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Working Group Report

Recommendations on the management of the asymptomatic patient with valvular heart disease

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Introduction

The management of asymptomatic patients with valve disease has become an important medical problem. There are two main reasons for this: firstly such patients are currently being diagnosed more frequently because of the widespread availability of echocardiography; secondly, the opportunity to perform less invasive interventions is an incentive to intervene earlier. However, data concerning the management of asymptomatic patients are limited. For this reason this topic remains a particularly rich source of debate.

There are no specific guidelines on the management of asymptomatic patients with valvular heart disease and recommendations can be drawn only from general guidelines such as those produced by the ACC/AHA[1] and some national societies in Europe[2–4]. Moreover, published guidelines are not always consistent due to the lack of randomized trials and also the constant evolution of practice. It is for this reason that the Working Group on Valvular Heart Disease of the European Society of Cardiology have produced these recommendations. The major types of acquired valve disease will be dealt with in the following order: aortic stenosis (AS), aortic regurgitation (AR), mitral stenosis (MS), mitral regurgitation (MR).

Key Words: Valvular heart disease, aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation.

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General comments

Evaluation of the patient

Definition of the asymptomatic patient

In patients with valve disease the asymptomatic state is often a difficult one to establish in practice. This may be due to a gradual decrease in activity or a sedentary lifestyle. Symptoms, which are in reality due to valve disease, may be considered atypical and attributed to other non-valvular causes, especially in the elderly.

Clinical examination

Careful clinical examination should search for signs which suggest a severe valve disease, such as a systolic thrill or an abolition of the aortic second heart sound in AS, a loud murmur or a third sound in MR, and peripheral signs of increased pulse pressure in AR. Finally good clinical judgement strongly suggests the presence of severe valve disease in patients who have a history of prior embolism or pulmonary oedema even if they claim that they are currently asymptomatic. The same applies in the presence of objective signs such as cardiomegaly, atrial fibrillation or pulmonary hypertension. Such findings should be an incentive for complete and early evaluation. These remarks concern both initial examination and follow-up.

Echocardiography

Echocardiography is the key examination. It is of crucial importance to confirm the diagnosis, assess the severity using a quantitative assessment[5–7], and evaluate left ventricular function. However, before indicating surgery on the basis of echocardiography it should be ensured

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that the recordings are of good quality and repeated before the final decision. Finally, echocardiography will identify aetiology and mechanisms and may allow selection of the most appropriate intervention. This is particularly important for valve repair in MR, percutaneous mitral commissurotomy (PMC) in MS, and valve sparing operation in AR[8–12].

Radionuclide angiography
Radionuclide angiography is useful in the initial and serial assessment of left ventricular function, in particular in AR and MR in the rare cases when echocardiography provides suboptimal or equivocal data.

Exercise testing
Before considering whether a patient is truly asymptomatic it is often useful to perform an exercise test for the objective assessment of functional capacity, i.e. the ability to reach 80% of the predicted heart rate without symptoms. Exercise testing is also indicated in asymptomatic patients to ascertain the recommended level of physical activity.

Exercise testing is contraindicated in patients with symptomatic AS, but was shown to be useful in asymptomatic patients[1,13]. Abnormal haemodynamics, particularly hypotension or inadequate rise in blood pressure, arrhythmias, marked ST-segment depression, or an inadequate exercise tolerance can be elicited in up to one third of patients[14–19]. Furthermore, in a total of about 600 asymptomatic patients with AS no complications have been reported[14–19].

In MS stress echocardiography can be used to assess the evolution of mitral gradient and pulmonary artery pressures[20,21]. The usefulness of stress echo in the evaluation of asymptomatic patients with AR or MR is less well established.

Magnetic resonance imaging
This is a useful and non-invasive examination enabling the morphology of the aorta, left ventricular geometry, and the degree of regurgitation to be accurately measured. However, its use in routine practice is limited by its availability and cost[22].

Holter ECG
This is useful to detect asymptomatic arrhythmias[23].

Cardiac catheterization
Currently, the indications for catheterization are limited to the rare cases where there are discrepancies between clinical and echocardiographic findings in defining the severity of stenosis or regurgitation. Coronary angiography is required prior to surgery in patients over 40 and/or in those with coronary risk factors[1–4].

Indications for intervention

In patients with valvular heart disease intervention comprises valve replacement but also less invasive interventions such as surgical repair in MR, and PMC in MS which are of special interest in patients who are asymptomatic.

In contrast to patients with symptoms in whom there is general agreement that surgery is the only effective treatment to improve symptoms and survival, there is still ongoing discussion about the indication for intervention in the asymptomatic patient. The decision to operate on a truly asymptomatic patient is always difficult. Early surgery exposes the patient to perioperative morbidity and mortality and the long-term complications of a prosthetic valve if valve replacement is performed. However, waiting for the patient to experience symptoms would expose them to the advent of rare but dramatic complications, such as sudden death or embolism with sequelae in the case of AS or MS, or may allow time for the development of irreversible depression of left ventricular function in valve regurgitation, which in turn, leads to a high incidence of postoperative left ventricular dysfunction and heart failure.

