Original Article

Hemostatic abnormalities in adult patients with Marfan syndrome

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Background: Aortic root ectasia might induce hemostatic disorders in patients with Marfan syndrome (MFS) via altered blood flow and rheology. The aim of this study was to explore the hemostasis in patients with MFS compared with healthy controls.

Methods: In this cross-sectional case-control study we included patients with verified MFS (n=51) and sex- and age-matched healthy controls (n=50). Main criteria were the aortic root in echocardiography and cardiac magnetic resonance imaging (MRI), and the coagulation status.

Results: When compared with healthy controls, patients with MFS showed significantly increased diameters of the aortic roots (43.0±7.72 *vs.* 28.8±3.74 mm, P<0.001) and aortic Z-scores (4.36±2.77 *vs.* 0.948±1.09, P<0.001), considerably higher values of Multiplate® tests (e.g., MP-ADP: 878.4±201.7 *vs.* 660.4±243.6 AU*min, P<0.001) and PFA-100® tests (PFA Col/ADP: 102.5±45.5 *vs.* 91.1±46.2 s, P<0.05), PTT (30.0±3.91 *vs.* 28.7±2.50 s, P<0.05) and D-dimers (0.488±0.665 *vs.* 0.254±0.099 mg/L, P<0.001). In MFS von Willebrand factor (VWF) activity (81.9%±41.8% *vs.* 106.3%±41.5%, P<0.05) and antigen (93.8%±43.9% *vs.* 118.8%±47.8%, P<0.05) and factor VIII activity (108.9%±29.6% *vs.* 126.7%±28.4%, P<0.05) were reduced. Significant positive correlations were found between aortic diameters and D-dimers (all P<0.05), as well as PFA Col/ADP (all P<0.01) in MFS patients. Factor VIII activity correlated significantly negatively with the diameter of the aortic root in MFS (r=–0.55, P<0.05).

Conclusions: In conclusion, our study reveals hemostatic deviations in patients with MFS. Further studies are necessary to understand the causal relationship and the exact pathomechanism.

Keywords: Marfan; coagulation; aortic root dilatation

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Introduction

Marfan syndrome (MFS) is an autosomal dominant genetic disease with a prevalence of 1–5 per 10,000 (1). In classic MFS, up to 95% of the disease-causing mutations are located in the *FBN1* gene on chromosome 15q21. The typical characteristic of MFS is the ectatic or aneurysmatic deformation of the aortic root. Other cardiovascular manifestations include aneurysm formation in more distally located aortic segments and the pulmonary artery (2,3), as well as disorders of the heart valves (3).

The typical aortic root ectasia or aneurysm associated with patients with MFS may induce hemostatic deviations. In contrast to the laminar blood flow with homogeneous shearing forces as observed in the normal aorta, aortic dilatation induces changes in blood flow and rheological parameters (4). Moreover, other clinical manifestations of MFS, such as aortic valve insufficiency or severe thoracic scoliosis, may lead to regurgitation, and flow turbulence (5,6) and increased shear stress (7), respectively. These rheological disturbances affect hemostasis by interfering with platelet activation or behaviour, the transport of clotting factors, and cell-to-cell interactions (8-10). Moreover, Heyde syndrome, a combination of an acquired aortic valve stenosis and angiodysplasias of the gastrointestinal tract, demonstrates a similar relationship between rheology and hemostasis in a clinical context. In this disease, the altered shear forces affect the von Willebrand factor (VWF) and thus the hemostasis (11,12). However, after surgical correction of such an aortic valve stenosis, the tendency toward increased bleeding, which is generally associated with Heyde syndrome, is significantly reduced (12).

Increased markers for platelet and thrombin activation, fibrinolysis, as well as a correlation of the parameters to the size of the aortic aneurysm have already been described in thoracic aortic aneurysms of different etiology and in abdominal aortic aneurysms (4,13,14).

Thus, a correlation between rheology and hemostasis can be assumed and this correlation may also be present in MFS patients with aortic pathologies. Due to the increased diameter of the aortic root, the blood flow patterns in MFS are altered and thus it can be argued that the aortic dilatation has the ability to influence hemostasis. Changes in hemostasis, probably also playing a causal role in the development and progression of aneurysms, may complicate cardiovascular and other surgical procedures in MFS patients.

To assess the feasibility of a correlation between rheology and hemostasis, laboratory parameters from MFS patients were compared with data from healthy, age- and sex-matched controls and further correlated with the size of the aortic root diameter in the MFS patients.

