VALVE DISEASE

Timing of aortic valve surgery

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The timing of aortic valve surgery is described for patients presenting with two conditions: aortic stenosis and chronic aortic regurgitation.

Aortic stenosis

Aortic stenosis may be caused by rheumatic disease, a congenital bicuspid valve or calcification of a trileaflet valve. In Europe and North America, the aetiology of aortic stenosis most often is increased leaflet stiffness, without commissural fusion, caused by lipo-calcific deposits on the aortic side of the valve leaflets. This active disease process affects both congenitally bicuspid and normal trileaflet aortic valves and represents the extreme of a spectrum of disease that includes both aortic sclerosis without outflow obstruction and severe valvar aortic stenosis. Aortic valve sclerosis and stenosis are the most common valve diseases in Europe and North America, with sclerosis present in about 25% of all people over age 65 years and stenosis present in 2–7% of this population.¹ Significant outflow obstruction tends to occur at a younger age in patients with a bicuspid valve, possibly related to increased mechanical stress on the valve leaflets.

At the tissue level, aortic valve stenosis is characterised by focal areas of displacement of the subendothelial elastic lamina on the aortic side of the leaflet; there is protein and lipoprotein deposition and an inflammatory cell infiltrate with macrophages, T lymphocytes, and production of proteins, such as osteopontin, that are associated with tissue calcification. Ongoing studies of this active disease process will further clarify mechanisms of disease.

Aortic sclerosis

The initial phase of the disease process leading to aortic stenosis is mild leaflet thickening without obstruction to ventricular outflow, defined as aortic sclerosis. 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 Clearly, valve surgery is not indicated in these subjects as there is no outflow obstruction. Although there have been no studies of medical treatment to decrease cardiovascular risk in these subjects,

the prudent physician will evaluate and treat conventional coronary risk factors.

Haemodynamic progression

Once mild aortic stenosis is present (defined as an aortic jet velocity > 2.5 m/s), a gradual increase in the severity of outflow obstruction is seen in most patients (fig 1). 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 cm^2 per year.³ However, there is wide individual variability in the rate of haemodynamic progression. Some patients have little change in the degree of outflow obstruction over several years, while others have a relatively rapid rate of disease progression. Factors that predict the rate of haemodynamic progression in an individual patient have not yet been identified.

Symptom onset

At some point, the degree of outflow obstruction prevents an adequate increase in cardiac output with exertion, and the patient becomes symptomatic. Interestingly, some patients develop clear symptoms with obstruction that traditionally has not been considered “critical”, while others remain asymptomatic with apparently severe obstruction. We now recognise that there is substantial overlap in haemodynamic severity between symptomatic and asymptomatic patients, even though clinical outcome is most dependent on the presence or absence of symptoms. Thus, a difficult clinical problem is the patient who has symptoms compatible with aortic stenosis but has outflow obstruction that traditionally would be considered only moderate. In this situation it can be difficult to separate symptoms caused by outflow obstruction from symptoms caused by other comorbidity. Exercise testing can be helpful in providing an objective measure of exercise tolerance and in documenting the haemodynamic response to exercise in these patients. However, it is incumbent on the physician to assume that symptoms are caused by aortic stenosis unless other explanations are evident or the degree of stenosis is so mild that

Figure 1. Continuous wave Doppler recording of aortic jet velocity in an elderly patient with severe aortic stenosis. Non-invasive Doppler evaluation of jet velocity, mean pressure gradient, and valve area are key to the evaluation and management of adults with aortic stenosis.

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Indications for surgery in valvar aortic stenosis

- 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 high 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

valve replacement would not improve haemodynamics.

There is widespread agreement that valve replacement is indicated for symptomatic severe aortic stenosis. Both historical series before the availability of valve surgery and more recent series of patients who refused intervention for severe symptomatic aortic stenosis show that outcome is extremely poor, with survival rates as low as 50% at two years and 20% at five years after symptom onset.

