REVIEW ARTICLE

Bicuspid Aortic Valve: In Search of Valve Dysfunction and Aortic Dilatation Determinants

Válvula aórtica bicúspide: En busca de los determinantes de la disfunción valvular y la dilatación de aorta

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INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital heart disease, with an estimated prevalence ranging from 0.5% to 1.4% of the population. This abnormality is genetically passed down through an autosomal dominant pattern with familial aggregation of 1 out of 8 first-grade relatives and 3:1 predominance in the male gender. (1) Bicuspid aortic valve usually occurs as an isolated cardiac abnormality but can be associated to other congenital defects resulting from alterations with the fetal stage of the left ventricular outflow tract, such as aortic coarctation, hypoplasia of the left heart, or ventricular septal defect. Approximately 40% to 50% of the patients with aortic coarctation have BAV. There are a number of genetic syndromes whose cardiac involvement includes BAV, such as the Turner syndrome, with 30% prevalence.

Isolated BAV is a clinically relevant entity not only because of the complications associated with the valve (valve dysfunction, infective endocarditis) but also because it is associated with many vascular abnormalities such as aortic dilatation (Figure 1). Transthoracic echocardiography (TTE) is the usual method for BAV diagnosis, with sensitivity and specificity of 92% and 96%, respectively, in non-severely calcified aortic valves. (2) This imaging technique is also useful to identify other anatomical abnormalities in the aortic root, the proximal portion of the ascending aorta, and other associated congenital malformations, as well as the degree of valve dysfunction.

Bicuspid aortic valve may present different valve morphologies depending on the fusion of the right and left cusps (Figure 2). No raphe is present in 15-20% of BAV cases. Type I is the most common valve morphology (70-80% of cases) and is the result of right and left coronary cusp fusion, determining anteroposterior valve opening. Type II morphology is less common (20-30%) and is the result of right and non-coronary cusp fusion, determining a latero-lateral opening. Type III is an uncommon variant (2-3%) caused by the left and non-coronary cusp fusion. (3)

Valve dysfunction

The most common complication in patients with BAV is valve dysfunction. Except for severely dysmorphic valves that cause aortic valve stenosis at pediatric age, most stenoses are the consequence of valve calcification that typically appears 15-20 years earlier than in patients with tricuspid aortic valve. Immunohistochemical studies on excised valves have demonstrated the presence of inflammation, lipid infiltration, and protein production as mediators in the calcification of the valve tissue. Thus, the mechanism of calcification is similar to that in tricuspid valves, also targeting T lymphocyte infiltration in histology. (4) Results in the literature are controversial regarding the relationship between valve morphology and calcification. (5-6) Pediatric series have reported that morphology with fusion of the right-sigmoid and non-coronary cusps is associated with more significant valve stenosis. (7) In our experience, this is also evident in the adult population, with increased valve calcification. Further studies should be carried out to confirm if this type of configuration causes greater hydrodynamic stress on the valve.

Aortic regurgitation is a common manifestation in young adults, and can occur in isolation or together with stenosis. Depending on the population studied, aortic regurgitation has been described as moderate or severe in 20-35% of the patients. (5-6) Mechanisms of aortic regurgitation include prolapse, endocarditis, myxomatous or functional degeneration secondary to dilatation of the aortic root or ascending aorta. It is common for young patients with valve regurgitation who have valve calcification throughout the years to end up with severe aortic stenosis.

When the BAV is pure (without raphe), both cusps are symmetric and progress with lower prevalence of valve dysfunction, particularly with reduced aortic

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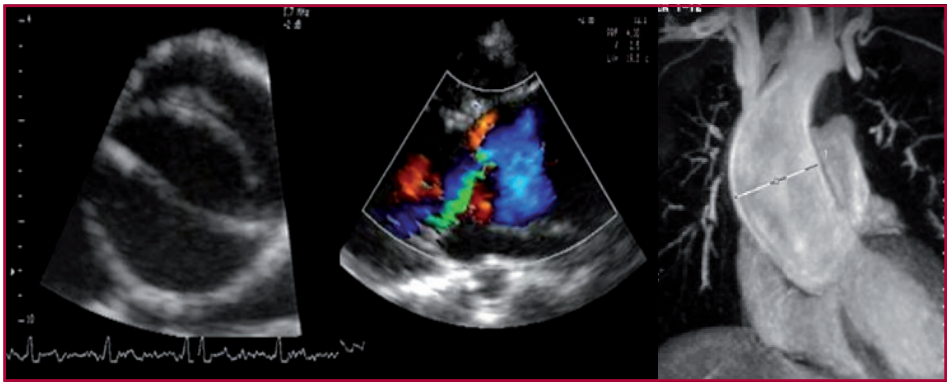

Fig. 1. BAV associated to valve regurgitation and dilatation of the ascending aorta.

