2022

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Canadian Journal of Cardiology 38 (2022) 688–694

Clinical Research

Regional Vascular Changes and Aortic Dilatation in Pediatric Patients With Bicuspid Aortic Valve

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See editorial by Bradley, pages 557–559 of this issue.

ABSTRACT

Background: Bicuspid aortic valve (BAV) is the most common congenital heart disease, often associated with valve dysfunction, coarctation of the aorta, and ascending aorta dilatation. Aortic dilatation might result from abnormal regional hemodynamics or inherent vascular disease. Vascular function in pediatric BAV remains poorly characterized.

Methods: A cross-sectional study was performed to evaluate vascular function in 142 children with BAV aged 7-18 years compared with healthy control children. Echocardiography was performed to assess aortic dimensions, BAV function, and vascular function (aortic arch

RÉSUMÉ

Contexte : La bicuspidie valvulaire aortique (BVA) est la cardiopathie congénitale la plus fréquente. Elle est souvent associée à une dysfonction valvulaire, à une coarctation de l'aorte et à une dilatation de l'aorte ascendante. La dilatation aortique peut résulter d'une anomalie de l'hémodynamique locale ou d'une vasculopathie intrinsèque. La fonction vasculaire des enfants atteints de BVA demeure mal caractérisée.

Méthodologie : Une étude transversale a été menée afin de comparer la fonction vasculaire de 142 enfants atteints de BVA âgés de 7 à 18 ans à celle d'enfants du groupe témoin en bonne santé. Les sujets ont

Bicuspid aortic valve (BAV) is the most common congenital cardiac malformation, with a prevalence of 1%-2%.[1] It is associated with coarctation of the aorta (CoA), ascending aorta dilatation in up to 80% of patients, and an 8- to 9-fold risk of aortic dissection.[2-4] There is considerable debate regarding the etiology of aortic dilatation. Two proposed mechanisms are hemodynamic flow disturbances, resulting in increased wall shear stress in the proximal aorta,[4-8] and genetic abnormalities resulting in intrinsic weakness of the aortic wall.[4,9] Our group and others have reported valve morphology, aortic stenosis (AS), and aortic insufficiency (AI) to be independently associated with ascending aortic dilatation.[10] However, even in BAV with no AS or AI, and in patients with trileaflet valves but a family history of BAV, there might be significant ascending aorta dilatation.[5,8,10-12]

Structural changes in aortic wall composition in BAV include cystic medial necrosis and disruption of extracellular matrix,[4] changes that might translate to increased arterial stiffness and an increased risk for cardiovascular events and mortality.[13,14] Increased arterial stiffness and impaired elasticity have been described in children and adults with BAV and are independent of the degree of aortic dilatation[15-19] and

Received for publication November 18, 2021. Accepted January 18, 2022.

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See page 693 for disclosure information.

https://doi.org/10.1016/j.cjca.2022.01.020

pulse wave velocity [PWV]), carotid intima media thickness, and aortic stiffness and distensibility). Carotid-femoral and carotid-radial PWV were assessed using tonometry. Vascular function was compared for 4 patient groups stratified according to aortic dilatation and a history of coarctation of the aorta. Multivariate regression analysis was performed to determine predictors of aortic dilatation.

Results: Children with BAV had stiffer and less distensible ascending aortas with higher aortic arch PWV compared with control children. Carotid-femoral and carotid-radial PWV were not increased in patients with BAV, and the vascular assessment of the abdominal aorta was unremarkable. Multivariate regression revealed that aortic arch PWV was the only vascular function parameter that was associated with aortic dilatation.

Conclusions: Children with BAV have differences in vascular function that are confined to their proximal aorta, even in normal functioning BAV. The observed differences in vascular function are likely multifactorial, with contributions from abnormal regional flow and a potential localized primary aortopathy.

subi une échocardiographie afin d'évaluer les caractéristiques suivantes : dimensions de l'aorte, fonction de la valvule aortique et fonction vasculaire (vélocité de pouls [VOP] de l'arc de l'aorte, épaisseur de l'intima-média de la carotide ainsi que rigidité et capacité de dilatation de l'aorte). La VOP carotido-fémorale et carotido-radiale ont été évaluées par tonométrie. La fonction vasculaire a été comparée chez les quatre groupes de patients stratifiés en fonction de la dilatation aortique et des antécédents de coarctation de l'aorte. Une analyse de régression multivariée a été effectuée afin de déterminer les prédicteurs de la dilatation de l'aorte.

