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Tissue Doppler Imaging Identifies Myocardial Dysfunction in Adults with Marfan Syndrome

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Summary

Background: Successful prevention of aortic complications has lead to improved survival of Marfan syndrome (MFS). With increasing age, however, ventricular arrhythmia and heart failure are emerging as life-threatening manifestations of myocardial dysfunction.

Hypothesis: We sought to investigate whether echocardiography with tissue Doppler imaging (TDI) identifies myocardial dysfunction in adults with MFS.

Methods: We performed two-dimensional (2-D) and Doppler echocardiography with TDI in 141 individuals with suspected MFS and competent heart valves, including 28 persons with MFS who had not undergone surgery and 86 healthy controls without inherited connective tissue disorders.

Results: Demographic profile, 2-D, mitral and pulmonary venous flow indices, and left ventricular ejection fractions were similar in both groups. Conversely, isovolumic relaxation time ($p < 0.001$) and deceleration time of E velocity ($p = 0.005$) were longer, and atrial reversal velocities ($p = 0.02$), and systolic and early diastolic TD velocities were slower in MFS than in controls ($p < 0.01$). Multiple linear regression analysis excluded association of reduced systolic and early diastolic TD velocities with mitral valve prolapse or other clinical or echocardiographic features of MFS.

Conclusions: Our study identifies reduced systolic and early diastolic TD velocities in adults with MFS. Further studies are mandatory to elucidate whether TD velocities predict arrhythmia and heart failure in MFS.

Key words: Marfan syndrome, cardiomyopathy, genetics, systole, diastole

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Introduction

The Marfan syndrome (MFS) is an autosomal dominant disorder of the connective tissue that is caused by mutations in the fibrillin-1 gene (FBN1). Advances in the medical and surgical management of aortic complications increased average life-expectancy from 32 years to over 50 years.[1] However, longer survival reveals new manifestations, among which dysfunction of the myocardium is most life threatening.[2] Previous studies suggest primary heart muscle disease. For instance, *FBN1* is expressed in the myocardial cytoskeleton, and an animal model with abnormal *FBN1* exhibits hypertrophic cardiomyopathy.[3] Moreover, patients with MFS exhibit abnormal chordae tendinae,[4] left ventricular (LV) dilatation,[5] intraventricular conduction delay,[6] and increased prevalence of Wolff-Parkinson-White syndrome.[7–9] To assess systolic and diastolic LV performance, we conducted a controlled prospective study of

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adults with MFS and normal heart values using two-dimensional (2-D), Doppler, and tissue Doppler imaging (TDI).

Methods

Study Design

We evaluated 232 consecutive nonrelated adults with suspected MFS for presence of manifestations listed in the Ghent nosology.[10] We included patients in the case group, with (1) MFS established by the Ghent criteria, (2) presence of functionally intact heart valves with no or at most hemodynamically irrelevant mitral valve regurgitation, and (3) without previous cardiovascular surgery or intervention except for isolated replacement of the aortic root. Many subjects referred with clinical suspicion of MFS did not have MFS or any other disorder; thus we assigned patients to the control group with (1) exclusion of MFS; (2) absence of other inherited connective tissue diseases as listed in the Ghent nosology;[10] (3) absence of any previous cardiovascular surgery or intervention; (4) presence of functionally and morphologically intact heart valves with no or at most hemodynamically irrelevant mitral valve regurgitation; and (5) with normal physical examinations including systolic and diastolic blood pressures, electrocardiograms, and echocardiograms. We did not use TDI or Doppler indices as criteria for enrollment in this study. Most patients assigned to the control group exhibited a mild degree of a single minor manifestation listed in the Ghent nosology; this was tall body size or a mild degree of joint hypermobility, or mild pectus deformity, or mild scoliosis as an isolated skeletal manifestation (46 patients) or a mild degree of myopia as an isolated ocular anomaly (15 patients), or an isolated family history of sudden unexplained death (10 patients). All patients fulfilling criteria for inclusion were invited to a blinded 2-D, Doppler, and TDI study using an imaging protocol that was employed in a study that established myocardial dysfunction in mutation-positive, presymptomatic patients with familial hypertrophic cardiomyopathy.[11]

