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MRI-assessed regional pulse wave velocity for predicting absence of regional aorta luminal growth in marfan syndrome☆

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ABSTRACT

Background: In patients with Marfan syndrome (MFS), increased aortic wall stiffening may lead to progressive aortic dilatation. Aortic Pulse Wave Velocity (PWV), a marker of wall stiffness can be assessed regionally, using in-plane multi-directional velocity-encoded MRI. This study examined the diagnostic accuracy of regional PWV for prediction of regional aortic luminal growth during 2-year follow-up in MFS patients.

Methods: In twenty-one MFS patients (mean age 36 ± 15 years, 11 male) regional PWV and aortic luminal areas were assessed by 1.5 T MRI. At 2-year follow-up, the incidence of luminal growth, defined as mean luminal diameter increase >2 mm was determined for five aortic segments (S1, ascending aorta; S2, aortic arch; S3, thoracic descending aorta, S4, supra-renal and S5, infra-renal abdominal aorta). Regional PWV at baseline was considered increased when exceeding age-related normal PWV (healthy volunteers (n = 26; mean age 30 ± 10 years, 15 male)) by two standard-errors. Sensitivity and specificity of regional PWV-testing for prediction of regional luminal growth were determined.

Results: Regional PWV at baseline was increased in 17 out of 102 segments (17%). Significant luminal growth at follow-up was reported in 14 segments (14%). The specificity of regional PWV-testing was ≥78% for all aortic segments, sensitivity was ≤33%.

Conclusions: Regional PWV was significantly increased in MFS patients as compared to healthy volunteers within similar age range, in all aortic segments except the ascending aorta. Furthermore, regional PWV-assessment has moderate to high specificity for predicting absence of regional aortic luminal growth for all aortic segments in MFS patients.

1. Introduction

Marfan syndrome (MFS) is an autosomal connective tissue disease caused by mutations in the gene encoding for fibrillin-1 [1]. In MFS patients, fibrillin-1 deficiency leads to impaired aortic elasticity (i.e. aortic stiffness), increased transforming growth factor beta (TGF-β) signalling [2,3] and smooth muscle cells apoptosis, degrading the support of the aorta [4]. Aneurysm formation is the result. Indeed, the leading cause of premature death in MFS patients is aortic dissection after progressive dilatation due to the local increased aortic wall stiffness [5]. Accordingly, clinical management aims for prevention of aortic dissection by regular evaluation of local aortic diameter and screening for abnormal luminal growth in combination with ß-blocker treatment to slow down aortic growth [6–8]. However, many MFS patients even when treated, develop eventually aortic dilatation and even dissection. Furthermore, aortic dissection may also occur in non-dilated aortas [6]. Therefore, investigation of other risk factors, such as aortic stiffness, is recommended for predicting progressive aortic dilatation [9–11].

A marker of aortic stiffness is the aortic pulse wave velocity (PWV), defined as the propagation speed of the systolic velocity wave front through the aorta. PWV-assessment by magnetic resonance imaging (MRI) is a well-validated method to non-invasively quantify arterial stiffness [12]. Recently, an improved MRI-technique

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with two-directional in-plane velocity-encoding (VE) covering the whole aorta in a multi-slice volume scan has been introduced for the assessment of regional and local PWV [13]. This approach results in dense PWV-sampling at 200 points along the aorta centerline, thereby enabling global, regional and local PWV-assessment [13]. It is expected that in MFS patients, with local variability of disease manifestation, PWV-assessment with in-plane VE MRI potentially allows for the detection of subtle changes in local aortic stiffness and thereby the identification of areas at risk. To our knowledge, the predictive value of regional aortic stiffness described by PWV, for luminal aortic growth in MFS patients has not been reported before.

The purpose of the current study was therefore to investigate whether increased regional PWV at baseline (increased with respect to age-related normal values) can predict regional aortic luminal growth at 2-year follow-up in patients with MFS.

2. Methods

2.1. Patient population and protocol

Twenty-one MFS patients and 26 healthy volunteers (without history of cardiac diseases) were prospectively studied with MRI in our institution. Written informed consent was obtained from each subject and the study protocol conformed to the Declaration of Helsinki and was approved by the Medical Ethical Committee. MFS patients were eligible for inclusion when 1) the diagnosis of MFS has been established according to the Ghent criteria [14], 2) they had no history of aortic surgery and 3) significant aortic valve or mitral valve insufficiency was excluded by echocardiography. Patients were diagnosed with MFS in specialized outpatient clinics in the Netherlands (Leiden University Medical Center, Leiden, the Netherlands (n = 18); Amsterdam University Medical Center, Amsterdam, the Netherlands (n = 3)). Patients temporarily refrained from beta-adrenergic blocking medication and were at least 24 hours without this medication prior to MRI.