Résultats : L'aorte ascendante des enfants atteints de BVA était plus rigide et moins distensible que celle des enfants du groupe témoin, et la VOP de leur arc aortique était plus élevée. Les VOP carotido-fémorale et carotido-radiale n'étaient pas plus élevées, et l'évaluation vasculaire de leur aorte abdominale n'a rien révélé de particulier. L'analyse de régression multivariée a indiqué que la VOP de l'arc aortique était le seul paramètre de la fonction vasculaire associé à une dilatation aortique.

Conclusions : Les enfants atteints de BVA présentent des différences de fonction vasculaire qui se limitent à la portion proximale de l'aorte, même si la valve aortique bicuspide fonctionne normalement. La cause de ces différences de fonction vasculaire est probablement multifactorielle, s'expliquant entre autres par une anomalie du flux régional et une possible aortopathie primaire localisée.

valve function.[16,20] The increase in stiffness seems to precede the onset of aortic dilatation, and pediatric patients with significant aortic dilatation might therefore represent a more severe vascular phenotype. Children with BAV and CoA represent another subset of patients whose vascular function is abnormal, although it is not clear if the abnormal elastic properties in this population are due to the coarctation alone or other factors related to BAV.[21-23] Providing a comprehensive evaluation of aortic vascular function in different phenotypes of pediatric patients with BAV might help to identify aortic wall anomalies that confer greater cardiovascular risk as adults.

The aim of this study was to describe vascular function in pediatric patients with different presentations of BAV (with or without aortic dilatation and CoA) compared with normal control children. We hypothesized that children with BAV have abnormalities in their vascular function and that these abnormalities are more pronounced in children with dilatation or CoA.

Methods

Participant recruitment and inclusion criteria

The study was approved by the Research Ethics Board at the Hospital for Sick Children. Written informed consent was obtained from all participants. A cross-sectional study was performed in 142 children recruited from a single centre (Hospital for Sick Children, Toronto, Ontario, Canada) between 2014 and 2017. Inclusion criteria were age between 7 and 18 years and a diagnosis of BAV. Exclusion criteria included: associated congenital heart disease (not including CoA) and known genetic syndromes. Patients were classified into 4 groups: presence or absence of ascending aortic dilatation (z-score $>$ 2), and presence or absence of CoA or history of CoA. Patients underwent a vascular and functional echocardiogram. A total of 142 age- and sex-matched healthy control children underwent similar cardiovascular imaging. Clinical data including associated congenital heart disease, history of CoA, history of cardiac procedures, and the presence of genetic abnormalities were collected from the electronic patient records.

Echocardiography

All cardiovascular imaging was performed prospectively with the participant in a quiet room after 10 minutes of supine rest by 2 experienced cardiovascular sonographers (C.S., W.H.) or a pediatric cardiologist (M.G.). Echocardiography was performed using a standardized functional protocol[24] using a GE Vivid 7 or Vivid E9 system (General Electric Medical Systems, New York, NY). Images were stored in RAW data format and all measurements were conducted offline using EchoPAC version 110.1.3 (General Electric Medical Systems). Echocardiograms were analyzed to determine BAV morphology, maximal aortic dimensions (annulus, sinus of Valsalva, sinotubular junction, and ascending aorta at the level of the right pulmonary artery), and the presence and severity of AS, AI, and CoA. All measurements were converted into z-scores on the basis of the Hospital for Sick Children z-scores (Supplemental Table S1). The degree of AI was determined from the echocardiography report on the basis of published guidelines.[25] The severity of AS was categorized on the basis of the highest reported mean pressure gradient obtained using continuous wave Doppler (none: $<$ 10 mm Hg, mild: 10-25 mm Hg, moderate: 25-40 mm Hg, and severe: $>$ 40 mm Hg).[26] The presence of CoA was determined from the echocardiography report, and was on the basis of the isthmus dimension, peak instantaneous gradient across the isthmus, and the abdominal aorta Doppler flow pattern.

