REVIEW ARTICLE

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Bicuspid aortic valve: theoretical and clinical aspects of concomitant ascending aorta replacement

Valva aórtica bicúspide: fundamentos teóricos e clínicos para substituição simultânea da aorta ascendente

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Abstract

Bicuspid aortic valve (BAV) is associated with annulo-aortic ectasia, dissection and ascending aortic aneurysm. The high incidence of this congenital malformation and aortic disease suggests a close correlation between the two phenomena. Abnormalities in different phases of cell migration of the neural crest might be responsible for the occurrence of abnormalities in the aortic valve, media layer of the ascending aorta and vessels of the aortic arch. Previous studies have shown that patients with normal BAV or slight dysfunction may present with dilation of the aortic root. The hemodynamic changes caused by BAV without stenosis or insufficiency seem to be an insufficient explanation for these findings. Several mechanisms have been proposed to explain the molecular and hystological aspects of this disease. We found a reduced fibrillin-1 content in both ascending aorta and pulmonary trunk as a possible cause. Histologically, the ascending aorta can present cystic medial necrosis and elastic fragmentation, similar to Marfan's disease. Some authors concluded that many patients, mainly those with aortic regurgitation, should have the aortic valve and the ascending aorta replaced at the same procedure, even if a mild dilatation (45 mm) is present in patients with BAV if life expectancy is anticipated to be greater than 10 years to prevent further aneurysms or ruptures.

Descriptors: **Aortic valve. Aortic aneurysm, thoracic. Aortic valve insufficiency. Aorta/pathology.**

Resumo

A valva aórtica bicúspide (VAB) está associada à ectasia ânulo-aórtica, aneurisma e dissecção da aorta ascendente. A alta incidência desta malformação congênita e doença da aorta sugere íntima relação entre os fenômenos. Anormalidades ocorrendo em diferentes fases da migração das células da crista neural podem ser responsáveis pela ocorrência em anormalidades na valva aórtica, na camada média da aorta ascendente e nos vasos do arco aórtico. Estudos prévios revelam que mesmo indivíduos com VAB normal ou com disfunção leve podem apresentar dilatação da raiz aórtica. Os autores acreditam que somente as alterações hemodinâmicas produzidas por uma VAB sem estenose ou insuficiência parecem ser insuficientes para as graves complicações vasculares observadas nos portadores de VAB. Vários mecanismos têm sido propostos para explicar os achados moleculares e histológicos desta doença.

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Encontramos a redução da fibrilina-1 na aorta ascendente e artéria pulmonar como possível causa. Histologicamente, a aorta ascendente pode apresentar necrose cística da média e fragmentação elástica, semelhante àquela encontrada em portadores de síndrome de Marfan. Vários autores atualmente recomendam que em se operando um paciente com VAB, especialmente aqueles com insuficiência aórtica, mesmo na presença de uma discreta dilatação (45 mm) deve-se substituir a valva aórtica e a aorta ascendente concomitantemente quando a expectativa de vida exceder 10 anos, para se prevenir futuros aneurismas ou rupturas.

Descritores: **Valva aórtica. Aneurisma da aorta torácica. Insuficiência da valva aórtica. Aorta, patologia.**

INTRODUCTION

Frequently, we find differences of opinions about the ideal surgical treatment to be offered to patients with bicuspid aortic valve (BAV). A significant number of these patients present, in addition to aortic valve dysfunction, aortic diameter near the upper limit of normal, and others present root ectasia or ascending aortic aneurysm. In clinical practice, we have reoperated several patients who had undergone previous aortic valve replacement, in relatively short periods of time, who are guided to our Service with ascending aortic aneurysms and/or aortic root.

In the last decade, a reasonable number of articles in the English-language literature brought to the discussion the complexity of this disease, seen over the years as an isolated change of the aortic valve morphology and whose presence of associated aneurysms was believed to be only result from hemodynamic changes.

This review raises the embryological aspects of this malformation, discusses the molecular and histological findings related to the fragility of the aortic wall and presents the experience of several authors in the surgical treatment of carriers of the BAV.

EMBRYOLOGICAL ASPECTS OF THE BICUSPID AORTIC VALVE AND GREAT VESSELS

The bicuspid presentation of the aortic valve is the most common heart valve abnormality [1-4], however, its morphogenesis is still cause for investigation. Sans-Coma et al. [5] concluded in an animal model that all morphological variants are developed from three mesenchymal cushions: right, left and dorsal, after the normal trunk-conal septation.

According to the authors, the bicuspid presentation of the aortic valve is not a result of improper development of the trunk-conal islets, bad trunk-conal septation, agenesis of the valvar cushions or valve lesions acquired after normal valvulogenesis. The fusion of right and left cushions in the beginning of valvulogenesis seems to be the key factor in the formation of bicuspid aortic valve (BAV). Each aortic valve acquires its configuration before the end of its formation process, in addition to the existence of a wide spectrum of valvular phenotypes, ranging from the bicuspid to tricuspid condition, with intermediate stages.

