Early impairment of left ventricular long-axis systolic function demonstrated by reduced atrioventricular plane displacement in patients with Marfan syndrome†

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Introduction

Marfan syndrome (MFS) is an autosomal dominant disorder of fibrillin-1 deficiency which chiefly affects the ocular, musculoskeletal and cardiovascular systems.1 Recent research on the molecular physiology of fibrillins has advanced our understanding of transforming growth factor-β (TGF-β) and the role of fibrillins in the extracellular matrix.2 Fibrillin-1 is one of the major constituents of the 10–12 nm microfibrils, which compose the cardiac connective tissue scaffold and endow it with long-range elastic recoil.3 Mutations in the FBN1 gene may lead to loss of fibrillin-rich microfibrils in the cardiac extracellular matrix. Absence of sufficient microfibrils causes excessive activation of TGF-β which in turn induces phenotypic consequences in MFS.4 However, more information is needed about the way molecular mechanisms lead from a mutation in FBN1 gene to the clinical disease.

It has been reported in the literature that cardiac function remains preserved in MFS, with only a minority of patients presenting with some involvement of the left ventricle (LV).5 In contrast, De Backer et al.6 recently reported primary mild impairment of LV function in MFS unrelated to valvular heart disease, utilizing sensitive techniques such as magnetic resonance imaging and pulsed wave (PW) tissue Doppler imaging (TDI).

M-mode and TDI techniques have been shown to be sensitive tools in the assessment of atrioventricular plane displacement (AVPD) both in healthy individuals and in patients with cardiac disorders other than MFS.7–9 To date, no
study has determined AVPD utilizing M-mode, anatomical M-mode, and TDI (obtained from the lateral, septal, inferior, anterior, and posterior mitral annular portions) to quantify LV systolic function in patients with MFS. We therefore conducted a case-control study to comprehensively assess the LV systolic function in unoperated patients with MFS without significant valvular disease.

Methods
The study population consisted of 66 Caucasian patients between ages 15 and 58 years with an established diagnosis of MFS according to the Gent criteria. Sixty-one healthy Caucasian volunteers with normal electrocardiographic (ECG) and echocardiographic findings were also selected to form our control group. There were no statistical differences in age, sex, height, and weight between the two study groups.

Twenty-nine (44%) of the 66 MFS patients had previously been genotyped and were known to have causative FBN1 mutations confirming their diagnosis. All patients were recruited from three different tertiary cardiac centres specialist outpatient clinics for MFS. For ethical reasons, patients were allowed to continue all their regular medication including β-blockers. Patients with coronary heart disease, persistent arrhythmias, hypertension, diabetes mellitus, thyroid disorders, renal impairment, or any other significant medical conditions were excluded from the study. Normal volunteers were enrolled from the general population residing within our geographical area.

None of the study subjects had undergone cardiac surgery or aortic root/valve replacement or had more than mild valvular disease. All patients and normal volunteers underwent echocardiographic examination at rest in the left decubitus position using the Vivid 7 ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway) equipped with a 4S-MHz probe.

Standard views from parasternal and apical acoustic windows were obtained to acquire 2D, colour Doppler and colour tissue Doppler images. Frame rate of colour tissue Doppler images was optimized to 180 (±15) frames using the narrowest possible sector and the appropriate velocity scale to avoid any aliasing within images.

Three consecutive cardiac cycles from each view were recorded and stored in a cine-loop format with simultaneous ECG recording at a sweep speed of 100 mm/s. Digitally stored images were analysed offline using the widely accepted Echopac (6.0.0) software. All the measurements were averaged over three consecutive cardiac cycles.

The study was approved by the local ethics committee of St George’s Hospital. All participants gave written informed consent before enrolment in the study.