Patients

Of the 232 patients assessed for suspected MFS, 91 did not participate in the study, because they did not fulfill inclusion criteria in 86 cases, and because they refused to participate or did not appear for echocardiography in 5 cases. The remaining 141 patients constituted our study group that comprised 73 men and 68 women at a mean age of 39 ± 13 years. Of these, 86 patients were assigned to the control group, whereas the other 55 patients had classical MFS, either without any cardiovascular surgery (28 cases), or with isolated replacement of

TABLE 1 Patient characteristics

Variable	Controls (n = 86)	Marfan		ANOVA P Value
		No surgery (n = 28)	Post surgery (n = 27)	
Age, years	38 ± 12	40 ± 14	43 ± 14	0.07
Men, n, (%)	45 (52)	12 (43)	16 (59)	0.5
Heart rate, beats/min	72 ± 12	72 ± 13	69 ± 8	0.5
Systolic blood pressure, mmHg	120 ± 15	118 ± 12	117 ± 10	0.6
Diastolic blood pressure, mmHg	73 ± 11	70 ± 13	71 ± 8	0.2
BMI, kg/m^2	20.7 ± 2.8	21.5 ± 2.3	22 ± 2.5	0.1
BSA, m^2	1.91 ± 0.23	2.02 ± 0.26	2.02 ± 0.19	0.06
LVEDD/BSA, mm/m^2	25.8 ± 2.6	25.6 ± 3.3	27 ± 2.5	0.2
LVESD/BSA, mm/m^2	15.6 ± 2.3	16 ± 2.9	16.9 ± 2.9	0.2
LVEF, %	67 ± 5	69 ± 6	67 ± 4	0.8
Septal thickness/BSA, mm/m^2	4.6 ± 0.9	4.4 ± 0.7	5 ± 0.9	0.06
Posterior wall thickness/BSA, mm/m^2	4.3 ± 0.9	3.9 ± 0.8	4.6 ± 0.9	0.08
LA diameter/BSA, mm/m^2	17.5 ± 2.5	15.6 ± 4.1	20.5 ± 2.7	<0.001[a]
LV mass/BSA, g/m^2	79 ± 3	86 ± 3	146 ± 12	<0.001[b]
Aortic ratio	1.0 ± 0.09	1.1 ± 0.08	0.9 ± 0.12	<0.001[c]
MVP, n (%)	—	14 (50)	11 (41)	<0.001[d]

Bonferroni test:
[a] B vs. controls $p = 0.001$, and vs. A $p < 0.001$.
[b] B vs. controls $p = 0.001$, and vs. A $p = 0.01$.
[c] A vs. the other two groups $p < 0.001$;
[d] controls vs. A and B $p < 0.001$ (Freeman-Halton test with the Bonferroni correction).
Abbreviations: ANOVA = analysis of variance BMI = body mass index, BSA = body surface area, LV = left ventricular, EDD = end-diastolic diameter, ESD = end-systolic diameter, LA = left atrial, postsurgery, previous aortic root replacement.

the aortic root (27 cases). Aortic root replacement had been performed as a composite graft procedure with a mechanical valve in 18 subjects, as a David procedure in 7 subjects, and as a Yacoub procedure in 2 subjects.[12] The average age at surgery was 34 years, and all patients had surgery at least 5 years before inclusion in the study. No patient was on beta blockers, calcium antagonists, or angiotensin-converting enzyme inhibitors since at least 1 week before echocardiography (Table 1).

Echocardiography

All patients were imaged and all data were assessed blinded to clinical information and final diagnoses, and all measurements were averaged over five cardiac cycles. Wall thickness, left ventricular (LV) end-diastolic diameter, LV end-systolic diameter, left atrial diameter, LV ejection fraction, LV mass, and classic mitral valve prolapse (MVP) were assessed on 2-D images.[13,14] We adjusted for differences in body size by dividing LV diameters, wall thickness and LV mass by body surface area (BSA).[15] We computed aortic ratios to assess presence of aortic root dilatation.[16] Peak early (E) and late (A) transmitral filling velocities, E/A ratio, and deceleration time of E velocity (DT), atrial filling fraction, and isovolumic relaxation time (IVRT) were determined from mitral inflow velocities. We assessed peak, duration, and time-velocity integrals of pulmonary venous flow velocities and computed pulmonary venous flow systolic filling fraction as the systolic/total forward time-velocity integral. The difference between the duration of atrial reversal and the transmitral A wave was assessed as the atrial reversal minus mitral A duration. We applied TDI for spectral display of mitral annulus velocities at septal and lateral corners to measure systolic (Sa), early diastolic (Ea), and late diastolic (Aa) velocities and to compute Ea/Aa and E/Ea ratios.[11]

