Original Research

Effect of Aortic Stiffness on Left Ventricular Long-Axis Systolic Function in Adults with Marfan Syndrome

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Applanation tonometry, augmentation index, pulse wave velocity.

Introduction: Several studies have documented increased aortic stiffness in patients with Marfan syndrome (MFS) using echocardiography and magnetic resonance imaging. Recent studies have also shown primary myocardial impairment in MFS. We investigated whether left ventricular (LV) function could be further impaired when acting against a stiff vascular system.

Methods: Twenty-six MFS patients (mean age 30 ± 2 years, 17 males) and 30 normal controls were examined. Mitral annular displacement, as a surrogate for LV systolic function, was evaluated from septal, anterolateral, anterior and inferior regions using M-mode and tissue Doppler imaging. Septal/anterolateral and anterior/inferior M-mode displacement measurements were normalised by dividing them by the longitudinal inner distance obtained at end diastole from the 4- and 2-chamber views, respectively. Carotid-femoral and carotid-radial (CF and CR) pulse wave velocities (PWV) were determined using an automated applanation tonometry device. Central aortic pressure was assessed by recording radial waveforms with the tonometer and central waveforms were reconstructed using a generalised transfer function.

Results: CF- and CR-PWV were significantly increased in the patient group ($p<0.001$), whilst mitral annular displacement measurements were significantly reduced ($p<0.001$, all regions). Regression analysis demonstrated that the disease status and CF-PWV were strongly associated with reduced LV systolic function ($p<0.001$, $p=0.002$, respectively).

Conclusions: Our study showed reduced LV systolic function and increased aortic stiffness in MFS patients. The efficiency of a fibrillin-1 deficient heart may be further reduced by ejection into a stiff vascular system. Care should be taken to ensure that any treatment regime addresses both increased aortic stiffness and myocardial dysfunction in MFS.

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Marfan syndrome (MFS) is an autosomal dominantly inherited disorder of connective tissue characterised by ocular, musculoskeletal and cardiovascular manifestations and caused by mutations in the FBN1 gene that encodes for the protein fibrillin-1.[1] Fibrillin-1 is the major constituent of the extracellular microfibrils that act as a scaffolding for the formation and maintenance of elastic fibres. Molecular studies by Dietz et al have demonstrated that fibrillin-1 haploinsufficiency and subsequent dysregulated transforming growth factor-β signalling are the key factors in the disease progression.[2]

Aortic complications, such as aortic root dilatation and dissections, have long been recognised as the main cause of premature death from MFS and have been studied extensively. Several studies have documented increased arterial stiffness in patients with MFS using echocardiography and cardiovascular magnetic resonance (CMR).[3,4] Recent studies have also shown primary myocardial impairment in MFS in the absence of significant valvular disease. De Backer et al reported convincing controlled data for left ventricular (LV) systolic and diastolic dysfunction in patients with MFS. Despite the small number of patients investigated, their study was powerful, as they implemented a more sensitive ultrasound technique and their findings were confirmed using CMR.[5] Other research centres also demonstrated impaired myocardial function in larger series of adult patients without valvular disease or other clinical comorbidities, using advanced echocardiographic techniques and CMR.[6-9]

However, LV function could be further impaired when acting against a stiff vascular system. Experimental studies on the Marfan syndrome mouse model showed fragmentation of the elastic fibres and increased collagen deposition, which result in increased aortic stiffness.[10] Previous studies on humans with MFS have demonstrated increased aortic stiffness and decreased aortic distensibility using echocardiographic, cardiac magnetic resonance, and invasive techniques.[3,4,11] Though pulse wave velocity (PWV) is considered to be the gold standard measurement of aortic stiffness,[12] measurements of central pulse pressure, central systolic blood pressure, augmentation index, along with PWV, are of critical importance in assessing aortic stiffness. However, applanation tonometry is a simpler, non-invasive, validated and reproducible technique for assessing all these parameters.[12]

The aim of this study was to investigate the effect of aortic stiffness on LV systolic function in adult unoperated patients with MFS using echocardiography and applanation tonometry.

Methods

Study population

In this study 26 Caucasian patients with MFS (mean age 30 ± 2 years, 17 males and 9 females) were enrolled. The diagnosis of MFS was established according to the internationally accepted Ghent criteria.[13] The studies were performed at St. George's, University of London, in collaboration with St. George's Hospital NHS Trust, prior to the start of β-blocker therapy. None of the patients were on any other medications. Patients were recruited from the MFS clinics at St. George's, Royal Brompton and Harefield Hospitals in London, UK. In each case, the clinical diagnosis was confirmed by three experienced observers (MM, AK and AHC). None of the patients had a history of dissection, any previous cardiac surgery, systemic or pulmonary hypertension, persistent arrhythmia or any clinical disorders known to compromise myocardial function, such as coronary heart disease, diabetes mellitus, renal impairment, anaemia, thyroid or liver disorder. In addition, smoking and excessive alcohol consumption were considered as exclusion criteria.