Methods

Study design and study subjects

For this cross-sectional case-control study, 78 patients with proven MFS were recruited between December 2012 and July 2017 from a tertiary care centre for adults with congenital heart disease. The control group consisted of 50 healthy age- and sex-matched persons recruited from March to June 2017 at various health care locations. Inclusion requirements were a clinically and molecular genetic based MFS diagnosis, according to the 2010 revised Ghent-criteria, and ≥18 years of age. Exclusion criteria for both patient and control groups were the use of anticoagulant as well as acetylsalicylic acid, the occurrence of inflammatory, coagulation and malignant diseases, lack of cognitive competency and refusal to consent. An additional exclusion criterion for the control group was the occurrence of cardiovascular diseases.

Ethical standards

All participants gave informed consent. The study complies with the requirements of the Declaration of Helsinki and was approved by the local ethical committee (number 5313/12).

Clinical data and imaging

Clinical data, cardiovascular imaging with magnetic resonance imaging (MRI) and echocardiography, as well as laboratory parameters were collected for each participant. The clinical data of the MFS patients were recorded retrospectively using patient files, while the clinical data of the controls were collected using partially standardized questionnaires. Both the MFS patients and control group underwent echocardiographic examinations (device type: Philips Epic 7G and GE Vivid E9 4D), either on or near the date on which blood was drawn. Additionally, the cardiac MRI results from the MFS patients were also evaluated (device type: 1.5 Tesla scanner, Avanto, Siemens Healthcare). If the patients had already undergone cardiac

surgery, echocardiographic and cardiac MRI findings from a time point prior to surgery were analyzed. In each case we studied the diameter of the aortic root in diastole, always regarding the largest diameter in the three-dimensional measurement and measuring inner edge to inner edge. Z-scores were calculated based on patient's body surface area (15). Furthermore, the cardiac valves were examined for the presence of insufficiency, prolapse or stenosis and the aorta for the presence of dissection.

Blood collection and laboratory assays

Venous blood was collected from each study participant and directly analyzed. The platelet count was measured by resistance impedance measurement, the platelet function by the Multiplate® and the PFA-100® systems. The Multiplate® test is usually used to monitor and differentiate an anticoagulation therapy. In this test, the platelet aggregation is measured after stimulating different receptors on platelets with different reagents (ADP, arachidonic acid and TRAP-6 as internal control). The PFA-100® measures the closure time after stimulating the platelets with collagen, shear stress and either ADP or epinephrine. In this test all values above 300 s are given as 300 s by the laboratory. D-dimers and VWF antigens and activity were determined by particle-enhanced immune-turbidimetry. Factor VIII activity, PTT and fibrinogen were measured by clotting assays at the Siemens BCS XP instrument. Prothrombin fragment 1+2 were determined by enzyme-linked immunosorbent assays (ELISA).

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics for Mac 2016, version 24.0 (Armonk, NY: IBM Corp.). All data were represented by mean and standard deviation, as well as median, minimum and maximum. Nominal data were described by relative and absolute frequencies. For the comparison of variables between two or more groups the Mann-Whitney U-test, the *t*-test or the Chi-square test were used depending on the characteristics of the groups and the variables of the *t*-test. The correlation between two continuous, non-normally distributed data were calculated with the Spearman correlation; the relationship between two continuous, normally distributed variables with the Pearson correlation. The correlation is purely descriptive and uncorrected for multiple testing. Statistical testing was performed at the 2-tailed alpha level of 0.05.

Results

Study subjects

Of the 78 primary MFS patients surveyed, 27 were excluded for various reasons. These included the use of anticoagulants in 15 cases, sequence analysis detected MFS variants of uncertain significance in eight cases, missing data in the main target variables in three cases, and age <18 years in one case.

Clinical, echocardiographic and cardiac MRI data are summarized in *Table 1*. There were no significant differences in age (P=0.846) and gender (P=0.617) between the MFS patients and the control group. Height (P<0.001), weight (P=0.041), and body surface area (P<0.001) at the time of echocardiography imaging differed significantly between both groups. Sixteen of the 51 MFS patients underwent cardiac surgery.

Imaging

MFS patients showed significantly higher Z-scores (P<0.001) and aortic root diameters (P<0.001) (*Table 1*). The mitral valve (86.3%, n=44) in MFS patients was most commonly found to be pathological (in 56.9% insufficiency and prolapse, in 15.7% only a insufficiency, in 13.7% only a prolapse), followed by the tricuspid valve (78.4%, n=40), the aortic valve (43.1%, n=22), and finally the pulmonary valve (27.5%, n=14). Only two of the MFS patients had no abnormality of any of the four valves. The valves of the control group showed very few abnormalities (in total 1% of all valves, n=2) including one aortic valve insufficiency and one mitral valve prolapse. Two MFS patients had a chronic aortic dissection type Stanford B. No aortic dissection type Stanford A was found in any of the patients.

A total of 19 cardiovascular operations for MFS-related cardiovascular manifestations were performed in 16 (31%) of the 51 MFS patients. In each of these operations at least one transfusion was necessary.

