



Review

Magnetic Resonance Imaging for Aortic Function Evaluation in Thoracic Aortic Aneurysms

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ABSTRACT

Thoracic aortic aneurysm is a common cardiovascular disease consisting of marked dilation of the aorta. Aortic aneurysms carry a high risk of life-threatening complications such as aortic dissection or rupture. Classically, maximum aortic diameter has been used as the sole descriptor of aneurysm severity and is considered the main predictor of complications. However, maximum aortic diameter measurement is often poorly reproducible and about 60% of type A and 80% of type B aortic dissections occurred in patients with an aortic diameter inferior to that recommended for the indication of elective surgical treatment. Therefore, new biomarkers for risk stratification in thoracic aortic aneurysm are needed. Cardiovascular magnetic resonance (CMR) imaging is a non-invasive imaging technique widely used for diagnosis, clinical follow-up and research in thoracic aortic aneurysms. CMR applications to thoracic aortic aneurysms are generally based on either cine CMR images, which are time-resolved images providing dynamic structural visualization, or phase-contrast images, which utilise a flow-encoding gradient to assess time-resolved velocity data. Particularly with 3D velocity encoding (4D flow MRI), phase-contrast imaging permits detailed study of haemodynamic in thoracic aortic aneurysms while cine CMR is often used to assess aortic geometry and its changes through the cardiac cycle or during follow-up. The possibilities offered by CMR for studying thoracic aortic aneurysms and a description of their applications in Bicuspid Aortic Valve (BAV) and Marfan patients are here reviewed.

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1. THORACIC AORTIC ANEURYSMS

Thoracic aortic aneurysm is a common cardiovascular disease consisting of marked dilation of the aorta. Aortic aneurysms carry a high risk of life-threatening complications such as aortic dissection or rupture, and constitute the 15th cause of death in developed countries and a common cause of premature death [1].

Classically, maximum aortic diameter has been used as the sole descriptor of aneurysm severity and is considered the main predictor of complications. Therefore, the Clinical Practice Guidelines recommend maximum aortic diameter for clinical management guidance [2]. In particular, the clinical management of aortic aneurysm with maximum diameter <50 mm consists of (i) reducing modifiable risk factors, such as through the administration of antihypertensive drugs, (ii) watchful follow-up of aortic diameter evolution with echocardiography, Cardiovascular Magnetic Resonance imaging (CMR) or Computed Tomography (CT), and (iii) lifestyle changes, e.g. moderate physical activity and smoking cessation. When aneurysm diameter is above 55 mm, preventive surgical or endovascular treatment is suggested. This threshold is lower (50 mm) in patients with Marfan Syndrome (MFS) or Bicuspid Aortic Valve (BAV) with other risk factors, such as family history of aortic dissection, coarctation of the aorta, or a rapid increase in aortic diameter [2].

However, accurate maximum aortic diameter measurement has several limitations, is often poorly reproducible, at least in certain aortic regions [3] and imaging modalities [4], and various experts question its usefulness as a predictor of acute aortic events. Indeed, results from the International Registry of Aortic Dissection showed that about 60% of type A [5] and 80% of type B [6] aortic dissections (i.e. those involving the ascending and descending aorta, respectively) occurred in patients with an aortic diameter inferior to that recommended for the indication of elective surgical treatment. Therefore, new biomarkers for risk stratification in thoracic aortic aneurysm are needed.

Several risk factors have been related to thoracic aortic aneurysm, with the most common being systemic hypertension, male sex, smoking and a family history of aortic aneurysm [2]. Apart in cases of family history, aneurysms ensuing from these established risk factors are often referred to as degenerative or arteriosclerotic, with the accumulation of damage in the aortic wall in a process of progressive *fatigue* being the most commonly accepted aetiology [7]. Other widely established risk factors for thoracic aorta aneurysm are aortic valve diseases, namely stenosis and regurgitation. Furthermore, two congenital conditions have been linked to an increased prevalence of thoracic aorta aneurysms: BAV and connective tissue disorder, the most common of which is MFS.

The possibilities offered by CMR for studying thoracic aortic aneurysms and a description of their applications in BAV and MFS patients are reviewed below.

