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Edited by Bernard Prendergast, consultant cardiologist,
The John Radcliffe Hospital, Oxford and
Philip MacCarthy, consultant cardiologist, Kings Health Partners,
Kings College Hospital, London

Changing epidemiology and natural history of valvular heart disease

Simon Ray, *consultant cardiologist/honorary reader in cardiology, Department of Cardiology, North West Heart Centre, University Hospitals of South Manchester*

The marked change in the epidemiology of valvular heart disease (VHD) over the last 50 years has been the dramatic reduction in the incidence of rheumatic heart disease in developed countries.[1] Rheumatic disease remains a major problem in developing countries, but most VHD in industrialised nations is now degenerative which, until recently, was thought to be relatively unimportant as a public health problem.[1–3]

US data on the prevalence of valvular heart disease

There are surprisingly little good quality data on the epidemiology of VHD. One difficulty in obtaining such data is that accurate diagnosis of the occurrence and severity of VHD requires high quality echocardiography in large numbers of patients.[1,3] In a landmark paper in 2006, Nkomo *et al* analysed pooled data from 12,000 subjects in three US population-based studies and a separate cohort of 16,500 patients from a well defined community setting.[1] The principal findings are summarised in Fig 1. It is evident from these data that VHD in the US population is a disease of increasing age (particularly the over-75s) and that mitral regurgitation (MR) and aortic stenosis (AS) make up the bulk of disease. Males and females are equally affected. Mitral stenosis (MS), highly prevalent in populations affected by rheumatic disease, is now uncommon.[1–3] It is important to emphasise that only moderate to severe VHD was included in the Nkomo analysis, reflected in the fact that subjects demonstrated evidence of cardiac chamber remodelling and reduced survival.

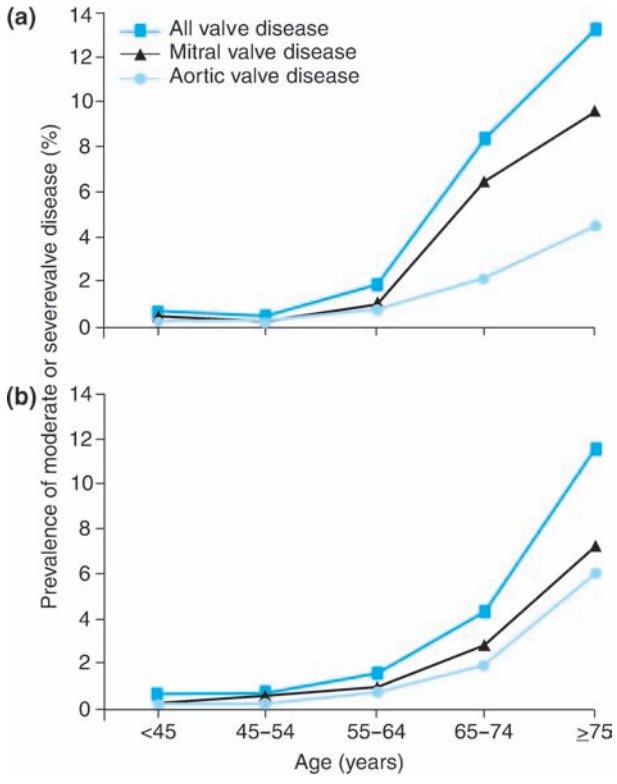

Fig 1. The rising prevalence of valvular heart disease with age in (a) three US population studies; (b) the community of Olmsted County, MN. Reproduced from the Lancet with permission from Elsevier.[1]

Extrapolation to the UK

The Nkomo study found a population prevalence of moderate to severe valve disease of 8.5% in the 65–74 age group and 13% in those over 75 years. There are currently no equivalent data for the UK population but extrapolation from the US figures would give an estimate of around one million affected individuals over the age of 65 years.[4] It is worth noting that the UK population aged over 75 years is projected to increase by around 50% by 2025 so the healthcare impact of valve disease is likely to increase substantially (Fig 2(a)–(c) and 3).[5]