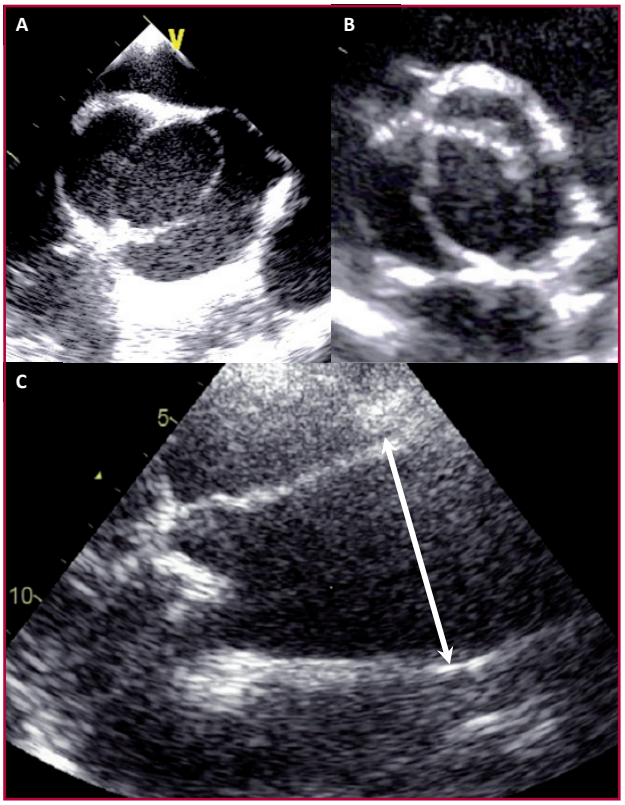

Fig. 2. A: Transesophageal echocardiography showing BAV with fusion of right and left coronary cusps. **B:** TTE showing BAV with right and non-coronary cusp fusion. **C:** TTE showing dilatation of the tubular aorta.

stenosis and regurgitation. (8) The main reasons accounting for a more benign course are that raphe tends to initiate the calcification process, and that valves with raphe tend to be more asymmetric, with a larger sigmoid that facilitates valve prolapse and regurgitation.

Aortic dilatation

Bicuspid aortic valve patients are at higher risk for dissection and dilatation of the ascending aorta. The prevalence of aortic dilatation associated with BAV ranges from 33% to 80%. (9-11) This great variability is attributed to the difference in the thresholds used to define dilatation, populations studied, imaging techniques used, values considered normal by age and body surface area, portion of the aorta analyzed, as well as the heterogeneous nature of the disease itself.

Aortic dilatation can be basically classified into two phenotypes. The most common is the tubular phenotype, which shows greater dilatation of the ascending aorta than of the aortic root. The root phenotype occurs in only 20-30% of the patients and is associated mainly with men, young patients, and patients with significant aortic regurgitation. Both aortic stenosis and type II valve morphology, fusion of the right-sigmoid and non-coronary cusps protect aortic root dilatation. Dilatation of the aortic root and the proximal ascending aorta occurs mainly in type I BAV patients, while dilatation of the tubular ascending aorta and proximal arch is common in type II BAV patients. (12) Although some studies have failed to identify valve morphology as a predictor of aortic dilatation, (13) the ascending aortic flow evaluations from 4D-flow MRI confirm that the type of propeller of the ascending aortic flow generated by the valve morphology determines a different location in the shear stress of the aortic wall.

Pathogenesis of aortic dilatation

Pathogenesis of aortic dilatation in BAV patients remains controversial between two theories. One of these theories argues that aortic dilatation could be the result of blood flow turbulence, and that this major hemodynamic effect would be acting since fetal life, resulting in different degrees of stress-induced aortic degeneration. Flow evaluation from 4D-flow MRI has demonstrated the tangential force of blood flow on the vessel wall, which has been estimated by wall shear stress (14-15) (Figure 3). This would explain the tendency tendency of aneurysm to develop in different locations depending on the valve morphology pattern. In fact, there are histological studies performed on explanted aortas of BAV patients reporting pathological alterations in the areas subjected to greater wall stress, with lower amount of elastin fibers, less thickness and greater distance between them.

