



# Bicuspid aortic valve disease: A simple embryonic defect or a complex syndrome? Paradigm or certainty?

**\*Corresponding Author(s): Carmela Rita Balistreri,**

Department of Pathobiology and Medical  
Biotechnologies, University of Palermo, Corso Tukory  
211, Palermo, 90134 Italy  
Tel: +39-091-655-5903; Fax +39-091-655-5933 ;  
Email: [carmelarita.balistreri@unipa.it](mailto:carmelarita.balistreri@unipa.it)

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## Mini Review

Cardiovascular diseases (CVDs) show a growing incidence in Western populations due to ongoing ageing [1,2]. Precisely, it is estimated that the CVD incidence will reach 36.9% to 40.5% by 2030, without changes in prevention or treatments [3]. Thus, CVDs are a very challenge. However, advances have been made in recent years in the management of some CVDs, such as ischemic heart diseases [3]. Differently, for a large CVD group, the management and the outcome still are complex. Typical examples are the aneurysms with heterogeneous etiology and increasing incidence, especially in elderly people [4]. Among these, it is possible to include the thoracic aortic aneurysms (TAA) associated with bicuspid aortic valve (BAV), that, indeed, represent the most common complication of this congenital

heart disease. BAV is known as a relatively frequent congenital disorder, with an incidence in the general population between 0.6-2%, and with a male prevalence of 3:1, that determines the appearance of a malformed aortic valve with only two cusps, usually of unequal size [5]. About the 33% of BAV cases shows valvular and vascular diseases, such as TAA, with cellular and molecular mechanisms not completely discovered and cleared [5]. However, our common hypothesis is that typical molecular, cellular and genetic profiles characterize the onset and progression of TAA in BAV patients, as demonstrated in our studies [4, 6-9]. In addition, we sustain that the keystone in identifying these mechanisms stays in detecting those related to BAV itself disease condition. BAV has been initially considered the result of a simple embryonic defect during the valvulogenesis. Today, it is emerging the concept to consider BAV as a *heterogeneous*



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and complex disease, a syndrome, with a great clinical impact, being associated with the onset of a large range of serious diseases, such as TAA and aortic dissection [5]. Accordingly, different BAV phenotypes and related aortic complications have been reported in literature [5], as well as distinct genetics alterations [5]. These last appear to large interest in the complex BAV pathophysiology. Regarding this issue, it has been evidenced a typical BAV feature of co-occurring with other congenital heart defects, ranging from left-sided heart defects integrated by aortic stenosis, coarctation of the aorta, mitral valve abnormalities, to Shone's complex and hypoplastic left heart, even if in 50% of BAV cases the most common is the coarctation of the aorta [amply quoted in 5]. In addition, BAV is also associated with connective tissue disorders, such as Marfan or Loeys-Dietz syndromes, and other syndromes, such as Turner and Williams [5]. As a result, a strong involvement of genetic component in the BAV onset seems to emerge. Consistent with this, the most common forms of familial BAV have been associated with an autosomal-dominant pattern, but with incomplete penetrance and variable expressivity [5]. In addition, the male predominance and the association of BAV with Turner syndrome have been demonstrated to be linked to a possible X-linked inheritance [5]. Accordingly, the screening of first-degree family members of BAV patients is recommended by the consensus guidelines, linked to its relatively high heritability rates [5], with the possibility to detect a 9% unknown BAV in these first-degree relatives [5]. Furthermore, it is imperative to recommend that BAV first-degree relatives, even with normal tricuspid aortic valves (TAV), may develop aortic dilatation [5]. Despite the recognized heritability of BAV, the genetic factors associated with the typical BAV complications remain to be defined. However, it retains that diverse genes are involved. On the other hand, in the aortic valvulogenesis are involved several evolutionally conserved pathways, such as members of the TGF- $\beta$  superfamily, VEGF, Notch, Wnt/ $\beta$ -catenin, bx20, and Gata4 [5]. Many other genes, including genes involved in connective tissue disorders, cell signaling (i.e. Toll-like receptors, particularly TLR4), and the extra-cellular matrix, have also been associated with BAV [5]. Modifications or alterations in these pathways may determine or be related to BAV onset. Of relevance appear the studies that evidence mutations in *NOTCH1* gene and polymorphisms in some genes (precisely encoding TLR4, angiotensin-converting enzyme and matrix metalloproteinases, endothelial oxide nitric synthase) significantly associated in subjects with BAV, and with TAA, as complication [5]. Consistent with this, accumulating lines of evidence demonstrated that an impairment of Notch signaling is involved in both onset and progression of aortic aneurysm, showing a dual effect [10]. On the one hand, Notch 1 appears to be activated in aortic aneurysms and either genetic or pharmacological attenuation of this pathways delays aneurysm progression [10]. On the other hand, the effects of Notch 1 activation appears to be cell-dependent, cell microenvironment-dependent, and are critical for the maintenance of vascular integrity and promotion of vascular repair. In fact, Notch 1 is also involved in the maintenance, survival, proliferation and maturation of endothelial progenitor cells (EPCs), as described in our monograph [11]. Thus, its alterations may reflect changes in the activity and number of these cells. In mediating the vascular effects, Notch pathway cross-talks with other pathways, such as TLR4 pathway, as amply discussed in our recent review and the related model. In fact, our and other groups have proposed the crucial role of chronic inflammation in both aneurysm onset and progression. Inflammatory cytokines and immune/inflammatory cells have been, indeed, detected in human aneurysm specimens [4,6-9].

In particular, we and He's group have recently observed a significant infiltrate of CD3+CD4+CD8+CD68+CD20+ cells in aorta tissues from patients with Marfan syndrome, familial and sporadic TAA [4, 6-9]. Moreover, we have observed significant amounts of immune/inflammatory cells in aorta tissues from 24 BAV patients with TAA than control aortas, but with higher levels in individuals with tricuspid aortic valve (TAV) and affected by TAA [7]. This might be linked to presence in BAV cases of alterations in Notch pathway that can be responsible of altered circulating ad tissue levels of immune cells, whose T and B cell development, in both central and peripheral lymphoid organs, requires the activity of Notch 1 pathway [10]. Interestingly, we recently examined in BAV and TAV cases with or without TAA the levels of some T and B subsets and evidenced that BAV subjects show significantly lower levels of these T and B subsets analyzed [12]. Accordingly, some experimental studies in animal models have demonstrated that the attenuation of aortic immune/inflammation prevents or delays the progression of aortic aneurysm [4,6-9].

We hypothesize that interplay between Notch pathway, inflammation and altered EPC function is characteristic of BAV condition and can be cause of increased TAA onset. Certainly, additional and larger studies are needed for confirming our ambitious hypothesis. However, we recently obtained very promising data in a larger study on BAV vs. TAV condition with TAA or not, that would suggest as close interplay among an altered Notch pathway, inflammation and a compromised cardiovascular self repair system may be associated to BAV itself condition and its most common complication, such as TAA (study submitted [13]).

Based on these observations, different mechanisms are suggested to be involved in BAV condition and its most common complication, that is TAA. Genetic predisposition, local stress in the valve tissue related to the bicuspid aortic valve, which alters blood flow, as well as alterations in evolutionally conserved pathways, such as Notch pathway, have been evidenced. However, numerous questions remain opened. Thus, further researches with multidisciplinary approaches are imperative, for a better understanding of BAV syndrome in order to facilitate its management and complications, such as TAA.

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