Timing for surgery in asymptomatic aortic valvular diseases – a matter of controversy

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I. INTRODUCTION

In the last decades, major advances have occurred in the diagnosis and interventional or surgical management of valvular heart disease. Despite the fact that the informational database has expanded in recent years, there are still a scarcity of large-scale multicenter trials addressing the treatment of valvular disease. Consequently, diagnostic and management issues remain controversial.

The Euro Heart Survey has shown that, in current practice, the aortic pathology is the most frequent (FIGURE 1).

After clinical examination, the echocardiographic evaluation is the key examination for diagnosis and assessment of severity and prognosis, but for a correct estimation we need to check consistency between the different echocardiographic findings such as severity, mechanism, anatomy. In the absence of evidence from randomized clinical trials, the decision to intervene in such patients, with aortic disease, relies on an individual risk-benefit analysis, suggesting that improvement of prognosis compared with natural history outweighs the risk of intervention and prosthesis-related complications (1).

In this article we review the present literature about current recommendations of the surgical management in asymptomatic patients with aortic valvular diseases. The timing of aortic valve surgery will be described for patients presenting with two conditions: aortic stenosis and chronic aortic regurgitation.


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II. AORTIC STENOSIS

Introduction

Aortic stenosis (AS) has become the most frequent type of valvular heart disease in Europe and North America. AS may be caused by rheumatic disease, a congenital bicuspid valve or calcification of a trileaflet valve, with a final common pathway of significant aortic outflow tract obstruction (FIGURE 2).

It primarily presents as calcic AS in adults of advanced age (2-7% of the population > 65 years) (1). The second most frequent aetiology, in the younger age group, is congenital, whereas rheumatic AS has become rare (1,2).

The stenotic lesion tends to progress slowly, a minimal valve gradient is present until orifice area becomes less than half of normal, but once symptoms develop clinical deterioration can ensue rapidly (2).

The natural history of aortic stenosis therefore begins with a prolonged asymptomatic period associated with minimal mortality. In general, symptoms in patients with aortic stenosis and normal left ventricular systolic function rarely occur until the stenosis is severe as defined by valve area < 1.0 cm², aortic jet velocity over 4.5 m/sec, and/or mean transvalvular gradient exceeds 50 mmHg (2).

Survival is excellent during the prolonged asymptomatic phase. After the development of symptoms, mortality exceeds 90% within a few years. Aortic valve replacement prevents this rapid downhill course (FIGURE 3).

Braunwald et al. showed that average survival after the onset of symptoms was < 2-3 years. In these symptomatic patients, valve replacement results not only in dramatic symptomatic improvement but also in favorable long-term survival (2,4).

On the other hand, it has been shown that patients with asymptomatic aortic stenosis may be followed conservatively until symptoms develop. However, there are concerns about the possibility of irreversible myocardial damage or sudden death when proceeding in such a way.

Assessing severity of aortic stenosis

Patient history and physical examination remain essential.

Echocardiography has become the key diagnostic tool. It confirms the presence of AS, assesses the degree of valve calcification, number of aortic cusps, planimetric area, size of aortic annulus/supravalvular ascending aorta, LV function and wall thickness, and detects the pres-
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ence of other associated valve disease, and provides prognostic information (1).

Doppler echocardiography is the preferred technique to assess severity through parameters such as:

- Peak aortic velocity
- Mean pressure gradient
- Aortic valve area (continuity equation)
- LVOT/AoV VTI ratio (see FIGURE 4)

All the above variables are derived from maximal aortic velocity, so that a meticulous search for this is essential. The VTI ratio is more useful because it is independent of changes in stroke volume and LV function impairment did not significantly alter the ratio (5).

According to the current ESC guidelines for diagnosis and management of valvular heart disease, the definition of severe AS is:

1. Peak aortic velocity \( \geq 4.5 \text{ m/s} \)
2. Mean pressure gradient \( \geq 50 \text{ mmHg} \)
3. Aortic valve area \( \leq 1 \text{ cm}^2 \)
4. Aortic valve area adjusted to the body surface area (BSA) \( \leq 0.6 \text{ cm}^2/\text{m}^2 \) – for patients with either unusually small or large BSA
5. LVOT/AoV VTI ratio \( \leq 0.25 – 0.3 \)

Critical aortic stenosis has been defined hemodynamically as a valve area <0.75 cm² and/or an aortic jet velocity >5.0 m/sec. However, the decision about valve replacement is not based solely on hemodynamics as some patients who meet these criteria are asymptomatic, while others with less severe measurements are symptomatic.