Laboratory measurements

Markers of hemostasis

Platelet count and function

No difference in the platelet count was observed between

Table 1 Clinical data, echocardiography, cardiac MRI in MFS and controls

Variables	MFS		Controls		P
	Mean ± SD; median [Min–Max]	n	Mean ± SD; median [Min–Max]	n	
Age, years	34.9±8.95; 34.3 [18–52.1]	51	35.3±8.26; 35.1 [22.8–54.4]	50	0.846
Men, %	27.5	51	31	50	0.617
Body height, cm	182.8±11.3; 181 [159–217]	51	173.4±8.94; 173.1 [156–195.4]	50	*<0.001*
Body weight, kg	73.4±12.2; 73 [39–103.7]	51	68.5±11.6; 67 [51.9–101.7]	50	*0.041*
BSA, m^2	1.94±0.194; 1.92 [1.40–2.43]	51	1.82±0.182; 1.81 [1.56–2.2]	50	*<0.001*
Syst BP, mmHg	122±11.2; 120 [101–160]	50	117.4±14.1; 118.5 [85–150]	50	0.076
Diastol BP, mmHg	70.7±7.81; 70 [55–92]	50#	76.1±8.06; 75.5 [53–90]	50#	*<0.001*
Echocardiography					
Z-score	4.36±2.77; 3.73 [–0.48 to 12.41]	51#	0.948±1.09; –0.975 [–3.71 to 1.4]	50	*<0.001*
Aortic root, mm	43.0±7.72; 41.0 [30.0–67.0]	51#	28.8±3.74; 28 [22–38]	50#	*<0.001*
Cardiac-MRI					
Aortic root, mm	43.7±7.04; 43.0 [28–57]	39	–		–

#, not normally distributed data. The italicized P values showed statistical significance. BSA, body surface area; Syst BP, systolic blood pressure; Diastol BP, diastolic blood pressure; MFS, Marfan syndrome; MRI, magnetic resonance imaging.

MFS patients and controls, nor did the values correlate with aortic diameter (*Table 2*).

The MFS patients showed significantly higher values in all three Multiplate® tests compared to the control group (P<0.001) (*Figure 1*, *Table 2*). None of these values showed a correlation to the aortic diameter.

The PFA Col/ADP test was significantly longer in the MFS patients compared to the controls (P=0.044) (*Figure 2*), whereas PFA Col/Epi did not differ between the MFS patients and the control group (*Table 2*). PFA Col/ADP also correlated positively with the size of the aortic root in the echocardiography (r=0.43, P<0.01) and the related Z-score (r=0.45, P<0.01) (*Figure 3*).

VWF

VWF activity (P=0.015) and antigen (P=0.014) were significantly reduced in MFS patients compared to controls (*Figure 2*). The VWF activity/VWF antigen ratio did not differ significantly between the MFS patients and the control group (*Table 2*). No significant correlation could be found with the size of the aortic root either.

Factor VIII activity

Factor VIII activity was significantly decreased in MFS patients compared to controls (P=0.016) (*Figure 2*, *Table 2*). Factor VIII activity correlated significantly negatively with the diameter of the aortic root in cardiac MRI (r=–0.55, P<0.05) (*Figure 3*). There was no correlation to the diameter of the aortic root and the Z-score in echocardiography.

Partial thromboplastin time

PTT was significantly higher in MFS patients compared to controls (P=0.047) (*Figure 2*, *Table 2*). A correlation to the diameter of the aorta was not found.

D-dimers

The D-dimers were significantly elevated in MFS patients when compared to the control group (P<0.001) (*Table 2*) and also correlated positively with the diameter of the aortic root (r=0.28, P<0.05) and the Z-scores in the echocardiography (r=0.29, P<0.05) (*Figure 4*).

Fibrinogen

Fibrinogen levels were similar in MFS patients and the control population (*Table 2*).

Prothrombin fragments 1 and 2

Prothrombin fragments 1 and 2 showed no significant differences between the two groups (*Table 2*).

Subgroup analysis

Subgroup 1: VWF

Eight MFS patients (subgroup 1) showed VWF antigen levels and VWF activity levels below the respective minimum values of the control group. For these eight

