Normal left ventricular ejection fraction and mass but subclinical myocardial dysfunction in patients with Friedreich’s ataxia

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Aims
Myocardial involvement in Friedreich’s ataxia (FRDA) is characterized by iron deposits, diffuse fibrosis, and focal necrosis. We hypothesized that subclinical left ventricular (LV) dysfunction may occur in FRDA patients who have normal LV ejection fraction (LVEF) and mass.

Methods
Twenty patients homozygous for the GAA expansion in the frataxin gene (mean age: 35 ± 16 years) and twenty age- and sex-matched controls (mean age: 34 ± 15 years) were studied using conventional echocardiography and speckle-tracking imaging. The two groups did not differ in terms of the LVEF (68 ± 6 vs. 67 ± 6%, in patients and controls, respectively) or LV mass (91 ± 20 vs. 82 ± 17 g/m²). Global systolic longitudinal (−15.3 ± 2.1 vs. −17.5 ± 1.6%, P = 0.001) and circumferential (−19.5 ± 2.9 vs. −21.4 ± 2.6%, P = 0.034) strain, and peak LV twist (9.2 ± 3.3 vs. 11.7 ± 2.3, P = 0.008) were significantly reduced in patients compared with controls. Indexed stroke volume was also significantly lower in patients (36 ± 5 vs. 43 ± 8 mL/m², P = 0.0012) and this decreased LV pump performance was associated with a concentric remodelling pattern (relative wall thickness: 0.47 ± 0.08 vs. 0.35 ± 0.05, P < 0.001).

Conclusion
There is evidence of morphological and functional abnormalities in FRDA patients with normal LVEF and mass.

Keywords
Friedreich ataxia • Ventricular function • Twist • Strain • Ventricular remodelling

Introduction
Friedreich’s ataxia (FRDA) is an autosomal recessive degenerative disease affecting the nervous system, the heart, and glucose metabolism.1 Patients have a shortened life expectancy and, in addition to bulbar dysfunction, cardiac involvement is a major cause of death. Hypertrophic cardiomyopathy (seen in two-thirds of patients) may progress into dilated cardiomyopathy, but the hypokinetic-dilated form has also been reported in patients without left ventricular (LV) hypertrophy.2,3 Likewise, arrhythmias may occur in the absence of overt cardiomyopathy.4

Myocardial involvement in FRDA is characterized by diffuse fibrosis, focal necrosis, and iron deposits.5 A recent MRI study demonstrated abnormal perfusion reserve and fibrosis as early manifestations of cardiomyopathy, in the absence of significant hypertrophy or reduced LV ejection fraction (LVEF).6 We hypothesized that this pathology may cause subclinical LV dysfunction even in FRDA patients with normal LVEF and mass. Strain-derived parameters and LV rotational mechanics analysis, which enable even subtle myocardial anomalies to be detected,7–10 could be useful to assess this subclinical LV dysfunction. However, there are only limited published data related to myocardial strain and rotational mechanics in FRDA patients.11,12 Moreover, none of the previous studies has specifically addressed FRDA patients without LV hypertrophy and with normal LVEF.

We, therefore, assessed cardiac status in FRDA patients with normal LVEF and LV mass by characterizing LV morphology and function using conventional echocardiography and speckle-tracking imaging.
Methods

Patients
Twenty consecutive FRDA patients referred to our neurology department who met the following echocardiographic criteria were prospectively included: normal LVEF (>55%) and normal indexed LV mass (men <115 g/m² and women <95 g/m²).13 Patients with a history of hypertension or with any unrelated other cardiac diseases were excluded. The diagnosis of FRDA was confirmed in all cases by the presence of GAA repeat expansions in both alleles of the FXN (Frataxin) gene. No patients in this series had other types of mutation. FRDA had been diagnosed a mean of 16 ± 13 years before inclusion of the study. Eleven patients were being treated with idebenone (2250 mg/day, mean duration of treatment: 26.4 ± 17.6 months) and two with deferiprone (20 mg/kg/day for one patient and 40 mg/kg/day for the other, duration of treatment 6 months for both). No patients were receiving β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor inhibitors, or calcium antagonists.

Imaging data were prospectively collected in these 20 patients and in 20 age- and sex-matched healthy controls. None of the control subjects was receiving any medication. All participants were in sinus rhythm.

The study protocol was approved by our local Ethics Committee. All participants provided written informed consent.