The three classical symptoms of aortic stenosis are angina, heart failure, and syncope. However, in patients followed prospectively, symptom onset is insidious and may not be recognised by the patient or physician unless a careful, directed history is performed. Specifically, the physician needs to ask what activities the patient is doing now compared to 1–3 years ago. If there has been any decrease in physical activity, the possibility of symptom onset should be considered. Patients often ascribe their decrease in activity to “the flu” or “getting old”, rather than recognising the subtle symptoms that led to their change in lifestyle.

The most common initial symptom in adults followed prospectively is a decrease in exercise tolerance or dyspnoea on exertion. Angina also is common but may not be recognised as such unless the physician has educated the patient about the significance of chest “discomfort” or “heaviness”. When severe aortic stenosis is present on echocardiography, surgical intervention should be performed promptly once even these minor symptoms occur. Symptoms of pulmonary oedema and syncope are late manifestations of the disease process, most often occurring in patients without appropriate access to medical care or who have ignored earlier symptoms. If the symptom status of the patient is unclear, exercise testing is helpful to determine exercise duration and the haemodynamic response to exercise. A fall or only minimal rise in blood pressure indicates symptomatic disease.

Valve replacement for symptomatic aortic stenosis

Aortic valve replacement remains the definitive treatment for symptomatic aortic stenosis. In recent surgical series, operative mortality averages 2–9 % with long term survival rate of 80% at three years (table 1). Aortic stenosis in adults is rarely amenable to repair although commissurotomy may be an option in carefully selected young adults with non-calcified valves. Alternative procedures, such as balloon aortic valvuloplasty and surgical or ultrasonic valve debridement have not been successful. The choice of valve substitute in an individual patient is based on the balance between the durability of a mechanical valve compared to a tissue valve versus the need for long term anticoagulation. Newer, stentless tissue valves offer improved haemodynamics and the promise of increased longevity without the need for anticoagulation, although long term outcome data are not yet available. Other options include an aortic homograft in young women desiring pregnancy and the pulmonic autograft procedure in carefully selected younger patients at some experienced centres.

Table 1 Aortic valve replacement for aortic stenosis in the elderly and in those with impaired left ventricular function (selected series)

Series			n	30 day operative mortality	Event free survival
Culliford 1991	Age ≥ 80 years	AVR	35	5.7%	93.3% at 1 year
		AVR+CABG	36	19.4%	80.4% at 3 years
Azariades 1991	Age ≥ 80 years	AVR±CABG	88	16%	5 years 64 (7)%
Olsson 1992	Age ≥ 80 years	AVR±CABG	44	14%	2 years 73%
	Age 65–75 years	AVR±CABG	83	4%	2 years 90%
Elayda 1993	Age ≥ 80 years	AVR	77	5.2%	1 year 90.8%
		AVR+CABG	75	24%	5 years 76%
Logeais 1994	Age ≥ 75 years	AVR±CABG	675	12.4%	
Connolly 1997	EF ≤ 35%	AVR±CABG	154	9%	EF improved in 76%

AVR, aortic valve replacement; CABG, coronary artery bypass graft; MI, myocardial infarction; EF, ejection fraction.

Sources: Culliford AT, *et al. Am J Cardiol* 1991;67:1256–60; Azariades M, *et al. Eur J Cardiothorac Surg* 1991;5:373–7; Olsson M, *et al. J Am Coll Cardiol* 1992;20:1512–16; Elayda MA, *et al. Circulation* 1993;88:II-1–6; Logeais Y, *et al. Circulation* 1994;90:2891–8; Connolly HM. *Circulation* 1997;95:2395–400.

Figure 2. Kaplan–Meier survival curves for patients with aortic stenosis and reduced left ventricular function with and without significant coronary artery disease (two vessel disease or greater or left main coronary disease) in comparison with expected survival. Number of patients alive at each point is shown on the x axis. CAD, coronary artery disease. Reproduced with permission from Connolly HM, et al. *Circulation* 1997;95:2395–400.

