Does Altered Aortic Flow in Marfan Syndrome Relate to Aortic Root Dilatation?

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Purpose: To examine possible hemodynamic alterations in adolescent to adult Marfan syndrome (MFS) patients with aortic root dilatation.
Materials and Methods: Four-dimensional flow MRI was performed in 20 MFS patients and 12 age-matched normal subjects with a 3T system. The cross-sectional areas of 10 planes along the aorta were segmented for calculating the axial and circumferential wall shear stress (WSS_{axial}, WSS_{circ}), oscillatory shear index (OSI_{axial}, OSI_{circ}), and the nonroundness (NR), presenting the asymmetry of segmental WSS. Pearson's correlation analysis was performed to present the correlations between the quantified indices and the body surface area (BSA), aortic root diameter (ARD), and Z score of the ARD. $P < 0.05$ indicated statistical significance.
Results: Patients exhibited lower WSS_{axial} in the aortic root and the WSS_{circ} in the arch ($P < 0.05$–0.001). MFS patients exhibited higher OSI_{axial} and OSI_{circ} in the sinotubular junction and arch, but lower OSI_{circ} in the descending aorta (all $P < 0.05$). The NR values were lower in patients ($P < 0.05$). The WSS_{axial} or WSS_{circ} exhibited moderate to strong correlations with BSA, ARD, or Z score ($R^2 = 0.50$–0.72) in MFS patients.
Conclusion: The significant differences in the quantified indices, which were associated with BSA, ARD, or Z score, in MFS were opposite to previous reports for younger MFS patients, indicating that altered flows in MFS patients may depend on the disease progress. The possible time dependency of hemodynamic alterations in MFS patients strongly suggests that longitudinal follow-up of 4D Flow is needed to comprehend disease progress.

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Marfan syndrome (MFS) is an autosomal dominant condition exhibiting complete penetrance, but with a variable expression.[1,2] In the majority of cases a mutation in the fibrillin 1 (FBN1) gene, discovered at chromosome 15, promotes fibrillinopathy.[3] In the aorta, the defective tissues showed increased alcianophilic glycosominoglycans, vacuoles secondary to the loss of smooth muscle cells, and disordered adhesive proteins.[4] This makes patients more susceptible to shear stress, leading to aortic dilatation and dissection over time.[4] At present, FBN1 molecular analysis is a valuable diagnostic method for obtaining information regarding MFS in clinical practice, especially for children who may not present initially with aortic dilatation.[5]

The aorta is a critical area for interactions between structural microfibril matrix abnormalities heightened by the failure of standard maintenance programs by TGF-β and beat-to-beat hemodynamic stressors.[1] A dangerous environment for abnormal connective tissue emerges following endothelial shear stress, wall strain, torsion, and intrinsic wall stress, resulting in thinning of the aortic wall that progressively dilates and loses

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TABLE 1. Characteristics of the Study Cohort

	Normal ($n = 12$)	MFS ($n = 20$)	P value
Number (male:female)	12 (6:6)	20 (14:6)	
Age (years)	26 ± 8 (range: 20 - 48) (median = 23)	30 ± 12 (range: 12 - 54) (median = 26)	0.149
Height (cm)	170.2 ± 8.7	178.9 ± 11.0	0.013
Weight (kg)	60.5 ± 10.4	70.0 ± 17.5	0.038
BSA (m^2)	1.7 ± 0.2	1.9 ± 0.2	0.013
Systolic pressure (mmHg)	122.3 ± 14.3	125.8 ± 10.1	0.241
Diastolic pressure (mmHg)	75.4 ± 7.1	70.6 ± 11.8	0.085
Heart rate (bpm)	81.8 ± 9.2	72.8 ± 14.8	0.031
Aortic root diameter (cm)	2.5 ± 0.4 (median = 2.6)	3.9 ± 0.9 (median = 3.7)	< 0.001
Z score (a.u.)	-1.7 ± 1.0 (median = -1.8)	2.9 ± 3.0 (median = 2.0)	< 0.001

BSA = body surface area; bpm = beats per minute.

