CLINICAL RESEARCH

Assessment of valvular surfaces in children with a congenital bicuspid aortic valve: Preliminary three-dimensional echocardiographic study

Estimation des surfaces valvulaires en cas de bicuspidie aortique chez l’enfant : une étude préliminaire d’échocardiographie tridimensionnelle

Thomas Cognet\textsuperscript{a,b,1}, Pierre-Emmanuel Séguéla\textsuperscript{a,*,1}, Emilie Thomson\textsuperscript{a,b}, Frédéric Bouisset\textsuperscript{b}, Olivier Lairez\textsuperscript{b}, Sébastien Hascoët\textsuperscript{a,b}, Didier Carrié\textsuperscript{b}, Philippe Acar\textsuperscript{a}

\textsuperscript{a} Paediatric Cardiology Unit, Children’s Hospital, Toulouse University Hospital, Toulouse, France
\textsuperscript{b} Department of Cardiology, Toulouse University Hospital, Toulouse, France

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KEYWORDS
Bicuspid aortic valve; Transthoracic three-dimensional echocardiography; Aortic stenosis; Aortic valve area

Summary
Background. — Congenital bicuspid aortic valve (BAV) is the most common congenital heart defect and may be responsible for aortic stenosis early in life. However, its pathogenesis remains unclear. A relationship between the severity of aortic stenosis and valvular surfaces has not been reported in the paediatric population.
Aims. — To assess the feasibility of three-dimensional transthoracic echocardiographic planimetry in congenital BAV in children and to evaluate the influence of valvular asymmetry and aortic valve area (AVA) on stenosis severity.
Methods. — Seventy consecutive children with BAV were included in this prospective single-centre study. Using the multiplanar review mode, surfaces were measured by planimetry (in systole for AVA and diastole for cusp surfaces). The degree of stenosis was assessed by instantaneous aortic Doppler. Results are expressed as medians and first and third quartiles.

Abbreviations: 2DE, two-dimensional echocardiography; 2DTTE, two-dimensional transthoracic echocardiography; 3DE, three-dimensional echocardiography; AVA, aortic valve area; BAV, bicuspid aortic valve; CI, confidence interval; MPR, multiplanar review mode; MRI, magnetic resonance imaging; RT-3DTTE, real-time three-dimensional transthoracic echocardiography.

* Corresponding author. Paediatric Cardiology Unit, Children’s Hospital, Toulouse University Hospital, 330, avenue de Grande-Bretagne, TSA 70034, 31059 Toulouse cedex 9, France. Fax: +33 5 34 55 86 63.
E-mail address: peseguela@yahoo.fr (P.-E. Séguéla).
1 Thomas Cognet and Pierre-Emmanuel Séguéla contributed equally.

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Background

Bicuspid aortic valve (BAV) is the most common congenital heart disease, observed in 0.4 to 2.25% of the general population [1,2]. The clinical spectrum is wide, ranging from asymptomatic valvular disease to severe heart failure. The severity of the valve dysfunction is related to the morphology of the BAV [3]. Moreover, the phenotype of the BAV is predictive of surgical timing [4]. Thus, the challenge is to assess valvular function and determine its probable evolution. Three-dimensional echocardiography (3DE) was reported as an efficient means of assessing valvular morphology in BAV [5]. Indeed, using multiplanar analysis, this technique allows precise measurement of valvular areas [6]. In adults, real-time three-dimensional transthoracic echocardiography (RT-3DTTE) using the biplane mode was consistent with both transoesophageal 3DE and catheterization for measurement of the aortic valve area (AVA) [7]. Although previous studies have demonstrated that the severity of aortic stenosis closely depends on the structural geometry of the aortic valve, the exact pathogenesis remains unclear. The aims of this study were to evaluate the feasibility of RT-3DTTE for the assessment of aortic surfaces in congenital BAV and to assess the relationship between valvular asymmetry, AVA and aortic stenosis.

