JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 82, NO. 5, 2023

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Mechanisms of Aortic Dilation in Patients With Bicuspid Aortic Valve

JACC State-of-the-Art Review

Jose F. Rodríguez-Palomares, MD, PhD,[a,b,c,d,*] Lydia Dux-Santoy, PhD,[b,*] Andrea Guala, PhD,[b,c] Laura Galian-Gay, MD, PhD,[a] Arturo Evangelista, MD, PhD[a,b,c,d,e]

ABSTRACT

Bicuspid aortic valve is the most common congenital heart disease and exposes patients to an increased risk of aortic dilation and dissection. Aortic dilation is a slow, silent process, leading to a greater risk of aortic dissection. The prevention of adverse events together with optimization of the frequency of the required lifelong imaging surveillance are important for both clinicians and patients and motivated extensive research to shed light on the physiopathologic processes involved in bicuspid aortic valve aortopathy. Two main research hypotheses have been consolidated in the last decade: one supports a genetic basis for the increased prevalence of dilation, in particular for the aortic root, and the second supports the damaging impact on the aortic wall of altered flow dynamics associated with these structurally abnormal valves, particularly significant in the ascending aorta. Current opinion tends to rule out mutually excluding causative mechanisms, recognizing both as important and potentially clinically relevant.
(J Am Coll Cardiol 2023;82:448–464) © 2023 by the American College of Cardiology Foundation.

Bicuspid aortic valve (BAV) is the most common congenital heart disease and is typically diagnosed incidentally during transthoracic echocardiography.[1] Its estimated prevalence is 0.7% to 1.4% in the general population,[2,3] with an approximate 2:1 to 3:1 predominance in men.[2-5] A recently standardized nomenclature[6] recognizes 3 types of BAV (**Figure 1**): the fused type, further divided according to the location of the fusion in right-left coronary cusp (RL), right-noncoronary cusp (RN), and left-noncoronary cusp; the 2-sinus type, and the partial fusion (forme fruste) type, where the fusion does not cover the whole leaflet border. The fused type represents the vast majority of BAVs, with RL fusion being present in approximately 70% to 80% of cases, RN in 20% to 25%, and left to noncoronary cusp being rare (≈2%).[2,7] Between 70% and 90% of BAVs present a raphe between the fused cusps.[2,8-10] Recently, attention has focused on the analysis of the extent of the fusion,[11-14] as reflected by the standardized nomenclature.[6]

The most important clinical implications of BAV are valve dysfunction, aortic dilation, infective endocarditis and aortic dissection. Aortic dilation, the central topic of this review, is very prevalent in BAV patients and will be thoroughly discussed in the next sections. Aortic dissection is the most-feared complication related to BAV. Although the incidence of aortic dissection in absolute numbers is very low,[1,5,15-18] the age-adjusted relative risk is 8.4 times

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From the [a]Department of Cardiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [b]Vall d'Hebron Institut de Recerca, Barcelona, Spain; [c]Biomedical Research Networking Center on Cardiovascular Diseases, Instituto de Salud Carlos III, Madrid, Spain; [d]Departament of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain; and the [e]Instituto del Corazón, Quirónsalud-Teknon, Barcelona, Spain. *Drs Rodríguez-Palomares and Dux-Santoy contributed equally to this work.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 31, 2022; revised manuscript received October 7, 2022, accepted October 20, 2022.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2022.10.042

HIGHLIGHTS

- Genetic and hemodynamic alterations have been suggested as causes of aortic dilation in patients with bicuspid aortic valve.
- Evidence supports a genetic basis for aortic root dilation, and ascending aortic expansion is associated with altered flow dynamics.
- Prospective studies are needed to assess the predictive value of biomarkers and potential interventions to slow the progression of aortopathy in patients with bicuspid aortic valves.

ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional
4D = 4-dimensional
AR = aortic regurgitation
AS = aortic stenosis
AscAo = ascending aorta
BAV = bicuspid aortic valve
CMR = cardiovascular magnetic resonance
CT = computed tomography
FDR = first-degree relatives
RL = right to left coronary cusp
RN = right to noncoronary cusp
TAV = tricuspid aortic valve
WSS = wall shear stress

higher in BAV compared with the general population.[16] Nonetheless, the long-term survival rate in these patients is comparable to that of the general population,[1,15-17] likely as a result of adherence to prophylactic surgical indications.[1,5,17] The main risk factors associated with aortic dissection in BAV are uncontrolled hypertension, a personal history of coarctation, a family history of aortic dissection or early unexplained sudden cardiac death, and a confirmed aortic diameter increase of >3 mm/year.[5,19,20] In these high-risk cases, prophylactic ascending aorta (AscAo) replacement is recommended at a lower threshold (aortic diameter of ≥50 mm) compared to the generally recommended value (≥55 mm).[21,22]

Aortic stenosis (AS) and regurgitation (AR), the most frequent aortic valve complications,[5] predict adverse events[15] and frequently require aortic valve repair or replacement.[8,15] The reported AR prevalence ranges from 23% to 70%,[1,2,8,9,16] is higher in male patients,[2,8,23] and increases with aortic root diameters.[24] Approximately a quarter of ARs are considered the result of aortic root dilation.[9] The age-adjusted long-term survival of BAV patients with moderate-severe AR is similar to that of tricuspid aortic valve (TAV) patients with the same degree of AR.[25,26] AS is the leading cause of valvular dysfunction, with a prevalence between 14% and 50%,[1,2,8,9,16,27] increases with age,[1,2] and is associated with cardiovascular risk factors.[2] AS has been reported more frequently in RN compared to RL BAV.[2,24] In BAV, AS severity is particularly associated with the calcification of the aortic valve.[28]

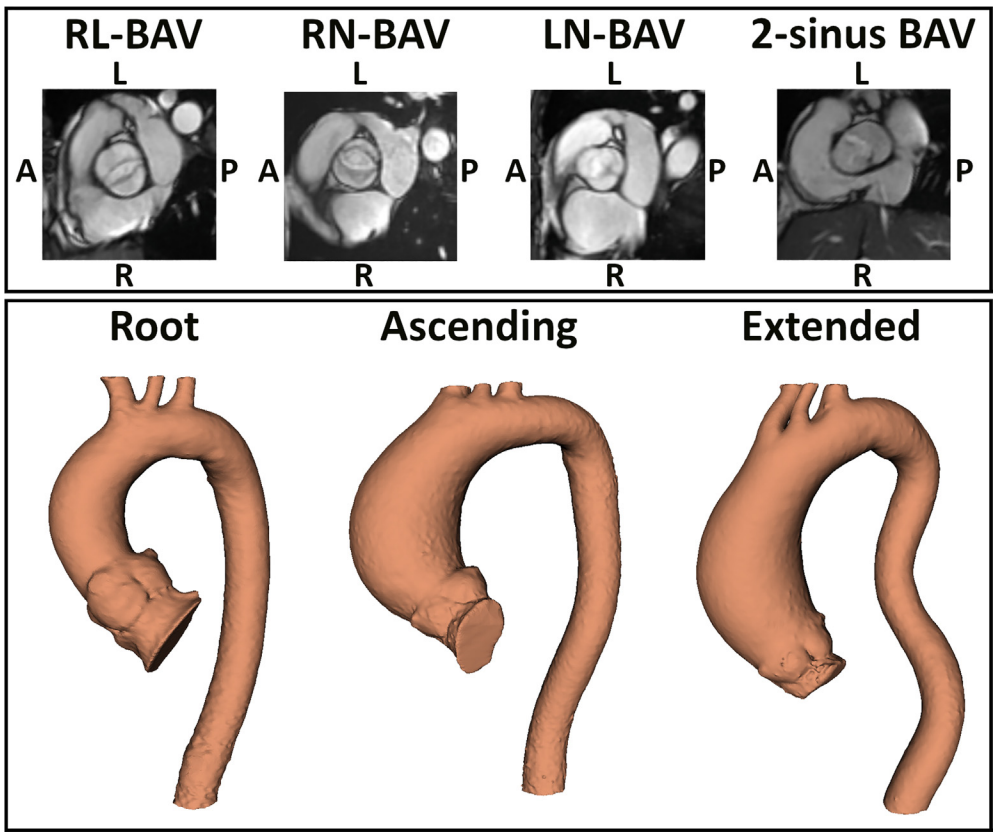
This review attempts to summarize and contextualize the scientific evidence regarding the presence and evolution of aortopathy in BAV, as well as the pathophysiologic mechanisms by which several factors induce structural changes in the aorta wall that contribute to its dilation. Better understanding of the mechanisms associated with this disease is crucial for optimizing the management and follow-up of these patients.

