

Early Regional Myocardial Dysfunction in Young Patients With Duchenne Muscular Dystrophy

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Background: In young patients (aged <12 years) with Duchenne muscular dystrophy (DMD), cardiac systolic function is generally described to be within the normal range. Recent studies have suggested the presence of subclinical dysfunction in these young patients using cardiac magnetic resonance imaging, tissue Doppler measurements, and myocardial velocity gradients. The aim of this study was to further assess regional myocardial function in a young group of patients with DMD using myocardial velocity and deformation imaging.

Methods: Thirty-two patients with DMD (mean age, 7.9 years; range, 3-12 years) and 29 age-matched normal controls were studied with echocardiography. Standard echocardiographic measurements of left ventricular (LV) systolic and diastolic function were performed. Myocardial velocity and deformation data, including peak systolic and early and late diastolic myocardial velocities, peak systolic strain rate (SR), and peak systolic strain (ϵ), were calculated in the radial direction in the inferolateral LV wall and in the longitudinal direction in the interventricular septum, the LV anterolateral wall, and the right ventricular (RV) free wall.

Results: Higher heart rates and increased LV end-systolic dimensions were seen in patients with DMD compared with controls. Significant decreases in radial and longitudinal peak systolic SR, peak systolic ϵ , and peak systolic and early diastolic myocardial velocities were found in the LV inferolateral and anterolateral walls in patients with DMD. No significant differences in longitudinal function could be found in the interventricular septum or in the RV free wall.

Conclusion: In young patients with DMD who have global normal systolic function, reductions in systolic deformation parameters as well as reduced early diastolic myocardial velocities can be detected in the anterolateral and inferolateral LV walls. The prognostic significance of these findings warrants further longitudinal follow-up. (J Am Soc Echocardiogr 2008;21:1049-1054.)

Keywords: Duchenne muscular dystrophy, Cardiomyopathy, Echocardiography, Doppler tissue imaging

Duchenne muscular dystrophy (DMD) is an X-linked recessive disease affecting approximately 1 in 3,500 live-born male children worldwide.¹ The disease is caused by a mutation in the dystrophin gene on chromosome Xp21.1,² with a resulting deficiency of the subsarcolemmal protein dystrophin. In skeletal and cardiac muscle, dystrophin is critical for muscle membrane stability, because it links actin (part of the sarcomere) with the sarcolemma and thus is actively involved in the contraction-relaxation process. Without dystrophin, muscle contraction causes progressive membrane damage and ultimately muscle necrosis and fibrosis through a complex pathophysio-

logic cascade.³ Clinically, DMD is associated with skeletal myopathy and dilated cardiomyopathy. The latter leads to congestive heart failure and is the cause of death in nearly 30% of patients with DMD. The dystrophin-deficient myocardium seems to work normally at younger ages, but progressive damage results in severe cardiac dysfunction later in life. It is possible that subclinical dysfunction progressively develops early in life and that the early identification and detection of cardiac dysfunction could result in earlier treatment, improving the long-term cardiovascular outcomes of these patients.

In young patients with DMD, cardiac systolic function is generally described to be within the normal range if one uses global measurements for cardiac function, such as fractional shortening or the ejection fraction.⁴ Subtle early changes in diastolic function have been reported in young patients to precede the development of chamber enlargement and systolic dysfunction.⁵ Also, regional myocardial dysfunction was described to be present in patients with DMD using Doppler tissue imaging (DTI), ultrasound backscatter imaging, and cardiac magnetic resonance imaging using myocardial tagging.⁶⁻¹⁰ In a dog model of DMD, deformation imaging was more sensitive than conventional echocardiographic parameters for detecting early subclinical myocardial abnormalities before left ventricular

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(LV) dilatation and dysfunction occurred.¹¹ Finally, magnetic resonance tagging studies have shown that myocardial deformation or strain (ϵ) was reduced in patients with DMD who had preserved global systolic function.¹² Both myocardial backscatter techniques and magnetic resonance tagging are not widespread and thus may not be readily available.