The control group consisted of 30 normal controls without significant differences in age, sex, race, or body surface area (BSA) from the patient group. The control group was enrolled from the general population and genetically unrelated family members of our patients. All normal volunteers also underwent a thorough physical, electrocardiographic and echocardiographic examination. Written informed consent was obtained from each subject, and the institutional ethics committee approved the study protocol.

Echocardiography

A two-dimensional echocardiographic examination was performed for each subject, using the Vivid 7 Vingmed General Electric ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway) equipped with a 4S probe. Three consecutive cardiac cycles were recorded for each view, with breath held at end expiration. An ECG was recorded simultaneously at a sweep speed of 100 mm/s. LV size and function were both assessed in accordance with the combined ASE/ESC guidelines.[14] Mitral annular displacement, which is often utilised to express LV systolic function, was evaluated from inferoseptal, anterolateral, anterior, inferior and inferolateral regions using M-mode echocardiography. The amplitude of regional displacement was calculated 60 ms after the beginning of the QRS complex to the first peak of the mitral annular waveform.[15] Inferoseptal and anterolateral displacement measurements were normalised by dividing them by the longitudinal inner distance obtained at end diastole from the apical 4 chamber view, and anterior and inferior displacements were divided by the inner distance obtained from the 2-chamber view (Figure 1).[16] Similar normalisation of the inferolateral mitral annular displacement was not performed,

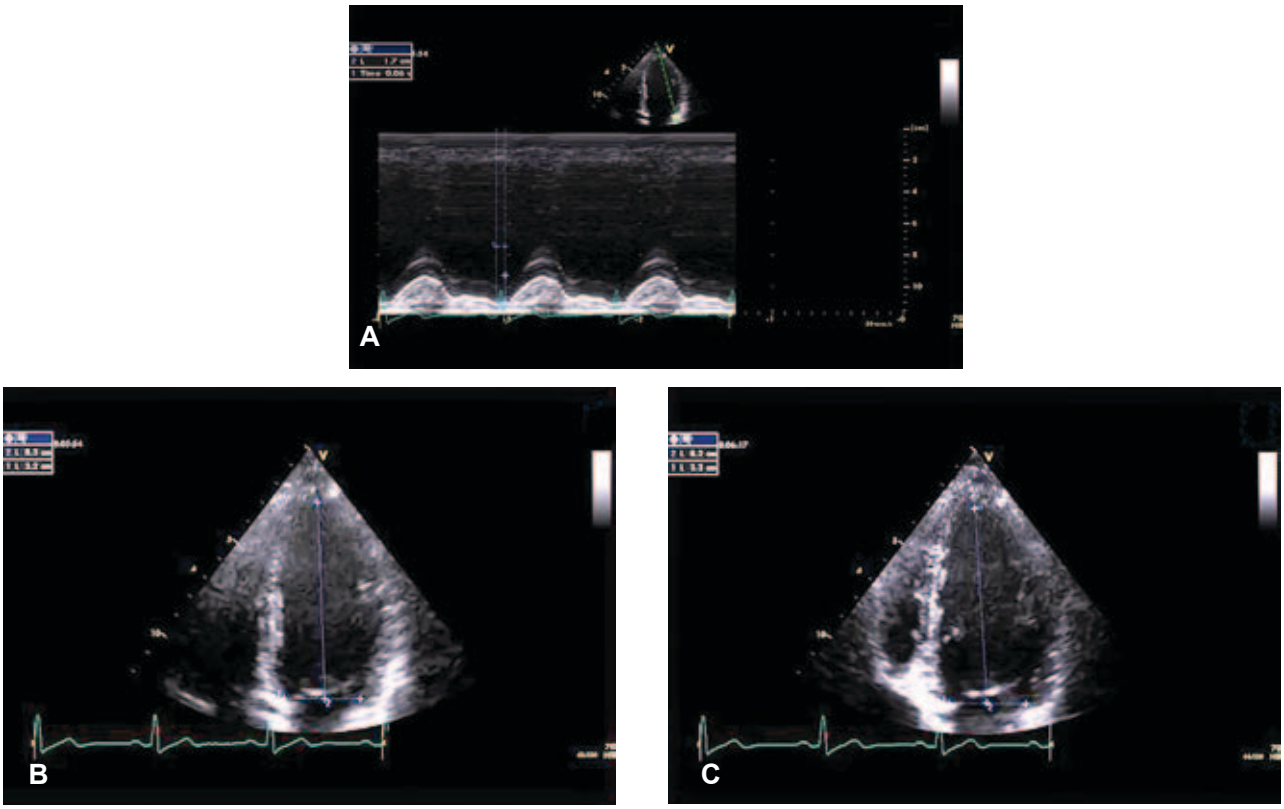

Figure 1. A. Regional displacement was calculated 60 ms after the beginning of the QRS complex to the first peak of the mitral annular waveform. B. Anterolateral and inferoseptal displacement measurements were normalised by dividing them by the longitudinal inner distance obtained at end diastole from the 4 chamber view. C. Anterior and inferior displacements were divided by the inner distance obtained from the 2-chamber view.

because it is not always possible to clearly visualise the LV apex in the three-chamber view and the plane of the long axis in this view is generally oblique. For this reason, we have presented the latter displacement in absolute values (cm).

