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ORIGINAL PAPER

# Abnormal aortic stiffness in patients with bicuspid aortic valve: phenotypic variation determined by magnetic resonance imaging

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## Abstract

The aim of this study was to assess aortic stiffness in patients with bicuspid aortic valve (BAV), and to determine if differences exist among the BAV phenotypes. Stiffness was measured by pulse wave velocity (PWV) determined using velocity-encoded magnetic resonance imaging (VENC-MRI). VENC-MRI was performed in 100 BAV patients and 45 normal controls. PWV was determined between the mid ascending and mid descending aorta. The BAV phenotypes were characterized using steady-state free precession (SSFP) images acquired across the face of the aortic valve, and classified as follows: right-left cusp (R-L) fusion, right and non-coronary cusp (R-NC) fusion, and left and non-coronary cusp (L-NC) fusion. The following BAV phenotypes were identified: 76 R-L, 23 R-NC, and 1 L-NC fusion. BAV patients demonstrated significantly greater PWV compared to normal controls, after adjusting for age (9.16 vs. 3.83 m/s; $p < 0.0001$). Furthermore, PWV was significantly greater in patients with R-NC fusion than those with R-L fusion phenotype (12.27 vs. 7.97 m/s; $p < 0.001$). There was significantly increased PWV from VENC-MRI in BAV patients compared to normal controls. Thisis the first to demonstrate the association of different BAV phenotypes and aortic stiffness. VENC-MRI PWV assessment potentially represents a novel parameter for enhanced surveillance and may alter surgical triage of aorta in this high risk group.

**Keywords** Bicuspid aortic valve · Valve phenotype · Aortic stiffness · Pulse wave velocity

## Introduction

Bicuspid aortic valve (BAV) is the most common congenital cardiac abnormality, with a prevalence of 1–2% in the general population [1–3]. BAV may be associated with valvular dysfunction including regurgitation and stenosis as well as aortic diseases. Associated abnormalities of the aorta in the BAV population include congenital anomalies such as coarctation of the aorta, interrupted aortic arch, and hypoplasia of the aorta along with acquired anomalies, for instance, aortic aneurysm, dissection, and rupture [4–8]. Further these abnormalities manifest earlier in life than tricuspid aortic valves. These established associations lead to the hypothesis of an underlying common developmental defect involving both intrinsic valvar and aortic pathologies. Despite the presence of BAV, the impact of BAV phenotype on valvar dysfunction and associated aortic anomalies either congenital or acquired have not been well-elucidated [4, 9–13].

Aortic stiffness is an important parameter that is abnormal in various aortopathies, including atherosclerotic aortic aneurysms and Marfan syndrome [14]. In addition, this abnormal aortic stiffness is predictive of progressive aortic dilation [15–20]. Similar abnormalities of aortic stiffness have been described in the setting of BAV using a variety of non-invasive techniques. To date, however, velocity-encoded magnetic resonance imaging (VENC-MRI) has been used sparingly in the study of aortic stiffness in BAV, and further there is scant data on the impact of BAV morphology on aortic stiffness.

Aortic pulse wave velocity (PWV) measurements obtained from velocity-encoded magnetic resonance imaging (VENC-MRI) is a promising non-invasive technique to determine aortic stiffness, particularly considering that these measurements do not depend on knowledge of central

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arterial pressure or geometrical assumptions that may limit other alternative measurement tools [15, 21–24].

In this study, we sought to assess aortic stiffness from VENC-MRI derived PWV measurements in patients with BAV, and to determine if there are differences in aortic stiffness among the BAV phenotypes.

## Methods

### Patient population

100 consecutive patients with BAV, and 45 normal controls, were included in this retrospective study which was approved by the local Institutional Review Board with a waiver of individual informed consent. Diagnosis of BAV was defined as partial or complete fusion of 2 aortic valve leaflets, with or without a central raphe [1]. Exclusion criteria included fusion of more than 2 leaflets (unicommisural), or concomitant aortic diseases, such as coarctation or Marfan syndrome. Classification of the severity of aortic stenosis and regurgitation was based on composite evaluation by Doppler echocardiography as: none, mild, moderate, or severe. Normal controls all had normal trileaflet aortic valves without any identified cardiac or aortic abnormalities.

### MR imaging

The MRI studies were performed using a 1.5-T MRI scanner (Avanto; Siemens Medical Solutions, Erlangen, Germany). ECG-triggered, free breathing black blood prepared HASTE (Half Fourier Acquisition in Steady State) images were acquired in 40 axial slices with the following scan parameters: TE = 20 ms, TR = 800 ms, refocusing flip angle = 160°, slice thickness = 6 mm, FOVx = 240–360 mm, FOVy = 300–380 mm; typical matrix size = 124 × 192, and typical acquired spatial resolution = 2.4 × 1.8 mm.

In order to classify the BAV phenotypes, balanced steady-state free precession (SSFP) cine images were acquired across the face of the aortic valve: TE = 1.2 ms, TR = 2.4 ms, flip angle = 70°, slice thickness = 6 mm, FOVx = 240–360 mm, FOVy = 300–380 mm; typical matrix size = 124 × 192, and typical acquired spatial resolution = 2.4 × 1.8 mm.

To measure through-plane flow in the mid-ascending and mid-descending thoracic aorta, VENC-MRI images were acquired using a breathhold, retrospectively ECG-gated gradient echo pulse sequence at the level of the pulmonary trunk. The scan parameters were as followed: TE = 3.1 ms, TR = 5.0 ms, flip angle = 30°, slice thickness = 6 mm, FOVx = 240–360 mm, FOVy = 300–380 mm; typical matrix size = 128 × 256, and typical acquired spatial resolution = 2.3 × 1.3 mm; temporal resolution = 25–35 ms depending on heart rate, and velocity encoding = 200 cm/s.