The neural crest is responsible for the formation of cardiac and non-cardiac structures. The neural crest-derived ectomesenchyme, occupying the III, IV and VI pharyngeal arches, participates in the formation of the carotid arteries, the aortic arch and ductus arteriosus, respectively. The muscle-connective tissue of the tunica media of arteries from the aortic arch are derived from neural crest. Furthermore, the neural crest cells play an important role in the formation of the trunk-conal. Anomalies occurring in different stages of migration of neural crest cells could be responsible for isolated or combined defects of the aortic arch, ascending aorta and aortic valve [6-8].

ANATOMOPATHOLOGICAL ASPECTS OF THE ASCENDING AORTA

In 1844 the particular susceptibility of the bicuspid aortic valve (BAV) to pathological processes had already been found, but little attention was given to this observation. In 1858, Peacock reported that the BAV tended to become thickened and calcified, leading first to the stenosis and subsequently, the incompetence. Osler in 1886, emphasized the vulnerability of the BAV to infective endocarditis. Since then, the tendency to infectious processes by this malformation of the aortic valve was recognized [9].

Previous pathological studies [10-12] point to the BAV as the most common cause of aortic valve disease in patients under 70 years of age in North America. It is also associated with higher prevalence of aortic coarctation [13], aortic dissection [14], annuloaortic ectasia [4,15-17] and spontaneous dissection of the innominate, carotid and vertebral arteries [18].

The high incidence of patients with congenital malformation of the aortic valve and aortic disease suggests a correlation between the two phenomena [18-20]. Larson and Edwards [21] demonstrated in anatomical study that the risk of aortic dissection was 9 times higher in patients

with BAV and 18 times higher in patients with unicommisural aortic valve when compared to patients with normal aortic valve, considering the valve malformation as an independent risk factor for aortic dissection. This same study pointed to the fact that the degeneration of the tunica media of the aorta is not determined by the functional status of the aortic valve or systemic arterial hypertension.

The other disease that severely compromises the aortic media layer is the Marfan syndrome, whose ocular and skeletal manifestations were described by Antoine Marfan in 1896. Etter and Glover, in 1943, and, posteriorly, Bear pointed to the serious cardiovascular manifestations of this autosomal dominant syndrome [22]. Only more than 50 years after Marfan description, it was observed that the development and subsequent rupture of an ascending aortic aneurysm were the most complications to be treated to protect the patient's lives with this syndrome, with reduction in life expectancy to one third. Vascular complications result from the weakness of the connective tissue [23.24], due to the reduction of fibrillin-1 in vascular matrix.

The research on Marfan syndrome pointed to the fact that the affected gene product would be expressed in structures common to different organ systems, allowing the appearance of skeletal, ocular and cardiovascular abnormalities, in addition to microfibrillar system abnormalities [25.26]. The main cardiovascular complications include dilation of the aortic root, dilation or dissection of the ascending aorta. Heart failure can occur associated with mitral and tricuspid valve insufficiency in the infantile form of the disease, resulting from the loss of support of the fibrous skeleton of the heart [27-29]. So intriguing, the histological changes found in the aortic medial layer in patients with Marfan syndrome (fragmentation of elastic fibers, cystic medial necrosis or accumulation of mucopolysaccharides and disorganization in smooth muscle cells) are nonspecific and commonly described, with intensity close to those found in some patients with BAV and ascending aortic aneurysms.

McKusick [30] reported the association between bicuspid aortic valve and cystic medial necrosis or Erdheim cystic necrosis in the aorta. Holman [31] believed that the histological changes of the aortic wall were result from the turbulence and the impact of the high-speed flow, due to the presence of a morphologically changed valve. Posteriorly, other researchers have shown that these changes occurred in patients with BAV with normal function or with changes in minimal functions [4,32,33]. The same author [30] questioned the hemodynamic stress as a causative factor of histological changes, since these changes were also found in the segment of abdominal aorta, mesenteric arteries, subclavian artery and, curiously, in the pulmonary artery.

Pachulski et al. [4] showed the occurrence of dilation of the aortic root in patients with normal BAV or minimal stenosis, whose systolic gradient was lower than 25 mmHg. Hahn et al. [32] confirmed these findings and affirmed that the phenomenon occurs regardless of age. Keane et al. [33] pointed to the possibility that the aortic dilation results primarily from intrinsic disease of its vessel wall and suggests that aortic valve regurgitation can play a favoring role in the development of such process. However, this study shows an association between aortic root diameter and males, age and increase in body surface.