All these parameters are available for a normal cardiac output. In the presence of low flow, usually due to depressed LV function, low pressure gradients may be encountered in patients with severe AS.

Another definition of severe AS, recently published, could be seen in TABLE 1.

Stress echocardiography using low-dose dobutamine may be helpful in this setting to distinguish truly severe AS from a functionally small valve area (pseudosevere AS). Truly severe AS shows only small changes in valve area (increase < 0.2 cm²) with increasing flow rate but significant increase in gradients, whereas pseudosevere AS shows marked increase in valve area but only minor changes in gradients (1,6).

In addition, this test may detect the presence of contractile reserve in AS with low ejection fraction (EF) (increase > 20% of stroke volume during low-dose dobutamine test), which has prognostic implications. There is poor perioperative mortality for no contractile reserve (50% vs. 7%) (1,6).

Exercise stress echocardiography and exercise testing has been proposed for risk stratification in asymptomatic AS.

Three-dimensional echocardiography has been applied for anatomic assessment of the aortic valve and root morphology and to calculate the valve area in aortic stenosis. The technique has been used to delineate aortic flow patterns and has demonstrated feasibility and accuracy in quantifying aortic regurgitation (7).

CT and MRI could improve assessment of the ascending aorta, and multislice CT may be useful in quantifying valve calcification, as well as in measuring valve area. More data are required to determine the full role of these imaging techniques in AS (1).

Asymptomatic patient with severe aortic stenosis - recommendation for aortic valve replacement

There is widespread agreement that valve replacement is indicated for symptomatic severe aortic stenosis. For these patients it has been shown that outcome is extremely poor, with survival rates as low as 50% at two years and 20% at five years after symptom onset (2).

The current AHA/ACC and ESC guidelines for the management of patients with valvular heart disease recommend aortic valve surgery in all patients with symptomatic severe aortic stenosis (class I indication). (See TABLE 2).

**TABLE 1.** Severity of aortic stenosis in adults

<table>
<thead>
<tr>
<th>Aortic jet velocity, m/sec</th>
<th>Mean gradient, mmHg</th>
<th>Valvular area, cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≤ 1.5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Mild</td>
<td>&lt; 3.0</td>
<td>&gt; 25</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.0-4.0</td>
<td>25-40</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt; 4.0</td>
<td>&gt; 40</td>
</tr>
</tbody>
</table>

**TABLE 2.** Indicators for surgery in valvar aortic stenosis. Adapted from Catherine M Otto, Timing of aortic valve surgery, Heart 2000; 84:211-218

- **Definite indications:**
  - symptoms caused by aortic stenosis (even if mild)
  - asymptomatic severe aortic stenosis with left ventricular systolic dysfunction
  - severe aortic stenosis at the time of other cardiac surgery

- **Selected patients:**
  - asymptomatic patients with severe stenosis and anticipated levels of exertion, plans for pregnancy, poor access to medical care, etc.
  - patients with moderate aortic stenosis undergoing coronary bypass surgery

- **Not accepted:**
  - prevention of sudden death in asymptomatic patients

**TABLE 3.** Evaluation of the patient with aortic stenosis and left ventricular dysfunction.
Adapted from Catherine M Otto, Timing of aortic valve surgery, Heart 2000; 84:211-218

- Calculate standard measures of stenosis severity and left ventricular ejection fraction
- Look at the severity of aortic valve calcification
- Consider the risk: benefit ratio of valve replacement in this patient
- Undertake dobutamine stress echocardiography to assess leaflet flexibility in selected cases

The only effective treatment for severe symptomatic aortic stenosis is valve replacement (AVR). In such patients who refuse or are not candidates for surgical intervention, therapeutic options are limited and of only marginal benefit. Percutaneous valve replacement may be an option for high risk patients in the future; this approach is currently being evaluated in clinical trials.