AORTIC STENOSIS IN THE ELDERLY

Aortic valve replacement is indicated for symptomatic severe aortic stenosis, regardless of age. In comparison with outcome on medical treatments, operative mortality rates are acceptable even in octogenarians (5–15%). Comorbid conditions are common in the elderly and some patients have strong preferences regarding surgical intervention—both are factors that need to be taken into account in decision making in this patient group. On the other hand, the rate of calcification of tissue valves decreases with age so that long term anticoagulation usually can be avoided by using a tissue valve with an expected longevity greater than the patient's expected survival.

Despite the compelling evidence that aortic valve replacement is both appropriate and feasible in the elderly, recent studies have highlighted its underuse. Elderly adults with severe symptomatic aortic stenosis often are not referred for surgical consideration because of misconceptions about the risks and benefits of valve replacement. Many primary care physicians are unaware that elderly patients with aortic stenosis and heart failure are the most likely to benefit from relief of outflow obstruction. It also is important to review tables of expected longevity for the patient's current age, as many patients (and physicians) are not aware of the expected further life span. For example, an 80 year old woman can expect to live an additional 10 years. Quality of life also is improved, even when operative mortality and morbidity are considered.

AORTIC STENOSIS WITH LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

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

Evaluation of the patient with aortic stenosis and left ventricular dysfunction

- 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

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 (fig 2).⁴ Since left ventricular afterload is increased when aortic stenosis is present, with relief of obstruction, ventricular function improved in 76% of patients, with an increase in mean (SD) ejection fraction from 27 (6)% to 39 (14)%.

Aortic stenosis with a low pressure gradient and left ventricular dysfunction is even more problematic. If the low pressure gradient is associated with severe stenosis resulting in left ventricular dysfunction and a low transaortic volume flow rate, the patient will improve after aortic valve replacement. 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. Dobutamine stress echocardiography, with measurement of pressure gradient and valve area at baseline and at an increased flow rate (typically with 10 µg/min/kg of dobutamine), 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. However, this approach has not yet been validated on the basis of clinical outcome. In addition, if stroke volume fails to increase, it remains unclear whether the primary problem is increased valve stiffness or myocardial dysfunction.

A pragmatic approach in this patient group is to look at the degree of valve calcification, either by transthoracic or transoesophageal echocardiography or by fluoroscopy. Severe valve calcification is consistent with severe stenosis. Focal areas of thickening or only mild calcification suggest that valve surgery is not indicated. Unfortunately, patients with low gradient aortic stenosis have a poor outcome with both medical and surgical treatment. Given this prognosis, my bias is to err on the side of surgical intervention, in the hope that ventricular function will improve at least to the extent that afterload is reduced.

MILD TO MODERATE AORTIC STENOSIS IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY

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. Surgical mortality rates for repeat surgery for aortic valve replacement are high (14–30%), further supporting the suggestion that “prophylactic” valve replacement be considered. However, we need to be cautious in applying this approach without consideration of the clinical factors in each patient. 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 (16)% 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 (18)%, suggesting that valve replacement is appropriate (fig 3). 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. In the future, it is possible that aggressive medical treatment to slow disease progression will provide an alternative to valve replacement in this patient group.

RATIONALE FOR SURGERY BEFORE SYMPTOM ONSET

There clearly are a few situations in which aortic valve replacement 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 or who live in areas remote from medical care, and adults with very severe stenosis, in whom symptom onset is inevitable in the short term and in whom an elective procedure is preferred.

