Age-related Morphological Changes in Cardiac Valves

Jagdish Butany, MBBS, MS, FRCPC, Departments of Pathology, Toronto General Hospital, University Health Network and University of Toronto, Toronto, ON.

Manmeet S. Ahluwalia, MBBS and Vidhya Nair, MBBS, MD, Departments of Pathology, Toronto General Hospital, Toronto, ON.

Christopher Feindel, MD, FRCPC, Cardiovascular Surgery, Toronto General Hospital, University Health Network and University of Toronto, Toronto, ON.

Valvular heart disease is a common cardiac problem. There are many age-associated changes that can occur in otherwise healthy heart valves. These commonly develop in the aortic valve and, to a lesser extent, in the mitral valve. In both cases there is fibrosis and thickening of the tissues with the deposition of calcium salts in the aortic valve cusps and in the annulus of the mitral valve. These changes can contribute to progressive secondary changes in the heart (left ventricle and left atrium), which can be associated with significant morbidity related to complications of valvular disease, such as congestive heart failure, infective endocarditis and sudden death.

Key words: heart valves, age-related changes, calcified aortic valve, mitral annular calcification.

Introduction

The mandate of quality health care includes improved neonatal survival, better maternal and neonatal health and an improved life expectancy, resulting in an increasingly older population with the largest growth in the 65+ age group. Therefore, there is a growing need for an improved awareness of age-related changes in the body in general and in the heart in particular. In addition to risk factors such as diabetes mellitus, abnormal lipid levels and hypertension,[1] increasing age is a major independent risk factor for cardiovascular disease. In a previous issue of *Geriatrics & Aging*, the age-related changes in the myocardium were highlighted.[2] In this paper we review age-related cardiac valvular changes and briefly discuss their sequelae and treatment.

Heart Valves: Structure and Function

Heart valves serve the important function of preventing backflow, or regurgitation, in the healthy heart. It is well known that cardiac valves can and do suffer congenital and acquired disease (Table 1) and that neoplasms are exquisitely rare. Congenital valvular disease manifesting in childhood is usually seen in right-sided valves, while acquired disease is more common in left-sided valves (higher pressure). All four valves have a similar basic structure and are divided morphologically into atrioventricular valves (mitral [MV] and tricuspid [TV]) and the semilunar valves (aortic [AV] and pulmonary [PV]). The valves on the left side (MV, AV) are exposed to higher closing pressures than those on the right side (TV, PV), and they consequently show structural differences such as a thicker zona fibrosa, a thicker spongiosa and a more prominent nodulus Arantius.

The valve function of maintaining unidirectional blood flow requires the integrated movement of all anatomic components of the valve, collectively referred to as the valve apparatus. The atrioventricular valve apparatus is comprised of the annulus, leaflets, chordae tendineae, papillary muscles and the myocardium of the chamber on either side. The semilunar valve apparatus is comprised of the annulus (aortic valve only), cusps, commissures, vessels and the ventricular myocardium. Endothelial cells cover the valve surfaces. While appearing structurally similar throughout the cardiovascular system, endothelial cells likely have different functional effects at different sites, including the heart valves.[3]

Histologically, all valves have four basic layers: the soft compressible spongiosa; the firm collagen-rich fibrosa; the ventricularis (continuation of the ventricular endocardium) and; the atrialis (continuation of the left and right atrial endocardium, the aorta or the pulmonary arterial intima). The tip of the AV is composed only of fibrosa and spongiosa. The fibrosa, the central layer of the valve composed of collagen and elastic fibres, provides strength and structural support to the valve. The zona spongiosa provides flexibility and allows the valve to "fold and unfold" as it opens and closes.[4] Chordae tendineae are thin, cord-like (or tendon-like) structures composed of endothelium-covered collagen and elastic tissue extending from the valve leaflet to the endocardial surface of papillary muscles. They are the "tensor" apparatus that allows the MV to stay closed against the left ventricular closing or ejection pressures.