Symptomatic patients with severe AS have a high mortality. In these patients AVR is associated with improvement in survival, LVEF, functional class, and regression of LV mass (8). Perioperative mortality is only 2% (11,14).
In contrast, the management of asymptomatic aortic stenosis remains controversial. The occurrence of sudden death and the potential risk of irreversible myocardial damage argue for early elective surgery. However, prospective studies suggest that, in the absence of preceding symptoms, sudden death may be uncommon (14).

Considering the wide variation in individual outcomes, the potential risk of complications related to the prosthetic valve, and the risk of valve surgery itself, the decision whether to operate on an asymptomatic patient remains difficult.

The identification of predictors of outcome that could help in the selection of patients who are likely to benefit from early surgery would be highly desirable. The ideal time to operate is immediately before symptoms develop (11).

Asymptomatic patients have been defined as those that can achieve 80% predicted maximum heart rate without developing symptoms. Among asymptomatic patients, there are no medical therapies that have been proven to delay progression of the leaflet disease.

In severe asymptomatic aortic stenosis the risks of perioperative morbidity, mortality, and long term complications related to the prosthesis have to be weighed against the risk of sudden cardiac death and the morbidity and mortality experienced on lengthy surgical waiting lists.

Patients with asymptomatic, severe aortic stenosis are at risk of cardiac death. AVR should be considered in these patients, if surgery is likely to prolong life expectancy. Although these patients do not have cardiac symptoms, they still are at increased risk for adverse cardiovascular outcomes. In the population based Cardiovascular Health Study, subjects with aortic sclerosis on echocardiography and no known cardiovascular disease had an approximately 50% increased risk of myocardial infarction and cardiovascular death over an average follow up of 5.5 years (2).

Recent prospective studies have demonstrated that about 75% of patients with initially asymptomatic aortic stenosis develop symptoms requiring valve replacement within the next five years. This observation has led to the suggestion that valve replacement be performed at the time of coronary artery bypass surgery when mild to moderate stenosis is present to preclude the need for repeat surgery in the next few years (2,14).

Surgical mortality rates for repeat surgery for aortic valve replacement are high (14–30%), further supporting the suggestion that “prophylactic” valve replacement be considered.

The likelihood of progression to symptoms is strongly correlated with the baseline aortic jet velocity. Those with a velocity < 3.0 m/s have a five year event free survival of 84% suggesting that valve replacement is not necessary, while those with a jet velocity > 4.0 m/s have a five year freedom from valve replacement of only 21%, suggesting that valve replacement is appropriate (2).

The decision about valve replacement in those patients with intermediate jet velocities (3–4 m/s) should be individualised, based on the risk of valve surgery, expected prosthetic valve haemodynamics and longevity, the extent of valve calcification, and patient preferences.

Overall, the average annual rate of increase in aortic jet velocity is 0.3 m/s per year, with an increase in mean transaortic pressure gradient of 7 mm Hg per year and a decrease in valve area of 0.1 cm² per year (2,14). However, there is wide individual variability in the rate of haemodynamic progression.

There clearly are a few situations in which AVR is appropriate in asymptomatic patients. Examples include patients with evidence of left ventricular systolic dysfunction caused by aortic stenosis, young women with severe stenosis who desire pregnancy, patients with asymptomatic severe disease who plan activities that involve severe exertion, and adults with very severe stenosis (14).

Risk stratification of the asymptomatic aortic stenosis patient remains inadequate, however, and the decision to operate must be individualized, particularly in the elderly.

The most important predictor of postoperative left ventricular systolic function is preoperative systolic function, and most patients with aortic stenosis show an increase in ejection fraction after valve replacement.

In the study by Otto et al. the only predictors of outcome were aortic-jet velocity, the rate of change in this velocity, and functional status, but not age, sex, cause of aortic stenosis, left ventricular mass, or ejection fraction.

However, the extent of valvular calcification was found to be a strong independent predictor of outcome. Assessment of the rate of progression of aortic-jet velocity by serial echocardiographic examination may yield im-
important prognostic information in addition to the degree of calcification (14).

Studies in the modern era have used echocardiographic measures of severity, and outcomes have been based on the combined end point of death or the need for replacement of the aortic valve. Increased peak aortic velocity (more than 400 cm/s), a fast rate of increase in peak aortic velocity (more than 30 cm/s per year), calcification of the valve, and increased age of the patient are predictors of outcome (2,11).

