REVIEW

Clinical significance of the bicuspid aortic valve

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The association of bicuspid aortic valve with aortic stenosis, aortic regurgitation, and infective endocarditis has been known for almost 150 years and with dissection of the aorta for 75 years.[1] These complications are mentioned only briefly in cardiology textbooks[3] and a standard work on medical insurance underwriting[4] implies that it is usually a benign lesion: when diagnosed at routine medical examination and if the valve is functionally normal, insurance is offered at ordinary rates. The authors also state "If there is no stenosis by age 20 years (defined as a peak gradient of less than 40 mm Hg) and only trivial insufficiency, there is an excellent chance that significant haemodynamic change will not develop before age 70." However, on the basis of published reports by this age the majority of patients will have died or developed serious symptoms requiring surgical intervention. This review summarises the major studies that provide information on the incidence, pathology, and natural history of the bicuspid aortic valve. Clinical diagnosis of this condition was unsatisfactory before the widespread use of cross sectional echocardiography approximately 15 years ago. Most of the information in this paper therefore comes from large necropsy series and from reports on patients who have undergone aortic valve replacement. It has to be accepted that conclusions based on these reports may be inaccurate, because of non-uniformity of diagnostic criteria and varying age range, source/selection of patients studied, and study objectives.

A small percentage of malfunctioning congenitally abnormal aortic valves are unicuspid or unicommissural,[5] but as most reports do not distinguish this from bicuspid aortic valve the abbreviation "bicuspid aortic valve" will used to include both types of valve unless stated otherwise.

Anatomy and pathology

Early pathology studies[1 6] documented three characteristics of bicuspid aortic valve: inequality of cusp size, the presence of a central raphé (ridge), usually in the centre of the larger of the two cusps, and smooth cusp margins even in diseased valves. Subsequently bicuspid aortic valve was differentiated from an initially tricuspid valve,[7] two cusps of which had become fused as a result of rheumatic or other inflammatory processes. Other necropsy series have confirmed, elaborated, and refined these characteristics,[5 8] and have also described the features of degenerative valve disease, the third major aetiological group:

- Calcification increases with age and is largely confined to the raphé (which does not extend to the commissure) and base of the cusps, as it is in degenerative valves. It is more diffuse in postinflammatory disease. Calcification is conspicuous in virtually all adults with a severely stenosed bicuspid aortic valve but is uncommon in isolated aortic regurgitation.[9 10]
- Only in postinflammatory valves are cusp margins severely distorted and fused, resulting in the valve often having a central triradiate orifice.
- In virtually all cases, the aetiology of aortic stenosis can be determined by naked eye examination of the valve.[8]
- Where doubt exists, histological examination shows no valve tissue in the raphé of a congenital bicuspid aortic valve, whereas postinflammatory valves show evidence of previous valvitis.[7 8] These criteria have been consistently applied in subsequent pathological studies, thus providing a high level of consistency to the identification of those valves which are congenitally bicuspid.

The orientation of the valve cusps, anteroposterior or left-right in approximately equal numbers,[5 7] may have some bearing on complication rates. The coronary arteries usually arise in front of the anterior cusp[5] which is the cusp with the raphé. Stenosis usually develops in bicuspid valves containing no redundant cusp tissue, and incompetence often in valves in which redundancy and prolapse are prominent.[1] This had been confirmed by more recent studies.[9] Unicommissural aortic valves are of two types, both of which are dome shaped.[10] One has no commissure, and the other a single commissure which only partially divides the cusps. Most have some evidence of two raphés, suggesting that they may have been tricuspid at an early stage of development.

Many vascular abnormalities have been associated with bicuspid aortic valve but only two are of common practical importance in adult cardiology.

First, a bicuspid aortic valve occurs in 20–85% of cases of coarctation of the aorta.[11 12] The presence of an untreated, inadequately treated, or recurrent coarctation increases the likelihood of developing aortic stenosis, aortic regurgitation, or dissection of the aorta (see below). Bicuspid aortic valve has also been

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reported in 27% of 52 cases of interrupted aortic arch,[13] suggesting a common developmental pathogenesis for congenital abnormalities of the aorta and aortic valve.