In asymptomatic patients the indications for surgery should be individualized and take into account the following factors:

- the operative risk resulting from the cardiac and extra cardiac condition. For example, surgery is rarely considered in elderly patients, (over 75) without symptoms, and is contraindicated in the presence of important comorbidities influencing life expectancy
- the patient's wishes. The decision should be preceded by extensive discussion with the patient and relatives about the balance of risks and benefits;
- the patient's satisfactory communication of symptoms, and the potential for regular follow-up.

Medical treatment

Infective endocarditis prophylaxis is indicated in all patients with significant valve disease with a special emphasis in cases with regurgitant lesions[24].

Rheumatic fever prophylaxis is indicated in young patients with evidence of rheumatic aetiology, particularly in countries with a high prevalence of rheumatic disease. There is no consensus regarding the exact duration of prophylaxis.

Specific valve disease

Aortic stenosis

Calcific AS has become the most common cardiac disease in developed countries after hypertension and coronary artery disease. In most European countries moderate AS is present in 5% of the population over the age of 75 and severe AS in 3%, half of them being asymptomatic[25–28]. The decision to intervene in asymptomatic patients with AS remains a source of hot debate. However, recent prospective series using echocardiography provide important information for decision making.

Table 1 Natural history of asymptomatic patients with moderate–severe aortic stenosis*

Author	n	Severity of AS	Sudden death (n=)/ No. years follow-up	Event-free survival (%)/ No. years follow-up
Chizner *et al.*[35]	8	AVA <1·1 cm^2	0/5·7*	—
Turina *et al.*[33]	17	AVA <0·9 cm^2	0/2·0*	75/5
Horstkotte *et al.*[34]	35	AVA 0·8–1·5 cm^2	3/—	80/10
Kelly *et al.*[36]	51	PV 3·5–5·8 m . s^{-1}	0/1·5	90/2
Pellikka *et al.*[37]	143	PV >4·0 m . s^{-1}	0/1·8	62/2
Kennedy *et al.*[38]	66	AVA 0·9 ± 0·1 cm^2	0/2·0	59/4
Faggiano *et al.*[39]	37	AVA 0·85 ± 0·15 cm^2	0/1·7	—
Otto *et al.*[18]	123	− PV 3–4 m . s^{-1}	0/2	66/2
		− PV >4 m . s^{-1}	0/2	21/2
Rosenhek *et al.*[40]	128	PV >4 m . s^{-1}		
		− No/Mild calc	0/4	75/4
		− Mod /Severe calc.	1/4	20/4

AS=aortic stenosis; AVA=aortic valve area; PV=peak aortic velocity; event-free survival=freedom from surgery or cardiac death; Calc=calcification; Mod=moderate; *operated only with symptoms.

Table 2 Positivity criteria of exercise in ECG in patients with aortic stenosis

Exercise test is considered to be abnormal when:
1. Patient develops symptoms of dyspnea, angina pectoris, syncope or near syncope[18,19].
2. Rise in systolic blood pressure during exercise is less that 20 mmHg[1,18,19] or a fall in blood pressure during exercise occurs[18].
3. Patient does not reach 80% of the normal level of exercise tolerance according to age and gender adjusted levels[13,18].
4. More than 2 mm horizontal or down-sloping ST-segment depression occur during exercise in comparison to baseline levels[13,18,19], which are not attributable to other causes than severe AS.
5. Complex ventricular arrhythmias occur (ventricular tachycardia, more than four PVC in a row)[18,19]

The implications of an abnormal exercise test for the indication for surgery are strongest for the occurrence of symptoms and abnormal blood pressure reactions.
PVC=premature ventricular contraction.

Natural history

Progression of the degree of AS varies markedly. The average increase in mean gradient is 7 mmHg per year. The mean decrease in valve area ranges from 0·02 cm^2 per year in 'slow progressors' to 0·3 cm^2 per year in 'fast progressors'. Progression is usually faster in degenerative AS than in bicuspid valves or rheumatic disease. The main predictors of rapid progression are the presence of coronary artery disease, old age, hypertension, smoking, and hyperlipidaemia[29,30].

Natural history studies in symptomatic patients have shown that prognosis is markedly impaired after the occurrence of symptoms and sudden death is the major concern[31–41]. Three retrospective and six prospective studies of the natural history of asymptomatic patients have shown that the incidence of sudden death is low: only four out of 503 patients followed for an average of 2·4 years suffered sudden death without prior symptoms (0·3% per year) (Table 1). However, it should be stressed that symptoms occurring before death may not have been reported by the patients, which emphasises the importance of education and close follow up.