The histological findings of Marfan syndrome are nonspecific, and had been described by several authors in patients with BAV [30,34-37]. However, its intensity may be different, presenting itself with both mild changes found in young and healthy patients, as external changes, such as those described in patients with Marfan syndrome. However, we believe that it is a result of improper synthesis of the protein responsible for skeletal microfibrillar of the elastic tissue and fibrous skeleton of the heart - the fibrillin-1 [38].

Although other proteins constituting the microfibrils associated with elastin, fibrillin-1 is the most intensely investigated between them because of its association with the aforementioned syndrome [39]. It is also known that this glycoprotein is the main component of the microfibrils structures of the extracellular matrix and also serves as a framework for deposition of elastin [40].

McKusick was also the first to describe the association between the BAV and cystic necrosis in the medial layer of pulmonary artery. Excepting this case reported by the aforementioned author, the possibility of involvement of the pulmonary artery in this congenital malformation, involving the aortic valve, the ascending aorta and pulmonary artery, had never been investigated. During the fulfillment of the study published by David et al. [41], we noted that five patients with BVA, who had undergone Ross operation, presented dilation of the pulmonary autograft. This fact, combined with knowledge of the common embryological origin of the aortic and pulmonary roots, led to the extension of that study to the molecular structure of the large vessels of the base, confirming the reduction of fibrillin-1 in the ascending aorta and pulmonary artery of patients with BVA compared to the patients with normal or impaired tricuspid aortic valve, in addition to the increase in activity of metalloproteinase 2, enzymes responsible for elastic matrix components degradation [38]. Even more intriguing was the finding on these changes had no relation with age and that there was no difference in the amount of collagen between the studied groups.

Schmid et al. [42], assessing apoptosis in smooth muscle cells of large vessels in patients with BAV, did not describe that the dilation of the pulmonary autograft was result of pathological or molecular processes intrinsic to

the vessel walls. Similarly, Della Corte et al. [43] when studing only patients with aortic stenosis, concluded that the disarrangement of smooth muscle cells and apoptosis are secondary to the stress caused by flow. The presence of aortic stenosis and aneurysm seems to be related to reduction of collagen in the aorta of patients with BAV, confirming our findings.

Cotrufo et al. [44] analyzing the composition of the extracellular matrix in different sites of the ascending aorta, described reduction of collagen type I and III of patients with BAV with aortic dilation and aortic insufficiency in relation to the normal specimens obtained from donors for transplantation and patients with BAV with stenosis.

Despite the apparently conflicting studies, clinical experience suggests that the group of patients with BAV and ascending aortic aneurysm may be a heterogeneous group, consisting of patients with ectasia or true aneurysms of the aortic root or also others who presented relatively normal aortic sinuses, with ascending aortic aneurysms from the sinotubular junction. The different anatomical locations of these vascular complications may reflect different mechanisms, or also different intensity of the same phenotypic expressions, resulting in distinct therapeutic implications [45].

The evidence points to the fact that vascular complications may represent part of a more complex malformation. In such cases, the histological changes of the vessels would not primarily caused by changes of flow, but a result of profound structural changes [37.38] determined during embryo formation. It is believed that different mechanisms may be involved in the physiopathology of aortic disease and these can be influenced but not determined by the functional state of the valve.

CLINICAL IMPLICATIONS IN AORTIC VALVE AND ASCENDING AORTIC SURGERY

The molecular and histological changes in vessels of the base in patients with BAV, although of controversial etiology, were recognized as important criteria for defining the surgical treatment, as occurs in patients with Marfan syndrome. These changes, although similar, differ in the intensity of clinical and laboratory manifestations.

According to Yasuda et al. [46], the aortic valve replacement, either by stenosis or failure, did not prevent the progressive dilation of the proximal aorta, which differs from that observed in patients with tricuspid aortic valve. The authors also suggest that in patients with aortic insufficiency, the aortic dilation progresses more acutely than in valvular stenosis.

Russo et al. [47], when following-up more than a hundred patients who underwent aortic valve replacement, also reported higher incidence of sudden death and aortic dissection in a group of patients with BAV, increase in aortic diameter significantly higher in this same group, suggesting that prophylactic surgery for replacement of the ascending aorta concomitant with valve replacement should be performed, even in the presence of mild dilation of the ascending aorta.

Borger et al. [48] in a clinical retrospective study assessing the aortic complications in patients with BAV, concluded that patients with aortic BAV with aortic diameter exceeding 45 mm should undergo combined surgery, or that is, aortic valve replacement and replacement of the ascending aorta to avoid reinterventions due to vascular complications, either aneurysms and dissections of the ascending aorta.

