Cardiac torsion-strain relationships in fatigued primary biliary cirrhosis patients show accelerated aging: a pilot cross-sectional study

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THE AUTOIMMUNE CHOLESTATIC liver disease primary biliary cirrhosis (PBC) is associated with life-altering fatigue in ~50% of patients. Previous work suggests that fatigued PBC subjects have evidence of autonomic dysfunction and may be at a higher risk of sudden cardiac death. The manifestation of this risk is not clear. This pilot study investigated whether alterations in cardiac torsion and strain could be detected in fatigued or nonfatigued early-stage PBC patients. We performed cardiac tissue tagging and anatomical cine-imaging in 13 early-stage PBC patients (including 7 with significant fatigue) and 10 control subjects to calculate cardiac torsion and strain throughout systole and diastole. From the cardiac tagging, we calculated the torsion-to-shortening ratio (TSR), a measure of subepicardial torsion exerting mechanical advantage over subendocardial shortening. Autonomic function testing was performed to evaluate baroreceptor effective index on standing. TSR was markedly increased in the fatigued PBC patients (0.70 ± 0.13) compared with both controls (0.46 ± 0.11, P = 0.002) and nonfatigued PBC patients (0.44 ± 0.12, P = 0.003). Decreased baroreceptor effective index on standing strongly correlated with increased TSR within the whole PBC group (r = −0.71, P = 0.007). Fatigued PBC patients demonstrate a redistribution of myocardial strain characteristic of a reduced relative contribution to contraction from the subendocardium. This is analogous to the changes found in healthy aging for subjects ~16 yr older than the fatigued PBC patients. Hence the hearts of fatigued PBC patients may be subject to processes of accelerated aging.

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fatigue severity was assessed by means of a validated questionnaire, the Fatigue Impact Score (FIS) (30). The FIS is a 40-item symptom-specific measure of health-related quality of life, commonly used in medical conditions in which fatigue is a prominent symptom. This scale allows patients to rate each item on a scale of 0 to 4, with 0 representing no problem and 4 representing an extreme problem, summed to provide a total score running from 0 (no fatigue) to 160, with higher scores indicating worse fatigue. Patients were divided into two groups: those without significant fatigue (defined as FIS < 25), and those with severe fatigue (FIS > 50). All controls had FIS < 25. The same experimental subjects had had phosphorus-31 (31P) MRS of the heart carried out at the same experimental session, and this has been reported elsewhere (16). Written, informed consent from all participants and institutional ethics approval were obtained.

Cardiac cine MRI. Cardiac examinations were performed using a 3T Philips Intera Achieva scanner (Best, NL). A dedicated 6-channel cardiac coil (Philips, Best, NL) was used with the subjects in a supine position and electrocardiogram gating. Cardiac cine MRI was acquired to assess cardiac morphology and systolic and diastolic function. A stack of balanced steady-state free precession images was acquired to estimate LV mass, systolic and diastolic parameters, including the ratio of early to late ventricular filling velocity (E/A ratio) and early filling percentage, have been detailed elsewhere (16). The ratio of the LV mass to the end-diastolic volume was calculated as this parameter is a measure of concentric remodeling (5). Preload, afterload, contractility, and ventricular-arterial coupling were also estimated: preload was determined by the end-diastolic volume, afterload by arterial elastance [Ea = end-systolic pressure (systolic BP × 0.9)/stroke volume (normalized to body surface area)], contractility by end-systolic elastance [Ees = end-systolic pressure/end-systolic volume (normalized to body surface area)], and ventricular-arterial coupling by the ratio of Ees/Ea.

Cardiac tagging. Tagged short-axis images were acquired at the same session as the morphological imaging (Fig. 1A). A turbo-field echo sequence with acceleration factor 9 was used (repetition time/echo time 4.9/3.1, flip angle 10°, number of averages 1, SENSE factor 2, field of view 350 × 350 mm, voxel size 1.37 × 1.37 mm with an orthogonal complementary spatial modulation and magnetization grid with tag spacing of 7 mm) (8). Two adjacent short-axis slices of 10-mm thickness were acquired at midventricle with a 2-mm gap. The Cardiac Image Modelling package (Auckland UniServices, New Zealand) was used to analyze the tagging data by aligning a mesh on the tags between the endo- and epicardial contours. Circumferential strain and the rotation of the two planes were calculated throughout the cardiac cycle. Circumferential strain is quoted for both the whole myocardial wall and the endocardial one-third of the wall thickness. The epicardial torsion between the two planes (taken as the circumferential-longitudinal shear angle defined on the epicardial surface, γ) was calculated (4).