The predominant glycosaminoglycans (GAGs) in heart valves are hyaluronic acid, chondroitin sulphate and heparan sulphate. With advancing age, there is a striking increase in elastin and GAGs with a concomitant decrease in collagen in the MV.[5] Increased thickness of valves is noticed with aging in both males and females.[5] This thickening is more prominent in left-sided valves (MV, AV) that are subject to higher pressures compared to right-sided valves (PV,

TV), as well as in the basal or annular third compared to the rest of the valve (greater stress localization). The PV shows the least noticeable change with aging (Table 1). The PV differs from the other three valves in that its cusps arise from the right ventricular outflow tract endomyocardium and not from the PV "annulus". This is relevant to the way the tissues are removed for the Ross or "valve switch" procedure for treating aortic valve disease.

Aortic Valve: Age-related Changes

The aortic valve shows the most significant age-related changes, often requiring valve replacement with prostheses (Figure 1). The AV cusps thicken with age, with fibrosis most marked in the posterior or non-coronary aortic cusp (Figure 2).[6] Histologically, the thickening is seen primarily in the fibrosa and in the ventricularis (Figure 3).[6] Thickening also is seen as plaque-like lesions on the cusps, especially at their bases. These plaques show a striking increase in elastin with a modest decrease in collagen, but no change in GAGs.[5]

The late morphologic hallmark is a heaped-up or nodular calcific mass(es) along the aortic or non-flow surface of the cusps that gradually becomes anchored to the annulus and prevents the smooth opening of cusps. Calcific deposits are often seen at the base and body of the cusps, especially along the "line of closure or rough zone" and rarely at the free edges (Figure 2). In addition, there is an increase in the number of adipocytes in the leaflet and increased prominence of the nodulus Arantius. This thickening and calcification of the AV is referred to as aortic sclerosis, which increases with age and is associated with mineral deposits (calcium apatite salts) in the zona fibrosa.

Aortic sclerosis is seen in over 20% of people older than 65 years and in 35% of people older than 75 years.[7] In the Helsinki Aging study, some degree of calcification was seen in 53% of people older than 75 years, and age was found to be a significant independent predictor of aortic valve calcification[7]—findings that were confirmed by the Cardiovascular Health Study.[8] This calcification is believed to be a degenerative change and can lead to significant aortic valve stenosis. Aortic valve sclerosis and stenosis are considered to be stages in calcific valve disease and occur in valves that were apparently previously normal and had three well-functioning cusps.[8] Hemodynamically significant aortic stenosis is seen in 2–3% of the population older than 65 years.[8] Calcific AV disease is the most common valvular lesion among older people, accounting for over half the number of cases needing prosthetic replacement of aortic valves.[9] Most of these patients present in the seventh decade with symptoms of exercise intolerance (most common), angina syncope and orthopnea.

Calcific AV disease needs to be differentiated from aortic stenosis secondary to calcification of the congenitally abnormal AV. The bicuspid (congenitally abnormal) aortic valve (BAV) is seen in 2–3% of the population and undergoes relatively accelerated calcification compared to a three-cuspid AV. Why some BAVs progress more rapidly to the symptomatic stage remains to be clarified. However, only a small percentage of this group will need AV replacement. Patients with a calcific BAV present in their 50s and 60s. Commissural fusion is usually absent in degenerative aortic valve disease. Occasionally there is extension of the AV calcific deposits onto the ventricular aspect of the anterior mitral leaflet or onto the adjacent ventricular septal myocardium.