Methods

Definition of bicuspid aortic valve

The term BAV includes different morphological phenotypes. Indeed, the valve may be composed of either two cusps (purely bicuspid) or three cusps (falsey bicuspid) with fusion (partial or complete) of two of them. The term raphes defines the conjoint or ‘fused’ area of the two underdeveloped cusps. For this study, we used the anatomical classification proposed by Sievers and Schmidtke [8], which is based on the presence and position of the raphes. Thus, a BAV

Results. – Median age was 5.6 years (2.2—11.5). Feasibility was 97%. Intra- and interobserver concordances were excellent for the measurement of cusp surfaces and AVA. Among the 70 children, 25 had aortic stenosis. The small/large cusp ratio was strongly associated with aortic stenosis ($P < 0.001$). The area under the receiver operating characteristic curve was 0.89 (95% confidence interval 0.82–0.97). The best cut-off value for differentiating stenotic from nonstenotic valve was 0.75, with 84% sensitivity and 83% specificity. When indexed for body surface area, AVA was significantly smaller ($P = 0.031$) in case of stenotic BAV (1.51 cm² [0.99–2.28]) compared with non-stenotic BAV (1.99 cm² [1.57–2.52]).

Conclusions. – Three-dimensional echocardiographic planimetry is a feasible and reproducible method for assessing aortic surfaces in congenital BAV. Aortic stenosis seems to strongly depend on the asymmetry of the valve.

Résumé

Contexte. — La bicuspidie aortique (BVo) est la malformation cardiaque congénitale la plus fréquente. Elle peut être responsable de sténose aortique (SAo) dès le plus jeune âge. Cependant, sa pathogénie reste encore incertaine. La relation entre sévérité de la SAo et importance des surfaces valvulaires n’a jamais été montrée chez l’enfant.


Résultats. — L’âge médian était de 5,6 ans (2,2–11,5). La faisabilité était de 97% avec une excellente variabilité inter- et interobservateur tant pour la mesure des feuillet valvulaires que pour celle de l’orifice aortique. 25 enfants avaient une SAo. Le ratio petit-grand feuillet était corrélé à l’existence d’une SAo ($p < 0,001$), l’aire sous la courbe ROC étant de 0,89 (IC à 95% : 0,82–0,97). La meilleure valeur seuil permettant de différencier une valve sténosante d’une non sténosante était de 0,75 (sensibilité 84 % et spécificité 83 %). Indexé à la surface corporelle, l’orifice valvulaire était significativement ($p = 0,031$) plus petit en cas de BVo sténosante (1,51 cm² [0,99–2,28 vs 1,99 cm² [1,57–2,52]] pour les non sténosantes).

Conclusions. — La mesure planimétrique des surfaces valvulaires par 3DE est une technique faisable et reproductible en cas de BVo chez l’enfant. La SAo semble dépendre étroitement du caractère asymétrique de ces valves.
type 0 (true BAV) has only two cusps with no raphe and BAV types 1 and 2 have three cusps with one and two raphes, respectively.

Patients

This was a single-centre prospective study performed in our paediatric cardiology unit. From April 2010 to April 2011, we enrolled all children with an echocardiographic diagnosis of BAV. These children were initially referred for the exploration of a cardiac murmur or for follow-up of an already known congenital heart disease. Exclusion criteria were age > 18 years, history of endocarditis, concomitant subaortic obstruction, previous surgical aortic commissurotomy and previous percutaneous aortic dilation. Only BAV types 0 and 1 (with 0 raphe and one raphe, respectively) were included because BAV type 2 (three cusps and two raphes) may be considered as a functional unicusp aortic valve. The study was approved by our local ethics committee. A written consent form was not required according to French law, given that echocardiographic evaluation was part of the regular management of the children and was required for management of their medical conditions. No additional examination was performed for the sole purpose of the study.