Assessment of LV systolic function
Left ventricular end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD) were derived from conventional 2D and M-mode or anatomical M-mode in subjects with off-axis 2D images. Values for LVEDD and LVESD were corrected for each individual according to their age and body surface area (BSA) using Henry’s regression equations. The measured LVEDD and LVESD were expressed as percentage of the predicted value according to the formula:

\[
\text{Percentage of predicted LV dimension} = \frac{\text{observed dimension/predicted normal dimension}}{100} \times (1 - \frac{1}{\text{BSA}^{0.3}}) - \frac{\text{age}}{10} - 7.2
\]

Predicted normal LVEDD = (45.3 × BSA0.3) − (0.03 × age) − 7.2, and predicted normal LVESD = (28.8 × BSA0.3) − (0.03 × age) − 4.1.

Dilated cardiomyopathy was defined as percentage of predicted LVEDD ≥ 112% and fractional shortening (FS) < 25%; LV enlargement was defined as percentage of predicted LVEDD ≥ 112% and FS ≥ 25%; and normal was defined as percentage of predicted LVEDD < 112% and FS ≥ 25%. Fractional shortening was calculated using the formula (100 × (LVEDD − LVESD)/LVEDD). Ejection fraction (EF) was calculated by Simpson’s biplane method using standard apical four- and two-chamber views. Left ventricular end-diastolic and systolic volumes (LVEDV and LVESV) were measured by tracking the endocardial border during diastolic and systolic phases of the cardiac cycle.

Left ventricle wall thickness was measured using M-mode in the standard parasternal long-axis view (septal and posterior wall) and 2D images in short-axis views (basal, mid, and apical levels). Left ventricular mass was calculated as per the recommendations in the combined ASE/ESC guidelines. Hypertrophy was diagnosed if LV mass (g)/BSA (m2) ratio was >88 for women and >102 for men. Meridional end-systolic stress (ESS) was calculated according to the formula: ESS = 0.334 × SBP × LVIDs/PWTs × (1 + (PWTs/LVIDs))1, where LVIDs and PWTs are LV internal dimension and posterior wall thickness at end-systole, respectively. The systolic blood pressure (SBP) was measured at the end of echocardiographic record.

Evaluation of AVPD
Standard M-mode
2D-targeted M-mode beam was directed from the apex along the hinge points of the mitral valve apparatus and lateral, septal, inferior, anterior, and posterior LV walls in four-, two- and three-chamber views. The regional displacement was calculated after 60 ms from the beginning of the QRS complex to the first peak of the mitral annular waveform, these points corresponding to mitral and aortic valve closure respectively.

To normalize AVPD measurements, the longitudinal LV inner distance was measured from the apical endocardial border to the atrioventricular plane at the end of diastole. The endocardial border was chosen for measurements since the epicardial contour is not always clearly seen. AVPD values obtained from the lateral-septal and inferior-anterior mitral annular regions were normalized by dividing these values by the LV longitudinal inner diameters obtained from the four- and two-chamber views respectively. Normalization of the posterior wall displacement was omitted because it is not always possible to clearly visualize the LV apex in the three-chamber view and the plane of long axis in this view is generally oblique.

Anatomical and colour anatomical M-mode
Anatomical M-mode was used to overcome limitations with regards to parallel alignment of the M-mode beam to the cardiac walls. Colour tissue Doppler M-mode was used as an additional method to assess the amplitude of AVPD as this technique ensures high spatial and temporal resolutions.

Systolic velocities of the mitral annulus
Mitrail annular longitudinal velocities were recorded using PW mode by positioning the Doppler cursor with a 5 mm sample volume at the lateral, septal, inferior, anterior, and posterior atrioventricular margins in LV TDI apical images. Care was taken to ensure that the ultrasound beam was kept parallel to the mitral annular motion. The filters and gains were set low in accordance with the recommendations for quantification of Doppler echocardiography. Peak systolic velocity was measured avoiding the initial peak that is observed during isovolumic contraction time.