BICUSPID AORTOPATHY

The clinical expression of BAV-related aortopathy is the dilation of the thoracic aorta, which is the consequence of a complex pathologic process associated with disruption in elastin and collagen fibers, smooth muscle cell loss, metalloproteinase release, and loss of fibrillin 1 microfibrils.[29] Aortic dilation may affect all aortic segments from the root to the proximal midaortic arch,[30] with aortic root dilation being observed in approximately 20% to 30% of BAVs and AscAo dilation in 60% to 80%[2,9,15] and present even in the pediatric population without valve dysfunction.[31] The age-adjusted relative risk of aneurysm formation is 80 times higher in BAV than in the general population.[16] Dilation progression is more rapid in BAV than in TAV patients with degenerative aneurysms,[18,32] ranging from 0.2 to 2 mm per year, with an average of 0.3 to 0.8 mm/year,[4,9,32-35] and a small percentage of patients have a particularly fast dilation rate (mainly in the root).[4] The aortic growth rate has been associated with different risk factors such as age, hypertension, family history of aortic disease, and the degree of valvular disease.[4,9,35,36] Clinical and demographic variables associated with dilation and its progression rate are summarized in **Table 1**.

Depending on the region predominantly affected, 3 types of aortic phenotypes are identified[6]: the ascending phenotype, the root phenotype, and the extended (or effaced) phenotype (**Figure 1**). The ascending phenotype represents approximately 70% of BAV-related aneurysms.[2,4] It is the most frequent dilation phenotype in any valve morphotype; develops mainly in the anterior aortic wall; and, particularly in RN BAV, often extends to the aortic arch.[2,39] The ascending phenotype has been related to older age at diagnosis[40] and AS[2,40,41] (**Table 1**). The root phenotype, present in approximately 20% of BAV-related aneurysms, is associated with earlier age at diagnosis,[2] male sex,[2,9,15] and AR,[2,9,40-42] whereas AS is inversely related.[2,40] It is relatively frequent in RL and rarely present in RN BAV.[4,7,9,43] The root phenotype has been proposed as the most likely form associated with a genetic cause and may represent a

FIGURE 1 Bicuspid Aortic Valve Fusion Morphotypes and Dilation Phenotypes



(Top) Different BAV fusion morphotypes. **(Bottom)** Root, ascending, and extended aortic dilation phenotypes. A = anterior; BAV = bicuspid aortic valve; L = left; LN = left to noncoronary cusp; P = posterior; R = right; RL = right to left coronary cusp; RN = right to noncoronary cusp.

more malignant form, with faster growth rates[4] and higher risk of adverse aortic events.[44-46]

The 2 main phenotypes of aortic dilation may have different genetic bases[44,47,48] and different flow patterns.[49,50] Both genetic and hemodynamic alterations have been suggested as primary mechanisms responsible for aortopathy in BAV, as discussed in detail later. Establishing the cause of BAV-associated aortopathy is crucial to determine the optimal time for surgery in patients with isolated aortic aneurysms or the need to include aortic repair or substitution in patients undergoing aortic valve surgery.

PEDIATRIC POPULATION. Recent studies documented a trend in BAV fetuses toward larger aortic diameters at the aortic valve level[51] and that a third of newborns with BAV presented aortopathy.[3] These data suggest that aortic dilation could develop earlier than previously described, possibly supporting the genetic hypothesis and the need for screening in childhood. In fact, BAV was reported as the most common association with aortic dilation in the fetal period.[52] A recent study on BAV children showed that 50% presented aortic root or AscAo dilation, with the latter being more common.[31] AscAo dilation was independently associated with the RN BAV morphotype and increasing AR and AS severity, while root dilation was independently associated with the RL morphotype and increasing AR severity and was inversely related to AS. A history of coarctation was associated with smaller root and AscAo diameters.[31] Dilation is present even in children with normally functioning valves: a recent study reported aortic dilation in 37% of cases (z-score of >2.0), being severe (z-score of >4.0) in 4%.[31] In that study, aortic dilation severity increased with age, and valve interventions affecting the degree of AS or AR did not influence the growth rate.

Data on the evolution of aortic disease in childhood are scant. Aortic diameter progression was recently reported as very slow: 0.05 z-score units/year in the

TABLE 1 Clinical and Demographic Characteristics Associated With Bicuspid Aortic Valve and Related Aortopathy

		Associated With Aneurysms		Predicts Aneurysm Growth Rate or Formation			
	Mechanism	Aortic Root	Ascending Aorta	Aortic Root	Ascending Aorta	Predict Relevant Adverse Events	Potentially Modifiable
Age	Wall degeneration	↑[9,15,40]	↑[4,9,31,40]	↓[9] No[35]	↓[9,35]	↑ CV events[15] and dissections[16]	No
Sex	?	↑ in ♂[2,4,9,50]	↑ in ♀[2] ↑ in ♂[9]	↑ in ♂[35] No[9]	Similar[9,16,35] ↑ in ♂[82] ↑ in ♂[23]	♂ ↑ CV events,[15] dissections,[16] and BAV-related morbidity[23] ♀ ↑ mortality[23]	No
Hypertension or high(er) blood pressure	Wall stress	↑[2,4,15]	↑[2,4]	↑[35] No[9,36,40]	↑[35,40] No[9,33,36] ↑[23]	↑ CV[15] but not aortic[16] events	Yes
Aortic stenosis	Hemodynamic stress	↓[4,31,36,40]	↑[2,31,37,40,41,83]	No[9,35]	↑[35,36,38] No[9] ↑[23]	↑ CV[15] and aortic[16,38] events ↑ mortality in ♂[23]	Yes
Aortic regurgitation	Hemodynamic stress	↑[2,4,31,36,37,40,134]	↑[2,4,31,36]	No[9,35]	↑[4] No[9]	↑ CV[15] but not aortic[16] events ↑ mortality in ♀[23]	Yes

The ↑ symbol indicates a positive association, ↓ means a negative association, ♀ represents female sex, and ♂ represents male sex. "No" means no association/differences. The presence of aortic aneurysms in bicuspid aortic valve patients is related to different clinical variables. Aortic root dilation has been associated with male sex, hypertension, and aortic regurgitation and is reportedly less prevalent in patients with aortic stenosis. Ascending aorta dilation has been related to age, hypertension, and both aortic stenosis and regurgitation. Results regarding the role of these variables as predictors of aneurysm growth or formation are not always consistent. Age, male sex, hypertension, and aortic stenosis and regurgitation are established predictors of adverse CV events. Age and male sex are also established predictors of aortic dissection.

? = there is no evidence to support this information; BAV = bicuspid aortic valve; CV = cardiovascular.