In the healthy heart, torsion occurs such that there is homogeneity of fiber shortening across the myocardial wall and is a marker of the dominance of epicardial fibers over endocardial fibers as a consequence of the greater radius in the epicardium. This can be quantified by a ratio of the peak torsion (in radians), defined as the shear angle between two planes on the epicardial surface (22), and the peak circumferential strain in the endocardial one-third of the myocardium, which is referred to as the torsion-to-shortening ratio (TSR) (22, 33). This ratio has been shown to be near constant among healthy subjects of the same age, and to increase with both healthy aging and disease. The rate at which torsion dissipates after systole is an important

Table 1. Morphological parameters for controls and PBC subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (a)</th>
<th>PBC Nonfatigued (b)</th>
<th>PBC Fatigued (c)</th>
<th>ANOVA Significant Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>51 ± 8</td>
<td>51 ± 10</td>
<td>54 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27 ± 3</td>
<td>26 ± 3</td>
<td>25 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71 ± 7</td>
<td>69 ± 9</td>
<td>63 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>121 ± 13</td>
<td>126 ± 23</td>
<td>116 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>77 ± 11</td>
<td>73 ± 7</td>
<td>80 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>96 ± 16</td>
<td>93 ± 6</td>
<td>88 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>LV index, g/m²</td>
<td>54 ± 7</td>
<td>53 ± 3</td>
<td>53 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>64 ± 12</td>
<td>65 ± 6</td>
<td>65 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>62 ± 7</td>
<td>65 ± 5</td>
<td>65 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Mass-to-end-diastolic volume, g/ml</td>
<td>0.78 ± 0.07</td>
<td>0.75 ± 0.09</td>
<td>0.85 ± 0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>76 ± 13</td>
<td>81 ± 10</td>
<td>68 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>4.8 ± 0.6</td>
<td>5.3 ± 1.0</td>
<td>4.4 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>End-diastolic volume, ml</td>
<td>123 ± 21</td>
<td>124 ± 14</td>
<td>105 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>End-systolic volume, ml</td>
<td>47 ± 14</td>
<td>43 ± 9</td>
<td>37 ± 10</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SD; N, no. of subjects. Where ANOVA indicates significant differences between at least two groups, the letters a, b, and c are used to specify the post hoc Bonferroni corrected significance between two specific groups. PBC, primary biliary cirrhosis; BMI, body mass index; LV, left ventricular; NS, no significant difference between any pair of groups.
Table 2. Wall motion, diastolic function, and autonomic function parameters for controls and PBC subjects

<table>
<thead>
<tr>
<th></th>
<th>Control (a)</th>
<th>PBC Nonfatigued (b)</th>
<th>PBC Fatigued (c)</th>
<th>ANOVA Significant Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>6</td>
<td>7</td>
<td></td>
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<tr>
<td>Torsion-to-shortening ratio</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Peak torsion, °</td>
<td>0.46 ± 0.11</td>
<td>0.44 ± 0.12</td>
<td>0.70 ± 0.13</td>
<td>P = 0.002 a/c, P = 0.003 b/c</td>
</tr>
<tr>
<td>Peak torsion, °</td>
<td>6.2 ± 1.7</td>
<td>5.6 ± 1.4</td>
<td>7.9 ± 1.4</td>
<td>P = 0.05 b/c</td>
</tr>
<tr>
<td>Peak endocardial circumferential strain, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual torsion at 150% ES, °</td>
<td>1.7 ± 0.7</td>
<td>2.9 ± 1.0</td>
<td>3.4 ± 2.0</td>
<td>P = 0.07 b/c</td>
</tr>
<tr>
<td>Longitudinal shortening, %</td>
<td>18.3 ± 3.1</td>
<td>18.6 ± 2.3</td>
<td>19.8 ± 3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Radial thickening, %</td>
<td>61 ± 17</td>
<td>60 ± 16</td>
<td>59 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.73 ± 0.60</td>
<td>1.95 ± 0.60</td>
<td>1.47 ± 0.52</td>
<td>NS</td>
</tr>
<tr>
<td>Early filling percentage, %</td>
<td>72 ± 5</td>
<td>73 ± 4</td>
<td>67 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial elastance, mmHg m⁻²·m⁻¹</td>
<td>2.6 ± 0.5</td>
<td>2.5 ± 0.5</td>
<td>2.6 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Contractility, mmHg m⁻²·m⁻¹</td>
<td>4.5 ± 1.1</td>
<td>4.7 ± 1.4</td>
<td>4.9 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular-arterial coupling</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Baroreflex effectiveness index on standing, %</td>
<td>55.5 ± 21.5</td>
<td>71.9 ± 14.1</td>
<td>47.7 ± 23.1</td>
<td>NS</td>
</tr>
<tr>
<td>Low-frequency heart rate variability on standing, ms²</td>
<td>241 ± 239</td>
<td>631 ± 283</td>
<td>272 ± 257</td>
<td>P = 0.06 a/b P = 0.08 b/c</td>
</tr>
</tbody>
</table>

Values are means ± SD; N, no. of subjects. Where ANOVA indicates significant differences between at least two groups, the letters a, b, and c are used to specify the post hoc Bonferroni corrected significance between two specific groups. ES, end-systolic time; E/A, ratio of early to late ventricular filling velocity.