There is marked variability in the duration of event-free survival. The occurrence of symptoms ranges between 5% and 23% per year. In addition to the variability of the anatomic progression this is also due to the heterogeneity of severity of AS in the different studies and the fact that in several studies approximately one-fourth of patients were operated on during follow-up while still asymptomatic, surgery being counted as an event. The main predictors of outcome derived from echocardiography are: peak aortic jet velocity at baseline reflecting the initial degree of AS severity, and rate of change in peak jet velocity. For example, in the study by Otto *et al.*[18], the 2-year event-free survival in patients with a peak jet velocity of <3 m . s^{-1} was 84%, whilst in those with >4 m . s^{-1} survival without surgery was only 21%. Left ventricular ejection fraction of <50% is also a predictor of poor outcome.

Functional status score[18] as well as exercise parameters are also predictive of clinical outcome. The criteria for an abnormal exercise test in asymptomatic patients with AS are outlined in Table 2. These criteria

are derived from studies in patients with asymptomatic AS[18,19] as well as studies in patients with coronary artery disease and other forms of heart disease. An increase in blood pressure of less than 20 mmHg or a fall in blood pressure during exercise is associated with a poor prognosis regardless of the aetiology of the heart disease[13,18,19]. As an illustration, in the study by Amato *et al*, after 24 months the probability of a patient with a positive stress test surviving event free was only 19% compared with 85% in those with a negative test[19].

More recently, it has been shown that the combination of moderate to severe calcification and a rapid increase in peak aortic jet velocity of $\geq 0{\cdot}3$ m . s^{-1} within 1 year, provides important prognostic information. The presence of these two parameters identified 79% of patients who either underwent surgery or became symptomatic within 2 years[40].

Results of early intervention

Operative mortality of aortic valve replacement for AS has dramatically decreased in recent years[42–44]. As an illustration, operative mortality is less than 2% in patients in NYHA Class I or II in a recent surgical data base[43]. However, the operative risk is higher in the elderly and in the presence of comorbidities such as coronary artery disease. In addition, the long term results of early intervention are excellent. This holds to be true for the functional capacity and for survival which is comparable to the control population[44].

Indication for intervention

Surgery should only be considered in asymptomatic patients with severe AS. According to the ACC/AHA guidelines[1] reduction in valve area to $<1{\cdot}0$ cm^2 has been considered as severe AS. However, it is advised to adjust the valve area to the body surface area (BSA), the threshold for severity being $<0{\cdot}6$ cm . m^{-2} BSA[45].

Even if the benefit is not definitely proven, surgery is recommended in the following circumstances:

1. patients with an abnormal response to exercise: development of symptoms, blood pressure fall, inadequate blood pressure rise, markedly impaired exercise tolerance (Table 2).
2. patients with moderate to severe calcification, a peak jet velocity >4 m . s^{-1}, and with an accelerated rate of progression of peak velocity ($\geq 0{\cdot}3$ m . s^{-1} per year) because of their fast progression towards symptoms;
3. patients with left ventricular dysfunction (left ventricular ejection fraction <50%). This situation is however rare in asymptomatic AS.

Even if there is a lower level of evidence, surgery can probably also be considered in the following situations:

- Severe left ventricular hypertrophy (>15 mm wall thickness) unless this is due to hypertension;
- Severe ventricular arrhythmias for which no other cause than severe AS can be identified.

The decision for prophylactic valve surgery before major non-cardiac surgical procedures should be taken on an individual basis[46]. Conception should be discouraged in female patients with severe AS. If pregnancy occurs, however, systematic surgery or percutaneous intervention should not be performed if the patients remains asymptomatic. However, great care in needed during delivery and it may be safer to carry out an elective caesarean section. Finally, percutaneous aortic valvuloplasty is not indicated in asymptomatic patients because it is of limited efficacy, does not change the natural course of the disease, and finally carries high procedural risk.

Medical management

All patients should be carefully educated about the implications of symptoms, so that they report to their doctor, should the situation change, and they also need to adapt their physical activity. The level of exercise allowed can be derived from the findings of the stress test.

It is of particular importance to control the risk factors for atherosclerosis even though further studies are needed to assess the preventive value of aggressive lipid lowering therapy on the clinical outcome[47,48].

Serial testing

Type and interval of follow-up should be determined on the basis of the initial examination.

- In cases of moderate to severe calcification of the valve and peak aortic jet velocity >4 m . s^{-1} at initial evaluation, patients should be re-evaluated every 6 months for the occurrence of symptoms, change in exercise tolerance or in echo-parameters. If peak aortic jet velocity has increased since the last visit, or if other evidence of progression is present, surgery should be considered. If no change has occurred and the patient remains asymptomatic 6 monthly clinical and 6–12 monthly clinical and echocardiographic re-evaluation are recommended.
- In the patients who do not meet these criteria, a yearly follow-up visit is sufficient, follow-up being closer in those with borderline values.