In this study, we sought to determine whether radial or longitudinal systolic myocardial dysfunction could be detected in young patients diagnosed with DMD using ultrasound-based myocardial velocity and deformation imaging.

METHODS

Study Group

We cross-sectionally studied 32 patients with DMD aged 3 to 12 years, without histories of cardiac involvement, followed at the Neuromuscular Centre of the University Hospitals Leuven, Leuven, Belgium. In all patients, the clinical diagnosis of DMD was confirmed by genetic mutational analysis and/or muscle biopsy showing complete absence of dystrophin by immunofluorescence. As a control group, 29 age-matched normal subjects were studied (mean age, 7.7 ± 2.6 years; range, 3-12 years). The study was approved by the local institutional ethics committee.

Echocardiographic Data Acquisition

All echocardiograms were obtained using a System 5/Vivid 7 ultrasound scanner (GE-Vingmed Ultrasound AS, Horten, Norway) equipped with a 2.5-MHz transducer. In every patient, standard parasternal and apical views were obtained.

To obtain LV end-diastolic and end-systolic dimensions, septal and inferolateral wall thickness, left atrial dimension, and fractional shortening, M mode using the parasternal LV short-axis view was used. All dimensions were corrected for calculated body surface area. The modified Simpson's method was used for the determination of the LV ejection fraction. Diastolic LV function was assessed by blood-pool Doppler measurements of mitral flow and pulmonary venous flow. On mitral flow tracings, the peak velocities of early (E wave) and late (A wave) filling, the E/A ratio, and the deceleration time of early filling were measured. The transmitral E wave/basal lateral and basal septal myocardial velocity ratio was measured as a marker of left atrial filling pressures. On pulmonary venous recordings, peak systolic velocity and peak diastolic velocity were measured. Isovolumic relaxation time was obtained from a recording between LV inflow and outflow. Because isovolumic relaxation time is heart rate dependent and patients with DMD often have sinus tachycardia, a correction for heart rate was made, and the value is expressed as a percentage of the expected value for a given heart rate, as recommended by others.¹⁰ The duration of the pre-ejection period was calculated as time from beginning of the QRS complex to opening of the aortic valve and corrected for the square root of the RR interval.

The myocardial performance index, an index of systolic and diastolic function, was calculated in the left and right ventricles, as previously described.¹³

DTI Data Acquisition

Standard apical 4-chamber views were used to obtain real-time 2-dimensional color DTI data in the interventricular septum, the LV anterolateral wall, and the right ventricular (RV) free wall. The parasternal short-axis view was used to acquire DTI data in the LV inferolateral wall.

DTI Data Analysis

The DTI data sets were analyzed using dedicated research software (Software Package for Echocardiographic Quantification Leuven 4; Catholic University of Leuven, Leuven, Belgium), allowing the computation of regional myocardial velocities and natural strain rate (SR) and ϵ values. Longitudinal peak systolic SR, peak systolic ϵ , peak systolic myocardial velocity, and peak early diastolic and late diastolic myocardial velocities were estimated in the basal, mid, and apical segments of the interventricular septum, the LV anterolateral wall, and the RV free wall by measuring the spatial velocity gradient over a computation area of 10 mm. For the measurement of radial peak systolic SR; peak systolic ϵ ; and peak systolic, peak early diastolic, and late diastolic myocardial velocities in the inferolateral wall, a computation area of 5 mm was chosen. The high temporal resolution of DTI makes it possible to identify abnormal timing of myocardial events, including postsystolic shortening. The postsystolic thickening index (in the radial direction) or shortening index (in the longitudinal direction) was calculated. The postsystolic thickening or shortening index was defined as $[(\text{maximal } \epsilon \text{ after aortic valve closure} - \text{end-systolic } \epsilon) / \text{end-systolic } \epsilon] \times 100$. As a marker of mechanical dyssynchrony, the time from the beginning of the QRS complex to maximal ϵ (corrected for the square root of the RR interval) was measured in each myocardial segment. A more comprehensive description of the DTI data acquisition and analysis is presented in previous studies from our group.¹⁴

Statistical Analysis

Data are reported as mean \pm standard deviation. We used unpaired 2-sided *t* tests to assess differences between groups (patients with DMD vs controls) for normally distributed continuous data. Parametric Mann-Whitney tests were used if data were not normally distributed. Linear correlation analysis was used to assess the relationship between age and peak systolic ϵ . Receiver-operating characteristic analysis was performed to determine the sensitivity and specificity of deformation parameters to detect myocardial dysfunction. A *P* value $< .05$ was considered statistically significant.