Aortic stenosis

Pathophysiology

AS results from a gradual reduction in the mobility of the cusps of the aortic valve, leading to reduced systolic excursion and reduction in the area of the open valve from the normal of 3–4 cm^2. As the valve becomes progressively narrowed, left ventricular (LV) systolic pressure rises and a pressure gradient develops between the ventricle and the

aorta. The ventricle compensates for this pressure rise with an increase in wall thickness and patients may remain asymptomatic for a long time despite a severely narrowed valve (<1 cm^2). Progressive hypertrophy eventually causes the ventricle to become less compliant, resulting in symptoms, most commonly exertional breathlessness. Most patients develop these symptoms before a reduction in ejection fraction but some present with poor ventricular function and overt heart failure.[6]

Aetiology and progression

The three main causes of AS in developed countries are:

- calcification of a congenitally bileaflet (or occasionally single leaflet) valve
- calcification of a trileaflet valve and,
- less commonly, rheumatic disease.

Thickening of the aortic valve without obstruction (or aortic sclerosis) is present in 25% of patients over 65 years and is associated with age, male gender, hypertension, smoking, low-density lipoprotein levels and diabetes mellitus.[7] Over five years, around 9% of such patients progress to AS.[8] Prediction of the rate of progression in any individual patient is difficult, although surgical data suggest more rapid change in single and bileaflet valves.[9] Excluding rheumatic valves, just over half of all stenotic valves are morphologically abnormal:

- below 50 years: two-thirds a bileaflet and one-third a single leaflet valve
- 50–70 years: two-thirds a bileaflet and one-third a trileaflet valve
- over 70 years: 40% a bileaflet and 60% a trileaflet valve.

Despite initially promising results for treatment with statins there is no convincing evidence that any medical treatment slows the progression of AS.[10] Valve replacement is the only effective treatment for severe AS.

Aortic regurgitation

Pathophysiology

Aortic regurgitation (AR) is caused by inadequate coaptation of the aortic valve cusps during diastole. It may arise either from primary abnormality of the valve or from abnormality of the aortic root causing disruption of normal valve closure. As a result, a proportion of LV stroke volume (±50% in severe AR) leaks back through the aortic valve in diastole. This in turn induces a compensatory response of ventricular dilatation and wall thickening which maintains efficient ventricular pump function. If regurgitation progresses unchecked, this compensatory response eventually becomes inadequate, resulting in progressive ventricular enlargement and the onset of exertional breathlessness.