All patients underwent baseline and follow-up MRI examination (median follow-up: 24 months (25-75%: 23-25 months)) to assess both regional aortic stiffness (PWV), by using velocity-encoded MRI and regional aortic lumen area, by using contrast-enhanced magnetic resonance angiography (MRA). In addition, twenty-six healthy volunteers were included to acquire age-related normal PWV-values. Of note, the healthy volunteers underwent only the baseline velocity-encoded (VE) MRI examination to acquire age-related normal PWV values and they did not undergo MRA examination.

For patients, first the regional PWV were compared against these age-related normal values and were considered to be increased if PWV exceeded age-related normal values by 2 standard errors of the regression coefficients. Second, the incidence of regional luminal growth in the MFS patients, between baseline and follow-up MRI was assessed. Consecutively, the predictive value of PWV at baseline for regional luminal growth at follow-up was analyzed.

2.1.1. MRI acquisition

MRI was performed with a 1.5 T scanner (Philips Intera, release 11 and 12; Philips Medical Systems, Best, the Netherlands; pulsar gradient system with amplitude 33 mT/m, 100 mT/m/ms slew rate, and 0.33 ms rise time). Imaging sequences were previously described [13]. In short, after acquisition of a series of thoracic survey images which were used for planning purposes, a three-slice volume slab (covering a double-oblique sagittal view of the aorta) was obtained with a steady-state free precession (SSFP) sequence and used for planning the VE MRI acquisitions [13].

2.1.2. Pulse wave velocity

PWV was assessed by means of two consecutive multi-slice two-directional in-plane VE MRI acquisitions of the three-slice double-oblique sagittal volume slab of the aorta. Velocity-encoding was performed in phase-encoding (i.e., anterior-posterior (AP)) direction and in frequency-encoding (i.e., feet-head (FH)) direction consecutively. The velocity-sensitivity was set to 150 cm/s. The body coil was used for signal reception. Scan parameters encompassed 60% rectangular field-of-view FOV 450×270 mm^2, 10 mm slice thickness, echo time TE 2.4 ms, repetition time TR 4.3 ms, flip angle α 10º, acquisition voxel size 3.5×2.1×10.0 mm^3, sampling bandwidth 495 Hz and number of signal averages NSA 2. Retrospective gating was performed with maximal number of phases reconstructed. The true temporal resolution (TRes) amounted to 8.6 ms (equals 2×TR). Acquisition was performed with free breathing and mean scan time of a single acquisition amounted to 7 minutes 8 seconds at a typical heart rate of 65 bpm.

2.1.3. Contrast-enhanced magnetic resonance angiography

In addition, contrast-enhanced magnetic resonance angiography (CE-MRA) of the full aorta was performed by first-pass imaging of a 25 mL contrast bolus Dotarem (Guerbet, Gorinchem, the Netherlands) with a molarity of 0.5 mmol/mL. Contrast was intravenously injected in the basilic, brachial or cephalic vein at an infusion rate of 2 mL/s, and subsequently flushed by 20 mL saline at 2 mL/s, using Spectris Powerinjector (Medrad, Warrendale, USA). Contrast arrival time for the CE-MRA acquisition (i.e. the appropriate scan delay time after contrast injection) was obtained by imaging a transection of the proximal descending aorta continuously for one minute during injection of a 2 mL timing bolus, which was injected with the same infusion rate and saline flush. The contrast arrival time was determined by using region of interest analysis of the aortic lumen, to produce a time-intensity curve and obtain the *time-to-peak* arterial contrast enhancement. Consecutively the CE-MRA of the full aorta was performed with 3D T1-weighted fast gradient-echo sequence (85% rectangular FOV 500×80 mm^2, 50 slices of 1.6 mm slice thickness, TE 4.6 ms, TR 1.3 ms, α 40°, acquisition voxel size 1.25×2.46×3.20 mm^3, sampling bandwidth 238 Hz and NSA 1). Breath-holding at end-expiration was performed.