RESULTS

Patient Characteristics

The results of cardiovascular physical examinations were normal at the time of echocardiography. Electrocardiographic results were normal in 21 patients and showed tall R waves in lead V_1 in 11 patients. All patients were in sinus rhythm at the time of evaluation. None were taking any cardiac medications; 15 were receiving stable, long-term steroid treatment with deflazacort to improve skeletal muscle function.

Standard Echocardiographic Measurements of Systolic and Diastolic Function

Data from standard echocardiography are summarized in Table 1. Heart rates were significantly higher in patients with DMD compared with controls. Also, LV end-systolic dimensions were significantly higher in patients compared with controls. The LV end-diastolic dimension, the left atrial dimension, and the end-diastolic wall thickness of the inferolateral wall did not differ between patients with DMD and control subjects. Fractional shortening and ejection fractions were not different between both groups. No differences in parameters of LV diastolic function were noted between patients and controls except for the transmitral E/E' ratio at the basal lateral wall, which was higher in patients than in controls. Pre-ejection periods

Table 1 Standard echocardiographic measurements of systolic and diastolic function

Variable	Patients with DMD (n = 32)	Controls (n = 29)	P value
Age (yr)	7.9 ± 2.7	7.7 ± 2.8	.95
Heart rate (beats/min)	102.2 ± 9.9	82.6 ± 13.8	<.01
LV end-diastolic dimension/BSA (mm)	42.9 ± 6.5	41.0 ± 6.1	.29
LV end-systolic dimension/BSA (mm)	29.0 ± 4.7	26.4 ± 3.84	.03
Inferolateral wall thickness/BSA (mm)	7.2 ± 1.1	7.1 ± 1.2	.82
LV fractional shortening (%)	33.7 ± 3.2	35.6 ± 3.7	.09
LV ejection fraction (%)	63.9 ± 5.6	66.5 ± 5.6	.11
Left atrial dimension/BSA (mm)	23.3 ± 3.3	24.1 ± 2.9	.25
Mitral E velocity (cm/s)	95.0 ± 19.2	102.1 ± 12.4	.17
Mitral A velocity (cm/s)	47.5 ± 9.2	48.6 ± 14.1	.63
Mitral E/A ratio	2.1 ± 0.6	2.2 ± 0.6	.44
Isovolumic relaxation time (% of predicted)	98.7 ± 18.3	101.0 ± 13.9	<.01
Mitral E deceleration time (ms)	126.6 ± 29.4	131.6 ± 22.8	.51
Systolic pulmonary venous velocity (cm/s)	48.8 ± 10.5	53.6 ± 9.7	.07
Diastolic pulmonary venous velocity (cm/s)	63.8 ± 10.3	67.1 ± 10.7	.16
Mitral E/basal septal E' ratio	11.8 ± 2.7	10.8 ± 2.7	.31
Mitral E/basal lateral E' ratio	11.6 ± 4.9	8.3 ± 2.0	.03
Pre-ejection period (ms)	148.3 ± 31.7	107.9 ± 22.2	.01
LV myocardial performance index	0.39 ± 0.08	0.31 ± 0.12	.01
RV myocardial performance index	0.30 ± 0.10	0.28 ± 0.07	.48

Data are expressed as mean ± standard deviation.

BSA, Body surface area; DMD, Duchenne muscular dystrophy; LV, left ventricular; RV, right ventricular.

