



## Abnormal aortic hemodynamics are associated with risk factors for aortic complications in patients with marfan syndrome

Mitzi M. van Andel<sup>a,1</sup>, Pim van Ooij<sup>b,1</sup>, Vivian de Waard<sup>c,1</sup>, Lukas M. Gottwald<sup>b,1</sup>, Roland R.J. van Kimmenade<sup>d,1</sup>, Arthur J. Scholte<sup>e,1</sup>, Michael G. Dickinson<sup>f,1</sup>, Aeilko H. Zwinderman<sup>g,1</sup>, Barbara J.M. Mulder<sup>a,1</sup>, Aart J. Nederveen<sup>b,1</sup>, Maarten Groenink<sup>a,b,\*,1</sup>

<sup>a</sup> Department of Cardiology, Amsterdam University Medical Center, Amsterdam, the Netherlands

<sup>b</sup> Department of Radiology & Nuclear Medicine, Amsterdam University Medical Centers, Amsterdam, the Netherlands

<sup>c</sup> Department of Medical Biochemistry, Amsterdam University Medical Center, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands

<sup>d</sup> Department of Cardiology, St. Radboud University Hospital, Nijmegen, the Netherlands

<sup>e</sup> Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands

<sup>f</sup> Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands

<sup>g</sup> Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam University Medical Center, Amsterdam, the Netherlands

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### ABSTRACT

**Background:** It is difficult to assess the risk for aortic dissection beyond the aortic root in patients with Marfan syndrome (MFS). To aid risk assessment in these patients, we investigated aortic flow and wall shear stress (WSS) by 4D flow magnetic resonance imaging (MRI) in patients with MFS and compared the results with healthy volunteers. We hypothesized that MFS patients with a high-risk profile for aortic dissection would show abnormal hemodynamics in aortic regions associated with aortic dissection.

**Methods:** MFS patients (n = 55) and healthy subjects (n = 25), matched for age and sex, prospectively underwent 4D flow MRI. 4D flow maps were constructed to detect elevated (defined as higher than the three-dimensional 95 % confidence interval) and deviant directed (defined as vector angle differences higher than 120°) WSS in MFS patients as compared to the controls. Univariate and multivariate associations with risk factors for aortic dissection in MFS patients were assessed.

**Results:** The maximum incidence for elevated WSS was 20 % (CI 9 %-31 %) and found in the ascending aorta. The maximum for deviant directed WSS was 39 % (CI 26 %-52 %) and found in the inner descending aorta. Significantly more male patients had deviant directed WSS in the inner proximal descending aorta (63 % vs 24 %, p = 0.014). Multivariate analysis showed that deviant directed WSS was associated with male sex (p = 0.019), and a haplo-insufficient FBN1 mutation type (p = 0.040). In 60 % of MFS patients with a previous aortic root replacement surgery, abnormal hemodynamics were found in the ascending aorta. No significant differences between hemodynamics were found in the descending aorta between operated and non-operated patients.

**Conclusion:** Deviant directed WSS in the proximal descending aorta is associated with known risk factors for aortic dissection in MFS patients, namely male sex and a haploinsufficient FBN1 mutation type.

### 1. Background

Marfan syndrome (MFS) is an inherited connective tissue disease,

caused by a wide range of Fibrillin-1 (FBN1) mutations. This condition may lead to aortic aneurysm formation, aortic dissection and subsequent sudden death at a relatively young age when untreated surgically.

**Abbreviations:** CI, confidence interval; CMR, cardiac magnetic resonance; DN, dominant-negative; FBN1, fibrillin-1; HI, haploinsufficient; IRQ, interquartile range; MAP, mean arterial pressure; MFS, Marfan syndrome; MRI, magnetic resonance imaging.

\* Corresponding author at: Amsterdam UMC, University of Amsterdam, Department of Cardiology and Radiology, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.

E-mail address: [m.groenink@amsterdamumc.nl](mailto:m.groenink@amsterdamumc.nl) (M. Groenink).