AscAo and 0.01 *z*-score units/year in the root.[53] Severity of the valvular disease and presence of an uncorrected coarctation constituted the main predictors of increased dilation rates at both levels, with no impact of the BAV morphotype. It is worth noting that only 1.7% of patients had severe AscAo dilation (*z*-score of >8.0) in the absence of valve dysfunction vs 9.1% of those with valve dysfunction,[53] thus supporting the hypothesis that factors other than genetics may be involved in aortic dilation progression. Related aortic events such as dissection or primary replacement of the proximal aorta are extremely rare in children and adolescents.[31,53]

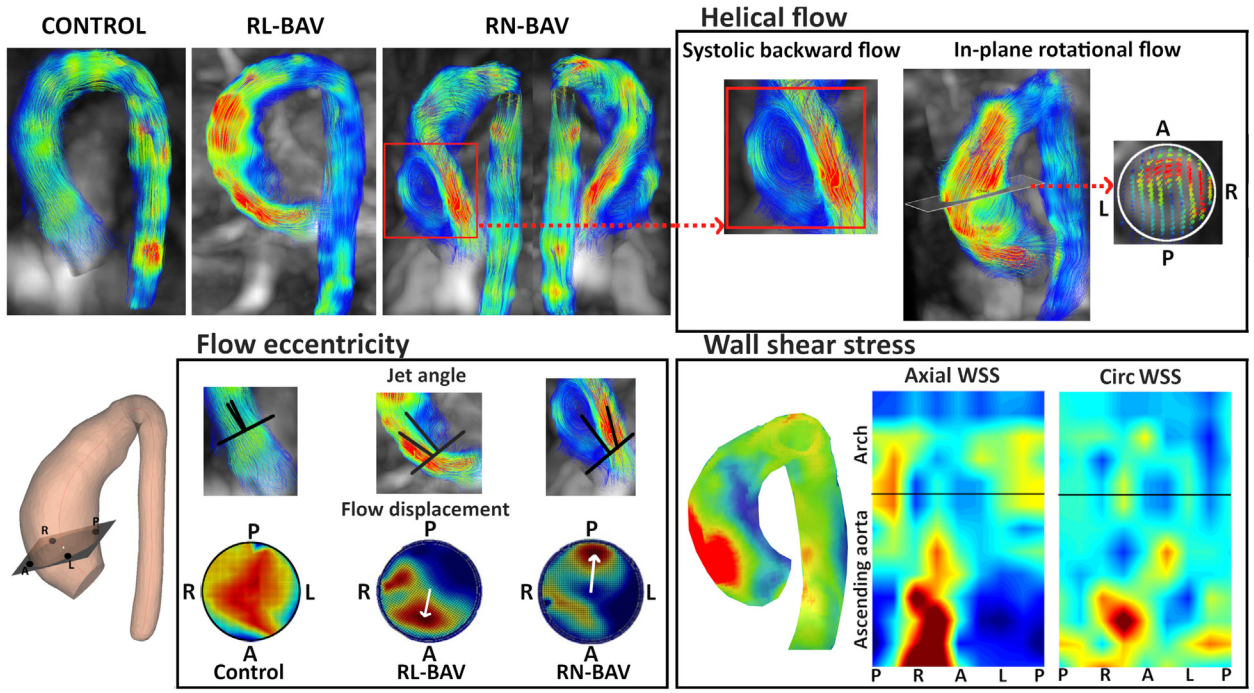
NONINVASIVE IMAGING IN THE EVALUATION OF BAV AORTOPATHY

Noninvasive imaging techniques such as transthoracic echocardiography, cardiovascular magnetic resonance (CMR), and computed tomography (CT) permit the assessment of aortic size and growth together with the identification of possible predictors of aneurysm formation and evolution.

AORTIC DILATION DETECTION. The evaluation of aortic dilation requires accurate and reproducible measurement of diameters from the annulus to the thoracic descending aorta (because of possible aortic coarctation) and periodic, lifelong evaluation to assess the dilation process.[19]

Transthoracic echocardiography is the first-line imaging technique used to evaluate the aorta; however, it is less precise in the measurement of aortic diameters, particularly beyond the aortic root.[9,19] Furthermore, marked aortic root asymmetry, common in BAV because of dilation opposite the commissural fusion, induces underestimation in the evaluation of its diameter in transthoracic echocardiography on the parasternal long-axis view, especially in the RN morphotype because the maximum aortic root diameter is approximately perpendicular to the valve opening.[54,55] However, the short-axis view by transthoracic echocardiography may be useful as an initial evaluation of root asymmetry.[56] CMR and CT have become the gold standard in aorta size evaluation because of their superior specificity and sensitivity. After multiplanar reformatting, they permit exact measurement of the thoracic aorta.[57] Controversy exists on how to assess aortic diameters, and various conventions have been considered,[21,57,58] while aortic diameters measured by different imaging modalities are not always comparable.[59] It is important to note that guidelines on aortic intervention are based on traditional manual measurements of mid ascending aortic diameters on axial images and aortic root dimensions on coronal images, which overestimate aortic diameters compared to current double-oblique and centerline measurements. Thus, some researchers suggested that the systematic underestimation of current double-oblique and centerline diameters compared to traditional assessment can be offset by a "left shift" on aortic diameter thresholds to indicate surgery at smaller dimensions than previously recommended.[57]

FIGURE 2 Altered Flow Dynamics by 4-Dimensional Flow CMR in BAV Patients



(Top left) Streamlines showing typical systolic flow in a healthy volunteer and eccentric flow in patients with BAV, with an anterior jet in RL BAV and a posterior outflow jet shifting anteriorly in the mid-distal ascending aorta in RN BAV. **(Top right)** Systolic retrograde flow and vortical (helical) flow. **(Bottom left)** Flow eccentricity, assessed by jet angle and flow displacement, showing a well-centered jet in a healthy control and eccentric jets toward the anterior or posterior wall in RL or RN BAV, respectively. **(Bottom right)** WSS maps. Magnitude (3 dimensional), axial, and circumferential WSS projections over 2-dimensional maps. Circ = circumferential; CMR = cardiac magnetic resonance; WSS = wall shear stress; other abbreviations as in Figure 1.

Because of the natural variability of aorta size related to patient age, sex, and body size, nomograms (or reference values) for aortic diameter have been developed.[60-63] Their adoption has been broad in pediatric patients, in whom changes in body size are substantial, whereas their use in adults is more limited. Reference values are often reported in terms of the *z*-score, which quantifies how many standard deviations below or above the population mean a measurement is. Aortic dilation is often defined as a *z*-score of ≥2.[31,60,61] The transition of aorta size assessment from childhood and adolescence to adult life is challenging because of different measurement conventions and different normal values, which rarely encompass such a transition.

A protocol for follow-up imaging in BAV patients has not been well established and should be individualized, with a frequency between 1 and 2 years depending on aortic diameters and cardiovascular risk factors.[64,65] When there is agreement in aortic diameters between transthoracic echocardiography and CMR/CT, echocardiography should be used for follow-up, but it needs to be confirmed by CT or CMR approximately every 3 years. CT or CMR should be indicated if aortic dilation is not confined to the aortic root or the proximal AscAo or in the case of disagreement with echocardiography. Also, CT or CMR should be used to confirm any diameter of ≥45 mm by echocardiography, regardless of its location (root or proximal AscAo) and to assess aortic root diameters when the short-axis view by echocardiography suggests an asymmetric aortic root.