Table 2 Radial myocardial function of the inferolateral wall

Variable	Patients with DMD (n = 32)	Controls (n = 29)	P value
Peak systolic velocity (cm/s)	3.1 ± 0.7	3.6 ± 0.8	.02
Peak early diastolic velocity (cm/s)	-5.5 ± 1.1	-6.9 ± 1.0	.01
Peak late diastolic velocity (cm/s)	-1.3 ± 0.7	-1.1 ± 0.5	.22
Peak systolic strain rate (s ⁻¹)	3.5 ± 0.5	4.4 ± 1.0	<.01
Peak systolic strain (%)	37.1 ± 11.7	62.3 ± 13.5	<.001
Postsystolic thickening (%)	24.6 ± 19.8	4.0 ± 3.6	<.001
Time to peak strain (ms)	392 ± 58	367 ± 27	<.01

DMD, Duchenne muscular dystrophy.

were significantly longer in patients compared with controls. The LV myocardial performance index was significantly increased in patients compared with controls.

Myocardial Velocity and Deformation

Tissue Doppler myocardial velocity data sets could be obtained in all patients with DMD (n = 32). After postprocessing, 10% of myocardial segments were excluded because of reverberation artifacts, poor signal/noise ratios, or poor alignment with the direction of myocardial motion.

Radial Myocardial Function in the Inferolateral Wall

Table 2 summarizes the peak systolic and early and late myocardial velocities, peak systolic SR, and peak systolic ε in the inferolateral wall as measured from the parasternal short-axis view. Peak systolic and early diastolic myocardial velocities, peak systolic SR, and peak systolic ε in the inferolateral wall were significantly lower in patients with DMD compared with controls. The postsystolic thickening index was significantly higher in patients compared with controls. Time to peak ε was significantly longer in patients compared with normal controls. Figure 1 shows the individual radial peak systolic ε

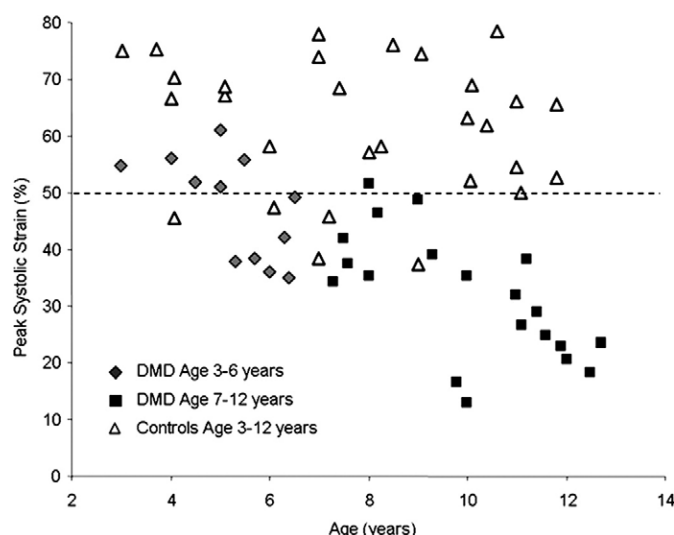


Figure 1 Individual radial peak systolic strain in patients with Duchenne muscular dystrophy (DMD) and controls. In patients with DMD, there was a significant reduction in radial peak systolic strain compared with controls. Dividing patients with DMD into a young group (aged 3-6 years; gray diamonds) and an older group (aged 7-12 years; black squares), one can note the progressive nature of the process. The lower limit of normality was 50% (average of controls minus 1 standard deviation; dashed line). In only 1 patient with DMD ≥7 years, peak systolic strain was ≥50%.

values in the inferolateral wall. Higher peak systolic ε values were more frequently observed in the youngest patients (aged 3-6 years) and overlapped with controls. In older patients (aged 7-12 years), lower peak systolic ε values were observed. A negative correlation between radial peak systolic ε in the inferolateral wall and age was found in patients with DMD (r = -0.74; P < .01). No correlation

