



Diagnosis and Treatment of Bicuspid Aortic Valve Disease

REVIEW

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ABSTRACT

Bicuspid aortic valve disease is the most common congenital cardiac anomaly. The prevalence in the general population is between 0.46% and 1.37%. There is significantly high cardiac morbidity associated with bicuspid aortic valve disease, predominantly due to progressive valve dysfunction (stenosis or regurgitation) that requires surgical intervention for symptom relief or prevention of left ventricular dysfunction, or less commonly, for complications of endocarditis. Bicuspid aortic valve disease is clinically important not only because of valve disease but also because of its association with many vascular abnormalities, such as aortic dilatation and aortic coarctation.

Keywords: Bicuspid aortic valve, aorta aneurysm, diagnosis and therapy

INTRODUCTION

Bicuspid aortic valve (BAV) is a hereditary pathology and the most common congenital cardiac anomaly; its prevalence in the general population is reported to be between 0.46% and 1.37%. Its familial recurrence rate is 35%. This congenital anomaly was first identified by Sir William Osler (1-3). Normally, aortic valve comprises three equal-sized valvular leaflets (or cusps) and has three coaptation lines where these three valves meet. In congenital BAV, however, there are usually two different-sized functional valvular leaflets and one coaptation line. In approximately half of the cases, there is a short raphé. Valvular stenosis or partially fused leaflets that develop due to inflammatory process as a secondary response to rheumatic fever are not evaluated in this group. BAV is not only a valvular disease but also an aortic disease that is particularly characterized by the defect on the medial layer of the ascending aorta. The cooccurrence of BAV together with the other left-sided obstructive heart lesions, such as aortic coarctation or interrupted aortic arch, indicates that it is a developmental defect (4).

Morphology and Pathophysiology

In BAV, the leaflets are usually not the same size. There is a false commissure or raphé on the larger leaflet. In histological studies, there is no valvular tissue on the raphé (5, 6). Generally, the left and right coronary valves fuse together and form the larger leaflet. The non-coronary valve becomes the other leaflet. In BAV, the free edges are straighter and less moving and their calcification increases with age. They fuse with the raphé and leaflets base to form the degenerative leaflet. The aortic sinus and ascending aorta are wider in patients with two cusps than in patients with three cusps. Abnormal aortic elasticity causes progressive aortic dilatation and dissection. Dilatation is usually progressive with an increment between 0.2-1.2 cm. Its increase rate is higher in the elderly population, hypertension (HT) patients, accompanying valvular disease patients, and males (7).

One-third of the BAV cases can develop complications throughout their lives; therefore, it must be observed and followed closely (8). Morphology of the valve can be an indicator of stenosis, dysfunction, or both. Stenosis or dysfunction is usually not observed in children with fused right and left cusps. Aortic coarctation is more often observed in such children. Pathological changes such as stenosis and dysfunction are more often observed in children where right and non-coronary cusps fused.

Incidence

Bicuspid aortic valve is a common congenital cardiac anomaly. The prevalence in the general population is between 0.9% and 2%. Its prevalence in patients over 15-year-old who have aortic stenosis is 54% (9). Many researchers have questioned the genetics of BAV (10). Generally, a genetic multifactorial inheritance and an autosomal dominant condition are observed. Emanuel et al. (11) determined the minimum familial incidence of bicuspid aorta to be 14.6%. Latest studies have shown that the prevalence in the immediate family of an individual with BAV is 9.1%. This is quite high compared to the prevalence in the general population (1%-2%). It is twice as common in males as it is in females. It has the same prevalence for males and females, who have a BAV history in the family (12).

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Bicuspid aortic valve can develop at all ages and may be coincidentally spotted during the autopsy. It may be asymptomatic and identified coincidentally during an echocardiographic examination. It can be responsible for severe aortic stenosis at infancy. BAV is usually diagnosed after infective endocarditis is developed along with systemic embolization. Stenosis in BAV generally starts after 20 years of age and the stenosis at the valve develops as a result of progressive sclerosis and calcification (13). High serum cholesterol levels are shown to accelerate the sclerosis in congenital BAV patients. In children with BAV exhibiting pathological changes, dysfunction is observed more often than is stenosis.