ASSESSMENT OF AORTIC FLOW PATTERNS. The assessment of blood flow characteristics in BAV patients witnessed a revolution in the early 2000s, when 3-dimensional (3D) cine (ie, time-resolved) phase-contrast CMR with 3-directional velocity encoding, commonly called "4-dimensional (4D) flow CMR," was introduced.[66-68] This sequence provides a complete description of time-resolved blood velocity in the entire thoracic aorta (Figure 2) and permits the assessment of established parameters such as velocity, flow, and regurgitant fraction, with results comparable

to those obtained by conventional phase-contrast CMR.[66] Furthermore, 4D flow CMR permits the quantitative evaluation of more advanced flow parameters, with good to excellent reproducibility.[69-72] Among these, the most studied are jet angle (the angle of the jet relative to the centerline), normalized displacement (the distance between the center of the lumen and center of the velocity, often normalized to the lumen diameter), wall shear stress (WSS) (the force per unit of area acting tangentially to the aortic wall), in-plane rotational flow (the integral of vorticity over the cross-sectional area), systolic retrograde flow, viscous energy loss (energy dissipation associated with abnormal laminar flow), and turbulent kinetic energy (the intensity of turbulent velocity fluctuations).[66]

The quantification of these complex parameters in cohort studies has dramatically increased the understanding of the pathophysiology of aortic dilation. This is especially relevant in BAV, where the obtained flow descriptors have added understanding of the complex flow patterns and insight into a potential mechanism of aortic dilation, as will be detailed. Notably, this knowledge could not have been achieved without the development of 4D flow CMR sequences.[66,73]

ASSESSMENT OF AORTIC STIFFNESS. Several aortic stiffness descriptors such as distensibility, circumferential and longitudinal strain, and pulse wave velocity can be evaluated from CMR or transthoracic echocardiography images. Distensibility and circumferential strain quantify the circumferential deformation experienced by the aorta wall during the cardiac cycle, with or without normalization for pulse pressure, respectively.[74] Longitudinal strain evaluates the deformation enforced on the AscAo by contraction of the left ventricle, which moves the aortic valve plane downward and cyclically elongates the AscAo.[75,76] Pulse wave velocity assesses the overall structural stiffness of the analyzed region[77] and is considered the gold standard for aortic stiffness quantification. It can be measured by 4D flow CMR in any aortic region, by 2D phase-contrast CMR, normally through the aortic arch, or by tonometry in the region between the carotid and femoral arteries.

MECHANISMS OF AORTIC DILATION

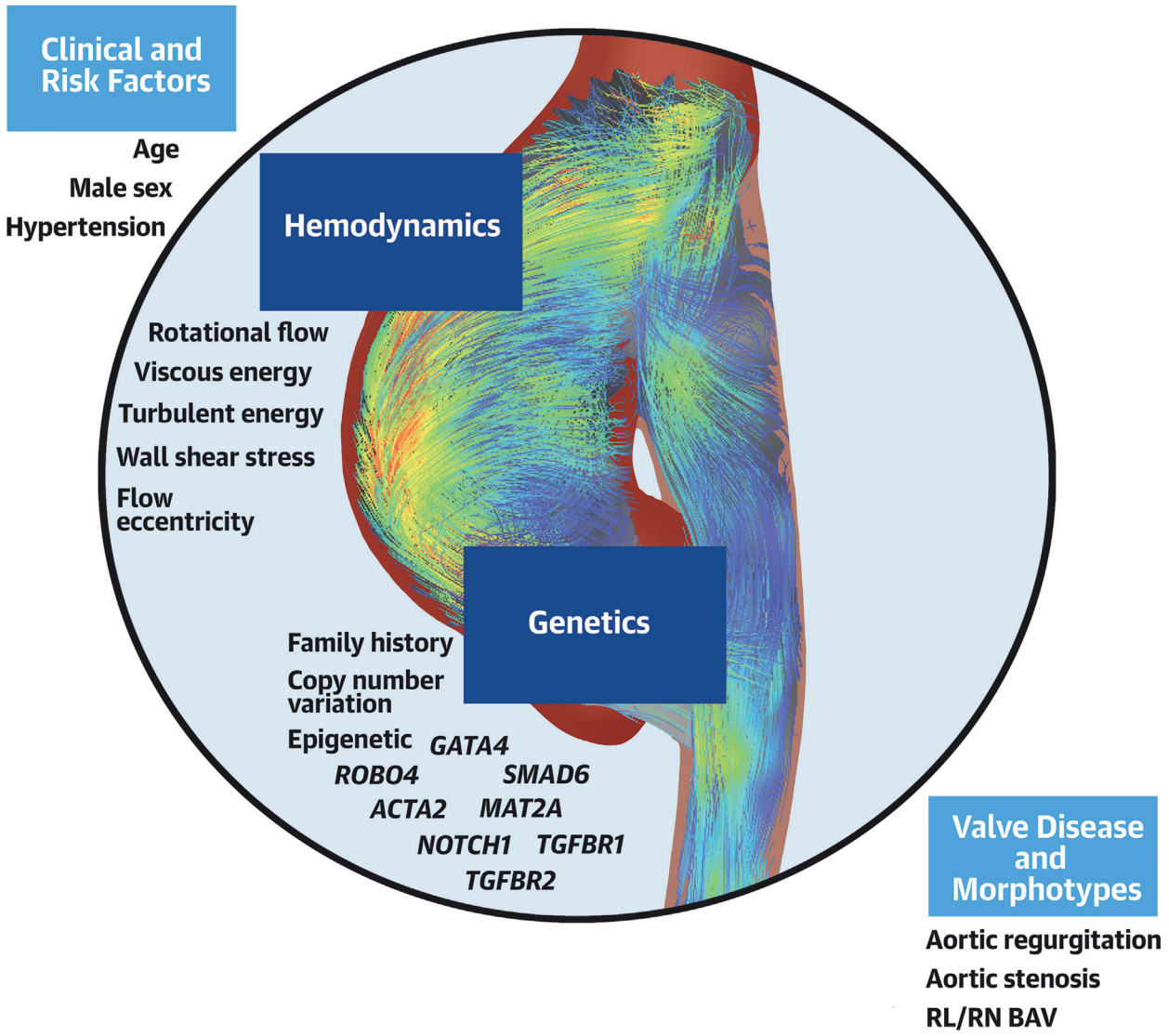
Different hypotheses have been proposed regarding the cause of aortic dilation in BAV, with 2 main theories being consolidated: 1) the genetic hypothesis postulates that genetic factors linked to BAV are responsible for intrinsic alterations of the aorta wall components that cause aortic dilation, thereby implying a need for a more aggressive surgical approach than in TAV,[47,48,78-81] as occurs in Marfan syndrome or other genetically mediated aortopathies; and 2) the hemodynamic hypothesis postulates that aortic dilation in BAV is a consequence of changes in the composition of the aortic wall caused by altered flow dynamics linked to the BAV,[33,34,49,73,82-84] which suggests that the indication for surgery should be more similar to that for TAV patients and possibly based on different risk factors, including flow biomarkers. These hypotheses are not mutually exclusive, and current evidence indicates a role for both mechanisms in the setting of BAV aortopathy.[27] In the next section, an in-depth discussion of the main factors playing a relevant role in aortic dilation is provided (**Central Illustration**).

GENETIC FACTORS. Beyond the hemodynamic bases of BAV, whereby altered blood flow through the valve during its formation determines an abnormal cusp formation,[85] the contributing role of genetics to the development of the disease has also been recognized.