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2. CARDIOVASCULAR MAGNETIC RESONANCE IMAGING

Cardiovascular magnetic resonance imaging is a non-invasive imaging technique exploiting tissue-specific response to a magnetic field to provide detailed imaging of cardiovascular structures. Owing to its ability to differentiate between blood flow and vessel wall, CMR is widely used for aortic aneurysm diagnosis and evaluation [2] and thus plays a fundamental role in the clinical follow-up of this condition, especially when the cumulative exposure to radiation and ionised contrast medium are of concern, as in congenital patients. CMR scientific applications to thoracic aortic aneurysms are generally based on either cine CMR images, which are two-dimensional time-resolved images providing dynamic structural visualization, or phase-contrast images, which utilise a flow-encoding gradient to provide time-resolved velocity data in 1, 2 or 3 directions.

3. CINE CMR IN THORACIC AORTIC ANEURYSM

Cine CMR is the widely used for the evaluation of aortic structure. Based on breath-holding, ECG-gated cine CMR acquisition do not need the administration of an external contrast agent and provides slice images with a spatial resolution of \approx a millimetre and temporal resolution of 15–35 ms. In the clinical management of aortic disease, double-oblique cine CMR is most often used to quantify thoracic aneurysm diameter and characterise the aortic valve. Regarding research on aortic aneurysm, cine CMR images are widely used for feature-tracking, most often to quantify distensibility and circumferential strain, with good reproducibility [8]. Furthermore, a technique utilising cine CMR images for the evaluation of proximal aorta longitudinal strain was recently presented [9].

4. THREE-DIMENSIONAL PHASE-CONTRAST CMR IN THORACIC AORTIC ANEURYSM

Three-dimensional, time-resolved Phase-Contrast (PC) Magnetic Resonance Imaging (MRI), also referred to as 4D flow MRI, is a magnetic resonance sequence able to provide a full velocity field in a large volume of interest and a 3D phase-contrast enhanced angiogram. The velocity field is “full” because every possible velocity can be described by three orthonormal components, thus removing potential errors arising from the choice of a specific velocity encoding direction, often occurring in Doppler echocardiography and PC-MRI with one velocity encoding. A 3D angiogram, which is needed for off-line identification of vessels or volumes of interest, is most often obtained by enhancing the 3D magnitude angiogram by phase contrast data, which allows for increased brightness of regions where blood flows. This sequence is applied during free-breathing, with or without respiratory gating and without the need for the administration of an external contrast agent. The interested reader is referred to a recent consensus document for aspects related to the choice of acquisition parameters, data pre-processing and possible applications not related to aortic haemodynamic [10].

4.1. Haemodynamic

Owing to its full coverage of the velocity field, 4D flow MRI permits the quantification of a wide range of simple and complex flow descriptors. Regarding relatively simple measures, 4D flow MRI has been shown to provide accurate quantification of blood velocity and flow [11]. Moreover, quantification of blood flow asymmetry can be obtained by computing jet angle, the angle between flow direction and local centreline, and normalised displacement, the radial displacement of the centre of velocity with respect to the centreline divided by the local vessel radius [12–15]. Normalised flow displacement may be more reproducible and clinically useful than jet angle for measuring aortic flow eccentricity [12,15].

Descriptors of complex flow patterns can also be obtained by 4D flow MRI. This is the case of parameters describing vortical, helical and rotational flow which may be useful for discriminating between physiological and pathological flow patterns. Several parameters have been proposed. Using the centreline as a reference system, any 3D flow rotation can be divided into in-plane (quantifying the rotational component of helical flow) and through-plane (retrograde to anterograde vortices) rotational components. The in-plane rotational component is most often quantified by computing the circulation, which is the integral of vorticity over the cross-sectional area [12,13,16], or by simply isolating the velocity component tangential to the wall [17]. Through-plane vortical structures have been quantified by computation of rotational flow along the centreline [18] or by quantifying the relative amount of backward flow during systole [12,19]. Researchers should be aware of the implications of analysing vortices with these projections and that 3D rotational flow descriptors with no prior choice of the rotation axis may convey more detailed information [20].

