Bicuspid aortic valve associated aortopathy: a genetic disease?

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Abstract

The present paper briefly reviews the literature supporting the pathogenetic importance of hemodynamics in the development of bicuspid aortic valve-associated aortopathy. The hypothesis of a genetic basis for this disease, whether it is a common defect for bicuspid malformation and predisposition to aortic aneurysm or not, should not be discarded. However, a more complex, multifactorial pathogenesis model is here proposed, based on the hypotheses raised by recent studies both on clinical and pre-clinical aspects of bicuspid aortopathy, whereby in at least some forms of the disease the biomechanical factors capable to induce aortic wall maladaptive remodeling may be necessary to the development of the aortopathy. The main scope of this review is to underscore the importance of trying to advance the scientific knowledge not only on the genetic bases but also on the peculiar aspects of hemodynamics of bicuspid aortic valve and flow-induced vascular remodeling.

Introduction

It is undeniable that the bicuspid aortic valve (BAV) is a genetically determined disorder.[1] Experimental studies on animal models have shown that different disturbances in different phases of valve embryogenesis may cause the two major morphological types of BAV, namely the left-right fusion (RL) and the right-noncoronary fusion (RN), suggesting possible genetic heterogeneity underlying the most common congenital cardiac malformation.[2] Those developmental discoveries have confirmed previous evidence that a defect of the neural crest cells contributing in both valve and ascending aorta embryological evolution may represent the explanation for the association of congenital aberrant valve morphology with both congenital aortic coarctation and the onset of aortopathy in the adulthood.[3] Further genetic complexity is believed to underlie the development of complications of BAV, including valve calcification and stenosis, regurgitation and aortopathy, and the level of inheritability of these associated conditions has been found to be by far lower compared to inheritability of the BAV itself.[4] Altogether, these pieces of evidence imply that both BAV malformation and its associated diseases may share a common genetic background; however, they also imply that the identification of BAV malformation as a genetic disorder should not be considered as an argument to discard other non-genetic causal factors of the aortopathy.

Pathogenesis of bicuspid aortic valve-associated aortopathy: from concepts to facts

The current knowledge about the pathogenesis of the aortopathy associated with BAV is limited.[5] Despite a growing interest of researchers for this disease, as testified by the ever-increasing number of publications per year on this topic,[6] no BAV-specific mechanism of aortic dilatation onset is known at present. Unlike Marfan syndrome, no precise pathogenetic mechanism underlying the progression of aortic dilatation has been identified for BAV aortopathy. It is easy to speculate that such limitations in our understanding of the disease are consequence of either inadequate method of research or inappropriate starting hypothesis and/or theoretical approach. Indeed, the conceptual approach has been characterized by a dichotomy between a genetic theory and a hemodynamic theory and there has often been a tendency to over-interpretation of the findings, making conclusions that were not fully justified by the methods employed and results observed. Several small observational studies, based on imaging data, from series often affected by referral bias, have proposed firm conclusions about the pathogenesis,[7-10] while merely observing the clinical manifestations of BAV aortopathy. Similarly, studies addressing the morphological or molecular aspects of the end-stage disease, namely aneurysm of the ascending aorta with BAV, have often quite arbitrarily inferred on its genetic bases, neglecting that between the genetic predisposition and the tissue or molecular phenotype several levels of regulation exist.[11-13]

Such a lack of strictness in data interpretation and statement of findings has exerted effects also in the clinical setting, where our common tendency to simplify problems when translating knowledge into practical principles has further polarized the dichotomy between the genetic and hemodynamic theories: the supporters of the former endorse greater aggressiveness when giving indication for elective surgical replacement of the aorta, while those supporting the latter suggest a more conservative posture.[14] This direct transferal of concepts from hypotheses to theories and from theories to practice, has led to the current situation, characterized by lack of standardization in the surgical treatment of this disease and lack of robust evidence to support official guidelines in recommending consistent criteria.[15]

Indeed, even the occurrence of aortic dilatation in BAV subjects with no degree of aortic valve dysfunction (or disproportionate to the degree of valve dysfunction) does not disprove the hemodynamic theory, since flow alterations other (and subtler) than detectable by echocardiography have been demonstrated.[10,16] However, the hemodynamic theory apparently cannot explain some aspects of the aortic disease associated with BAV, including the occurrence of mild aortic dilatation in first degree relatives of BAV patients, as reported by Biner *et al.*,[17] and the fact that aortic valve replacement (AVR) fails to prevent progression of the aortopathy or acute aortic events.[7,18] On the other side, the argument of BAV aortopathy being different in clinical severity and frequency compared to the other known genetically mediated aortopathies, like typically the one occurring in Marfan's syndrome, is easily neutralized by the hypothesis of a complex genetic background, with no single gene mutation directly causing aortopathy but rather a number of possible combinations of common and/or unique variants[19] leading to a spectrum of different severities and modalities of clinical presentation.