Echocardiographic acquisitions and off-line analysis

All patients underwent standardized and complete two-dimensional transthoracic echocardiography (2DTEE), performed using high-quality commercially available ultrasound systems (iE33, Philips Medical Systems, Andover, MA, USA). When a BAV was diagnosed, the examination was completed by RT-3DTTE. X3-1 and X7-2 matrix probes (Philips Medical Systems, Andover, MA, USA) were used, depending on the age of the patient. The best short-axis cross-sectional view was selected to see the most circular annulus and the commissural areas. RT-3DTTE data were acquired—as much as possible considering the extreme youth of some children—during end expiratory. When necessary, 3D zoom was used to improve image resolution. Q-Lab software (Philips Medical Systems, Andover, MA, USA) was used for off-line analysis. In the multiplanar review (MPR) mode, three orthogonal cutting planes can be moved independently of each other through the data set. The MPR mode allows better morphological analysis because the valve can be seen in the best 2D cutting plans at any stage of the cardiac cycle. 3D images were acquired by triggering to the electrocardiogram R-wave and quality was improved using gain and compression controls. Two 3D volumes were acquired for each patient. Cusp surfaces and AVA were determined by planimetry. The degree of asymmetry was assessed by manually surfacing the leaflets (Fig. 1). Aortic cusp surfaces were measured in diastole. For BAV type 1, the sum of the two fused cusps was considered as a single functional cusp. The ratio between the surfaces of the two functional cusps was calculated to express the degree of asymmetry (small/large cusp ratio). AVA was measured at the inner leaflet edges at the time of maximal opening in systole. All areas were corrected for body surface area. Mean and maximal instantaneous aortic Doppler gradients were measured to evaluate aortic stenosis. Aortic Doppler values were obtained from an apical five-chamber view. The valve was defined as stenotic for a maximal instantaneous aortic Doppler gradient > 20 mmHg. The ascending aorta, measured in parasternal long-axis view, was defined as dilated if the Z-score of the diameter was > 2.

Operators

RT-3DTTE acquisitions were performed by a single cardiologist. Two independent operators performed the off-line analysis, randomly and on separate days, to assess inter-observer variability. To evaluate intraobserver variability, the same observer performed measurements twice, on different days, in a random order and blinded to the prior results.

Statistical analysis

Statistical analysis was performed on STATA statistical software, version 11.1 (Stata Corporation, College Station, TX, USA). Continuous variables are summarized as medians and interquartile ranges. Categorical variables are presented as proportions. In univariate analysis, qualitative variables were compared with the Chi² test (or Fisher’s exact test; when necessary). The Mann—Whitney U test was used to compare ranges of continuous non-normally distributed variables according to qualitative variables. Reproducibility of the measurements was tested on 16 randomly selected patients by calculating intraclass correlation coefficients. Receiver operating characteristic curves were used to determine the best threshold values for sensitivity and specificity. Linear regression analyses expressing Doppler gradients according to AVA or small/large cusp ratio are presented. A P value < 0.05 was considered statistically significant.