Mitral annular systolic velocities were also assessed from the above 5 mitral annular regions using tissue Doppler imaging (TDI) in accordance with the recommendations for quantification of Doppler echocardiography.[17] Peak systolic velocity was measured avoiding the initial peak that is observed during isovolumic contraction time (Figure 2).

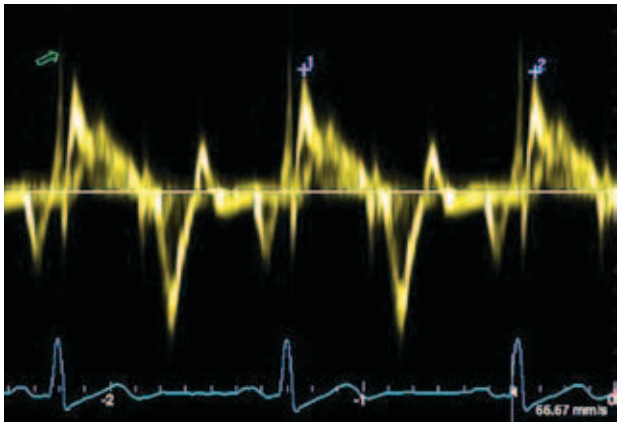

Figure 2. Assessment of systolic mitral annular velocities using tissue Doppler imaging. Peak systolic velocity was measured avoiding the initial peak that is observed during isovolumic contraction time, as indicated by the green arrow.

Blood pressure measurements

Brachial artery blood pressure was measured twice for each patient, using a standard mercury sphygmomanometer on the right arm while the subject was in a sitting position after 15 min of rest. Appropriate cuff sizes were chosen for each subject's arm circumference. An average was calculated for each participant and was used for the analyses.

Measurement of PWV

Participants were investigated in our vascular laboratory. After their echocardiographic examination,

they stayed at rest for at least 10 minutes in a recumbent position. The room temperature was maintained at a level of 22 ± 1° C and noise levels were kept to a minimum for subjective comfort. The study subjects had to refrain from eating for at least 3 hours before the examination, particularly from drinking beverages containing caffeine. They had also to refrain from alcohol intake 10 hours before the tests.

Carotid-femoral PWV (CF-PWV) was determined with the foot-to-foot velocity method from various waveforms using the SphygmoCor system (AtCor Medical, Sydney, Australia). Consecutive recordings of the carotid and femoral artery pulse waves were ECG-gated, and thus the time shift between the appearance of the wave at the first and second sites could be calculated. The distance between the two sites was measured on the body surface for the calculation of CF-PWV in metres/second (m/s). PWV was calculated by dividing the distance (D) between these two sites by the time delay (Dt or transit time) measured between the feet of the two waveforms: PWV = D (metres) / Dt (seconds).

Carotid-radial PWV (CR-PWV) was also determined by obtaining ECG-gated consecutive recordings of the carotid and radial artery pulse waves, following the same methodology as for the CF-PWV assessment.

Figure 3 shows some representative waveform recordings and measurements taken using this equipment.

Pressure waveform analysis

The assessment of arterial wall properties and wave reflection characteristics was performed non-invasively using the SphygmoCor system. Radial artery pressure waveforms were recorded at the wrist, using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Houston, TX, USA). After the recording and averaging of 20 sequential waveforms, a validated generalised mathematical transfer function (TF) was used to reconstruct the corresponding central aortic pressure waveform (Figure 4). Augmentation index (AIx) and augmentation pressure were derived using the peripheral waveform and the incorporated SphygmoCor TF. The merging point of the incident and the reflected wave (the inflection point) was identified on the generated aortic pressure waveform. Augmentation pressure was the maximum systolic pressure minus pressure at the inflection point. AIx was defined as the augmentation pressure divided by pulse pressure and expressed as a percentage. Larger values of AIx indicate increased wave reflection from the periphery or earlier return of the reflected wave as a result of increased PWV (attributable to increased arterial stiffness). AIx is dependent upon the elastic properties of the entire arterial tree (elastic and muscular arteries).[18]

Reproducibility of pressure wave analysis

All measurements were performed by the same person (AK), with the patient in the supine position in a quiet, temperature-controlled room after a brief rest period of at least 10 min. Prior to commencing this study, there was an initial learning period of 25 repeated measurements until satisfactory reproducibility was achieved (<5% variability between duplicate measurements). As a further check for quality control, the Sphygmocor® software incorporates a quality control feature that is displayed on the screen.

Reproducibility of AVPD measurements

The reproducibility of atrioventricular plane displacement (AVPD) measurements was assessed in 28 randomly selected study patients and normal controls. These measurements were performed blindly by two observers on two different occasions. The intra- and inter-observer reproducibility was calculated using unsigned relative errors ($2 \times |A - B| / (A + B)$), where A and B were the repeated measurements using the same method.[19] Statistical analysis of the reproducibility of methods was based on comparisons of the absolute values of relative errors using the Mann-Whitney test.