2.2. Image analysis

Regional PWV and aortic luminal area were obtained from MRI data. MRI analysis of MFS patients with respect to the patient characteristics was performed blinded. A schematic representation of image acquisition and analysis in a MFS patient is provided in Fig. 1. The aorta was divided into five segments (Fig. 1A); the ascending aorta (S1), which included the aortic root, the tubular portion of the ascending aorta and extending to the brachiocephalic artery origin; the aortic arch (S2), which begins at the origin of the brachiocephalic artery, extending to the left common subclavian artery; the thoracic descending aorta (S3) which begins at the left common subclavian artery extending to the level of the diaphragm; the suprarenal abdominal aorta (S4) from the level of the diaphragm to the origin of the renal arteries; the infrarenal abdominal aorta (S5). The aortic segments for CE-MRA (at both baseline and follow-up) and PWV-analysis (at baseline) were registered manually by registration of the aortic centerline that was calculated during PWV- and CE-MRA image processing. Only after this image analysis was completed, results for PWV and CE-MRA analyses were combined.

2.2.1. Regional pulse wave velocity

Regional PWV was obtained from the two-directional, three-slice in-plane velocity-encoded MRI data using in-house developed MASS software, as described [13] (Fig. 1D). The aorta was segmented in all three double-oblique sagittal views and the aortic centerline was automatically defined from this segmentation. Perpendicular to this centerline, at 200 sampling positions along the aorta, equidistant lines were automatically placed. Along each of these lines, the velocity was sampled and the maximal velocity per line was recorded, resulting in the maximal velocity wave form (constructed from the velocity components in AP and FH direction in each phase of the cardiac cycle) of blood flowing along the aortic centerline. Wave propagation analysis was performed to determine the pulse wave arrival at each sampling position automatically, by foot detection of the wave. The diastolic flow velocity was modeled as a horizontal line and the upslope of the wave front was modeled by linear regression of 20% to 80% of all values along the slope. The pulse wave arrival time was then determined by the intersection of both lines. Regional PWV per segment was obtained from the relation between pulse wave arrival time versus sampling location along the aortic centerline. This relation was determined by linear regression. PWV was then defined by the inverse of the slope of this linear relation between pulse wave arrival time and the sampling position. This regional PWV was obtained for each of the five aortic segments (Fig. 1E).

Normal values of regional PWV per segment were determined from the healthy volunteer data. The age-relation of these normal values was determined by linear regression (PWV = A x Age + B). Consecutively, regional PWV of the MFS patients were compared against these age-related normal values. The PWV assessed in MFS was considered increased if this value exceeded the predicted normal PWV (predicted according to the age of the patient) with two