Table 2 Laboratory measurements

Variables	MFS		Controls		P	Cohen's d
	Mean ± SD; median [Min–Max]	n	Mean ± SD; median [Min–Max]	n		
Platelet count and function						
Platelets, 10^9/L	260.6±54.7; 250 [178–387]	51#	264.4±76.4; 260 [96–599]	50	0.781	
MP-ADP, AU*min	878.4±201.7; 876.5 [294–1,351]	48	660.4±243.6; 642.5 [255–1,312]	50	*<0.001*	0.975
MP-ASPI, AU*min	1,033.5±262.4; 1,084 [125–1,388]	49#	866.2±263; 884 [129–1,420]	49	*<0.001*	0.637
MP-TRAP, AU*min	1,290.5±205.3; 1,279 [886–1,683]	49	1,098.9±250.2; 1,100.5 [492–1,711]	50	*<0.001*	0.837
PFA Col/ADP, s	102.5±45.5**; 85.5 [62–300]	50#	91.1±46.2; 81.5 [59–300]	50#	*0.044*	0.249
PFA Col/Epi, s	177.12±72.4; 151.5 [74–300]	50#	153.6±52.1; 144 [93–300]	49#	0.242	
Von Willebrand parameters						
VWF activity, %	81.9±41.8; 81 [9.3–171]	51	106.3±41.5; 99.5 [48–226]	50#	*0.015*	0.586
VWF antigen, %	93.8±43.9; 94.8 [16.3–210]	51	118.8±47.8; 108 [53–266]	50#	*0.014*	0.545
VWF activity/VWF antigen	0.857±0.17; 0.897 [0.11–1.08]	51#	0.90±0.099; 0.889 [0.59–1.13]	50	0.429	
Factor VIII activity, %	108.9±29.6*; 110 [59–167]	23	126.7±28.4; 127.5 [70–248]	50	*0.016*	0.614
PTT, s	30.0±3.91; 29.8 [19.9–44.4]	51#	28.7±2.50; 28.7 [24.3–34.2]	50	*0.047*	
Markers of fibrinolysis und thrombin activation						
D-dimers, mg/L	0.488±0.665*; 0.3 [0.19–4.4]	51#	0.254±0.099; 0.19 [0.19–0.60]	50#	*<0.001*	0.407
Fibrinogen, mg/dL	293.9±72.0; 278 [170–447]	51#	278.6±44.0; 278 [222–438]	50	0.411	
Prothrombin fragment 1+2, pmol/L	302.8±588.9; 162.5 [70–3,921.2]	51#	165.2±64.8; 147.2 [68–346.1]	50#	0.411	

#, not normally distributed data. */**, significant correlation with the aortic root in the echocardiography or the aortic root in the cardiac MRI or the Z-score: *, P<0.05; **, P<0.01. The italicized P values showed statistical significance. VWF, von Willebrand factor; MFS, Marfan syndrome; PTT, partial thromboplastin time.

MFS patients, the VWF activity/VWF antigen ratio was significantly smaller (P<0.001) compared to the control group and the aortic root showed values above the mean and the median of the control group. In seven of these patients, the echocardiographic Z-score was above the maximum value of the control group (*Figure 4*). Seven of these eight patients had prolonged values in the PFA Col/Epi test and five in the PFA Col/ADP test. No specific correlation could be found with factor VIII activity.

Subgroup 2: D-dimers

Subgroup 2 was formed from eight MFS patients with D-dimer values above the maximum value of the control group. In seven patients of this subgroup, the aortic root and the associated Z-score were larger than the respective maximum value of the controls (*Figure 4*). Six patients from the subgroup also had elevated levels of prothrombin fragment 1+2.

Discussion

This study demonstrates the presence of hemostatic alterations in a large group of patients with proven MFS in relation of the size of the aortic root and in comparison with data from a group of healthy, sex- and age-matched controls. To the best of our knowledge there is only one case control study exploring this issue in MFS patients (4) and in addition several single case reports (4,16-18).

The main finding of the study is the possible presence of an acquired von Willebrand syndrome type 2A in patients with MFS. This syndrome is characterized by a qualitative and quantitative defect of large VWF multimers followed by a dysfunctional interaction with platelets (19,20). It