Patients with no or only mild calcification represent a low-risk subgroup. They may remain asymptomatic for many years, and early elective surgery is definitely not justified. Follow-up visits at annual intervals and instruction to report the development of symptoms promptly appear to be appropriate for these patients.

In contrast, patients with severe, asymptomatic aortic stenosis and moderately or severely calcified valves represent a subgroup of patients with a poorer prognosis. Rapid progression of the disease can be expected, and approximately 80 percent of these patients will require valve replacement or die within four years (14).

Recently, the degree of aortic valve calcification combined with a rapid increase in aortic velocity from 1 visit to the following within 1 year has been shown to identify a high-risk group of patients, with ~ 80% death or requirement of surgery within 2 years (2,12).

Exercise testing was found the best predictor of outcome - a positive test had a high sensitivity of 92% but a relatively low specificity of 68% (11). Exercise testing should be included in the evaluation of asymptomatic severe aortic stenosis patients, as it may help to uncover functional and hemodynamic impairment that may be silent 20-30% of the patients (12).

Symptom development on exercise testing in physically active patients, particularly those younger than 70 years, predicts a very high likelihood of symptom development within 12 months. Recent data demonstrates a lower positive predictive value for abnormal blood pressure response, and even more so for ST-segment depression, than symptoms for poor outcome guidelines (1).

Natriuretic peptides have been shown in preliminary studies to predict symptom-free survival in AS. However, more data are required before recommending their serial measurement to identify optimal timing of surgery (1).

However, there remains concern about the risk of irreversible myocardial damage or sudden death among such patients who do not undergo surgery. The true incidence of sudden death approaches 5% per year for these patients (8,11).

In contrast to patients with valvular regurgitation, patients with severe aortic stenosis who are still asymptomatic but already have impaired left ventricular function are very rare. Nevertheless, myocardial fibrosis or severe hypertrophy may not be reversible after delayed surgery and may preclude an optimal postoperative outcome. However, the outcome after valve replacement is excellent in patients with normal preoperative left ventricular function (14).

Therefore, the potential benefit of preventing myocardial fibrosis and severe hypertrophy by early intervention is unlikely to outweigh the risk of perioperative and late complications of valve replacement in asymptomatic patients (14).

Surgery is recommended for asymptomatic severe aortic stenosis, in the following situations:

1. an abnormal response to exercise
   — symptoms develop,
   — systolic blood pressure falls
   — blunted systolic blood pressure response (less than 20 mm Hg) occurs when exercise capacity is poor;

2. impaired left ventricular systolic function (LVEF less than 50%).

3. moderate to severe calcification of the valve, peak aortic velocity more than 400 cm/s, and a rate of progression more than 30 cm/s per year;

Replacement of the aortic valve is also recommended in severe disease with the presence of marked left ventricular hypertrophy (more than 15 mm), unless the hypertrophy is due to hypertension or severe ventricular arrhythmias, although less evidence supports these strategies (2,12,14).

Patients not fulfilling the above criteria should have follow up with echocardiography and exercise testing at intervals of 6-12 months, depending on the severity of disease.

These recommendations are a consensus statement rather than strong evidence based guidelines.
Another difficult clinical situation is the patient with aortic stenosis and left ventricular systolic dysfunction. When stenosis is severe and there is a high pressure gradient across the aortic valve (maximum gradient > 50 mm Hg), surgery is indicated regardless of the degree of left ventricular systolic dysfunction. In the series from the Mayo clinic of 154 patients with an ejection fraction < 35%, operative mortality was only 9% and overall survival was 69% at five years in those with coexisting coronary artery disease, compared to 77% in those with isolated aortic stenosis (2).

Aortic stenosis with a low pressure gradient and left ventricular dysfunction is even more problematic. The depressed EF in this group is predominantly caused by excessive afterload (afterload mismatch). If the low pressure gradient is associated with severe stenosis resulting in left ventricular dysfunction, the patient will improve after AVR. However, if the pressure gradient is low because of moderate aortic stenosis with concurrent primary myocardial dysfunction, valve replacement is less likely to be beneficial. Distinguishing these two groups of patients is not easy as both have a small calculated valve area since, in both cases, valve opening is impaired (2).