Vascular measurements

Vascular echocardiographic measurements were obtained using a GE Vivid 7 system (General Electric Medical Systems) using a standardized vascular functional protocol.[27,28] Briefly, the common carotid arteries were imaged with a 12-MHz linear-array transducer, and carotid intima media thickness (CIMT) was calculated using an automatic edge detection algorithm averaged over 10 cardiac cycles (Carotid Analyser; Medical Imaging Applications, Coralville, IA). The mean of 3 CIMT measurements was calculated for the right and left common carotid arteries. Central (aortic arch) pulse wave velocity (PWV) was measured from the suprasternal notch aortic arch view as previously described.[29] The maximum and minimum luminal diameters of the ascending and abdominal aorta were measured using M-mode echocardiography and the elastic pressure modulus (EPM), stiffness index, and distensibility were calculated (Supplemental Table S2).[27] Peripheral carotid-radial and carotid-femoral PWV were measured using applanation tonometry (SphygmoCor; AtCor Medical, Sydney, New South Wales, Australia).

Statistical analysis

Categorical data are reported as frequency and percentage, and continuous variables are expressed as the median and interquartile range or mean and standard deviation as appropriate. The Mann−Whitney test or student *t* test were used to assess the differences in aortic parameters for children with BAV compared with healthy control children. Differences in frequencies among the different phenotypes of BAV were assessed using Fisher exact test, whereas differences in continuous variables were assessed using the Kruskal-Wallis test. Multivariable regression was used to determine associations between ascending aorta or aortic sinus z-score and various clinical, vascular, and valvular characteristics including a history of CoA, the previously mentioned vascular measurements, BAV morphology, and the degree of AS and AI. Significance level of 5% was applied to all analyses. Data analysis was conducted using SAS version 9.4 (SAS Statistical Software, Cary, NC) and GraphPad Prism (GraphPad Software, San Diego, CA).

Results

Participant characteristics

Table 1 includes a summary of the demographic and baseline clinical characteristics of the cohort. Mean age at baseline assessment was 13.4 years (SD, 3.2 years), and 72% were male. Sixty-four percent had right and left coronary cusp fusion BAV morphology and 60% had less than mild AS and AI. Approximately half of the population had a history of CoA, with 15% having residual CoA. The ascending aorta was dilated (z-score $>$ 2) in 81 (57%) patients, and moderately or severely dilated (z-score $>$ 4) in 21 (15%) patients.

Vascular function parameters

The measures of vascular function are shown in Table 2. There was trend for aortic arch PWV to be higher in BAV children compared with control children with significantly higher PWV in patients with isolated BAV with ascending aorta dilatation. Carotid-femoral PWV was lower in children with BAV compared with control children with no differences between subgroups. Children with BAV had higher ascending aorta EPM and stiffness and lower distensibility with no differences between subgroups. Patients with isolated BAV had less stiff, more distensible abdominal aortas compared with control children with no differences in the dilated vs non-dilated groups. CIMT was significantly higher in children with BAV compared with control children. Children with BAV and CoA had higher CIMT than those with isolated BAV, regardless of dilatation. These parameters of vascular function were influenced by the presence of AS and AI (Supplemental Figs. S1-S3). There were no differences between male and female children.

Association of valve characteristics and vascular function with aortic dilatation

Multivariable regression analysis is shown in Table 3. Increasing severity of AI was independently associated with ascending aortic dilatation. History of CoA was inversely associated with ascending aortic dimension. BAV valve morphology and AS were not associated with increased ascending aortic dimensions. In terms of vascular function, only aortic arch PWV was independently associated with ascending aortic dilatation. Similar analysis for aortic sinus z-score showed increasing AI severity and aortic arch PWV to be independently associated with aortic sinus dilatation. Carotid-femoral PWV was not associated with either aortic sinus or ascending aortic dimension.

PWV measurements were similar in patients with well functioning BAV compared with control children (Supplemental Fig. S1). Aortic arch PWV was increased in patients with moderate or severe AS with a weakly positive correlation with AS mean gradient ($r = 0.19$; $P = 0.04$). Carotid-femoral PWV was decreased in patients with moderate or severe AS and moderate or severe AI. There was a weakly negative correlation between AS mean gradient and carotid-femoral PWV ($r = -0.22$; $P = 0.02$).

Children with well-functioning BAVs had a higher ascending aorta EPM and stiffness index, and a lower ascending aorta distensibility compared with control children. There was a lower EPM and stiffness index, and a higher distensibility in patients with moderate or severe AI (Supplemental Fig. S2). Moderate or severe AI was also associated with a lower EPM and stiffness index, and a higher distensibility in the abdominal aorta (Supplemental Fig. S3).