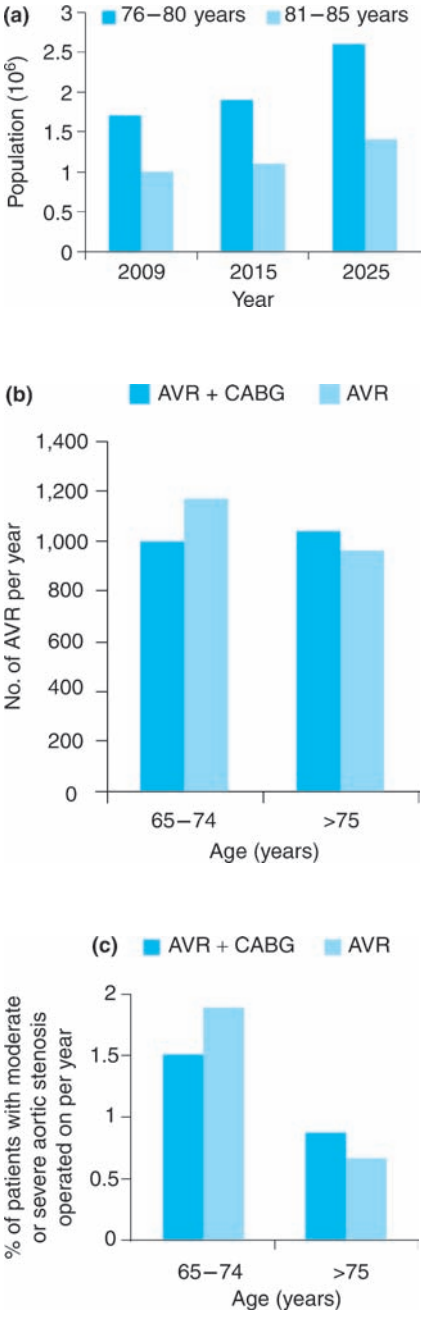

Fig 2. (a) Population estimates for England and Wales for 2009, 2015 and 2025, illustrating the anticipated growth in the 76–80 and 81–85 age groups; (b) number of aortic valve replacements (AVRs) per year in the UK for age 65–74 and over-75; (c) number of aortic valve replacements per year as a percentage of the population estimated to have moderate or severe aortic stenosis. A relatively smaller proportion of the over-75 age group undergo surgery. CABG = coronary artery bypass grafting. Reproduced with permission from SCTS and Dendrite Clinical Systems.[5]

Key Points

Rheumatic heart disease is now uncommon in industrial nations but still a major burden in the developing world

Valvular heart disease (VHD) is a disease of advancing age in the developed world and particularly prevalent over the age of 75 years

Aortic stenosis usually results from progressive valvular calcification. Congenitally abnormal (single and bileaflet) valves stenose more rapidly than those which are morphologically normal (trileaflet)

Mitral regurgitation (MR) is the most common form of moderate to severe VHD in the community setting

Ischaemic MR is common after myocardial infarction, often difficult to detect and associated with an adverse outcome

KEY WORDS: aortic stenosis, epidemiology, mitral regurgitation, valve disease

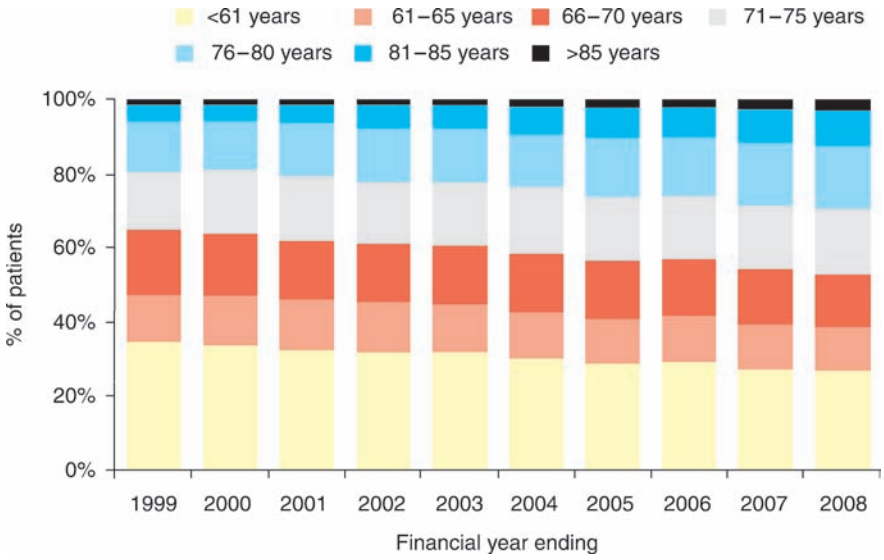

Fig 3. Advancing age of patients undergoing aortic valve surgery in the UK. Isolated aortic valves: age categories (n=31,200). Reproduced with permission from SCTS and Dendrite Clinical Systems.[5]

Aetiology and progression

About half of patients undergoing valve replacement for pure AR have an abnormality of the valve itself while the rest have an abnormality of the aortic root (most commonly of non-specific cause).[11] Of the valvular causes, bileaflet valves constitute about 60% and infective endocarditis 20% (rheumatic heart disease now accounts for <10%). There is conflicting evidence that treatment with vasodilating agents (eg angiotensin-converting enzyme inhibitors) may slow the progression of AR.[6]

Mitral regurgitation

MR is the most commonly occurring valve abnormality.[1] The epidemiology and natural history are critically dependent on aetiology. It may be classified into:

- primary: an abnormality of the valve itself, or
- secondary: an abnormality of the left ventricle.