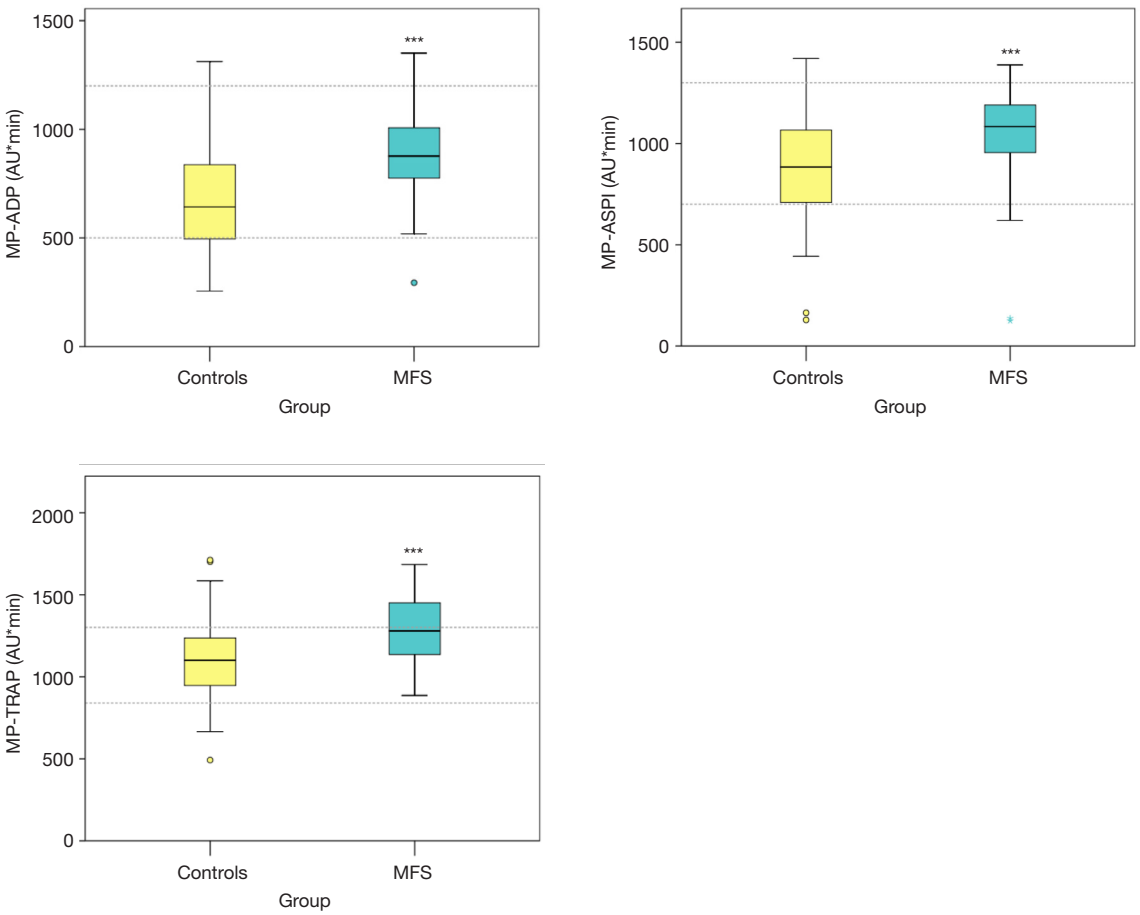

Figure 1 Boxplots showing the results of the Multiplate® tests in patients with MFS (cyan) *vs.* controls (yellow). The grey lines symbolize the upper and lower normal ranges of each parameter. MFS, Marfan syndrome. ***, P<0.001. The small circles indicate mild deviations from the median, and the small stars indicate extreme deviations from the median.

may be induced by increased shear stress caused by the ectatic aortic root in MFS patients (9) which gives rise to a conformational change of the VWF antigens and results in an increased susceptibility to proteases (ADAMTS13) (10,11,21-24).

Further evidence supporting an acquired von Willebrand syndrome type 2A was found in the laboratory findings (25,26). These included an abnormal PFA-100® test, significantly VWF antigen and activity (the VWF activity was more frequent and its mean more decreased than that of the VWF antigen), normal to moderately decreased factor VIII activity and normal platelet counts. PFA Col/ADP also correlated positively with the aortic root size as determined by echocardiography and the related Z-scores. Through the analysis of a selected patient subgroup (subgroup 1) these specific patterns became more apparent.

Various other studies have shown similar laboratory deviations in patients with aortic valve stenosis (12,27), dysfunctional aortic or mitral valve replacement, severe aortic or mitral valve regurgitation (28,29) and in patients with acquired von Willebrand syndrome type 2A (30). It was also reported that the altered laboratory parameters normalized after the repair of an aortic valve stenosis (30-32).

In order to confirm our theory, further investigations will be necessary. A standardized, universally accepted diagnostic criteria for acquired von Willebrand disease is still lacking (24) and there are different opinions about the sensitivity of the laboratory tests (33-36). Another point which may add greatly to this field will be the development of further laboratory tests to differentiate between different subtypes of the von Willebrand syndromes. Analyzing the laboratory parameters before and after surgery in one patient could determine a possible regression of hemostatic changes after the correction of aortic aneurysm