Assessment of aortic root size, motion and aortic stiffness
Aortic root size was measured in accordance with the combined ASE/ESC guidelines. Aortic valve and root motion were assessed using the M-mode technique that has been described in previous studies. Aortic stiffness was determined from the changes of the aortic diameters from systole to diastole, and changes of the
arterial pressure using the formula: Stiffness index = \log \frac{(systolic blood pressure)/(diastolic blood pressure)}{(changes aortic diameter)/(diastolic aortic diameter)}.^20\)

**Reproducibility of AVPD measurements**

The reproducibility of AVPD measurements was assessed in 28 randomly selected study patients and normal controls. These measurements were blindly performed 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 of the same study groups. Statistical analysis of reproducibility of methods was based on comparisons of the absolute values of relative errors using Mann-Whitney test. \(P\)-value < 0.05 was considered statistically significant.

**Statistical analysis**

Continuous variables were summarized as means ± standard deviation (SD). To test for the hypothesis of normality, the Shapiro-Wilk test was used. Differences in continuous variables between patients with MFS and normal volunteers were investigated using a \(t\)-test for independent samples or Mann-Whitney test when appropriate. Categorical variables were expressed as absolute numbers and percentages. The statistical test in these cases was the \(x^2\)-test.

For each wall (lateral, septal, inferior, anterior, posterior) and each method (M-mode, anatomical M-mode and colour anatomical M-mode), the displacement was tested using multiple regression analysis to detect differences between patients with MFS and normal controls, being adjusted for age, sex, heart rate (HR), SBP, BSA, and aortic root size. Age, sex, \(5\) and HR are known confounders, and therefore all analyses were adjusted for these variables. SBP, BSA and aortic root size were identified as other possible confounders after using multiple regression models keeping the variables of MFS diagnosis, age, sex, and HR constant in all models. LVEDV (as an indicator of LV preload), \(\beta\)-stiffness, beta-blockade and myocardial thickness were also assessed to explore the possible impact of other confounders on LV long-axis systolic function.

In our study, we used three different M-mode techniques to assess mitral motion obtained from five annular regions. Hence, to detect the overall effect of different variables, meta-analysis was performed. The estimates from the posterior wall were not included in the meta-analysis because the displacement was not normalized. \(P\)-values less than 0.05 were considered significant. The statistical analysis was performed using STATA.24

**Results**

**Baseline characteristics**

The baseline characteristics of the study subjects are listed in Table 1.

Heart rate was slower in patients with MFS compared to normal controls \((P < 0.01)\). No differences were found between both groups in any of the remaining clinical parameters.

**Conventional echocardiographic measurements**

The conventional echocardiographic parameters are listed in Table 2.

**LV size, thickness, and function**

With regards to conventional echocardiographic measurements (Table 2), LVEDD and LVESD were not significantly different between the patients and normal volunteers.

However, after correcting for age and BSA, the LV end diastolic diameters expressed as percentage of the predicted value were significantly higher in patients with MFS in comparison to normal controls. There were also statistically significant differences in LVEDV and LVESV measurements between the study groups.

Eleven patients with MFS (17%) had LV enlargement in the absence of significant valvular disease as compared to normal volunteers. None of the patients however fulfilled the criteria for dilated cardiomyopathy.

Twenty-two (33%) out of 66 MFS patients met the criteria for LV hypertrophy (LVH). Of these, 20% \((n = 13)\) had mild, 9% \((n = 6)\) moderate and 5% \((n = 3)\) severe LVH as categorized using conventional criteria.

Ejection fraction evaluated by biplane Simpson’s method was found significantly reduced in MFS (mean 66.33 ± 5.98 vs. 71.85 ± 4.38%, \(P < 0.001)\), although it was within the normal range. FS was comparable between the study groups.

**AVPD**

Table 3 illustrates the AVPD measurements assessed by M-mode, anatomical M-mode and colour anatomical M-mode techniques. Normalized lateral, septal, inferior and anterior AVPD and absolute values obtained from the posterior side of the mitral annulus were significantly reduced in MFS \((P < 0.001, in all wall regions)\).