Aortic regurgitation

Indications for operating on patients with asymptomatic AR were clarified in the 1980s. The thresholds based on left ventricular function are now widely used to indicate

Table 3 Studies of the natural history of asymptomatic patients with aortic regurgitation

Study	No. of patients	Mean follow-up (years)	Progression to symptoms, death, or LV dysfunction per 100 patients/year (%)	Progression to asymptomatic LV dysfunction per 100 patients/year (%)
Siemienczuk *et al.*[53]	50	3·7	4·0	0·5
Bonow *et al.*[51]	104	8·0	3·8	0·5
Scognamiglio *et al.*[52]	74	6·0	5·7	3·4
Tornos *et al.*[55]	101	4·6	3·0	1·3
Ishii *et al.*[56]	27	14·2	3·6	—
Borer *et al.*[57]*	104	7·3	6·2	0·9

LV=left ventricular; *20% of patients in Class II.

surgery even though there is currently a trend towards earlier intervention. With the decline of rheumatic fever in western countries the degenerative origin, which is frequently associated with aneurysm of the ascending aorta, is now the most frequent aetiology of AR. This has implications on the decision to operate.

Natural history

Past studies on the natural history of AR showed that patients remain without symptoms for many years and that once symptoms develop the prognosis is poor[49,50]. In those studies however, the status of left ventricular function was not described. More recent series[51–58] have prospectively studied the natural history of aortic regurgitation with normal left ventricular systolic function, determined by invasive or non invasive techniques (Table 3).

Asymptomatic AR with normal left ventricular function is a disease with a slow progression and the number of events during follow-up is low. The development of asymptomatic left ventricular dysfunction is unusual (<1·3% per year), sudden death is rare (<0·2% per year) and progression to symptoms, left ventricular impairment or death occurs at a rate of 4·3% per year[1]. It has also been shown that progression to symptoms or left ventricular dysfunction is preceded by a period of left ventricular enlargement[55].

Age, left ventricular end-systolic diameter or volume, end-diastolic diameter or volume, and ejection fraction at rest are predictors of outcome[51–59]. In multivariate analysis, age and end-systolic diameter at initial study predicted outcome. A left ventricular end-systolic diameter >50 mm was a predictor of poor outcome with an incidence of 19% per year of death, or symptoms, or left ventricular dysfunction[54]. Contemporary data suggest that it is more appropriate to use thresholds related to BSA for the measurements of left ventricular dimensions. The proposed value is an end-systolic diameter $>25\ mm\ .\ m^{-2}$ BSA. This will generally lead to an earlier intervention than with non-indexed thresholds but the use of such values is supported by the good long-term results, in particular in young patients at low risk for surgery[60].

Degenerative AR is frequently associated with an aneurysm of ascending aorta. The progression of the dilatation of ascending aorta has been well documented in patients with Marfan syndrome, in whom aortic complications are the main cause of mortality[61–63]. In these patients the strongest predictor of the occurrence of aortic complications is the diameter of the aortic root as measured at the level of Valsalva sinuses[62]. The presence of a family history of cardiovascular event is also an important risk factor[64], On the other hand, degenerative AR associated with an aneurysm of the ascending aorta in patients without Marfan is known as annulo-aortic ectasia[65]. The risk of annulo-aortic ectasia is less well known than in Marfan disease, but complications related to aortic aneurysm have also been reported in such patients. Finally, dilatation of the ascending aorta out of proportion to co-existent valvular lesion is observed in patients with bicuspid valves[66].

Results of early intervention

Operative mortality of aortic valve replacement for AR is low (1–3%) when it is performed at an early stage of the disease, in particular in patients in NYHA Class I or II who have only a moderate impairment of left ventricular function[60,67–69]. Long-term survival is good and comparable to the general population and functional results are excellent. It has been shown that late results after surgery for AR were less satisfactory in women than men[70]. This is probably because intervention is undertaken later in women than men because figures for ventricular size, validated mainly in men, are applied to women who have a lower BSA. Thus by the time these absolute values are reached the real degree of dilatation normalized for BSA is much higher in women than men.

In cases of aneurysm of ascending aorta with and without Marfan syndrome, aortic valve replacement and replacement of the ascending aorta with re-implantation of coronary arteries carries a low operative risk when performed on an elective basis and late survival is good[63,71,72]. More recently, valve-sparing operations have been proposed in patients who have aneurysm of the ascending aorta with mild or moderate AR and

Table 4 Predicted size of aortic root according to age and body surface area. From Roman et al.[62]

Age (years)	Diameter of aortic root (cm)
<18	1·02+(0·98 × BSA)
18–40	0·97+(1·12 × BSA)
>40	1·92+(0·74 × BSA)

BSA=body surface area (m^2).

no structural abnormalities of the valve. Operative mortality is low and mid-term results are promising[73] .