However, other authors suggest that hemodynamic

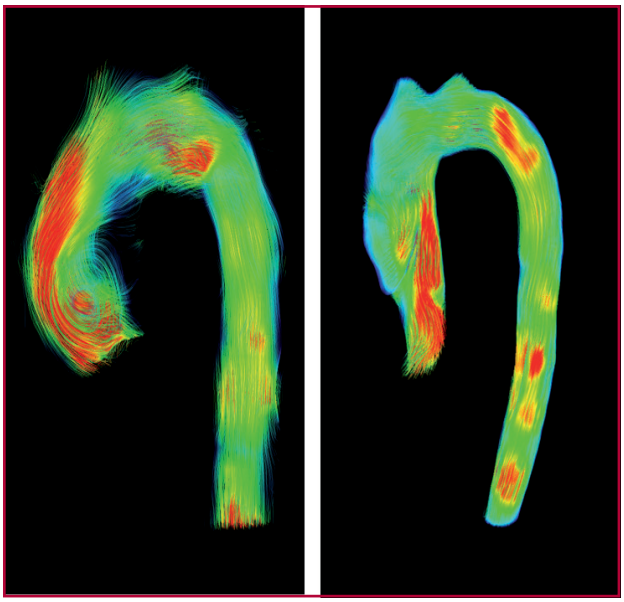

Fig. 3. 4D-flow cardiac MRI in BAV patients.

alterations alone cannot be responsible for aortic dilatation in these patients (16) and hypothesize the presence of a congenital heart defect inherent to the aortic structure. The association between cusp structure and ascending aorta disease could be explained by abnormal development patterns of cells derived from the neural crest with structural abnormalities at the cellular level, regardless of from hemodynamics. (17) Although advocates of this theory argue that normofunctional BAV are associated with significant aortic dilatations, it must be recognized that a "normofunctional" BAV is intrinsically stenotic, with eccentric flow causing abnormal helical flow patterns in the proximal aorta. (9) It has also been reported that BAV has high heredability, and its determinants are almost entirely genetic. Large familial studies have documented a BAV prevalence of 9% in first-degree relatives (FDR) of BAV patients. In addition, some studies have reported aortic valve dilatation, thoracic aortic aneurysm, or aortic dissection in up to one third of FDR of BAV patients, regardless of the presence or absence of BAV. (18-19) However, a recent surgical study demonstrated a high incidence of small raphes in patients with ascending aortic aneurysm. (20) These small raphes were not identified via transthoracic echocardiography, and therefore we cannot rule out that some relatives with ascending aortic dilatations and tricuspid valve could not present dilatation as a result of blood flow alterations secondary to small raphes without implying a wall weakness of genetic origin. In any event, in the light of current knowledge, we cannot rule out that a combination of both factors can account for the development of this complication. Furthermore, we should also consider the alterations typical of aortic valve dysfunction since, while valve regurgitation tends to dilate the aortic root and proximal ascending aorta, stenosis produces less aortic dilatation located in the distal tubular aorta. (21)

Risk of aortic dissection

Aortic dissection is the most dreaded complication in BAV patients owing to to its high associated mortality rate. The incidence reported in two large population series is low, between 0-0.1%. (5, 6) Although the probability of dissection is much lower than in patients with Marfan syndrome, where BAV is 100 times more common, it can cause a significant number of aortic dissections at the population level. Aortic dissection in BAV patients typically affects the dilated aorta in undiagnosed patients. Aortic dissection is exceptional in patients with aortic diameter <55 mm or <33 mm/m2. Other than aortic dilatation, risk factors for dissection include family history of aortic dissection, aortic coarctation, Turner's syndrome, and severe aortic regurgitation with aortic root morphology.

Medical treatment

In addition to routine imaging follow-up, BAV patients should be informed about lifestyle and evolution of their disease. In patients with aortic dilatation, validation of diameters obtained by echocardiography with a different imaging technique (CT scan, CMR) is recommended aimed at more accurate measurement with the double-oblique technique. A reference value is important for a reliable comparison of measurements in case of progression of aortic dilatation. (22) (Figures 4).

In BAV patients, aggressive control of blood pressure and other cardiovascular risk factors should be performed. The latest 2014 ESC Guidelines on aortic diseases suggest the use of beta-blocking agents in patients with BAV and aortic root > 40 mm, although with low level of evidence (22) and based on extrapolation of study results in patients with Marfan syndrome.