distensibility, thereby increasing the risks of aneurysm and dissection throughout its length, particularly at the root.[1] In clinical practice, the aortic root diameter (ARD) usually is measured through transthoracic echocardiography at the level of the aortic annulus, sinus of Valsalva, sinotubular junction, and ascending aorta (AAo), according to a report by the American Society of Echocardiography.[6] The mortality and event rates are significantly higher in adults with MFS when the absolute ARD is >5 cm.[1,7]

The entire aorta can be imaged using time-resolved 3D (4D) flow MRI acquired with phase-contrast imaging,[8] and complications including aneurysm formations, dissection, and previous operations are usually well visualized, rendering it suitable for longitudinal follow-ups. Several previous studies have qualitatively and quantitatively identified abnormal flow patterns or have reported flow-related indices in MFS patients. Groenink et al indicated decreased aortic distensibility and increased flow wave velocity at specified levels of normal-sized aorta for patients with a dilated aortic root.[9] Geiger et al investigated MFS flow patterns and reported that local helix flow in the AAo, which can be observed in young asymptomatic MFS patients, was closely associated with an enlarged aortic sinus.[10] Geiger et al also reported that young asymptomatic MFS patients had a mild reduction in peak systolic velocity as well as a significant increase in regional wall shear stress (WSS) in specific segments in the AAo.[11] The aortic characteristics of MFS patients may change, possibly leading to different alterations in aortic hemodynamics.

At present, quantitative analysis of hemodynamic parameters, WSS, and oscillatory shear index (OSI) for relatively young MFS patients has been performed.[11] However, systematic investigations on adolescent to adult MFS patients are lacking. Moreover, the association of the WSS and OSI with body surface area (BSA), dilated ARD, and Z score remains deficient, resulting in difficulties in evaluating the risk of aortic dissection in this group of patients. Therefore, the purpose of this study was to examine the possible hemodynamic alterations in adolescent to adult MFS patients with aortic root dilatation. We analyzed the WSS, OSI, and other hemodynamic parameters from aortic root to descending aorta (DAo) through noninvasive 4D Flow MRI.

Materials and Methods

Study Cohort

We recruited 20 MFS patients (age = 30 ± 12 [range = 12–54, median = 26] years, male:female = 14:6) who had no history of aortic dissection and 12 normal subjects who had no history of cardiovascular disease (age = 26 ± 8 [range = 20–48, median = 23] years, male:female = 6:6). The BSA of each participant was calculated using the method proposed by Du Bois et al.[12] This study was approved by the local ethics board, and informed consent was obtained from all participants, including their parents if subjects were younger than 18 years old. Table 1 lists a summary of the demographics of MFS patients and normal subjects.

MRI Acquisition

All images were acquired on a 3T system (Tim Trio, Siemens, Erlangen, Germany). To reliably measure the ARD, cine images with retrospective ECG-gating and breath-hold were acquired in the left ventricular outflow track (LVOT) view.[13] The imaging sequence was balanced steady-state free-precession (SSFP): repetition time (TR) = 16.1 msec, echo time (TE) = 1.57 msec, flip angle = 50°, and spatial resolution = 1.17 × 1.17 × 6 mm^3.

Aortic blood flow was measured by using 4D Flow MRI with three-directional velocity encoding in a sagittal oblique volume covering the entire thoracic aorta. Prospective ECG-triggering (sampling 90% of the cardiac cycle) and respiratory navigator-echo gating were used to synchronize cardiac and breathing motions, respectively. The scanning parameters were: TR = 10 msec,

TE = 2.7 msec, flip angle = 7°, temporal resolution = 40 msec, spatial resolution = (1.36–1.44) × (1.36–1.44) × 3.5 mm^3, 32–40 slices/slab, acceleration factor = 5, and velocity sensitivity encoding (VENC) = 1.5 m/s in three directions. No contrast agent was administered. The total 4D Flow MRI scanning time was ~15 minutes.