Inheritance of aortic dilation in BAV. Despite most BAV cases being sporadic,[14,81] early studies identified familial clustering and its presence in monozygotic twins, thereby supporting an underlying genetic abnormality.[14,86,87] An autosomal dominant pattern of inheritance with incomplete penetrance has been described for BAV,[88] with its heritability estimated between 47% and 89%.[14,87] Additionally, the prevalence of BAV in first-degree relatives (FDRs) is around 6%, more frequent in men than women and not related to BAV morphotypes.[14] This higher male prevalence suggests that the loss of genes on the X chromosome may predispose to BAV formation[89]; however, these genes have not been identified to date. The highest penetrance of BAV in a genetic syndrome occurs in women with Turner syndrome, caused by partial or complete absence of one X chromosome.[89] Up to 30% of patients with Turner syndrome have a BAV,[90,91] presenting a higher prevalence of associated coarctation, aortic aneurysms, and acute aortic dissections than sporadic BAV cases.[92]

A higher prevalence of aortic dilation, around 10%, compared to the general population has also been observed in FDRs even with tricuspid aortic valves, with a root phenotype in 3% and an ascending phenotype in 7%.[14] Notably, the presence of small (<50%) valve leaflet fusion (partial fusion) has been documented in approximately 30% of patients initially considered as having TAV referred for surgery because of an AscAo aneurysm[93] and in FDRs of patients with BAV with dilated AscAo.[14] Along with

CENTRAL ILLUSTRATION **Mechanisms of Aortic Dilation in Bicuspid Aortic Valve Patients**



Rodríguez-Palomares JF, et al. J Am Coll Cardiol. 2023;82(5):448-464.

Several clinical and risk factors have been associated with aortic dilation. Ascending aortic dilation has been consistently associated with altered hemodynamics. Different genetic alterations have been found in BAV and partially explain dilation, mainly in the aortic root phenotype. BAV = bicuspid aortic valve; RL = right to left coronary cusp; RN = right to noncoronary cusp.

the presence of dilation in newborns with BAV,[3] these data support the hypothesis of an underlying genetic predisposition for aortic dilation. However, those newborns also presented higher flow velocities across the BAV without significantly smaller aortic valve areas compared to those with TAV, which indicates abnormal valve hemodynamics,[3] and a small valve leaflet fusion is also related to altered flow dynamics.[12] Based on this evidence, FDRs of individuals with BAV are advised to undergo echocardiographic screening to detect BAV and potential valvular and extravalvular complications.[19,20]

Genetic and molecular basis of BAV. *NOTCH1* was the first gene to be associated with inherited aortic valve disease and with other left-sided and right-sided congenital heart defects (such as tetralogy of Fallot, truncus arteriosus, or hypoplastic left heart syndrome)[94,95] in both familial[78] and sporadic BAV

cases.[79] However, *NOTCH1* variants explain only a small proportion of familial (2%) and sporadic (0.05%-0.08%) BAV cases, suggesting incomplete penetrance.[96] In this regard, genetic testing in patients with hereditary thoracic aortic aneurysm and BAV found no difference in the proportion of qualifying *NOTCH1* variants compared to control individuals.[80]

In families with inherited BAV, the mutated gene usually correlates with specific features and prognoses. Mutations in smooth muscle alpha actin (ACTA2) cause a syndrome that may include BAV and different vascular diseases.[97] Patients with Loeys-Dietz syndrome (TGFβR1 and TGFRβ2 mutations) have a higher prevalence of BAV than the general population.[81,98] Similarly, a 4-fold increase in BAV prevalence was described in patients with Marfan syndrome (FBN1 mutations) compared with the general population,[99] although other studies did not confirm this finding.[100] Because BAV and aortopathy often occur together, different underlying genetic variants may interact in an additive manner in BAV, thus increasing the risk for complications. Several other genes have been reported to be associated with BAV, although some of these associations may result from coexisting diseases. Recently, targeted sequencing of the coding regions of 9 genes previously associated with BAV (*NOTCH1*, *AXIN1*, *EGFR*, *ENG*, *GATA5*, *NKX2-5*, *NOS3*, *PDIA2*, and *TGFBR2*) showed they were not associated with BAV in a case-control population.[101] Whether the presence of BAV further influences the risk of aortic-related events in syndromic and nonsyndromic familial thoracic aortic aneurysm has not been systematically examined. A recent study in patients with Marfan syndrome found that the presence of BAV increases aortic diameters at any given age, thus requiring earlier prophylactic surgery.[100]

The uncertain functional status of identified genetic variants has nurtured further sequencing studies in BAV patients with more severe phenotypes, including the coarctation and root phenotype.[47] Larger genetic studies, including whole-exome sequencing and genome-wide association studies, have been conducted to identify genetic variants associated with BAV and aortopathy.[102,103] A whole-exome sequencing study failed to identify high-effect coding sense variants in multiple individuals with BAV.[102] That analysis in distant relatives from a large family with an autosomal-dominant inheritance of thoracic aortic aneurysm variably associated with BAV identified a rare variant in the *MAT2A* gene. However, further studies are required to establish the potential mechanisms by which this abnormality is associated with aortic diseases.[104] Also, based on a genome-wide single nucleotide polymorphism array, a study identified 47 recurrent copy number variations in BAV patients with thoracic aortic aneurysm that were absent or extremely rare in control individuals.[105] These findings suggest that rare copy number variations may disrupt the expression of cardiac or vascular developmental genes in these regions, further highlighting the genetic heterogeneity of BAV and the multiple disease mechanisms leading to aortopathy.

In BAV patients with a root phenotype, a cross-sectional next-generation sequencing study reported a wide spectrum of rare, potentially or likely pathogenic variants in 30% of patients, with NOTCH1 being the most common.[47] Other deleterious variants were revealed in AXIN1, NOS3, ELN, FBN1, and FN1. These results support the potential genetic origin of the associated aortopathy in this specific BAV cohort.

Recent data revealed that some epigenetic alterations may also contribute to the pathogenesis of the aortic dilation.[106,107] In BAV, a decrease in specific microRNAs has been associated with aortopathy.[108,109] Aortopathy, however, is also associated with aortic valve calcification and stenosis, which have been related to specific genetic alterations in TAV[110] and BAV[78] patients. Well-established cardiovascular risk factors such as smoking, hypertension, and dyslipidemia can also influence the development of valve disease and associated aortic dilation.[2,4,9,35,36] Thus, the interaction between a genetic substrate and valve-related flow abnormalities is very likely to be responsible for the ultimate expression of AscAo dilation.

The variety and complexity of BAV inheritance and genetic mediation in aortopathy are under intense investigation but remain to be fully clarified.[111] Collectively, available evidence supports the notion that the clinical heterogeneity of BAV aortopathy involves complex interactions among primary genetic defects, other genetic modifiers, and epigenetic factors as well as hemodynamic abnormalities. Consequently, genetic testing is not recommended for the typical BAV presentation, even if familial, unless there is a family history of aortic dissection or early or unexplained sudden cardiac death or syndromic features.[112] Nonetheless, it has recently been suggested that very young BAV patients (eg, <30 years old) with the root phenotype should undergo genetic testing in light of the potential absence of syndromic features with certain pathogenic variants associated with BAV (eg, transforming growth factor beta receptor, Loeys-Dietz syndrome).[112]

TABLE 2 Hemodynamic Characteristics Associated With Bicuspid Aortic Valve and Related Aortopathy

		Associated With Aneurysms		Predicts Aneurysm Growth or Formation		
	Abnormal in Bicuspid Aortic Valve	Aortic Root	Ascending Aorta	Aortic Root	Ascending Aorta	Predict Relevant Adverse Events
Jet angle	↑[50,83,131,142]	No[50]	↑[49,50,83,131]	?	?	?
(Normalized) flow displacement	↑[49,50,142]	↑[50,135]	↑[49]	?	↑[141]	?
Retrograde flow	↑[50,125]	?	↑[50,126]	?	?	↑ Surgery[126]
Rotational (helical) flow	↑[50,67,83,123,142]	No[50]	↑[50,67]	?	?	?
Turbulent kinetic energy	↑[128]	?	No[128]	?	?	?
Viscous energy loss	↑[125]	?	↑[125]	?	?	?
Wall shear stress						
Magnitude	↑[34,49,50,83,84,123,124,130,134,136,142] No[82]	No[50,134]	↑[124,125,134,136] No[84]	?	↑[33,34,82]	?
Axial	↑[50,82,123,130] No[142]	↑[50]	↑[125]	?	No[33,82]	?
Circumferential	↑[50,82,123,125,130,142]	No[50]	↑[50,83,125]	?	↑[33] No[82]	?
Angle	↑[82]	?	?	?	↑[82]	?
Distribution	↑[34,49,50,83,132]	↑[135]	↑[134]	?	?	?