### Image analysis

#### Pulse wave velocity

VENC-MRI images were analyzed using dedicated cardiovascular image analysis software (Argus, Siemens Medical Solutions, Erlangen, Germany). In each image, the mid-ascending and mid-descending aorta were contoured, and the volume flow rate at these two locations was computed in all phases of the cardiac cycle. From the resulting flow-time curves, the arrival of the foot of the flow wave was measured as the point of interception of the linear extrapolation of the steep early systolic slope and the baseline (Fig. 1).

The path length between the mid-ascending and mid-descending thoracic aorta, corresponding to the same levels as the VENC-MRI image, was derived from multiplanar reconstructions of the axial HASTE images in an oblique sagittal view. These images were analyzed using dedicated image analysis software (3D, Siemens Medical Solutions, Erlangen, Germany).

PWV was calculated according to the following formula:

$$\mathrm{PWV} = \frac{\Delta x}{\Delta t}(\mathrm{m/s})$$

where $\Delta x$ was the aortic path length between the mid-ascending and mid-descending thoracic aorta, and $\Delta t$ was the time delay between the arrival of the foot of the flow wave at these levels [21, 25].

### BAV phenotypes

The 3 BAV morphologic subtypes were classified using a cine-SSFP across the face of the aortic valve. The fusion of cusps, right and non-coronary cusps was categorized as: right and left coronary cusp fusion (R-L fusion), right and non-coronary cusp fusion (R-NC fusion), and left and non-coronary cusp fusion (L-NC fusion), respectively (Fig. 2).

#### Intra and inter-observer reproducibility

Intra-observer and inter-observer reproducibility were determined using 20 randomly selected BAV patients and 20 randomly selected normal controls. The data were reanalyzed by the same observer four weeks after the initial analysis, and by a second independent observer blinded to the initial results.

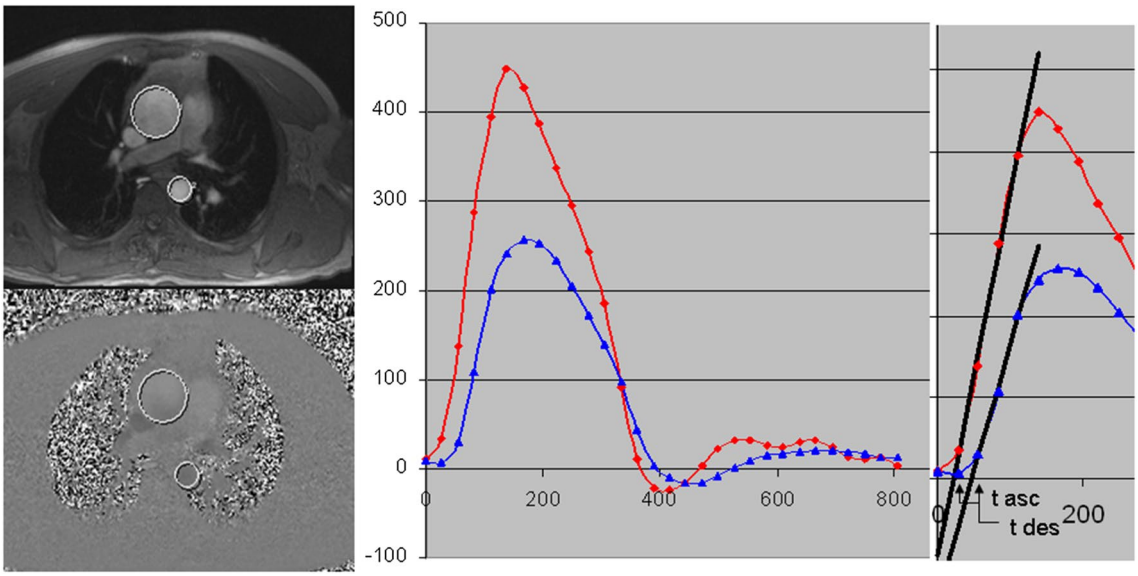


**Fig. 1** Measurement of flow in the mid-ascending and mid-descending aorta from VENC-MRI. Through-plane velocity encoded magnetic resonance imaging at mid-ascending (red circle) and mid-descending thoracic aorta (blue circle). Corresponding flow measurement at mid-ascending (red line) and mid-descending thoracic aorta (blue line). The arrival of the foot of the pulse wave was measured as the point of interception of the linear extrapolation of the steep early systolic slope and the baseline

### Statistical analysis

Continuous variables were presented as mean values and corresponding standard deviations, whereas categorical data were summarized as numbers and percentages. Patient characteristics relative to the morphologic subtypes of BAV and normal controls were compared using Chi square test and analysis of variance (ANOVA), where appropriate. The analysis of covariance (ANCOVA) was used to demonstrate the difference in PWV between BAV patients and normal controls, and PWV between the phenotypes, all adjusted for age.

Intra-observer and inter-observer reproducibility for PWV measurements was determined as the mean differences, and a Bland–Altman method plot was generated to demonstrate the agreement between the PWV measurements by the same and different observers [26]. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the SAS software Version 9.3 (SAS institute, Cary, North Carolina).

## Results

### BAV phenotypes

Image quality was good for all image types acquired in all patients—thus, no patients were excluded on this basis. BAV phenotypes were distributed as follows: 76 R-L, 23 R-NC, and 1 L-NC fusion. As only 1 patient in our population exhibited the L-NC phenotype, a rate of occurrence consistent with previous studies [2, 22], the L-NC phenotype was excluded from further analysis. Mean age was not significantly different between the remaining patient groups (R-L, R-NC) and normal controls (49.0, 49.6, and 49.3 years, respectively; p = NS). The mid-ascending and mid-descending aortic diameters were larger in BAV patients compared to normal controls, but there was no difference between the R-L fusion and R-NC fusion subgroups. Baseline characteristics are summarized in Table 1.