Anamnesis

Patients with BAV may be completely asymptomatic. However, some BAV patients (30%) develop complications (14). If a symptom develops, it is usually due to aortic stenosis, dysfunction, or both. There is usually a serious aortic stenosis, which is caused by congenital BAV behind a severe congestive heart failure, at the early infancy. This critical form is often associated with unicommissural valve.

Bicuspid aorta generally functions well in coexisting cases leading to left heart obstruction, such as aorta coarctation and interrupted aortic arch. Symptoms develop in accordance with the accompanying pathology.

Associated syndromes:

- Coarctation or interrupted aortic arch (In 50% of these lesions, BAV is present)
- Williams syndrome (In 11.6% of supravalvular aortic stenosis cases, BAV is present)
- Patent ductus arteriosus
- In 30% of patients with Turner syndrome, BAV is present

Diagnosis

Bicuspid aortic valve diagnosis is highly important for clinicians in cases with aortic valve disease. Transthoracic echocardiography (TTE) is the gold standard for its diagnosis (Figure 1a). The diagnosis depends on finding two leaflets and two commissures on short-axis cardiac images. Features such as eccentric valve closure and one coaptation line support the diagnosis. With an appropriate TTE, the sensitivity of diagnosing bicuspid aorta is 78% and the specificity is 96%. In approximately 25% of the cases, the morphology of the aortic valve cannot be detected with TTE. In their latest studies, Tamborini et al. (15) showed that sensitivity and specificity of TTE increased when more windows are used. When patients' TTE image quality is limited, transesophageal echocardiography helps for diagnosis and evaluation of the aorta (Figure 1b). Magnetic resonance imaging (MRI) is better than echocardiography in detecting the morphology of the aortic valve (96% and 73%). MRI is more sensitive than echocardiography in BAV diagnosis (0.75 and 0.55) (15).

Prognosis and complications

Congenital BAV can be asymptomatic for life time, or calcification and stenosis may develop progressively. BAV is the most common cause of isotonic aortic stenosis. In two-third of non-rheumatic aortic stenosis patients, bicuspid aorta can be observed. BAV with severe stenosis are very rigid due to fibrosis and severe calcification and calcification fibrosis progresses with age. In most patients, abnormal valvular calcification advances until the patient is 20 years

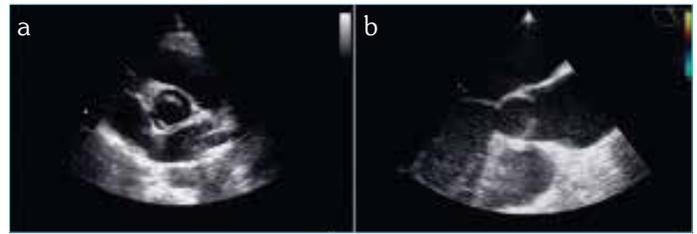


Figure 1. (a) Parasternal short-axis image of bicuspid aortic valve. (b) Transesophageal long-axis image of abnormal systolic dilatation

old. In their 30s, calcification can be detected. Progress of stenosis is quite rapid. High low density lipoprotein and lipoprotein a levels and smoking are independent risk factors for aortic stenosis, which clinically deteriorates with age. In particular, if the leaflets are asymmetrical and have an anteroposterior location, development of the stenosis is faster. The need for surgical intervention is five years earlier for patients with aortic stenosis developing secondary to bicuspid aorta than normal cases with three cusps.

The incidence for aortic insufficiency amongst BAV patients is 1.5%-3%. It usually develops due to the prolapsus of the wider cusp. It can also be associated with aortic root dilatation, aortic coarctation, and infective endocarditis. Pachulski et al. (16) observed that, in BAV patients, aortic root dilatation is significantly high, even when there is aortic stenosis. Aortic root dilates with the dissociation of the elastic tissue on the aortic valve and aortic insufficiency develops. In the 43%-60% of the BAV cases with severe aortic stenosis, secondary infective endocarditis is detected. Infective endocarditis is a well-known complication of bicuspid aorta. Its frequency is found to be between 7% and 25% in autopsy series. It usually develops during the 4th or 5th decade of life. In majority of the cases, surgical intervention is required and the mortality rate is approximately 9%. Prevalence of bicuspid aorta endocarditis is higher in young people and its incidence is higher in males. Average age of incidence is between 38 and 53 years. In three-fourth of natural valve endocarditis cases, the responsible agents are *Staphylococcus* and *Streptococcus*. Heart failure and valvular or myocardial abscess are the common complications. Latest studies show that 25%-54% of the infected aortic valves are bicuspid. BAV is found in 13% of the aortic dissection cases. Aortic dissection develops nine times more often in BAV patients compared with that in general population. Aortic dissection can be observed on the normal cusp and even in the patients who have undergone aortic valve replacement surgery because of bicuspid aortic stenosis. Smooth muscle cell apoptosis is detected on the ascending aorta premature medial layer that forms in BAV, and the prevalence of aortic dissection is found to be higher amongst these patients.