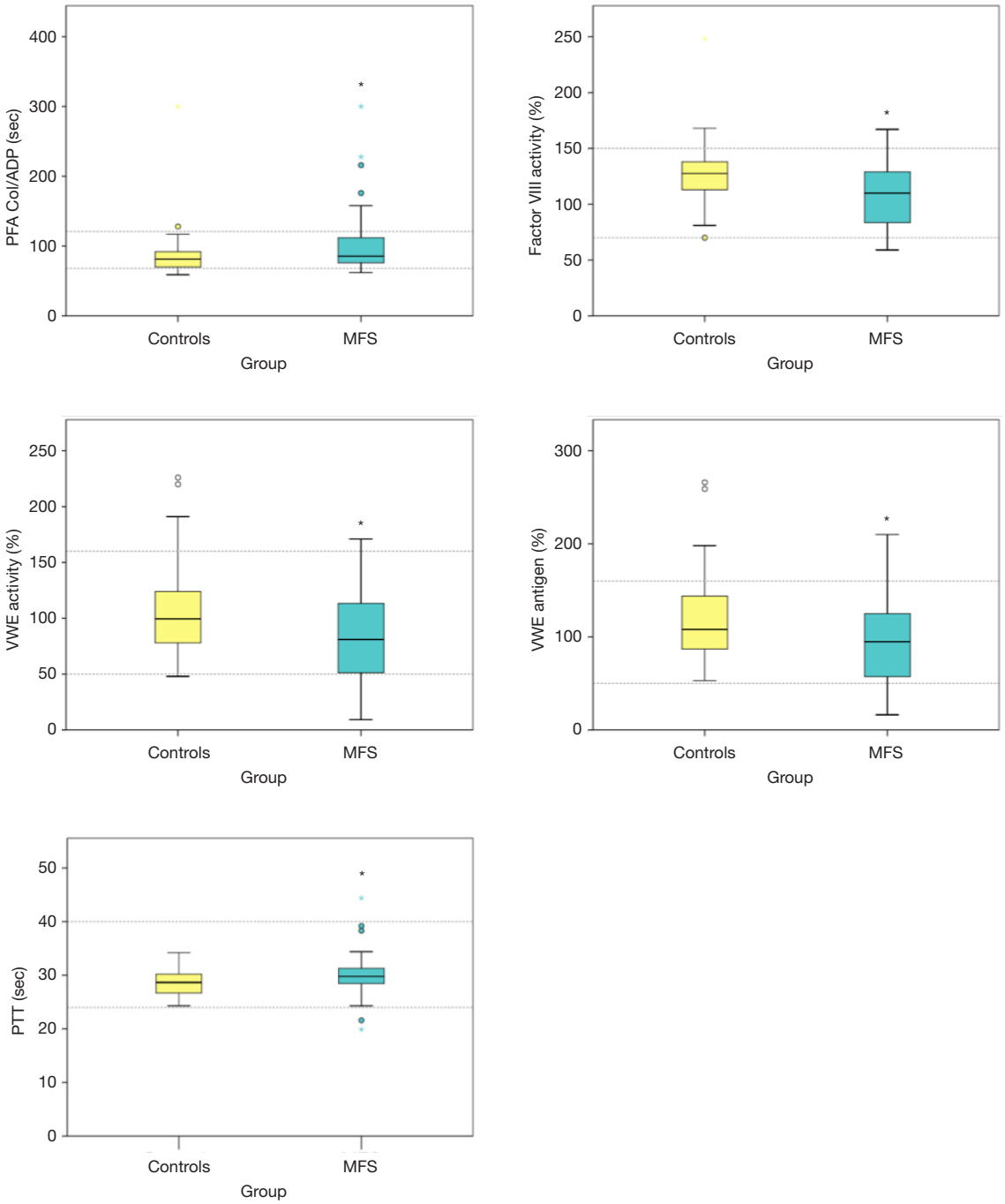

Figure 2 Boxplots showing the results of different tests in patients with MFS (cyan) *vs.* controls (yellow), showing hints to an acquired von Willebrand syndrome type 2A. The grey lines symbolize the upper and lower normal ranges of each parameter. MFS, Marfan syndrome. *, P<0.05. The small circles indicate mild deviations from the median, and the small stars indicate extreme deviations from the median.