Statistical Analysis

We used analysis of variance (ANOVA) to compare variables across patient groups; with this global test significant at $p < 0.05$, we performed the Bonferroni *t* test for post hoc multiple comparisons. To identify potential confounders of LV performance, we conducted a multiple linear regression analysis with indices of diastolic function and TDI values as dependent variables and normalized left atrial diameters, normalized LV mass, MVP, surgery of the aortic root, and presence of MFS as independent variables; $p < 0.05$ was considered significant. All data were presented as the mean value $\pm$ standard deviation (SD) or frequencies. We used SPSS software (Statistical Package for Social Sciences for Windows, Release 10.0.7, SPSS Inc. 1989 to 1999, Chicago, Ill.) for statistical analysis.

Results

All study patients had 2-D, Doppler, and TDI studies satisfactory for analysis. Mean age, gender, heart rate, systolic and diastolic blood pressures, body mass index, BSA, LV ejection fraction, and normalized values of LV end-diastolic diameters, LV end-systolic diameters, and septal and posterior wall thicknesses were similar in all groups. Conversely, normalized left atrial diameters and LV mass were larger in MFS after aortic root replacement than in the other groups, and the aortic ratio was larger in MFS without any surgery than in the other groups (Table 1).

Patients with MFS had longer IVRT and longer DT than controls. Similarly, the atrial and systolic filling fractions tended to be increased, and atrial reversal velocity was mildly prolonged in MFS. Other Doppler measurements including peak E and peak A transmitral filling velocities, and E/A ratios were similar in all groups (Table 2). Both MFS groups had reduced Sa and Ea velocities but similar Aa velocities at both corners of the mitral annulus compared with controls. Accordingly, in both MFS groups the Ea/Aa ratio was lower and the E/Ea ratio higher at both corners of the mitral annulus than in controls (Table 3, Fig. 1). Multiple linear regression analysis established an independent influence of MFS on lateral Sa (standardized coefficient $ß = -0.406$; $p = 0.012$), lateral Ea ($ß = -0.502$; $p = 0.003$), septal Sa ($ß = -0.714$; $p < 0.001$), septal Ea ($ß = -0.325$; $p = 0.035$), IVRT ($ß = 0.757$; $p < 0.001$), and DT ($ß = 0.35$; $p = 0.04$), excluding an impact of left atrial diameter, LV mass, MVP, and aortic surgery.

Discussion

Our study identifies abnormal TDI contraction and relaxation velocities in adults with MFS. These abnormalities are present despite competent heart valves and are not related to diameters of the left atrium, LV mass, MVP, or previous aortic root replacement. It is interesting that the decrease of TDI velocities was similar in MFS irrespective of previous aortic root replacement. This may be due to timing of surgery already at aortic root diameters $\geq$50 mm (45 mm in high-risk patients), preventing myocardial dysfunction related to aortic valve regurgitation.[9]

Tissue Doppler imaging has not been used previously to scrutinize LV performance in MFS, and diastolic Doppler parameters were obtained only in children[15] and in a heterogeneous group of younger adults with MFS or mitral aortic skin skeletal (MASS) phenotype.[17] These Doppler studies, however, corroborate a normal LV ejection fraction with prolonged IVRT[17] and DT[15] and document presence of impaired LV relaxation in MFS.[18] Our TDI studies further establish an impaired early diastolic function and document reduced systolic

contraction velocities. Of interest, reduced systolic TDI velocities were shown to predict LV dysfunction in mutation-positive subjects with presymptomatic familial hypertrophic cardiomyopathy.[11,19]