However, some investigators have suggested that valve replacement be performed in patients with severe aortic stenosis before symptom onset in order to prevent irreversible left ventricular hypertrophy and left ventricular systolic and diastolic dysfunction, and to decrease the risk of sudden death. There are little convincing data to support this approach. 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. It is clear that diastolic dysfunction persists for years after aortic valve surgery, with histologic studies showing persistence of increased myocardial fibrosis.⁵ However, it is unclear how early the intervention would need

to be performed in order to prevent these changes, and there have been no trials demonstrating clinical benefit of early intervention. The risk of sudden death in the absence of antecedent symptoms is extremely low in adults with aortic stenosis and certainly is lower than the operative mortality of valve replacement surgery.

At this time, it is difficult to advocate routine early surgery in asymptomatic adults with severe aortic stenosis. This issue is further confused by our changing understanding of the definition of severe stenosis. Some patients develop symptoms at a pressure gradient and valve area that traditionally have been considered moderate, while other patients with apparent severe stenosis remain asymptomatic. Thus, it is problematic to define a specific numerical measure of stenosis severity that could be used to justify earlier surgical intervention. Of course, the other side of the risk-benefit equation in the timing of aortic valve replacement includes operative mortality and morbidity and the suboptimal haemodynamics and longevity of prosthetic valves. As surgical techniques improve and better valve substitutes are developed the argument for early surgery may become more persuasive.

Chronic aortic regurgitation

Chronic aortic regurgitation may be caused by abnormalities of the valve leaflets, most often a congenitally bicuspid valve, or by enlargement of the aortic root (fig 4). 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. For example, in a patient with Marfan syndrome, the extent and rate of aortic root dilation are the primary determinants of the timing of aortic root and valve replacement. Acute aortic regurgitation differs from chronic disease both in clinical presentation and management. Acute aortic regurgitation may be caused by leaflet destruction (for example, endocarditis) or by lack of commissural support (for example, aortic dissection).

Figure 3. Cox regression analysis showing event free survival in 123 initially asymptomatic adults with valvar aortic stenosis, defined by aortic jet velocity at entry ($p < 0.001$ by log rank test). Reproduced with permission from Otto CM, et al. *Circulation* 1997;95:2262–70.

Figure 4. Colour flow Doppler image showing severe aortic regurgitation with a broad regurgitant jet and dilated left ventricle in a patient with a bicuspid aortic valve. Doppler measures of regurgitant severity are most helpful in identifying patients in whom periodic evaluation of left ventricular size and systolic function is warranted.

Acute aortic regurgitation caused by aortic dissection is a surgical emergency. Severe aortic regurgitation caused by endocarditis also should be treated promptly with surgical intervention as outcome with medical treatment alone is poor.

SYMPTOM ONSET

Patients with chronic aortic regurgitation may remain asymptomatic for many years despite haemodynamically significant backflow across the valve. The increased volume load on the left ventricle leads to a gradual increase in left ventricular dimension so that a normal forward stroke volume is maintained. Most patients eventually develop symptoms as a result of aortic regurgitation, with an average rate of symptom onset of 5–6% per year in prospective studies.^{6,7} The most common initial symptom is dyspnoea on exertion or a decrease in exercise tolerance. In previously asymptomatic

Figure 5. Cumulative actuarial incidence of progression to aortic valve replacement in 143 initially asymptomatic patients with severe aortic regurgitation randomised to treatment with digoxin 0.25 mg daily or nifedipine 20 mg twice a day. Reproduced with permission from Scognamiglio et al.⁸

patients with severe aortic regurgitation, 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.

Echocardiography provides a useful non-invasive approach to risk stratification in adults with chronic aortic regurgitation since the rate of symptom onset is directly related to the extent of left ventricular dilation. In one study, patients with an initial end systolic dimension < 40 mm had an annual rate of symptom onset of 0%, compared to 6% in those with an end systolic dimension of 40–49 mm and 19% in those with an end systolic dimension > 50 mm.⁶ In another study, the strongest predictor of clinical outcome in chronic aortic regurgitation was the change in left ventricular ejection fraction from rest to exercise, normalised for the exercise change in end systolic wall stress.⁷ However, measurement of this parameter is difficult and cumbersome in the clinical setting, as it requires both echocardiographic and radionuclide data acquisition during exercise testing. The simpler measure of the exercise left ventricular ejection fraction is also strongly predictive of clinical outcome, with an exercise ejection fraction > 56% indicating a low rate of symptom onset (0% per year) compared to those with an exercise ejection fraction < 50% in whom symptoms occurred at a rate of 8.8% per year.