Discussion

This study provides a comprehensive assessment of vascular function in a large cohort of children with BAV with varying degrees of aortic dilatation, CoA, and valvular dysfunction. We found changes in vascular function in the pediatric BAV population, that were confined to the ascending aorta without any significant abnormalities more distally. Increased aortic arch PWV was independently associated with ascending aorta and aortic root dilatation. However, no other measure of vascular function was independently associated with aortic dilatation, and the differences in other measures of vascular function were more related to valve dysfunction and the presence of CoA. Taken together, our results suggest that pediatric patients with BAV have evidence

Table 1. Characteristics of children with BAV compared with control children

	BAV baseline visit	Control	*P* (if significant)
Male sex, n (%)	142 (72)	142 (68)	
Age (SD), years	13.4 (3.2)	13.6 (2.8)	
Systolic blood pressure (SD), mm Hg	109.8 (12.8)	108.4 (10.0)	
Diastolic blood pressure (SD), mm Hg	58.9 (6.3)	57.1 (7.5)	0.025
BAV morphology, n (%)			
R-L	90 (64)		
R-N	47 (33)		
L-N	4 (3)		
AS			
None	74 (52)		
Mild	40 (28)		
Moderate or greater	27 (19)		
AI			
None	55 (39)		
Mild	66 (47)		
Moderate or greater	20 (14)		
≤ Mild AS and AI	85 (60)		
Aortic coarctation	68 (48)		
Aortic sinus dilatation			
None (%)	124 (87.3)		
Mild (%)	18 (12.6)		
Moderate or greater (%)	0 (0)		
Ascending aortic dilatation			
None (%)	61 (43)		
Mild (%)	59 (41.5)		
Moderate or greater (%)	22 (15.5)		
Aortic diameter			
Annulus Z (SD)	1.0 (1.7)	0.2 (1.3)	< 0.001
Aortic sinus Z (SD)	0.5 (1.4)	−0.4 (1.0)	< 0.001
Aortic STJ (SD)	0.6 (1.5)	−0.3 (0.9)	< 0.001
Ascending aorta (SD)	2.3 (1.6)	0.6 (0.8)	< 0.001

AI, aortic insufficiency; AS, aortic stenosis; BAV, bicuspid aortic valve; L-N, left and noncoronary cusp; R-N, right and noncoronary cusp; R-L, right and left coronary cusp; STJ, sinotubular junction.

of vascular remodelling and dysfunction localized to the proximal aorta

We found evidence of vascular functional changes in all phenotypes of BAV regardless of presence of CoA or aortic dilatation. There was evidence of vascular abnormalities in other proximal vessels, specifically increased CIMT, although these were most related to the presence of CoA and might be related to physiologic adaptation to increased blood pressure rather than vascular dysfunction.[30] Vascular functional changes were not observed in the more distal aorta. Our findings are consistent with other pediatric studies that reported increased stiffness parameters in BAV in the absence of significant valve dysfunction.[16] Our findings support the theory of a more localized disease process in childhood and not a generalized vascular disease. We could not demonstrate increased carotid-femoral PWV in children with BAV, an abnormality that has been reported in the adult BAV population[13,14,31] but not seen in recent data from a mixed population including younger adults and children.[32] The discrepancy between adult and pediatric data might stem from the fact that the full phenotype of aortic disease might take more time to manifest, or that measurement of PWV might be less sensitive for detecting subtle changes in vascular stiffening in the pediatric age range.

Measurement of aortic PWV is a strong predictor of future cardiovascular events and all-cause mortality in a variety of adult populations.[13,14,19,33,34] In adults, the increased carotid-femoral PWV is restricted to patients with BAV and aortic dilatation,[19,33-35] with some studies reporting more extensive systemic vascular abnormalities in this subgroup including systemic endothelial dysfunction, and higher plasma matrix metalloproteinase-2 levels.[33] These data suggest more diffuse aortic remodelling in this subgroup later in life, and a greater cardiovascular risk compared with nondilated BAV patients. Greater aortic stiffness measured according to carotid-femoral PWV was independently associated with faster aortic aneurysm growth in patients with BAV.[31] Adult patients might have additional etiologies for increased carotid-femoral PWV including atherosclerosis, and it is not clear how these factors interact with the BAV phenotype. Young children with significant aortic dilatation are likely to have significant dilatation as adults and will hence also have a high risk for dilatation-related complications as adults. However, long-term longitudinal studies with repeated vascular assessments are needed to determine whether vascular dysfunction and aortic dilatation in childhood correlates with adverse aortic outcomes in adulthood.