Mutations in MFS affect proteins of the myocardial cytoskeleton and extracellular matrix, whereas mutations in familial hypertrophic cardiomyopathy involve different sarcomeric proteins. Left ventricular endomyocardial biopsies are unavailable in both diseases, and thus molecular mechanisms of TDI-defined myocardial dysfunction remain speculative.[11,19] Savolainen *et al*. presume that in MFS weakened elastic recoil caused impaired LV relaxation.[15,20] Moreover, an increased prevalence of Wolff-Parkinson-White syndrome,[7–9] QT-prolongation,[6,7] abnormal chordae tendinae,[4] eccentric LV dilatation,[5] and intraventricular conduction delay[6] indicate a role of fibrillin-1 during myocardial development.[21] Alteration of transforming growth factors (TGF-ß) causes mitral valve prolapse[22] in mouse models of MFS and may also cause myocardial dysfunction.

Study Limitations

We did not use Doppler or TDI to assess systolic or diastolic performance of the right ventricle; however, 2-D measurements including diameters and systolic contractions were normal in all patients.

TABLE 2 Doppler echocardiography

Variable	Controls (n = 86)	Marfan		ANOVA p Value
		No surgery (n = 28)	Post surgery (n = 27)	
Peak E velocity, cm/s	85 ± 17	85 ± 18	92 ± 20	0.3
Peak A velocity, cm/s	56 ± 16	58 ± 20	56 ± 15	0.8
E/A ratio	1.6 ± 0.4	1.6 ± 0.6	1.8 ± 0.7	0.3
IVRT, ms	76 ± 11	106 ± 19	95 ± 14	<0.001[a]
DT, ms	162 ± 38	183 ± 41	182 ± 52	0.02[b]
AFF	0.25 ± 0.05	0.28 ± 0.05	0.27 ± 0.06	0.08
Ar velocity, cm/s	27 ± 6	31 ± 5	30 ± 8	0.05
SFF	0.36 ± 0.05	0.39 ± 0.08	0.38 ± 0.08	0.05
Ar-A duration, ms	4 ± 16	9 ± 11	12 ± 18	0.09

Bonferroni test:
[a] Controls vs. the other two groups, $p < 0.001$, Group A vs. Group B, $p = 0.01$.
[b] Controls vs. the other two groups, $p = 0.04$.
Abbreviations: ANOVA = analysis of variance, IVRT = isovolumic relaxation time, DT = deceleration time, AFF = atrial filling fraction, Ar = atrial reversal, SFF = systolic filling fraction.

TABLE 3 Tissue Doppler velocities

Variable	Controls (n = 86)	Marfan		ANOVA p Value
		No surgery (n = 28)	Post surgery (n = 27)	
Lateral Sa, cm/s	15 ± 4	12 ± 3	11 ± 2	<0.001[a]
Lateral Ea, cm/s	20 ± 6	16 ± 6	17 ± 6	0.002[b]
Lateral Aa, cm/s	12 ± 5	12 ± 4	10 ± 5	0.2
Lateral Ea/Aa	1.8 ± 0.6	1.4 ± 0.5	1.8 ± 0.7	0.02[c]
Lateral E/Ea	4.5 ± 1.3	6.3 ± 3.8	5.9 ± 2.2	<0.001[d]
Septal Sa, cm/s	12 ± 3	10 ± 2	10 ± 2	<0.001[e]
Septal Ea, cm/s	16 ± 4	14 ± 6	11 ± 4	<0.001[f]
Septal Aa, cm/s	10 ± 3	11 ± 4	10 ± 5	0.5
Septal Ea/Aa	1.6 ± 0.4	1.3 ± 0.4	1.3 ± 0.6	0.001[g]
Septal E/Ea	5.6 ± 1.4	7.5 ± 4.5	8.9 ± 3.5	<0.001[h]

Bonferroni test:
[a] Controls vs. A and B, $p < 0.001$.
[b] Controls vs. A, $p = 0.005$ and vs. B, $p = 0.049$.
[c] Controls vs. A, $p = 0.02$.
[d] Controls vs. A, $p = 0.001$, and vs. B $p = 0.01$.
[e] Controls vs. A and vs. B, $p = 0.001$.
[f] Controls vs. B, $p < 0.001$.
[g] Controls vs. A, $p = 0.008$, and vs. B, $p = 0.01$.
[h] Controls vs. A $p = 0.008$, and vs. B, $p = 0.001$.