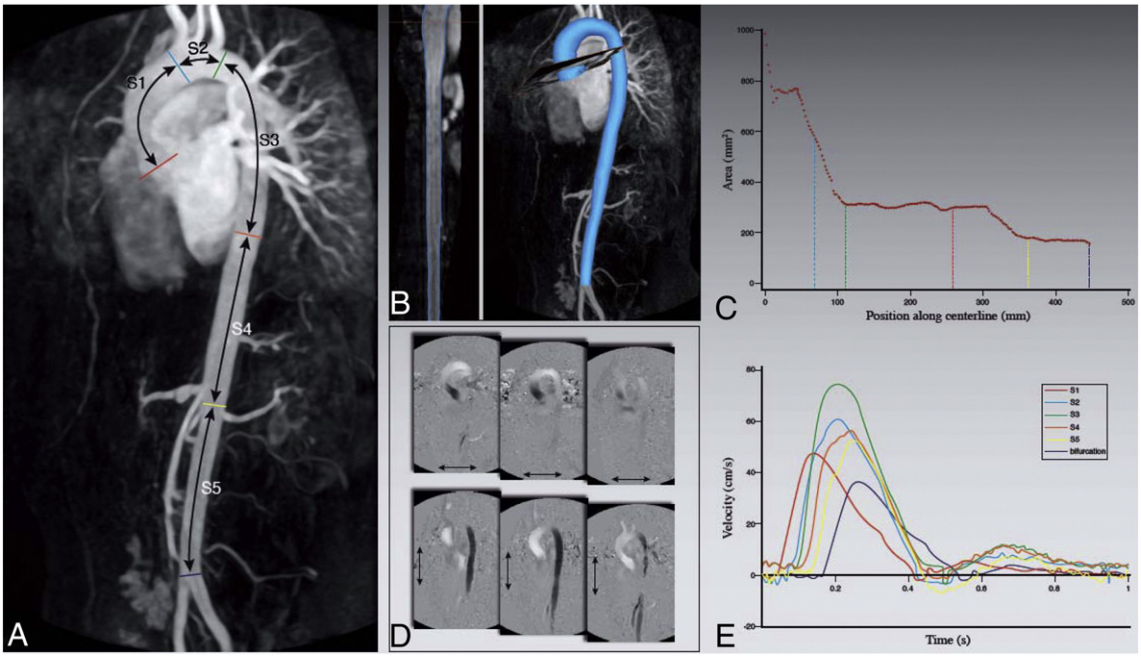

Fig. 1. Representation of image acquisition and analysis in a MFS patient. Regional aortic luminal area and regional PWV were obtained from MRI data. **Fig. 1A.** Maximum-intensity-projection of contrast-enhanced (CE) MRA data of an MFS patient. Five aortic segments were evaluated: ascending aorta (S1), aortic arch (S2), thoracic descending aorta (S3) suprarenal abdominal aorta (S4) and infrarenal abdominal aorta (S5). **Fig. 1B.** The CE-MRA image analysis was performed using in-house developed LAVA software with automated centerline detection and 3D deformable modeling. **Fig. 1C.** From CE-MRA data, cross-sectional luminal area was determined at 200 equidistantly-spaced sample points along the aortic centerline. For both baseline and 2-year follow-up, the mean lumen area per segment was determined. **Fig. 1D.** PWV was obtained from two-directional, three-slice in-plane velocity-encoded MRI data using in-house developed MASS software, by calculating the relation between pulse wave arrival time at 200 equidistantly-spaced sample points along the aortic centerline and the position of these sample points along the centerline (**Fig. 1E).** The centerline of PWV analysis was registered manually to the MRA centerline, and MRA centerline at baseline and follow-up were also manually registered. Regional PWV was determined for each of the five aortic segments.

standard errors for each of the regression coefficients. Accordingly, PWV is increased if PWV > $((A + 2 \times SE_A) \times AGE + (B + 2 \times SE_B))$.

2.2.2. Aortic luminal growth

From CE-MRA data in patients, the mean cross-sectional luminal area per aortic segment was determined at baseline and at 2-year follow-up (Fig. 1B.). Image analysis was performed using in-house developed and validated LAVA software with automated 3D centerline detection and automated segmentation using deformable tube modeling [15]. The required user-interaction for centerline detection and lumen segmentation was limited to the placement of start and end point in the 3D data. Automated lumen segmentation resulted in a tube fit of the aorta. Next, the cross-sectional luminal area was determined at 200 equidistantly-spaced positions along the centerline (Fig. 1C.). When required, the lumen segmentation was corrected manually on the cross-sectional view of the aorta. Image analysis resulted in a mean luminal area per segment. Assuming a circular shape, the mean diameter was calculated for each segment, both for baseline and follow-up.

A mean aortic luminal diameter increase from baseline to follow-up (2 years) of more than 2 mm was considered significant growth. This cut-off represents a substantial increase, based on typical MFS aortic growth characteristics [16] and a comparable definition (mean aortic diameter increase > 1 mm/year) has been used previously [10].

2.2.3. Intra- and inter-observer analysis

Intra- and inter-observer analysis for repeated image analysis was performed. Five patients were selected at random; one observer performed image analysis twice (with inter-examination time more than 6 months) and another observer repeated the analysis, blinded to the results of the other observer. For each patient, baseline MRA and PWV-analysis was repeated. Regional aortic lumen area and PWV were obtained, for aortic segments 2 to 5 (segment 1 was not taken into account, as for this segment, no anatomical start point marker was defined), resulting in a total of 20 evaluable measurements.

Table 1
Characteristics of MFS patients.

Characteristics	MFS Patients (n = 21)	Healthy volunteers (n = 26)	p-value
Demographics			
Male/female	11 (52%) /10 (48%)	16 (62%) /10 (39%)	0.5
Age at baseline MRI (years)	36 ± 15	30 ± 10	0.12
Brachial blood pressure (mmHg)			
Systolic	124 ± 11	122 ± 15	0.6
Diastolic	73 ± 9	71 ± 11	0.5
Heart rate (beats/minute)	66 ± 10	67 ± 10	0.95
Height (cm)	187 ± 10	177 ± 10	0.003
Body surface area (m^2)	2.11 ± 0.27	1.9 ± 0.2	0.005
Body mass index (kg/ m^2)	25 ± 5	23 ± 3	0.2
Ectopia Lentis	8 (38%)		
Mitral valve prolapse	9 (43%)		
Aortic root diameter by MRI (mm)	40.0 ± 3.4		
Genetic mutation	18 (86%)		
Fibrillin-1	17 (81%)		
Transforming growth factor-2 receptor	1 (5%)		
ß -blocker use	14 (66%)		
ACE inhibitors	5 (24%)		

Data are presented as number (percentage) or as mean ± standard deviation. Abbreviations: MFS: Marfan syndrome; MRI: magnetic resonance imaging; ACE: Angiotensin converting enzyme.