The haemodynamic parameter that has received the most attention to date is Wall Shear Stress (WSS). WSS is a vector describing the force per unit of area acting tangentially to the aortic wall [10]; it arises any time a viscous flow has a relative movement with respect to a surface. WSS has been related to extracellular matrix dysregulation and elastic fibre thinning in the aortic wall [21,22] and to angiogenesis and endothelial cell-mediated remodelling [23]. The computation of WSS in most of the previous works was based on the technique proposed by Stalder et al. [24]; however, intense research is underway to improve WSS quantification [25]. WSS is mainly visualised and studied by mapping it over the surface of the aorta, thereby providing specific location information, and is often divided into axial and circumferential components.

4.2. Aortic Stiffness

Pulse Wave Velocity (PWV), a physical quantity related to aortic stiffness, may play a role in aneurysm formation and rupture. PWV is the velocity of propagation of any information (here flow velocity) in a hollow structure, and is most often evaluated as the ratio of the distance between two measurement sites to the time needed for information displacement (transit time). PWV can be measured by 2D PC MRI [26] or by 4D flow MRI, with the latter allowing for the off-line choice of measurement locations [26,27]. Transit time quantification is the most delicate aspect in the evaluation of PWV by PC MRI owing to the relatively limited temporal resolution of these images. In CMR applications, transit

time is commonly measured in the frequency domain, pairing two velocity waveforms via Fourier analysis or their systolic upslope via wavelet analysis [26,28].

5. MAGNETIC RESONANCE IMAGING FOR BICUSPID AORTOPATHY EVALUATION

Bicuspid aortic valve is a congenital defect consisting of the anatomical fusion of two aortic valve leaflets. It is the most common congenital heart defect in adults, with a prevalence of around 1–2% in the general population and is responsible for more deaths and complications than all other congenital heart defects combined [29,30]. The most common morphology (80% of cases) consists of the fusion of right and left coronary cusps (RL-BAV) followed by the fusion of right and non-coronary cusps (RN-BAV, 20% of cases [31]), while the fusion of left and non-coronary cusps is rare [31]. The prevalence of proximal aorta dilation in patients with normally-functioning BAV has been estimated at between 33% and 80% [29,32,33] depending on dilation definition and specific aortic region. Two main theories have been proposed to explain this high prevalence: one argues that dilation arises from abnormal blood flow impinging on the aortic wall (haemodynamic theory) while the other advocates the presence of intrinsic (congenital) aortic wall defects.

The haemodynamic theory is sustained by a number of 4D flow MRI studies showing that the presence of BAV entails abnormal flow patterns consisting of marked flow asymmetry, which leads to uneven WSS distribution at the aortic wall, even in the absence of aortic valve disease or dilation [12,13,16,34]. Elevated WSS has been related to extracellular matrix dysregulation and elastic fibre thinning in the ascending aorta of BAV patients [21,22], possibly providing a mechanism through which these abnormal stresses are translated into dilation. Furthermore, flow conditions associated with different fusion patterns matched regions of higher dilation prevalence, i.e. proximal/mid ascending aorta in RL-BAV and distal ascending aorta and aortic arch in RN-BAV [12,13,29]. However, the clinical significance of these results should be confirmed by 4D flow MRI-based, prospective longitudinal studies, which remain lacking.

The second theory, i.e. the one favouring the existence of intrinsic abnormalities in the aortic wall, is sustained by histological findings of vascular smooth muscle cell apoptosis [35] and fibrillin-1 deficiency [36] in the aortic wall (as in Marfan patients), higher-than-normal prevalence of dilation in BAV first-degree relatives [37,38] and an increased dilation rate following aortic valve replacement in BAV compared to tricuspid aortic valve patients [39]. These early findings led to extensive research into possible intrinsic alterations in the aortic wall of BAV patients. That research was based on aortic stiffness. However, aortic distensibility, a proxy of aortic stiffness, was found reduced in BAV only when aortic diameter was larger compared to the control population [40–42], while being similar in diameter-matched comparisons [16,26,43]. Similarly, PWV, the leading marker of aortic stiffness, was found altered in dilated [44–46] but not in non-dilated [26,45,47] BAV patients compared to healthy controls. Although this picture has been clouded by the confounding factor of dilation, recent larger datasets increasingly support the absence of intrinsic differences in aortic stiffness in BAV patients.

The balance between these two theories has significant clinical implications and has indeed been mirrored by clinical guidelines.