In a multiple regression analysis including age, sex, HR, BSA, SBP and aortic root size the diagnosis of MFS correlated strongly with reduced AVPD \((P < 0.001)\). Moreover, the effect of SBP, BSA and HR on AVPD measurements was consistently negative. The aortic root size also showed a statistically negative association with reduced AVPD obtained from the septum \((P < 0.004, in all M-mode methods)\), (Figure 1). LVEDV, \(\beta\)-stiffness, \(\beta\)-blockade and myocardial thickness had no significant impact on AVPD measurements.

Meta-analysis of the results showed that MFS patients had reduced AVPD as compared to normal volunteers, (95% confidence interval \((-0.046, -0.039)\), \(P < 0.001)\). Meta-analysis also demonstrated that SBP and BSA were negatively correlated to AVPD \((P < 0.001, for all variables)\), while the aortic root had a negative association only to AVPD obtained from the septum \((P < 0.001)\).

**Intra- and inter-observer variability**

The mean intra- and inter-observer variability was less than 5% for all AVPD measurements, as shown in Table 4.

**Systolic TDI velocities of the mitral annulus**

Peak systolic velocities obtained from lateral, septal, inferior, anterior, and posterior sites of the mitral annulus by TDI were significantly reduced in patients with MFS as compared with normal volunteers \((P < 0.001)\).

**Aortic root size and motion**

The aortic root size at the sinuses of Valsalva level was increased in patients with MFS \((P < 0.001)\). After adjusting for BSA, aortic root diameter remained significantly higher in MFS patients \((P < 0.001)\) as compared with normal subjects. MFS patients with dilated aortic root exhibited backward motion of the posterior aortic wall during early systole.
Table 1 Baseline characteristics for MFS patients and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>MFS (n = 66)</th>
<th>Controls (n = 61)</th>
<th>P-value (MFS vs. Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male/Female)</td>
<td>37/29</td>
<td>27/34</td>
<td>0.184^a</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31 ± 13</td>
<td>30 ± 7</td>
<td>0.680^b</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.8 ± 13.5</td>
<td>78.2 ± 14.6</td>
<td>0.382^b</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>186 ± 10</td>
<td>184 ± 9</td>
<td>0.246</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>56.41 ± 8.66</td>
<td>60.41 ± 9.5</td>
<td>0.014</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.97 ± 0.21</td>
<td>1.99 ± 0.22</td>
<td>0.583</td>
</tr>
<tr>
<td>β-blockers (Atenolol)</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114.94 ± 11.38</td>
<td>114.34 ± 7.6</td>
<td>0.732</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74.79 ± 7.82</td>
<td>74.36 ± 6.2</td>
<td>0.735</td>
</tr>
</tbody>
</table>

DBP, Diastolic blood pressure.
Results are presented as Mean ± SD.
^aχ²-test.
^bMann–Whitney test.