Indications for surgery

Surgery is recommended in asymptomatic patients with severe AR in the following circumstances:

1. evidence of progressive left ventricular dysfunction. Surgery is recommended in patients who have an end-diastolic diameter >70 mm, or an end-systolic diameter >50 mm or even better >25 mm . m^{-2} BSA, or a resting left ventricular ejection fraction ≤50%. A rapid increase in left ventricular diameters on serial testing is a further incentive to consider surgery;
2. in patients with aortic root dilatation >55 mm, surgery should be undertaken irrespective of the degree of AR or left ventricular function. In patients with bicuspid aortic valves or with Marfan syndrome an even lower degree of root dilatation (50 mm) can be used as a threshold for surgery, in particular if a valve-sparing operation is possible or if there is a rapid increase of aortic diameter. In non-Marfan patients undergoing operation because of severe AR with left ventricular dilatation, the threshold of dilatation of the ascending aorta is less well established (50 or 55 mm) and in addition to the size of the aorta, the decision should also take into account the shape and thickness of the ascending aorta as well as the status of the rest of the aorta. As the normal size of the aortic root varies according to age and BSA, it seems even more appropriate to compare the observed diameter of the aortic root to the predicted value. Surgery should be considered when the ratio observed/predicted diameter of the aortic root is >1·3, because this is associated with an increased risk of aortic complications[63] (Table 4).

The tolerance of AR in itself is usually good during pregnancy and does not require intervention. The problem is totally different in women with Marfan syndrome who have an aneurysm of the ascending aorta. There is a risk of aortic complications when the diameter of the aortic root exceeds 40 mm, and pregnancy should be discouraged in such cases. When the aortic diameter is ≤40 mm, close clinical and echocardiographic follow-up is mandatory and beta-blockers should be used throughout pregnancy[74].

Medical treatment

Vasodilator therapy should not be used in asymptomatic patients with mild to moderate AR unless the patients are hypertensive. These patients have an excellent prognosis and a beneficial effect of vasodilator therapy has not been demonstrated.

Vasodilators can be used in asymptomatic patients with severe AR and moderate or severe left ventricular enlargement. In this group of patients vasodilators seem to prolong the compensated phase thereby delaying surgery, although the weight of the evidence is quite low and based on very few studies[75–78].

Beta-blockers should be systematically prescribed to patients who have a Marfan syndrome with an ascending aortic aneurysm because they reduce the progression of the aneurysmal dilatation[61]. Conversely, patients who have a severe AR the use of beta-blockers should be very cautious because of the lengthening of diastole increases the regurgitant volume.

Serial testing

- Patients with mild to moderate AR can be seen on a yearly basis with echocardiography performed every 2 years.
- Patients with severe regurgitation and moderate ventricular enlargement (left ventricular end-diastolic diameter 60–65 mm) should be seen every 6 months and echocardiography performed every year. When dimensions approach the thresholds for surgery end-diastolic diameter >70 mm and end-systolic diameter >50 mm, or preferably end systolic diameter >25 mm . m^{-2} BSA, it is recommended that echocardiographic examinations are more frequent.
- In patients with aortic root dilatation <50 mm, serial echocardiograms are also needed to evaluate progression of the aortic root size on a yearly basis.

Mitral stenosis

It has generally been accepted that the spontaneous prognosis of patients with asymptomatic MS is good and when the only intervention available was surgery indications were generally considered only after the onset of symptoms. However, it is now possible to have a different outlook in the light of our knowledge of asymptomatic MS, in particular regarding the embolic

risk, and also because of the development of PMC enabling effective treatment to be performed at low risk.

Natural history

The progression of MS has been evaluated in only a few studies comprising serial haemodynamic or echocardiographic measurements[79,80]. The stenosis progressed in 32% of the patients at a mean rate of $0{\cdot}3 \pm 0{\cdot}2\ cm^2$ per year, while there was no significant change in the remaining patients. The higher rates were observed in those who already had significant stenosis at the initial examination.

Studies on natural history are old and they are based only on clinical data from young patients, with no information on valve area[81,82]. Furthermore there are no comparisons available with control populations. In the series from Rowe *et al.*[81], survival of asymptomatic patients was 84% at 10 years, but only 38% at 20 years. Among patients who had few symptoms survival was 42% at 10 years and 8% at 20 years.

It should be noted that the patient may deteriorate very gradually but there may be a sudden change of the clinical picture as a result of a complication in half of the patients. Atrial fibrillation may occur in asymptomatic patients[23,83,84] and it is often preceded by supraventricular arrhythmias. In a study of 65 patients with MS in sinus rhythm, 56% had transient atrial arrhythmias on Holter recordings, 95% of the episodes being asymptomatic, but embolic events occurred in 14%[23]. The risk of atrial fibrillation increases with age and left atrial enlargement[84]. Thromboembolic events are the most dramatic complications, their incidence being estimated between 1·5 and 6 per 100 patients-year[81–83,85]. They are most often cerebral in location and they leave permanent neurological deficits in 30 to 40% of cases. More importantly, thromboembolism may be the initial event in 20% of the patients. The risk of thromboembolic events is increased by age, the presence of atrial fibrillation, a larger left atrium, and a smaller valve area, but the strongest predictor is the presence of left atrial spontaneous echo contrast, as assessed by TEE[11,86]. Thrombophilic conditions in the left atrium may also contribute to the thromboembolic risk[87].

