Impaired cardiovascular function in primary biliary cirrhosis

David E. J. Jones, Kieren Hollingsworth, Gulnar Fattakhova, Guy MacGowan, Roy Taylor, Andrew Blamire, and Julia L. Newton

1Institute of Cellular Medicine, 2Newcastle Magnetic Resonance Centre, and 3Institute for Ageing and Health, Newcastle University, Newcastle, United Kingdom

Submitted 10 December 2009; accepted in final form 3 February 2010

Impaired cardiovascular function in primary biliary cirrhosis. Am J Physiol Gastrointest Liver Physiol 298: G764–G773, 2010. First published February 4, 2010; doi:10.1152/ajpgi.00501.2009.—Cardiovascular system dysregulation in the form of autonomic dysfunction is common at all stages of the disease process in the autoimmune liver disease primary biliary cirrhosis (PBC) and associates with the symptom of fatigue. The mechanisms underpinning autonomic dysfunction in PBC are, however, at present unclear. In this study we set out to explore, for the first time, cardiac structure and function in PBC using impedance cardiography (ICG) and magnetic resonance methodologies. ICG was assessed beat to beat in response to orthostasis (by head-up tilt) in age and sex case-matched high-fatigue and low-fatigue PBC groups (assessed by Fatigue Impact Scale), normal control subjects (n = 15 each group) and a liver disease control cohort (primary sclerosing cholangitis). Cardiac structure and bioenergetics were examined in 15 of the PBC subjects and 8 of the normal control subjects by magnetic resonance spectroscopy and cine imaging. Capacity of the left ventricle to respond to orthostasis [left ventricular ejection time (LVET)] was impaired in PBC compared with matched normal control subjects (P = 0.05). This was a PBC-specific phenomenon unrelated to fatigue status. PBC patients exhibited significantly lower cardiac muscle phosphocreatine-to-ATP ratio (PCr/ATP ratio; measure of cardiac bioenergetic integrity) compared with control subjects (P < 0.01). PCr/ATP <1.6 (indicative of increased risk of death in cardiomyopathy) was present in 6/15 (40%) PBC patients (0/8 control subjects; P < 0.05). Cardiac structure and function were similar in all measures of left ventricular morphology between control subjects and PBC. The close relationship between PCr/ATP and LVET seen in normal subjects (r² = 0.6; P < 0.05) was lost in PBC patients, a finding compatible with myocardial dysfunction. Significant correlation was seen between fatigue severity in PBC and fall in cardiac output on orthostasis (r² = 0.25; P = 0.005). Our hypothesis therefore was that PBC patients have cardiac impairment that occurs as a result of a bioenergetic abnormality that accounts (at least in part) for the autonomic dysfunction and increased cardiac risk seen in those with PBC. To explore this, we used two complementary dynamic assessment approaches: impedance cardiography (ICG) and magnetic resonance spectroscopy (MRS) and imaging. ICG measures noninvasive changes in thoracic impedance generated by fluctuating blood volumes on a beat-to-beat basis, allowing noninvasive assessment of cardiac function and calculation of preload, myocardial contractility, and afterload. Magnetic resonance technology allows both real-time imaging of cardiac anatomy during the cardiac cycle but also assessment of myocardial metabolic function. A combination of these approaches, together with clinical assessment of the symptoms of PBC, provides a novel insight into derangement of cardiovascular function in PBC.

SUBJECTS AND METHODS

Subjects

Impedance cardiography was performed in fully age and sex case-matched groups of PBC patients with high and low perceived fatigue severity (n = 15 each group), normal control subjects (also America and the UK and the almost universal presence of hypercholesterolemia (albeit elevation typically of HDL and lipoprotein X) (16). Epidemiological studies in PBC performed by both our group and others have, however, reopened this debate. Two large, community-based epidemiological studies from Newcastle and Nottingham in the UK have shown significantly increased all-cause mortality rates in comprehensive PBC patient groups, with a significant component of this increased mortality coming from non-liver-related causes (11, 28). These studies were not designed to address the cause of this increase in non-liver-related mortality. There is, however, convincing evidence from the same populations to suggest that malignant disease makes little or no contribution to this excess nonliver mortality (9, 11). Given the importance of cardiovascular mortality in the general population, the possibility must be considered that cardiac mechanisms contribute to the excess nonliver mortality rates seen in these UK populations.

The limitation shared by the existing studies of cardiovascular disease in PBC is that they fail to address the issue of cardiovascular function (as distinguished from structure). Where dynamic aspects of cardiovascular system function have been addressed in PBC, such as autonomic nervous system regulation of the hemodynamic response to standing, significant abnormality has been observed (12, 13, 20–22). Furthermore, autonomic dysfunction of the type seen in PBC is associated with increased cardiac mortality risk in nonliver chronic disease states (25, 32). We have also recently reported significant peripheral muscle bioenergetic abnormality in PBC (7) raising the possibility that similar bioenergetic abnormality may also be present in cardiac muscle.