It is evident that, put in the wrong terms, the

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debate on the pathogenesis of BAV aortopathy has only led to cultural uncertainty, without any positive contribution to the clinical practice. Thus, unpredictability of the dilatation based on common echocardiographic parameters of valve dysfunction does not necessarily exclude a triggering role of altered hemodynamics; however admitting it should not necessarily imply relative *benignity* of the condition. Lack of systemic involvement and existence of BAV patients not developing ascending aortic dilatation throughout their lifetime do not reject an association between BAV and a genetically determined aortopathy; however recognizing this must not entail systematically addressing BAV aortopathy with similar surgical aggressiveness as towards Marfan aortopathy.

Bicuspid aortic valve aortopathy: polygenic? or rather *multifactorial?*

Why does a patient with BAV present with an aortic stenosis that already requires intervention in pediatric age while another one is referred to surgery for aortic valve stenosis only slightly earlier in life than the usual tricuspid aortic valve (TAV) stenosis patient? Similarly, why does a young patient need ascending aorta replacement with a normally functioning BAV whereas another one has to undergo AVR in his/her elder age and presenting only mild degree of ascending aorta dilatation? In a recent study, the rate of progression of the BAV ascending aorta diameter over time, commonly interpreted as a surrogate parameter for the severity of the aortopathy,[20] ranged between 0 and nearly 0.5 cm/year,[21] indicating a wide variability in the tendency towards aneurysm development and possibly acute complication occurrence. The general recognition of such an heterogeneity in terms of severity, time of onset, extent of the aortopathy etc. has gradually led to a greater awareness of the fact the BAV is more similar to a cluster of diseases of the aorta than to a single syndrome.[22] A polygenic model could explain clinical heterogeneity from the genetic perspective, however, beside a *possible* set of genetic variants, an altered biomechanical environment is present *for sure* at the ascending aorta level, with BAV.

The systems used by cells to adapt their biology to the biomechanical environment are complex, involving different signaling pathways.[23] Therefore, defective mechano-sensing and/or mechano-transduction by the resident cells of the aortic wall (endothelial cells? smooth muscle? myofibroblasts?) could be caused by a combination of different genetic variants, polymorphisms or haplo-insufficiencies. According to the burden of such variants in the individual patient, a lesser or greater degree of hemodynamic derangement would be necessary for the aortopathy to become phenotypically evident.

Blood flow, with the consequent biomechanical cues, is known to have a regulatory role also in valve and aortic arch embryogenesis,[24,25] hence the association of a congenital malformation of the valve (with possible association with coarctation) with a predisposition to aortopathy in the adulthood. This theory could also explain the presence of increased aortic diameter and stiffness in the TAV relatives of BAV probands reported by Biner and colleagues:[17] both parameters in the first degree relatives were intermediate between the values observed in the probands and those in the normal population, which is compatible with a common underlying genetic defect in the family, whose expression is exacerbated by the local hemodynamic alterations accompanying BAV but not TAV. Also the evidence from a recently growing body of literature that AVR can at least slow down, if not halt, the progression of the aortic diameter, fits well with the hypothesis of a defect in the response of the aortic wall to biomechanical stimuli.[26-29] In particular, a rate of aortic growth not differing from the normal progression in the healthy general population has been recently reported in a mean 10-year follow-up after AVR by Ross operation in a large BAV series.[26] This is intriguingly consistent with a 4D-Flow magnetic resonance imaging (MRI) study showing that while the most commonly employed heart valve prostheses fail to restore a normal flow pattern (in terms of vorticity and helicity, eccentricity of jet flow and consequently aortic wall shear stress), the only surgical solution yielding a normal wall shear stress was autograft implantation, which is indeed the method employed in the Ross operation.[30]

A variable degree of alteration in the remodeling response to (more or less abnormal) biomechanical stress could also explain the typical asymmetric configuration of the BAV-associated dilatation of the tubular tract of the ascending aorta, characterized by predominant involvement of the greater curvature, or convexity,[31] which almost invariably represents the area where flow jet impacts and shear stress is more disturbed.[32] Moreover, the two most common anatomical variants of BAV, namely the RL and RN cusp fusion are associated with different patterns (but apparently not significantly different *risk*) of aortic dilatation, the former being associated with tubular ascending dilatation in about 60% of cases and with dilatation of the sinuses of Valsalva in 35-40%, the second with much lower prevalence of root dilatation (20%), but more frequent involvement of the proximal arch.[33-35] These differential patterns of involvement of the various aortic segments strictly mirror the distinct flow patterns demonstrated by 4D-Flow MRI between patient groups with the two valve morphotypes.[32]

Therefore, although genetic heterogeneity and complexity could suffice to explain the clinical heterogeneity and phenotypic variability of BAV aortopathy, the interaction between genetic substrate and hemodynamic factors is very likely to be responsible for the ultimate expression of the aortopathy, in terms of age of onset, severity of the progression, risk for acute dissection, extent of the disease.