In particular, the early suggestion of a smaller diameter for preventive aortic surgery in BAV (50 vs. 55 mm in the general population) reflected the predominant belief in the theory of intrinsic wall abnormalities [48]. Thus, BAV patients were considered at increased risk of adverse events and should have been treated more aggressively. Considering the last studies supporting haemodynamic as the main trigger of dilation in BAV, clinical guidelines are increasingly suggesting a similar threshold in BAV and TAV [49].

Apart from the need for the stratification of BAV patients regarding the risk of life-threatening aortic events, another major clinical aspect is related to BAV heritability, the understanding of which is fundamental for the widely-discussed need to screen First-Degree Relatives (FDR) of BAV patients [2]. Several studies reported BAV inheritance in around 5–10% of cases [37,50–52]; however, whether it is an autosomally-dominant inheritance pattern [51,52] or is polygenic with incomplete penetrance and variable expression [52] remains unclear. Even less known is whether intrinsic alterations in the aortic wall of BAV patients could be inherited. This may be supported by evidence of the prevalence of dilation in FDR of BAV patients with tricuspid aortic valve (identified by echocardiography) being around 10–30% in different series [37,38]. However, the presence of partial fusion of the aortic valve was recently reported in 40% of BAV FDR with aortic valve diagnosed as tricuspid by echocardiography [50]. Importantly, even minor fusion of the aortic valve has been related to an abnormal flow pattern [53], which was already proposed as a potential explanation for the prevalence of aortic dilation in BAV FDR with tricuspid aortic valve [54].

6. MAGNETIC RESONANCE IMAGING IN MARFAN SYNDROME PATIENTS

Marfan syndrome is a hereditary connective tissue disorder caused by mutations in the *FBNI* gene [55]. Unless treated, MFS patients are at high risk of acute aortic events, especially involving the aortic root. Life expectancy in MFS increased dramatically following advances in diagnosis, treatment and elective aortic replacement [56].

Driven by early evidence regarding implication of the *FBNI* gene in extracellular matrix synthesis, research on aortic stiffness in MFS has been extensive. This research was based mainly on CMR since this imaging technique is widely used in the clinical management of these patients. Most studies reported increased stiffness in MFS patients, either as reduced distensibility [26,57–61] or longitudinal aortic strain [9], or as an increase in PWV [26,59,60,62]. However, despite the relatively large number of cross-sectional studies available, only two longitudinal CMR studies evaluated the potential predictive role of increased aortic stiffness in aortic dilation or aortic events in MFS patients. One study related reduced proximal aorta longitudinal strain to aortic root dilation and aortic events (dissection + need for aortic surgery) [9], while the other related descending aorta distensibility to local dilation [63].

Conversely, studies regarding haemodynamic alterations in MFS patients are scant, and results more conflicting. Despite reported evidence regarding the presence of abnormal vortices in the aortic root [64] and in the ascending [65] and descending [62,64,66] aorta, leading to altered WSS in the root [67], ascending [65] and descending [62,66] aorta, the sole 4D flow MRI-based longitudinal study conducted to date failed to record progressive dilation

in a small group of young patients ($n = 19$; mean age: 12.7 years; range: 2–17 years) [66] and consequently its relationship with flow pattern or WSS. With very few exceptions, all these haemodynamic studies were conducted in a limited number of MFS patients. The main reasons for the lack of large population studies are thought to be the relatively short time elapsed since 4D flow MRI became available for clinical research, the need to exclude patients with previous surgery and severe aortic valve disease so as not to confound the analysis and the relative rarity of MFS.

7. CONCLUSION

Cardiac magnetic resonance is a powerful non-invasive imaging technique for the clinical assessment and research of thoracic aortic aneurysm. Cine CMR sequences are useful for evaluating aortic structures and their deformation, while phase contrast CMR, particularly with 3D encoding velocity (4D flow MRI), permits detailed study of the potential role of haemodynamic in thoracic aortic aneurysm. Despite promising results in both bicuspid aortic valve and Marfan patients, large longitudinal studies, and thus possible causative associations, are lacking and should be pursued.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

AG contributed in literature search, manuscript writing, final approval. GTT, AE and JRP contributed in literature search, manuscript review, final approval.