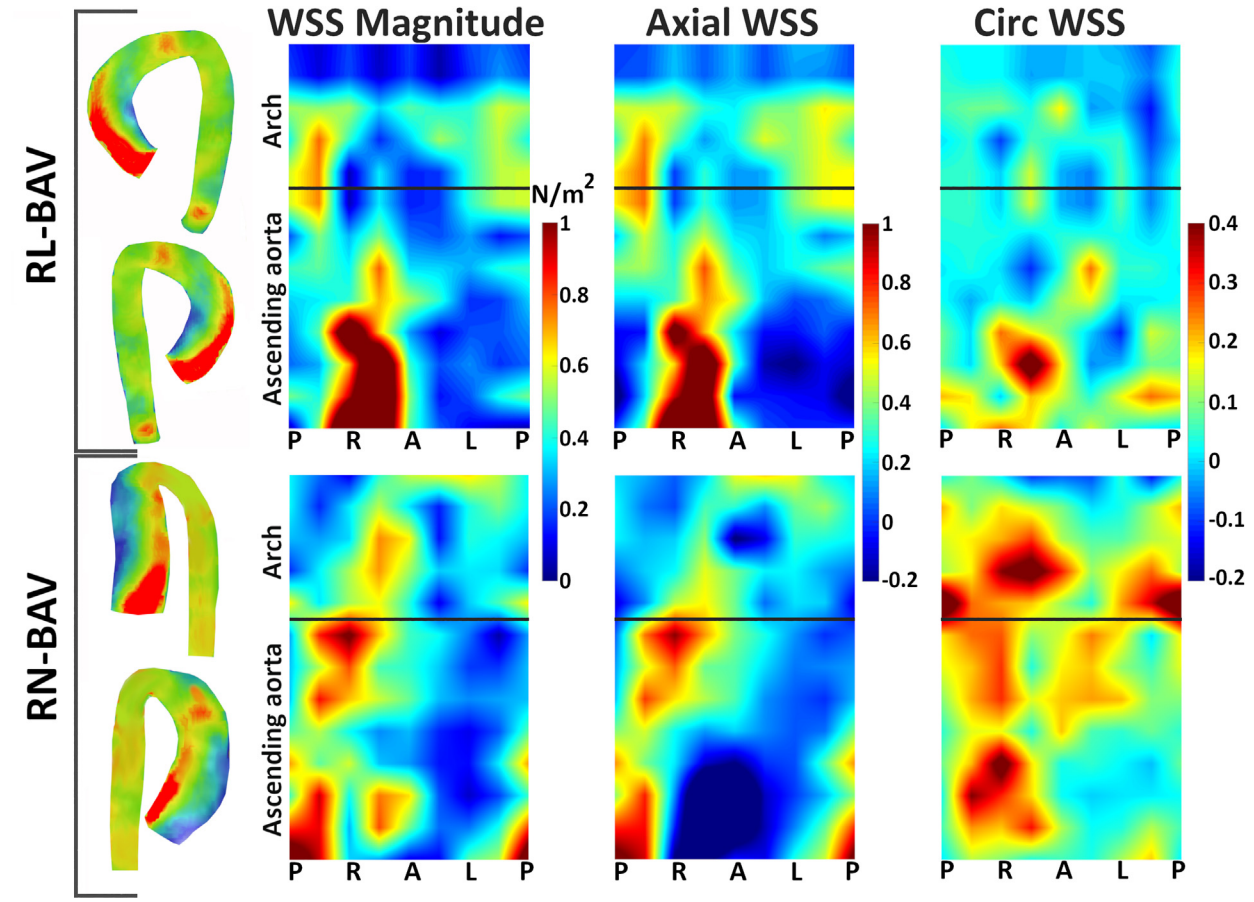
The symbol ↑ indicates a positive association or higher. "No" means that studies showed an absence of association. BAV produces abnormal flow dynamics, including a predominantly eccentric jet, helical flow, retrograde flow in systole, and increased turbulent kinetic energy and viscous energy loss that result in an asymmetrically increased wall shear stress. Several studies have associated these flow alterations with ascending aorta dilation. Normalized flow displacement and wall shear stress abnormalities have also been related to ascending aorta growth. The potential of these markers to predict adverse aortic events remains to be established.

? = there is no evidence to support this information.

AORTIC BIOMECHANICS. Biomechanical properties of the aorta wall represent a potential marker of intrinsic wall defect and susceptibility to aortopathy. Thus, recent advances in the understanding of BAV aortopathy included the analysis of aortic biomechanics, particularly aortic stiffness, a predictor of cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort.[113] Patients with BAV have been reported to have a stiffer aorta compared to healthy volunteers,[77,114-118] and aortic stiffness was shown to predict faster dilation rates and need for aortic replacement[76] and correlate with aorta wall degeneration.[84] Nonetheless, further research consistently showed that the positive relationship between aortic stiffness and diameter seen in BAV patients[77,83,114,115,117-120] was, notably, also true in healthy subjects,[114,115,119] thereby indicating that at least some of that relationship could be physiologic. Moreover, these results warned that the increase of stiffness in BAV compared to healthy subjects may be caused by differences in diameter between the compared groups, thus highlighting the need for diameter-matched (or -adjusted) comparisons. The largest study performed in BAV patients further showed that the stiffening of the AscAo with increasing diameter was limited to large aneurysms, whereas in the mild to moderate aortic dilation spectrum, a negative relationship was evident.[77] Nonetheless, once properly matched for aortic diameter, the vast majority of studies reported the absence of differences in aortic stiffness related to BAV,[83,119-122] regardless of the used aortic stiffness descriptor. An exception is the aortic root, reported to be stiffer in BAV patients even after correction for local diameter,[119] thus supporting the evidence for genetic triggering of aortopathy in this phenotype. Differently, AscAo aortopathy has been associated with BAV-induced altered aortic flow dynamics, as explained in the next section.

HEMODYNAMIC FACTORS. BAV produces flow disturbances in both the aortic root and AscAo,[13,49,50,67,83,123-125] which may persist in the aortic arch.[39,126] AscAo BAV-induced flow abnormalities include an increase in flow velocity in the absence of aortic valve stenosis[3,125]; predominantly eccentric jet[13,49,50,67,83]; sustained, mainly right-handed helical flow[13,67,83,127]; large retrograde flow in systole[13,50]; and increased turbulent kinetic energy[128] and viscous energy loss[125] (**Figure 2**). These abnormal flow characteristics may result in the WSS increase seen in BAV patients,[13,49,50,83,123,125,129] which is associated with aorta wall elastic fiber thinning and degeneration and extracellular matrix dysregulation.[73,84] WSS can be decomposed into the axial and circumferential directions.[130] Circumferential WSS is higher in BAV compared to TAV,[50,82,83,123,125] whereas axial WSS may be increased, normal, or decreased depending on the extent of local dilation.[13,50,82,123,125] WSS angle was proposed as a measurement of the relative importance of

FIGURE 3 **WSS in BAV Patients With Nonsignificant Valve Dysfunction**



The magnitude and axial WSS maps show right-anterior maximum WSS in a RL BAV patient **(top)**, and a proximal-posterior maximum shifting anteriorly at the mid-distal ascending aorta in a RN BAV patient **(bottom)**. Circumferential WSS is higher in RN compared to RL BAV in the ascending aorta and proximal arch. Abbreviations as in Figures 1 and 2.

circumferential over axial WSS and was reported to be abnormally high in BAV.[82] Flow abnormalities in BAV and their association with aortic dilation, growth rate, and adverse events are summarized in Table 2.