Second, 90% of patients with a normal (tricuspid) aortic valve have right coronary artery dominance, that is the right coronary artery supplies the crux of the heart, and the left main stem averages 10 mm in length. With a bicuspid aortic valve, left dominance is more common (between 29% and 56.8%[14 15]) and in 90% of such cases the left main stem is less than 5 mm in length.[16] Failure to recognise these associations may result in inadequate myocardial preservation at the time of aortic valve replacement and an increased risk of perioperative myocardial infarction.[16]

Clinical diagnosis

A clinical diagnosis of bicuspid aortic valve based purely on the presence of an aortic ejection click, with or without an ejection systolic murmur, lacks predictive accuracy as it may be heard in tricuspid aortic valve stenosis, or in aortic dilatation from any cause, and is absent when the valve cusps are rigid.[17 18] The reliability of diagnosis has been significantly improved by the introduction of cross sectional and Doppler echocardiography—a specificity of 96%, a sensitivity of 78%, and a predictive accuracy 93% have been reported.[19] Diagnosis is based on the demonstration of two cusps and two commissures during short axis visualisation. Supportive features include cusp redundancy and eccentric valve closure, and a single coaption line between the cusps during diastole. However, the usually bicuspid nature of a valve may be obscured by severe fibrosis or calcification and false negative results may be produced by a prominent raphé (which can give the appearance of a third coaption line); a false positive diagnosis may occur when one coaption line of a tricuspid valve is unclear.

The incidence of bicuspid aortic valve and complications

Four necropsy series[5 6 8 20] provide the only basis we have for estimating the incidence of bicuspid aortic valve in the adult population, as diagnosis by auscultation is insufficiently accurate and no relevant echocardiographic study has been published. The incidence of normally functioning bicuspid aortic valves is 0.6% to 0.9%.[5 6 21] This is probably the minority of bicuspid aortic valves, as only 15–28%[5 6] are reported as normal in necropsy series. The incidence of the various fatal complications in cohorts of patients with bicuspid aortic valve has been published (although many of these patients would nowadays survive following surgery): aortic stenosis, 15%[21] to 71%[5]; aortic regurgitation, 1.5%[5] to 3%[21]; infective endocarditis, 9.5%[5] to 40%[18]; and aortic dissection, 5%.[18] The wide range reported for aortic stenosis and infective endocarditis is explained by their age related incidence. Aortic stenosis occurs predominantly in middle age, and the lower figure is derived from a young population. Conversely, infective endocarditis is a complication of the young and the upper figure is from this age group. In the light of these figures the statement that "this is a very common defect, being found once in every 100 to 200 autopsies"[7] is reasonable and provides a valid basis for the generally accepted figure of an overall incidence of 1–2%.

Because of case selection, some of the figures quoted will have overestimated the incidence of complications but they are the only relevant published data. They indicate that, at a conservative estimate, one third and possibly the majority of patients with bicuspid aortic valve will develop serious complications.

Specific complications

AORTIC STENOSIS

Four reports define the clinical and pathological characteristics of bicuspid aortic valve stenosis, three based on necropsy data[5 8 22] and one on surgical specimens.[23] There is broad agreement that approximately 50% of adults with severe aortic stenosis have a bicuspid aortic valve. Severely stenosed bicuspid aortic valves are very rigid because of fibrosis and heavy calcification, but are not narrowed.[8 20 23] Both calcification and fibrosis (and thus deteriorating valve function) are age related.[23] In a clinical series a third of initially asymptomatic patients with bicuspid aortic valve deteriorated during a mean period of 10.9 years.[24] Echocardiographic studies[25 26] have shown that sclerosis of the valve begins in the second decade, and calcification is increasingly prominent from the fourth decade onwards; the average aortic valve gradient increases concurrently by 18 mm Hg per decade. Stenosis progressed more rapidly (27 mm Hg per decade) if the cusps were asymmetrical in size and in the anteroposterior location.[26] In a second report[27] of 31 patients with an initially functionally normal valve (mean gradient < 25 mm Hg), four had an undefined increase in gradient and three required aortic valve surgery during a median follow up time of 21 months. High serum low density lipoprotein cholesterol, high serum lipoprotein (a), and smoking are independent risk factors for aortic stenosis and presumably contribute to the age related deterioration.[28]