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Clinical management is directed at prophylactic aortic root replacement, based on threshold values for aortic diameters [1]. As a result of aggressive root replacement, the main threat for recognized patients is now the aorta beyond the aortic root, where dissection is very difficult to predict by aortic diameter alone [2]. Several potential additional risk factors, including: male sex, haploinsufficient (HI) type of FBN1 mutation, and history of aortic root replacement have been shown to negatively affect prognosis in MFS patients. However, none of these factors have reached the level of clinical importance to justify surgical intervention at aortic diameters below 50 mm, although rapid aortic aneurysm growth and family history of aortic dissection are generally accepted as an additional risk factor for aortic dissection according to current guidelines [3]. It is of great importance to establish parameters that could help to determine aortic disease severity beyond the aortic root in MFS patients [4].

Beside mentioned risk factors, altered aortic elastic function and geometry are probably both the cause and the result of the degenerative changes in the aortic wall in patients with MFS. Interactions between mechanic aortic wall properties and aortic geometry will probably result in altered aortic flow patterns, as shown in previous 4D flow magnetic resonance imaging (4D flow MRI) studies [5,6].

Over the past decade, several studies using 4D flow MRI have demonstrated the usefulness of this technique for the assessment of abnormal 3D flow patterns and wall shear stress (WSS) in MFS patients [5–7]. Multiple studies have shown altered WSS at predilection sites for aortic dissection in these patients [5,6,8–14]. However, it remains a challenge to interpret these findings and to assign elevated or deviant directed WSS to be a cause (by affecting endothelial function) or just a result of aortic degeneration and aneurysm formation in MFS.

In this study, we present an aortic 4D flow MRI analysis, providing a comprehensive quantification and visualization of abnormal aortic velocity and WSS magnitude and direction with state-of-the-art techniques [15,16] in MFS patients. We hypothesize that an abnormal hemodynamic profile could be found in aortic regions which are known predilection sites for aortic dissection (aortic root and proximal descending aorta). Furthermore, we hypothesize that abnormal hemodynamics are associated with higher risk profile for aortic dissection among patients with MFS.

## 2. Methods

### 2.1. Study design and participants

Sixty patients with MFS with a genetically confirmed FBN1 mutation were prospectively included in the RESVcue Marfan study (NL66127.018.18). The RESVcue Marfan study aims at obtaining sufficient data on beneficial effects of Resveratrol on aortic degenerative disease in patients with MFS to justify a randomized trial. The RESVcue MFS study included patients from four Dutch university hospitals with a specialized multidisciplinary MFS screening clinic (Amsterdam UMC – Academic Medical Center, Amsterdam; Radboud University Medical Center, Nijmegen; University Medical Center Groningen, Groningen; Leiden University Medical Center, Leiden) from December 2018 to October 2020. Eligible patients were adults ( $\geq 18$  years) who were diagnosed with MFS according to the revised Ghent criteria [17] and with a known FBN1 mutation. Patients were ineligible if they (i) had an aortic root diameter  $> 50$  mm, (ii) had a history of aortic dissection, (iii) had more than one vascular prosthesis, (iv) had aortic surgery in the last 6 months prior to inclusion, (v) were likely to have aortic surgery within 6 months of inclusion, or (vi) were pregnant or planning pregnancy. The study was approved by the local ethics board and informed consent was obtained from all participants. Twenty-five healthy subjects were prospectively included as part of an earlier study [18]. The healthy subjects were recruited based on the absence of cardiovascular disease or surgery.

### 2.2. Magnetic resonance imaging

Study subjects were examined in supine position in a 3 T MR scanner (Ingenia, Philips, Best, The Netherlands). All MRI scans were performed at one center (Amsterdam UMC – Academic Medical Center). Localization of the aorta was performed by balanced steady-state free precession imaging sequences. The entire aorta was then visualized using an ECG gated Dixon 3D sequence with specific read-outs for water, fat, in phase and out phase MR signals. The spatial resolution was  $0.73 \times 0.73 \times 1.25$  mm. Timing was at end-diastole and triggered on end-expiration by a navigator sequence. The aortic diameters of the MFS patients were measured on water images and the maximum value was considered for analysis. For the control group, diameter measurements were performed on the modulated images of 4D flow data. A 4D-Flow phase contrast sequence was applied to the entire thoracic aorta. Parameters for MFS patients: spatial resolution:  $2.5 \times 2.5 \times 2.5$  mm<sup>3</sup>; temporal resolution: 33 ms (30 timeframes); echo time, repetition time / flip angle (TE/TR/FA) 2.1msec/3.9msec/8°; velocity encoding: 150–250 cm/s; acceleration with Prospective Undersampling in Multiple Dimensions (PROUD) [19] R = 8. Parameters for healthy subjects: spatial resolution: (TE/TR/FA)  $2.5 \times 2.5 \times 2.5$  mm<sup>3</sup>; 42 ms (24 timeframes); VENC = 150 cm/s; k-t PCA acceleration factor: 8 [20]. Brachial systolic (SBP) and diastolic (DBP) blood pressure were measured every 10 min during the entire MRI study.