### Pulse wave velocity

PWV was significantly greater in BAV patients compared to normal controls, adjusting for age ($9.16 \pm 5.86$ vs. $3.83 \pm 0.81$ m/s; $p < 0.0001$). Within the 2 BAV phenotype subgroups, PWV was significantly greater in patients with R-NC fusion, as compared to those with R-L fusion phenotypes ($12.27 \pm 6.47$ vs. $7.97 \pm 4.89$ m/s, respectively; $p < 0.001$) (Fig. 3). The presence of aortic stenosis and aortic regurgitation did not differ significantly between these 2 BAV phenotypes.

#### Intra and inter-observer reproducibility

There was good intra-observer and inter-observer reproducibility for the PWV measurements. The mean PWV ± SD values were $6.41 \pm 4.15$ and $6.45 \pm 4.22$ m/s ($r = 0.99$) for

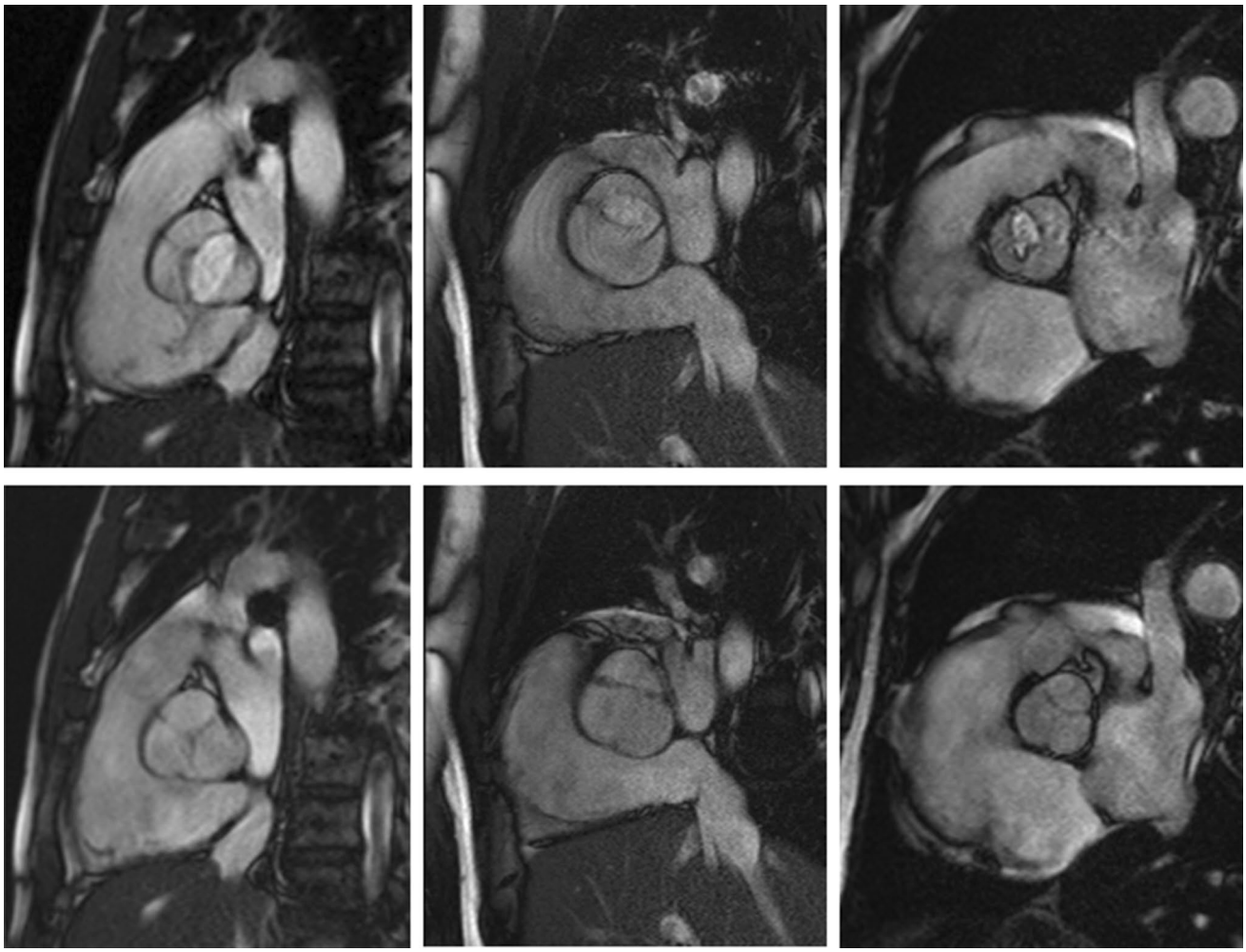

**Fig. 2** Identification of the BAV morphologic subtypes from cine-SSFP images. Fusion between right and left coronary cusps (R-L fusion)—systole (Top) and diastole (Bottom). Fusion between right and non-coronary cusps (R-NC fusion)—systole (Top) and diastole (Bottom). Fusion of left and non-coronary cusps (L-NC fusion)—systole (Top) and diastole (Bottom)

the first observer in the initial and repeated analyses, respectively. Mean PWV was $6.55 \pm 3.89$ m/s ($r = 0.98$) for the second observer. Using the Bland–Altman method, intra-observer mean differences for two measurements of PWV were $0.04 \pm 0.23$ ($p = 0.24$), and inter-observer mean differences were $0.14 \pm 0.84$ ($p = 0.29$), respectively (Fig. 4).