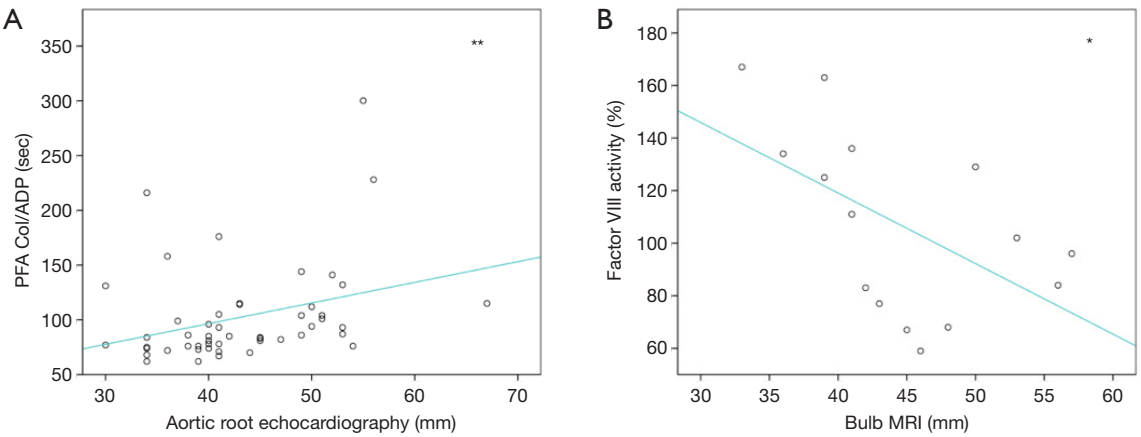

Figure 3 Scatterplots showing the relationship in MFS between (A) PFA Col/ADP and the aortic root in echocardiography and (B) factor VIII activity and the aortic root in cardiac MRI. The cyan lines represent the linear regression. MFS, Marfan syndrome; MRI, magnetic resonance imaging. *, P<0.05; **, P<0.01.

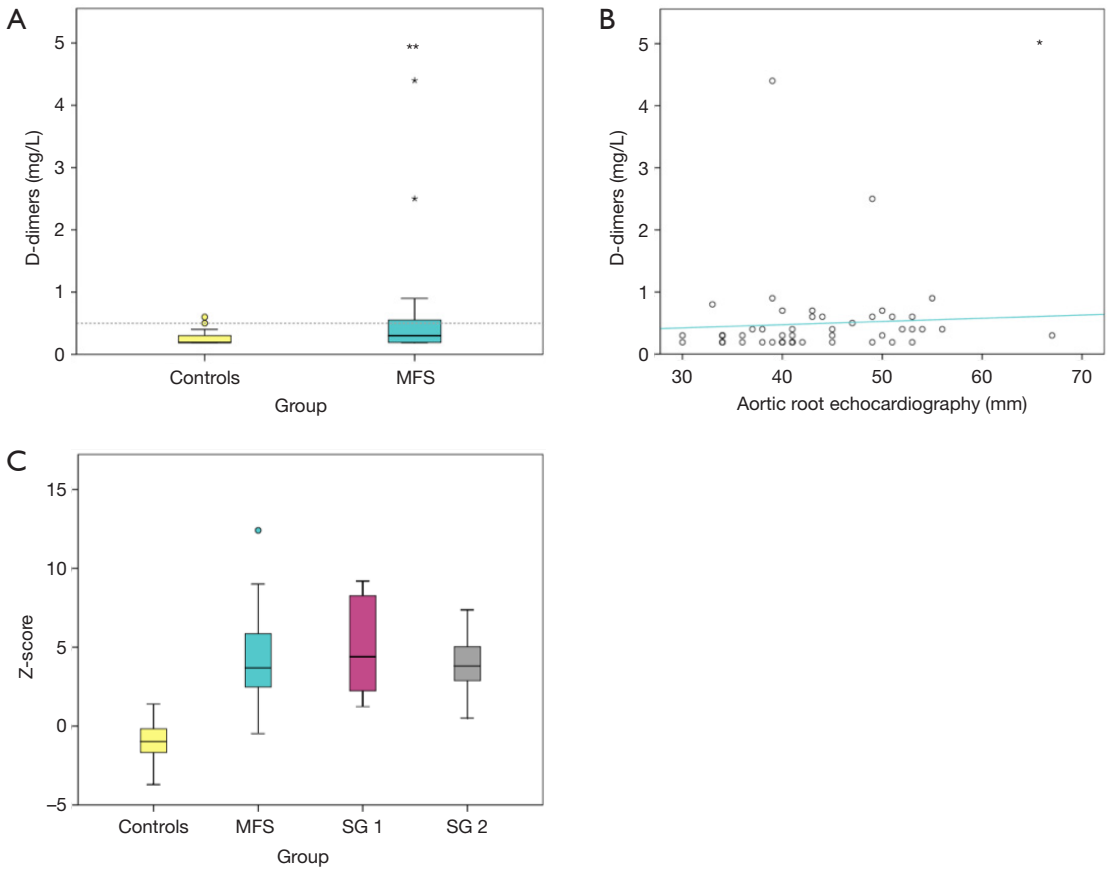

Figure 4 Boxplots and scatterplot showing the results of the D-dimers and of the subgroup analysis. (A) Boxplot showing significantly elevated values of D-dimers in patients with MFS (cyan) *vs.* controls (yellow). The grey lines symbolize the upper and lower normal ranges of the parameter. (B) Scatterplot showing the relationship between D-dimers and the aortic root in echocardiography in MFS. The cyan line symbolizes the linear regression. (C) Boxplot showing the Z-scores in controls (yellow) *vs.* MFS (cyan) *vs.* Subgroup 1 (SG 1) (magenta) *vs.* Subgroup 2 (SG 2) (grey). MFS, Marfan syndrome. *, P<0.05; **, P<0.01. The small circles indicate mild deviations from the median, and the small stars indicate extreme deviations from the median.

or pathological cardiac valves. This would be important to prevent acquired coagulation changes, such as the mentioned von Willebrand syndrome type 2A, by early correction of pathological heart valves or aortic aneurysms. Lastly, the majority of the MFS patients had pathological heart valves, which might also have an effect on shear stress and thereby on hemostasis. In future studies it would be interesting to examine the correlation between hemostasis and parameters like regurgitant volume or pressure half time in MFS patients.