Data Processing

The ARD was determined manually at the end-systolic phase at the midpoint between the sinotubular junction and the sinus of Valsalva in LVOT view (see Supplementary Information Fig. S1). The Z score, describing the aortic diameter with minimal relation of residuals to age, gender, and BSA, was calculated according to the regression model proposed by Devereux et al.[14]

The acquired 4D Flow MRI datasets were corrected for eddy currents, Maxwell terms, and velocity aliasing, as described previously.[15,16] The 3D blood flow visualization was achieved by reconstructing a 3D PC MR angiogram from 4D Flow MRI data by using commercial software (EnSight 9.2, CEI, Apex, NC). This program enables the placement of different cut-planes in the areas of interest along the aorta, allowing subsequent quantification of hemodynamic flow data for each plane. Ten 2D planes were placed manually according to the landmarks listed in Table 2 on the 3D MRA; the planes were perpendicular to the long axis of the aorta. These locations were determined according to the Stanford and De Bakey classification of aortic dissection.[4] We placed 10 planes along the thoracic aorta, including three in the AAo (Planes 1–3, including two planes in the aortic root and one plane in the middle AAo), three in the aortic arch (AA: Planes 4–6), and four in the descending aorta (DAo: Planes 7–10). The cross-sectional area of each plane was segmented manually with an in-house analysis tool programmed with MatLab (MathWorks, Natick, MA).

In this study we calculated several hemodynamic indices to describe the aortic flow in MFS patients. The vorticity $\vec{C}(r,t)$ was an index describing the vortex flow and was calculated using the curl of velocity $\vec{V}(r,t)$[17]:

$$\vec{C}(\mathbf{r},t)=\nabla\times\vec{V}(\mathbf{r},t) \quad (1)$$

where **r** and t denote the space and time coordinates of the velocity field, respectively.

An index of relative helicity was estimated from the angle between the velocity and vorticity vectors:

$$\text{Relative Helicity} = \cos\varnothing \quad (2)$$

where Ø is the angle between the velocity and vorticity vector.[18] Angle Ø ranged from 0° to 180°, resulting in relative helicity values that were between +1 (maximum clockwise rotation when viewed in the direction of the flow) and –1 (maximum counterclockwise rotation). We report the mean relative helicity averaged over the cardiac cycle.

The WSS vector $\vec{\tau}$ was evaluated by an analysis tool developed in a previous study[19] and was defined as:

$$\vec{\tau}=2\eta\dot{\varepsilon}\cdot\vec{n} \quad (3)$$

where η represented blood viscosity, $\vec{n}$ is the inward unit normal, and $\dot{\varepsilon}$ is the deformation tensor. The WSS vector $\vec{\tau}$ could be divided into axial (WSS_{axial}) and circumferential (WSS_{circ}) components. As described in a previous study,[19] if a 1D problem was considered, $\vec{\tau}$ was simplified to:

$$\vec{\tau}=\eta\frac{\partial\vec{V}}{\partial h} \quad (4)$$

where h is the height of the boundary. In this study we report WSS values averaged over the cardiac cycle to compare the different WSS values between MFS and normal groups.

To evaluate temporal oscillations in the WSS, the OSI, the WSS deviated from its averaged direction during one cardiac cycle, was defined as:

$$\text{OSI}=\frac{1}{2}\left(1-\frac{\left|\int_0^T\vec{\tau}\cdot dt\right|}{\int_0^T|\vec{\tau}|\cdot dt}\right) \quad (5)$$

where T is the duration of the cardiac cycle. The innermost curvature was determined as the reference point and the circumference of each vessel plane was divided equally into 12 segments along the lumen circumference, starting at the reference point, as described in the previous study.[19] Subsequently, the segmental WSS and OSI could be calculated.[19]

The nonroundness (NR), describing the asymmetry of the 12 segmental WSS values of each plane, was defined as:

$$\text{NR}=\sqrt{\frac{1}{N}\sum_{i=1}^{N}(\tau_i-\bar{\tau})^2} \quad (6)$$

where τ represents the WSS, and $N=12$.

TABLE 2. Positions of 10 Transaxial Planes Along the Aorta

Plane	Position
1	Sinus of Valsalva
2	Sinotubular junction
3	Middle of Planes 2 and 4
4	Proximal aortic arch
5	Middle of innominate artery and left common carotid artery
6	Middle of left common carotid artery and left subclavian artery
7	2 cm distal to left subclavian artery
8	Middle of Planes 7 and 9
9	At the level of diaphragm
10	2 cm distal to diaphragm

Statistical Analysis

A Student's *t*-test was performed to compare the differences between two groups. The correlations between quantified flow-