## Discussion

This study, which involves the largest cohort of BAV patients studied with MRI to date, has identified significantly increased aortic stiffness in BAV patients compared to normal controls. Further, this is the first to demonstrate that patients with the R-NC fusion phenotype exhibited a greater abnormality of aortic stiffness than patients with R-L fusion, emphasizing the importance of aortic valve morphology.

### Aortopathies in the setting of BAV

In addition to the morphologic and functional abnormalities of valves in BAV, there also is an intrinsic pathology of the aortic wall, manifested by a range of abnormalities including coarctation of the aorta, interrupted aortic arch, and hypoplastic aorta, as well as potentially lethal complications such as aortic aneurysm, dissection, and rupture [27, 28]. The extent of aortic dilation in BAV has been demonstrated to be beyond that attributable to coexistent valvar lesions, consistent with the hypothesis that intrinsic aortic wall pathology is in large part responsible for aortic dilation [29, 30]. Moreover, progressive aortic dilation can occur despite normal valve function in BAV patients [16, 31, 32].

The underlying common developmental defect leading to both intrinsic valvar and aortic pathologies has been described in prior studies [28, 33–38]. One animal study suggested the involvement of neural crest cells in the

**Table 1** Characteristics of patients with BAV and controls

| | Patients with BAV | | Controls (n = 45) | p value |
|---|---|---|---|---|
| | R-L fusion (n = 76) | R-NC fusion (n = 23) | | |
| Age (years) | 49.0 ± 13.9 | 49.6 ± 17.2 | 49.3 ± 15.7 | 0.68 |
| Male/female | 54 (71)/22 (29)* | 17 (57)/13 (43) | 24 (53)/21 (47)* | 0.046 |
| Height (cm) | 173.9 ± 12.4 | 176.1 ± 10.8 | 172.8 ± 10.5 | 0.537 |
| Weight (kg) | 87.8 ± 18.9 | 86.8 ± 16.8 | 88.9 ± 17.0 | 0.489 |
| Body surface area ($mm^2$)+ | 2.0 ± 0.3 | 2.1 ± 0.2 | 2.1 ± 0.3 | 0.885 |
| Systolic blood pressure (mmHg) | 123 ± 17 | 129 ± 18 | 121 ± 17 | 0.605 |
| Diastolic blood pressure (mmHg) | 74 ± 10 | 78 ± 12 | 75 ± 12 | 0.478 |
| Heart rate (beats/min) | 67 ± 12 | 69 ± 12 | 70 ± 11 | 0.098 |
| Medications | | | | |
| Betablocker | 44 (57.9) | 15 (65.2)* | 14 (31)* | 0.230 |
| Calcium blocker | 6 (7.9) | 2 (8.7) | 5 (11.1) | 0.093 |
| ACEI | 20 (26.3) | 6 (26.1) | 4 (9.0) | 0.924 |
| ARB | 6 (7.9) | 2 (8.7) | 4 (9.0) | 0.753 |
| Diameter of mid-ascending aorta (cm) | 3.9 ± 0.7* | 4.1 ± 0.6** | 2.9 ± 0.5*,** | < 0.001 |
| Diameter of mid-descending aorta (cm) | 2.3 ± 0.4 | 2.2 ± 0.4 | 2.2 ± 0.4 | 0.098 |
| Aortic stenosis | 20 (26.3)* | 7 (30.4)* | 0 (0)*,** | 0.002 |
| Aortic regurgitation | 42 (55.3)* | 16 (69.6)* | 0 (0)*,** | < 0.0001 |

Continuous data represent as mean ± SD

Categorical data represent as number of patients, and percentages in parenthesis

*BAV* bicuspid aortic valve, *R-L fusion* right and left cusp fusion, *R-NC fusion* right and noncoronary cusp fusion, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker

*,**Define a pair with $p < 0.05$

+According to the formula: $\sqrt{}$ [height (cm) × weight (kg)/3600]