Statistical analysis. Image analysis was performed blinded to the status of patients and controls. Statistical comparisons were made using SPSS version 17. Data are presented as means and SD. Data were tested for normality using the Shapiro-Wilk test, and comparisons were drawn between groups using ANOVA (or Kruskal-Wallis where nonparametric) with post hoc Bonferroni correction for multiple comparisons. Correlations were executed as two-tailed tests using the Pearson correlation method (or Spearman’s rank if nonparametric). Statistical significance level was set at P < 0.05.

RESULTS

Cardiac MR data for the groups are presented in Tables 1 and 2. Cardiac tagging strain and torsion measurements. Peak LV torsion was increased by 27% in the fatigued PBC group compared with the control group, and peak endocardial circumferential strain was reduced by 9% in the fatigued PBC group, although these changes did not reach individual statistical significance (Table 2). The TSR was significantly increased in the fatigued PBC group compared with either the age-matched control group (by 52%, P = 0.002) or the nonfatigued PBC group (by 59%, P = 0.003, Fig. 2). There was no difference in torsion, strain, or TSR between the controls and the nonfatigued PBC group. Longitudinal shortening and radial thickening were not different between the three groups.

Fig. 2. Torsion-to-shortening ratio (TSR) in the control, nonfatigued, and fatigued primary biliary cirrhosis (PBC) groups. Boxes indicate lower and upper quartiles, the median value is indicated by the central line, whereas stems indicate outlying values.

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There were no significant differences in diastolic function as measured by the E/A ratio or the early filling percentage (Table 2). The residual torsion at 150% of the end-systolic time was significantly longer in the PBC group as a whole (3.1° ± 1.6°) compared with the control group (1.7° ± 0.7°, P = 0.02); there was no significant difference between the nonfatigued and fatigued PBC groups (Fig. 3), with the greatest difference between the control group and the fatigued PBC patients (P = 0.07). There was no correlation between the residual torsion at 150% of the end-systolic time and either measure of diastolic function (early filling percentage, E/A ratio) or the TSR.

**Relationship between cardiac tagging measurements and autonomic function tests.** There was a strong inverse relationship between baroreflex effectiveness index upon standing and the TSR (r = -0.71, P = 0.007, Fig. 4) in the PBC group as a whole. The baroreflex effective index on standing (which measures the number of times that the baroreflex is effective in overcoming the nonbaroreflex influences that regulate the sinus node) indicated that the baroreflex was less effective in those with the most impaired ratio between torsion and endocardial strain at rest.

There was also a strong inverse relationship between low-frequency beat-to-beat interval variance on standing and the TSR (r = -0.70, P = 0.007, Fig. 5). The low-frequency beat-to-beat interval variance after orthostatic loading represents peripheral sympathetic activity/sympathetic vasomotor control, and this association indicated that those patients with the most abnormal TSR in the resting state also had the greatest impairment of sympathetic vasomotor control.

There was no correlation between TSR and autonomic function results with patients at rest.

**Cardiac morphology and function by standard cine-MRI.** As reported previously, parameters relating to cardiac morphology (LV mass, end-diastolic and end-systolic volume) were not significantly different between the control group and PBC patients, regardless of fatigue status. Table 1 summarizes the main parameters, which can be found in more detail in Ref. 16: there was no significant difference in systolic or diastolic BPs between any groups. When the PBC group was divided into those with and without significant fatigue, there was no significant difference between LV mass, LV index, or mass-to-volume ratio, eliminating the possibility of overt concentric hypertrophy in the fatigued PBC group. Likewise, ejection fractions, stroke volume, cardiac output, heart rate, arterial elastance, contractility, and ventricular-arterial coupling were equivalent in the three groups.

**DISCUSSION**

This study demonstrated that there are abnormalities in the ratio of torsion to endocardial circumferential strain in a group of severely fatigued PBC patients compared with groups of matched controls and nonfatigued PBC patients. This finding arose from raised peak torsion and lower circumferential strain. The release of LV torsion in early diastole was delayed in PBC patients compared with controls, despite no significant defect in diastolic filling.