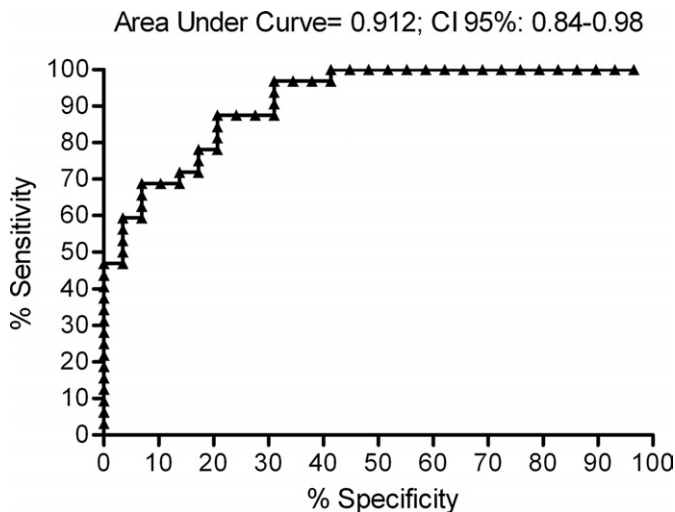


Figure 2 Receiver-operating characteristic analysis for the detection of myocardial dysfunction in patients with Duchenne muscular dystrophy. Area under the curve and 95% confidence interval (CI) are given for radial peak systolic strain.

between age and peak systolic ε could be found in the control group ($r = -0.16$, $P = .69$). **Figure 2** shows the results of receiver-operating characteristic analysis. Peak systolic ε was the best parameter to detect myocardial dysfunction in this group of young patients with DMD (area under the curve, 91%; 95% confidence interval, 84% to 98%).

Longitudinal Myocardial Function in the LV Anterolateral Wall, Interventricular Septum, and RV Free Wall

Table 3 shows peak systolic, early diastolic, and late diastolic myocardial velocities; peak systolic SR; peak systolic ε ; time to peak ε ; and the postsystolic shortening index in the basal, mid, and apical segments of the LV anterolateral wall and the interventricular septum. Peak systolic and early diastolic myocardial velocities, peak systolic SR, and peak systolic ε were significantly lower in the 3 myocardial segments of the LV anterolateral wall in patients with DMD, but there were no changes in these parameters in the interventricular septum. The postsystolic shortening index was significantly higher and time to peak ε significantly longer in the 3 segments of the LV anterolateral wall in patients with DMD. **Table 4** shows DTI data in the basal, mid, and apical segments of the RV free wall.

DISCUSSION

Our study shows that early abnormalities in regional myocardial function can be detected using ultrasound-based deformation in young patients with DMD who have preserved ejection fractions or fractional shortening. Especially in the anterolateral and inferolateral segments, abnormalities in different parameters assessing radial as well as longitudinal systolic and diastolic LV function can be observed. In these walls, we observed reduced myocardial velocities, reduced peak systolic SR and end-systolic ε values, and increased postsystolic thickening or shortening and increased times to peak ε . On the basis of our longitudinal measurements, the function of the interventricular septum and RV free wall is better preserved at this early disease stage. We also found some evidence for early desynchronization in these patients, with delayed time to peak ε in the inferolateral segments compared with normal controls, while the

Table 3 Longitudinal myocardial function in the LV anterolateral wall and interventricular septum