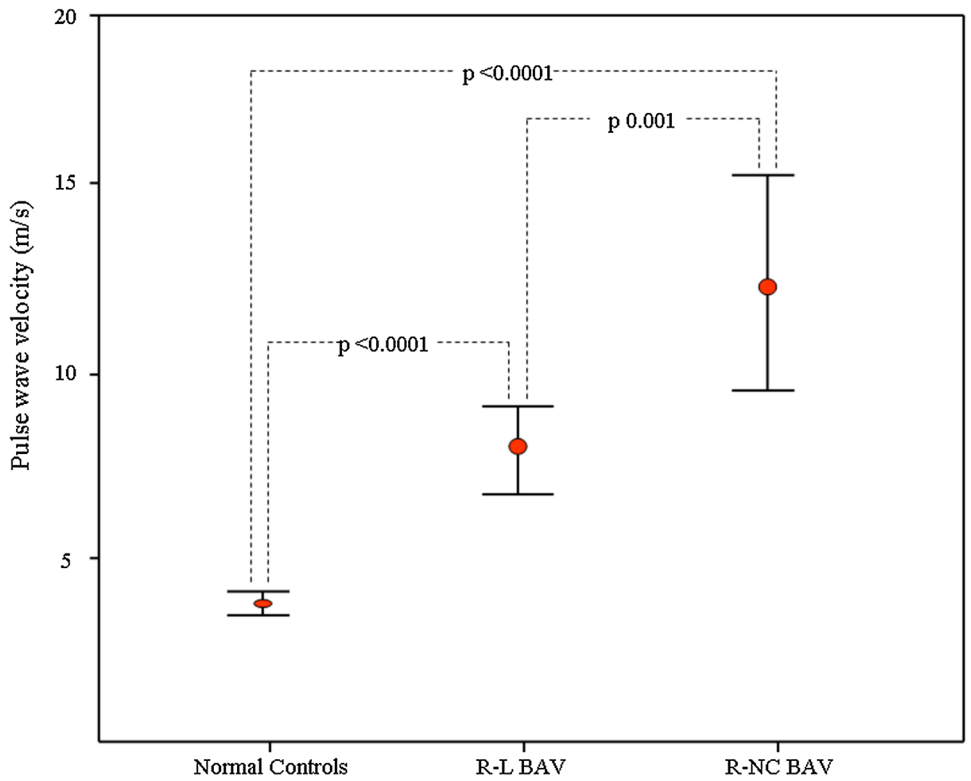


**Fig. 3** PWV in normal controls, BAV patients with R-L fusion phenotype, and R-NC fusion phenotype. The PWV (mean ± SD) in normal controls, and BAV patients with R-L fusion phenotype and R-NC fusion phenotype were 3.85 ± 0.89, 7.97 ± 4.89 and 12.27 ± 6.47 m/s, respectively. Circle, mean and whiskers, and 95% confidence intervals

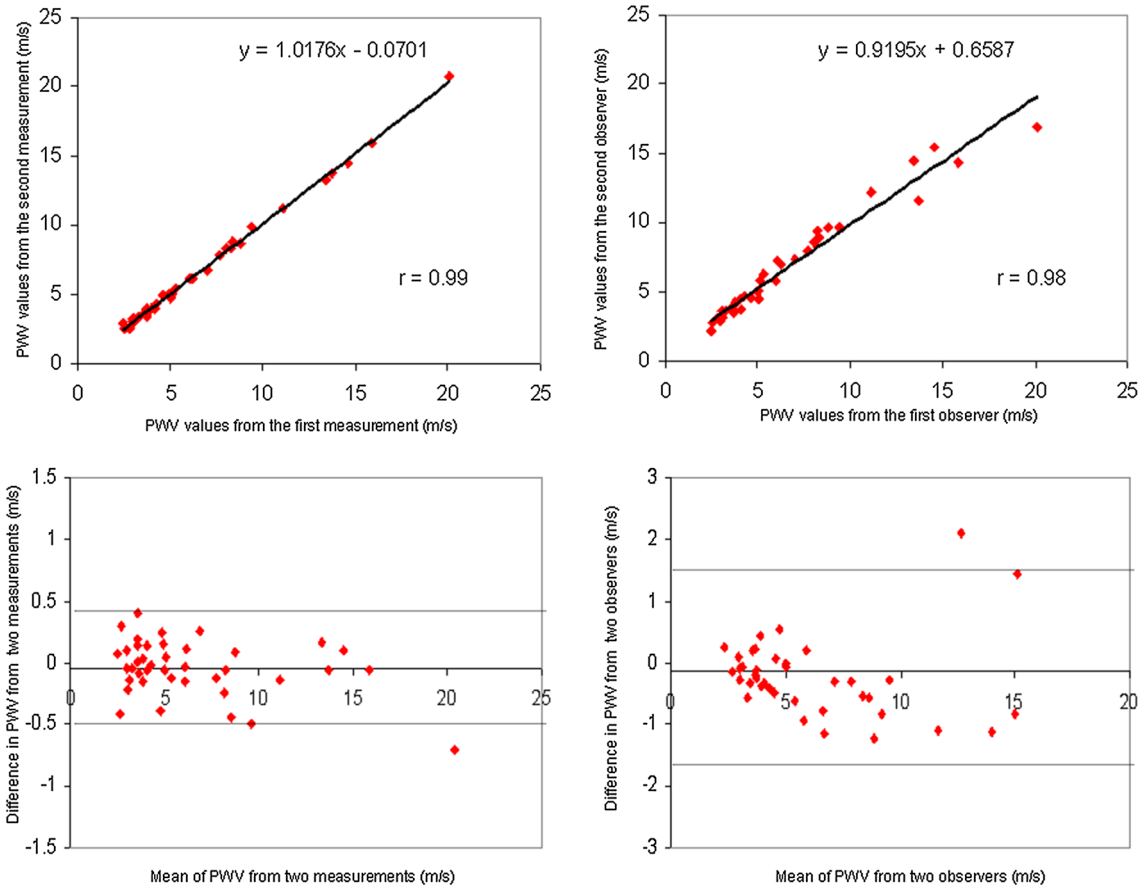


**Fig. 4** Intra-observer and inter-observer reproducibility of PWV measurements. The correlation of PWV measurements in the same observer and between two independent observers, respectively. Bland–Altman plot of the PWV measurements in the same observer and between two independent observers, respectively

development of the aortic valve and ascending aorta [33]. Disruption of fibroblast growth factor 8 expression was related to great vessel and coronary artery abnormalities, as well as BAV [34]. Histological characteristics of abnormal aortic pathologies, including Erdheim's cystic medial necrosis, premature medial smooth muscle cell apoptosis, fragmented elastin, increased ground substances, and elevated matrix metalloproteinase, have been described in BAV patients [28, 35–37].

Aortic PWV is a robust and well-accepted measure of arterial stiffness [15]. Increased aortic stiffness has been established in various aortopathies such as atherosclerotic aortic aneurysm and Marfan syndrome [14]. Though there is increasing evidence of abnormal aortic stiffness in the BAV population, limited data exists from MRI [16–19, 39]. Using VENC-MRI, PWV can be derived without estimates of central arterial pressure, and without any geometric assumptions regarding the aortic path, both of which are limitations of alternate PWV measurement techniques. Furthermore, errors resulting from these geometric assumptions of aortic path length may be more pronounced in the setting of BAV where tortuous, aneurysmal aortas may be present [40].

One previous MRI study demonstrated increased PWV in 20 patients with BAV, compared to age-matched control subjects, and clearly supported the concept that BAV pathology is not confined only to the valve itself, but also involves the aorta [21]. However, this study presented no data comparing among different valvar morphologies.

