Analysis of Hemodynamic Parameters for Symptomatic Marfan Syndrome Patients by Phase-Contrast MRI

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Introduction: The Marfan syndrome (MFS) is a heritable gene mutation of FBN1 that encodes fibrillin-1 protein which is in charge of specifying the synthesis or processing of a constituent of the extracellular matrix (1). One of the most life-threatening complications is aortic dissection or rupture (2). Medical therapy to reduce the rate of aortic dilatation and risk of dissection, once MFS has been diagnosed, is now advocated (3). In previous study, noninvasive phase-contrast magnetic resonance imaging (PC-MRI) has been used to derive several reliable hemodynamic parameters (4). A previous study has qualitatively investigated the flow patterns of MFS by flow-sensitive 4D MRI (5). Geiger et al. has reported that asymptomatic MFS patients revealed significant increased regional wall shear stress (WSS) in ascending aorta (AAo) (6). However, a quantitative analysis of hemodynamic parameters for symptomatic MFS patients is still deficient, leading to the difficulty to monitor the risk of aortic dissection for MFS patients. The purpose of this study is to analyze regional WSS and oscillatory shear index (OSI) along the aorta of MFS patients with usage of noninvasive PC-MRI. The analyzed regional hemodynamic parameters of MFS were compared with normal controls so as to establish potential indices to predict specific sites in aorta with high risk of dissection or rupture.

Methods: The study cohort included 5 normal controls (age: 23.8±4.7 y/o, female/male: 3/2) and 15 MFS patients (age: 32.7±14.0 y/o, female/male: 4/11). The mean aortic root diameter were measured in MR left ventricular outflow track (LVOT) view and the values are 23.4±3.5 and 40.9±9.7 mm ($p<0.001$) for controls and MFS, respectively. The datasets of 3 normal controls (age: 24.7±6.4 y/o, female/male: 2/1, aortic root diameter: 21.13±2.33 mm) and 4 MFS patients (age: 30.5±12.7 y/o, male: 4, aortic root diameter: 47.23±14.33 mm) were used to compute regional distribution of WSS. All subjects underwent flow-sensitive 4D PC-MRI with FLASH sequence to acquire flow data in a 3.0 Tesla MR scanner (Trio, Siemens, Erlangen, Germany). The parameters are TR/TE = 43.2/2.92 ms, flip angle = 7°, VENC=1.5 m/s, voxel size = 1.17×1.17×3.5 mm^3, sampling 90% of the cardiac cycle. Prospective ECG-triggering and navigator-echo gating technique were performed to synchronize with heart beating and respiratory motion. The analysis of hemodynamic indices was accomplished by commercial software for 3D flow and vascular visualization (EnSight, CEI, Apex, NC) and home developed program (7) for quantification of hemodynamic indices. Ten vessel planes were placed at specific sites along the aorta, as listed in Table 1. The WSS, expressing as the tangential force per unit area that is exerted by the flowing blood on the arterial wall, has been proved to be associated with gene expression and extracellular matrix remodeling (8). The WSS vector ($\vec{\tau}$), whose absolute value is WSS magnitude (WSS_{mag}), can be divided into axial (WSS_{axial}) and circumferential (WSS_{circ}) components and is defined as: $\vec{\tau} = \eta\dot{\varepsilon}\cdot\vec{n}$, where η is viscosity, $\vec{n}$ is inward unit normal and $\dot{\varepsilon}$ is deformation tensor (7). The OSI, showing the deviation of the WSS from its averaged direction during one cardiac cycle, is defined as: $OSI = \frac{1}{2}\left(1 - \frac{\left|\int_0^T \vec{\tau}\cdot dt\right|}{\int_0^T |\vec{\tau}|\cdot dt}\right)$, where T is the duration of the cardiac cycle (7). The circumference of each vessel plane was divided into 12 segments so that the regional WSS and OSI can be derived. Student's t-test was performed to compare the difference between two groups and $p<0.05$ indicates statistically significant difference.

Table1. Positions of 10 planes.

Plane	Location
1	Sinuses of valsalva
2	Sinotubular junction
3	In the middle of plane#2 and #4
4	Proximal aortic arch
5	In the middle of innominate artery and left common carotid artery
6	In the middle of left common carotid artery and left subclavian artery
7	2 cm distal to left subclavian artery
8	In the middle of plane#7 and #9
9	At the level of diaphragm
10	2 cm distal to diaphragm

Results: As shown in Fig. 1(a-c), MFS patients revealed significant lower WSS_{axial}, WSS_{circ}, and WSS_{mag}, particularly in AAo and aortic arch (AA), representing significantly lower tangential force is exerted on the arterial wall at these sites in MFS patients. In Fig. 1(d-f), OSI_{circ} values of normal controls and MFS patients were significant different in plane#6 (6.4±4.2% vs. 15.1±4.7%, $p<0.05$) and plane#7 (24.9±4.1% vs. 13.2±5.5%, $p<0.01$). Figure 2 displayed the regional distribution of WSS_{axial} for two groups. In general, MFS patients demonstrated lower WSS_{axial} compared to normal controls, particularly in AAo and AA. Besides, in descending aorta (DAo), MFS patients presented lower WSS_{axial} in specific sites of plane#7,8,10 (Fig.2). The spider charts also illustrated that normal controls revealed asymmetric WSS_{axial} values along circumference of aortic wall. The long-axis of the ellipses in spider charts rotated from segment#5-11 in AAo to segment#3-9 in DAo. In contrast, MFS showed relatively symmetric circles in spider charts.