Even in the absence of randomized trials there is no debate on the efficacy of anticoagulant therapy in patients with atrial fibrillation. However, anticoagulation does not offer complete protection from thromboembolism to patients in atrial fibrillation, who have a residual rate of 1 per 100 patients-year of embolic events which is higher than in non valvular atrial fibrillation. Conversely, in patients in sinus rhythm, the embolic risk is low <1 per 100 patients-year without anticoagulation[83] .

Results of early intervention

The intervention considered in asymptomatic patients is generally PMC. This procedure has been shown to be effective at a low risk[88–93] and there is a worldwide trend towards performing PMC at an early stage of the disease.

Most series reporting late follow-up after PMC have identified the functional class before the procedure as one of the strongest predictors of the occurrence of clinical events[91,93]. An early treatment also decreases the occurrence of other predictors of adverse outcome such as small valve area or atrial fibrillation.

There are very limited data on PMC in patients with few or no symptoms. Therefore, an illustration of the results which can be obtained with this technique, is shown in a series of 432 consecutive patients[94] who underwent PMC while in NYHA Class I or II, 9% with a history of embolism and 25% in atrial fibrillation. The safety of the procedure is of particular importance when facing patients who have few or no symptoms. In this series no patient experienced death, tamponade or embolism, but severe MR occurred in 2% of cases. After the procedure, 94% of the patients had a valve area $\geq 1{\cdot}5\ cm^2$ with no MR >2/4. After 9 years, 95% of the patients were alive and 77% were asymptomatic. This should be put in perspective with the natural history, as in the series from Rowe *et al.*[81], in which only 21% of the patients with few symptoms had a stable condition after 10 years.

Additionally, some data suggest a specific value of PMC in reducing the risk of embolic events. In a prospective series of 402 patients with mitral stenosis in atrial fibrillation, the multivariate analysis showed that the performance of PMC was associated with a decrease in the risk of embolic events[85]. These findings are consistent with the favourable effect of PMC on factors which influence the thromboembolic risk: decrease in the incidence and the intensity of spontaneous echo contrast; decrease in the size of the left atrium; improvement of left atrial function; and a decrease in the activation of coagulation in the left atrium[95–97]. The favourable effect of PMC on atrial fibrillation has not been definitively proven.

Indications for intervention

When intervention is considered PMC is the treatment of choice in patients with few or no symptoms.

It should be performed only in patients with severe MS, the threshold usually accepted being $1{\cdot}5\ cm^2$ or better $1\ cm^2\ .\ m^{-2}$ BSA.

The following can be regarded as contraindications for the procedure: presence of left atrial thrombosis, mitral regurgitation $\geq$2/4, and severe valve calcification.

PMC can be considered in carefully selected asymptomatic patients who have severe MS and:

1. increased risk of thromboembolic events: prior embolism, dense spontaneous echo contrast in the left atrium, or to a lesser extent recent or paroxysmal atrial fibrillation. In such cases PMC should be preceded by at least 4 weeks of effective

anticoagulant therapy and the performance of TEE immediately before the procedure to exclude a thrombus in the left atrium;
2. risk of haemodynamic decompensation: pulmonary hypertension (systolic pulmonary pressure >50 mmHg at rest or >60 mmHg on exercise, as defined in the AHA/ACC guidelines[1], wish for pregnancy, or need for major cardiac surgery.

In patients with few or no symptoms the importance of an experienced operator in avoiding complications must be stressed. Therefore the procedure performed in asymptomatic patients should only be carried out by experienced teams. The probability of good results must be high as assessed by clinical and anatomic parameters, i.e. mainly young patients with suitable anatomy.

Surgery, especially valve replacement, is seldom considered in asymptomatic patients with MS because of the inherent risks. Surgery can be considered in patients in NYHA Class II with a tight mitral stenosis if there is a contraindication to PMC and a very high embolic risk, such as recurrent episodes of embolism, or a severe haemodynamic impairment.

Medical treatment

Anticoagulant therapy, with a target INR between 2·5 and 3·5[98], is indicated in patients with MS with atrial fibrillation while in the patients with sinus rhythm, the decision should be made on an individual basis taking into account the risk/benefit ratio of long-term treatment. There is a consensus to consider anticoagulation in case of prior embolic event or thrombus in the left atrium; there are strong arguments in patients who have an enlarged left atrium (>50 mm[99], or >55 mm[1] in diameter, and this will probably require more precise measurements such as the left atrium area); or finally in the presence of dense spontaneous echo contrast.

Cardioversion should not be performed before intervention in patients with severe MS because it will not restore sinus rhythm, or may do so only for a short period if obstruction is not relieved. Cardioversion should be performed early after intervention if atrial fibrillation is of short duration and when the left atrium is only moderately enlarged. In patients with mild to moderate stenosis in whom atrial fibrillation has developed for the first time, it is appropriate to attempt cardioversion.

Serial testing

Patients with moderate to severe MS should be regularly followed-up yearly, by means of clinical and echocardiographic examinations while the follow-up could be performed at longer intervals in cases with stenosis of a lesser degree.