## Effects of different BAV phenotypes

The majority of prior studies assessing valvar dysfunction and aortic dilation have not differentiated among the different BAV phenotypes [2, 41, 42]. However, several recent studies have elucidated the impact of different valvar morphologies on the severity of valvular stenosis and regurgitation, freedom from valve intervention, associated coarctation, and aortic dilation [4, 9–11, 17, 43–45]. In two studies, BAV patients with R-NC fusion exhibit an increased incidence of aortic stenosis and regurgitation, and decreased freedom from valvar intervention [4, 9, 38], findings that

suggest R-NC fusion may represent a more severe form of BAV. Conflicting data existed regarding pathology of aorta among different phenotypes. R-NC phenotype established aortic dilation involving ascending aorta, whereas R-L phenotype involved predominately root dilation [11–13, 46, 47]. One study demonstrated greater diameter of ascending aorta in R-NC phenotype [45], while other two studies revealed the contrary result [12, 13].

Our study demonstrated significantly increased aortic stiffness in BAV patients with R-NC fusion compared to R-L fusion, irrespective of the severity of aortic stenosis, aortic regurgitation, or aortic size. Although the underlying mechanism for this finding is unclear, one potential contributor might be genetic differences between BAV phenotypes. An alternative explanation might be that differences in blood flow hemodynamics caused by the phenotypic variations in valve morphology could lead to variations in wall shear stresses [46–48]. R-NC phenotype revealed eccentric posterior flow, higher systolic flow angle and higher in-plane wall shear stress [46–48].

There was only one study evaluating the association of valve phenotypes and aortic stiffness, however local stiffness was measured [17]. Differences in aortic diameter and stiffness were found to vary regionally between BAV phenotypes. Using transthoracic echocardiography, this study reported R-L patients to exhibit significantly greater aortic diameter and stiffness at the sinuses of Valsalva and aortic arch, relative to R-NC patients. However, differences in the ascending aorta, where maximal dilatation typically occurs in BAV patients, were not significant. Furthermore, this study did not use PWV as its measure of stiffness, instead relying on a local stiffness index which has not been as widely applied or validated as PWV, and requires knowledge of central aortic pressure (brachial cuff pressure was used as a surrogate). In contrast, PWV measurements using MRI represent an average stiffness between the mid-ascending and mid-descending thoracic aorta, and are not dependent on central, or other, pressure measurements.

### Importance of abnormal aortic stiffness in BAV

Patients with BAV typically exhibit a larger ascending aorta diameter compared to the trileaflet aortic valve population, and a substantial number of BAV patients demonstrate aortic dilation independent of hemodynamically significant valvar dysfunction [29, 31, 32, 49]. Further, aortic dissection will develop in 5% of BAV patients during their lifetime [50]. Similarly, some aortopathies, such as Marfan syndrome, have seen abnormal aortic stiffness as an independent predictor of progressive aortic dilation [20]. Given the significance of aortic complications, it is clinically relevant to establish predictive parameters for the development of aortic dilation. Abnormal aortic stiffness and aortic sequelae such as dilation and dissection in BAV need further investigation.

Indications for aortic surgery alone in the absence of valvar criteria for valve surgery in BAV patients have not been well-established. Considering that the aortic dilation in the BAV population can be attributed in part to collagen vascular diseases, as in Marfan syndrome, optimal surgical strategy in this population may involve a smaller aortic diameter than in the general population, but remains controversial [51–55]. Moreover, aortic dilation and dissection are frequent complications even after BAV replacement, therefore more aggressive concomitant aortic replacement has been recommended [56].

### Clinical implication

BAV is increasingly recognized as a disease of the aortic valve, entire aortic root, and ascending aorta contributing to both valvular and vascular sequelae. One-third of patients with BAV have significant complications during their lifetime [27] Consequently, patients with BAV require heightened assessment of valve function and aortic involvement. MRI or computed tomography (CT) is considered the preferred assessment tool for the aorta according to ACC/AHA and ESC guidelines [57]. In addition to morphologic evaluation, the PWV measurements described in this study provide a novel role for MRI in the assessment of vascular function. More aggressive aortic involvement of the R-NC phenotype, as manifested in our study by the greater abnormality of aortic stiffness, suggests aortic PWV as a novel parameter of aortic pathology. Future studies assessing the direct impact of this pronounced abnormal aortic stiffness on progressive aortic dilation, development of complications, and clinical outcomes will further clarify the utility of VENC-MRI PWV measurements.

## Conclusions

Abnormal aortic stiffness as measured by VENC-MRI PWV in patients with BAV has been clearly established in this study. In addition, the R-NC phenotype has significantly greater alterations in aortic stiffness lending further evidence to consider it a more malignant form of BAV. VENC-MRI determined PWV measurements represent a further complementary parameter in diagnostic strategies for BAV, and may help direct better targeted therapeutic options.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References