Subgroup 2 of MFS patients with enlarged aortic root and Z-score had increased fibrinolysis and thrombin activation with elevated levels of D-dimer and prothrombin fragment 1+2. Other studies on patients with ectatic or aneurysmatic thoracic and abdominal aortic segments have also revealed increased fibrinolysis and thrombin activation (4,13,37-40). Indeed, studies on the thoracic aortic aneurysms typical of MFS are rare: Touat *et al.* [2008] studied 52 Marfan patients and found increased platelet and thrombin activation in patients with aortic diameter over 45 mm. In patients with thoracic aortic aneurysm significantly elevated levels of D-dimers and a correlation to the aneurysmal size were found (37,41). In contrast to abdominal aortic aneurysms, this location is not characterized by the formation of mural thrombi contributing to coagulation (4), thus implying that other mechanisms must be responsible for this occurrence.

The patients represented in subgroup 1 and subgroup 2 did not overlap, indicating that both previous discussed theories may exist independently in MFS. Both situations were positively correlated with the size of the aortic root. Identifying and comparing the exact genotypes of the two subgroups would be an interesting topic for future studies. However, it remains unclear whether the altered hemostasis is a consequence of the ectatic aortic root or whether it plays a causal role in the development and progression of an enlarged aortic root. If the altered hemostasis leads to an enlarged aortic root, it may be due to microthrombosis in the vessel wall inducing a necrosis.

Other inherited diseases leading to thoracic aortic aneurysm, like Ehlers-Danlos syndrome, were also associated with platelet dysfunction, measured, e.g., by PFA-100® tests. In contrast, von Willebrand disease or factor VIII deficiency could be excluded in Ehlers-Danlos patients (42,43). There are no studies available on hemostasis in Loeys-Dietz syndrome as the third important genetic disease with aortic aneurysm. Patients with bicuspid aortic valve and thoracic aortic dilatation showed increased fibrinolysis and thrombin activation (4). Bilen *et al.* [2012] found increased platelet activation measured by mean platelet volume and a correlation to aortic wall stiffness in patients with bicuspid aortic valve (44).

Limitations

This study has various limitations: the data collection was partly done in a retrospective manner. The recruitment of a part of the control population in the Outpatients' Clinic for Prevention, Rehabilitation and Sports Medicine, may have led to a selection bias, as patients at this clinic are often more physically active than normal controls. Furthermore, the controls did not undergo cardiac MRI screening. However, there was no clear need for this, as echocardiography did not reveal an aortic root ectasia or aneurysm in any case. A biological, pre-analytical and analytical variability must be considered, especially when analysing manually measured coagulation parameters.

In addition other contributing factors for the findings must be considered: in this study we focused on the correlation between hemostatic parameters and aortic dilatation, but also the pathological cardiac valves play a decisive role in the development of shear forces and thus influence the hemostasis. Second, in MFS patients altered wall shear stress was found in absence of changes in aortic morphology (45), which may indicate an intrinsic coagulation disorder. Third, the effects of the occurred surgical interventions and patient's blood group were not considered. As endothelial cells synthesize von VWF, endothelial dysfunction found in MFS patients might cause reduced VWF levels (46-48). PTT did not show relevant abnormalities, so a haemophilia as another cause for the findings could be excluded. Lastly, multiple linear regression analyses using hemostasis parameters as dependent variables and gender, weight, height, body surface area, age and blood pressure as independent variables did not show statistically significant and relevant findings (data not shown).

Conclusions

The current study reveals relevant hemostatic deviations in MFS patients, which could be attributed to either an acquired von Willebrand syndrome type 2A or a nonspecific coagulation activation with increased fibrinolysis and thrombin activation. The hemostatic deviations are associated with increased diameters of the aortic root,

possibly explicable by the altered blood flow patterns present in these patients.

These novel findings may help to reduce peri- and postoperative bleeding complications and improve common therapeutic and preventive measures for MFS patients. However, the clinical relevance of the findings needs further definition. Until then the hemostatic parameters should be carefully monitored when use of anticoagulants or surgical interventions are necessary.

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Footnote

Conflicts of interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study complies with the requirements of the Declaration of Helsinki and was approved by the local ethical committee (number 5313/12). All participants gave informed consent.

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