2.3. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). Parameters describing blood pressure (BP) and PWV were compared between MFS patients and healthy volunteers using unpaired t-tests. For the healthy volunteers, linear regression analysis was performed (PWV = A x Age + B) in each of the five aortic segments. Age-related normal values were defined from this data for each segment, with PWV within limits of 2 standard errors of the regression coefficients. In MFS patients, the incidence of increased PWV per aorta segment was calculated as well as the incidence of aortic luminal growth over 2-year follow-up. In addition, sensitivity, specificity, positive and negative predictive value of regional PWV-assessment for predicting aorta luminal growth were calculated. Statistical analysis was performed using SPSS v 18.0 (SPSS Inc., Chicago, IL).

3. Results

Twenty-one MFS patients (mean age: 36 years (min-max: 18-63 years)), diagnosed according to the Ghent criteria, were evaluated [14]. Patient characteristics at the time of inclusion are summarized in Table 1. Eleven patients (52%) were male and all patients were adults at time of inclusion. Marfan genetic mutations were found in 18 patients (86%). Pathologic mutations in the fibrillin-1 gene were identified in 17 patients (81%), whereas in 1 patient (5%) a pathologic mutation in transforming-growth factor-2 receptor was found. A positive family history for MFS was found in 17 (81%) of the patients. Fourteen (66%) of the patients were on ß-blocker medication.

In addition, the clinical characteristics of the twenty-six healthy volunteers (mean age: 30 years (min-max: 15-58 years)), are also provided in Table 1. Gender, mean age, blood pressure, heart rate and BMI were not significantly different between patients and volunteers. Patients with MFS were generally taller compared to the healthy volunteers, which was also evident from the larger body surface area.

3.1. Pulse wave velocity

Mean regional PWV-values for MFS patients and volunteers are presented in Table 2.

In twenty-six healthy volunteers, regional PWV was determined for five aortic segments. Of note, in three volunteers, the most distal segment S5 (infrarenal aorta) was not included in the PWV acquisition volume due to elongation of the aorta.

In twenty-one MFS patients, a total of 102 aortic segments was evaluated. In three patients, S5 was not included in the PWV acquisition volume due to elongation of the aorta. Mean regional PWV was significantly increased in patients with Marfan syndrome as compared to the healthy volunteers in similar age range, in all aortic segments. However, although the mean value of PWV in the ascending aorta (segment 1) was higher for MFS patients as compared to healthy volunteers, these values were not statistically significantly different, due to the wide standard deviation.

Age-related normal PWV values were acquired from the results of the linear regression analyses for the relation between age and regional PWV in the healthy volunteer cohort (Table 3). Regional PWV values significantly correlated with age (Pearson R between 0.39 and 0.57), except for segment 2 (aortic arch) and segment 5 (infrarenal abdominal aorta). In MFS patients, regional PWV at baseline was increased when compared with age-related normal values in 17 segments (17%) of 13 MFS patients.

3.2. Cross-sectional luminal area of the aorta

In the MFS patients, a mean aorta trajectory of 44 ± 4 cm was evaluated. For all MFS patients, mean aortic diameter measurements for baseline and follow-up per aortic segment are provided in Table 4. Significant luminal growth at follow-up was reported in 14 out of 102 aortic segments (14%) and in 7 (33%) of the MFS patients.

3.3. Prediction of aortic luminal growth with PWV

The incidence of increased PWV per aortic segment is presented in Table 5. For the ascending aorta (segment 1), PWV was increased in five MFS patients, for the aortic arch (segment 2) in four MFS patients, for the thoracic descending aorta (segment 3) in three MFS patients, for the suprarenal abdominal aorta (segment 4) in two patients and for the infrarenal abdominal aorta (segment 5), three patients showed increased baseline PWV. The incidence of luminal increase per aortic segment is presented in Table 5. Significant luminal growth was present in three MFS patients for segment 1, in six patients for segment 2 and in 1 patient for segment 4. In the other segments (S3 and S5), no significant luminal increase was observed. Of note, two patients (S1: n = 1; S2: n = 1) presented with both increased PWV at baseline and luminal increase at follow-up.

