Valvular heart disease (VHD) is common and it is essential that hospital pharmacists understand the disease and the role of pharmacotherapy in its treatment and prevention.

The heart is composed of four chambers (two atria and two ventricles) and contains four valves (mitral and aortic valves on the left, tricuspid and pulmonary valves on the right). The valves prevent blood flowing backwards within the systemic (left side) and pulmonary (right side) circulations (see Figure 1, p120).

Many disease processes affect the cardiac valves. Disease may cause valve stenosis (narrowing) or regurgitation (blood leaking in the wrong direction), with haemodynamic consequences. Acute or subacute infection, most commonly bacterial endocarditis, can destroy heart valves, as can connective tissue diseases. Diseases of the chambers can also affect the valves and cause functional disease.

Thirty years ago, the most common cause of VHD in people under the age of 60 years was rheumatic heart disease — an immunological reaction to streptococcal infection. Widespread antibiotic use has reduced the incidence of rheumatic heart disease, and the most common form of VHD is now degenerative valvular disease in elderly patients.1,2 Comorbidity is common; atherosclerosis, renal impairment and chronic obstructive pulmonary disease are the most frequent conditions found in VHD patients.3

Increasing numbers of patients are now undergoing valve replacement operations, and optimizing cardiac function in patients awaiting these operations has become an important aspect of patient care. Following surgery, there is a strong emphasis on anticoagulation monitoring and antibiotic prophylaxis against endocarditis.

This article will describe how the six most common forms of VHD are managed. A second article (p127) focuses on anticoagulation and prophylaxis of endocarditis.

Aortic stenosis

Aortic stenosis (AS) is the most common form of VHD in the western world, affecting 2–7 per cent of people over 65 years of age.1 It is most commonly caused by senile degeneration and calcification of valves. Aortic sclerosis, in which the valves become thickened but do not obstruct blood flow, is similar to AS and can be considered to be an earlier stage of the disease. Patients with AS are typically asymptomatic for long periods. Patients who present with symptoms of breathlessness, chest pain, palpitations or dizziness may have had mild AS for many years.

**Special features**

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Valvular heart disease — pathophysiology and management

By Sukhjinder Nijjer, MB ChB, M RCP, Jasdeep Gill, MB ChB, and Sandeep Nijjer, M Pharm, M RPharmS

The valves of the heart can be affected by a number of diseases and drugs. This article describes the most common types of valvular heart disease, the symptoms and diagnosis, and how the disease is managed with drugs and surgical intervention.

Widespread antibiotic use has reduced the incidence of rheumatic heart disease, and the most common form of VHD is now degenerative valvular disease in elderly patients.1,2 Comorbidity is common; atherosclerosis, renal impairment and chronic obstructive pulmonary disease are the most frequent conditions found in VHD patients.3

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**Aortic stenosis**

Aortic stenosis (AS) is the most common form of VHD in the western world, affecting 2–7 per cent of people over 65 years of age.1 It is most commonly caused by senile degeneration and calcification of valves. Aortic sclerosis has a disease process similar to atherosclerosis, involving lipid infiltration and inflammation.2,3 Younger patients (ie, those under 65 years of age) affected by AS may have bicuspid valves (the valve has two leaflets rather than the usual three) which undergo stenosis more quickly, or they may have congenital problems.

AS is strongly associated with coronary artery disease. Aortic sclerosis, in which the valves become thickened but do not obstruct blood flow, is similar to AS and can be considered to be an earlier stage of the disease.

Patients with AS are typically asymptomatic for long periods. Patients who present with symptoms of breathlessness, chest pain, palpitations or dizziness may have had mild AS for many years.
Atherosclerosis risk factor management is recommended for patients with AS, because of the similarity in the disease processes. Hypertension, hypercholesterolemia and diabetes should be treated, and smoking cessation is advised. Statins and angiotensin converting enzyme (ACE) inhibitors may slow the progression of AS caused by calcification, but this has not been confirmed in randomised controlled trials.

Symptomatic patients, or those with a valvular pressure gradient of \( \geq 50\) mmHg, should undergo surgical valve replacement ideally before left ventricular (LV) dysfunction occurs. Those with a dilated aortic root over 5.5 cm should be considered for surgery. The main surgical treatment is valve replacement. In aortic dilation, the ascending aorta must be replaced; the valve may be replaced or spared. An aortic diameter of \( \geq 55\) mm (or \( \geq 45\) mm in those with Marfan’s syndrome) indicates that surgery is necessary.