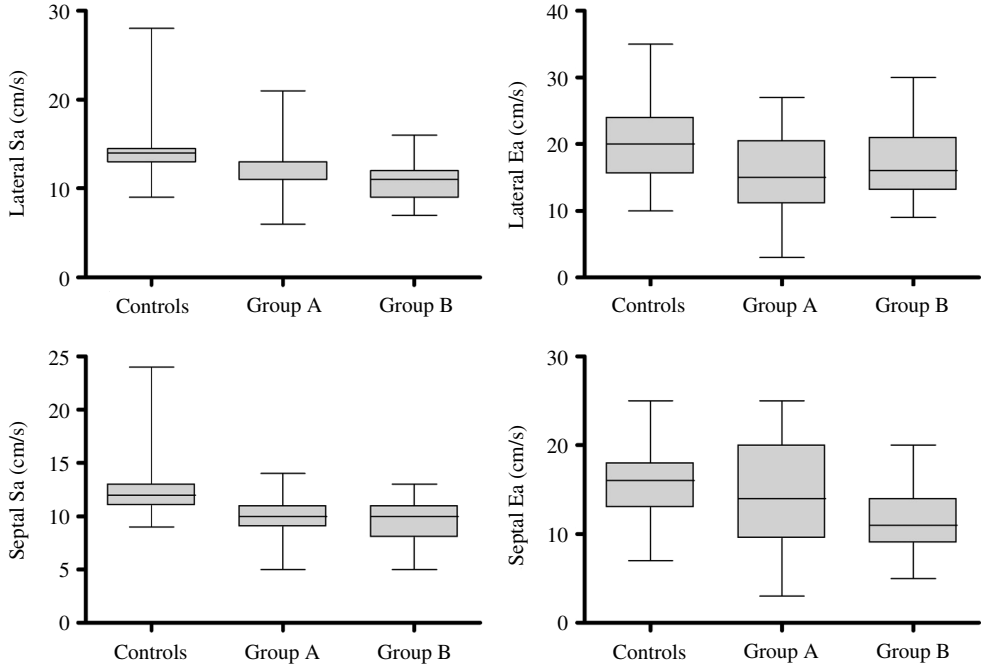

FIG. 1 Box plot for systolic and early diastolic tissue Doppler velocities. Abbreviations: Group A = MFS with no surgery, Group B = MFS post surgery.

We observed overlap of TDI velocities measured in patients with MFS and in controls. To some extent this may be explained by the fact that our controls were initially suspected of having MFS (see Methods). Our diagnostic algorithm for suspected MFS relies on separating three patient groups: first, those with classical MFS; second, those with other inherited connective tissue disorders comprising MASS phenotype, familial aortic aneurysms, familial ectopia lentis, familial Marfan-like habitus, or Ehlers-Danlos syndromes; and third, patients without any inherited connective tissue disease. Only the latter group constituted our controls. As indicated in Methods, some of these healthy individuals exhibited isolated mild manifestations, such as isolated myopia or isolated tall stature. These isolated features are frequent in the general population, and current nosology precludes diagnosis of connective tissue disease consistently.[10,23] All controls exhibited normal cardiovascular findings including heart valves, blood pressures, heart rates, electrocardiograms, and standard echocardiography. Moreover, the TDI measurements in our controls were similar to those reported in other studies.[11,24] Thus, the overlap of TDI measurements is unlikely to result form connective tissue disease in controls but rather from the circumstance that only a subgroup of MFS suffers myocardial dysfunction.

Conclusions

There is increasing evidence that late survivors of MFS suffer severe complications of myocardial dysfunction. For instance, Pyeritz reports cases of MFS with cardiomyopathy out of proportion to their valvular lesions,[25] and a surgical series of 353 adults with MFS identifies 12 cases with transplantation for primary cardiomyopathy.[26] Moreover, a recent study of the natural history of MFS reports ventricular arrhythmia in 21% of patients, with lethal outcome in 4%.[2] Our study provides further evidence of potential myocardial dysfunction. Follow-up investigations need to assess whether TDI predicts symptomatic cardiomyopathy in MFS. Mounting evidence for myocardial dysfunction, however, may justify extending patient care to a surveillance of heart rhythm and myocardial function.

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