Notably, the few studies that included patients with no valve diseases and/or no aortic dilation showed that these flow abnormalities were still present,[39,67,83,125,132] even in pediatric patients.[83]

Impact of valvular morphotypes. Different flow patterns have been described depending on the valve morphotypes. Compared to RL, RN BAV presents more severe flow abnormalities, showing a more eccentric outflow jet and increased rotational flow in the AscAo[49,50,83] and proximal midaortic arch.[39] Thus, circumferential WSS is increased in the mid- and distal AscAo[50,83] and the aortic arch in RN compared to RL BAV[39] (Figure 3). Moreover, the velocity profile and maximum axial WSS are homogeneously distributed right-anteriorly in RL BAV, whereas RN presents more variable profiles with a mainly proximal-posterior distribution shifting anteriorly in the mid-distal AscAo.[49,50]

The presence of a small fusion between valve leaflets (partial fusion)[14,93] may also influence flow dynamics. FDRs of BAV patients with a partial fusion present higher flow eccentricity in the proximal mid-AscAo and vortexes in the distal AscAo.[12] Moreover, the length of fusion between leaflets is variable and has been related to flow asymmetry, vortexes, and circumferential WSS, as well as dilation of the root and AscAo, thereby possibly providing a pathophysiologic link with aortic dilation.[13]

Impact of valvular dysfunction. Aortic valve disease further exacerbates AscAo flow alterations, possibly contributing to dilation.[24,133,134]

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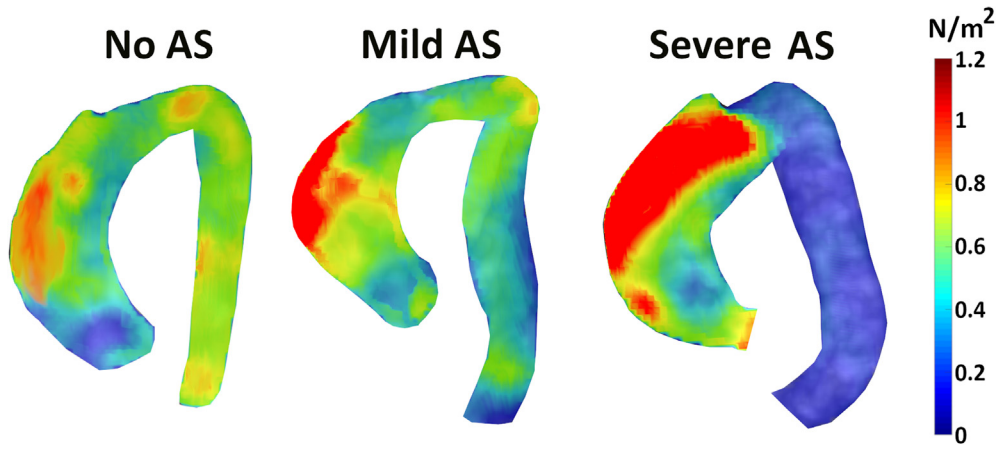
FIGURE 4 Effect of Aortic Stenosis on Wall Shear Stress in Bicuspid Aortic Valve



Example of wall shear stress maps in right to left coronary cusp bicuspid aortic valve patients with no valvular disease and mild or severe aortic stenosis and no aortic regurgitation.

The presence of AS has been associated with pronounced high-velocity eccentric jet, leading to markedly elevated flow velocities throughout the AscAo and arch (an extended flow jet).[83,133-137] These alterations in transvalvular flow are associated with an increase in flow turbulence[128,138] and a markedly asymmetrical increase in WSS both in BAV and TAV patients.[133,136] Van Ooij et al[133] showed that any degree of AS leads to an increase in regional WSS in BAV (**Figure 4**) and TAV patients, whereas moderate or severe AS blurred WSS differences between these valves, thus suggesting that the presence of AS dominates AscAo hemodynamics regardless of valve type. Similar findings were obtained in a study on BAV patients with AS, where a higher prevalence of arch dilation was found in cases of significant AS.[135] The potential contribution of AS-induced hemodynamics in the pathophysiology of aortic dilation is supported by histologic studies showing that increased WSS correlates with fiber thinning, particularly in AS,[84] and that regions where the jet impacts the wall are more affected by histologic alterations.[24]

Regional AscAo WSS variability increases with AS, reflecting the variability of stenotic transvalvular flow and associated complex flows.[133] In patients with AS, both viscous energy loss[125,139] and turbulent kinetic energy[128,138] are increased, indicating augmented cardiac afterload.[139] Turbulent kinetic energy may capture hemodynamic effects of the valvular morphotype and aortic morphology that are not assessable with echocardiography.[128]

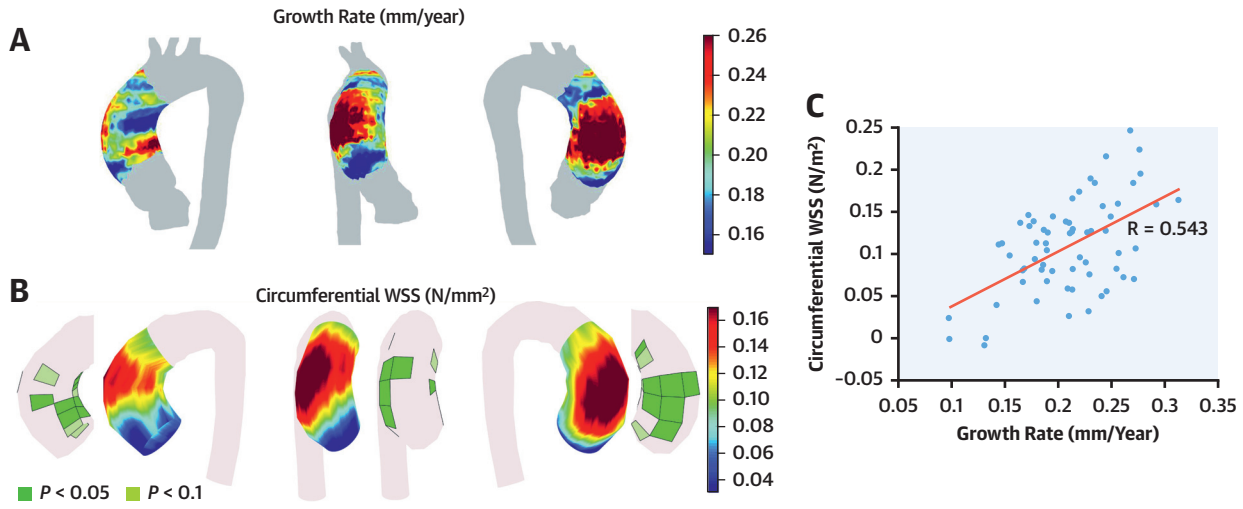
To date, very limited data are available regarding the specific flow variables and associated WSS patterns in patients with AR.[134] AR and AS have a different impact on aortic flow dynamics in RL BAV patients, with those with severe AR presenting a homogeneous (not eccentric) increase in regional WSS correlated positively with stroke volume.[134] Despite the limited data, there is evidence that AR leads to histologic aorta wall lesions in the AscAo[24,140] regardless of the aortic dilation.[140]

Therefore, the presence of valvular disease, common in BAV, is related to flow and hemodynamic disturbances that produce structural alterations of the aorta wall, which may predispose it to dilation.