Dobutamine stress echocardiography has been advocated for evaluation of these patients. If there is an increase in valve area with an increase in stroke volume, the valve leaflets are flexible and stenosis is not severe. Conversely, if valve area remains fixed despite an increase in flow rate, severe stenosis is present.

Octogenarians face more difficult issues. They have a shorter life expectancy and have a higher incidence of co-morbid conditions. At 4 years, the mortality of those with moderate to severe AS was 59%. Thus AVR by itself can be expected to reduce ~ 52% of all death (8).

A schematic approach of asymptomatic severe aortic stenosis is illustrated in the FIGURE 5.

![FIGURE 5. Surgical indication in AS. Adapted from ESC Guidelines of Management of Valvular Heart Disease](image-url)
In conclusion, it is reasonable to recommend AVR for asymptomatic patients with severe valvular AS if they are in higher risk group.

## III. AORTIC REGURGITATION

### Introduction

Chronic aortic regurgitation (AR) may be caused by abnormalities of the valve leaflets, most often a congenitally bicuspid valve, or by enlargement of the aortic root. When aortic root disease is the cause of aortic regurgitation, timing of surgical intervention is more dependent on aortic root pathology than on the severity of aortic regurgitation.

Patients with severe aortic regurgitation may remain asymptomatic for many years despite haemodynamically significant backflow across the valve. The increased volume overload leads to a gradual increase in left ventricular dimension so that a normal forward stroke volume is maintained. Most patients eventually develop symptoms, with an average rate of symptom onset of 4.3% per year in prospective studies (TABLE 4).

AVR has clearly been shown to prolong survival and improve functional class in patients with severe symptoms (1).

The optimal timing for valve replacement in asymptomatic patients is more controversial. In recent years, advances in surgical techniques and valve prostheses have led to progressive improvements in outcomes. Earlier intervention has been advocated to improve survival and functional outcomes.

LV function improves after aortic valve replacement with correction of the volume after load.

The benefits of preserving contractile function must be weighted against the immediate operative risks associated with prosthetic valves. Asymptomatic patients with normal LV function have an excellent long-term prognosis: 90% are asymptomatic at 3 years, 81% at 5 years and 75% at 7 years. The percentage of them requiring AVR was < 4% per year. Asymptomatic Patients with impaired LV ejection performance: 66% require surgery within 3 years (15).

Survival benefits for surgery in the asymptomatic AR patient can only be inferred from observational comparisons. Considering the lack of any randomized clinical trial data and the obvious risk for even asymptomatic patients, we admitted that the timing of surgery is a “moving target.”

### Assessing severity of aortic regurgitation and LV function

Clinical evaluation is the first step in diagnosis and assessment of severity, but echocardiography is the key diagnostic tool. It confirms the presence of AR, the anatomy of aortic cusps, the image of the aorta at four different levels: annulus, sinuses of valsalva, sinotubular, ascending aorta, evaluates LV function and wall thickness, and detects the presence of other associated valve disease, and provides prognostic information (1).

Doppler echocardiography is the preferred technique to assess severity. (See FIGURE 6 and TABLE 5)

Transthoracic echocardiography diagnoses and quantifies the severity of AR, using colour Doppler (extension or width of regurgitant jet) and CW Doppler (rate of decline of AR flow and holodiastolic flow reversal in the descending aorta. All this indices are influenced by loading condition and the compliance of the ascending aorta and the LV. Quantitative Doppler echocardiography, using the continuity equation or analisys of PISA is less sensitive to loading conditions, but this evaluation are less established than in mitral regurgitation. The best predictor for severity estimation, compared to angiographic study is the ratio between jet width and ejection tract width (LVOT) (1).

### Criteria for AR severity are:

1. Specific signs of severe regurgitation
   - Central jet width ≥ 55% of LVOT
   - Vene contracta > 6 mm

### TABLE 4.

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year(s)</th>
<th>N</th>
<th>Rate</th>
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<td>Bonow</td>
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<td>104</td>
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<td>Scagnamiglio</td>
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<td>1995</td>
<td>101</td>
<td>3.0%/yr</td>
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<tr>
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<td>2003</td>
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<td><strong>Total</strong></td>
<td></td>
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<td>565</td>
<td>4.3%/yr</td>
</tr>
</tbody>
</table>

TABLE 4. Asymptomatic aortic regurgitation with normal LV function. Rate of progression to symptoms and/or LV dysfunction.