With aging, whisker-like projections called Lambl's excrescences (single or multiple thin, papillary projections) appear along the lines of valve closure.[10] They also can be seen along the free surface and are most common on the nodule of Arantius on the AV. They are believed to consist mainly of fibrous tissue, contain some elastic tissue[11] and are believed to represent organized thrombi.[12]
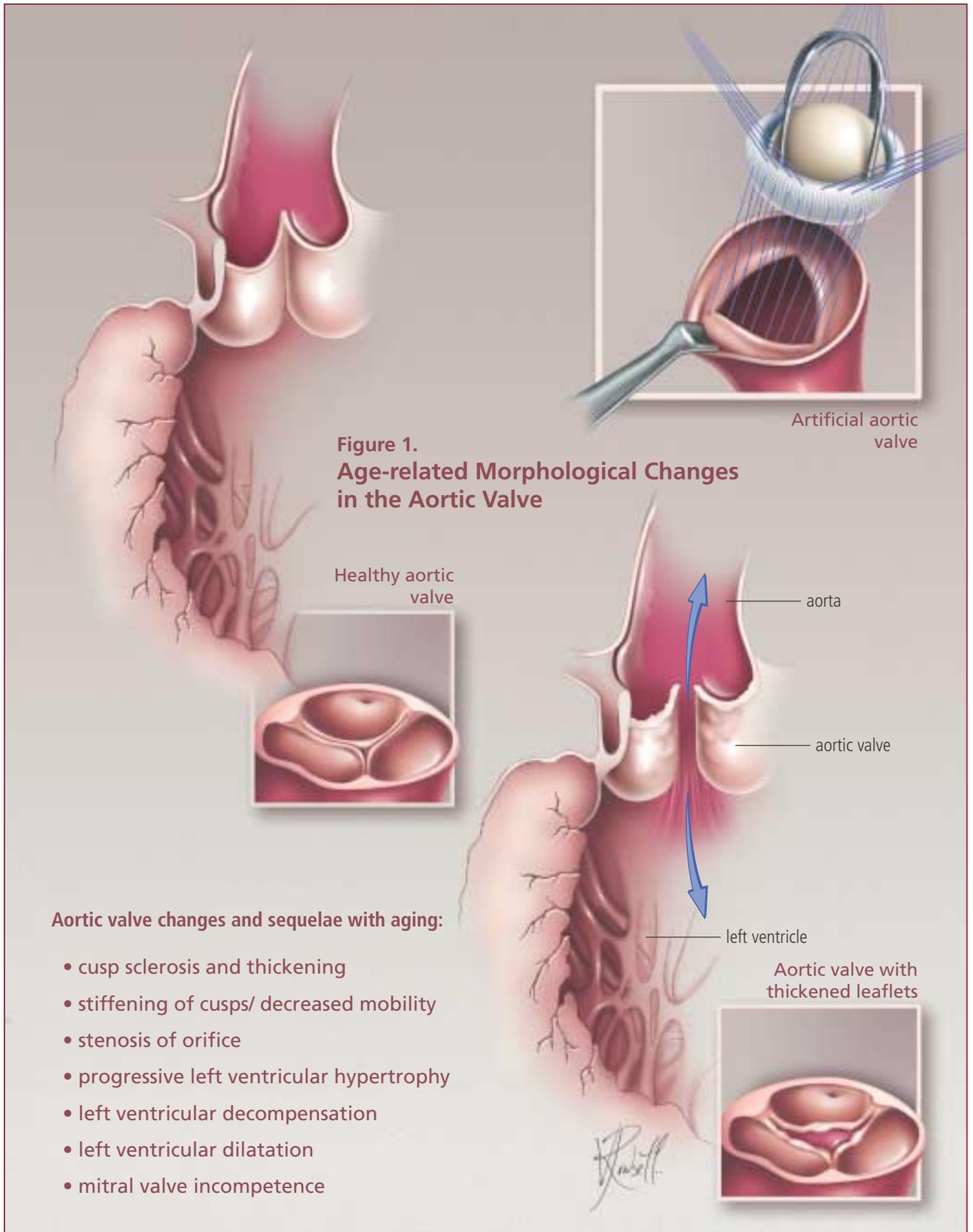
In a study by Christie, *et al.*, maximum radial elastic extensibility (also referred to as stretch) of human aortic valves decreased with age.[13] Stretch loss in the leaflets can be a contributing factor to the development of aortic incompetence.[13] Fenestrations are variably sized defects in the lunules of valve cusps ranging in size from pinpoint to over 1.0cm in diameter, and are increasingly apparent with advancing age. They may be congenital defects that gradually increase in size or may form due to wear and tear. Fenestrations are usually seen near commissures, in the lunule above the line of closure. If they extend beyond the line of closure they

Table 1

Native Heart Valve Disease				
	Valve			
Lesions	**Aortic**	**Mitral**	**Tricuspid**	**Pulmonary**
Congenital	yes	very rare	yes*	yes**
Acquired	yes	yes	rare	rare
Chronic inflammation†	yes	yes	rare	very rare
Acute inflammation††	yes	yes	yes	yes**
Age-related	yes	yes	no	no

* In association with other changes; isolated valvular abnormality is rare.
** In pulmonary valve, congenital changes and infective endocarditis are common.
† Rheumatic process.
†† Infective endocarditis.