There have been no prospective studies showing that quantitative evaluation of the severity of regurgitation is predictive of clinical outcome. Of course, these studies only included patients with “severe” regurgitation as defined by clinical and echocardiographic criteria. As with aortic stenosis, the availability of non-invasive quantitative measures of valve disease is changing our understanding of the relation between regurgitant severity and clinical outcome. Many patients with “severe” aortic regurgitation remain asymptomatic with little change in ventricular size or function for many years. Thus, severe chronic aortic regurgitation should be defined as the degree of backflow across the aortic valve that results in progressive left ventricular dilation in association with adverse clinical outcomes. Doppler criteria alone should not be used to define severity until prospective studies are available that show the value of these quantitative measures in predicting clinical outcome.

On the other hand, Doppler measures of aortic regurgitant severity are extremely helpful when the degree of left ventricular dilation seems out of proportion to the severity of regurgitation. Quantitative measurements may then allow distinction between severe aortic regurgitation resulting in left ventricular dilation and mild to moderate aortic regurgitation with concurrent primary myocardial dysfunction caused, for example, by myocarditis or ischaemic disease. When clinical and Doppler data are discordant, evaluation of aortic regurgitation in the catheterisation laboratory also can be helpful.

Table 2 Timing of valve replacement in chronic aortic regurgitation

Study	n	Symptoms at entry	Mean (range) age (years)	Conclusions
Henry 1980	49	Yes	46 (19–68)	Pre-op ESD > 55 mm and FS < 25% were associated with poor outcome post AVR
Henry 1980	37	No	35 (17–64)	ESD and FS predicted which patients became symptomatic and required AVR
Bonow 1983	77	No	37 (16–67)	AVR is not needed until symptoms or LV dysfunction occurs
Bonow 1984	37	Yes	41 (20–46)	Duration of pre-op LV dysfunction is an important predictor of reversibility of LV function
Taniguchi 1987	62	Yes	43 (18–64)	Pre-op LV-ES volume index was most important predictor of subsequent cardiac death
Bonow 1988	61	Yes	43 (19–72)	Long term improvement in LV function is related to early reduction in EDD post-op
Siemieniczuk 1989	50	No	48 (16)*	Patients can be risk stratified for “early progression to AVR” based on measurement of LV size and function
Taniguchi 1990	35	Yes	43 (15–60)	The post-op increase in EF correlated with the decrease in ESS. Contractile dysfunction persisted
Bonow 1991	104	No	36 (17–67)	Multivariate predictors of outcome (death, ventricular dysfunction or symptoms) were age, initial ESD, and rate of change in ESD and rest EF
Pirwitz 1994	27	Yes	(18–72)	The peak systolic pressure to ESV ratio was the strongest predictor of postoperative (post-op) functional class
Klodos 1996	31	Yes	50 (15)*	Pre-op EF (not EDD) predicted late survival and post-op EF. Severe LV dilation is not a contraindication to surgery
Borer 1997	104	No	46 (15)*	Change in EF from rest to exercise (normalise to the change in wall stress) was the strongest predictor of outcome
Dujardin 1999	264	No	56 (19)*	Predictors of outcome were age, functional class, comorbidity, AF, and ESD

AF, atrial fibrillation; AVR, aortic valve replacement; EF, ejection fraction; EDD, end diastolic dimension; ESD, end systolic dimension; ESS, end systolic stress; ESV, end systolic volume; FS, functional shortening; LV, left ventricular; *SD.