Ongoing patient-specific computational fluid dynamic studies are demonstrating that even in accurately selected patient subsets, homogeneous for clinical characteristics, including valve morphotype and function and ascending aortic dimensions, flow patterns may differ in terms of degree of eccentricity, helicity, vorticity, and ultimately stress acting on the wall (A. Redaelli et al., unpublished material, 2014; Figure 1). Future studies should focus on investigating the possible prognostic significance of those differences in terms of occurrence and severity of the aortopathy.

At one end of the range of possible pathogenetic associations of gene defects with hemodynamic determinants there may also be a sub-clinical aortopathy, whereby the patients with a low burden of genetic variants will not develop overt dilatation unless their BAV will become significantly stenotic (thus occurring as the so called *post-stenotic dilatation*); at the other end, a multifactorial model would also imply that patients with a normally functioning BAV might have a strong propensity to dilatation due to a particular combination of genetic variants affecting vessel response to biomechanical cues, so that the intrinsic flow pattern abnormalities accompanying BAV are enough to induce aortic enlargement.

Biomechanical regulation of vascular biology

Both in the evolution of vertebrates and in human embryological development, the shift from an open circulatory system with continuous flow to a closed system with pulsatile flow coincides with the appearance of the expression of elastic fibers in the arterial wall.[36] Already in the late nineteenth century it was postulated that each type of biomechanical stimuli prompts a specific mechanism of arterial response, leading to modification of the vessel length, wall thickness, lumen size.[37] The mechanisms of both physiological and maladaptive flow-induced and stress-mediated vascular remodeling have since been extensively studied, mainly by means of experimen-

tal models and *in vitro* studies. Just to mention some examples of demonstrated paradigms of vascular responses to alterations of the hemodynamic forces: endothelial nitric oxide (NO) synthase expression/activity,[38] matrix metalloproteinases 2 and 9 (MMP-2, MMP-9) expression (in part through the NF-kB signaling pathway) and TGF-β production/release are all known to be regulated by wall shear stress pattern and magnitude;[39] MMP-2 expression is also induced by mechanical stretch,[40] and recently the evidence has been reported that the activity of MMP-2 promoter, but not MMP-9 promoter, is induced by increased wall tension;[41] smooth muscle cells (SMC) can change their phenotype from contractile to synthetic, when subjected to chronic increased wall stress, through mechanisms mediated by growth factors like CTGF and PDGF;[42] vascular cell apoptosis is inducible by alterations in local intraluminal pressure.[37]

It is worthy of mention, in this perspective, that while no pathogenetic sequence has ever been traced for BAV aortopathy, a large number of studies have addressed its features at the molecular and tissue levels. To thoroughly review those features goes beyond the aims and possibilities of the present paper, but few examples of how aortic wall changes in BAV aortopathy could be explained by an hemodynamic mechanism of causation will be hereunder briefly listed. In BAV disease altered eNOS expression in the ascending aortic wall has been reported, interestingly also varying according to the site of retrieval of the specimens in the single aorta (*e.g.* convexity *vs* concavity);[43,44] MMP-2, and not MMP-9, has been demonstrated to typically increase in the early phase of aortic dilatation with BAV, unlike aortic dilatations with TAV;[45] loss of SMCs differentiation (*i.e.* loss of their mature contractile phenotype) has been reported in aortic specimens from BAV patients.[46] The evidence of early smooth muscle cell apoptosis in the BAV aorta, traditionally reported as a proof for a *genetic program* causing aortic dilatation with BAV,[12] was forwarded in an era when the awareness of the aortic biomechanical alterations intrinsic to the presence of a BAV (potentially enough to cause increased apoptotic indexes) was still low.[47]

An elegant study demonstrated, through a process called *expression screening*, that several genes that were differentially expressed between the BAV and TAV dilated aorta (including genes codifying for constituents of endothelial mechano-sensory complex) showed consistent co-expression with well-known flow-regulated genes from public microarray datasets and about half of them was differentially expressed in regions of the aorta exposed to different stress patterns.[48] Beside affecting the aortic wall biology at the transcriptional level, hemodynamic environment could importantly affect the phenotype at the epigenetic level, which indeed, excluding a few studies on micro-RNAs,[49] is still a relatively unexplored field in BAV aortopathy research.