Management

The onset of symptoms (shortness of breath or angina) is the trigger for surgery in AR. In asymptomatic patients, a falling LV ejection fraction (LVEF) or an increasing end-diastolic LV diameter (as measured by echocardiography) are triggers for surgery. The main surgical treatment is valve replacement. In aortic dilation, the ascending aorta must be replaced; the valve may be replaced or spared. An aortic diameter of \( \geq 55\) mm (or \( \geq 45\) mm in those with Marfan’s syndrome) indicates that surgery is necessary.

Asymptomatic patients should be monitored annually. Those with hypertension should be treated with ACE inhibitors or dihydropyridine calcium channel blockers (eg, nifedipine). It has been suggested that nifedipine delays the need for aortic valve replacement. However, this was contested in a study of non-hypertensive patients, in which long-term nifedipine did not reduce or delay the need for valve replacement in severe AR. Enalapril has been shown to slow aortic root dilation in patients with Marfan’s syndrome. Beta-blockers have been shown to slow the progression of aortic dilation and these should be continued after surgery. However, they should be used with caution because they prolong diastole and therefore increase the regurgitant volume in severe AR. All patients with AR must be advised about endocarditis prevention and antibiotic prophylaxis.

Mitral regurgitation

Mitrval regurgitation (MR) is the second most common form of VHD. It may affect the valve leaflets (organic MR), the valve annulus (functional MR) or the valve

Examination

An examination, a harsh ejection systolic murmur is heard. Severe AS classically causes loss of the second heart sound. The pulse pressure (ie, the difference between the systolic and diastolic pressures) may be narrow. Sudden cardiac death may occur in 10–20 per cent of symptomatic patients but this reduces to 1 per cent per year in asymptomatic patients.

Calcium from the valve can affect underlying conducting tissues, causing ventricular arrhythmias, and heavily stenosed valves can cause haemolytic anaemia. About 10 per cent of AS patients develop infective endocarditis.

Electrocardiograms may demonstrate left ventricular hypertrophy in response to the difficulty in pumping the blood through the stenosed valve. Echocardiography with Doppler studies is essential to assess the valve area — less than 1 cm\(^2\) is classed as severe stenosis. The average rate of progression of AS is a decrease in valve area of 0.1 cm\(^2\) per year, but this is variable. Echocardiography can also be used to calculate the pressure gradient across the stenosed valve. Values of \( > 50 \) mmHg indicate stenosis, and values of \( > 100 \) mmHg indicate severe stenosis. Exercise testing is contraindicated in patients with symptomatic AS, but may be performed in asymptomatic patients under expert guidance.

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Mitral stenosis

Rheumatic heart disease remains the most common cause of mitral stenosis (MS), but rates have decreased with the reduction in rheumatic fever. It is also caused by senile degeneration of the valve. Stenosis occurs slowly without causing symptoms for many years before leading to reduced activity and breathlessness. Symptoms may occur once the valve area is <1.5 cm². Development of AF or a left atrial thrombus can lead to sudden deterioration. Once symptoms develop the prognosis is poor.

Examination

Echocardiography is used to calculate the severity of MS; an area of <1 cm² is defined as critical stenosis. Before surgery is undertaken in patients with MS, a transoesophageal echocardiogram (in which the Echo probe is passed into the oesophagus to a position behind the heart) must be performed, to exclude the presence of a left atrial thrombus.

Treatment

Drug therapy for MS includes diuretics or long-acting nitrates to relieve dyspnoea. Beta-blockers or rate-controlling calcium channel blockers (eg, diltiazem) improve exercise tolerance — slowing the heart rate prolongs diastole and therefore prolongs the time available for LV filling through the stenosed valve.

Patients in AF should be anticoagulated (target INR 2.5–3). If the patient has had an embolic event or is found to have a left atrial thrombus, he or she should be anticoagulated even if in sinus rhythm (the normal regular electrical activity of the heart). Warfarin should also be started if the left atrial diameter is greater than 50 mm.

In most patients with AF, the aim is to restore normal sinus rhythm (cardioversion) with drugs such as amiodarone, or with electrical shocks to the chest. It is usual to try cardioversion once the MS has been treated surgically. Surgery is usually performed when the valve area falls below 1.5 cm² and symptoms develop.

Surgery in MS typically requires valve replacement. Alternatively, the stenosed valves may be opened up during open or closed heart surgery. Another alternative, percutaneous mitral commissurotomy (PMC), is used if the valve is pliable and non-calcified, with minimal MR and no left atrial thrombus. PMC involves passing a catheter across the stenosed valve, inflating a balloon at the end and then pulling it back. This ruptures the valve and provides at least a 100 per cent increase in valve area, or results in a valve area of at least 1.5 cm².