### 3. 4D flow data analysis

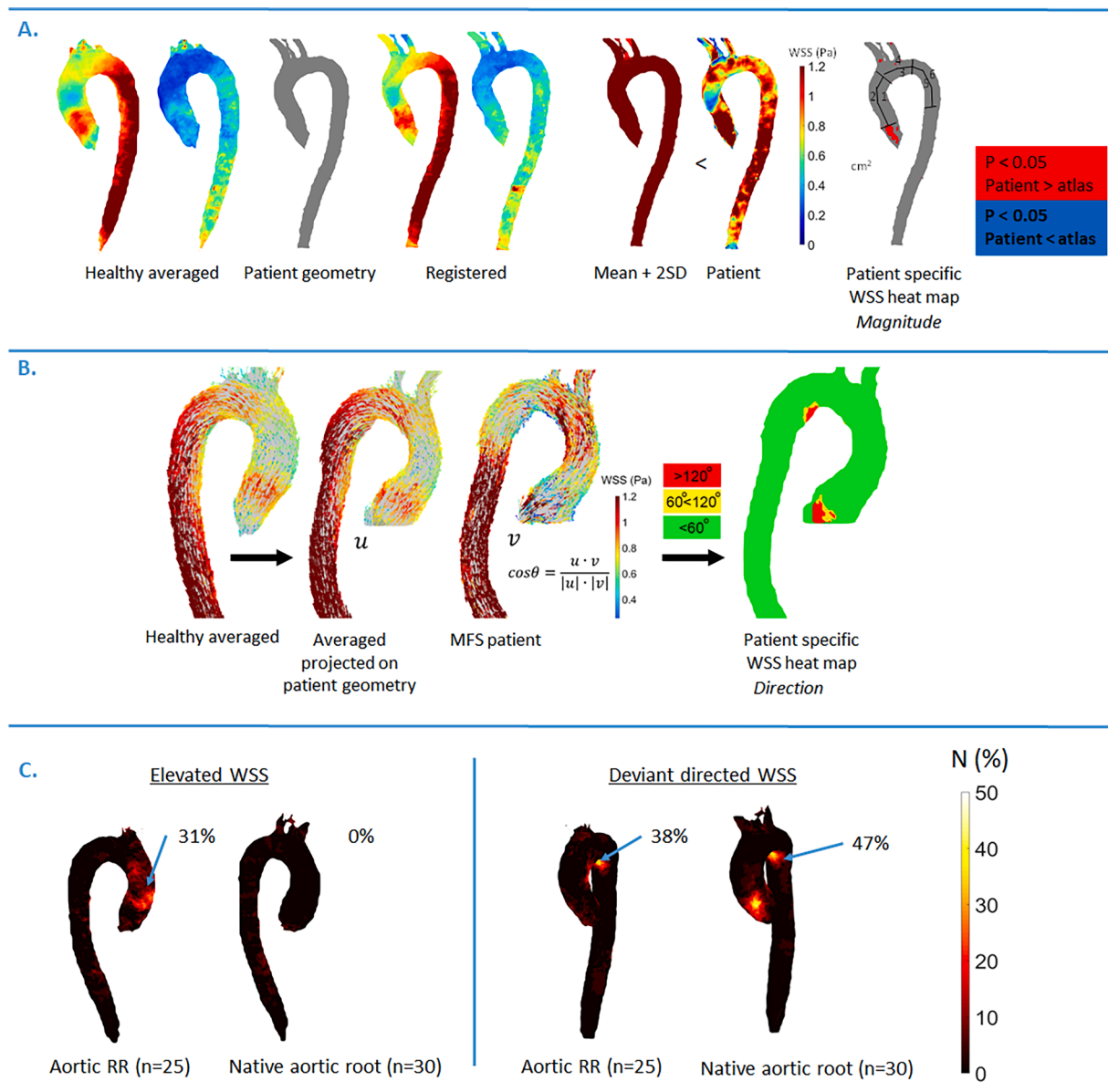
All 4D flow data were corrected for eddy currents, Maxwell terms, and velocity aliasing using custom built software programmed in Matlab (The Mathworks, Inc, Natick, MA). The aorta was manually segmented on time-averaged phase contrast MR angiogram images (phase contrast magnitude images multiplied by absolute velocity) by threshold, watershed and manual voxel in-/exclusion in Mimics (Materialise, Leuven, Belgium). The segmentations were used to mask the velocities, calculate WSS and co-registration for quantification of abnormal hemodynamics using previously described algorithms [21]. Briefly, the WSS vector was estimated at the wall based on the 3D spatial velocity gradient perpendicular to the vessel wall. Systolic 3D WSS magnitude along the entire aorta surface was then calculated at peak systole [22].