Artificial aortic valve

Figure 1.
Age-related Morphological Changes in the Aortic Valve

Healthy aortic valve

aorta

aortic valve

left ventricle

Aortic valve with thickened leaflets

Aortic valve changes and sequelae with aging:

- cusp sclerosis and thickening
- stiffening of cusps/ decreased mobility
- stenosis of orifice
- progressive left ventricular hypertrophy
- left ventricular decompensation
- left ventricular dilatation
- mitral valve incompetence

Figure 2. Three surgically excised aortic valve cusps (flow surface) from a 76-year-old male showing diffuse sclerosis and yellow areas of calcification (arrowheads). These changes lead to cusp thickening, "stiffening" and stenosis of the valve orifice to which the myocardium responds with circumferential ventricular hypertrophy.

may cause valve incompetence or regurgitation. The size of the aortic valve ring or annulus increases with advancing age.[14] Although rare, the aortic valve ring has been reported to be as large as the mitral valve in patients older than 90 years.[15]

Mitral Valve: Age-related Changes

In the MV, the closing edge (rough zone) of each leaflet is thicker than the rest of the valve and this is more pronounced in the anterior leaflet than in the posterior.[16] MV leaflets become less translucent with age and adipocytes and lipid deposits accumulate within the leaflet tissue, especially on the ventricular surface and in the zona spongiosa. Nodular thickening often can be seen along the lines of closure on both leaflets, likely due to repeated trauma caused by valve closure.[17] With increasing age, collagen deposition, degeneration, lipid accumulation and dystrophic calcification of the annulus is seen (Figure 4). Lambl's excrescences are increasingly found with advancing age and were reported in almost all subjects

over 60 years of age.[18] They are found on the atrial surface of the leaflets, usually along the line of closure.[6]

Mitral annular calcification (MAC) is considered a degenerative disease similar to aortic sclerosis or stenosis.[19] The prevalence of MAC increases with aging. Crescent-shaped calcific deposits of varying severity and significance can be seen at the basal end and in the annulus of the MV leaflets in about half of the older population, on echocardiography.[20] Any condition that increases the stress on the MV (e.g., hypertension, mitral valve prolapse) enhances this degenerative process. Increasingly, the basal part of the posterior mitral leaflet (PML) adheres to this annular calcific mass that bulges into the left ventricular cavity, immediately behind the PML.

Complications of MAC include calcific erosion of the PML, perforations of the PML, infective endocarditis and "liquefaction" necrosis of this calcific mass.[21] MAC can result in mitral regurgitation and/or mitral stenosis,[22] left atrial enlargement,[23] atrial fibrillation[23] and an increased incidence of thromboembolic phenomena. In the prospec-

tive Framingham Heart Study, MAC was found to be associated with stroke; this association was found to be independent of atrial fibrillation, congestive heart failure (CHF) and coronary heart disease.[24] The risk of stroke, embolic in two-thirds of cases, was found to double in the presence of MAC.[24] Other complications of MAC include complete heart block or other conduction defects because of extension of calcification from the mitral ring into the conduction system.[25] Other changes in the mitral annulus include annular dilatation (often seen in CHF and dilated cardiomyopathy).

Redundancy of the leaflet tissue, with increasing hooding of the MV leaflets (occurring due to increased closing pressures over the years) and MV incompetence, is seen in older patients.[6] This is due partly to shortening of the overall base to apex length of the left ventricle, causing the mitral valve chordae to become "redundant" and to appear longer, leading to mild mitral leaflet tissue prolapse.