Statistical analysis

Continuous variables were summarised as means ± standard deviation (SD). The Kolmogorov-Smirnov test was used to test for the hypothesis of normality. Differences in continuous variables between patients with MFS and normal volunteers were investigated using a t-test for independent samples. Categorical variables were expressed as absolute numbers and percentages. The statistical test in these cases was the chi^2-test.

To investigate and compare the ability of M-mode and TDI mitral annular motion measurements to predict the presence of LV dysfunction caused by MFS, receiver operating characteristic (ROC) curves were constructed.

In order to investigate possible factors influencing the LV longitudinal systolic function in addition

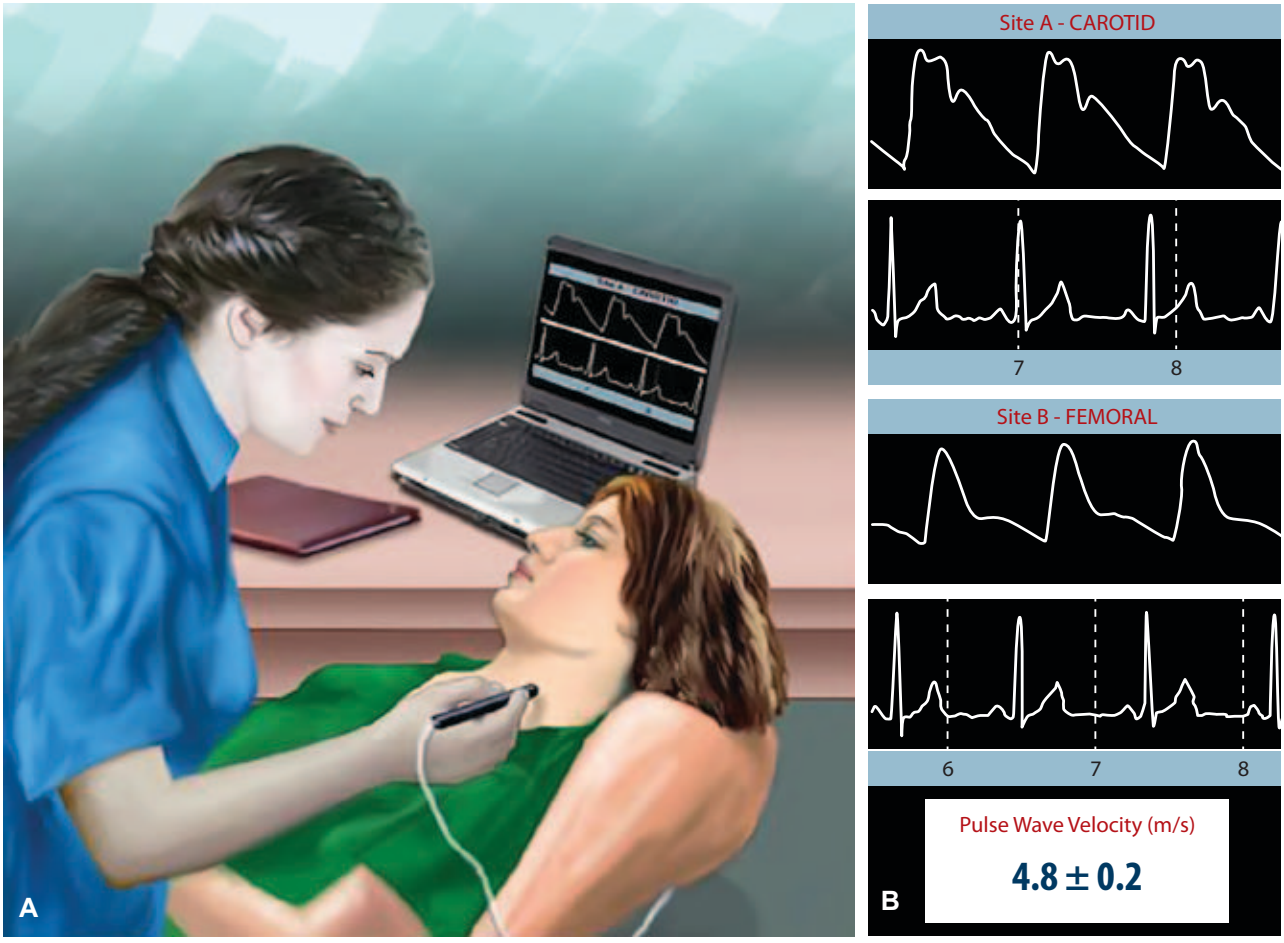

Figure 3. Some representative waveform recordings (A) and measurements (B) taken using the equipment.

to the disease status (MFS), multiple regression analysis models were constructed with the averaged normalised AVPD measurements obtained from the anterolateral, inferoseptal, inferior and anterior mitral annular regions as the dependent variable and MFS diagnosis, age, sex, systolic blood pressure (SBP), diastolic blood pressure, BSA, heart rate, AIx, CF-PWV and CR-PWV as possible confounders. Absolute AVPD measurements (in cm) obtained from the inferolateral mitral annular region were also tested separately as a dependent variable against the aforementioned possible confounders.