Furthermore, the sensitivity, specificity and positive and negative predictive value (confidence interval) for PWV predicting regional luminal growth are presented in Table 5. Specificity of regional PWV-testing in

Table 2
Comparison of mean PWV per aortic segment between MFS patients and healthy volunteers.

Aortic Segment	MFS patients (n = 21)	Healthy Volunteers (n = 26)	p-value
PWV S1 (m/s)	6.1 ± 3.5	5.4 ± 1.2	0.3
PWV S2 (m/s)	5.9 ± 3.3	4.2 ± 1.9	0.03
PWV S3 (m/s)	6.3 ± 2.9	4.9 ± 1.1	0.02
PWV S4 (m/s)	6.3 ± 2.1	5.1 ± 1.1	0.01
PWV S5 (m/s)	7.4 ± 3.3	5.1 ± 1.6	0.007

Data are presented as mean ± standard deviation.
Abbreviations: MFS: Marfan syndrome; PWV: Pulse Wave Velocity; S1: ascending aorta; S2: aortic arch; S3: thoracic descending aorta; S4: suprarenal abdominal aorta; S5: infrarenal abdominal aorta.

Table 3
Linear regression analysis PWV in healthy volunteers per aortic segment: PWV = A x Age + B.

Aortic Segment	A ± SE	B ± SE	Pearson R
PWV S1 (m/s)	0.05 ± 0.02	3.76 ± 0.66	0.46 (p = 0.017)
PWV S2 (m/s)	-0.02 ± 0.04	4.63 ± 1.19	-0.09 (p = 0.672)
PWV S3 (m/s)	0.06 ± 0.02	3.12 ± 0.55	0.57 (p = 0.003)
PWV S4 (m/s)	0.06 ± 0.02	3.39 ± 0.55	0.55 (p = 0.004)
PWV S5 (m/s)	0.06 ± 0.03	3.39 ± 0.95	0.39 (p = 0.067)

Data are presented as mean ± standard error (SE).
Abbreviations: PWV: Pulse Wave Velocity; SE: standard error; S1: ascending aorta; S2: aortic arch; S3: thoracic descending aorta; S4: suprarenal abdominal aorta; S5: infrarenal abdominal aorta.

Table 4
Aortic Diameter measurements in MFS Patients for baseline and follow-up.

Aortic Segment	Baseline	Follow-up	p-value
Diameter S1 (mm)	27.1 ± 2.8	27.7 ± 3.1	0.14
Diameter S2 (mm)	22.3 ± 2.5	23.4 ± 2.9	0.002
Diameter S3 (mm)	20.4 ± 2.4	20.8 ± 2.4	0.001
Diameter S4 (mm)	18.7 ± 2.3	19.1 ± 2.1	0.028
Diameter S5 (mm)	14.9 ± 1.3	15.0 ± 1.3	0.161

Data are presented as mean ± standard deviation.
Abbreviations: MFS: Marfan syndrome; S1: ascending aorta; S2: aortic arch; S3: thoracic descending aorta; S4: suprarenal abdominal aorta; S5: infrarenal abdominal aorta.

Table 5
Diagnostic performance of regional PWV-testing for prediction of luminal aortic growth at 2-year follow up in MFS patients.

Aortic Segment	Incidence of Increased PWV	Incidence of Luminal Increase	Sensitivity (CI)	Specificity (CI)	Positive Predictive Value (CI)	Negative Predictive Value (CI)
Aorta S1	5 (24%)	3 (14%)	33% (2-88%)	78% (52-93%)	20% (1-70%)	88% (60-98%)
Aorta S2	4 (19%)	6 (29%)	17% (1-64%)	80% (51-95%)	25% (1-78%)	71% (44-89%)
Aorta S3	3 (14%)	0 (0%)	NA	86% (63-96%)	NA	100% (78%-100%)
Aorta S4	2 (10%)	1 (5%)	0% (0%-90%)	90% (67%-98%)	0% (0-80%)	95% (72%-99%)
Aorta S5	3 (17%)	0 (0%)	NA	83% (58%-96%)	NA	100% (75%-100%)

Abbreviations: MFS: Marfan syndrome; S1: ascending aorta; S2: aortic arch; S3: thoracic descending aorta; S4: suprarenal abdominal aorta; S5: infrarenal abdominal aorta; CI: confidence interval; NA: not applicable.

patients with Marfan syndrome was ≥78% for all aortic segments. For segments 3 and 5, sensitivity and positive predictive value are not provided, since for those segments, none of the MFS patients presented an increased aortic luminal area at follow-up.

