that between 39 and 100% of patients develop a hypertrophic or ataxia affecting 1 in 50,000 live births. Various studies have reported

Introduction. Friedreich's ataxia (FA), an autosomal recessive neurodegenerative disorder, is the most common form of inherited ataxia affecting 1 in 50,000 live births. Various studies have reported the ratio of phosphocreatine (PCr) to ATP is a measure of the energetic state of cardiac muscle (4,5).

To determine if the frataxin defect in FA led to abnormal cardiac energetics, we measured PCr to ATP ratios non-invasively by 31P-MRS in the hearts of 17 FA patients, all homozygous for the GAA expansion.

Methods. Seventeen FA patients (mean age 33; 7 males) (Table 1) and 18 controls (mean age 30; 8 males) were studied in a 2T Oxford magnet interfaced to a Bruker Avance spectrometer. Patients lay prone in the magnet and standard spin-echo MRI was used to position the heart in the centre of the magnet. Cardiac 31P spectra were acquired using a 7 cm circular surface coil placed below the chest. Data were acquired following shimming using a slice selective, 1D spectroscopic imaging sequence. A single oblique outer volume suppression slab was positioned using the MR images and was used to pre-saturate 31P signal from the lateral chest wall to improve the localisation (6). Spatial resolution was set to 1cm and encoding was performed in the anterior-posterior direction. Spectroscopic imaging rows corresponding to the heart were identified from the MR images and extracted from the data set. Data were analysed using a purpose written interactive frequency domain fitting program. Spectral fitting included adjustments for mixed Gaussian-Lorentzian lineshapes and first order phase changes due to phase encode duration. PCr to ATP ratios were calculated including a correction to the ATP signal for blood contamination (as determined from the 2,3-DPG resonance). The ratios were corrected for saturation, based on excitation profile of the surface coil, literature values of T1 for PCr and γ-ATP, distance of slices from the coil and heart rate (7). Left ventricular dimensions were measured from echocardiograms using a HP5500 system and fractional shortening (FS) was calculated. Data are presented as mean ± SD. Statistical analysis was performed by Student t test for unpaired data, and p < 0.05 was taken to be significant.

Table 1. Clinical details from FA patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age of onset (years)</th>
<th>Duration of disease (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA with normal</td>
<td>31 ± 9</td>
<td>18 ± 9</td>
</tr>
<tr>
<td>PW4 and IVD4</td>
<td>(n=5)</td>
<td></td>
</tr>
<tr>
<td>FA with increased</td>
<td>31 ± 10</td>
<td>16 ± 10</td>
</tr>
<tr>
<td>PW4 and IVD4</td>
<td>(n=12)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Results. Five patients had normal echocardiograms, while the rest showed left ventricular hypertrophy (posterior wall, PW4 or septal IVD4 thickness equal or greater than 1.1 cm) (Table 2). Except for one patient all had normal end-systolic (LVes) and end-diastolic (LVad) dimensions, and fractional shortening (FS) (Table 2). The figure shows a spectrum from a patient and a control. In FA patients the mean PCr/ATP ratio was 1.88 (0.77) compared to controls in whom it was 2.85 (0.32) (p<0.001). PCr/ATP ratios in both group of FRDA patients with normal (1.33 ± 0.68) and hypertrophied heart (1.99 ± 0.75) was significantly reduced compared to controls (p<0.001 for both groups) (Table 2). There was no statistical difference in PCr/ATP ratio between FRDA patients with and without left ventricle hypertrophy (p= 0.1).

Discussion. In FA patients the intrinsic X25 GAA repeat expansion is associated with abnormal in vivo cardiac bioenergetics in the absence of any discernible deterioration in contractile performances. The bioenergetic defect is present in FA patients without left ventricle thickening, indicating that cardiac metabolic dysfunction in FA precedes the development of the hypertrophic process.

Previous studies demonstrated low PCr/γ-ATP ratios in patients with impaired left ventricular function (4). In aortic valve disease, patients with reduced ejection fractions had lower ratios compared to controls (4). In mitral regurgitation, a significant correlation was found between fractional shortening and PCr/γ-ATP ratios (5). PCr/γ-ATP is normal in non-failing hypertrophied ventricles in hypertension and HCM, but is reduced in patients with impaired left ventricular function. It has been suggested that the biochemical abnormality is a consequence of the mechanical abnormality.

In our FA patients PCr to γ-ATP ratios were decreased irrespective of echocardiographic findings, suggesting that the metabolic mitochondrial defect may initiate the myocardial abnormalities. Intramitochondrial iron content has been found to be increased in myocardium of FA patients. Iron is known to promote the generation of damaging oxygen species which probably are the cause of the bioenergetic abnormality we have described.

References