Primary mitral regurgitation

Pathophysiology

Primary MR results from failure of systolic coaptation of the mitral leaflets as a result of abnormalities of the valve apparatus. A proportion of the LV stroke volume (±50% in severe MR) is ejected into the left atrium which enlarges as a result. The left ventricle also enlarges to accommodate the increased stroke volume and a compensated state develops during which patients may remain asymptomatic for many years. This compensatory response is eventually inadequate and patients develop exertional breathlessness and/or echocardiographic signs of ventricular decompensation. No current medical treatment slows the progression of primary MR.

Aetiology and progression

The most common form of primary MR in the developed world is degenerative mitral valve disease (also known confusingly by other names, including mitral valve prolapse or myxomatous mitral valve disease). The term 'degenerative' combines a variety of pathologies that lead to varying degrees of leaflet redundancy, thickening or thinning, and lengthening or rupture of the chordae. The second most common cause is infective endocarditis. Rheumatic MR is rare in the industrial nations but highly prevalent in the developing world.[2,3] Other less common causes are congenital abnormalities, trauma and drug-induced MR.[12]

The prevalence of primary MR depends critically on the method of assessment. Definitions in the early days of echocardiography were lax, resulting in an apparent prevalence as high as 30% in young women. Using carefully standardised criteria, the true prevalence appears to be around 2%, roughly equal between males and females and with a fairly even age distribution.[13] However, natural history is highly variable. Life expectancy is normal in about half of subjects, with minimal health impact.[14] About 20% have an adverse prognosis and are at high risk of progression to surgery, heart failure or death. The principal predictors of a more aggressive course are moderate or severe MR at diagnosis and any reduction in LV ejection fraction.[14] Patients with a flail mitral leaflet due to chordal rupture tend to progress particularly rapidly.[15] Women generally have a more benign form of disease, with fewer flail leaflets and less severe MR, but those who develop severe MR fare worse than men with equivalent MR and are less likely to undergo surgery.[16] Successful valve repair in patients with no more than mild symptoms and normal LV function restores normal life expectancy.[17]

Secondary mitral regurgitation

Secondary MR results from distortion of ventricular anatomy, usually as a result of myocardial infarction (MI) but also as a result of ventricular dilatation or hypertrophic cardiomyopathy. Pathophysiology depends upon the underlying aetiology.

Ischaemic MR is common, but often clinically silent and only detected using echocardiography. Scarring of the left ventricle distorts chamber anatomy, with consequent dysfunction of the mitral apparatus and failure of leaflet coaptation (though the leaflets themselves remain normal). The haemodynamic load of the resultant MR is imposed on an already damaged ventricle. About 50% of patients have some MR 30 days after MI, moderate or severe in 12%.[18] MR is more frequent in women, older patients and those with

triple vessel disease[19] and just as common after both non-ST segment elevation MI (NSTEMI) and STEMI.[20] Over a five-year follow-up after MI, moderate or severe MR is associated with a substantial risk of heart failure or death independent of age, sex or baseline ejection fraction.[18] Paradoxically, there is minimal long-term symptomatic or survival benefit associated with the addition of mitral valve repair to coronary grafting in patients with ischaemic MR,[21] although appropriate medical treatment for heart failure may reduce the degree of regurgitation in some patients.

Mitral stenosis

Pathophysiology

MS results from fusion, thickening and reduced mobility of the mitral leaflets and chordae tendinae. The major cause worldwide is rheumatic fever, but congenital abnormalities of the valve make up a larger proportion of cases in industrialised nations. Valve area decreases from the normal of about 4 cm^2 to 1 cm^2 or less, producing a diastolic gradient between the left atrium and left ventricle, raised left atrial pressure (and consequent enlargement), secondary pulmonary hypertension and right heart failure. The primary symptom is breathlessness on exertion.

Aetiology and progression

MS tends to develop within a few years of rheumatic fever in the developing world[2] but the interval is longer in industrialised nations. Once MS has developed, the average fall in valve area is approximately 0.1 cm^2 per year.[22]

Conclusions

Rheumatic fever has declined sharply as a cause of chronic VHD in industrialised nations and most valve pathology is now degenerative. Symptomatic VHD (particularly aortic valve disease) is generally a disease of increasing age and will become more common in forthcoming decades. As a consequence, VHD is now a major public health issue.