A p-value <0.05 was considered statistically significant. Data were analysed using SPSS® version 16.0.2, 2008 (SPSS Inc., Chicago, IL, USA). Bland-Altman plots, linear regression analyses and relevant curves were generated using the "Analyse it" package for the Excel programme. The "Analyse-it" software uses the DeLong nonparametric approach for the analysis of areas under correlated ROC curves.[20]

Results

Recordings were successfully obtained from all participants and they all tolerated the investigation tests well. The clinical characteristics of the study subjects are presented in Table 1. There were no differences in the baseline characteristics between the two groups except for the weight, which was lower in patients with MFS, as expected (p=0.046). Body surface area measurements however, showed no significant differences. The echocardiographic parameters are illustrated in Table 2. Patients with MFS had higher LV end-diastolic volume and LV end-systolic volume indexed to BSA (p<0.05). Ejection fraction measurements were significantly lower in the patient group, although they were still within the normal range (p=0.002). Normalised and absolute AVPD measurements were also significantly lower in patients with MFS when compared with normal controls (p<0.001). PWV measurements and pulse

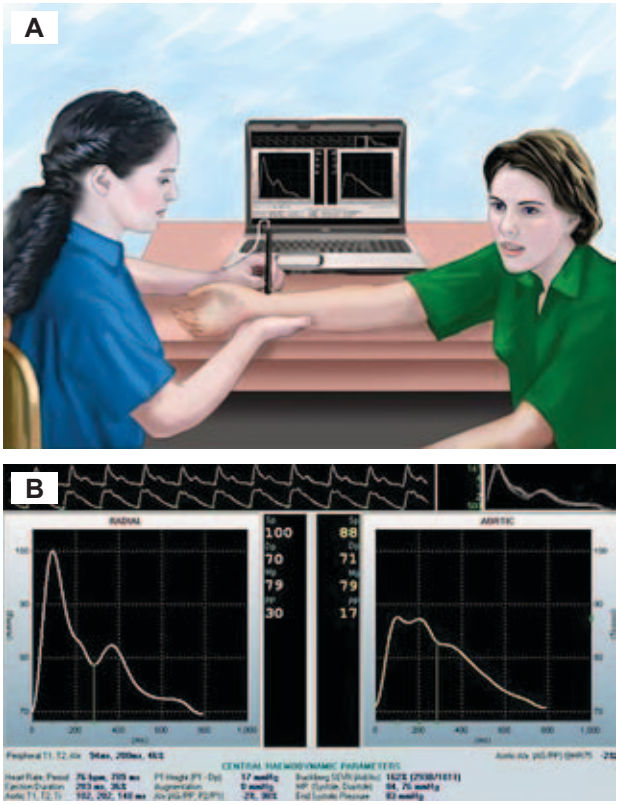

Figure 4. Central aortic pressure was assessed by recording radial waveforms with the tonometer (A) and central waveforms were reconstructed using a generalised transfer function. Figure 4B shows the corresponding recordings and measurements.

waveform analysis for patients with MFS and normal controls are given in Table 3. Carotid-femoral-PWV, CR-PWV and AIx values were significantly elevated in the patient group ($p<0.001$). However, peripheral and central blood pressure measurements were similar in the two groups. Distance measurements from the suprasternal notch to the point where carotid arterial waveforms were recorded showed no differences between patients and controls. The distances from the suprasternal notch to left radial and femoral recording sites also showed no differences between the study groups. Thus, the increased PWV in patients with MFS could be attributed to a decreased time interval between the appearance of the wave at the first and the second sites.

ROC analysis

For the averaged normalised AVPD and TDI measurements obtained from the inferoseptal, anterolateral, inferior and anterior mitral annular regions, the largest area under the curve was obtained with AVPD using M-mode echocardiography, as shown in Figure 5A. Similarly, with regard to the absolute inferolateral mitral annular displacement measurements and TDI systolic velocities, the largest area under the curve was obtained with M-mode echocardiography (Figure 5B).

Regression analysis

Since the ROC analysis showed significant differences between the M-mode and TDI echocardiographic techniques, only the data obtained from the former method (averaged normalised AVPD obtained from 4 mitral annular regions and absolute measurements from the inferolateral LV wall) were included as dependent variables in the multiple regression analyses.

The results of the multiple regression models demonstrated uniformly that MFS diagnosis was strongly associated with reduced LV longitudinal systolic function (measured by AVPD). These analyses also showed that CF-PWV had a significant negative association with LV longitudinal systolic function. In addi-

Table 1. Baseline characteristics for Marfan syndrom patients and controls.