Altered flow dynamics and aortic dilation. The aforementioned differences in flow characteristics among BAV fusion morphotypes are mirrored by differences in location of the dilation, thus supporting flow dynamics as a key player in the development of dilation phenotypes, even in the absence of valve disease.[39,49,50,83]

In cross-sectional studies, flow alterations associated with BAV have been postulated to exacerbate dilation.[13,39,50,67,83,128,141] Mahadevia et al[49] showed increased eccentricity to be locally related to aortic dilation, reporting higher flow displacement in the proximal and mid-AscAo of patients with the AscAo dilation phenotype, extending to the distal AscAo in cases of arch dilation. Rodríguez-Palomares et al[50] found the radial displacement of the jet and axial WSS to be independently associated with the root dilation phenotype, whereas circumferential WSS and systolic flow reversal were associated with AscAo dilation. Dux-Santoy et al[39] confirmed the association of aortic arch dilation with greater eccentric flow and

FIGURE 5 Aortic Growth and WSS in BAV Patients



Average regional maps of **(A)** aortic growth and **(B)** circumferential WSS, together with the significance of their regional statistical association. **(C)** Relationship between regional circumferential WSS and aortic growth. Adapted with permission from Guala et al.[33] BAV = bicuspid aortic valve; WSS = wall shear stress.

further showed that the presence of high rotational flow and circumferential WSS were independently associated with arch dilation. This study also showed that flow alterations associated with aortic dilation in BAV tend to disappear in the regions not affected by BAV aortopathy (ie, distal arch and descending aorta), further supporting the role of flow in aortic dilation.

Recently, 3 independent longitudinal studies established the predictive value of WSS and/or its components for future dilation rates[33,34,82] (**Table 2**). A retrospective longitudinal study reported that the fraction of AscAo wall exposed to abnormally high WSS was associated with an increased AscAo diameter growth rate.[34] A prospective longitudinal study further found that WSS, and particularly its circumferential component, predicts colocalized AscAo diameter growth rate, regardless of baseline AscAo diameter (**Figure 5**).[33] Another prospective study enrolling BAV patients with at least moderate valve disease showed WSS magnitude and WSS angle to be predictors of future AscAo volume growth irrespective of baseline AscAo volume.[82]

Whether flow alterations are induced by the presence of BAV or by the related aortic dilation has been controversial. However, there is now evidence suggesting that BAV per se is responsible for severe flow alterations. A study by Dux-Santoy et al[39] demonstrated that nondilated BAV patients had a higher normalized displacement, systolic flow reversal ratio, and circumferential WSS and a lower axial WSS compared to the control group. More data supporting this hypothesis are the normalization of flow disturbances after BAV replacement or repair.[142,143]

The increasing evidence of the role of altered flow dynamics in BAV aortopathy suggests that BAV patients may benefit from comprehensive hemodynamic assessment. In particular, WSS and its circumferential component are emerging as potential risk markers of AscAo dilation in this population. An initial 4D flow CMR at diagnosis may help to identify BAV patients with increased risk of dilation, which may deserve a closer follow-up.

LIMITATIONS AND FUTURE DIRECTIONS

Despite the promising results of the very recent 4D flow CMR longitudinal studies showing that hemodynamic alterations in BAV patients correlate with future ascending aortic growth,[33,34,82] these were still single-center studies with a limited number of patients. Furthermore, because of current technical limitations, the potential of hemodynamics to predict aortic root dilation remains largely unexplored. Prospective multicenter studies are needed to assess the predictive value of hemodynamic parameters in BAV aortopathy, including a deeper analysis of the clinical impact (prognosis) of valve disease. Differences in flow parameters among vendors and sequences,[144] as well as the limited availability of 4D flow CMR, have hindered the extrapolation of results and multicenter studies. To overcome this limitation, consensus on the acquisition and analysis of 4D flow CMR has to be

reached. Furthermore, the introduction of fast acquisition methods[145] and artificial intelligence-guided analysis,[146-148] still tedious and time-consuming, is expected to expand the adoption of these sequences into clinical practice.

Current clinical assessment of aorta size and growth is restricted to standardized analysis planes referenced to anatomic landmarks.[149] However, maximum dimensions and growth frequently occur at other sites[150] and are thus likely missed. Also, different morphologic parameters beyond aortic diameters, such as left ventricular outflow angle[24,151] and aortic tortuosity,[152] may play a role in BAV aortopathy. Thus, a comprehensive 3D aortic assessment, both in terms of morphologic analysis and dilation mapping,[150,153] could contribute significantly to the identification of predictors of adverse events.

Despite extensive efforts in the study of genetics in BAV, the identified genes account for only a small proportion of familial and sporadic cases of BAV and aortopathy. The analysis of large and well-phenotyped cohorts of BAV patients and relatives, along with the use of the standardized classification of BAV morphology and dilation phenotypes,[6] may help to identify genes that cause BAV and the associated complications.[81]

Understanding the contribution of flow dynamics and genetics in the pathophysiology of BAV aortopathy is likely to have implications for clinical practice by empowering risk stratification and the development of new preventive and therapeutic approaches based on hemodynamics or genetic risk profiles.

CONCLUSIONS

Whether BAV aortopathy has a genetic basis or results from altered hemodynamics has been widely debated, and current evidence highlights that both contribute to aortic dilation. Underlying genetic alterations have been able to explain only a small proportion of BAV cases and associated aortopathy. In particular, dilation of the aortic root, which has been found to be a more malignant form of BAV aortopathy, has been mainly related to genetic alterations. On the other hand, dilation of the ascending aorta has been consistently related to altered flow dynamics, shown to locally correlate with histologic aortic wall disruption and aortic growth rate. A comprehensive 3D assessment of aortic morphology and flow dynamics in future prospective multicenter studies is warranted to confirm these findings, which may greatly improve the clinical management of BAV patients.

ACKNOWLEDGMENT The authors are grateful to Christine O'Hara for English revision.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by funding from the Instituto de Salud Carlos III (projects ICI14/00197, PI17/00381 and PI20/01727); the Spanish Ministry of Science, Innovation, and Universities (RTC2019-007280-1); the Spanish Society of Cardiology (SEC/FEC-INV-CLI 20/015 and SEC/FEC-INV-CLI 21/030); and the Biomedical Research Networking Center on Cardiovascular Diseases. Dr Guala has received funding from the Spanish Ministry of Science, Innovation and Universities (IJC2018-037349-I) and from "la Caixa" Foundation (LCF/BQ/PR22/11920008). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Jose Fernando Rodriguez-Palomares, Department of Cardiology, Hospital Universitari Vall d'Hebron, Paseo Vall d'Hebron 119-129, 08035 Barcelona, Spain. E-mail: jfrodriguezpalomares@gmail.com. Twitter: @JRodriPalomares. OR Dr Andrea Guala, Department of Cardiology, Hospital Universitari Vall d'Hebron, Paseo Vall d'Hebron 119-129, 08035 Barcelona, Spain. E-mail: andrea.guala@vhir.org. Twitter: @andreaguala6.

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KEY WORDS aortic dilation, aortopathy, bicuspid aortic valve, pathophysiology, state of the art