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REFERENCES

- [1] Eleftheriades JA, Farkas EA. Thoracic aortic aneurysm: clinically pertinent controversies and uncertainties. *J Am Coll Cardiol* 2010;55:841–57.
- [2] Erbel RA, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2014;35:2873–9126.
- [3] Vis JC, Rodríguez-Palomares JF, Teixidó-Tura G, Galian-Gay L, Granato C, Guala A, et al. Implications of asymmetry and valvular morphotype on echocardiographic measurements of the aortic root in bicuspid aortic valve. *J Am Soc Echocardiogr* 2019; 32:105–12.
- [4] Rodríguez-Palomares JF, Teixidó-Tura G, Galuppo V, Cuéllar H, Laynez A, et al. Multimodality assessment of ascending aortic diameters: comparison of different measurement methods. *J Am Soc Echocardiogr* 2016;29:819–26.e4.
- [5] Pape LA, Tsai TT, Isselbacher EM, Oh JK, O'gara PT, Evangelista A, et al. Aortic diameter ≥ 5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). *Circulation* 2007;116:1120–27.
- [6] Trimarchi S, Jonker FHW, Hutchison S, Isselbacher EM, Pape LA, Patel HJ, et al. Descending aortic diameter of 5.5 cm or greater is not an accurate predictor of acute type B aortic dissection. *J Thorac Cardiovasc Surg* 2011;142:e101–e7.
- [7] Nichols WW, O'Rourke MF, Vlachopoulos C. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 6th ed., London, UK: Hodder Arnold; 2011.
- [8] Dogui A, Kachenoura N, Frouin F, Lefort M, De Cesare A, Mousseaux E, et al. Consistency of aortic distensibility and pulse wave velocity estimates with respect to the Bramwell-Hill theoretical model: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* 2011;13:11.
- [9] Guala A, Teixidó-Tura G, Rodríguez-Palomares JF, Ruiz-Muñoz A, Dux-Santoy L, Villalva N, et al. Proximal aorta longitudinal strain predicts aortic root dilation rate and aortic events in Marfan syndrome. *Eur Heart J* 2019;40:2047–55.
- [10] Dyverfeldt P, Bissell MM, Barker AJ, Bolger AF, Carlhäll CJ, Ebbens T, et al. 4D flow cardiovascular magnetic resonance consensus statement. *J Cardiovasc Magn Reson* 2015;17:72.
- [11] Ebel S, Hübner L, Köhler B, Kropf S, Preim B, Jung B, et al. Validation of two accelerated 4D flow MRI sequences at 3 T: a phantom study. *Eur Radiol Exp* 2019;3:10.
- [12] Rodríguez-Palomares JF, Dux-Santoy L, Guala A, Kale R, Maldonado G, Teixidó-Tura G, et al. Aortic flow patterns and wall shear stress maps by 4D-flow cardiovascular magnetic resonance in the assessment of aortic dilatation in bicuspid aortic valve disease. *J Cardiovasc Magn Reson* 2018;20:28.
- [13] Dux-Santoy L, Guala A, Teixidó-Tura G, Ruiz-Muñoz A, Maldonado G, Villalva N, et al. Increased rotational flow in the proximal aortic arch is associated with its dilation in bicuspid aortic valve disease. *Eur Hear J Cardiovasc Imaging* 2019;20:1407–17.
- [14] Mahadevia R, Barker AJ, Schnell S, Entezari P, Kansal P, Fedak PW, et al. Bicuspid aortic cusp fusion morphology alters aortic three-dimensional outflow patterns, wall shear stress, and expression of aortopathy. *Circulation* 2014;129:673–82.
- [15] Sigovan M, Hope MD, Dyverfeldt P, Saloner D. Comparison of four-dimensional flow parameters for quantification of flow eccentricity in the ascending aorta. *J Magn Reson Imaging* 2011;34:1226–30.
- [16] Bissell MM, Hess AT, Biasioli L, Glaze SJ, Loudon M, Pitcher A, et al. Aortic dilation in bicuspid aortic valve disease: flow pattern is a major contributor and differs with valve fusion type. *Circ Cardiovasc Imaging* 2013;6:499–507.