Following the procedure, subcutaneous heparin is required for 24 hours. Those at risk of thrombosis will need warfarin. PMC may be considered in younger patients keen to avoid surgery or in elderly patients who have contraindications to surgery.

Panel 1: Replacement valves

<table>
<thead>
<tr>
<th>Valve type</th>
<th>R replacement valves can be mechanical or biological. Biological valves can be xenografts (eg, porcine or bovine, using pericardial or valvular tissue), homografts (preserved human aortic valves from cadavers) or autografts (eg, in the Ross procedure the patient's pulmonary valve is used to replace the aortic valve). Mechanical valves are metal or carbon alloys and are classified by structure (types include the “caged ball” [see illustration on p119] or “tilting disc” valve). There are a number of different valve manufacturers and valves differ in terms of haemodynamics and durability. Mechanical valves are more durable than biological valves and may last 20–30 years, but patients with these valves require lifelong anticoagulation. They are used in young patients, patients with a life expectancy of greater than 10–15 years and those already on warfarin. Biological valves are less thrombogenic and do not require anticoagulation. However, they are less durable, lasting for approximately 10 years. Biological valves deteriorate quickly in younger patients and should be avoided in patients under 40 years of age. They are used in the very elderly and in patients who cannot tolerate warfarin or who have a significant haemorrhage risk due to their lifestyle (eg, contact sports) or comorbidities.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choice of valve</td>
<td>The choice of valve in a particular patient requires a tailored approach. Age and lifestyle are significant considerations in valve choice, as described above. Mechanical and biological valves have similar long-term survival statistics, although re-operation (for a failed or deteriorating valve) is more common with the biological type. The need for future operations must be considered when making initial choices — repeat operations have a higher risk with longer recovery periods.</td>
</tr>
<tr>
<td>Pregnant patients</td>
<td>Valve procedures in pregnant women and those who are of child bearing age need expert guidance and patients need careful counselling. Biological valves may be used in pregnant women to avoid the need for warfarin (teratogenic in the first trimester). The valve is likely to have a short lifespan, but re-operation risks are lower in the younger age group. Those requiring a metallic prosthesis should take low dose warfarin (≤5 mg/day) during the second and third trimesters of pregnancy, until the 36th week, to reduce the risk of fetal malformation.</td>
</tr>
</tbody>
</table>
Tricuspid regurgitation

Tricuspid regurgitation (TR) is most commonly functional, secondary to annular dilation and right ventricular volume overload. Causes include pulmonary hypertension and atrial septal defects, which allow high blood pressures on the left side of the heart to be transmitted to the right side of the heart. Other causes include acute valvular destruction by endocarditis (commonly due to intravenous drug use) and a congenital defect known as Ebstein's anomaly, in which the right atrium extends down into right ventricle. Carcinoid syndrome (a neuroendocrine tumour which secretes chemicals that affect blood pressure) and rheumatic disease can also affect the tricuspid leaflets leading to TR.1,2 Patients generally tolerate TR well, but may present with signs of right heart failure. A pansystolic murmur may be heard at the lower left sternal edge. As right heart failure ensues, the patient will develop peripheral oedema and ascites. Despite being well tolerated, severe TR has a poor prognosis.

Treatment

Diuretic therapy is required to treat the symptoms of right heart failure. The cause of the TR should be identified and treated; reducing right heart dilation may diminish or stop TR.

Tricuspid stenosis

Tricuspid Stenosis (TS) is rare in the UK, but occurs in countries where rheumatic disease is common. Since rheumatic disease affects any valve, TS may accompany other types of VHD. A mean gradient of >5mmHg across the valve is defined as significant TS. Patients may present with heart failure and will need treatment with diuretics. Surgical intervention involves valve replacement with a biological prosthesis. The lower pressure in the right side of the heart means that biological prostheses have a sufficiently long life.1

Replacement valves

The types of replacement valve available are described in Panel 1 (p121). Replaced valves have a number of complications, listed in Panel 2 (p123). It is essential to consider the possibility of these complications when a patient with a replaced valve is unwell.