Results

Population characteristics

Among the 70 patients included in the study, 44 (62.9%) were male. Median age was 5.6 years (2.2–11.5) and median weight was 16.5 kg (11–32) (Table 1). The most common associated cardiac lesion was coarctation of the aorta, encountered in 21 (30%) patients (Table 2). Aortic stenosis was noted in 25 patients (35.7%). The median value of the mean instantaneous aortic Doppler gradient was 16 mmHg (10–30) for stenotic BAV and 2 mmHg (2–3) for non-stenotic valves. The median value of the maximal instantaneous aortic Doppler gradient was 30 mmHg (24–50) in case of aortic stenosis and 4 mmHg (4–5) in case of non-stenotic BAV. Dilatation of the ascending aorta occurred in 22 patients (31.4%) and was more frequent in case of aortic stenosis (48.0% vs. 22.2%; P = 0.03). Four patients were excluded from the study because they had BAV type 2; three of them had aortic stenosis (one patient underwent a surgical commissurotomy). According to standard cross-sectional echocardiography, all patients had normal left ventricular function.
Figure 1. Measurement of aortic cusp surfaces by planimetry using the multiplanar review mode. A. Schematic representation of the different types of bicuspid aortic valve (BAV) according to the classification described by Sievers and Schmidtke. BAV type 0 has two cusps with no raphe and BAV type 1 has three cusps with one raphe. Raphes are represented by black lines. In type 0, ap and lat refer to the spatial position of the cusps. In type 1, the position of the raphe is indicated by L-R (between the left and right coronary sinuses), R-N (between the right and non-coronary sinuses) and N-L (between the non-coronary and left coronary sinuses). The small/large cusp ratio corresponds to the surface of the white cusp/surface of the blue cusp ratio. Adapted from Sievers and Schmidtke [8]. B. Real-time transthoracic three-dimensional echocardiography of a pure BAV (type 0 ap). This valve is perfectly symmetrical as shown by measurement of the cusp surfaces. C. Multiplanar review mode from three-dimensional acquisition with the three orthogonal cutting plans. Cropping allows perfect visualization of the valve in a short-axis plane. Ap: anterior-posterior; lat: lateral; L: left coronary sinus; N: non-coronary sinus; R: right coronary sinus.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Population characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aortic stenosis (n = 25)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>4.2 [1.8–9.7]</td>
</tr>
<tr>
<td>Men</td>
<td>15 (60.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>14.8 [10.4–31.6]</td>
</tr>
<tr>
<td>Type of bicuspid aortic valve</td>
<td></td>
</tr>
<tr>
<td>Type 0 lat</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Type 0 ap</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Type 1 L-R</td>
<td>9 (36.0)</td>
</tr>
<tr>
<td>Type 1 R-N</td>
<td>9 (36.0)</td>
</tr>
<tr>
<td>Type 1 N-L</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>8 (32.0)</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dilation of the ascending aorta</td>
<td>12 (48.0)</td>
</tr>
<tr>
<td>Associated congenital heart defect</td>
<td>4 (16.0)</td>
</tr>
</tbody>
</table>

Data are median [interquartile range] or number (%). Ap: anterior-posterior; lat: lateral; L: left coronary sinus; N: non-coronary sinus; NA: not applicable; R: right coronary sinus.
Feasibility

Cusp surface and AVA measurements were feasible for 97% of patients. RT-3DTTE analysis was not possible for only two patients because of poor image resolution attributed to poor echogenicity; these two patients were aged 14.9 and 15.7 years. Tachycardia was not a limiting factor in our population.

Reproducibility

Intra- and interobserver concordances were excellent for the measurement of the cusp areas and the orifice area. Indeed, intraclass correlation coefficients estimated for the assessment of intraobserver variability were 0.992 (95% confidence interval [CI] 0.979–0.997) for the small cusp surface, 0.998 (95% CI 0.993–0.999) for the large cusp surface and 0.998 (95% CI 0.995–0.999) for the AVA. Correlation coefficients expressing the interobserver variability were also excellent: 0.964 (95% CI 0.900–0.987) for the small cusp surface, 0.961 (95% CI 0.892–0.986) for the large cusp surface and 0.983 (95% CI 0.953–0.994) for the AVA.

Valvular asymmetry and aortic stenosis

According to the functional status of the valve (stenotic/non-stenotic), there was no difference between cusp areas for the large cusp (1.27 cm² vs. 1.31 cm²; \( P = 0.93 \)) or for the small cusp (0.72 cm² vs. 1.13 cm²; \( P = 0.15 \)). However, the small/large cusp ratio was strongly associated with aortic stenosis (\( P < 0.001 \)). Indeed, the median ratio was 0.59 [0.52–0.68] for aortic stenosis and 0.86 [0.79–0.91] for non-stenotic valves (Table 3). Showing the ability of this ratio to predict aortic stenosis, the area under the receiver operating characteristic curve (Fig. 2) was excellent at 0.89 (95% CI 0.82–0.97) and the best cut-off value to distinguish stenotic valves from non-stenotic valves was 0.75, with 84% sensitivity and 83% specificity. When considering only valvular asymmetry, 20 of 25 patients (80%) with stenotic BAV had a small/large cusp ratio < 0.75 (\( P < 0.001 \)). For a small/large cusp ratio < 0.75, the odds ratio, calculated using a logistic regression, was 21.7 (95% CI 6.1–77.2; \( P < 0.001 \)). Finally, the degree of asymmetry correlated well with the maximal instantaneous aortic Doppler gradient (\( r = 0.6379, P < 0.001 \)) and the mean instantaneous aortic Doppler gradient (\( r = 0.6102, P < 0.001 \) (Fig. 3).