Clinical images provided by the American College of Cardiology Foundation

*Patients receiving digoxin.
**LV function not reported in all patients.
LV=left ventricular
TIMING FOR SURGERY IN ASYMPTOMATIC AORTIC VALVULAR DISEASES – A MATTER OF CONTROVERSY

2. Supportive signs
   - Pressure half time < 200 ms
   - Holodiastolic aortic flow reversal in descending aorta
   - Moderate or greater LV enlargement in the absence of other aetiologies of dilation

3. Quantitative parameters
   - Regurgitant volume ≥ 60 ml/beat
   - Regurgitant fraction ≥ 50%
   - ERO (cm²) ≥ 0.30

TEE may be performed only to define the anatomy of the valve and ascending aorta, especially when a valve reconstruction is considered (1).

At present, clinical decision should not be based on changes in EF on exercise, nor on data from stress echocardiography because these indices, although potentially interesting, have not been adequately validated (guidelines position).

CT or MRI is recommended for the evaluation of the aorta in patients with an enlarged aorta, especially in cases of bicuspid valves or Marfan’s syndrome.

**Asymptomatic patient with severe aortic regurgitation – recommendation for aortic valve replacement**

Patients with severe AR, there is a small risk of sudden death occurring in 2–4% of patients over 7–8 years of follow up, typically in patients with severe left ventricular dilation. They have an excellent prognosis if their resting EF is greater than 45-50%. The annual mortality rate is less than 0.5%, but such patients are not homogenous group (16).

Echocardiography provides a useful non-invasive approach to risk stratification in adults with chronic AR. The simpler measure of the exercise left ventricular ejection fraction is strongly predictive of clinical outcome, with an exercise ejection fraction > 50% indicating a low rate of symptom onset compared to those with an exercise ejection fraction < 50% in whom symptoms occurred at a rate of 8.8% per year (2).

Asymptomatic AR with normal LV function has an excellent long-term survival rate, and < 4% of pts per year requires AVR. Asymptomatic AR with impaired LV function, have a considerably more aggressive clinical course and should be referred for elective AVR to avoid progression to irreversible contractile dysfunction.

80% of asymptomatic pts with an end-systolic dimension > 55 mm required surgery within 34 months compared with 20% of pts with an end-systolic dimension < 55 mm. No patient with an end-diastolic dimension = 40 mm required aortic valve replacement at 4 years (1).

The report best predictor of subnormal left ventricular performance in asymptomatic patients with severe AR are a decrease in EF on exercise, by more than 5% and a low EF on exercise, less then 50%, coupled with inappropriately high wall stress assessed by echocardiography (2).

Mortality was also higher than expected for asymptomatic patients with LV ejection fraction (LVEF) < 55% (5.8% yearly, p=0.03) or with end-systolic diameter normalized to body surface area 25 mm/m² (7.8% yearly, p=0.004). Restrictive mitral inflow pattern also predicts outcome in severe AR (17).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mild</th>
<th>Moderate</th>
<th>Mod-Severe</th>
<th>Severe</th>
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</thead>
<tbody>
<tr>
<td>JH @ origin (mm)</td>
<td>&lt;2</td>
<td>2-3.5</td>
<td>3.5-5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>JH / LVOT (%)</td>
<td>&lt;25</td>
<td>25-40</td>
<td>40-55</td>
<td>&gt;55</td>
</tr>
<tr>
<td>JA / LVDA (%)</td>
<td>&lt;5</td>
<td>5-10</td>
<td>10-20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>JL (cms)</td>
<td>&lt;2</td>
<td>2-4</td>
<td>4-6</td>
<td>&gt;6</td>
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<tr>
<td>Reg. Fract. (%)</td>
<td>&lt;20</td>
<td>20-40</td>
<td>40-60</td>
<td>&gt;60</td>
</tr>
<tr>
<td>EROA (mm²)</td>
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<td>10-20</td>
<td>20-30</td>
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<tr>
<td>PHT (msec)</td>
<td>&gt;500</td>
<td>500-350</td>
<td>350-200</td>
<td>&lt;200</td>
</tr>
<tr>
<td>VDS (m/sec)</td>
<td>&lt;2</td>
<td>2-2.75</td>
<td>2.75-3.5</td>
<td>&lt;3.5</td>
</tr>
</tbody>
</table>