Bicuspid aortic valve is the commonest aetiology of aortic stenosis between the ages of 60 and 75 years (59% of cases); it was also the cause in 40% of those aged under 60 years and 32% of those aged more than 75 years.[8] The relation between age and bicuspid aortic valve stenosis was also shown in another necropsy series[26]: it occurred in 15% of individuals aged 20–29 years, 55% aged 40–49 years, and 73% aged over 70 years. Likewise in a surgical series it occurred in 14% of patients aged 40–49 years, 30% aged 50–59 years, and 35% aged 60–69 years.[23]

Patients with aortic stenosis secondary to a bicuspid aortic valve require aortic valve replacement five years before those with a tricuspid aortic valve (59 (9) years *v* 64 (9) years (mean (SD)).[25] The unicommissural aortic valve deteriorates more rapidly than the bicuspid aortic valve[10]: the average age at death or aortic valve replacement in 21 patients, 13%

of a cohort of congenitally abnormal valves who had survived childhood, was 44 years (range 16 to 62).

Although most cases of aortic stenosis occur in adults, serious problems may arise in infancy. Bicuspid or unicommissural aortic valves are responsible for 80–95% of cases of aortic valve disease detected in early life.[29 30] Aortic stenosis in infancy may be rapidly progressive[31] but deterioration over a period of years is more usual. In a study of 239 patients born with aortic stenosis[32] (excluding "mild stenosis" and presumably also normally functioning bicuspid aortic valves), 95% of those with an initial gradient of 41–80 mm Hg and 30% with a lesser gradient became symptomatic after a mean of 9.2 years. After surgery or valvoplasty in childhood, 26% required further intervention after approximately 10 years[33] and 39% after 18 years.[34] It is likely that most patients who are symptomatic in childhood will require a second operation before the age of 40.

AORTIC REGURGITATION

The aetiology of aortic regurgitation in patients with a bicuspid aortic valve is more complex than that of aortic stenosis. It may occur in isolation,[35] usually as a result of prolapse of the larger of unequally sized cusps,[1] but also in association with aortic root dilatation,[36 37] coarctation of the aorta,[38] or infective endocarditis.[6]

Regurgitation of a bicuspid (or tricuspid) aortic valve may cause diffuse dilatation of the ascending aorta. The reverse, aortic regurgitation secondary to root dilatation, also occurs. This results specifically from disruption or dissolution of elastic tissue within the upper aortic ring (sinotubular junction), as this structure provides the main support for the valve cusps.[36] When this occurs in association with a bicuspid aortic valve the cusps are usually of equal size. Approximately half of young adults with a bicuspid aortic valve have aortic root dilatation[39] and are thus potential candidates for resultant aortic regurgitation.

As an isolated phenomenon a bicuspid aortic valve is a relatively uncommon cause of severe aortic regurgitation (between 1.5%[35] and 10.7%[37]), but the incidence found in various studies increases significantly if cases with associated pathology are added—from 1.5% to 10%,[5] from 8% to 21%,[35] and from 3% to 40%.[20] Because of the declining incidence of rheumatic heart disease, it appears that bicuspid aortic valve may be associated, directly or indirectly, with the majority of cases of severe aortic regurgitation.[21 36]

Probably because of its association with coarctation of the aorta, and especially with infective endocarditis, patients with aortic regurgitation die or have surgical intervention at an earlier age than those with aortic stenosis: in necropsy series, 35 years[21] *v* 46 years[5]; in surgical series, 48 years[9] *v* 59 years.[23]

INFECTIVE ENDOCARDITIS

Between 10% and 30% of bicuspid aortic valves develop infective endocarditis,[6 7 9 26 40 41] and 25% cases of infective endocarditis develop on a bicuspid aortic valve.[11 15] These figures are based on selected case series and the true incidence is likely to be less. Bicuspid aortic valve as a substrate for infective endocarditis is predominantly a complication in children and young adults. It was the cause of death in 55% of patients aged under 30 years but in only 13% of those aged over 70 years.[21] In infancy and childhood, four lesions—tetralogy of Fallot, ventricular septal defect, bicuspid aortic valve, and mitral valve prolapse—are the substrate for 80–90% of cases.[42–44] In children bicuspid aortic valve may be second only to tetralogy of Fallot in order of importance,[42] and in young adults it is comparable to mitral valve prolapse. Infective endocarditis is responsible for between 43%[9] and 60%[35] of cases of severe aortic regurgitation in patients with bicuspid aortic valve, the result of cusp perforation in the majority of cases.[16] The bicuspid aortic valve is the usual site of vegetations in patients with coarctation of the aorta who have infective endocarditis.

AORTIC DISSECTION

Dissection of the aorta was the cause of death in between 19%[38] and 23%[45] of cases of coarctation of the aorta in the presurgical era, but in 50% when there was a coexisting bicuspid aortic valve.[38] A bicuspid aortic valve is present in 1%[46] to 13%[2] of unselected cases of aortic dissection. In three other large series, the figure was approximately 7%,[47–49] but in 15% of proximal dissections.[49] The presence of a bicuspid aortic valve increases the risk of dissection ninefold (6.14% *v* 0.67%), and this rises to 18-fold if there is a unicommissural aortic valve (12.5% *v* 0.67%).[49] Aortic dissection occurs at a younger age in patients with a bicuspid aortic valve (54 *v* 62 years).[47] In one study it occurred a decade earlier with bicuspid than with tricuspid aortic valve, and two decades earlier with a unicommissural aortic valve.[50] Twenty four per cent of a group of patients who died from aortic dissection before the age of 40 had a bicuspid aortic valve,[51] and 13% of (young) military personnel.[2] Most patients with aortic dissection have hypertension,[46–48 50] which explains the high incidence of dissection when bicuspid aortic valve and coarctation coexist. Aortic dissection usually occurs in the presence of a normally functioning bicuspid aortic valve[49 50] but it may also occur with stenosed bicuspid aortic valves[47] and following aortic valve replacement, at a site remote from surgical access to the valve.[52] Aortic root dilatation, a precursor of dissection, occurs in 50–60% of patients with a normally functioning bicuspid aortic valve[39 53] and has been reported as often with normally functioning bicuspid aortic valves as in patients with associated mild aortic regurgitation or mild to moderate aortic stenosis.[54]

The reason for the high incidence of aortic dissection in patients with bicuspid aortic valve is unclear. Although the susceptibility of patients with Marfan's syndrome to develop aortic dissection has been attributed to cystic medial necrosis, current opinion is that the histological differences between overtly abnormal aortas and the normal aging process are only

quantitative. Patients with more extreme changes are now said to have "genetically inferior" aortas which are prone to dilate in response to the effects of normal (and abnormal) haemodynamic stresses.[55] Presumably the same applies to people with bicuspid aortic valves. Even before these observations, the reported incidence of medial necrosis in patients with bicuspid aortic valves and aortic dissection varied widely.[2 47 50]

Approximately 40% of patients with Marfan's syndrome have aortic dissection, but only 5% of patients with a bicuspid aortic valve. However, because the prevalence of bicuspid aortic valve is much higher (1–2% *v* 0.01%), it is the more common aetiology.[48 50]

Conclusions

Although some of the data reviewed may overestimate the incidence of complications, the patterns of valve involvement and age related complication rates are probably correct. Complications requiring intervention occur at some stage in many patients with bicuspid aortic valve. In childhood and early adult life, critical aortic stenosis and infective endocarditis are the commonest problems. From early adulthood to early middle age, aortic regurgitation—especially secondary to infective endocarditis—and aortic dissection are the major causes of morbidity; thereafter aortic stenosis is increasingly common until the 70s. Bicuspid aortic valve is the commonest aetiology of aortic stenosis and perhaps also of aortic regurgitation. It is a major substrate for infective endocarditis and is associated with more cases of aortic dissection than Marfan's syndrome. Aortic root dilatation is common in bicuspid aortic valve, even when the valve is haemodynamically normal, and consequently aortic dissection usually occurs in previously asymptomatic patients. All patients should therefore be regularly reviewed to identify progressive root dilatation with a view to preempting dissection by prophylactic surgery. Likewise hypertension should be meticulously controlled. Smoking should be discouraged and control of hypercholesterolaemia considered, in view of the impact of these factors on the development of aortic stenosis. Because of familial clustering[56] it might also be appropriate to screen first degree relatives.

Excluding bicuspid aortic valve, the incidence of all congenital cardiac defects is approximately 0.8% of live birth.[5 57] If it is accepted that the incidence of bicuspid aortic valve is 1–2% and that serious complications occur in at least one third of cases, this condition may be responsible for more deaths and morbidity than the combined effects of all other congenital heart defects.

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