1. Roberts WC (1970) The congenitally bicuspid aortic valve. A study of 85 autopsy cases. Am J Cardiol 26(1):72–83
2. Sabet HY, Edwards WD, Tazelaar HD, Daly RC (1999) Congenitally bicuspid aortic valves: a surgical pathology study of 542 cases (1991 through 1996) and a literature review of 2,715 additional cases. Mayo Clin Proc. 74(1):14–26
3. Basso C, Boschello M, Perrone C, Mecenero A, Cera A, Bicego D et al (2004) An echocardiographic survey of primary school children for bicuspid aortic valve. Am J Cardiol 93(5):661–663
4. Fernandes SM, Sanders SP, Khairy P, Jenkins KJ, Gauvreau K, Lang P et al (2004) Morphology of bicuspid aortic valve in children and adolescents. J Am Coll Cardiol 44(8):1648–1651
5. Friedman T, Mani A, Elefteriades JA (2008) Bicuspid aortic valve: clinical approach and scientific review of a common clinical entity. Expert Rev Cardiovasc Ther 6(2):235–248
6. Tzemos N, Therrien J, Yip J, Thanassoulis G, Tremblay S, Jamorski MT et al (2008) Outcomes in adults with bicuspid aortic valves. JAMA 300(11):1317–1325
7. Michelena HI, Desjardins VA, Avierinos JF, Russo A, Nkomo VT, Sundt TM et al (2008) Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. Circulation 117(21):2776–2784
8. Forsell C, Bjorck HM, Eriksson P, Franco-Cereceda A, Gasser TC (2014) Biomechanical properties of the thoracic aneurysmal wall: differences between bicuspid aortic valve and tricuspid aortic valve patients. Ann Thorac Surg 98(1):65–71
9. Fernandes SM, Khairy P, Sanders SP, Colan SD (2007) Bicuspid aortic valve morphology and interventions in the young. J Am Coll Cardiol 49(22):2211–2214
10. Ciotti GR, Vlahos AP, Silverman NH (2006) Morphology and function of the bicuspid aortic valve with and without coarctation of the aorta in the young. Am J Cardiol 98(8):1096–1102
11. Schaefer BM, Lewin MB, Stout KK, Gill E, Prueitt A, Byers PH et al (2008) The bicuspid aortic valve: an integrated phenotypic classification of leaflet morphology and aortic root shape. Heart 94(12):1634–1638
12. Della Corte A, Bancone C, Dialetto G, Covino FE, Manduca S, Montibello MV et al (2014) The ascending aorta with bicuspid aortic valve: a phenotypic classification with potential prognostic significance. Eur J Cardiothorac Surg 46(2):240–247 (**Discussion 7**)
13. Della Corte A, Bancone C, Buonocore M, Dialetto G, Covino FE, Manduca S et al (2013) Pattern of ascending aortic dimensions predicts the growth rate of the aorta in patients with bicuspid aortic valve. JACC Cardiovasc Imaging 6(12):1301–1310
14. Groenink M, de Roos A, Mulder BJ, Verbeeten B Jr, Timmermans J, Zwinderman AH et al (2001) Biophysical properties of the normal-sized aorta in patients with Marfan syndrome: evaluation with MR flow mapping. Radiology 219(2):535–540
15. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D et al (2006) Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 27(21):2588–2605
16. Nistri S, Grande-Allen J, Noale M, Basso C, Siviero P, Maggi S et al (2008) Aortic elasticity and size in bicuspid aortic valve syndrome. Eur Heart J 29(4):472–479
17. Schaefer BM, Lewin MB, Stout KK, Byers PH, Otto CM (2007) Usefulness of bicuspid aortic valve phenotype to predict elastic properties of the ascending aorta. Am J Cardiol 99(5):686–690
18. Nistri S, Sorbo MD, Basso C, Thiene G (2002) Bicuspid aortic valve: abnormal aortic elastic properties. J Heart Valve Dis 11(3):369–373 (**Discussion 73–74**)
19. Yap SC, Nemes A, Meijboom FJ, Galema TW, Geleijnse ML, ten Cate FJ et al (2008) Abnormal aortic elastic properties in adults with congenital valvular aortic stenosis. Int J Cardiol 128(3):336–341
20. Nollen GJ, Groenink M, Tijssen JG, Van Der Wall EE, Mulder BJ (2004) Aortic stiffness and diameter predict progressive aortic dilatation in patients with Marfan syndrome. Eur Heart J 25(13):1146–1152
21. Grotenhuis HB, Ottenkamp J, Westenberg JJ, Bax JJ, Kroft LJ, de Roos A (2007) Reduced aortic elasticity and dilatation are associated with aortic regurgitation and left ventricular hypertrophy in nonstenotic bicuspid aortic valve patients. J Am Coll Cardiol 49(15):1660–1665
22. Rogers WJ, Hu YL, Coast D, Vido DA, Kramer CM, Pyeritz RE et al (2001) Age-associated changes in regional aortic pulse wave velocity. J Am Coll Cardiol 38(4):1123–1129
23. Petersen SE, Wiesmann F, Hudsmith LE, Robson MD, Francis JM, Selvanayagam JB et al (2006) Functional and structural vascular remodeling in elite rowers assessed by cardiovascular magnetic resonance. J Am Coll Cardiol 48(4):790–797
24. van der Meer RW, Diamant M, Westenberg JJ, Doornbos J, Bax JJ, de Roos A et al (2007) Magnetic resonance assessment of aortic pulse wave velocity, aortic distensibility, and cardiac function in uncomplicated type 2 diabetes mellitus. J Cardiovasc Magn Reson 9(4):645–651
25. Stevanov M, Baruthio J, Gounot D, Grucker D (2001) In vitro validation of MR measurements of arterial pulse-wave velocity in the presence of reflected waves. J Magn Reson Imaging 14(2):120–127
26. Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1(8476):307–310
27. Ward C (2000) Clinical significance of the bicuspid aortic valve. Heart 83(1):81–85
28. Fedak PW, Verma S, David TE, Leask RL, Weisel RD, Butany J (2002) Clinical and pathophysiological implications of a bicuspid aortic valve. Circulation 106(8):900–904
29. Keane MG, Wiegers SE, Plappert T, Pochettino A, Bavaria JE, Sutton MG (2000) Bicuspid aortic valves are associated with aortic dilatation out of proportion to coexistent valvular lesions. Circulation 102(19 Suppl 3):III35–III39
30. Ferencik M, Pape LA (2003) Changes in size of ascending aorta and aortic valve function with time in patients with congenitally bicuspid aortic valves. Am J Cardiol 92(1):43–46
31. Cecconi M, Manfrin M, Moraca A, Zanoli R, Colonna PL, Bettuzzi MG et al (2005) Aortic dimensions in patients with bicuspid aortic valve without significant valve dysfunction. Am J Cardiol 95(2):292–294
32. Beroukhim RS, Kruzick TL, Taylor AL, Gao D, Yetman AT (2006) Progression of aortic dilation in children with a functionally normal bicuspid aortic valve. Am J Cardiol 98(6):828–830
33. Jiang X, Rowitch DH, Soriano P, McMahon AP, Sucov HM (2000) Fate of the mammalian cardiac neural crest. Development 127(8):1607–1616
34. Macatee TL, Hammond BP, Arenkiel BR, Francis L, Frank DU, Moon AM (2003) Ablation of specific expression domains reveals discrete functions of ectoderm- and endoderm-derived FGF8 during cardiovascular and pharyngeal development. Development 130(25):6361–6374
35. McKusick VA (1972) Association of congenital bicuspid aortic valve and erdheim's cystic medial necrosis. Lancet 1(7758):1026–1027
36. Niwa K, Perloff JK, Bhuta SM, Laks H, Drinkwater DC, Child JS et al (2001) Structural abnormalities of great arterial walls in congenital heart disease: light and electron microscopic analyses. Circulation 103(3):393–400