**TABLE 5.** Parameters of AR severity, adapted from Atlas of Perioperative Echocardiography, www.manbit.com

**FIGURE 6.** Assessment of AR severity, adapted from Atlas of Perioperative Echocardiography, www.manbit.com
TTTTTIMING FOR S S S S SURGERY IN A A A A ASYMPTOMATIC AAAAAORTIC V V V V VALVULAR D D D D DISEASES – A MMMMMATTER OF C C C C CONTROVERSY

Taking in consider all this information, an algorithm for the timing of surgery in asymptomatic patients with AR was done. See TABLE 6 and TABLE 7 (18).

Chronic AR represents a condition of combined volume and pressure overload. The balance between afterload excess, preload reserve, and hypertrophy cannot be maintained indefinitely in many patients, and afterload mismatch, depressed contractility, or both ultimately result in a reduction in EF. The transition to LV systolic dysfunction presents a continuum and no single hemodynamic measurement represents the absolute boundary between normal LV systolic function and systolic dysfunction. This transition may be insidious, and it is possible for patients to remain asymptomatic until severe LV dysfunction has developed.

To justify the risk of surgery, the ideal timing for surgical intervention in patients with AR is therefore at the onset of contractile dysfunction, yet early enough to prevent the development of irreversible contractile dysfunction.

Echocardiography in conjunction with a thorough history and physical examination provides accurate, reproducible, and cost-effective methodology for the serial assessment of contractile dysfunction in patients with aortic regurgitation.

According to present AHA/ACC and ESC guidelines, accepted indications for surgery in asymptomatic AR are (1) (FIGURE 7):

1. Severe AR with
   - impaired LV function at rest, LVEF ≤ 50% - class I

2. Whatever the severity of AR for patients who have aortic root disease with maximal aortic diameter
   - ≥ 45 mm or patients with Marfan’s syndrome – class I
   - ≥ 50 mm for patients with bicuspid valves - class IIa
   - ≥ 55 mm for other patients - class IIa

3. A rapid increase in ventricular parameters on serial testing

Sub clinical LV contractile dysfunction may develop when the LV ejection fraction remains normal. It is a challenge to recognize patients with sub clinical myocardial dysfunction in order to operate early enough to prevent post-operative heart failure.

Several studies, which have been based on all the currently used indices (volumetric, performance, contractility) measure the overall myocardial function and not the local elastic properties of the myocardium and the regional myocardial contraction on radial, circumferential, and longitudinal axis.

There are data suggesting that the mechanism of LV dysfunction in patients with AR is a result of subendocardial dysfunction, where the fibers are aligned longitudinally. Myocardial Doppler tissue velocity measurements can be used to measure long-axis function, which may

<table>
<thead>
<tr>
<th>Points</th>
<th>Clinical</th>
<th>LV Function</th>
<th>LV Size</th>
<th>Exercise Capacity</th>
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<td>None</td>
<td>&gt; 60%</td>
<td>&lt; 45</td>
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</tbody>
</table>

TABLE 6. Parameters for the Timing of Surgery in Asymptomatic Pts with Aortic Regurgitation.
Adapted from Bhudia SK et al., JACC 2007; 49:1465-1471
Clinical: Age > 65, Cardiothoracic ratio >= 0.58, LVH on ECG. Cardiac index <= 2.5 l/m/m2, LV ED Pressure > 20 mmHg.
Exercise Capacity: 8 METS on graded exercise treadmill

<table>
<thead>
<tr>
<th>Total Points</th>
<th>Decision Regarding Surgical Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>Delay Surgery; Clinical and Echocardiograph follow-up at 12 mo</td>
</tr>
<tr>
<td>2</td>
<td>Borderline; Recommend Clinical and Echocardiographic follow-up at 6 mo</td>
</tr>
<tr>
<td>≥ 3</td>
<td>Proceed with Surgery</td>
</tr>
</tbody>
</table>

TABLE 7. Algorithm for the Timing of Surgery in Asymptomatic Pts with AR
Adapted from Bhudia SK et al., JACC 2007; 49:1465-1471
**FIGURE 7.** Surgical indication in AR. Adapted from ESC Guidelines of Management of Valvular Heart Disease