### 4. 3D WSS atlas

Cohort-averaged 3D velocity and WSS “heat maps” were created from the healthy subjects, delineating elevated velocity and WSS in the aorta as previously described [15]. In short, a “shared” geometry of the control group was created. Each control was coregistered to the “shared” geometry, followed by interpolation of the peak systolic velocity and WSS values. After interpolation, the average and standard deviation (SD) of the velocity and WSS of the control cohort was calculated. Next, the average and SD velocity and WSS maps of the control cohort were projected onto the aortic geometry of each individual patient with MFS.

Elevated or decreased WSS was defined as higher or lower than the three-dimensional 95 % confidence interval (Fig. 1A). Deviant directed WSS was defined as vector angle differences higher than 120° (Fig. 1B). Patients that showed any vectors in different direction in the descending aorta were considered in the group of patients with a deviant directed WSS. The 3D maps with abnormal hemodynamics were co-registered and added to yield 3D maps that show the incidence of abnormal hemodynamics [18].

The aorta was subdivided in six regions of interest (ROIs): [1] the inner ascending aorta (AAo); [2] the outer AAo; [3] the inner aortic arch; [4] the outer aortic arch; [5] the inner descending aorta (DAo); [6] the outer DAo.



**Fig. 1.** Individual patients peak systolic WSS maps are compared with peak systolic 3D WSS atlases, resulting in patient specific WSS heat maps depicting regions with **A.** increased (red) or decreased (blue) WSS, or **B.** deviant directed WSS; >120° (red), 60-120° (yellow), <60° (green). **C.** Incidence maps for elevated and deviant directed WSS in patients with previous aortic RR and patients with a native aortic root. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

#### 4.1. Statistical analysis

Statistical analyses were performed using SPSS V.26 (IBM, Armonk, NY, USA). Categorical data, reported in numbers and percentages were compared between groups using the Fisher's exact test. Continuous data were interpreted as median and interquartile range (IQR) or as mean and standard deviation, depending on the distribution of the data. Comparison of continuous variables between groups were executed with either parametric (Student's *t*-test) or non-parametric (Mann-Whitney U) tests, depending on the distribution.

We investigated whether the following clinical characteristics, that are potential risk factors for aortic complications, were significantly associated with deviant directed WSS in the descending aorta using univariate regression analyses: sex (male), age, body surface area (BSA, Dubois method), scoliosis (yes or no, if it exceeded an angle of >20°), family history of dissection (yes or no), cardiovascular medication use (yes or no), aortic root replacement (yes or no), mean arterial pressure,

heart rate, pulse pressure, FBN1 mutation (HI or DN), and aortic dimensions (mm). Variables with p-values < 0.20 in the univariate analyses were subsequently included in a multivariate regression analysis. Strengths of the associations were presented as odds ratios (OR) with 95 % confidence intervals (CI). All multivariate tests were two-sided and p-values < 0.05 were considered to indicate statistical significance.