Sources: Henry WL, *et al. Circulation* 1980;61:71–483; Henry WL, *et al. Circulation* 1980;61:484–92; Bonow RO. *Circulation* 1983;68:509–17; Taniguchi K, *et al. J Am Coll Cardiol* 1987;10:510–18; Bonow RO. *Circulation* 1988;78(II):108–20; Siemieniczuk D, *et al. Ann Intern Med* 1989;110:587–92; Taniguchi K, *et al. Circulation* 1990;82:798–807; Bonow RO. *Circulation* 1991;84:1625–35; Pirwitz MJ, *et al. J Am Coll Cardiol* 1994;24:1672–7; Klodos E, *et al. J Am Coll Cardiol* 1996;27:670–7; Borer JS, *et al. Circulation* 1997; 97: 525–34; Dujardin KS, *et al. Circulation* 1999; 99:1851–7.

Medical treatment

Medical treatment has been shown to be effective in slowing the rate of left ventricular dilation and delaying the timing of surgical intervention in adults with chronic aortic regurgitation. Aortic regurgitation represents both a volume and pressure overload state of the left ventricle as the increased stroke volume is ejected into the high resistance aorta. Thus, it makes physiologic sense that afterload reduction might decrease the severity of regurgitation and prevent progressive ventricular dilation. Several small studies have shown that angiotensin converting enzyme (ACE) inhibitors can slow the rate of left ventricular dilation. Further, in a randomised study of adults with severe aortic regurgitation and left ventricular dilation, treatment with nifedipine was associated with a six year event free survival rate of 85% compared to 65% in those treated with digoxin (fig 5).⁸ Afterload reduction treatment now is standard in patients with severe aortic regurgitation and evidence of left ventricular dilation.

Asymptomatic ventricular systolic dysfunction

In patients with chronic aortic regurgitation, valve replacement is indicated at symptom

onset. However, a small number of patients develop irreversible left ventricular systolic dysfunction in the absence of symptoms. The ideal measure of left ventricular systolic function would reflect contractility and be relatively independent of loading conditions, such as the end systolic pressure-volume relation or elastance. However, measurement of contractility is an elusive goal and measures that approximate this goal are impractical in the clinical setting. Thus, clinical decision making is based on parameters that have been shown to be predictive of postoperative outcome in series of patients undergoing valve replacement.

In studies of symptomatic patients who underwent valve replacement for severe aortic regurgitation, baseline predictors of postoperative left ventricular dysfunction include: (1) increased left ventricular size at end systole, defined either as end systolic dimension or end systolic volume index; (2) the duration of left ventricular dysfunction; (3) end systolic wall stress; and (4) ejection fraction. In a smaller number of studies that prospectively followed asymptomatic patients with chronic aortic regurgitation, the same factors (ventricular size and contractile function) were found to predict

the onset of symptoms or left ventricular dysfunction (table 2). Other predictors of outcome after valve replacement for aortic regurgitation include age, severity of symptoms, exercise tolerance, evidence of left ventricular hypertrophy on electrocardiography, an elevated left ventricular end diastolic pressure, and the ratio of wall thickness to chamber dimensions.⁹

Taken together, all these studies indicate that excessive ventricular dilation, particularly at end systole, is a marker of incipient systolic dysfunction. When ventricular end systolic dimension exceeds 55 mm or the end systolic volume index exceeds 60 ml/m², surgical intervention should be considered. Of course, it is important to verify the accuracy of these measurements and, in most cases, it is prudent to repeat the study after an appropriate time interval to confirm the degree and progression of ventricular dilation. Other clinical parameters that may be helpful in clinical decision making include overt evidence of systolic dysfunction (an ejection fraction < 50%), diastolic ventricular dilation (an end diastolic dimension > 80 mm), or an elevated end diastolic pressure (> 20 mm Hg).