Variable	N	MFS	N	Controls	p
Sex (male/female)	17/9		15/15		0.246†
Age (years)	26	30 ± 11	30	32 ± 8	0.450
Weight (kg)	26	74.28 ± 14.47	30	82.06 ± 14.04	0.046
Height (cm)	26	187.27 ± 10.69	30	187.87 ± 8.97	0.821
BSA (m^2)	26	1.96 ± 0.23	30	2.06 ± 0.22	0.083
Caucasian race	26	All	30	All	–
Smoking	26	No history	30	No history	–

MFS – Marfan syndrome; BSA – body surface area.
Results are represented as mean ± SD.
P-values are obtained from t-tests, adjusted for unequal variances if necessary; †Chi^2 test.

Table 2. Echocardiographic parameters in Marfan syndrom patients and controls.

Variable	N	MFS	N	Controls	p
LVEDD (cm)	26	5.06 ± 0.43	30	4.94 ± 0.44	0.325
LVESD (cm)	26	3.10 ± 0.47	30	2.99 ± 0.35	0.331
LVEDV (ml)	26	90.68 ± 19.95	30	86.28 ± 16.97	0.37
LVEDV/BSA (ml/m^2)	26	46.31 ± 8.90	30	41.82 ± 7.24	0.042
LVESV (ml)	26	30.78 ± 9.77	30	25.06 ± 6.07	0.010
LVESV/BSA (ml/m^2)	26	15.67 ± 4.63	30	12.13 ± 2.72	0.001
EF (%)	26	66.32 ± 5.24	30	70.42 ± 4.09	0.002
LV Anterolateral AVPD ratio	26	0.17 ± 0.03	30	0.21 ± 0.02	<0.001
LV Inferoseptal AVPD ratio	26	0.14 ± 0.19	30	0.19 ± 0.02	<0.001
LV Inferior AVPD ratio	26	0.17 ± 0.03	30	0.21 ± 0.03	<0.001
LV Anterior AVPD ratio	26	0.16 ± 0.03	30	0.19 ± 0.03	<0.001
LV Inferolateral AVPD (cm)	26	1.88 ± 0.21	30	1.52 ± 0.20	<0.001
Aortic root size (cm)	26	4.17 ± 0.69	30	3.18 ± 0.33	<0.001

MFS – Marfan syndrome patients; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LVEDV – left ventricular end-diastolic volume; BSA – body surface area; LVESV – left ventricular end-systolic volume; EF – ejection fraction evaluated by Simpson's biplane method; LV – left ventricle; AVPD – atrio-ventricular plane displacement.
Results are represented as mean ± SD.
P-values are obtained from t-tests, adjusted for unequal variances if necessary.

Table 3. Pulse wave velocity measurements and pressure waveform analysis for Marfan syndrome patients and controls.

Variable	MFS (n=26)	Controls (n=30)	p
Carotid-femoral PWV (m/s)	6.99 ± 1.71	5.30 ± 0.54	<0.001
Carotid-radial PWV (m/s)	7.67 ± 1.80	6.31 ± 0.86	0.001
Carotid to suprasternal notch distance (mm)	115.77 ± 8.09	120.33 ± 11.59	0.098
Suprasternal notch to femoral artery distance (mm)	573.46 ± 65.48	564.37 ± 29.84	0.497
Suprasternal notch to radial artery distance (mm)	766.92 ± 56.20	769.00 ± 39.68	0.872
Augmentation index (%)	12.35 ± 13.29	1.80 ± 7.99	0.001
Peripheral systolic blood pressure (mmHg)	112.85 ± 11.55	114.73 ± 7.75	0.471
Peripheral diastolic blood pressure (mmHg)	75.19 ± 8.17	75.40 ± 5.90	0.913
Peripheral pulse pressure (mmHg)	37.65 ± 7.91	39.33 ± 6.28	0.380
Peripheral mean arterial pressure (mmHg)	87.74 ± 8.66	88.51 ± 5.87	0.696
Central systolic blood pressure (mmHg)	100.92 ± 11.19	99.20 ± 6.31	0.473
Central diastolic blood pressure (mmHg)	75.58 ± 8.57	76.17 ± 5.22	0.753
Central pulse pressure (mmHg)	25.35 ± 8.69	23.03 ± 4.02	0.197
Central mean arterial pressure (mmHg)	86.42 ± 8.59	86.73 ± 5.29	0.870
Heart rate (bpm)	52 ± 12	51 ± 24	0.803
Ejection duration (ms)	295.04 ± 26.71	294.83 ± 21.72	0.975
Aortic Tr (ms)	152.15 ± 9.81	155.70 ± 11.06	0.213

Results are represented as mean ± SD. P-values are obtained from t-tests, adjusted for unequal variances if necessary. PWV – pulse wave velocity; MFS – Marfan syndrome; Tr – time between the start of the systolic curve and the inflection point.

tion, systolic blood pressure and BSA had a significant negative association with averaged normalised AVPD, whilst AIx had a borderline (p=0.05) positive association with inferolateral mitral annular displacement (Table 4).

Pressure wave analysis reproducibility

The variability for duplicate measurements was <5%.

AVPD reproducibility

The mean intra- and inter-observer variability was less than 5% for all AVPD measurements.