Mitral regurgitation

MR is the second most common heart valve disease after AS. Older studies of the natural history of MR were mainly based on rheumatic valve disease whereas the most frequent aetiology is now degenerative in western countries. Moreover, surgical results have improved dramatically by the steady development of valve repair. However, the timing of intervention in patients who have severe degenerative MR remains controversial.

We shall consider here only non-ischaemic MR since patients with severe MR of ischaemic origin are usually symptomatic.

Natural history

It has been widely assumed that some patients with severe MR may remain asymptomatic for a long period of time. This opinion, however, relies on old series which are difficult to interpret due to the lack of data on the initial severity of MR, the small population included, and the dominance of rheumatic origin[100,101]. Our knowledge has greatly improved due to recent observational studies evaluating the value of clinical and echocardiographic variables on outcome with and without surgery.

In a recent analysis of the natural history of degenerative MR, including 71% of patients in NYHA class I or II, there was a mortality rate of 6·3% yearly, associated with a high morbidity at 10 years since the incidence of heart failure and atrial fibrillation were 63% and 30% respectively[102]. Moreover, a linear rate of 1·8% per year of sudden death has recently been reported in patients with MR due to flail leaflets followed conservatively, the figure being 0·8% per year in patients with no or minimal symptoms[103].

Results of early intervention

It is widely accepted that valve repair is the optimal surgical treatment in patients with severe non-rheumatic MR. When compared with valve replacement it carries a lower perioperative mortality, provides improved survival, better preservation of postoperative left ventricular function than valve replacement, and lower long term morbidity since it obviates the need for long term anticoagulation in patients with sinus rhythm[104–110].

Recent series of surgery for severe non-ischaemic organic MR, which concentrate specifically on patients in NYHA Class I–II, showed a low operative mortality and excellent postoperative long-term survival, which appear significantly better than those in patients in Class III–IV[111–113] (Table 5). Furthermore, comparison with the expected survival shows that patients operated on in NYHA Class I–II had no excess long-term mortality[111]. The long-term morbidity was also very low as regards thromboembolism, endocarditis and need for

Table 5 Results of surgery in patients with severe mitral regurgitation, in NYHA Class I–II

	n	Valve repair (%)	Degenerative origin (%)	Operative mortality (%)	Maximum FU (years)	Late survival (%)
Tribouilloy *et al.*[111]	199	79	79	0·6	10	80
Sousa Uva *et al.*[112]	175	99	73	1	5	98
Garbarz *et al.*[113]	109	100	80	1	7	87 83* 78**

*Survival without reoperation
**Survival without reoperation and in NYHA Class I–II.

reoperation[111–113]. It should be noted that most of the patients in these series had degenerative MR and very few rheumatic MR.

Besides symptoms, the most important predictors of postoperative outcome after surgery for MR are age, atrial fibrillation, preoperative left ventricular function, and the reparability of the valve.

- Older age increases the operative risks and negatively influences late outcome. In the series by Tribouilloy *et al.*[111] the operative mortality for patients in NYHA class I–II was 0% below 75 and 3·6% over this age.
- Pre-operative atrial fibrillation is a predictor of an excess late postoperative morbidity and mortality, while duration of atrial fibrillation >1 year and left atrial diameter >50 mm are predictors of persistent postoperative atrial fibrillation which leads to the use of anticoagulant therapy cancelling one of the advantages of valve repair[105,106,111]. Similarly, in one study[114] left atrial dilatation was predictive of late postoperative mortality, but the precise dimensions of the left atrium which should not be exceeded have not clearly been determined.
- The most important predictors of postoperative outcome are left ventricular ejection fraction and end-systolic diameter[111,115–118]. A preoperative left ventricular ejection fraction <50% is associated with high postoperative mortality and a 'borderline' value between 50% and 60% is also associated, to a lesser degree, with an excess late mortality[115,116]. The best results of surgery are observed in the group with a preoperative left ventricular ejection fraction >60%, independently of the type of surgery.

A preoperative end-systolic diameter >45 mm is also closely correlated with a poor postoperative prognosis. Even a moderate increase of this diameter, between 35 and 45 mm, is associated with an increased risk of postoperative left ventricular dysfunction[115]. It would be much more appropriate to use left ventricular diameters indexed to BSA. The threshold of left ventricular end-systolic diameter of 26 mm . m^{-2} BSA has been suggested in one study including a limited number of patients and has yet to be confirmed[117].

For survival after surgery, data regarding ejection fraction have more power than those for end-systolic left ventricle dilatation. Systolic dysfunction is most likely when both values are abnormal. On the other hand, because MR produces complex haemodynamic alterations, left ventricular dysfunction can be concealed behind a normal ejection fraction and minimal or no symptoms. A value over which postoperative left ventricular dysfunction will not occur has not been demonstrated, rendering the prediction of the postoperative dysfunction, and thereby individual decision, difficult. In addition to the initial measurements, the temporal changes of left ventricular function should also been taken into account when making decisions about surgery.

Finally, progressive development of pulmonary hypertension is also a marker for a poor prognosis[1,118].