Variable	Patients with DMD (n = 32)	Controls (n = 29)	P value
Peak systolic velocity (cm/s)			
Basal lateral	5.3 ± 2.2	6.7 ± 1.8	.03
Mid lateral	4.6 ± 2.1	6.1 ± 1.6	.03
Apical lateral	3.1 ± 1.7	4.8 ± 2.1	.02
Basal septum	4.5 ± 0.8	4.7 ± 0.8	.87
Mid septum	3.8 ± 0.6	3.9 ± 0.7	.67
Apical septum	2.7 ± 1.0	2.5 ± 0.9	.59
Peak early diastolic velocity (cm/s)			
Basal lateral	-9.3 ± 3.4	-11.7 ± 2.5	.02
Mid lateral	-8.4 ± 2.5	-9.9 ± 2.7	.03
Apical lateral	-6.5 ± 2.9	-7.9 ± 2.5	.03
Basal septum	-8.3 ± 2.0	-8.8 ± 1.4	.33
Mid septum	-7.7 ± 2.1	-8.1 ± 1.8	.31
Apical septum	-6.8 ± 2.4	-7.2 ± 1.9	.33
Peak late diastolic velocity (cm/s)			
Basal lateral	-2.3 ± 1.5	-1.9 ± 1.2	.25
Mid lateral	-1.7 ± 1.5	-1.4 ± 1.0	.51
Apical lateral	-1.5 ± 1.0	-1.0 ± 0.6	.10
Basal septum	3.4 ± 1.2	-2.8 ± 0.9	.12
Mid septum	-3.1 ± 0.9	-2.6 ± 0.6	.07
Apical septum	-2.3 ± 0.9	-1.8 ± 0.5	.09
Peak systolic strain rate (s⁻¹)			
Basal lateral	-1.9 ± 0.6	-2.4 ± 1.0	.01
Mid lateral	-1.5 ± 1.1	-2.3 ± 0.8	<.01
Apical lateral	-1.6 ± 0.7	-2.3 ± 0.9	<.01
Basal septum	-2.1 ± 0.6	-2.2 ± 0.7	.72
Mid septum	-2.1 ± 0.7	-2.2 ± 0.7	.83
Apical septum	-1.9 ± 0.8	-1.9 ± 0.4	.85
Peak systolic strain (%)			
Basal lateral	-17.5 ± 7.4	-24.7 ± 10.6	<.01
Mid lateral	-16.1 ± 8.5	-24.1 ± 9.8	<.01
Apical lateral	-17.8 ± 6.4	-23.7 ± 8.4	<.01
Basal septum	-22.7 ± 7.9	-24.1 ± 7.6	.65
Mid septum	-21.6 ± 5.9	-23.4 ± 8.7	.34
Apical septum	-21.8 ± 8.3	-23.7 ± 7.7	.61
Postsystolic shortening (%)			
Basal lateral	13.9 ± 20.1	4.9 ± 4.3	.02
Mid lateral	29.1 ± 35.9	6.6 ± 8.3	<.001
Apical lateral	26.9 ± 37.3	4.7 ± 2.3	<.01
Basal septum	7.0 ± 5.9	4.5 ± 5.8	.12
Mid septum	5.2 ± 5.8	3.2 ± 3.8	.15
Apical septum	6.8 ± 9.0	6.3 ± 7.1	.83
Time to peak strain (ms)			
Basal lateral	398 ± 60	365 ± 28	<.01
Mid lateral	390 ± 51	358 ± 23	<.01
Apical lateral	391 ± 50	353 ± 23	<.01
Basal septum	362 ± 32	346 ± 21	.24
Mid septum	365 ± 35	347 ± 23	.33
Apical septum	370 ± 35	349 ± 23	.15

DMD, Duchenne muscular dystrophy; LV, left ventricular.

timing was preserved in the interventricular septum. This delayed activation in this wall is associated with increased postsystolic motion.

Global LV systolic function, as evaluated by fractional shortening and the ejection fraction, is still within the normal range in the