References

1 Nkomo VT, Gardin JM, Skelton TN *et al.* Burden of valvular heart disease: a population-based study. *Lancet* 2006;368:1005–11.
2 Nkomo VT. Epidemiology and prevention of valvular heart disease and infective endocarditis in Africa. *Heart* 2007;93:1510–9.
3 Marijon E, Ou P, Celermajer DS *et al.* Prevalence of rheumatic heart disease detected by echocardiographic screening. *N Engl J Med* 2007;357:470–6.
4 www.statistics.gov.uk
5 The Society for Cardiothoracic Surgery in GB and Ireland (SCTS). *The sixth national cardiac surgical database report*. Henley-on-Thames: Dendrite Clinical Systems, 2009.
6 Bonow RO, Carabello BA, Chatterjee K *et al*; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease); Society of Cardiovascular Anesthesiologists. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. A report of the ACC/AHA Task Force on Practice Guidelines (Writing Committee), developed in collaboration with the Society of Cardiovascular Anesthesiologists, endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2006;48:e1–148.
7 Stewart BF, Siscovick D, Lind BK *et al.* Clinical factors associated with calcific aortic valve disease: Cardiovascular Health Study. *J Am Coll Cardiol* 1997;29:630–4.
8 Novaro GM, Katz R, Aviles RJ *et al.* Clinical factors, but not C-reactive protein, predict progression of calcific aortic-valve disease: the Cardiovascular Health Study. *J Am Coll Cardiol* 2007;50:1992–8.
9 Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation* 2005;111:920–5.
10 Rosseb A, Pedersen T, Boman K *et al.* Intensive lipid lowering with simvastatin and eztimibe in aortic stenosis. *N Engl J Med* 2008;359:1343–56.
11 Roberts WC, Ko JM, Moore TR, Jones WH 3rd. Causes of pure aortic regurgitation in patients having isolated aortic valve replacement at a single US tertiary hospital (1993 to 2005). *Circulation* 2006;114:422–9.
12 Van Camp G, Flamez A, Cosyns B *et al.* Treatment of Parkinson's disease with pergolide and relation to restrictive valvular disease. *Lancet* 2004;363:1179–83.
13 Freed LA, Levy D, Levine RA *et al.* Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med* 1999;341:1–7.
14 Avierinos JF, Gersh BJ, Melton J 3rd *et al.* Natural history of asymptomatic mitral valve prolapse in the community. *Circulation* 2002;106:1355–61.
15 Ling LH, Enriquez-Sarano M, Seward JB *et al.* Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med* 1996;335;1417–23.
16 Avierinos JF, Inamo J, Grigioni F *et al.* Sex differences in morphology and outcomes of mitral valve prolapse. *Ann Intern Med* 2008;149:787–95.
17 Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D *et al.* Quantitative determinants of asymptomatic mitral regurgitation. *N Engl J Med* 2005;352:875–83.
18 Bursi F, Enriquez-Sarano M, Nkomo VT *et al.* Heart failure and death after myocardial infarction in the community: the emerging role of mitral regurgitation. *Circulation* 2005;111:295–301.
19 Pellizon GG, Grines CL, Cox DA *et al.* Importance of mitral regurgitation in patients underlying percutaneous coronary intervention for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complication (CADILLAC) trial. *J Am Coll Cardiol* 2004;43:1368–74.
20 Perez de Isla L, Zamorano J, Quezada M *et al.* Prognostic significance of functional mitral regurgitation after a first non-ST-segment elevation acute coronary syndrome. *Eur Heart J* 2006;27:2655–60.
21 Mihaljevic T, Lam BK, Rajeswaran J *et al.* Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. *J Am Coll Cardiol* 2007;49:2191–201.
22 Sagie A, Freitas N, Padial LR *et al.* Doppler echocardiographic assessment of long-term prognosis of mitral stenosis in 103 patients: valve area and right heart disease. *J Am Coll Cardiol* 1996;28:472–9.

Address for correspondence:
Dr S Ray, Department of Cardiology, University Hospitals of South Manchester, Manchester Academic Health Sciences Centre, Manchester M23 9LT.
Email: simon.ray@uhsm.nhs.uk