Analysis of the GAA expansion
All FRDA patients included in this study were genotyped for GAA repeat expansions in the FXN gene. Genomic DNA was extracted with the Invisorb Blood Universal Kit (Invitek GmbH). Polymerase chain reaction of GAA repeats was carried out using previously described primers Bam (5′-GAGGGATCCGTCTGGGCAAAGG-3′) and 2500F (5′-MTGCCAGGACAGTCAAGGCTTT-3′).14 Amplification was conducted with the Expand Long Template PCR System (Roche) Kit and protocol on a high quality 50 ng DNA. Different alleles were resolved by the analysis of PCR products on 1% agarose gels. The mean number of GAA repeats in the smaller allele was 635 ± 268 and in the larger allele, 869 ± 246.

Echocardiography
Images were acquired using an IE33 echocardiographic system (Philips Medical System, Andover, MA, USA). Data were acquired by two observers (C.D. and P.J.) and analysed by one (C.D.).

LV internal dimensions (LVID), septal wall thickness (SWT), and posterior wall thickness (PWT) were measured at end-systole and end-diastole from M-mode recordings in a longitudinal parasternal view13 and indexed to body surface area (BSA). The LVEF and LV volumes were evaluated using the bi-apical Simpson disk method.

LV mass was assessed using the American Society of Echocardiography recommended formula: LV mass = 0.8 × (1.04[(LVIDd + PWTd + SWTd)²-(LVIDd)²]) + 0.6 g, and indexed to the BSA. Relative wall thickness (RWT) was used to measure the degree of concentric remodelling and was calculated as: (SWT in diastole + PWT in diastole)/LVID in diastole. A concentric remodelling pattern was defined as the RWT > 0.42.

LV stroke volume was obtained using the formula: LV stroke volume = [(I) × (LV outflow tract diameter/2)² × LV outflow tract velocity time integral.

LV end-systolic wall stress was calculated as: 0.33× cuff systolic blood pressure × end-systolic LVID/(end-systolic PWT× [1 + (end-systolic PWT/end-systolic LVID)])}.
Recordings. The mean difference in peak systolic twist was 0.2 ± 0.7° (r = 0.97, P < 0.0001) and the mean difference in the GSLS was 0.1 ± 0.7% (r = 0.97, P < 0.0001). Intra-observer variability was 2.4% for LV twist and <1% for the GSLS. Inter-observer variability for peak LV twist and GSLS was assessed from measurements performed by a second operator on the same echocardiographic recordings. The mean difference in peak systolic twist was 0.4 ± 1.0° (r = 0.94, P < 0.0001) and the mean difference in the GSLS was 0.5 ± 1.0% (r = 0.91, P < 0.0001). Inter-observer variability was 3.8% for LV twist and 2.9% for the GSLS.

### Statistical methods

The results are expressed as mean ± standard deviation. Data were tested for normality using the Kolmogorov–Smirnov test. Student’s test for independent samples was used for comparison between FRDA patients and controls. Mann–Whitney’s test was used to examine differences in non-normally distributed data. Proportions were compared using a χ² test. Correlations were tested by linear regression analysis and Pearson correlation coefficient. A two-sided P-value of <0.05 was considered significant.

### Results

Clinical data for the FRDA patients and the healthy controls are shown in Table 1. The BSA was lower and the heart rate was higher in FRDA patients compared with controls.

### Standard echocardiography

The LVEF and LV mass were similar in the patients and controls. SWT and PWT tended to be higher and LV volume was smaller in FRDA patients, consistent with a concentric remodelling pattern. Among the 20 patients, 15 had a concentric remodelling pattern, compared with none in the control group (P < 0.0001) (Table 2).

Stroke volume was lower in the patients than in the controls. Cardiac index remained normal, as a result of the increased heart rate. End-systolic wall stress was significantly reduced in the patients as a result of the smaller LV diameter and greater wall thickness.

Mitral inflow Doppler measurements showed reduced E/A. The E-wave tended to be reduced in patients, whereas the A-wave tended to be increased. Ea was significantly lower and E/Ea significantly higher in FRDA patients than in controls.

### Rotational and strain measurements

Peak systolic LV twist and apical rotation were significantly reduced in patients compared with controls (Figure 1). Thirty-five per cent
of the FRDA patients had an LV twist more than two standard deviations below the mean value of the controls (namely, <7.1°). LV torsion tended to decrease in the patients as compared with the controls (1.3 ± 0.5 vs. 1.5 ± 0.3°/cm, respectively, P = 0.121). GSCirS and GSLS were reduced in patients compared with controls, but not GSRadS. Longitudinal strain was not significantly different in the LV septal wall when compared with the value in the lateral wall (−16.0 ± 2.8 vs. −15.0 ± 3.4%, respectively, P = 0.306) (Table 3).