- The probability of a successful outcome for valve repair is of crucial importance. Due to the lower risk and better results than valve replacement, surgery should be considered earlier in patients in whom repair is highly likely. Repair can now be successfully performed in more than 80% of patients in experienced centres. Degenerative MR due to valve prolapse, can usually be repaired[105,106,108,110,119,120]. The reparability of rheumatic lesion, particularly if there is a risk of further episodes of rheumatic fever[121,122], and even more so of MR with extensive leaflet or annulus calcification is not as consistent even in experienced hands[105]. When repair is not feasible, mitral valve replacement with chordal preservation is preferred[118].

Indications for surgery

Surgery can be recommended in selected asymptomatic patients with severe MR:

1. asymptomatic patients with signs of left ventricular dysfunction: ejection fraction <60% and/or left ventricular end-systolic dimension >45 mm. Surgery in this group should be considered, even in patients with a high likelihood of valve replacement, to prevent further

deterioration of left ventricular function;
2. patients with atrial fibrillation and 'preserved' left ventricular function;
3. patients with 'preserved' left ventricular function and pulmonary hypertension (pulmonary systolic pressure >50 mmHg at rest of 60 mmHg on exercise) with a high likelihood of valve repair.

The other indications are controversial:

- surgery is of debatable value in asymptomatic patients with no signs of left ventricular dysfunction. In this group of patients, surgical correction can be considered if the following conditions are present: high likelihood of valve repair on the basis of valve lesion and experience of the surgeon, and a low operative risk. Conversely, an attentive clinical follow-up is recommended for patients at relatively high operative risk (e.g. patients 75 years or older) or with doubt about the feasibility of valve repair. In this latter group of patients, operative risk and/or prosthetic valve complications probably outweigh the advantages of correction MR;
- in patients with mitral valve prolapse and 'preserved' left ventricular function with recurrent ventricular arrhythmias despite medical therapy, early surgery is controversial because solid data on the value of surgery are currently lacking.

Pregnancy is generally well tolerated in MR except in case with severe pulmonary hypertension, but data are lacking on this topic.

Medical treatment

Several studies have shown that vasodilator therapy is effective in patients with functional MR associated with left ventricular dilatation and depressed systolic function but the effects of vasodilator therapy to delay the onset of the deterioration of left ventricular function and to improve the outcome remain to be proven in patients with organic MR[123–125]. Therefore, at the present stage, in the latter group of patients, the use of long-term vasodilator therapy is not recommended and furthermore should not delay surgery if indicated.

Even though the risk of embolism is less than in MS, there is a consensus to recommend anticoagulation with an INR of 2·5 to 3·5 in patients with MR and permanent or paroxysmal atrial fibrillation or whenever there is a history of systemic embolism or evidence of left atrial thrombus[98,99].

Serial testing

Asymptomatic patients with moderate MR and preserved left ventricular function can be clinically followed-up on a yearly basis. Echocardiography should be performed every 2 years to monitor the size and function of the left ventricle, the severity of MR, and the pulmonary artery pressures.

Asymptomatic patients with severe MR and preserved left ventricular function should be seen every 6 months and echocardiography performed every 12 months. The follow-up being closer (6 months) in patients with borderline values such as left ventricular ejection fraction 60–65%, and left ventricular end-systolic diameter 40–45 mm. The patients should be instructed to report rapidly any change in functional status.

Conclusion

The management of asymptomatic patients with severe valvular heart disease should be based on individual assessment of the risk to benefit ratio. The first step of the evaluation is to confirm the absence of symptoms by an accurate assessment of the functional status. Exercise testing may be very useful as a method of achieving an objective insight into the true level of incapacity or the lack of it. The next step is to define the severity of the valve lesion using quantitative methods largely based on echocardiography. Currently these measurements are being adjusted for body size as much as possible as regards valve area in stenosis and left ventricular dimensions. The third step is to perform individual risk assessment to predict the chances of future adverse clinical events and left ventricular dysfunction and the risks and benefits of early intervention. Then, the patient will be advised to have intervention or to remain under careful follow-up. If intervention is decided the less invasive intervention will be chosen as often as possible, if appropriate, as is the case for PMC in MS and mitral valve repair in MR. If medical follow up is adopted then the clinician should decide in advance what changes will lead to intervention and discuss these with the patient.

Finally, the level of evidence available today underlines the remaining controversial issues in the management of asymptomatic patients with valvular heart disease. This void in our knowledge base should encourage further research in this area.

Addendum

There is a lack of clinical trials providing a high level of evidence in the field of asymptomatic patients with valvular heart disease and it is not possible to set guidelines with a ranked strength of evidence. Thus the representatives of the Working Group of Valvular Heart Disease elaborated recommendations according to an expert consensus statement procedure along the rules for the position document of the ESC committee for Scientific and Clinical initiative. These recommendations are based on an update of a Medline medical literature search and the opinion of seven committee members. A first draft was written by five members of the Working

Group of Valvular Heart Disease and was then circulated to the other members of the group for discussion and final approval.

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