## 5. Results

### 5.1. Study population

In total, 60 adult patients with MFS participated in the RESVcue Marfan study (2018–2021). Of these 60 patients, the scans of 55 patients were eligible for analysis; five scans were of insufficient quality to further analyse the 4D flow data. Characteristics of the cohort are shown in [Table 1](#). Included patients were adults (≥18 years) diagnosed with MFS according to the revised Ghent criteria of 2010 [17] and with a

**Table 1**  
Demographic and clinical characteristics of the patients with MFS.

	Total n = 55	Total n = 55
<i>General features</i>		<i>Aortic dimension by MRI</i>
Age at inclusion (years)	37 ± 9	Native aortic root (mm)
Sex (male)	28 (51 %)	Ascending aorta (mm)
Body surface area (m <sup>2</sup> )	2.12 ± 0.2	Aortic arch (mm)
Mean aortic pressure (mmHg)	84 ± 9	Descending aorta
Heart rate (bpm)	62 ± 10	Pulmonary artery (mm)
FBN mutation	55 (100 %)	Diaphragm (mm)
Dominant-negative	25 (45 %)	
Haploinsufficient	24 (44 %)	
Unknown	6 (11 %)	
Cardiac medication	42 (76 %)	
β-blocker	32 (58 %)	
Losartan	34 (62 %)	
β-blocker and Losartan	23 (42 %)	
Aortic root replacement	25 (46 %)	

known FBN1 mutation. Mean age at was 37 ± 9 years, of which 28 (51 %) patients were male. Twenty-five (46 %) patients had a history of prophylactic aortic root replacement, and 42 (76 %) of the patients used cardiac medication (β-blocker, angiotensin-II receptor blocker, or a combination). Furthermore, 25 healthy controls with a mean age of 37 ± 13 years, of which 16 (64 %) male participants, underwent 4D flow MRI to compare velocity and WSS values between patients with MFS and healthy controls. There were significant differences between BSA (MFS patients 2.12 ± 0.2, controls 1.9 ± 0.2, p < 0.001, and heart rate (MFS patients 62 ± 10, controls 74 ± 14, p < 0.001) between the two groups.

## 6. Thoracic aorta dimensions and the correlation with WSS

Mean aortic diameters in patients with MFS were 42 ± 4.4 mm at the Sinus of Valsalva in non-operated patients. For the entire cohort of patients with MFS, aortic diameters were 31 ± 3.4 mm in the mid-AAo, 26 ± 3.2 mm in the aortic arch, 26 ± 3.8 mm in the proximal DAo at the level of the pulmonary artery, and 22 ± 2.5 mm in the distal DAo at the level of the diaphragm (Table 1). Diameters in the aortic root and

**Table 2**  
Subgroup analysis for deviant directed WSS in the proximal DAo.

	Total n = 55	Deviant directed WSS		Normal directed WSS		Univariate		Multivariate	
		Inner DAo n = 38	Inner DAo n = 17	P*	OR	CI (95 %)	P*		
<i>Patient characteristics</i>									
Sex (male)	28 (51 %)	24 (63 %)	4 (24 %)	0.014	3.6	1.2–9.9	0.019		
Age at inclusion, years	38 (30–46)	38 (29–46)	39 (31–46)	0.590	1.0	0.9–1.03	0.286		
Body surface area (m <sup>2</sup> )	2.11 ± 0.24	2.2 ± 0.24	2.0 ± 0.20	0.213	0.3	0.02–5.5	0.439		
Scoliosis	13 (24 %)	9 (24 %)	4 (24 %)	0.704	0.7	0.2–2.5	0.581		
Skeletal involvement	25 (45 %)	16 (42 %)	9 (53 %)	0.793	1.3	0.4–5.0	0.657		
Family history of dissection	19 (35 %)	15 (39 %)	4 (24 %)	0.324	1.9	0.7–5.5	0.249		
Cardiovascular medication use	42 (76 %)	29 (76 %)	13 (76 %)	0.122	1.7	0.5–6.0	0.409		
Aortic root replacement	25 (45 %)	17 (45 %)	8 (47 %)	0.691	0.5	0.2–1.7	0.313		
Mean arterial pressure	84 ± 9.1	83 ± 9.1	85 ± 10.3	0.576	1.0	0.96–1.1	0.504		
Heart rate	62 ± 10.2	61 ± 9.9	63 ± 11.6	0.236	1.0	0.96–1.1	0.694		
Pulse pressure	48 ± 11.4	49 ± 11.1	50 ± 12.6	0.868	1.0	0.99–1.1	0.113		
FBN1 Mutation	n = 49	n = 33	n = 16						
Haploinsufficient	25 (51 %)	20 (61 %)	5 (31 %)	0.086**	3.0	1.1–8.2	0.040*		
Dominant-negative	24 (49 %)	13 (39 %)	11 (69 %)	0.086**	0.3	0.12–0.9	0.040*		
<i>Aortic dimension by MRI</i>	n = 30	n = 21	n = 9						
Native aortic root (mm),	41.3 ± 4.4	42.3 ± 4.2	39.8 ± 3.9	0.590	1.0	0.8–1.2	0.785		
	n = 55	n = 38	n = 17						
Ascending aorta (mm)	30.8 ± 3.5	31.3 ± 3.8	30.0 ± 2.3	0.703	0.9	0.8–1.1	0.483		
Aortic arch (mm)	26.4 ± 3.3	26.8 ± 3.4	25.8 ± 2.7	0.991	0.9	0.7–1.0	0.148		
Prox. descending aorta (mm)	26.5 ± 4.3	27.2 ± 3.9	24.5 ± 2.9	0.124	0.9	0.9–1.2	0.221		
Dis. descending aorta (mm)	22.0 ± 2.6	22.2 ± 2.6	21.7 ± 2.1	0.753	0.9	0.7–1.1	0.257		