Aortic arch PWV was independently associated with ascending aorta and aortic sinus dilatation. Aortic arch PWV is a marker of compliance of the ascending aorta and aortic arch, and it is certainly possible that vascular dysfunction in this area predisposes to aortic dilatation. Ascending aorta dilatation was also associated with moderate or severe AI and the absence of CoA, whereas aortic sinus dilatation was also associated with moderate or severe AI. Our group, along with others, have previously reported an association between the presence and severity of aortic dilatation (ascending aorta and aortic sinus) and valve dysfunction (AS and AI), BAV morphology (right and non coronary cusp fusion), and the absence of CoA.[10] There was no association in our current cohort with AS or BAV morphology and overall there are conflicting reports in the literature regarding the effect of these factors on aortic dilatation.[4,10,36] We suspect that our current study and some of the previous reports were underpowered to detect more subtle associations including the effect of AS and BAV morphology.

In our cohort, a history of CoA was associated with significantly less ascending aorta dilatation, despite having higher CIMT compared with other BAV subgroups. Several studies have previously reported a lower prevalence rate of aortic dilatation in patients with BAV and CoA compared with those with isolated BAV,[31,36] and a slower progression of aortic dilatation post CoA repair.[31] This might in part be related to lower rates of valve dysfunction in BAV associated with CoA compared with isolated BAV.[10] Although thicker vessels as evidenced by increased CIMT in patients with CoA might provide protection against aneurysm formation, this protective effect is not well supported in the adult BAV literature, which reports CoA as a risk factor for aortic events.[31,37] This might, however, suggest a different underlying pathophysiology for patients with isolated BAV and those with associated CoA, which merits further investigation.

Previous studies have suggested that a genetically inherited vasculopathy is the cause of ascending aorta dilatation in

Table 2. Vascular function parameters in "extreme phenotype" BAV groups

	All Bav (n = 142)	No CoA, no Dil (n = 19)	No CoA, with Dil (n = 54)	CoA, no Dil (n = 42)	CoA, with Dil (n = 23)	Control (n = 142)	*P* all BAV vs control	*P*, Bav subgroups
Aortic Z scores								
Ascending aorta	2.33	1.02	3.50	0.87	3.14	0.59	< 0.001	< 0.001
Aortic root	0.53	−0.49	0.80	0.15	1.29	−0.42	< 0.001	< 0.001
Pulse wave velocity								
Aortic arch	4.62	5.12	4.91	3.99	4.97	4.24	0.051	0.039
Carotid-femoral	4.63	4.90	4.25	4.30	5.30	5.20	< 0.001	0.005
Carotid-radial	6.50	6.65	6.45	6.45	6.80	6.70	0.048	
Ascending aorta biophysical profile								
EPM	355	353	333	369	454	309	0.002	
Stiffness index	4.43	4.52	4.27	4.57	5.59	3.81	0.003	
Distensibility	0.28	0.28	0.30	0.27	0.22	0.32	0.002	
Abdominal aorta biophysical profile								
EPM	228	217	201	254	275	255	0.012	0.013
Stiffness index	2.81	2.58	2.68	3.16	3.24	3.17	0.006	0.012
Distensibility	0.44	0.46	0.50	0.39	0.36	0.39	0.012	0.013
Right CIMT	0.46	0.43	0.46	0.46	0.49	0.44	0.001	0.003
Left CIMT	0.46	0.43	0.45	0.47	0.47	0.44	< 0.001	

BAV, bicuspid aortic valve; CIMT, carotid intima media thickness; CoA, coarctation of the aorta; Dil, dilatation; EPM, elastic pressure modulus.

patients with BAV. Studies on familial clusters of BAV showed isolated aortic dilatation and abnormal vascular properties of the aortic root in family members with trileaflet aortic valves.[12] Elevated central aortic stiffness is observed in pediatric patients with Turner and Marfan syndromes, even in the absence of aortic dilatation. Patients with Turner syndrome show increased stiffness that is localized to the ascending aorta and arch, whereas the entire ascending thoracic aorta and descending thoracic aorta are uniformly affected in patients with Marfan syndrome,[38] as expected in a generalized arteriopathy. Interestingly, the presence of a BAV in pediatric patients with Turner syndrome was associated with more pronounced aortic stiffness compared with patients with a tricuspid aortic valve, suggesting an additive effect of BAV and an intrinsic wall abnormality.[39] Our findings suggest that a generalized arteriopathy is not present in pediatric patients with BAV. They are more consistent with either a localized arteriopathy or other rheological factors as an etiology for aortic dilatation.