### Table 2 Cardiac anomalies associated with bicuspid aortic valves.

<table>
<thead>
<tr>
<th>Cardiac anomalies</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>Coarctation of the aorta</td>
<td>14</td>
</tr>
<tr>
<td>and subaortic membrane</td>
<td>3</td>
</tr>
<tr>
<td>and ventricular septal defect</td>
<td>3</td>
</tr>
<tr>
<td>and partial anomalous pulmonary venous connection</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary valve stenosis</td>
<td>2</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>2</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>2</td>
</tr>
<tr>
<td>Double orifice mitral valve</td>
<td>1</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
</tr>
</tbody>
</table>

### Table 3 Influence of valvular asymmetry and aortic valve area on stenosis in congenital bicuspid aortic valve.

<table>
<thead>
<tr>
<th></th>
<th>All the patients (n = 70)</th>
<th>Aortic stenosis (n = 25)</th>
<th>No aortic stenosis (n = 45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cusp surface (cm²)</td>
<td>0.91 [0.54–1.87]</td>
<td>0.72 [0.51–1.27]</td>
<td>1.13 [0.59–1.95]</td>
<td>0.15</td>
</tr>
<tr>
<td>Large cusp surface (cm²)</td>
<td>1.28 [0.76–2.19]</td>
<td>1.27 [1.04–2.09]</td>
<td>1.31 [0.73–2.34]</td>
<td>0.93</td>
</tr>
<tr>
<td>Small/large cusp ratio</td>
<td>0.79 [0.59–0.89]</td>
<td>0.59 [0.52–0.68]</td>
<td>0.86 [0.79–0.91]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Aortic valvar area (cm²)</td>
<td>1.43 [0.74–2.50]</td>
<td>1.0 [0.57–1.82]</td>
<td>1.82 [0.82–2.66]</td>
<td>0.048</td>
</tr>
<tr>
<td>Indexed aortic valve area (cm²/m²)</td>
<td>1.89 [1.36–2.48]</td>
<td>1.51 [0.99–2.28]</td>
<td>1.99 [1.57–2.52]</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Valvular asymmetry is represented by the small/large cusp ratio.
Aortic valve area and aortic stenosis

Indexed AVA was significantly smaller in patients with a stenotic BAV than in patients with a non-stenotic BAV (1.51 cm² [0.99–2.28] vs. 1.99 cm² [1.57–2.52]; P = 0.031). When not indexed, AVA was still significantly smaller in patients with a stenotic BAV than in patients with a non-stenotic BAV (1 cm² [0.57–1.82] vs. 1.82 cm² [0.82–2.66]; P = 0.048). However, both AVA and indexed AVA were weakly correlated with the maximal instantaneous aortic Doppler gradient (respectively, r = −0.2772, P = 0.011 and r = −0.2995, P = 0.006) or with the mean instantaneous aortic Doppler gradient (respectively, r = −0.2697, P = 0.012 and r = −0.2953, P = 0.007).

Aortic valve area and valvular asymmetry

The association between indexed AVA and valvular asymmetry was not significant (r = 0.0296, P = 0.16). BAV with a small/large cusp ratio < 0.75 had a non-significantly smaller indexed AVA than BAV with a small/large cusp ratio > 0.75 (1.43 cm² [1.06–2.48] vs. 1.93 cm² [1.72–2.49]; P = 0.09).

Asymmetry and aortic dilation

Children with aortic dilation (n = 22) had a significantly lower small/large cusp ratio than children without aortic dilation (0.68 [0.50–0.84] vs. 0.81 [0.65–0.9]; P = 0.027).