OR: Odds Ratio, CI (95 %) = 95 % Confidence Interval.

\*p < 0.05 according to the regression analyses, indicating a significant result.

\*\*p < 0.2 according to the regression analyses, indicating a possible trend.

ascending aorta were significantly different from the control group with a mean diameter of 31 ± 5, and 30 ± 5 respectively (both p-values < 0.0001). Furthermore, the inner proximal DAo negatively correlated with mean WSS (β = -0.481, p < 0.001), where lower mean WSS values correlated with increased aortic diameter.

In Fig. 1, the averaged normal WSS maps are shown, an example of a patient with elevated WSS value and an example with deviant directed WSS. Compared with controls, patients with MFS showed elevated and deviant directed WSS. The maximum incidence for elevated WSS was 20 % (CI 9 %-31 %) and found in the AAO. The maximum for deviant directed WSS was 39 % (CI 26 %-52 %) and found in the inner DAo.

## 7. Subgroup analysis for deviant directed WSS in the proximal DAo

Differences in characteristics between the MFS patients with deviant directed WSS in the inner proximal DAo (n = 38) and those with normal directed WSS in the inner proximal DAo (n = 17) are summarized in Table 2. Significantly more male patients showed deviant directed WSS in this subgroup analysis. Furthermore, there was a trend towards more patients with a HI mutation in the group with deviant directed WSS. In multivariate regression analysis, male sex (OR = 3.6 | 95 % CI: 1.2–9.9 | p = 0.019), and HI type of FBN1 mutation (OR = 3.0 | 95 % CI: 1.1–8.2 | p = 0.040) were significantly associated with deviant directed WSS in the proximal descending aorta. No differences were found in patients who used cardiovascular medication and patients who used no medication.

## 8. Aortic root replacement and WSS

Differences in hemodynamics in the AAO and aortic arch between patients with a native aortic root and previous aortic root replacement were observed (Table 3). Patients with previous aortic root replacement showed significantly elevated velocity and WSS in the inner and outer AAO (all p-values < 0.001). In the aortic arch, patients with previous aortic root replacement showed significantly elevated velocity in the inner and outer wall (p = 0.002, p < 0.001 respectively), and elevated WSS in the inner wall only (p < 0.001). In addition, deviant directed

**Table 3**  
Differences in abnormal hemodynamics for patients with MFS with aortic RR and patients with a native aortic root.

	Inner AAO			Outer AAO			Inner Arch			Outer Arch		
	Operated	Non-operated	p	Operated	Non-operated	p	Operated	Non-operated	p	Operated	Non-operated	p
Elevated velocity [cm <sup>3</sup> ]	3.1 ± 3.0	0.3 ± 0.9	<0.001*	7.2 ± 4.5	0.2 ± 0.5	<0.001*	0.6 ± 0.9	0.3 ± 0.8	0.002*	1.7 ± 2.9	0.4 ± 1.2	<0.001*
Elevated WSS [cm <sup>3</sup> ]	1.5 ± 3.2	0.1 ± 0.2	<0.001*	3.8 ± 5.0	0.0 ± 0.1	<0.001*	0.2 ± 0.4	0.1 ± 0.2	0.060**	0.3 ± 0.4	0.1 ± 0.5	<0.001*
Deviant directed velocity [cm <sup>3</sup> ]	0.8 ± 1.5	0.1 ± 0.3	0.021*	0.1 ± 0.2	0.1 ± 0.3	0.313	0.0 ± 0.1	0.0 ± 0.0	0.071**	0.1 ± 0.4	0.0 ± 0.0	0.132
Deviant directed WSS [cm <sup>2</sup> ]	3.2 ± 3.3	0.9 ± 1.4	<0.001*	0.7 ± 1.2	1.4 ± 2.0	0.178	0.3 ± 0.6	0.2 ± 0.4	0.107	0.4 ± 1.8	0.0 ± 0.04	0.003*