Medical treatment

There is a lot of evidence that show valve calcification develops secondary to inflammation, lipid accumulation, and extracellular bone matrix protein accumulation. Several retrospective studies claim that statin treatment prevents aortic valve calcification (17). The treatment of risk factors, such as smoking and hyperlipidemia, should be in the focus before finalizing randomized prospective studies. BAV patients, even those with mild aortic dilatation, should avoid isometric endurance exercises and competitive sports. Physi-

cally less demanding isokinetic exercises could be allowed to prevent obesity and hypertension. In asymptomatic patients with mild or moderate aortic dilatation, aggressive blood pressure control is necessary. In particular, in Marfan syndrome patients, β -blocker treatment hinders the slow development of the disease (18). However, there is no finding demonstrating that prophylactic β -blocker treatment prevents the aortic dilatation in BAV patients.

The presence of BAV is known to induce endocarditis susceptibility. A study shows that BAV is found in 7%-25% of endocarditis cases, with a significantly high mortality rate (9%) amongst the patients who require surgical intervention (19). Therefore, maintaining oral hygiene and prophylactic antibiotic treatment appear necessary.

Surgical treatment

There are some matters to be considered for an appropriate surgical treatment of BAV patients. First, majority of the patients are young when the surgery is planned. Therefore, because of the high life expectancy of these patients, valve-related morbidity risk will increase cumulatively, although the valve thrombosis, thromboembolism, and hemorrhage risks are low after the mechanical valve implantation. Second, the morphology of BAV, size of the ascending aorta, and degree and rate of aortic dilatation require a personalized surgical approach. Finally, accompanying comorbidities should be considered in the decision stage for surgery.

The repairment of the aortic valve

In pediatric BAV patients who have aortic stenosis, aortic valvuloplasty is usually preferred. If the patients are outside of the pediatric age group and have severe aortic stenosis or aortic failure, aortic valve replacement is an option. It is also defined in the valve disease treatment guide of the American College of Cardiology (ACC)/American Heart Association (AHA) (20).

Because the life expectancy is long for these patients, bioprosthetic or mechanic valve implantation is controversial. With the third generation bioprosthetic valves, in 80% of the patients, there was no need for another operation in the next 12 years (21). New generation stent-free bioprosthesis are more durable than previous ones. In patients with isolated aortic failure, valve repairment appears to be an alternative for valve replacement. Cosgrove et al. (22) have reported that the results were ideal at first (22) and that no reoperation was required in the following 5 years for 87% of the patients (23). Rao et al. (23) report that the durability rate in the following 10 years is 57%.

Recently, there have been several studies comparing valve replacement and repairment in BAV patients. Although the reintervention rate is similar in both groups in 5 years, recurrent moderate and severe failure rate is found to be higher in valve repairment group (24). Therefore, surgical repairment should only be performed in selected cases of BAV patients. Ross procedure (using patient's own pulmonary valve in aortic position and pulmonary allograft replacement) in BAV replacement has been used for many years and does not require anticoagulation. However, recent studies show that reoperation requirement in 10 years is 25% in autografts and 14% in allografts (25). This complication is more common in patients who are young and in patients with aortic dilatation before the surgery (26). To prevent posterior dilatation in patients who

underwent Ross procedure, using inclusion techniques, homograft and allograft wraps are suggested.