Surgical outcomes and effect on left ventricular function

Operative mortality for elective aortic valve replacement in chronic aortic regurgitation is 4–10% with five year survival rates of 70–85% in recent series, and is similar in women and men. Most patients experience a decrease in cardiac symptoms and an improved functional capacity postoperatively. Predictors of operative mortality include severe symptoms, renal failure, and atrial fibrillation.

If surgery is performed before the onset of irreversible left ventricular dysfunction, relief of the chronic volume overload leads to decreased ventricular volumes and mass. Ventricular volumes and myocardial mass decrease postoperatively by 30–35%, but this decrease occurs over a prolonged time period. Ventricular volumes decrease to near normal within 1–2 years, while ventricular mass continues to decrease up to eight years postoperatively. Thus, after valve replacement for aortic regurgitation, left ventricular geometry is characterised by concentric hypertrophy caused by the differing rates of decrease in ventricular volumes and mass. The early postoperative decrease in muscle mass is caused by regression of myocardial cell hypertrophy and a decrease in myocardial fibrous content, with the later decrease in myocardial mass caused by a continued decrease in fibrous tissue content.

Even in patients with excessive left ventricular dilation or a reduced ejection fraction at the time of initial diagnosis of aortic regurgitation, there is an improvement in ventricular function after valve replacement in most patients. In one study of 31 patients with chronic aortic regurgitation and a preoperative end systolic dimension > 80 mm, operative mortality was low and there was an improvement in ejection fraction postoperatively (from 43 (12)% to 53 (11)%, $p < 0.0001$).¹⁰ Ejection fraction also continues

Timing of surgery for chronic aortic regurgitation

- **Definite indications:**
 - symptomatic severe aortic regurgitation
 - asymptomatic severe regurgitation with evidence of early left ventricular systolic dysfunction (ejection fraction < 50%, left ventricular end systolic dimension > 55 mm)
 - symptomatic severe aortic regurgitation with left ventricular systolic dysfunction
- **Not accepted:**
 - asymptomatic aortic regurgitation without significant left ventricular dilation or systolic dysfunction

to improve over a long time period postoperatively, reaching a stable value only after 4–6 years.

Conclusions

It is clear that aortic valve replacement improves survival and quality of life in symptomatic patients with severe aortic stenosis or regurgitation. Surgery is deferred only if there is severe comorbidity limiting longevity or increasing surgical risk to an unacceptable degree. Even when left ventricular systolic dysfunction is present preoperatively, patients with both aortic stenosis and regurgitation show an improvement in systolic function after valve replacement; thus it is never “too late” to consider surgical intervention. Aortic valve surgery in the asymptomatic patient with aortic stenosis remains controversial except in patients with severe stenosis undergoing other cardiac surgical procedures. In patients with chronic aortic regurgitation, periodic echocardiography is indicated to identify the small number of patients who develop evidence of left ventricular dysfunction before symptom onset. If surgery is performed soon after the onset of ventricular dysfunction, left ventricular size and ejection fraction are likely to return to normal postoperatively.

Our understanding of the disease process in chronic valve disease is changing. New insights into the pathophysiology of calcific aortic stenosis may lead to medical treatments to prevent disease progression. In patients with chronic aortic regurgitation, afterload reduction treatment delays, and may prevent, the need for valve surgery.

1. Stewart BF, Siscovick D, Lind BK, *et al*. Clinical factors associated with calcific aortic valve disease. *J Am Coll Cardiol* 1997;29:630–634.

• In the population based Cardiovascular Health Study, aortic valve stenosis or sclerosis on echocardiography was associated with older age, male sex, hypertension, current smoking, elevated serum low density lipoprotein (LDL) and lipoprotein Lp(a) concentrations, shorter height, and the presence of diabetes.

2. Otto CM, Lind BK, Kitzman DW, *et al* for the Cardiovascular Health Study. Association of aortic valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 1999;341:142–7.