Development of "atheroma" on the MV anterior leaflet is increasingly noticed with aging.[26,27] Lipid deposits can occur in both leaflets, and are found on the ventricular surface and sometimes can involve the chordae tendinae.[27]

Surgical Management of Damaged Heart Valves

Cardiac surgery may be required to replace aging or damaged heart

Figure 3. Histologic sections of three aortic valve cusps showing marked fibrosis (arrowheads) and large areas of nodular calcification (arrows).
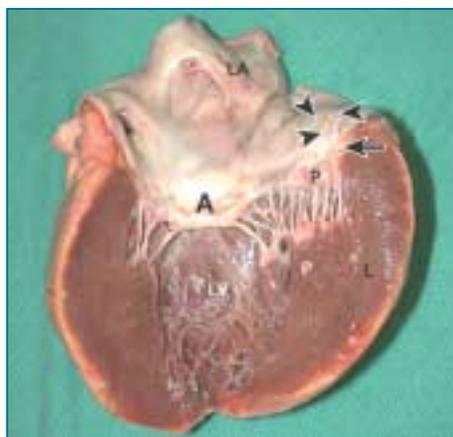
Figure 4. Left side of heart from a 78-year-old male shows fibrosis and thickening of the anterior mitral leaflet (A), fibrosis and thickening of the posterior leaflet (P) and a moderate degree of annular calcification (arrows). The posterior leaflet over a part of its extent had adhesed to the calcific annular mass.

valves. Although cardiac surgeons are very familiar with the location and distribution of calcium deposits in heart valves, removing these poses a number of problems. Multiple fragments of calcium may result during debridement of a calcified valve annulus. Great care must be taken to avoid embolization of these calcium fragments, which could otherwise cause a stroke. Calcium that extends deep into the annulus and surrounding tissues is particularly dangerous. If the calcium is not carefully removed, a new valve prosthesis may not seat well. On the other hand, radical debridement of the annulus can lead to aortoventricular or atrial ventricular separation which, if unrecognized, is usually fatal. Finally, older patients who require aortocoronary bypass surgery frequently have associated valvular sclerosis. Even though the main indication for surgery is the presence of coronary heart disease, there is often controversy about the best management of mildly sclerotic valves that are identified at the time of coronary bypass surgery. The surgeon must make a judgment about adding an unplanned valve replacement procedure to a planned aortocoronary bypass surgery. This has to be balanced against the likelihood that at some time in the future sclerotic valves eventually cause hemodynamically significant problems. This, in turn, may expose the patient to the risk of a re-operation, often in the face of functioning bypass grafts.

Conclusion

In this review, age-associated changes in cardiac valves have been summarized. Some of these, such as lipid insudation, may remain trivial morphological curiosities, while others, such as aortic valve calcification and mitral annular calcification, can lead to significant clinical consequences and often to heart valve replacement with one of the many excellent prosthetic heart valves available today.[28,29] Many other complications, such as thromboemboli and infective endocarditis, can occur on these diseased valves (Table 2). It is therefore essential to be aware of these changes, to order the appropriate investigations and to seek appropriate surgical intervention when required. ◆

No competing financial interests declared.

References

1. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. Circulation 2003;107:139-46.
2. Butany J, Ahluwalia MS. The morphology of the aging heart. Geriatrics Aging 2003;6(5):52-5.
3. Leask RL, Jain N, Butany J. Endothelium and valvular diseases of the heart. Microsc Res Tech 2003;60:129-37.
4. Thubrikar MJ, Heckman JL, Nolan SP. High speed cine-radiographic study of aortic valve leaflet motion. J Heart Valve Dis 1993;2:653-61.
5. McDonald PC, Wilson JE, McNeill S, et al. The challenge of defining normality for human mitral and aortic valves: geometrical and compositional analysis. Cardiovasc Pathol 2002;11:193-209.
6. Lester WA. Age-related cardiovascular changes. In: Silver MD, Gotlieb AI, Schoen FJ, editors. Cardiovascular pathology. New York: Churchill Livingstone, 2001: 54-68.
7. Lindroos M, Kupari M, Heikkila J, et al. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. J Am Coll Cardiol 1993;21: 1220-5.
8. 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.
9. Dare AJ, Veinot JP, Edwards WD, et al. New observations on the etiology of aortic valve disease: a surgical pathologic study of 236 cases from 1990. Hum Pathol 1993;24:1330-8.