Valve thrombosis

Patients with valve thrombosis may present with pulmonary oedema, poor peripheral perfusion or with systemic embolisation (stroke or transient ischaemic attack). About 1–2 per cent of patients per year with prosthetic valves will have valve thrombosis, despite taking warfarin.1,2 Once a clot has formed between the leaflets of a mechanical valve, the valve will sound abnormal. Diagnosis is proven with echocardiography. Anticoagulation should be optimised if the thrombus is small (<10mm) and non-obstructive.1,4 Large clots may require emergency surgery or fibrinolysis.

Mixed valve disease

It is possible for a valve to be both stenosed and regurgitant. This is more typical following rheumatic heart disease. Examinations including echocardiography will determine which lesion is most predominant, and treatment will be initiated according to the findings. Where both types of valve disease are prominent, management decisions are based on the patient’s symptoms and degree of ventricular dysfunction.

The aim of surgery is to prevent irreversible right ventricular dysfunction, and its timing can be difficult. Annuloplasty, where a prosthetic ring is inserted around the dilated annulus, is a popular method of repair with low rates of recurrence of TR. In some situations the tricuspid valve is replaced, usually with a biological prosthesis.
**Embolisation** Embolisation usually manifests as cerebrovascular events. It occurs at a rate of 1 per cent per year in patients on warfarin, and 4 per cent in those not on warfarin. The risk is greater in patients with prostheses in the mitral valve, with caged ball devices or with multiple prosthetic devices. Older patients, those with AF and those with poor LV function are also at risk from embolisation.

Patients with cerebral embolisation should have their anticoagulation stopped for 72 hours and be checked for intracerebral haemorrhage. If present, or if extensive infarction has occurred, anticoagulation should be withheld for seven to 10 days. Other emboli are treated with optimised anticoagulation. Patients on warfarin who suffer recurrent emboli will need additional aspirin.

**Bleeding** Major bleeds can occur if a patient’s INR is not monitored regularly. Major bleeds may occur in 1 per cent of patients with prosthetic valves and can lead to significant morbidity and mortality. Minor significant bleeds (eg, a nosebleed causing a drop in haemoglobin) occur more frequently.

**Prosthetic dysfunction** Mechanical failure is rare, but can cause sudden onset dyspnoea, loss of consciousness and acute shock with severe acute valvular regurgitation. One type of valve (a Bjork-Shiley model) was withdrawn from the market in 1986 following reports of strut fracture. Aortic valve failure will cause death within minutes, but mitral valve failure may be treated by emergency surgery. Biological valves become calcified and rigid over time and therefore may tear or rupture.

**Haemolysis** Haemolysis most commonly occurs with caged ball devices. The blood is haemolysed as it passes through the valve mechanism, and this can be severe enough to cause anaemia. Patients should receive iron and folate and may require blood transfusions. Severe haemolysis may occur in patients with paravalvular leaks caused by improper valve implantation or valve endocarditis. Severe anaemia can lead to transfusion dependence and heart failure. Surgical repair of any leaks may be necessary, but repeat surgery can be risky.

**Endocarditis** Prosthetic valve endocarditis can be classed as “early” or “late”. Early endocarditis occurs up to 60 days after the operation and is typically caused by perioperative bacteraemia from wound infections or contaminated central lines. The most common causative organisms are Staphylococcus epidermidis, Staphylococcus aureus or Gram-negative bacteria. Late prosthetic valve endocarditis (occurring more than 60 days post procedure) is commonly caused by Streptococcus viridans. These bacteria are the most common cause of endocarditis in the general population (ie, those without prosthetic valves). The risk of endocarditis is similar for mechanical and bioprosthetic valves. The mortality of prosthetic valve endocarditis is high (30-80 per cent) and requires urgent antibiotics and consideration for urgent surgery.

The second article in this feature (p127) focuses on the prevention of thrombosis and endocarditis.
It has been established that certain drugs can cause valvular heart disease through activation of 5-HT<sub>2B</sub> receptors, which appear to be essential in valvular development. The appetite suppressants fenfluramine and dexfenfluramine have been shown to cause valvular thickening with plaque development, chordal thickening and retraction. It is thought that valvular damage results from mitosis of normally quiescent valve cells, triggered by 5-HT<sub>2B</sub> receptor stimulation. The antiparkinsonian dopamine agonists pergolide and cabergoline are also potent 5-HT<sub>2B</sub> receptor agonists. Population studies have confirmed initial case reports that patients taking these drugs have an increased risk of valvular regurgitation. Ergot derivatives such as the anti-migraine drugs dihydroergotamine, methysergide and ergotamine, and other amphetamine derivatives (including the methylenedioxymethamphetamine “ecstacy”) have also been implicated in causing VHD.

References


