient or valve area. Generally, symptoms can be attributed to AS if the aortic valve area is < 1.0 cm<sup>2</sup> or if the transvalvar velocity > 4m.s<sup>-1</sup>.<sup>(10)</sup> There is significant overlap of all measures of haemodynamic severity between symptomatic and asymptomatic patients and it is not unusual to see asymptomatic patients with a transvalvar velocity > 4m.s<sup>-1</sup>. Furthermore, the rate of haemodynamic progression is highly variable between patients. On average, transvalvar velocities increase by 0.3m.sec/year and valve area decreases by 0.1cm<sup>2</sup>/year.<sup>(9)</sup>

### PITFALLS IN THE ASSESSMENT OF DISEASE

#### SEVERITY BY CARDIAC CATHETERISATION

Cardiac catheterisation is reserved for patients where echocardiographic data is non-diagnostic or when clinical and echocardiographic data are discrepant. Heavily calcified aortic valves should not be crossed with a catheter because of the risks of peripheral embolisation. A careful left ventricle to aorta pull-back is particularly useful to exclude subvalvar or supra-valvar AS. When the aortic valve cannot be crossed by a catheter and the diagnosis is still in doubt, a trans-septal puncture must be performed with simultaneous measurement of LV and aortic pressures. When performing a LV to aorta pullback it is important to measure transvalvar pressures in the ascending aorta just distal to the aortic valve using an end-hole catheter as peripheral amplification of aortic pressures may lead to false reduction in the peak and mean gradients. Calculation of aortic valve area using the Gorlin equation is flow-dependent. Therefore, patients with LV dysfunction and a low cardiac output may have a low calculated valve area even in the presence of mild AS (see AS with reduced EF below).<sup>(11)</sup>

### PITFALLS IN THE MANAGEMENT OF AS

#### Symptomatic AS

There is no debate with regards to the management of symptomatic, severe AS. Patients should have an aortic valve replacement as soon as the classic symptoms of angina, syncope or dyspnoea develop in the absence of surgical contra-indications. This recommendation is supported by the landmark survival data of Ross and Braunwald who showed a 75% 3 year mortality in symptomatic AS patients without valve surgery compared to near-normal age-corrected survival for patients who underwent valve surgery.<sup>(12)</sup> They clearly showed that 50% of patients with AS who present with angina survive 5 years; 50% of patients with syncope survive 3 years; and only 50% of patients with heart failure survive 2 years. Symptomatic patients with moderate AS that have no other explanations for symptoms should also be considered for valve surgery.

## Asymptomatic AS

The asymptomatic patient with moderate or severe AS has an excellent prognosis and should be followed up at 6 monthly intervals. They should be advised to report to their doctor or cardiologist as soon as symptoms develop because symptomatic patients, even for a period of a few months, have a poorer prognosis. The prognosis of asymptomatic patients is not completely benign as there is small incidence of sudden cardiac death (0.4%/year) with severe valve obstruction.<sup>(13)</sup> This risk is too low to recommend routine aortic valve replacement in every severe, asymptomatic patient as the operative risks of surgery (3-4%) and the risks of living with a prosthetic valve outweigh the small benefit of prevention of sudden cardiac death. The onset of symptoms can be difficult to assess as some patients may subconsciously adapt and reduce their daily activities. Approximately 1/3 of asymptomatic patients will become symptomatic within 2 years.<sup>(14)</sup> Asymptomatic patients with moderate or severe AS undergoing coronary artery bypass grafting, surgery of the ascending aorta or mitral valve surgery should undergo concomitant aortic valve replacement.

The use of exercise stress testing to further risk stratify asymptomatic patients with severe AS is controversial. The ACC/AHA guidelines recommend exercise stress testing when patients' symptoms are unclear but it is a Class IIb recommendation.<sup>(6)</sup> It does not form part of our routine practice for a number of reasons. There is currently no good evidence that this strategy decreases mortality in patients with severe asymptomatic AS as compared to watchful waiting. Although, exercise testing may be useful to predict symptom onset in patients with asymptomatic severe AS, a study by Das et al. showed that symptoms with exercise stress testing had a positive accuracy of only 65% and a negative accuracy of 73% to predict the onset of symptoms in the following 12 months.<sup>(15)</sup> Exertional dizziness rather than chest tightness or dyspnoea on exercise was a more reliable marker to predict symptoms in the following 12 months. The demonstration of breathlessness or chest tightness on a treadmill in an elderly patient with a limited exercise capacity is difficult to interpret as physical fitness clearly influences symptom interpretation and underlying coronary artery disease may mimic symptoms of AS. It has been stated that exercise stress testing is more useful in active patients  $\leq$  70 yrs of age, but

these are a group of patients where symptom onset is generally easier to define. Furthermore, the utility of ST-segment changes or an abnormal blood pressure response with exercise does not give additional prognostic information over symptoms alone.