Table 2		
Complications of Valvular Heart Disease		
Morphological Features	**Aortic Valve**	**Mitral Valve**
Cardiomegaly	yes	yes
Left ventricular hypertrophy	circumferential	late with mitral regurgitation
Left ventricle dilatation	late	late with mitral regurgitation
Congestive heart failure	yes	yes
Sudden death	aortic stenosis	yes
Infective endocarditis	yes	yes
Thrombosis	yes (usually minor)	left atrial
Cardiac rhythm changes	usually not seen	atrial fibrillation
Lambl's excrescences	yes	yes

10. Boone SA, Campagna M, Walley VM. Lambl's excrescences and papillary fibro-elastomas: are they different? Can J Cardiol 1992;8:372-6.

11. Rosnowski A, Wasiutynski A. [Elastic tissue in Lambl's excrescences]. Patol Pol 1965;16:223-34.

12. Hurle JM, Garcia-Martinez V, Sanchez-Quintana D. Morphologic characteristics and structure of surface excrescences (Lambl's excrescences) in the normal aortic valve. Am J Cardiol 1986;58:1223-7.

13. Christie GW, Barratt-Boyes BG. Mechanical properties of porcine pulmonary valve leaflets: how do they differ from aortic leaflets? Ann Thorac Surg 1995;60(Suppl):S195-9.

14. Krovetz LJ. Age-related changes in size of the aortic valve annulus in man. Am Heart J 1975;90:569-74.

15. Kitzman DW, Scholz DG, Hagen PT, et al. Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity): A quantitative anatomic study of 765 specimens from subjects 20 to 99 years old. Mayo Clin Proc 1988;63:137-46.

16. Sahasakul Y, Edwards WD, Naessens JM, et al. Age-related changes in aortic and mitral valve thickness: implications for two-dimensional echocardiography based on an autopsy study of 200 normal human hearts. Am J Cardiol 1988;62:424-30.

17. Schenk KE, Heinze G. Age-dependent changes of heart valves and heart size. Recent Adv Stud Cardiac Struct Metab 1975;10:617-24.

18. Magarey FR. On the mode of formation of Lambl's excrescences and their relation to chronic thickening of mitral valve. J Pathol 1949;61:203.

19. Roberts WC. The senile cardiac calcification syndrome. Am J Cardiol 1986;58:572-4.

20. Aronow WS, Ahn C, Kronzon I. Prevalence of echocardiographic findings in 554 men and in 1,243 women aged > 60 years in a long-term health care facility. Am J Cardiol 1997;79:379-80.

21. Namura M, Kanaya H, Ohka T. Spherical liquefaction necrosis of mitral annular calcification in a chronic dialysis patient—liquefaction necrosis of mitral annular calcification. Jpn Circ J 1992;56:866-70.

22. Labovitz AJ, Nelson JG, Windhorst DM, et al. Frequency of mitral valve dysfunction from mitral anular calcium as detected by Doppler echocardiography. Am J Cardiol 1985;55:133-7.

23. Nestico PF, Depace NL, Morganroth J, et al. Mitral annular calcification: clinical, pathophysiology, and echocardiographic review. Am Heart J 1984;107(5 Pt 1):989-96.

24. Benjamin EJ, Plehn JF, D'Agostino RB, et al. Mitral annular calcification and the risk of stroke in an elderly cohort. N Engl J Med 1992;327:374-9.

25. Mellino M, Salcedo EE, Lever HM, et al. Echographic-quantified severity of mitral anulus calcification: prognostic correlation to related hemodynamic, valvular, rhythm, and conduction abnormalities. Am Heart J 1982;103:222-5.

26. Pomerance A. Atheroma of the mitral valve. J Atheroscler Res 1967;7:151-60.

27. Pomerance A. Ageing changes in human heart valves. Br Heart J 1967;29:222-31.

28. Butany J, Ahluwalia MS, Munroe C, et al. Mechanical heart valve prostheses. Identification and evaluation. Cardiovasc Pathol 2003;12:1-22.

29. Butany J, Fayet C, Ahluwalia MS, et al. Biological replacement heart valves. Identification and evaluation. Cardiovasc Pathol 2003;12:119-39.