Discussion

In this study, we investigated the relationship between aortic stiffness and LV myocardial impairment in adult unoperated patients with MFS, using echocardiogra-

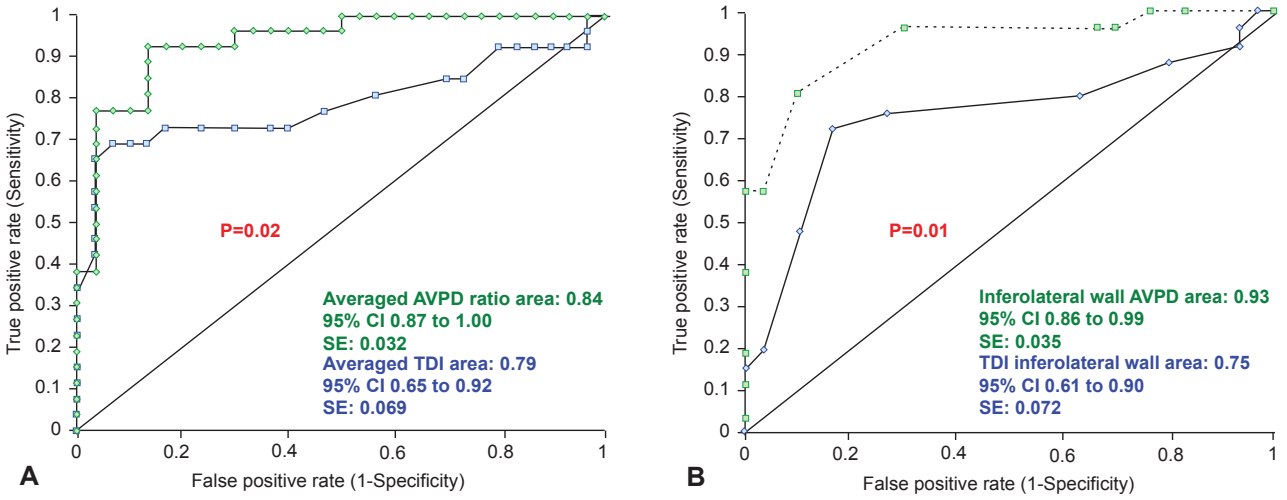

Figure 5. A. Data from ROC analysis for averaged atrioventricular plane displacement (AVPD) ratio calculated from the anterolateral, inferoseptal, inferior and anterior mitral annular regions and systolic velocities obtained from the same mitral annular regions using tissue Doppler imaging (TDI). The largest area under the curve was generated by M-mode echocardiography (AVPD): 0.94. B. Data from ROC analysis for absolute AVPD measurements (in cm) obtained from the inferolateral mitral annular region and systolic velocities obtained from the same mitral annular region using tissue Doppler imaging. As with panel A, the largest area under the curve was generated by M-mode echocardiography: 0.93.

phy and applanation tonometry. To the best of our knowledge, this is the first study to assess the impact of aortic stiffness on LV long-axis systolic function in MFS patients. Our findings showed reduced LV longitudinal systolic function and increased aortic stiffness in our patients when compared with normal controls.

In the literature, there are several studies demonstrating that M-mode echocardiography constitutes an established method for evaluating AVPD that is often utilised as a surrogate of LV systolic function.[21,22] The predictive value of this technique has also been reported in patients with coronary or non-coronary heart disease.[23-25]

Increased aortic stiffness was expected in our patients. Physiological ageing of the aorta is associated with a degeneration of smooth muscle cells and elastic tissue within the aortic wall known as cystic medial necrosis.[26] These changes become particularly profound early in life in patients with MFS, leading to increased aortic stiffness. Previous studies have demonstrated increased aortic stiffness and decreased aortic distensibility in patients with MFS using echocardio-

Table 4. Multiple regression analyses results demonstrating the effect of disease status and carotid-femoral pulse wave velocity on left ventricular atrioventricular plane displacement measurements. Regression coefficients show the effect of each confounder for one unit increase.

Variable	Method	B-coefficient	p
Averaged AVPD	MFS diagnosis	-0.643	<0.001
	CF-PWV	-0.304	0.004
	SBP	-0.207	0.029
	BSA	-0.222	0.017
Inferolateral wall AVPD	MFS diagnosis	-0.598	<0.001
	CF-PWV	-0.354	0.002
	AIx	0.194	0.05

AVPD – atrioventricular plane displacement; Averaged AVPD – averaged normalised AVPD measurements; MFS – Marfan syndrome; CF-PWV – carotid-femoral pulse wave velocity; SBP– systolic blood pressure; BSA – body surface area; Inferolateral AVPD – atrioventricular plane displacement in absolute values; AIx: augmentation index.

graphic, cardiovascular magnetic resonance, and invasive techniques.[3,4,11] Recent experimental studies on the MFS mouse model showed fragmentation of the elastic fibres and increased collagen deposition attributed to fibrillin-1 deficiency and associated excessive transforming growth factor-β bioactivity.[10]