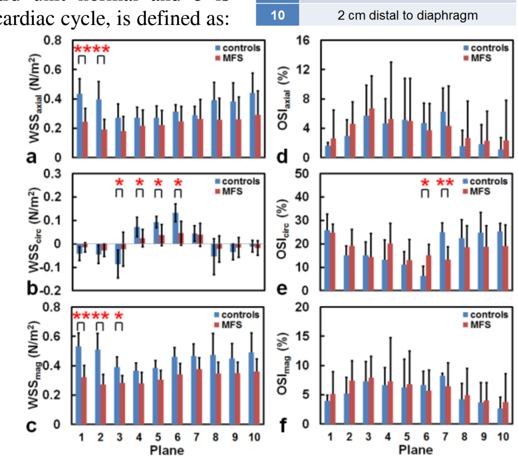

Fig. 1. The plots showed WSS (a-c), and OSI (d-f) in 10 planes along the aorta of normal controls (blue) and MFS patients (red). *$p<0.05$, **$p<0.01$.

Discussion & Conclusions: In this study, hemodynamic indices of WSS and OSI were analyzed for symptomatic MFS patients and normal controls. A previous study has reported that the shear stress was the most relevant endothelial-regulated hemodynamic force in vasoregulation (9). Low level of shear stress was discovered in regions of lesions (e.g. atherosclerosis), since blood separation and flow reversal occurred (10). In our work, WSS in the aorta of symptomatic MFS patients decreased at specific segments in certain planes, where may indicate the disturbed flows, particularly in AAo, in segment#10~12 of AA, and in segment#3~5 in DAo. However, Geiger et al. reported increased peak systolic WSS in AAo, which is inconsistent with our finding in this study. The discrepancy may result from the recruited MFS groups. Geiger et al. measured WSS of asymptomatic MFS patients while we analyzed hemodynamic parameters for symptomatic MFS group and try to establish potential indices for evaluating risk of dissection. Since our patient population has revealed significant symptom, saying increased aortic root diameter, disturbing flows and thus decreased WSS values are reasonable and expectable. Long-term follow-up experiments of patient group are needed to correlate the decreased WSS values with specific sites of dissection in MFS group. In conclusion, hemodynamic indices of WSS and OSI were analyzed for symptomatic MFS patients and compared with normal controls. The values of WSS were significant lower in MFS patients. Regional distribution of WSS_{axial} further displayed the chaotic flows in specific sites of the aorta, which may indicate potential sites with high risk of dissection. In the future, large number of MFS patients and normal controls shall be recruited and follow-up of patient group shall be conducted to convincingly establish predictive indices for aortic dissection in MFS patients.

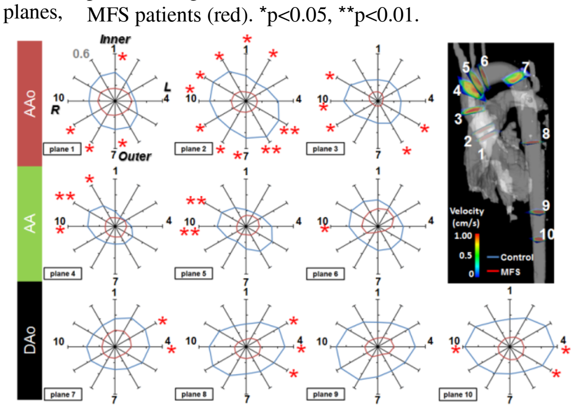

Fig. 2. The spider charts displayed regional WSS_{axial} in 12 segments of 10 planes along the aorta of normal controls (blue) and MFS patients (red).*$p<0.05$, **$p<0.01$.

References: **1.** Ammash et al. *Curr Probl Cardiol*. 33(1):7-39 (2008). **2.** Milewicz et al. *Circulation*. 111:e150-e157 (2005). **3.** Dormand et al. *J Cardiovasc Magn Reson*. 15:33 (2013). **4.** Gerald et al. *J Am Coll Cardiol*. 43: 5S–12S. (2004). **5.** Geiger et al. *J Magn Reson Imaging*. 35(3):594-600 (2011). **6.** Geiger et al. *Magn Reson Med*. 70:1137–1144 (2013). **7.** Stalder et al. *Magn Reson Med*. 60:1218–1231 (2008). **8.** Chiu et al. *Ann Med*. 41: 19-28 (2009). **9.** Koller et al. *Circ Res*. 72(6): 1276-1284. (1993). **10.** Zarins et al. *Circ Res*. 53(4): 502-514. (1983).