The ACC/AHA guidelines state that severe LV hypertrophy ( $\geq$  15mm) not due to hypertension, or ventricular arrhythmias for which no other cause can be identified, can be used to further risk stratify asymptomatic patients and receive Class IIb recommendations for valve replacement surgery.<sup>(8)</sup>

The utility of serial measurements of cardiac biomarkers (particularly N-terminal brain natriuretic peptide) to identify the optimal timing of aortic valve replacement in asymptomatic patients is still under investigation. More evidence is needed before the measurement of biomarkers as a risk stratifying tool is adopted in clinical practice.

AS has been shown to be an inflammatory process associated with cardiovascular risk factors with histopathological changes in the valve leaflets similar to atherosclerosis. Given the clear relationship between atherosclerosis and AS it would seem that modification of cardiovascular risk factors would seem an obvious method to retard the progression of aortic stenosis. However, there is currently no good evidence that any medical therapy can retard the progression of AS.

Although a number of small retrospective studies have suggested that statin therapy can possibly retard the progression of AS, two recent randomised controlled trials have failed to demonstrate a reduction in the progression of aortic stenosis or hard clinical end-points.<sup>(16,17)</sup>

In theory, ACE inhibition could play a role in preventing progression of AS as sclerotic aortic valves express Angiotensin II and ACE and pressure overload leads to progressive cardiac remodelling (hypertrophy and fibrosis). A single retrospective study failed to show a beneficial effect of ACE-inhibitors on the progression of AS.<sup>(18)</sup> Historically, ACE inhibition was said to be contraindicated in the patients with AS. The concern has been that ACE inhibitors would cause profound peripheral vasodilation and decreased coronary perfusion pressure that would result

in haemodynamic compromise, collapse and potentially death. A single study showed that patients with severe AS can tolerate ACE-inhibitors very well on initiation.<sup>(19)</sup> There is sufficient theoretical evidence to support a randomised control trial to explore the role of ACE inhibition and AS. It is our current practice not to commence ACE inhibitors in patients with severe asymptomatic AS but not to withdraw them if patients are tolerating them as many patients are often unknowingly established on such treatment without compromise.

No clinical trials have addressed whether interventions aimed at altering cardiovascular risk factors such as hypertension, diabetes or smoking have any effect on the progression of AS.

### AS with reduced ejection fraction

Reduced ejection fraction in patients with aortic stenosis can be caused either by the severe afterload or contractile dysfunction. It is important to differentiate between these two causes as a low ejection fraction caused by severe afterload usually responds to relief of the afterload and has a good prognosis because contractility is maintained and the ejection fraction improves post surgery. The mean transvalvular gradient is a good measure of afterload and, generally, the higher the gradient (mean gradient > 35mmHg), the greater the afterload and usually the better response to surgery.<sup>(20)</sup> Most of the above patients will be symptomatic. A minority may be asymptomatic and should undergo aortic valve replacement when the LVEF ≤50%.

Patients with AS and a reduced ejection fraction caused by contractile dysfunction generally have a poorer response to surgery because irreversible LV dysfunction rather than severe afterload is the cause of the reduced ejection fraction. These patients will typically have a small transvalvular gradient, with a small reduction in afterload and smaller improvement in ejection fraction post surgery. Low-flow, low-gradient AS is defined as a reduced ejection fraction (LVEF≤40%) and a low gradient (mean gradient < 30mmHg) with a valve area < 1.0cm<sup>2</sup>. As the calculation of valve area in the Gorlin's equation is flow dependent, aortic valve area is highly dependent on cardiac output. As cardiac output can be reduced by any cause of contractile dysfunction, it is important to identify patients with truly severe AS (whose severe valve disease has led to severe LV dysfunction)

or relative or pseudo-AS where the LV dysfunction is from another process, such as coronary artery disease, and the ventricle is unable to open a mildly but not severely stenotic aortic valve. Dobutamine stress testing with calculation of the mean transvalvular gradient and aortic valve area by echocardiography using the continuity equation has been used to help differentiate true AS from relative AS and, secondly, to further identify contractile reserve in patients with true AS. Dobutamine will increase cardiac output in relative AS but the mean gradient will increase slightly or not at all with a large increase in calculated valve area. This is in contrast to true AS where the cardiac output and mean gradient will increase with a minimal change in the calculated valve area (if there is contractile reserve).