Table 4 Longitudinal myocardial function in the RV free wall

Variable	Patients with DMD (n = 32)	Controls (n = 29)	P value
Peak systolic velocity (cm/s)			
RV basal	8.7 ± 2.3	9.0 ± 2.1	.76
RV mid	6.6 ± 2.0	6.9 ± 1.9	.71
RV apex	5.0 ± 2.5	4.8 ± 1.8	.86
Peak early diastolic velocity (cm/s)			
RV basal	-9.5 ± 2.6	-10.7 ± 2.6	.53
RV mid	-7.8 ± 2.7	-9.0 ± 1.1	.34
RV apex	-5.8 ± 2.7	-6.7 ± 1.2	.41
Peak late diastolic velocity (cm/s)			
RV basal	-6.1 ± 2.5	-5.2 ± 2.1	.48
RV mid	-5.7 ± 2.1	-4.7 ± 2.1	.48
RV apex	-3.9 ± 2.1	-3.2 ± 1.3	.39
Peak systolic strain rate (s ⁻¹)			
RV basal	-3.0 ± 1.1	-2.7 ± 0.8	.41
RV mid	-3.0 ± 1.1	-2.9 ± 0.8	.79
RV apex	-3.0 ± 1.6	-3.0 ± 1.2	.85
Peak systolic strain (%)			
RV basal	-38.5 ± 16.0	-38.2 ± 12.3	.89
RV mid	-41.7 ± 14.1	-46.7 ± 12.6	.62
RV apex	-43.2 ± 12.9	-41.5 ± 10.8	.77
Postsystolic shortening (%)			
RV basal	8.5 ± 9.2	5.7 ± 8.3	.26
RV mid	5.1 ± 5.3	3.9 ± 4.4	.40
RV apex	3.3 ± 6.4	3.1 ± 4.1	.88

DMD, Duchenne muscular dystrophy; RV, right ventricular.

majority of this young patient group.⁴ Only some of the “older” patients in the present study had mildly reduced ejection fractions or fractional shortening. Subtle differences in some of the other parameters assessing global ventricular function were observed: there was a small increase in LV end-systolic dimension, possibly reflecting early systolic dysfunction and remodeling. Also, the blood-pool Doppler indices for global LV function were abnormal, with a prolonged pre-ejection period and increased myocardial performance index. Both reflect an increase in isovolumic contraction time. When comparing the absolute values for the isovolumic relaxation times, the measured values were shorter in the patient group compared with the normal controls. This was due to increased heart rates, and when corrected for heart rate, isovolumic relaxation time did not differ between the 2 groups.

Because dystrophin deficiency is present from birth and the disease is a progressive disorder, it is not surprising to observe some abnormalities in ventricular systolic function at this early stage of the disease process. Dystrophin deficiency leads to progressive membrane destabilization and cellular damage, possibly caused by oxidative stress and inflammation. This process of muscle damage begins at (or even before) birth, and there is evidence of subclinical myocardial damage, with apoptosis and early regional fibrosis early in life. This has also been suggested by ultrasound backscatter studies, in which abnormalities in myocardial characteristics were measured in young patients with DMD.⁶ These changes in myocardial acoustic properties indicate changes in myocardial structure such as fibrosis. Similar changes could be observed in patients with Becker disease with preserved ventricular function.¹⁵ This suggests that subclinical myocardial damage precedes overt global cardiac dysfunction and that changes in the

ejection fraction and fractional shortening occur only after more extensive damage. This can be probably be explained by the compensation mechanisms present in the cardiac muscle.

One of the most interesting findings of the current study is the differences in regional myocardial function, with the most important changes in the inferolateral and anterolateral walls. In the longitudinal direction, we noted a more prominent reduction in myocardial velocities and SR and ϵ values in the anterolateral wall segments compared with the longitudinal parameters in the septal segments. Also, time to peak ϵ was reduced in the anterolateral wall, suggesting delayed activation and some discrete dyssynchrony within the left ventricle, with delayed contraction in the lateral wall compared with the interventricular septum. Unfortunately, our Doppler-based technique did not allow us to reliably analyze the radial deformation of the septum, because of reverberation artifacts.

Earlier reports based on grayscale imaging demonstrated that regional systolic function in the posterior or inferolateral wall was affected earlier compared with the other segments.⁴ Histologic studies have also confirmed that pathologic changes occur more prominently in this wall certainly compared with the septum.¹⁶ Different hypotheses could potentially explain this finding. One explanation might be the influence of the adjacent low-pressure right ventricle on longitudinal septal function. Our data show that longitudinal function in the RV free wall segments was preserved. The septum is the wall where the right and left ventricles interact, and preserved RV function might result in preserved global septal deformation. Another potential explanation for these regional differences is regional differences in mechanical activation resulting in regional differences in wall stress. The inferolateral wall is activated last during normal electrical activation.¹⁷ The fibers in this region might be pulled by other myocardial segments that are activated earlier, causing increased stretching of the fibers before they start to shorten. The lateral wall also has a higher regional radius of curvature, also adding to increased regional stress.