3.4. Intra- and inter-observer analysis

Results for intra- and inter-observer analysis for repeated image analysis are presented in Table 6. Intra-class correlation showed excellent agreement for intra- and inter-observer analysis for both PWV analysis as well as MRA-assessment for cross-sectional luminal area. The variation for PWV-assessment amounted to 12% and 9% for the MRA-assessment.

4. Discussion

In the present study, the diagnostic performance of regional PWV-sampling with velocity-encoded MRI for prediction of aortic luminal growth in MFS patients was evaluated. The main findings of this study are: (i) regional PWV was increased in MFS patients as compared to healthy volunteers in similar age range, in all aortic segments; (ii) regional PWV-assessment has moderate to high specificity for predicting absence of regional aortic luminal growth in MFS patients, as ≥78% of the cases of without regional aortic luminal growth at 2-year follow-up presented without increased regional PWV at baseline. Of note, regional PWV-assessment lacks sensitivity, since only ≤33% of the cases with aortic luminal growth presented with increased regional PWV at baseline.

In patients with MFS, aortic stiffness assessment can potentially provide complimentary prognostic value to the monitoring of the aortic diameter for disease progression. In our study, regional aortic stiffness at five aortic segments was expressed by PWV-assessment from in-plane velocity-encoded MRI. When compared to age-related normal values, the regional PWV at baseline was increased in 17% of all studied aortic segments of these selected MFS patients. Furthermore, significant luminal growth at follow-up was reported in 14% of the aortic segments. Of note, the diagnostic performance of regional PWV-testing for prediction of regional aortic luminal growth at 2-year follow-up showed moderate to high specificity for all aortic segments.

To our knowledge, the predictive value of regional aortic stiffness, described by PWV for luminal aortic growth in MFS patients, has not been reported before. In a previous study by Nollen et al. in 78 non-operated MFS patients, the predictive value of aortic stiffness both *locally* by distensibility assessment at a single position and *regionally* by PWV-assessment from through-plane velocity-encoded MRI was investigated for patients with progressive aortic dilatation [10]. Aortic stiffness, calculated at a *local* level by distensibility was an independent predictor of progressive descending thoracic aortic dilatation. However, in the same study, the authors reported that PWV from through-plane VE MRI did not hold predictive value for aortic luminal growth in the descending thoracic aorta. This fact may possibly be explained by the limited accuracy due to the low temporal resolution (i.e. 25 ms) of the MRI-sequence that was used by Nollen et al. A temporal resolution of 25 ms is low considering the transit-time between flow waves at ascending and proximal descending aorta is in the order of 20 ms. In comparison, we used a temporal resolution of 8.6 ms. Furthermore, they used the half-peak of the flow wave as definition of pulse wave arrival, whereas in our study the foot of the velocity wave was used, a definition that should be more robust when automated transit-time assessment is less corrupted by early wave reflections and not affected by distal damping of the wave front [17].

A previous study showed that regional PWV-assessment from in-plane VE MRI with high temporal resolution (i.e. 8.6 ms) shows higher agreement with invasive pressure measurements, the true gold standard for PWV-assessment [13], than PWV-assessment from through-plane VE MRI. Furthermore, regional aortic stiffness assessment with in-plane VE MRI at 200 sampling positions along the aorta centerline may be more sensitive in detecting regional stiffness variation. Of note, performing multiple local aortic stiffness assessment by distensibility calculations from maximal and minimal cross-sectional lumen area at 200 positions over the total aortic length is impracticable with respect of the extensive MRI planning and elaborate post-processing, and the local pulse pressure, which is required for distensibility calculations, may only be accurately assessed invasively. On the other hand, local PWV-assessment from in-plane VE MRI is feasible in terms of scan duration and post-processing time.

Groenink et al. showed that PWV from though-plane VE MRI was increased in MFS patients as compared to a control group with

Table 6
Intra- and inter-observer analysis for both PWV analyses as MRA-assessment for cross-sectional luminal area.