Table 2 Conventional echocardiographic measurements in patients with MFS and controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MFS (n = 66)</th>
<th>Controls (n = 61)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (cm)</td>
<td>4.95 ± 0.52</td>
<td>4.81 ± 0.41</td>
<td>0.09</td>
</tr>
<tr>
<td>Predicted</td>
<td>4.84 ± 0.19</td>
<td>4.87 ± 0.20</td>
<td>0.5</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>102.23 ± 9.41</td>
<td>98.76 ± 6.80</td>
<td>0.02</td>
</tr>
<tr>
<td>Predicted</td>
<td>3.15 ± 0.48</td>
<td>3.07 ± 0.36</td>
<td>0.3</td>
</tr>
<tr>
<td>LVEDS (cm)</td>
<td>3.09 ± 0.13</td>
<td>3.11 ± 0.13</td>
<td>0.4</td>
</tr>
<tr>
<td>Predicted</td>
<td>101.63 ± 14.3</td>
<td>98.51 ± 10.4</td>
<td>0.2</td>
</tr>
<tr>
<td>EF (%)</td>
<td>66.33 ± 5.98</td>
<td>71.85 ± 4.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FS (%)</td>
<td>38.30 ± 5.55</td>
<td>38.98 ± 4.96</td>
<td>0.4</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>89.98 ± 21.94</td>
<td>80.67 ± 20.79</td>
<td>0.02</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>30.66 ± 10.71</td>
<td>22.57 ± 7.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Meridional wall stress (mmHg)</td>
<td>56.85 ± 15.56</td>
<td>53.30 ± 13.14</td>
<td>0.2</td>
</tr>
<tr>
<td>Basal anterior septal thickness (cm)</td>
<td>1.02 ± 0.17</td>
<td>0.95 ± 0.08</td>
<td>0.002</td>
</tr>
<tr>
<td>Basal posterior septal thickness (cm)</td>
<td>0.99 ± 0.15</td>
<td>0.92 ± 0.07</td>
<td>0.001</td>
</tr>
<tr>
<td>Basal inferior wall thickness (cm)</td>
<td>0.94 ± 0.09</td>
<td>0.91 ± 0.07</td>
<td>0.1</td>
</tr>
<tr>
<td>LV mass/BSA (g/m²)</td>
<td>89.71 ± 18.5</td>
<td>78.78 ± 11.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative LV thickness</td>
<td>0.38 ± 0.05</td>
<td>0.38 ± 0.04</td>
<td>0.9</td>
</tr>
<tr>
<td>Aortic root diameter (cm)</td>
<td>4.02 ± 0.58</td>
<td>3.06 ± 0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic root diameter/BSA (cm²/m²)</td>
<td>2.06 ± 0.35</td>
<td>1.55 ± 0.15</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results are presented as Mean ± SD.

Discussion

To our knowledge, this is the first study to reveal findings of reduced LV long-axis systolic function in MFS. This study demonstrates significantly decreased LV long-axis systolic function in patients with MFS, using M-mode, anatomical M-mode, colour anatomical M-mode echocardiography and PW TDI. Our results show that all three methods of M-mode imaging used for AVPD assessment are comparable to each other.

Several studies have shown that M-mode echocardiography constitutes an established method to evaluate AVPD.
which is often utilized to express LV systolic function. AVPD may also predict mortality in patients with coronary heart disease and provide prognostic information in patients with non-ischemic heart disease.

In the last decade, significant progress in analysis of FBN1 mutant mice lines has elucidated the role of fibrillin-1 in MFS pathogenesis. Light and electron microscopic studies of human and rodent myocyte samples have shown that fibrillin-1 is an important glycoprotein component of microfibrils. Microfibrils form fibrous connections between myofibers and collagen and are orientated in the long axis of the cardiac muscle cells. These observations suggest that spatial arrangements of microfibrils play an important role in transmitting forces from myocytes to the extracellular connective tissue framework. Thus, the reduced ventricular long-axis function which was found in our patients

Figure 1  Meta-analysis showing effect of different clinical characteristics on AVPD measurements in MFS patients and Control group. (A) Reduced AVPD in MFS as compared with Controls. (B) Reduced septal AVPD in MFS patients with aortic root dilatation. (C) Negative effect of SBP on AVPD in both groups. (D) Negative effect of BSA on AVPD in both groups.
could be attributed to weak myofibre-collagen fibre linkages caused by deficiency of fibrillin-1 in the extracellular matrix of the myocardium.

Abnormal microfibrils also lead to inappropriate activation of TGF-β with deleterious consequences on tissue remodeling and cellular performance in MFS. TGF-β induced transcriptional responses in cardiovascular and myoskeletal systems result in myxomatous changes of the mitral valve, aortic aneurysm formation and skeletal muscle hypoplasia with impaired muscle regeneration. Dietz et al. found reduced preload in the mouse model correlated with increased TGF-β signalling (personal communication). It is likely that in patients with MFS similar mechanisms operate within the myocardium leading to progressive loss of contractile function (Figure 3). However, there are no studies at present to assess the impact of excessive TGF-β signalling on human myocardial function.

Valvular dysfunction, which is commonly seen in MFS patients, is also known to affect LV systolic function. However, none of our patients had clinically significant valvular regurgitation.