\*p < 0.05 according to the regression analyses, indicating a significant result.

\*\*p < 0.2 according to the regression analyses, indicating a possible trend.

WSS was significantly higher in the inner AAO and inner aortic arch in patients with previous aortic root replacement (p < 0.001, p = 0.003, respectively).

Fig. 1C shows percentages of elevated WSS in the AAO (31 %) of patients with previous aortic root replacement. Deviant directed WSS was observed in patients with aortic root replacement in the DAAO (38 %), and in patients with a native aortic root (47 %).

## 9. Discussion

This study shows elevated and deviant directed WSS at known predilection sites for aortic dissection, namely the ascending and proximal descending aorta, respectively, in patients with MFS. Patients with deviant directed WSS in the descending aorta were more frequently men, with a HI mutation type. Furthermore, 60 % of patients with a previous aortic root replacement showed abnormally elevated hemodynamics in the ascending aorta.

MFS is characterized by a great variability in phenotypical penetrance of aortopathy. Anomalies in WSS, both elevated and reduced, in the proximal descending aorta have been described in earlier MFS studies, using similar 4D flow MRI methodology [5,6]. Guala et al. showed that WSS correlates independently with proximal descending aortic diameter beyond age, BSA and regional stiffness [13], suggesting local hemodynamics as an independent measure of aortopathy in MFS. The correlation with known risk factors for aortic dissection in MFS, i.e., male sex and a HI mutation type [23,24], with deviant WSS in the proximal descending aorta may further strengthen this theory.

There is an ongoing debate on the relative roles of hemodynamics versus intrinsic genetic defects in aneurysm formation. WSS alterations in patients with MFS are likely part of a dynamic process that is either caused by the genetic mutation, which influences the integrity of the extracellular matrix and thus cellular function, promoting further vascular damage, which may both be present at the same time in MFS. Changes in WSS may therefore reflect aspects of aortic pathology and provide insight in aortic disease development in MFS. Interestingly, in multiple studies focusing on patients with a bicuspid aortic valve (BAV), it was shown that increased WSS was related to increased dilatation rate [25], which differed from patients with MFS. One study also showed that more severe aortic valve dysfunction resulted in a further increase of aortic WSS in BAV patients [26], which suggest that different WSS values (decreased or elevated) might be related to disease etiology, and whether its origin is in the vessel wall (MFS patients), or in the valve (BAV patients).

The non-compliant implanted graft, with stiff mechanical characteristics, may explain the observed increased incidence of elevated WSS in the ascending aorta in patients who underwent aortic root replacement. The graft is likely to influence blood flow patterns, which determine WSS, as previously shown [13]. Thereby, it seems reasonable that

patients with previous aortic root replacement are more severely affected, and therefore have a more dilated descending aorta and elevated WSS. Interestingly, changed direction of WSS in the distal aorta showed no differences between patients with a native aortic root and patients who underwent aortic root replacement. Since patients with aortic root replacement are known to be at enhanced risk for aortic dissection in the descending aorta [2], it was anticipated that hemodynamic changes in this region would be associated to this subpopulation of operated patients to explain disease severity. However, aortic diameters were larger in the descending aorta in patients with aortic root replacement compared to patients with a native aortic root, suggesting that the WSS values should be independently interpreted.