<b>Relative AS</b>	Area > 0.3cm <sup>2</sup> and/or area > 1.2cm <sup>2</sup>
<b>True AS with contractile reserve</b>	> = 20% increase in stroke volume and area < 1.2cm <sup>2</sup>
<b>True AS without contractile reserve</b>	< 20% increase in stroke volume and area < 1.2cm <sup>2</sup>

*Adapted from Bermejo et al.<sup>(21)</sup>*

Patients with relative AS should not undergo surgery, and the patient's prognosis is largely determined by the cause of the underlying LV dysfunction. Surgery is indicated if there is true AS and contractile reserve is demonstrated with dobutamine. The surgical risk is very high in patients without contractile reserve and surgery should not be recommended. Although division into these categories may help guide therapeutic decisions, we still lack large follow-up studies evaluating their effect on long-term prognosis. In the largest study published to date, Monin et al. showed that when contractile reserve was present, 6 year survival after aortic valve replacement was 75%.<sup>(22)</sup> When contractile reserve was absent, prognosis was much worse, although even some patients without contractile reserve improved post surgery. Methods to identify this latter group of patients whom may benefit still needs to be identified.

### AS in elderly patients

Symptom onset is often difficult to determine in the elderly. Fatigue rather than dyspnoea can be the sign of limited effort tolerance. History should also address patients' wishes and examination should focus on co-morbidities. Coronary angio-

graphy is indicated before surgery and is an important component of decision-making as coronary disease will influence operative risk and prognosis. The benefit of surgery on late outcome should be interpreted in the light of life expectancy. There have been many studies to date that have shown that there is almost no age limit for aortic valve surgery in patients with aortic stenosis in the absence of comorbid disease.<sup>(23)</sup> Operative mortality of aortic valve replacement is approximately 10% in patients over 80 years of age. The decision to operate relies on a team approach (cardiac surgeon, anaesthetist, cardiologist, geriatrician) with an accurate estimation of the risk/benefit ratio, comorbidity, operative mortality and life expectancy.

### AS and regurgitation

Many patients will have a combination of AS and regurgitation. These patients should be evaluated and managed with standard diagnostic approaches described above. It must be emphasised that symptoms may develop when AS and regurgitation is quantified as "moderate".<sup>(24)</sup> Aortic valve replacement is clearly indicated in patients who are symptomatic, LV systolic function is  $\leq 50\%$  or at the time of other cardiac surgery.

### AS and hypertension

AS and hypertension frequently co-exist in the same patient. Hypertension can mask the physical findings of AS especially in the elderly patient. Hypertension may result in the carotid pulse having a rapid upstroke and normal amplitude as well as a diminished murmur because of increased vessel stiffness and peripheral aortic impedance. The combined effect of aortic valvar obstruction (AS) and increased systemic vascular resistance (hypertension) on the double-loaded left ventricle is still not fully understood.<sup>(25)</sup> Hypertension may reduce aortic transvalvar flow rates and consequently transvalvar gradient. Therefore, calculation of aortic valve area by either the continuity equation during echocardiography or by cardiac catheterisation using Gorlins' equation may be more accurate than transvalvar gradients/velocities. Thus evaluation of AS severity should preferably be performed when patients are normotensive. The best drug for lowering blood pressure in the presence of AS has not been established. Anti-hypertensives should be started at low doses with careful dose escalation. We would begin with a diuretic with careful introduction of an ACE-inhibitor to control blood pressure (in patients who do not have severe AS).

### AS and coronary artery disease

Significant coronary disease occurs in about 30% of pre-operative cardiac catheterisation.<sup>(24)</sup> Patients with severe aortic stenosis should undergo coronary artery bypass grafting of significant lesions at the time of surgery. Patients due to undergo coronary artery bypass grafting with moderate/severe AS should undergo valve surgery. A challenging group are patients with a chest pain and both coronary artery disease and moderate AS. Studies testing for inducible ischaemia have a lower diagnostic accuracy in patients with AS.

### AS and noncardiac surgery

Patients with severe asymptomatic AS who require emergent non-cardiac surgery should undergo non-cardiac surgery without aortic valve evaluation. Patients with symptomatic AS should generally undergo valve replacement before elective surgery. There are small case series showing that surgery can be performed at an acceptable risk in patients with asymptomatic severe AS.<sup>(26)</sup>

## PERCUTANEOUS AORTIC VALVE REPLACEMENT

Percutaneous implantation of an aortic valve seems to offer a durable improvement in valve function at a lower risk than aortic valve replacement. Initial experience has demonstrated the feasibility of this approach in patients with severe co-morbidities and contra-indications to surgery. Growing experience and ongoing trials in patients at high operative risk will allow more accurate evaluation of this procedure.

## CONCLUSION

We have attempted to highlight some of the pitfalls in the diagnosis and management of AS. In many instances, the estimation of severity of aortic stenosis and the timing of valve replacement surgery is easy. In older patients and those with concomitant coronary, pulmonary or other disease it may be extraordinarily difficult. In truly asymptomatic patients the matter of severity of AS does not usually need to be pursued. In any symptomatic patient, once the possibility of AS has been entertained, investigation needs to be continued until the severity of the AS and its contribution to the symptoms has been clearly established.

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