Thus, there are many suggestions that altered hemodynamics from the malformed and intrinsically malfunctioning BAV (*i.e.* restricted opening motion even with normal echocardiographic function, causing eccentric systolic jet, in turn yielding altered flow patterns, including accentuated flow helicity and

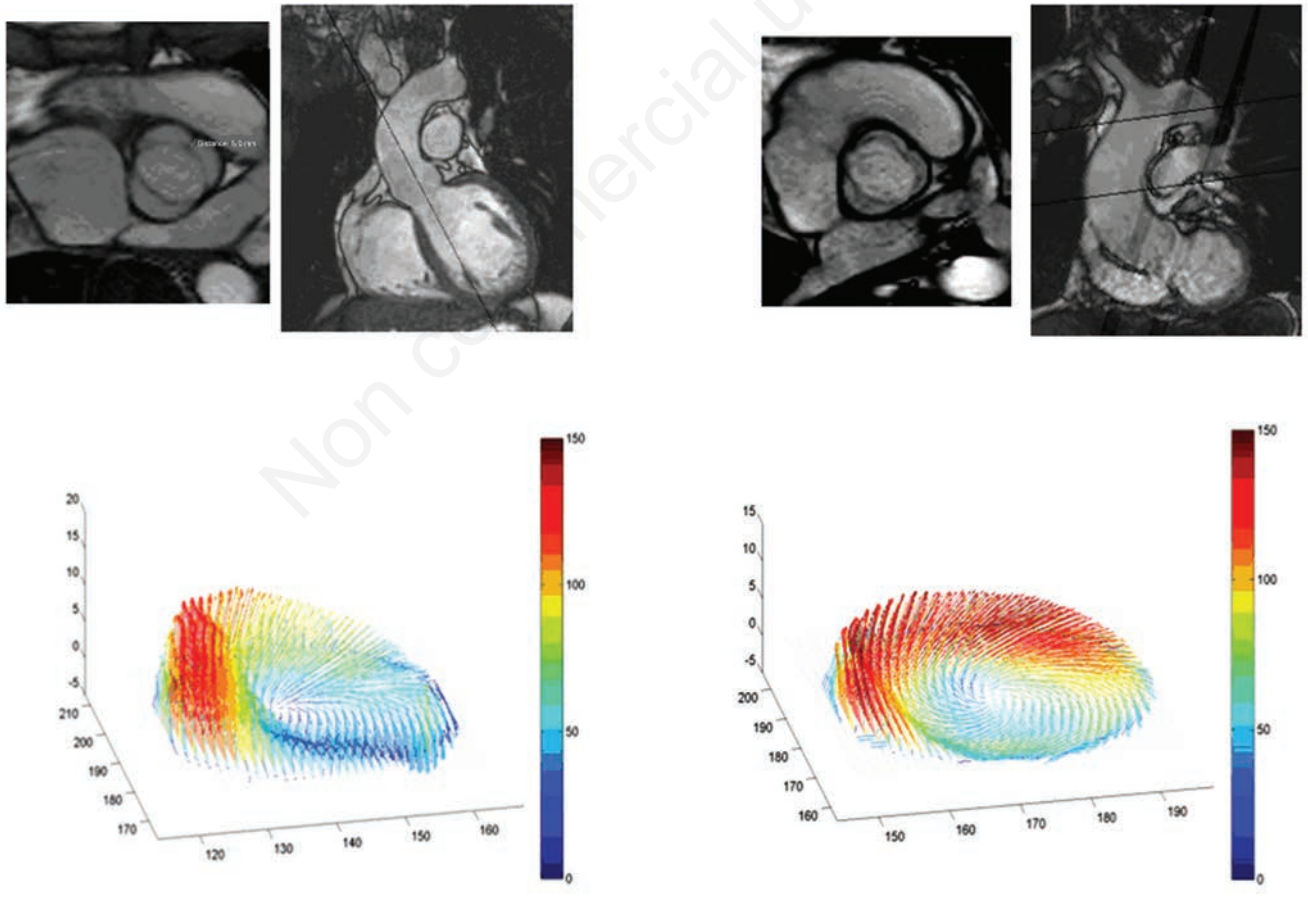

Figure 1. Patient-specific computational fluid dynamics. Comparison of peak systolic flow velocity vectors in a cross-section at the level of the sino-tubular junction in two bicuspid aortic valve (BAV) patients with echocardiographically normofunctional BAV with left-right type of fusion and non-dilated ascending aorta: marked eccentric flow is demonstrated in one, an helical pattern in the other. (Courtesy of Prof. Alberto Redaelli, PhD and Emiliano Votta, PhD, Politecnico di Milano, Milan, Italy).

increased wall shear stress) might play a relevant and, at least in a proportion of patients, *necessary* role in the determinism of the aortic wall tissue remodeling that ultimately prompts dilatation occurrence and progression.