In our laboratory’s previous work (11) on healthy subjects in young (mean age 31 ± 6 yr), middle-aged (mean age 48 ± 6 yr), and older groups (mean age 62 ± 2 yr), we found that the TSR remains constant between the young and middle-aged groups (mean 0.43 and 0.48, respectively), while it was raised by 44% in the oldest group (mean 0.62). Other authors have...
noted increases in torsion and TSR, notably Oxenham et al. (12), where a 38% increase in TSR and 33% increase in torsion were noted between two groups of healthy volunteers with mean ages of 23 and 68 yr old. Our group of fatigued PBC patients (mean age 54 yr) demonstrated an increase in TSR (52% compared with controls) in excess of that of a group of subjects who were 8 yr older on average. Under an assumption of linearly increasing TSR with age (as our laboratory reported in healthy control subjects (11)), we would estimate that the fatigued PBC hearts belonged to healthy individuals of mean age 70 yr, rather than their true mean of 54 yr, representing 16 yr of accelerated aging.

The timely release of torsion and strain during diastole is crucial for good diastolic function, and we evaluated this, as in other studies (27), by measuring the residual torsion at 150% of the end-systolic time. The PBC group as a whole had 89% more residual torsion at this time than the controls, although there was no significant difference between the nonfatigued and fatigued groups. By contrast, our work on healthy controls (11) indicated a 45% increase in residual torsion between mean age 48 and 62 yr. Similarly, a study with a wider age range (27) found a 56% increase in residual torsion between the ages of 22 and 69 yr old. This residual torsion did not significantly correlate with any measurement of cardiac morphology, function, or autonomic function in this study, although subject numbers are limited.

The increase in torsion and TSR in older adults indicated that there was an alteration in the transmural distribution of strain, and, in particular, that subendocardial fibers are not making a proportionate contribution to systolic ejection compared with the subepicardial fibers, with a consequent increase in torsion. It has been observed that the endocardium is particularly sensitive to insult, as has been shown in histopathology of ischemic tissue (13), by studies of transmural wall motion in stunned myocardium that has recovered from an ischemic insult (3, 23) and in patients with aortic valve stenosis (33).

Observation of raised TSR is not confined to healthy aging and has been shown to occur in overt cardiac diseases, where relative subendocardial contractile performance may be impaired. Compared with our observation of a 52% increase in TSR, in adult patients with severe aortic valve stenosis (33), TSR was increased by 91% compared with controls, while in patients 3 mo after valve replacement, TSR was only 39% increased compared with controls. In asymptomatic children with aortic stenoses, TSR was increased by 38% (6). In LV hypertrophy, a comparable measure of TSR was found to be increased by 24% in hypertrophic cardiomyopathy mutation carriers without hypertrophy (31), while a study of those with hypertrophy (34) found an approximate 50% increase in torsion compared with strain (although they did not calculate TSR itself). The magnitude of the changes we find are, therefore, comparable with examples of subclinical and overt disease.

Previous studies exploring potential biomarkers for cardiac risk have suggested that reduced baroreceptor function and reduced heart rate variability have the potential to identify those at increased risk of cardiac mortality (19, 20, 32). Interestingly, reductions in these parameters on standing were both associated with increased TSR at rest in the PBC patient group, indicating reduced relative subendocardial contribution. This provides a direct link between changes in baroreceptor function under stress and general contractile performance, confirming the potential role that TSR may have in predicting cardiac mortality. We acknowledge that we cannot draw conclusions about causation from this study, but it is interesting to speculate that increased TSR in PBC arises either as a consequence or cause of reduced baroreceptor function.

Previously, our laboratory had observed that myocardial energetics were impaired in two-thirds of the PBC cohort compared with a matched control group (16). There was no association between the abnormally high TSR found and the myocardial ratio of phosphocreatine to adenosine triphosphate in this group. Abnormalities in myocardial energetics may precede the development of motion abnormalities, as has been found in other diseases (9, 21).

The limitations of this study included that we did not perform tagging studies of the entire LV, and so we are unable to comment on differences that may exist in torsion and strain characteristics between apex and base. A small number of subjects were examined in this pilot study. To reduce the burden of the examination (which was one part of a larger MR protocol and medical assessment), we did not perform tagging with as fine a time resolution as other studies, so we are unable to detect small changes in the timing of the onset and release of torsion and systole. Given the findings of potentially altered contractile function, a study of a larger cross-sectional cohort of PBC subjects is indicated. We are unable to say how such differences may develop within the time course of PBC. This would demand an extensive longitudinal experiment: such experiments would now be highly desirable to establish the time course of changes.

Conclusions. This study has established that there are differences in myocardial mechanics present in both nonfatigued and fatigued PBC subjects, and that a larger characterization study is warranted, particularly focusing on those PBC subjects with fatigue and the relationship between cardiac torsion, strain, and autonomic function.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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