37. Bonderman D, Gharehbaghi-Schnell E, Wollenek G, Maurer G, Baumgartner H, Lang IM (1999) Mechanisms underlying aortic dilatation in congenital aortic valve malformation. Circulation 99(16):2138–2143
38. Shin HJ, Shin JK, Chee HK, Kim JS, Ko SM (2015) Characteristics of aortic valve dysfunction and ascending aorta dimensions according to bicuspid aortic valve morphology. Eur Radiol 25(7):2103–2114
39. Warner PJ, Al-Quthami A, Brooks EL, Kelley-Hedgepeth A, Patvardhan E, Kuvin JT et al (2013) Augmentation index and aortic stiffness in bicuspid aortic valve patients with non-dilated proximal aortas. BMC Cardiovasc Disord 13:19
40. Karamanoglu M (2003) Errors in estimating propagation distances in pulse wave velocity. Hypertension 41(6):e8.
41. Yener N, Oktar GL, Erer D, Yardimci MM, Yener A (2002) Bicuspid aortic valve. Ann Thorac Cardiovasc Surg 8(5):264–267
42. Pachulski RT, Chan KL (1993) Progression of aortic valve dysfunction in 51 adult patients with congenital bicuspid aortic valve: assessment and follow up by Doppler echocardiography. Br Heart J 69(3):237–240
43. Della Corte A, Bancone C, Dialetto G, Covino FE, Manduca S, D'Oria V et al (2014) Towards an individualized approach to bicuspid aortopathy: different valve types have unique determinants of aortic dilatation. Eur J Cardiothorac Surg 45(4):e118–e124 (**Discussion e24**)
44. Pees C, Michel-Behnke I (2012) Morphology of the bicuspid aortic valve and elasticity of the adjacent aorta in children. Am J Cardiol 110(9):1354–1360
45. Koenraadt WM, Grewal N, Gaidoukevitch OY, DeRuiter MC, Gittenberger-de Groot AC, Bartelings MM et al (2016) The extent of the raphe in bicuspid aortic valves is associated with aortic regurgitation and aortic root dilatation. Neth Heart J 24(2):127–133
46. Bissell MM, Hess AT, Biasiolli L, Glaze SJ, Loudon M, Pitcher A et al (2013) Aortic dilation in bicuspid aortic valve disease: flow pattern is a major contributor and differs with valve fusion type. Circ Cardiovasc Imaging 6(4):499–507
47. Mahadevia R, Barker AJ, Schnell S, Entezari P, Kansal P, Fedak PW et al (2014) Bicuspid aortic cusp fusion morphology alters aortic three-dimensional outflow patterns, wall shear stress, and expression of aortopathy. Circulation 129(6):673–682
48. Hope MD, Hope TA, Meadows AK, Ordovas KG, Urbania TH, Alley MT et al (2010) Bicuspid aortic valve: four-dimensional MR evaluation of ascending aortic systolic flow patterns. Radiology 255(1):53–61
49. Nistri S, Sorbo MD, Marin M, Palisi M, Scognamiglio R, Thiene G (1999) Aortic root dilatation in young men with normally functioning bicuspid aortic valves. Heart 82(1):19–22
50. Larson EW, Edwards WD (1984) Risk factors for aortic dissection: a necropsy study of 161 cases. Am J Cardiol 53(6):849–855
51. Hardikar AA, Marwick TH (2013) Surgical thresholds for bicuspid aortic valve associated aortopathy. JACC Cardiovasc Imaging 6(12):1311–1320
52. Adamo L, Braverman AC (2015) Surgical threshold for bicuspid aortic valve aneurysm: a case for individual decision-making. Heart 101(17):1361–1367
53. Hiratzka LF, Creager MA, Isselbacher EM, Svensson LG, Nishimura RA, Bonow RO et al (2016) Surgery for aortic dilatation in patients with bicuspid aortic valves: a statement of clarification from the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol 67(6):724–731
54. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA et al (2014) 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation 129(23):e521–e643
55. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology, European Association for Cardio-Thoracic Surgery, Vahanian A, Alfieri O, Andreotti F, Antunes MJ et al (2012) Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 33(19):2451–2496
56. Yasuda H, Nakatani S, Stugaard M, Tsujita-Kuroda Y, Bando K, Kobayashi J et al (2003) Failure to prevent progressive dilation of ascending aorta by aortic valve replacement in patients with bicuspid aortic valve: comparison with tricuspid aortic valve. Circulation 108(Suppl 1):II291–I4
57. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD et al (2008) 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 118(15):e523–e661