Taking into account the control subjects and patients, peak systolic twist correlated positively with apical rotation (r = 0.88, P < 0.001) and inversely with peak UT rate (r = −0.71, P < 0.001) and GSCirS (r = −0.59, P < 0.001). There was no relationship between peak systolic LV twist and GSLS. There was an inverse correlation between peak systolic twist and SWT (r = −0.43, P = 0.005), RWT (r = −0.35, P = 0.029), and indexed LV mass (r = −0.32, P = 0.046).

The GSLS was correlated with SWT (r = 0, P = 0.001), PWT (r = 0.59, P < 0.001), RWT (r = 0.48, P = 0.002), and indexed LV mass (r = 0.45, p = 0.004). GSCirS was correlated with SWT (r = 0.42, P = 0.007) and RWT (r = 0.36, P = 0.024).

In the FRDA patients group, peak systolic twist correlated positively with apical rotation (r = 0.88, P < 0.001). Peak systolic twist and peak apical rotation inversely correlated with peak UT rate (r = −0.71, P < 0.001) and GSCirS (r = −0.59, P < 0.001).
Friedreich’s ataxia and left ventricular function

LV deformation parameters and rotational mechanics assessed by speckle-tracking were consistent with the presence of LV dysfunction. Indeed, the assessment of global LV function by the LVEF is not sensitive enough to detect cardiac involvement and speckle-tracking imaging detected subtle myocardial dysfunction in these patients.

Left ventricular longitudinal, circumferential, and radial deformation

Global systolic LV longitudinal and circumferential deformations were reduced in the FRDA patients compared with age-matched controls. Unlike Mottram et al., we found no difference between the LV lateral and LV septal wall longitudinal strain and no correlation between GAA alleles and global or regional speckle-tracking-derived parameters. This could be explained by the exclusion of patients with LV hypertrophy, thus with a lesser range of myocardial involvement.

Noticeably, radial strain remained similar to that observed in controls. In contrast, Dutka et al. reported reduced tissue Doppler imaging (TDI)-derived systolic velocity gradients on the posterior LV wall, suggesting altered systolic function. In the current study, we excluded patients with LV hypertrophy, which may explain this apparent difference. A paradoxical discrepancy among altered systolic and circumferential deformation, and preserved or even increased radial deformation has been observed previously in the early stages of other diseases and has been ascribed to a compensatory mechanism in response to the impairment in global longitudinal function, with radial function deteriorating only in more advanced cardiac muscle disease.

Our results are in agreement with those of Weidemann et al. who found an altered myocardial longitudinal deformation pattern, as assessed by TDI, in FRDA patients with normal LV fractional shortening. Compared with normal age-related controls, this abnormality was present even in the non-hypertrophied segments, however, patients without LV hypertrophy were not excluded from their study.

Noticeably, former studies have been performed using TDI and not speckle-tracking imaging. Many differences exist between the two methods, but these techniques correlate well and therefore allow a reasonable comparisons of the results.

Rotational mechanics

LV twist was lower in FRDA patients compared with controls. LV twist deformation, related to the helicoidal architecture of LV myocardial fibres, is an important contributor to LV performance. Unique involvement of the endocardial fibres would have resulted in less opposition to the dominant epicardial action resulting in an increased LV twist. The observed reduction in LV twist likely results, therefore, from a process involving the three layers of the myocardium or, alternatively, from predominantly epicardial involvement. A transmural myocardial disease instead of an epicardial involvement is more consistent with previous histological studies, which reported diffuse myocardial involvement.