	Intra-observer		Inter-observer	
	PWV	MRA	PWV	MRA
Intra-class correlation	0.90 ($p<0.001$)	0.96 ($p<0.001$)	0.96 ($p<0.001$)	0.99 ($p<0.001$)
Mean difference ± SD	0.09 ± 0.64 (m/s)	3 ± 25 mm^2	0.12 ± 0.70 m/s	−3 ± 9 mm^2
95% CI (m/s)	−0.2 − 0.4 m/s	−8 − 14 mm^2	−0.2 − 0.4 m/s	−7 − 1 mm^2
p-value t-test	0.54	0.59	0.46	0.22
Coefficient of variation	12%	9%	13%	3%

Abbreviations: PWV: pulse wave velocity; MRA: magnetic resonance angiography; 95% CI: 95% confidence interval.

corresponding mean age for both the entire aorta and PWV in three segments of the aorta (ascending aorta-aortic arch, thoracic descending aorta and abdominal descending aorta) [6]. Similar to that study, we found that PWV was increased in MFS patients as compared to healthy volunteers in all aortic segments. However, for the ascending aorta (segment 1) the difference in mean PWV between MFS patients and volunteers was not statistically significant. This finding may be explained by the fact that MFS patients in this study cohort can be considered as relatively healthy (i.e., well regulated by medical treatment) since aortic surgery was not indicated yet for these patients at the time of study and MFS has a variable manifestation of disease. In addition, MRI in the ascending aorta is prone to respiratory blurring and movement of the aorta during the cardiac cycle, more than in other parts of the aorta. This might have reduced accuracy in this part of the aorta, both for MRA as well as PWV-assessment.

In adult MFS patients, current guidelines for prophylactic replacement of aortic root include excessive aortic growth, defined as growth of the aortic diameter of $\geq$5 mm/year [6,18]. In our study, we used the definition of significant luminal increase of $>$2 mm diameter growth at 2-year follow-up. Using this definition, 10 (14%) of the evaluated aortic segments showed significant luminal increase. In total, 7 patients (33%) presented with significant luminal growth in at least one aortic segment.

Some MFS patients experience acute dissections even in the presence of non- or moderately-dilated aortas [6]. Therefore, next to applying the current clinical guidelines, also monitoring of the entire aortic diameter with respect to other risk factors for aortic dissection, such as aortic stiffness, may prove to hold predictive value for disease progression [10,11,19]. In our study, at least 78% of the cases without regional aortic luminal growth at follow-up presented without increased regional PWV at baseline. Therefore, regional PWV-assessment by VE MRI has moderate to high specificity for all aortic segments in these MFS patients. This finding implies that regional PWV-assessment is good at demonstrating absence of progressive disease. In contrast, 33% or less of the cases which presented with increased regional PWV at baseline revealed regional aortic luminal growth at follow-up. This finding implies that regional PWV-assessment lack sensitivity as it seems marginal at detecting present disease. Consequently, the risk-stratification strategy presented (i.e., regional PWV-testing) can be used to rule out progressive disease, which potentially is very useful for managing patients. Therefore, regional PWV-testing may potentially be useful complimentary to other clinical parameters, i.e. aortic diameter assessment.

A potential limitation of our study is the selection of a relatively healthy population of MFS patients (which had not yet undergone elective aortic surgery at the time of study) and the short follow-up duration. By evaluating these selective patients during a longer follow-up duration, more patients might reveal progressive aortic dilatation. Typically studies show differences between healthy volunteers and *very abnormals*. The *near normals* (relatively healthy MFS patients) described in the present study represent a tougher cohort where imaging can be really of benefit. However, we need to acknowledge that our present findings are based on a relatively small study population and need to be validated in a larger and more challenging study population. Furthermore, since the healthy volunteers did not undergo a CE-MRA acquisition and no follow-up MRI examination, analysis between MFS patients and healthy volunteers was not performed blinded. However, analysis of MFS patients with respect to the patient characteristics was blinded. In addition, aortic segments for the PWV-analysis and the CE-MRA analysis were co-registered by the aortic centerline. Only after this image analysis was completed, results for PWV and CE-MRA analyses were combined. Of note, MRA aortic centerline detection is semi-automated [15]. Importantly, for PWV analysis, the arrival time of each of the 200 wave forms was automatically determined as previously described [13]. Of note, accuracy of regional PWV-assessment may depend on the segment length, since including a longer trajectory with more sampling points may result in more accurate weighting of the pulse wave transit-time over this particular segment. In addition, the curvature of the proximal aorta and the motion during the cardiac cycle that the proximal aorta is subjected to as compared to the more distal aorta is potentially an additional source of error, as well as the presence of branches that may lead to early wave reflections that can corrupt the automated definition of the foot of the pulse wave.

5. Conclusion

Regional PWV was significantly increased in selected MFS patients as compared to healthy volunteers within similar age range, in all aortic segments except in the ascending aorta. Furthermore, regional PWV-assessment has moderate to high specificity in MFS patients, as $\geq$78% of the cases without regional aortic luminal growth at 2-year follow-up presented without increased regional PWV at baseline.

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