This study has some limitations inherent to its cross-sectional design, which precludes any inferences on causality or temporality of the observed vascular changes. Our cohort was recruited from a tertiary care centre that follows patients with more severe BAV phenotypes, making recruitment of the patient with isolated BAV and no dilatation difficult. A potential strength of our study is the heterogenous study population; however, because of how inter-related measures of BAV function can be, it can be difficult to dissect the relative contribution of each factor on aortic dimensions.

Conclusions

In conclusion, in a large cohort of pediatric patients with BAV, we have shown that there are already abnormalities in

Table 3. Multivariable regression analysis for ascending aorta and aortic sinus Z scores in patients with BAV

	Ascending aorta		Aortic sinus	
Variable	Z score (95% CI)	*P*	Z score (95% CI)	*P*
Age, years	−0.02 (−0.11 to 0.07)	0.64	−0.03 (−0.12 to 0.05)	0.45
Male sex	0.37 (−0.13 to 0.86)	0.144	0.88 (0.41-1.36)	**< 0.001**
BAV morphology	0.05 (−0.20 to 0.29)	0.70	−0.04 (−0.27 to 0.20)	0.76
History of coarctation	−0.70 (−1.25 to −0.15)	**0.013**	0.09 (−0.43 to 0.62)	0.72
AI				
Mild	−0.92 (−1.47 to −0.37)	**0.001**	−0.70 (−1.22 to −0.17)	**0.010**
Moderate	1.09 (0.44-1.75)	**0.001**	0.96 (0.33-1.58)	**0.003**
Severe	1.10 (−0.11 to 2.32)	0.075	1.0 (−0.15 to 2.15)	0.089
AS	0.55 (−0.26 to 1.35)	0.182	−0.51 (−1.29 to 0.26)	0.194
AS mean gradient	−0.01 (−0.04 to 0.01)	0.38	−0.02 (−0.04 to 0.01)	0.142
Residual coarctation	1.70 (−0.67 to 4.06)	0.157	1.44 (−0.67 to 3.54)	0.180
Residual coarctation peak gradient	−0.02 (−0.08 to 0.03)	0.41	−0.02 (−0.07 to 0.03)	0.33
Carotid femoral PWV	0.08 (−0.27 to 0.42)	0.66	0.07 (−0.23 to 0.36)	0.66
Aortic arch PWV	0.15 (0.04-0.26)	**0.006**	0.10 (0.01-0.20)	**0.031**
Ascending aorta distensibility	−1.13 (−2.98 to 0.73)	0.23	−0.43 (−2.14 to 1.29)	0.62
Abdominal aorta distensibility	0.01 (−1.54 to 1.55)	0.99	0.05 (−1.41 to 1.51)	0.95
Left CIMT	−1.96 (−7.02 to 3.11)	0.44	−2.82 (−7.74 to 2.10)	0.26
Right CIMT	1.57 (−2.90 to 6.05)	0.49	3.17 (−1.35 to 7.69)	0.166

Bolded values: $P < .05$.

AI, aortic insufficiency; AS, aortic stenosis; BAV, bicuspid aortic valve; CIMT, carotid intima media thickness; PWV, pulse wave velocity.

vascular function, with abnormalities limited to the ascending aorta and proximal aortic arch. The distal aorta is less affected with normal peripheral PWV in patients with well-functioning BAVs. Aortic arch PWV, along with AI severity and the absence of CoA, are independently associated with increasing aortic dilatation in BAV patients. Taken together, our results suggest that pediatric patients with BAVs have evidence of vascular remodelling and dysfunction localized to the proximal aorta. Whether these abnormalities are a result of a primary localized aortopathy or secondary adaptation to flow disturbances caused by the BAV, as well as the prognostic value of these changes, require further prospective evaluation.

Funding Sources

This study was supported by a Fondation Leducq Network Grant (12 CVD 03).

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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