Our hypothesis therefore was that PBC patients have cardiac impairment that occurs as a result of a bioenergetic abnormality that accounts (at least in part) for the autonomic dysfunction and increased cardiac risk seen in those with PBC. To explore this, we used two complementary dynamic assessment approaches: impedance cardiography (ICG) and magnetic resonance spectroscopy (MRS) and imaging. ICG measures noninvasive changes in thoracic impedance generated by fluctuating blood volumes on a beat-to-beat basis, allowing noninvasive assessment of cardiac function and calculation of preload, myocardial contractility, and afterload. Magnetic resonance technology allows both real-time imaging of cardiac anatomy during the cardiac cycle but also assessment of myocardial metabolic function. A combination of these approaches, together with clinical assessment of the symptoms of PBC, provides a novel insight into derangement of cardiovascular function in PBC.

THE QUESTION AS TO WHETHER the autoimmune cholestatic liver disease primary biliary cirrhosis (PBC) is associated with abnormality in the cardiovascular system is a controversial one. Studies looking at the prevalence of ischemic cardiovascular disease have given contradictory results, with a current consensus that there is little, if any, increase in such disease risk in PBC (8, 24). This is despite the well-described increase in smoking frequency among PBC patients in both North
matched to the low-fatigue PBC patients for fatigue severity), and a cholestatic liver disease control cohort (primary sclerosing cholangitis, n = 13). PBC patients were consecutive appropriate, noncirrhotic patients identified from a specialist disease clinic with normal liver synthetic function (albumin, bilirubin, and prothrombin time). All had definite or probable PBC defined according to previously validated criteria [at least 2 of the 3 of cholestatic biochemical parameters, compatible liver histology and supportive serology (17)]. All participants in the present study were antimitochondrial antibody positive by immunofluorescence at a titer of ≥1:40 with M2 presence confirmed by ELISA. Normal control subjects were recruited via notices in the local press. No screening was performed in the control subjects. Primary sclerosing cholangitis (PSC) patients were recruited via the Freeman Hospital Liver Clinic database. Clinical details of PBC and PSC participants are given in Table 1. A 12-lead ECG including QTc was performed in all subjects.

Potential participants in all groups were excluded if they had a clinical history of diagnosed cardiovascular disease or hypertension or were taking medicines able to modulate blood pressure (including antihypertensives, antianginals, and antidepressants). None of the subjects was receiving statin therapy or had renal impairment and none had clinical evidence suggestive of the presence of valvular heart disease. Subjects were excluded from the study if found to have any of the following secondary causes for fatigue and/or autonomic abnormalities: hypothyroidism, multiple sclerosis, diabetes mellitus, anemia, Parkinson’s disease, rheumatoid arthritis. To participate in the study subjects also had to be capable of standing for the duration of the 40-min assessment. Ethical permission was obtained for the study of control subjects from the Newcastle and North Tyneside Local Research Ethics Committee; the protocol was reviewed and approved by the UK Medical Research Council.

Impedance Cardiography

The ICG signal was acquired via electrodes placed on the neck and the thorax, and the resultant signals were used to derive stroke volume and systolic time intervals (Taskforce, CNSYStems, Graz, Austria) (1). The electrical and impedance signals were processed to determine fiducial points, which were then utilized to measure and calculate hemodynamic parameters. These were then normalized for body surface area to provide the following.

Indicators of cardiac function. Cardiac output is output from the heart per minute, which is the product of heart rate and stroke volume, the output from the heart per beat.

Indicators of myocardial contractility. Left ventricular ejection time (LVET) is the time interval from the opening to the closing of the aortic valve (mechanical systole).

Table 1. Clinical details of liver disease patient groups included in the study

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Low-Fatigue PBC (n = 15)</th>
<th>High-Fatigue PBC (n = 15)</th>
<th>P</th>
<th>PSC (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % female in group</td>
<td>64 ± 14</td>
<td>62 ± 15</td>
<td>59 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Fatigue Score, FIS</td>
<td>5 ± 5</td>
<td>74 ± 30</td>
<td>23 (26)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AMA positivity, no. of subjects (%)</td>
<td>15 (100)</td>
<td>15 (100)</td>
<td>23 (26)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Clinical features of advanced disease, no. of subjects (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>6 (40%)</td>
<td>5 (33%)</td>
<td>7 (54%)</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>6 (46%)</td>
<td></td>
</tr>
<tr>
<td>No biopsy</td>
<td>9 (60%)</td>
<td>10 (67%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Biochemistry, median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>150 (41–192)</td>
<td>160 (60–250)</td>
<td>280 (110–248)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>9 (6–16)</td>
<td>10 (7–17)</td>
<td>30 (12–55)</td>
<td></td>
</tr>
<tr>
<td>Alanine transaminase</td>
<td>40 (35–45)</td>
<td>41 (30–52)</td>
<td>55 (32–52)</td>
<td></td>
</tr>
<tr>
<td>Medication, no. (%) taking Urs</td>
<td>12 (80%)</td>
<td>12 (80%)</td>
<td>10 (80%)</td>
<td></td>
</tr>
</tbody>
</table>

All values are means ± SD unless stated. