Editorial

The Bicuspid Aortic Valve
Adverse Outcomes From Infancy to Old Age

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The population frequency of a bicuspid aortic valve is ~0.9% to 1.36%, with a 2:1 male:female ratio. It is likely that the presence of a bicuspid aortic valve has a genetic basis, with the pattern of transmission in some families suggesting an autosomal dominant pattern of inheritance. Epidemiological data from the Baltimore-Washington Infant Study demonstrated the familial clustering of left heart obstructive lesions (including coarctation of the aorta, aortic valve stenosis, and hypoplastic left heart syndrome). More recently, the increased risk of identifying a bicuspid aortic valve in the parent or sibling of the proband with any form of left heart obstructive lesion was described. By inference, this also suggests the potential identification of a congenitally malformed aortic valve in the presence a family member with a more complex congenital heart lesion. In addition, a bicuspid aortic valve is present in >50% of patients with aortic coarctation and in 10% to 12% of women with Turner syndrome. The specific genetic locus and protein abnormality in patients with a bicuspid aortic valve have not yet been identified, however.

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The tissue abnormality in patients with a bicuspid aortic valve is not confined to the valve leaflets; these patients are at increased risk of aortic aneurysm and dissection. At the tissue level, the aorta shows cystic medial necrosis, loss of elastic fibers, increased apoptosis, and altered smooth muscle cell alignment. When compared with patients with a trileaflet valve, patients with a bicuspid valve have larger aortic root dimensions and an increased rate of aortic dilation over time, with the degree of aortic dilation independent of valve hemodynamics. The risk of aortic dissection in patients with a bicuspid valve is 5 to 9 times higher than in the general population, although some investigators hypothesize that this increased risk is limited to a subset of bicuspid valve patients. Even after valve replacement, surgery for a bicuspid valve is a strong risk factor for subsequent aortic dissection. The association of bicuspid aortic valve with aortic aneurysm and dissection suggests the possibility that a bicuspid valve, at least in some patients, is only the most identifiable manifestation of a systemic connective tissue disorder.

Most patients with a bicuspid aortic valve are unaware of the diagnosis until late in life because symptoms and physical findings often are absent for many years. Unless echocardiography is requested for other indications, the diagnosis often is made only at the time of an adverse cardiovascular outcome. On echocardiography, aortic valve anatomy can be reliably determined in a short-axis view, although care is needed to visualize the opening of all 3 leaflets in systole. Diastolic images can be misleading because the raphe in the larger leaflet of a bicuspid valve may simulate a trileaflet valve in the closed position (Figure). If images are suboptimal, then transesophageal imaging may be helpful for the accurate evaluation of valve anatomy.

Nearly all patients with a bicuspid aortic valve will require valve surgery during their lifetime. The clinical outcomes in patients with a bicuspid valve include significant valve regurgitation, endocarditis, aortic aneurysm and dissection, and in the majority of these patients, severe stenosis resulting from superimposed calcific changes. A small subset of patients with unicuspid or severely deformed bicuspid valves require intervention in childhood or adolescence. The vast majority of “hemodynamically significant” aortic valve disease in infancy and young children results from aortic stenosis of the bicuspid valve. In the current era, these children receive intervention via balloon aortic valvuloplasty rather than via surgery. Later in childhood and into adolescence, identification of aortic regurgitation is more frequent, often slowly evolving in the patient who previously received intervention in the cardiac catheterization laboratory. These children may eventually require valve repair or replacement, the latter group divided among the allograft, the autograft (Ross procedure), and the mechanical valve.

Another important issue in any discussion of the bicuspid aortic valve is that of the relative risk for the development of endocarditis. Although the population risk of endocarditis in the presence of an isolated, nonobstructive or regurgitant aortic valve may be as high as 3%, the exact prevalence remains controversial. Outcomes in children with an infected bicuspid aortic valve are poorer than they are in children with other types of congenital heart disease.

About 15% to 20% of bicuspid valve patients have incomplete valve closure and present at age 20 to 40 years with an asymptomatic diastolic murmur, cardiomegaly, or symptoms resulting from aortic regurgitation. Once significant regurgitation is present, the natural history is determined by the left ventricular response to chronic volume overload. In these patients, aortic valve surgery often is needed because of the
onset of symptoms at the rate of \( \approx 6\% \) per year or progressive left ventricular dilation in 3\% to 4\% per year.\(^{17,18} \) Some of these patients remain asymptomatic with normal left ventricular function, however, and they will subsequently develop valve stenosis.

The majority of patients with a bicuspid valve have relatively normal valve function and remain undiagnosed until late in adulthood, when stenosis develops because of superimposed leaflet calcification. The cellular and molecular mechanisms involved in the calcification of a bicuspid aortic valve appear to be similar to the process in a trileaflet valve.\(^{19} \) Aortic leaflet calcification starts as a focal area on the aortic side of the leaflet with subendothelial accumulation of lipoproteins and an inflammatory cell infiltrate. There is lipoprotein oxidation with infiltration of macrophages and T lymphocytes and local production of proteins associated with inflammation and tissue calcification, including bone matrix proteins such as osteopontin and osteocalcin, tenascin-C, upregulation of matrix metalloproteinases, and active tissue angiotensin-converting enzyme. Microscopic calcification in the subendothelium and adjacent fibrosa is seen early in the disease process, with marked calcification and even cartilage and bone formation as the disease progresses. The accumulation of calcium and lipid along with tissue fibrosis eventually leads to increased leaflet stiffness with a reduction in systolic valve opening. When patients present with symptoms resulting from valve obstruction, the treatment is valve replacement.

In this issue of *Circulation*, Roberts and Ko\(^{20} \) report that the prevalence of bicuspid aortic valve was 53\% in a consecutive series of 933 patients undergoing valve replacement for isolated aortic stenosis. In addition, 4\% had unicommissural valves. The authors intentionally excluded patients with a previous aortic valvulotomy; thus the prevalence of congenitally malformed aortic valves may be underestimated. Although we have long recognized that the 3 most common causes of aortic stenosis are a bicuspid valve, rheumatic disease, and calcification of a trileaflet valve, previous reports of the prevalence of a bicuspid valve were based on surgical series that likely included patients with rheumatic disease. In addition, both echocardiographic and surgical evaluation of valve anatomy can be misleading unless care is taken to distinguish a congenital raphe from inflammatory commissural fusion. The study by Roberts and Ko is the first that was restricted to nonrheumatic aortic stenosis with rigorous examination of the pathology of the explanted valve leaflets.

The study demonstrates a marked difference in the age distribution at the time of valve surgery, according to valve anatomy. Only 7\% of the total valve surgeries were performed in patients \( < 50 \) years old; of these patients, about one third had a unicuspid valve and two thirds had a bicuspid valve. About 40\% of valve surgeries were performed when the patient was between 50 and 70 years old, with about two thirds of these patients having a bicuspid valve and one third having a trileaflet valve, and rare cases having a unicuspid valve. More than 50\% of valve surgeries were performed in patients \( > 70 \) years old, with \( \approx 60\% \) of these patients having a trileaflet valve and 40\% having a bicuspid valve. Thus, these data demonstrate that increasing calcification results in severe valve obstruction before an individual is 50 years old for most unicuspid valves and before 80 years old for most bicuspid valves, whereas stenosis of a trileaflet valve may occur as early as 50 years old but typically presents in the 70- to 90-years-old range. This pattern of presentation is consistent with the hypothesis that abnormal mechanical and shear stresses, as expected with unicuspid and bicuspid valves, are associated with earlier leaflet calcification.

These data have important clinical implications. The \( \approx 50\% \) incidence of a congenitally malformed aortic valve in adults requiring aortic valve replacement suggests a significant issue of which both the public and the health professional should be aware. Clearly, an effective therapy to
prevent calcific aortic valve stenosis—focusing on patients with a bicuspid aortic valve—would have a major impact on the number of older adults requiring valve replacement. The study by Roberts and Ko study highlights another issue, that of the ongoing concern about the risk of developing aortic dilation and dissection in the presence of a bicuspid aortic valve.

Dr Roberts truly is a student of the aortic valve, and this study builds on his innumerable contributions to our understanding of aortic valve disease. As with Dr Roberts’s other pioneering articles, it is hoped that the present data will stimulate other investigators to find answers to the many questions remaining about the bicuspid aortic valve: What is the genetic basis of a bicuspid aortic valve? Is this a single phenotype or have we included more than one condition in the designation “bicuspid aortic valve”? Should relatives of a patient with a bicuspid valve undergo screening for valve disease? Why do some patients develop regurgitation and others stenosis? What recommendations should we make to a young patient with a bicuspid aortic valve? Can we prevent calcific stenosis of a bicuspid valve? Which patients are at risk of aortic dissection?

Although definitive answers to these questions may take years, a prudent approach to the patient with a normally functioning bicuspid valve is to educate the patient about the expected long-term prognosis, emphasize dental hygiene and endocarditis prophylaxis, evaluate and treat standard cardiovascular risk factors on the basis of evidence-based guidelines, and follow valve function with periodic echocardiography. When regurgitation or stenosis is detected, guidelines for evaluation and treatment of those conditions should be followed. Given the increased risk of identifying a bicuspid aortic valve in first-degree relatives having the same diagnosis, screening of this at-risk population should be considered. Echocardiographers should take particular care to identify bicuspid aortic valves in young patients because of the important long-term clinical consequences of this condition.

References

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