Statins have shown a reduction in levels of extracellular matrix metalloproteinases observed in aortic aneurysms. Several retrospective studies suggested the benefit of statins to reduce aortic dilatation in patients with BAV. (23, 24) At valvular level, clinical trials failed to demonstrate their efficacy to reduce the progression of valve calcification; however, isolated studies suggest greater benefit in individuals with mild valve involvement. (25) At present, we are coordinating a clinical trial to evaluate the effectiveness of atorvastatin in patients with BAV (BICATOR: Evaluating the Effectiveness of Atorvastatin on the Progression of Aortic Dilatation and Valvular Degeneration in Patients With Bicuspid Aortic Valve; ClinicalTrials.gov number NCT02679261). In the near future, it will also be possible to determine whether BAV treatment with beta-blocking agents and angiotensin II receptor antagonists (Beta Blockers and Angiotensin Receptor Blockers in Bicuspid Aortic Valve Disease Aortopathy study; ClinicalTrials.gov number NCT01202721) is feasible.

Surgical treatment

Indications for surgery in aortic valve dysfunction are the same as those for tricuspid aortic valve. Over the past two decades, aortic valve repair has been an

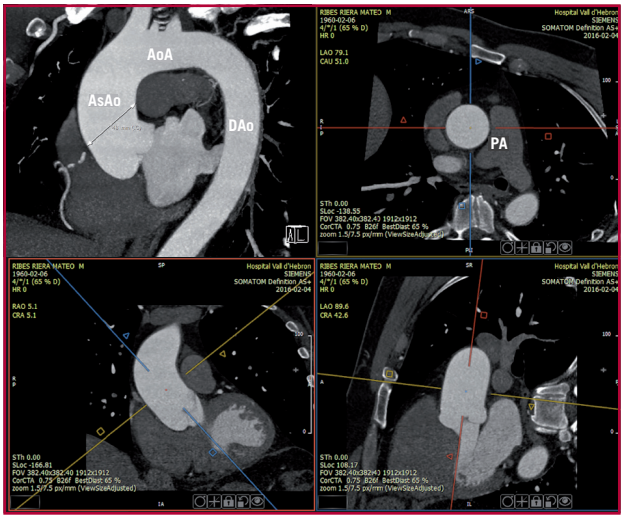

Fig. 4. CT angiography of the aorta. Curved multiplanar and double-oblique reconstruction showing accurate measurement of aortic diameters. Oblique measurement of ascending aorta (arrow), overestimating aortic diameters. AsAo (ascending aorta), AoA (aortic arch), DAo (descending aorta), PA (pulmonary artery).

option in patients with aortic regurgitation, with the advantage of avoiding long-term anticoagulant therapy in these patients. Multiple surgical techniques have been proposed, such as plication of redundant tissue, triangular raphe resection with cusp repair, pericardial repair with interposition graft, free margin resuspension, or annuloplasty. There is recent evidence that the anatomic characteristics play a key role in the durability of the repair. Thus, a coaptation height ≤9 mm or a coaptation surface <4 mm, aortoventricular diameter >28 mm and commissural orientation <160º are considered predictive echocardiographic factors for reoperation. Population studies reported that the need for surgery of the aorta at 25 years in asymptomatic BAV patients was 25%. (26) The ACC/AHA/ESC 2014 Guidelines (27) recommend surgical treatment of the aorta if the diameter is ≥55 mm (Class I, level of evidence B). In cases of aortic diameters >50 mm, treatment of aorthopathy is considered reasonable in cases of family history of aortic dissection or if growth is ≥5 mm/year (Class IIa, level of evidence C). In most cases, it is only necessary to replace the ascending aorta with a supracoronary tube implantation, with Bentall or rarely, David procedure when the aortic root is dilated. Aortic surgery is advisable when diameters are >45 mm, if surgery aortic valve surgery is indicated (Class IIa, level of evidence C). (28)

CONCLUSIONS

Survival rate of BAV is similar to that of the normal population, however, but the risk of associated complications, such as valve dysfunction, aortic aneurysm, endocarditis, or aortic dissection is significantly greater. Aortic stenosis caused by valve calcification occurs earlier particularly in patients with type-II BAV with raphe. Aortic regurgitation is more common in the young population. Valve repair techniques are rapidly evolving, offering a promising future for these patients. Dilatation of the tubular aorta affects more than 70% of patients, whereas dilatation of the aortic root is uncommon. Both aortic dilatation patterns are related to demographic variables, blood flow alterations of ascending aorta associated with BAV morphology and valve dysfunction. Transthoracic echocardiography is the method of choice for diagnosis and follow-up of BAV patients; however, in cases of aortic dilatation, a CT scan and a CMR are recommended to confirm TTE results and evaluate the whole aorta. An adequate baseline study will be a reference if in doubt about aortic growth. It is necessary to gain more knowledge on the pathogenesis of valve degeneration and aortic dilatation in order to develop new therapies that reduce the need for surgical treatment of most BAV patients.

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