It is well known from the literature that long-axis function is partly dependent on the subendocardial fibres which are highly susceptible to ischaemia. Allwork et al. showed that children with MFS had smaller diameter of coronary arteries, but it is unclear what impact this may have on myocardial perfusion. With regards to the incidence of ischemia in MFS, there are only a few case reports of coronary artery aneurysms, postoperative coronary artery spasm complicating aortic valve replacement and acute coronary syndromes associated with aortic dissection. Reduced long-axis function in our study is unlikely to be the result of ischaemia as none of the patients had clinical or ECG findings suggestive of reduced myocardial perfusion. However, since there was no indication to justify specific investigations, such as diagnostic coronary angiography, asymptomatic coronary artery disease cannot be ruled out in our patients.
Additionally, our data revealed that longitudinal (meridional) wall stress measurements were similar between the study groups. This may suggest that LV dysfunction in MFS is caused by impaired contractility rather than increased wall stress. Moreover, the SBP did not show any significant difference in either group. However, meta-analysis of our results showed that SBP had a significant negative relationship with the LV long-axis systolic function. SBP in MFS tends to be in the low normal range, but this data suggests that it is important to maintain levels lower than the currently acceptable limits for the normal population, while avoiding side effects.

It is well known that increased after load resulting from raised SBP leads to concentric hypertrophy. Verdecchia et al.\textsuperscript{35} on the other hand, demonstrated asymmetrical LV remodelling due to isolated septal thickening in patients with systemic hypertension. In our series, twenty-two of our MFS patients (33%) showed asymmetrical LVH despite normal blood pressure. There is paucity of data in the literature about interventricular septal hypertrophy in patients with MFS. Fujiseki et al.\textsuperscript{36} reported increased thickness and interstitial fibrosis in stained biopsy specimens of the septum which showed defective organization of collagen into fibrils, but no true hypertrophy of the cardiac myocytes. Thus, asymmetric LVH seen in our patients could be attributed to the same mechanism of defective fibre organization. On the other hand, it is likely that even normal levels of blood pressure play an important role in causing a true form of LVH, similar to that seen in patients with systemic hypertension. Further studies are needed to elucidate the effect of blood pressure on the myocardial structure in MFS.

In addition to SBP, meta-analysis of AVPD measurements showed that increased aortic root size was correlated with pronounced decrease of the septal displacement. Atsushi et al.\textsuperscript{37} reported a paradoxical (backward) motion of the posterior aortic wall and aortic valve in MFS patients with dilated aortic root which is similar to our findings. Since the aortic valve is in close relationship with the interventricular septum,\textsuperscript{38} paradoxical motion of the posterior aortic wall could probably explain a greater reduction in septal displacement in cases associated with dilated aortic root (Figure 2). BSA and HR also appear to significantly affect the AVPD measurements in contrast to other factors such as age, sex and β-blockade which had no effect.