We also observed that the LV UT rate was significantly reduced in our FRDA patients. The UT rate is an index of LV elastic recoil during isovolumic relaxation, which generates the suction force for efficient LV filling, but also, correlates closely with the time constant of LV relaxation (tau). Thus, a reduced UT rate provides further evidence for an impairment in early diastolic LV filling. Indeed, conventional but indirect markers of diastolic function, such as the E/A ratio and E/Ea ratio, were also significantly different from those of controls. A reduction in the LV UT rate has been previously ascribed, at least partly, to a reduction in LV twist.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>FRDA patients (n = 20) (mean ± SD)</th>
<th>Controls (n = 20) (mean ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak LV systolic twist (°)</td>
<td>9.2 ± 3.3</td>
<td>11.7 ± 2.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Peak apex systolic rotation (°)</td>
<td>6.0 ± 2.9</td>
<td>8.5 ± 2.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Peak base systolic rotation (°)</td>
<td>-3.5 ± 1.6</td>
<td>-3.4 ± 1.4</td>
<td>0.861</td>
</tr>
<tr>
<td>UT (%) at 5%</td>
<td>8.4 ± 7.9</td>
<td>12.7 ± 11.9</td>
<td>0.185</td>
</tr>
<tr>
<td>UT (%) at 10%</td>
<td>19.7 ± 13.0</td>
<td>30.6 ± 20.9</td>
<td>0.056</td>
</tr>
<tr>
<td>UT (%) at 15%</td>
<td>35.0 ± 17.4</td>
<td>46.9 ± 21.0</td>
<td>0.059</td>
</tr>
<tr>
<td>Peak UT rate (°/s)</td>
<td>-80.6 ± 29.4</td>
<td>-101.2 ± 29.6</td>
<td>0.035</td>
</tr>
<tr>
<td>GSLS (%)</td>
<td>-15.3 ± 2.1</td>
<td>-17.5 ± 1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>GSCirS (%)</td>
<td>-19.5 ± 2.9</td>
<td>-21.4 ± 2.6</td>
<td>0.034</td>
</tr>
<tr>
<td>GSRadS (%)</td>
<td>22.4 ± 4.3</td>
<td>24.1 ± 4.5</td>
<td>0.225</td>
</tr>
</tbody>
</table>

LV, left ventricular; UT, untwisting; GSLS, global systolic longitudinal strain; GSCirS, global systolic circumferential strain; GSRadS, global systolic radial strain.
Congruent with this observation, we found a negative correlation not only between the UT rate and systolic twist, but also with apical rotation. The altered mechanics of the apex during systole may thus predominantly contribute to the impairment in the suction force involved in diastolic LV filling. The clinical impact of these alterations in filling and diastolic parameters is, however, unclear, as LA size, a marker of LA pressure, was not significantly higher in the FRDA patients.

As a result from neurological dysfunction, the BSA was lower in FRDA patients. However, because strain parameters negatively correlate to the BSA, the finding of lower strain parameters in FRDA patients is, therefore, even more significant. There is also uncertainty on whether the reduced twist might be related to difference in body size rather than on intrinsic mechanical alteration. Indeed, the specific effect of the BSA on rotational mechanics, independently of age is, to the best of our knowledge currently unknown. Because chronotropic stimulation has little effect on rotational mechanics it is unlikely that the observed increased heart rate in FRDA patients had a significant impact on our results.

**Friedreich’s ataxia and left ventricular morphology**

A concentric LV remodelling pattern was found in the majority of our patients. This pattern may represent a compensatory mechanism for loss of LV contractility allowing reduced end-systolic wall stress to occur. Indeed, the ejection fraction may be preserved in patients with heart failure and LV hypertrophy. Furthermore, FRDA cardiomyopathy is characterized histologically by cardiomyocytes hypertrophy, replacement of cardiac cells by connective tissue, and focal necrosis. In hypertensive heart disease, the presence of concentric remodelling has been associated with loss of LV function. Similarly, in FRDA patients, this pattern might also contribute to the altered cardiac mechanics through a Frank–Starling-mediated mechanism resulting from decreased end-diastolic volume and thus preload reduction. However, the lack of correlation between the RWT and any of the strain parameters suggests that concentric remodelling geometry cannot fully explain the altered cardiac mechanics.

Importantly, these morphological and contractile changes are associated with decreased pump performance, since indexed stroke volume was inversely correlated with the extent of LV remodelling. A similar finding has been reported in patients with hypertension, and was associated with a poorer cardiovascular prognosis compared with hypertensive patients without concentric remodelling; however, the prognostic significance of this pattern in FRDA patients is currently unknown.

In conclusion, our prospective study demonstrates that, despite normal LVEF and mass, subtle LV systolic dysfunction as assessed by speckle-tracking imaging is present in FRDA patients. This myocardial dysfunction involves not only longitudinal, but also circumferential and rotational parameters, and is associated with a concentric remodelling pattern, as well as a reduced stroke volume. Whether these parameters will prove useful as predictors of future cardiac events and as outcome measures for the assessment and follow-up of new therapies in FRDA warrants further studies.

**Study limitations**

Two-thirds of the patients were receiving specific therapies (idebenone and deferiprone), reflecting the situation in the general population of FRDA patients. Although there are no definite data on the myocardial actions of these drugs, no deleterious effects have been reported, and they may even improve cardiac function. Therefore, one could hypothesize that the observed twist and strain reduction would have been even more striking without such medications. The present analysis focused on echocardiographic evaluation of FRDA patients in a small number of patients; further larger studies, using magnetic resonance imaging, might allow to assess the correlation between iron deposits and fibrosis, and the markers of LV dysfunction.

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