- [17] Ha H, Kim GB, Kweon J, Lee SJ, Kim YH, Kim N, et al. The influence of the aortic valve angle on the hemodynamic features of the thoracic aorta. *Sci Rep* 2016;6:32316.
- [18] Bieging ET, Frydrychowicz A, Wentland AL, Landgraf BR, Johnson KM, Wieben O, et al. In vivo three-dimensional MR wall shear stress estimation in ascending aortic dilatation. *J Magn Reson Imaging* 2011;33:589–97.
- [19] Guala A, Dux-Santoy L, Teixido-Tura G, Johnson KM, Evangelista A, Rodríguez-Palomares J. Raphe in bicuspid aortic valve without significant aortic valve disease is unrelated to aortic hemodynamics and stiffness. *Rev Española Cardiol (Engl Ed)* 2020;73:89–90.
- [20] Morbiducci U, Ponzini R, Rizzo G, Cadioli M, Esposito A, De Cobelli F, et al. In vivo quantification of helical blood flow in human aorta by time-Resolved three-dimensional cine phase contrast magnetic resonance imaging. *Ann Biomed Eng* 2009;37:516–31.
- [21] Guzzardi DG, Barker AJ, van Ooij P, Malaisrie SC, Puthumana JJ, Belke DD, et al. Valve-related hemodynamics mediate human bicuspid aortopathy: insights from wall shear stress mapping. *J Am Coll Cardiol* 2015;66:892–900.
- [22] Bollache E, Guzzardi DG, Sattari S, Olsen KE, Di Martino ES, Malaisrie SC, et al. Aortic valve-mediated wall shear stress is heterogeneous and predicts regional aortic elastic fiber thinning in bicuspid aortic valve-associated aortopathy. *J Thorac Cardiovasc Surg* 2018;156:2112–20.e2.
- [23] Resnick N, Yahav H, Shay-Salit A, Shushy M, Schubert S, Zilberman LCM, et al. Fluid shear stress and the vascular endothelium: for better and for worse. *Prog Biophys Mol Biol* 2003;81:177–99.
- [24] Stalder AF, Russe MF, Frydrychowicz A, Bock J, Hennig J, Markl M. Quantitative 2D and 3D phase contrast MRI: Optimized analysis of blood flow and vessel wall parameters. *Magn Reson Med* 2008;60:1218–31.
- [25] Sotelo J, Dux-Santoy L, Guala A, Rodríguez-Palomares J, Evangelista A, Sing-Long C, et al. 3D axial and circumferential wall shear stress from 4D flow MRI data using a finite element method and a laplacian approach. *Magn Reson Med* 2018;79:2816–23.
- [26] Wentland AL, Wieben O, François CJ, Bonczyk C, Muñoz Del Rio A, Johnson KM, et al. Aortic pulse wave velocity measurements with undersampled 4D flow-sensitive MRI: comparison to 2D and algorithm determination. *J Magn Reson Imaging* 2013;37:853–9.
- [27] Guala A, Rodríguez-Palomares J, Dux-Santoy L, Teixido-Tura G, Maldonado G, Galian L, et al. Influence of aortic dilation on the regional aortic stiffness of bicuspid aortic valve assessed by 4-dimensional flow cardiac magnetic resonance: comparison With Marfan syndrome and degenerative aortic aneurysm. *JACC Cardiovasc Imaging* 2019;12:1020–9.
- [28] Bargiotas I, Mousseaux E, Yu WC, Venkatesh BA, Bollache E, de Cesare A, et al. Estimation of aortic pulse wave transit time in cardiovascular magnetic resonance using complex wavelet cross-spectrum analysis. *J Cardiovasc Magn Reson* 2015;17:65.
- [29] Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. *N Engl J Med* 2014;370:1920–9.
- [30] Ward C. Clinical significance of the bicuspid aortic valve. *Heart* 2000;83:81–5.
- [31] Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg* 2007;133:1226–33.
- [32] Nistri S, Sorbo MD, Marin M, Palisi M, Scognamiglio R, Thiene G. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. *Heart* 1999;82:19–22.