Discussion

Feasibility of aortic planimetry using real-time three-dimensional transthoracic echocardiography

This study shows that RT-3DTTE is a feasible method for analysing cusp surfaces and AVA in children with a BAV. Proving the good reproducibility of the method, both intra- and interobserver variability were low. Our data are consistent with those from previous adult studies. When compared with catheterization and two-dimensional echocardiography (2DE), 3DE was proved to be accurate and reproducible for the quantification of AVA [9,10]. Moreover, using the MPR mode, 3DE has been reported to be more precise than 2DE because it overcomes the physiological deformation of aortic annulus during the cardiac cycle [11]. An excellent correlation was also reported between 3DE planimetry of AVA and 2DE planimetry of AVA, which require the use of the Doppler continuity equation [7,12,13].

Role of aortic valve area and valvular asymmetry in aortic stenosis

In a recent paediatric study, Bharucha et al. showed that the AVA value obtained by 3DE was not well correlated with 2DE Doppler gradients [14]. In agreement with these data, we found a poor relationship between the maximal and mean Doppler gradients and the AVA calculated by RT-3DTTE. Nevertheless, when considering aortic stenosis for a maximal instantaneous gradient > 20 mmHg, AVA was significantly smaller for the stenotic valves. Above all, our results suggest that, in children, aortic stenosis strongly depends on the valvular asymmetry. As proved by linear regression analysis, the degree of stenosis is well correlated with the severity of asymmetry and a small/large cusp ratio < 0.75 seems to be predictive of an increased risk of stenotic valve. Because aortic stenosis strongly influences prognosis, assessment of valvular symmetry would be of interest in these patients [15]. Furthermore, even if the prognosis depends on the severity of the valvular lesion at the time of diagnosis, a BAV may have the potential for evolution towards stenosis during life [16]. As 3DE is valuable for clearly depicting the valvular morphology of a BAV [17–19], this new technique seems to provide good quantification of valvular surfaces and clinicians must keep in mind that a very asymmetric valve might become more stenotic.

Aortic stenosis: pathology

As proved by a catheter-based study, the severity of the stenosis is influenced, in congenital BAV, by the
structural geometry of the leaflets [20]. Furthermore, four-dimensional flow magnetic resonance imaging (MRI) showed abnormal helical systolic flow in the ascending aorta of patients with a BAV [21,22]. This local flow pattern was also reported in isolated ascending aortic aneurysms [23], suggesting that modification of the aortic flow could be responsible for lesions of the ascending aorta. Because a disturbed flow may result in local changes in aortic wall stress and may cause aortic remodeling, asymmetry of the valve might explain the role of the BAV in aortic dilation. By showing a lower small/large cusp ratio in the population of BAV with aortic dilation, our results tend to support this hypothesis.

Study limitations

Several limitations must be outlined. First, even if this 3DE study is one of the largest ever conducted in children with a BAV, we did not show any relationship between the type of BAV and valvular asymmetry. Because certain types of BAV are rare, a study including more patients is necessary to identify whether one particular phenotype is more asymmetric than others. Secondly, no gold standard was used to compare the 3DE planimetric values. Indeed, it would have been ethically difficult to systematically perform cardiac MRI in these children, who are, for the most part, asymptomatic. Because cardiac MRI, which was proved to be efficient for the assessment of valvular morphology in a BAV population [24], sometimes requires general anesthesia, especially in young children, it did not appear ethical to perform this invasive examination for the sole purpose of the study. Third, we deliberately excluded patients with a BAV type 2 because measuring the small/large cusp ratio was impossible as these valves may be considered as monocuspid (no commissure individualized). However, in our experience, this type of BAV appears to be frequently stenotic: three of the four excluded patients with a BAV type 2 had aortic stenosis. Finally, planimetric measurements of valvar surfaces using 3DE is time consuming because of the off-line analysis.

Conclusions

RT-3DTTE is a feasible and reproducible method of assessing valvar surfaces in the population of children with a BAV. Our study shows that aortic stenosis seems to depend strongly on the asymmetry of the valve. Furthermore, a small AWA assessed by RT-3DTTE is also associated with aortic stenosis. When percutaneous balloon valvuloplasty is considered, this technique may be useful for accurately choosing the balloon size, according to the aortic annulus and the AWA. However, further prospective studies are needed to evaluate this non-invasive imaging technique in daily clinical practice.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