Eleven patients (17%) showed dilatation of the LV cavity, though none of these fulfilled the criteria for dilated cardiomyopathy. This data is consistent with findings by Meijboom.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{AVPD obtained from the septal mitral annular region of a normal subject and MFS patient showing significantly reduced long-axis systolic displacement.}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
LV sites & Method & MFS (n = 44) no β-blockers & MFS (n = 22) β-blockers & P-value \\
\hline
Lateral & M-mode (R) & 0.17 ± 0.004 & 0.17 ± 0.006 & 0.71 \\
 & AM-mode (R) & 0.16 ± 0.004 & 0.17 ± 0.006 & 0.17 \\
 & CAM-mode (R) & 0.17 ± 0.005 & 0.17 ± 0.007 & 0.43 \\
 & TDI m/s & 0.13 ± 0.004 & 0.11 ± 0.007 & 0.04 \\
 & M-mode (R) & 0.13 ± 0.005 & 0.14 ± 0.006 & 0.23 \\
 & AM-mode (R) & 0.13 ± 0.005 & 0.14 ± 0.005 & 0.36 \\
Septum & CAM-mode (R) & 0.14 ± 0.004 & 0.14 ± 0.005 & 0.73 \\
 & TDI m/s & 0.09 ± 0.003 & 0.09 ± 0.004 & 0.19 \\
 & M-mode (R) & 0.15 ± 0.004 & 0.17 ± 0.006 & 0.02 \\
 & AM-mode (R) & 0.16 ± 0.004 & 0.17 ± 0.007 & 0.29 \\
Inferior & CAM-mode (R) & 0.16 ± 0.004 & 0.17 ± 0.005 & 0.15 \\
 & TDI m/s & 0.11 ± 0.004 & 0.10 ± 0.004 & 0.11 \\
 & M-mode (R) & 0.15 ± 0.004 & 0.16 ± 0.006 & 0.23 \\
 & AM-mode (R) & 0.15 ± 0.004 & 0.16 ± 0.006 & 0.14 \\
Anterior & CAM-mode (R) & 0.15 ± 0.005 & 0.16 ± 0.006 & 0.24 \\
 & TDI m/s & 0.12 ± 0.004 & 0.10 ± 0.006 & 0.03 \\
 & M-mode cm & 1.39 ± 0.040 & 1.37 ± 0.050 & 0.81 \\
 & AM-mode cm & 1.39 ± 0.040 & 1.44 ± 0.060 & 0.45 \\
Posterior & CAM-mode cm & 1.45 ± 0.050 & 1.44 ± 0.060 & 0.87 \\
 & TDI m/s & 0.13 ± 0.005 & 0.11 ± 0.005 & 0.04 \\
\hline
\end{tabular}
\caption{Left ventricular AVPD measurements for Marfan patients not on therapy vs. on β-blocker therapy}
\end{table}

R, ratio of AVPD to LV end diastolic inner distance; AM-mode, anatomical M-mode; CAM-mode, colour anatomical M-mode.

Results are presented as Mean ± SE.
et al., who studied LV dimensions and systolic function in 234 patients with MFS without significant valvular disease. With regards to LV systolic function in MFS, De Backer et al.4 found mild impairment of LV contractile function (EF = 53.5 ± 9.0%). Our findings also revealed reduced EF, which though within the normal range, was significantly lower in comparison to the control group. This could have important clinical implications during situations of increased myocardial demand, such as febrile illnesses, arrhythmias or stress in peri-operative period, which may lead to rapid decompensation of the fibrillin-1 deficient myocardium.

Limitations

It is well acknowledged that M-mode is the most frequently used method to assess AVPD.Nevertheless, this measurement only estimates the total longitudinal displacement of a given ventricular wall and does not, per se, identify any segmental abnormalities. Studies involving strain rate imaging may provide additional insights into the spatial distribution of systolic abnormalities seen in MFS.

In our study, 29 (44%) out of 66 patients had a known causative FBN1 mutation confirming their diagnosis. This number was insufficient to demonstrate association of any particular type or location of mutations with impaired LV long-axis systolic function. Eventually all patients will be genotyped, but those in whom the clinical diagnosis required confirmation or whose families required mutation screening, were prioritized for this time-consuming test. Genotypic identification of all our MFS patients would allow potential correlation of the FBN1 mutations to LV systolic function.

Another possible limitation was the continuation of β-blocker therapy for 22 (33%) of the 66 MFS patients during the study. There was no evidence of significant differences in AVPD measurements between MFS patients on β-blockers vs. those not on β-blockers (see Table 5). There were some statistical differences in TDI measurements obtained from the lateral, anterior and posterior walls (P = 0.05). However, statistical analysis between normal controls and 44 (67%) MFS patients not on β-blockers showed significant differences in all AVPD and TDI measurements (P < 0.001).

Conclusions

Our study demonstrated that LV long-axis systolic function is reduced in MFS. Our observations suggest that AVPD assessment by 2D-targeted M-mode echocardiography is a useful tool in providing information about LV systolic function in MFS. These findings should prove useful in diagnosis, prognosis and optimum management of MFS patients. Treatment may need to be tailored to prevent further deterioration by supporting LV systolic function.

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