- [33] Carro A, Teixido-Tura G, Evangelista A. Aortic dilatation in bicuspid aortic valve disease. *Rev Esp Cardiol (Engl Ed)* 2012;65:977–81.
- [34] Hope MD, Hope TA, Meadows AK, Ordovas KG, Urbana TH, Alley MT, et al. Bicuspid aortic valve: four-dimensional MR evaluation of ascending aortic systolic flow patterns. *Radiology* 2010;255:53–61.
- [35] Nataatmadja M, West M, West J, Summers K, Walker P, Nagata M, et al. Abnormal extracellular matrix protein transport associated with increased apoptosis of vascular smooth muscle cells in Marfan syndrome and bicuspid aortic valve thoracic aortic aneurysm. *Circulation* 2003;108:II329–II34.
- [36] Fedak PW, de Sa MP, Verma S, Nili N, Kazemian P, Butany J, et al. Vascular matrix remodeling in patients with bicuspid aortic valve malformations: implications for aortic dilatation. *J Thorac Cardiovasc Surg* 2003;126:797–806.
- [37] Biner S, Rafique AM, Ray I, Cuk O, Siegel RJ, Tolstrup K. Aortopathy is prevalent in relatives of bicuspid aortic valve patients. *J Am Coll Cardiol* 2009;53:2288–95.
- [38] Loscalzo ML, Goh DLM, Loeys B, Kent KC, Spevak PJ, Dietz HC. Familial thoracic aortic dilation and bicommissural aortic valve: a prospective analysis of natural history and inheritance. *Am J Med Genet A* 2007;143A:1960–7.
- [39] Andrus BW, O'Rourke DJ, Dacey LJ, Palac RT. Stability of ascending aortic dilatation following aortic valve replacement. *Circulation* 2003;108:II-295–II-9.
- [40] Nistri S, Grande-Allen J, Noale M, Basso C, Siviero P, Maggi S, et al. Aortic elasticity and size in bicuspid aortic valve syndrome. *Eur Heart J* 2008;29:472–9.
- [41] Santarpia G, Scognamiglio G, Di Salvo G, D'Alto M, Sarubbi B, Romeo E, et al. Aortic and left ventricular remodeling in patients with bicuspid aortic valve without significant valvular dysfunction: a prospective study. *Int J Cardiol* 2012;158:347–52.
- [42] Li Y, Deng YB, Bi XJ, Liu YN, Zhang J, Li L. Evaluation of myocardial strain and artery elasticity using speckle tracking echocardiography and high-resolution ultrasound in patients with bicuspid aortic valve. *Int J Cardiovasc Imaging* 2016;32:1063–9.
- [43] Kurt M, Tanboga IH, Bilen E, Isik T, Kaya A, Karakaş MF, et al. Abnormal left ventricular mechanics in isolated bicuspid aortic valve disease may be independent of aortic distensibility: 2D strain imaging study. *J Heart Valve Dis* 2012;21:608–14.
- [44] Grotenhuis HB, Ottenkamp J, Westenberg JJM, Bax JJ, Kroft LJM, de Roos A. Reduced aortic elasticity and dilatation are associated with aortic regurgitation and left ventricular hypertrophy in nonstenotic bicuspid aortic valve patients. *J Am Coll Cardiol* 2007;49:1660–5.
- [45] Tzemos N, Lyseggen E, Silversides C, Jamorski M, Tong JH, Harvey P, et al. Endothelial function, carotid-femoral stiffness, and plasma matrix metalloproteinase-2 in men with bicuspid aortic valve and dilated aorta. *J Am Coll Cardiol* 2010;55:660–8.
- [46] Shim CY, Cho IJ, Yang WI, Kang MK, Park S, Ha JW, et al. Central aortic stiffness and its association with ascending aorta dilation in subjects with a bicuspid aortic valve. *J Am Soc Echocardiogr* 2011;24:847–52.
- [47] Warner PJ, Al-Quthami A, Brooks EL, Kelley-Hedgepeth A, Patvardhan E, Kuvin JT, et al. Augmentation index and aortic stiffness in bicuspid aortic valve patients with non-dilated proximal aortas. *BMC Cardiovasc Disord* 2013;13:19.
- [48] Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/

- STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation* 2010;121:e266–e369.
- [49] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 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. *J Am Coll Cardiol* 2014;e57–e185.
- [50] Galian-Gay L, Carro Hevia A, Teixido-Turà G, Rodríguez Palomares J, Gutiérrez-Moreno L, Maldonado G, et al. Familial clustering of bicuspid aortic valve and its relationship with aortic dilation in first-degree relatives. *Heart* 2019;105:603–8.
- [51] Huntington AK, Hunter AGW, Chan KL. A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. *J Am Coll Cardiol* 1997;30:1809–12.
- [52] Cripe L, Andelfinger G, Martin LJ, Shooner K, Benson DW. Bicuspid aortic valve is heritable. *J Am Coll Cardiol* 2004;44:138–43.
- [53] Guala A, Rodríguez-Palomares J, Galian-Gay L, Teixido-Tura G, Johnson KM, Wieben O, et al. Partial aortic valve leaflet fusion is related to deleterious alteration of proximal aorta hemodynamics: a 4-dimensional flow magnetic resonance imaging study. *Circulation* 2019;139:2707–9.
- [54] Schnell S, Smith DA, Barker AJ, Entezari P, Honarmand AR, Carr ML, et al. Altered aortic shape in bicuspid aortic valve relatives influences blood flow patterns. *Eur Heart J Cardiovasc Imaging* 2016;17:1239–47.
- [55] Dietz HC, Cutting CR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, et al. Marfan syndrome caused by a recurrent *de novo* missense mutation in the fibrillin gene. *Nature* 1991;352:337–9.
- [56] Silverman DI, Burton KJ, Gray J, Bosner MS, Kouchoukos NT, Roman MJ, et al. Life expectancy in the Marfan syndrome. *Am J Cardiol* 1995;75:157–60.
- [57] Teixido-Tura G, Redheuil A, Rodríguez-Palomares J, Gutiérrez L, Sánchez V, Forteza A, et al. Aortic biomechanics by magnetic resonance: early markers of aortic disease in Marfan syndrome regardless of aortic dilatation? *Int J Cardiol* 2014;171:56–61.
- [58] Fattori R, Bacchi Reggiani L, Pepe G, Napoli G, Bnà C, Celletti F, et al. Magnetic resonance imaging evaluation of aortic elastic properties as early expression of Marfan syndrome. *J Cardiovasc Magn Reson* 2000;2:251–6.
- [59] Jeremy RW, Huang H, Hwa J, McCarron H, Hughes CF, Richards JG. Relation between age, arterial distensibility, and aortic dilatation in the Marfan syndrome. *Am J Cardiol* 1994;74:369–73.
- [60] Groenink M, de Roos A, Mulder BJ, Verbeeten B, Timmermans J, Zwinderman AH, et al. Biophysical properties of the normal-sized aorta in patients with Marfan syndrome: evaluation with MR flow mapping. *Radiology* 2001;219:535–40.
- [61] Prakash A, Adlakha H, Rabideau N, Hass CJ, Morris SA, Geva T, et al. Segmental aortic stiffness in children and young adults with connective tissue disorders: relationships with age, aortic size, rate of dilation, and surgical root replacement. *Circulation* 2015;132:595–602.
- [62] Guala A, Teixido-Tura G, Dux-Santoy L, Granato C, Ruiz-Muñoz A, Valente F, et al. Decreased rotational flow and circumferential wall shear stress as early markers of descending aorta dilation in Marfan syndrome: a 4D flow CMR study. *J Cardiovasc Magn Reson* 2019;21:63.
- [63] Nollen GJ, Groenink M, Tjissen JGP, van der Wall EE, Mulder BJM. Aortic stiffness and diameter predict progressive aortic dilatation in patients with Marfan syndrome. *Eur Heart J* 2004;25:1146–52.
- [64] Geiger J, Markl M, Herzer L, Hirtler D, Loeffelbein F, Stiller B, et al. Aortic flow patterns in patients with Marfan syndrome assessed by flow-sensitive four-dimensional MRI. *J Magn Reson Imaging* 2012;35:594–600.
- [65] Geiger J, Arnold R, Herzer L, Hirtler D, Stankovic Z, Russe M, et al. Aortic wall shear stress in Marfan syndrome. *Magn Reson Med* 2013;70:1137–44.
- [66] Geiger J, Hirtler D, Gottfried K, Rahman O, Bollache E, Barker AJ, et al. Longitudinal evaluation of aortic hemodynamics in Marfan syndrome: new insights from a 4D flow cardiovascular magnetic resonance multi-year follow-up study. *J Cardiovasc Magn Reson* 2017;19:33.
- [67] Wang HH, Chiu HH, Tseng WYI, Peng HH. Does altered aortic flow in Marfan syndrome relate to aortic root dilatation? *J Magn Reson Imaging* 2016;44:500–8.