It has been suggested that increased stress in the absence of dystrophin might lead to earlier muscle damage.¹⁸⁻²⁰ In the current data sets, the prestretch could not be studied, because our Doppler-based methodology did not allow us to look at mechanical activation in all segments during the same cardiac cycle. Compatible with this hypothesis, we found no difference in regional deformation parameters in the RV free wall between the DMD group and normal controls. This would confirm previous observations suggested that the right ventricle is usually not involved in patients with DMD. Fiber stress in the right ventricle is lower compared with that in the left ventricle, probably protecting RV fibers from damage.

Reduced myocardial deformation in young patients with DMD was also demonstrated using magnetic resonance–based myocardial tagging.¹² In that study, reduced circumferential ϵ was observed in all segments studied in young patients with DMD with normal ejection fractions. These authors could not detect regional differences in circumferential ϵ . Thus, it seems that longitudinal function is affected differently from circumferential deformation. Further study is needed on how regional myocardial mechanics are affected by the underlying disease process.

The predictive value of early deformation abnormalities was demonstrated in 2 recent studies. First, in a dog model of DMD, the myocardial velocity gradient (MVG) was shown to be reduced in the inferolateral wall in animals with preserved LV fractional shortening.¹¹ The MVG corresponds to radial systolic SR. This reduction in MVG was associated with increased collagen content and apoptotic cells in the involved myocardial segment. This study only looked at myocardial deformation in a single myocardial segment but showed

that reduced regional deformation is associated with myocardial histological damage. Gitrakos et al⁹ provided the first data that a reduction in regional SR is predictive of clinical outcome, but additional studies are needed to corroborate this finding. Both studies indicate that the reduction in deformation we measured in our patient population is related to myocardial damage and has prognostic significance. In our patient group, we noted that the end-systolic radial ε values in the inferolateral wall were lower in the older patients compared with the younger ones, suggesting a progressive decrease in radial deformation with age. Further longitudinal follow-up of our population is required and currently being performed.

Heart rates were significantly higher in young patients with DMD, and this might be one of the first signs of myocardial dysfunction in patients with DMD.²¹ One may speculate the reduced deformation is secondary to reduced preload due to shortened diastole. However, ε and SR measurements are not affected by increases in heart rate within the range observed in our patients. This has been demonstrated in experimental models in which measurements were done at different heart rates.²² So the observed decreases in ε and SR cannot be attributed to the higher heart rates in the patient group. In addition, one would expect that changes in heart rate would equally affect all myocardial segments, not just the inferolateral and anterolateral LV walls.

Limitations of the Present Study

The main limitation of our study is its cross-sectional nature with a lack of follow-up data. Ongoing studies are looking at the clinical predictive value of the abnormalities detected. Second, patients with DMD usually have poor acoustic windows, making ultrasound imaging more challenging, so the quality of data is sometimes suboptimal. This led to excluding from our analysis 10% of the myocardial segments. Third, this study was performed using 1-dimensional techniques. Two-dimensional techniques have the advantage of being angle dependent but have not been validated in this age group.

Conclusion and Potential Clinical Implications

This study demonstrates the presence of subclinical regional myocardial dysfunction in young patients with DMD with normal fractional shortening and ejection fractions. The detection of early systolic dysfunction in this patient group has potential important therapeutic implications. For patients with DMD, these findings could offer a rationale for starting a trial looking at the potential benefit of early cardiac treatment. Reducing LV afterload and influencing cardiac remodeling by the use of angiotensin-converting enzyme inhibitors has been shown to be beneficial for this patient group, but further studies looking at long-term outcome are needed.^{23,24} Our findings suggest that subtle regional myocardial dysfunction in the inferolateral and anterolateral LV walls precedes global dysfunction. This could be used as an argument for starting treatment earlier in life, before a measurable reduction in the ejection fraction occurs. Reducing myocardial afterload might reduce stress and be protective against the progression of damage.

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