However, this field is particularly complex to understand, as the interactions between biomechanical environment and aortic wall cells are not static, but change as the aortopathy progresses: this concerns both the forces acting on the wall (*e.g.* the shear stress is inversely proportional to the vessel radius, thus it decreases as dilatation occurs, whereas wall tension increases by the Laplace law) and the way they are *sensed* by the wall (*e.g.* once remodeling has begun the mechanical properties of the extracellular matrix change and so does the matrix-mediated transmission of the mechanical stimulus to the cells). Therefore the role of hemodynamics might be different between the onset phase and the progression phase of BAV aortopathy, not to mention the biomechanical implications of the acute complications of the aortopathy, including aortic rupture and dissection.

Taking advantage of heterogeneity

Genetic heterogeneity and clinical heterogeneity make understanding the mechanisms of development and progression of BAV aortopathy an extremely difficult task. Very large series, with careful phenotyping and adequate follow-up time are needed, which implies the necessity for a multicenter and multidisciplinary effort.[5] However, the phenotypic heterogeneity that is strictly related to the above-discussed pathogenetic complexity may serve as a means to systematize this multiform disease, by classifying the different anatomical and clinical manifestations as different forms or types of *aortopathy*: this will be useful not only for nosology purposes and to find a common language in study result reporting, but also importantly for the future attempts to unravel the genetic background in details. Different molecular signaling pathways could be involved in the determinism of the diverse phenotypes of BAV aortopathy: beside large-scale genotyping studies addressing the possible mutations underlying BAV malformation occurrence, genotype-phenotype association studies in more selected series would be warranted to detect the specific variants involved in the causation of the various forms of aortopathy.

An entity that will be particularly interesting to address in further studies is what we have called the *root phenotype*, *i.e.* the dilatation predominantly or exclusively of the sinuses, usually occurring in young (about 30 years-old) male patients with either a normally functioning BAV or a significant pure regurgitation, usually of a RL valve type.[50] This form of aortopathy, occurring as 20-30% of aortic dilatations in BAV patients according to hospital series,[21,51] seems to be overrepresented in series of aortic dissection BAV patients,[52] has been reported as associated with increased risk of post-AVR *aortic events*, including need for reoperation for aortopathy, acute aortic dissection and sudden death,[53] and is an independent predictor of fast growth (>0.1 cm/year) of the ascending aorta.[54] In the study by Biner and colleagues suggesting a sub-clinical aortopathy in the first degree relatives (FDRs) of BAV patients, the percentage of probands and relatives having a root phenotype was particularly high (72% and 86% respectively), thus the suggestion that FDRs who do not have a BAV may be at risk for aortopathy actually should be limited to the root phenotype.[17]

All the above evidence confirms the suggestion that the root phenotype may represent the *strong genetic component* extremity of the spectrum of phenotypic expressions of BAV aortopathy, as opposed to the *ascending phenotype* that is associated with BAV stenosis, with a prevalence that increases with age, and is more likely subtended by a necessary effect of altered hemodynamics.[51,53] Further clinical studies should be undertaken to characterize the different forms of aortopathy and phenotypic associations, in a way to enhance our armamentarium of clinical criteria, to eventually improve decision-making in the surgical management, and to influence the designing of pathobiology studies and genetic research.

Conclusions

There is no doubt that the BAV is a genetically determined malformation. The most constructive approach to the research in the field of BAV-related disease cannot disregard this evidence, nor should it neglect the strong arguments, forwarded by the most recent studies, in favor of a pathogenetic role of hemodynamics in at least the most common subtypes of BAV aortopathy. A new vision of the pathogenesis of this disease should imply the coexistence in each individual BAV patient of both a variable degree of hemodynamic disturbance and a genetic predisposition prompting aberrant response to biomechanical stimuli onto the aortic wall. Genetic discoveries are desired and expected in this field, but until their translation into clinical practice, correct and consistent phenotyping is warranted both in the clinical setting and in research. Investigating the flow patterns in the BAV patients and the modalities of interaction between flow-related forces and aortic tissue pathobiology will likely have as strong an impact on the future clinical management of BAV patients as the improvement of our knowledge of the genetic bases of this complex syndrome.

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