- Aortic valve sclerosis, defined as irregular leaflet thickening without obstruction to outflow, was associated with an approximately 50% increase in risk for myocardial infarction and cardiovascular mortality in patients without known coronary disease at study entry.
- 3. **Otto CM, Burwash IG, Legget ME, et al.** A prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997;**95**:2262–70.
- In a prospective study of 123 adults with asymptomatic aortic stenosis the only predictors of symptom onset (and valve replacement) on multivariate analysis were the baseline aortic jet velocity, baseline functional status score, and the rate of increase in jet velocity over time.
- 4. **Connolly HM, Oh JK, Orszulak TA, et al.** Aortic valve replacement for aortic stenosis with severe left ventricular dysfunction. Prognostic indicators. *Circulation* 1997;**95**:2395–400.
- In 154 consecutive patients with aortic stenosis and a left ventricular ejection fraction $\leq 35\%$, operative mortality was 9% with predictors of operative mortality including coronary artery disease and reduced cardiac output at baseline. Left ventricular ejection fraction improved after valve surgery in 76% of survivors and only 7% were in New York Heart Association functional class postoperatively, compared to 88% at baseline.
- 5. **Lund O, Kristensen, Baandrup U, et al.** Myocardial structure as a determinant of pre- and postoperative ventricular function and long-term prognosis after valve replacement for aortic stenosis. *Eur Heart J* 1998;**19**:1099–108.
- Based on intraoperative transmural biopsies of the myocardium in 49 patients undergoing valve replacement for aortic stenosis, the authors propose that the degree of muscle hypertrophy is an important factor both for preoperative symptoms and for early and late mortality after valve replacement.
- 6. **Bonow RO, Lakatos E, Maron BJ, et al.** Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. *Circulation* 1991;**84**:1625–35.
- In 104 asymptomatic patients with chronic aortic regurgitation followed prospectively, 58 (9)% remained asymptomatic with normal left ventricular function at 11 years. Multivariate predictors of clinical outcome were age, initial end systolic dimension, and the rate of change in end systolic dimension and rest ejection fraction during serial studies.
- 7. **Borer JS, Hochreiter C, Herrold EM, et al.** Prediction of indications for valve replacement among asymptomatic or minimally symptomatic patients with chronic aortic regurgitation and normal left ventricular performance. *Circulation* 1997;**97**:525–34.
- The change in ejection fraction from rest to exercise, normalised for the change in end systolic wall stress, was the strongest predictor of clinical outcome in this prospective study of 104 adults with severe aortic stenosis followed for an average of 7.3 years.
- 8. **Scognamiglio R, Rahimtoola SH, Fasoli G, et al.** Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. *N Engl J Med* 1994;**331**:689–94.
- In order to evaluate the effect of afterload reduction treatment on clinical outcome, 143 patients with severe asymptomatic aortic regurgitation and normal systolic function were randomised to treatment with nifedipine or digoxin. After six years, 34 (± 6)% of the digoxin group and 15 (± 3)% of the nifedipine group have undergone aortic valve replacement.
- 9. **Donovan CL, Starling MR.** Role of echocardiography in the timing of surgical intervention for chronic mitral and aortic regurgitation. In: Otto CM, ed. *The practice of clinical echocardiography*. Philadelphia: WB Saunders, 1997:327–54.
- Comprehensive review (159 references) of the literature on timing of intervention for aortic regurgitation, with proposal of an algorithm for clinical decision making.
- 10. **Klodos E, Enriquez Sarano M, Tajik AJ, et al.** Aortic regurgitation complicated by extreme left ventricular dilation: long-term outcome after surgical correction. *J Am Coll Cardiol* 1996;**27**:670–7.
- In 31 patients with severe aortic regurgitation and extreme left ventricular dilation (end diastolic dimension ≥ 80 mm), operative mortality was only 5.6% with a 10 year survival of 73 (5)%, which is no different than expected for age. Ejection fraction increased from 44 (11)% to 49 (15)%.

website extra

Additional references appear on the Heart website

www.heartjnl.com