Brown et al. [49], assessing patients who had undergone Ross operation, of which 48% were under 19 years old, concluded that dilation of the pulmonary autograft is not common after this procedure, with 82% of patients free of dilation in 10 years of follow-up. The authors also commented that the major cause of aortic insufficiency in children and young adults is the presence of BAV and that an increased aortic annulus may be related to the enlargement of the autografting, in addition to technical failures in its fulfillment.

Article published by Davies et al. [50] in 2007 on the natural history of aneurysms of the ascending aorta in patients with BAV showed, after a mean follow-up of 65.1 months, that the aortic stenosis represents a risk factor in patients with BAV and aortic aneurysm. Despite the higher growth rate of aneurysms in this subgroup, the incidence of rupture, dissection or death was similar to the group with tricuspid aortic valve. The authors defined as aneurysm the diameter of the ascending aorta exceeding 3.5 cm and reported that approximately half of patients with BAV did not present aortic stenosis, considering the onset of aortic dilation in patients with normofunctioning BAV. It was not identified the association of the development of aneurysms between the age of the patients. This low rate of complications of the ascending aorta may have been influenced by the mean follow-up period relatively short of only 65.1 months.

Russo et al. [47] observed incidence of complications in the aorta significantly higher in patients with BAV compared to the group of patients with tricuspid aortic valve (TAV). This difference was evident only after a period of 10 years of follow-up. Also in the study of Davies et al., intervention rate of 77.1% in the aorta in patients with BAV was described. This intervention rate may have influenced the called natural history of the disease.

Study published by Etz et al. [51], including 206 carriers of BAV undergone Bentall operation, revealed important data from the clinical point of view: the patients were

relatively young, mean age of 53 ± 14 years, 84% male, who underwent surgery due to presentation of BAV with impaired or dilated of the aortic root. Of the total, 52% presented pure aortic insufficiency, 26%, double-aortic lesion, and only 12% presented pure aortic stenosis. The mean preoperative aortic diameter was 5.5 cm, ranging from 3 to 9 cm. The authors report that in cases of surgery due to aortic valve disease, associated with a diameter of the root or ascending aorta exceeding 4.0 cm and life expectancy exceeding 10 years, the option was to replace both the valve and aorta. In patients with normofunctioning BAV, the Bentall operation was performed when the aortic diameter was greater than or equal to 5.5 cm. These data confirm our impression that the most severe histological changes are found in young patients when they have aortic insufficiency associated with aneurysms or ascending aortic dissections [37].

Study published by Girdauskas et al. [52] showed greater need for reoperation after surgical treatment of ascending aortic dissection type A in patients non-carriers of Marfan syndrome, but who presented severe histological changes in the medial layer of the aorta, specially cystic medial necrosis, compared to the group with less severe histological changes.

Recent publication of Lad et al. [53] describes the echocardiographic, surgical and pathological findings of 29 patients with BAV and associated mitral insufficiency, who had undergone surgical treatment. The authors report the presence of large anterior leaflet of mitral valve with prolapse and aortic annulus dilated (over 30 mm) in 28/29 patients. The authors also describe that 19 presented aortic insufficiency and 11 ascending aortic or aortic root aneurysm. They concluded describing the embryological relationship between the anterior leaflet of the mitral valve, the intervalvar fibrous trigone, the aortic cusps and the fibrous portion of the left ventricle outflow tract.

Sievers, commenting on the study of Lad et al. [53], reports the interest of surgeons to better classify the BAV and disclosure important concepts. The author also adds that the association of BAV and mitral insufficiency, with the need for surgical treatment represents a continuous spectrum of changes of a specific entity, the BAV, associated with mitral and aortic weakness, fusion or prolapse of the aortic leaflets associated or not with aortic insufficiency, ascending aortic dilation associated or not with the dilation of the Valsalva sinus, misalignment of the non-coronary sinus in relation to the left ventricular outflow tract, dilation of intercommissural triangles, dilation of the anterior mitral and aortic annulus, increase of the anterior leaflet of the mitral valve with or without prolapse and mitral insufficiency, predominantly affecting males. The author concludes his comment stating that there is now consensus on the genetic character of the disease and that the tissue fragility seems to be determined by the impairment of the matrix and not a consequence of degeneration.

CONCLUSION

Patients with impaired bicuspid aortic valve, especially with aortic annulus exceeding 30 mm, should undergo concomitant ascending aortic replacement on the occasion of the aortic valve replacement. In young patients, even in the presence of mild dilation of the aorta (above 45 mm) mainly associated with aortic valve insufficiency, a more extensive procedure can be justified (Bentall), aiming to prevent vascular complications. According to the studies assessed, the mechanisms that result in changes of the aortic wall may differ functionally when the aortic valve presents itself with stenosis or insufficiency. Patients with bicuspid aortic valve who had undergone surgery should be more intensely monitored by echocardiography.

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