In our cohort, 76 % of the patients used cardiac medication ( $\beta$ -blockers, losartan, or a combination). These drugs have proven to be effective on slowing down aortic dilatation rate [27,28]. Little debate has been going on, whether the reduction of cardiac output caused by medication use would influence WSS. An earlier study has demonstrated that MFS patients with lower flow rates, did still show regionally higher systolic WSS [9]. The authors speculate that altered WSS reflects the presence of disturbed flow, which results in altered and elevated shear forces at the vessel wall. In a study focussing on WSS in patients with bicuspid aortic valves and the use of  $\beta$ -blockers, no differences were seen in average WSS in patients who used  $\beta$ -blockers or patients who did not [29]. It is however possible that mean WSS is not altered in patients with or without medication use, but that values of WSS velocity and direction are. It would also be interesting to investigate whether there is a difference in WSS between patients who use  $\beta$ -blockers and patients who use losartan.

Earlier studies show altered hemodynamics and WSS in predilection sites for aortic dissection in MFS [5,6]. Since these studies were conducted in children, it would be interesting to have a longer follow up, especially in male study subjects with a HI FBNI mutation, between ages of 16–30. Geiger et al., who provided one of the few longitudinal studies concerning 4D flow MRI in patients with MFS, reported generally stable hemodynamic findings in the thoracic aorta in a 3-year follow-up [6]. However, they did find significant WSS changes in the inner segment of the proximal descending aorta. Similarly, we observed deviant directed WSS in this aortic segment. These changes may also be explained by the location where the aorta is fixed at the level of the ligamentum arteriosum, a site prone to dissect. Due to this fixation and the often elongated aorta in MFS patients, continued pulling forces on the aortic wall due to aortic motion may be responsible for these local changes in hemodynamics and dissection risk.

Literature on the use of 4D flow MRI in patients with MFS is expanding, yet due to lack of longitudinal studies there is no consensus on how to interpret the hemodynamic parameters, such as flow patterns and WSS, and use them in clinical practice. Overall, these studies indicate that patients with abnormal flow patterns and low WSS (related to

increased diameter) have a higher risk of progressive disease and therefore early dissection [5,6], and may thus require more intense follow up. Since we face the limitations of measuring just aortic diameters to predict risk for aortic events, the usefulness of hemodynamic parameters obtained from 4D flow MRI to further optimize risk stratification in patients with MFS seems obvious, especially in combination with additional risk factors, such as male sex, and a HI mutation type. Longitudinal studies, with clinically relevant endpoints (e.g. aortic root replacement and dissection), are essential to further elucidate the diagnostic and prognostic value of hemodynamic parameters.

#### Future perspectives.

Follow up data on clinical endpoints (aortic surgery, aortic dissections, aortic ruptures or death) from the RESVcue Marfan study will be available after sufficient follow-up (at least 5 years).

#### Limitations

Limitations of the study are the relatively small number of patients who were included. Observer variability and test–retest were not assessed in this study because previous studies have demonstrated good inter-observer variability and test–retest reproducibility of the 3D WSS method and 3D WSS atlas concept [30]. Furthermore, it was not optimal to have two different 4D flow methods used for either patients or healthy subjects.

Moreover, the cross-sectional nature of the study implies the impossibility of supporting causal relationships among variables, which should be addressed in future longitudinal studies. Our results are influenced by the antihypertensive medication that results in changes in cardiac output.

## 10. Conclusion

Altered hemodynamics were localized at predilection sites for aortic dissection in patients with MFS compared to healthy controls. Deviant directed WSS in the descending aorta was more frequently seen in male patients, and in patients with a HI mutation type. Elevated WSS was detected in the ascending aorta in patients with previous aortic root replacement. In the descending aorta no differences in elevated hemodynamics were seen between operated and non-operated patients.

#### Declarations

##### Availability of data and materials

The datasets generated and analyzed during the current study will become available from the corresponding author upon reasonable non-commercial request.

##### Authors' contribution

VdW and MG proposed and initiated the RESVcue Marfan study. MMvA, AHZ, BJMM, MG and VdW defined the research strategy. AHZ and PvO provided statistical expertise. AJHAS, MPB, MD, RK, FBE, PvO are our collaborators. MMvA, PvO and MG drafted the manuscript. AHZ, BJMM and VdW revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

##### Ethics approval and consent to participate

This study was approved by the local ethics board of the Amsterdam UMC – AMC (Amsterdam, the Netherlands). All the institutional review boards of the local centers approved participation in the study. Written, informed consent to participate was obtained from all participants.

##### Consent for publication

Not applicable.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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