With regard to the observed reduction in LV longitudinal systolic function in MFS, previous studies provided evidence for primary LV myocardial impairment. De Backer et al reported primary mild impairment of LV systolic and diastolic function in patients with MFS. Assessment for possible confounding factors showed that reduced LV function could not be caused by valvular or ischaemic heart disease and/or increased meridional wall stress.[5]

In addition, our centre recently demonstrated reduced LV longitudinal systolic function in a relatively large series of unoperated adults with MFS, which again could not be attributed to valvular or ischaemic disease.[27] In our previous study, an interesting factor in the meta-analysis results was a significant negative correlation between blood pressure measurements and left ventricular systolic function, although the blood pressure measurements showed no differences between the study groups. Similarly, the multiple regression analysis in the current study demonstrated a negative association between systolic blood pressure and averaged AVPD. Systolic blood pressure measurements in MFS usually lie within the low normal range, even in the absence of β-blockade (personal observations of Dr. Child). Thus, the data from the above studies suggested that systolic blood pressure values even at the lower limits of normal would constitute an increased afterload for the fibrillin-1 deficient LV myocardium. Perhaps, in order to protect the LV, it is important to maintain systolic blood pressure levels lower than the currently acceptable limits for the normal population, while avoiding side effects. A large, prospective study is needed to better investigate the effect of systolic blood pressure on LV performance in MFS.

Several scientific reports stressed that compromised arterial-ventricular coupling affects cardiovascular reserve function.[28,29] In their elegant study, Patrianakos et al demonstrated that increased proximal aortic stiffness is correlated with LV function and reduced exercise capacity in dilated cardiomyopathy.[30] As stated earlier, our findings have shown increased aortic stiffness and decreased LV longitudinal systolic function in patients with MFS. The multiple regression analyses revealed that the disease status plays an important role in causing primary LV systolic dysfunction. This analysis also showed a negative association between the carotid-femoral PWV and LV longitudinal systolic function. These findings suggest that LV systolic function could be further impaired when acting against a vascular system with increased impedance.

Multiple regression analysis also demonstrated that BSA was negatively associated with AVPD, as we had observed in an earlier study on LV function in MFS.[27] Studies by Wong et al and Peterson et al, examining obese subjects, have also shown similar findings, although they showed a negative effect on LV function from body mass index rather than BSA.[31, 32]

Another important finding in our series of studied subjects was that the central systolic pressure and pulse pressure showed no significant differences between the two groups. However, AIx was significantly higher in the patient group. We do not know whether the higher AIx was due to increased aortic stiffness or increased wave reflections. Perhaps the higher AIx can be explained by increased aortic stiffness in our patients.

A large-scale study is underway to evaluate the prognostic value of arterial stiffening indices in MFS.

Suggested pathogenesis of the disease

Fibrillin-1 is one of the major structural constituents of the 10 nm microfibrils that compose the cardiovascular connective tissue scaffold and endow it with long-range elastic recoil.[33] Calcium binding sites located on fibrillin-1 help protect the microfibrils from the proteolytic action of serine proteases and matrix metalloproteinases.[34] In addition, recent experimental work provides evidence that fibrillin-1 also plays an important role in regulating transforming growth factor-β (TGF-β) bioactivity and signalling.[35]

Therefore, the LV dysfunction and increased aortic stiffness observed in patients with MFS could be explained by extracellular matrix remodelling and an abnormal TGF-β biological pathway due to a fibrillin-1 deficient environment. However, evidence to demonstrate the effect of these pathophysiological mechanisms on the human Marfan myocardium has yet to be established.

Limitations

One potential limitation was that the number of suitable subjects within our total MFS patient population was limited for reasons of patient comfort. Muscu-

loskeletal abnormalities, such as scoliosis and lower back pain, were the main barriers, since patients had to lie still in a supine position for more than 30 minutes for the examination of CF-PWV and CR-PWV in addition to their preceding echocardiogram.

In addition, the lack of assessment of myocardial impairment by imaging techniques such as CMR and radionuclide imaging or angiography constitutes another limitation of our study. Likewise, although none of the study subjects had any history or symptoms of diabetes, chronic obstructive pulmonary disease, atherosclerosis or Graves' disease, laboratory tests for the listed conditions were not performed and hence these entities cannot be totally ruled out as other factors affecting myocardial function.

For all patients with MFS the diagnosis was established on the basis of the Ghent criteria.[13] There is an ongoing project to confirm this diagnosis with a full genotypic analysis. A genotype/phenotype correlation will be commented on as the subject of a future scientific work.

Conclusions

Our study showed reduced LV long-axis systolic function and increased arterial stiffness in patients with MFS. The efficiency of a fibrillin-1 deficient heart may be further reduced by ejection into a stiff vascular system. As carotid-femoral PWV is an easy-to-use bedside technique and is the gold-standard assessment of arterial stiffness, it should be incorporated into the monitoring of all MFS patients. Care should be taken to ensure that any treatment regimen addresses both increased arterial stiffness and myocardial dysfunction in MFS.

Acknowledgments

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