The timing of repairment for the ascending aorta

The reason for operating an asymptomatic patient with a dilated aorta is to prevent the dissection and rupture that is in the natural course of the disease. In a study, the limit value for the development of aortic aneurysm complication was found to be 6 cm. Beyond this point, the annual risk rate for rupture, dissection, and mortality was calculated to be 14.1% (27). When Marfan syndrome or BAV is present, the suggested limit value for prophylactic aorta surgery is 5 cm (28) or 4 cm, according to a source (29). In a study, Borger et al. (30) reported increased aorta aneurysm, rupture, and sudden death rate in patients with aorta diameter of 4.5-4.9 cm compared with patients with aorta diameter below 4.5 cm who underwent isolated aortic valve replacement. In this matter, the evaluation should be based on the aortic ratios obtained by proportioning aorta diameter to body size and age. The replacement of aortic root has twice as much perioperative risk as isolated aorta replacement (30).

Below are the ACC/AHA 2006 suggestions regarding the treatment of BAV and dilate ascending aorta patients:

Class I

- Transthoracic echocardiography (TTE) should be performed to evaluate the diameter of ascending aorta and aortic root in patients who are diagnosed with BAV. Evidence level B
- Cardiac MRI and Blalock-Taussig (BT) shunting must be performed to evaluate the morphology of ascending aorta and aortic root for patients who cannot be evaluated with TTE. Evidence level C
- Echocardiography, cardiac MRI, or cardiac BT shunting must be performed annually for patients with BAV and aortic root and ascending aorta width >4 cm. Evidence level C
- Surgical repairment or replacement of the ascending aorta is suggested for BAV patients with aortic root or ascending aorta width >5 cm or annual increment >0.5 cm. Evidence level C
- Aortic root repairment or replacement of ascending aorta is suggested if the aorta or aortic root diameter is >45 mm in patients with severe aortic failure or stenosis. Evidence level C

Class II

- When surgery is not considered, β -blocker use is suggested for BAV patients who do not have moderate or severe aortic failure but have aortic root width >4 cm. Evidence level C
- Further examination with MRI and cardiac BT shunting is suggested to determine the severity level of the aortic dilatation in BAV patients who were diagnosed with aortic root dilatation using TTE. Evidence level B

The repairment of the ascending aorta

Bicuspid aortic valve is also an ascending aorta disease. In these patients, ascending aorta dilates faster, and dissection and rupture can occur at an early age. Therefore, the ascending aorta reaching 5 cm, as in Marfan syndrome, or the rapid expansion of the aorta (annually ≥ 0.5 cm) requires surgery. Shawl-Lapel with external wrapping or tailoring aortoplasty can be performed in patients with mild dilatation when valve replacement is required but the operation criteria for the aortic root is not fulfilled. A recent study

reports perfect results with this approach in a time-period of 8 years (31). However, it is still controversial whether to treat these aortas. When replacement of both aorta and aortic valve is necessary, there are two standard options. First is the Bentall and De Bono (32) replacement of the aortic root with composite valve graft or with stent-free bioprosthetic porcine (obtained from pigs) via coronary reimplantation or with homograft. The second valve replacement without replacement in the sinuses, and also, supra-coronary graft repairment. It is known that conservative treatment is more effective in elderly patients without aortic root dilatation. Bentall procedure appears to be more favorable compared with other methods for long-term positive results in young patients (33).

There are different alternatives for BAV patients with ascending aorta aneurysm that have normal functionality or dysfunction. Sinotubular component's anatomy can be corrected by aortic valve separation operations; thus, the coaptation of the cusps can be fixed. Its requirement for reoperation in 7 years is similar to that of Ross procedure. There is a requirement for more long term observations and studies to show the effectiveness of these surgical methods on BAV patients with aortic dilatation.

CONCLUSION

Congenital BAV is common. In most cases, it is not detected until infection or calcification develops. The most common complications are aortic stenosis and failure, infective endocarditis and aortic dissection. In patients with aortic valve disease, it is imperative to scan for BAV. Echocardiography should be planned if murmur is detected in first-or second-degree relatives of BAV patients. The timing of the replacement of the ascending aorta is controversial in BAV patients. However, prophylactic ascending replacement is recommended when the diameter of aorta exceeds 5 cm, when it exceeds 4.5 cm in the presence of certain risk factors, or when it exceeds 4 cm in cases that require aorta replacement.

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