**FIGURE 8.** Aortic valve replacement for asymptomatic patients with subnormal LVEF. ∆ indicates change from rest to exercise; ESS, end-systolic stress; and CHF, congestive heart failure. Reproduced from Lippincott, Williams & Wilkins. Borer JS, Bonow RO. Contemporary approach to aortic and mitral regurgitation. *Circulation* 2003; 108:2432-2438

**Schema for Selecting Asymptomatic Patients With Aortic Regurgitation for AVR**

- **Group I**
  - AVR Definite
  - Subnormal LVEF rest and/or ∆ESS → CHF; death = 25%/year

- **Group II**
  - AVR should be strongly considered; definite if ≥2 criteria met
  - LVIDd ≥80mm, "rapid" LVEF rest, FSS, or "rapid" LVIDs, LVIDd → subnormal LVEF, CHF, death = 7-10%

- **Group III**
  - AVR should be considered; definite if ≥1 Group II criteria also met
  - LVIDs ≥55mm, ≥ 25mm/m², ∆LVEF >5%
  - ∆LVEF-ESS Index ≥17% → subnormal LVEF, CHF, death >10-20%/yr

*Note: surgery must also be considered if significant changes occur during follow-up.*
be more sensitive than radial contraction to minor disturbances of LV function (13).

LV diameters, mass, and systolic function are the parameters that are routinely measured and represent the baseline information with which future serial measurements can be compared.

However, dynamic exercise echocardiography cannot be performed in patients with musculoskeletal problems, and acquiring data within 1 minute of peak exercise is difficult in patients with a poor echocardiographic window or severe breathlessness (16).

In patients with asymptomatic AR, the estimation of LV long-axis contraction at rest can unmask a subnormal LV functional status. The longitudinal motion of the septum might be influenced by the systolic function of the right ventricle (RV) as a result of the sandwiched position of the septum.

The most powerful variable to which LV functional reserve is related is the lateral mitral wall-motion velocity. Indeed, a lateral mitral wall-motion velocity of 9 cm/s seems to be the cutoff point and values below this suggest subnormal LV functional reserve (sensitivity 90%, specificity 100%) (13,16).

A systolic excursion of less than 12 mm had a sensitivity of 80% and a specificity of 82% for predicting a poor exercise response (16).

However, peak systolic velocity had a higher sensitivity and specificity in predicting a poor exercise response than systolic excursion (16).

Measurement of both LV and RV longitudinal contraction might be a reliable marker of ventricular subendocardial dysfunction. Thus, evidence of deteriorating long-axis contraction might be helpful in identifying the transition phase to ventricular dysfunction and patients who require more frequent and more careful re-evaluation.

Recently, strain/strain rate (S/SR) imaging was proved to detect early dysfunction in regional LV systolic deformation. Radial as well as longitudinal peak systolic SRs were significantly decreased in patients with moderate to severe AR compared with healthy subjects. Changes in regional LV deformation correlated inversely both with end-diastolic volume and with end-systolic volume (19).

In moderate to severe AR compensatory LV remodelling can occur with no increase in plasma BNP. Increased BNP is associated with more severe regurgitation and changes consistent with early LV dysfunction on exercise echocardiography.

Patients with elevated BNP levels had several echocardiographic measures suggesting LV dysfunction immediately after exercise. AR with elevated BNP had higher LV end-systolic and diastolic volume index and a trend to lower post-exercise ejection fraction than AR patients with normal BNP levels. However, the predictive value of both BNP and Nt-BNP for post-exercise LV dysfunction on echocardiography is modest. Patients with elevated BNP levels had lower global longitudinal strain rate and change in strain rate after exercise (9).

However, there was no significant association between S' velocity at rest or post-exercise and the plasma level of BNP. Large prospective study is needed to determine whether including serial measurements of BNP or Nt-BNP during follow-up improves the ability to detect early LV dysfunction and thereby allows more optimal timing of aortic valve replacement (9).

In conclusion, in the absence of evidence from randomized clinical trials, the decision to operate in patients with asymptomatic aortic disease relies on an individual risk-benefit analysis, suggesting that improvement of prognosis compared with natural history outweighs the risk of intervention and prosthesis-related complications.
REFERENCES

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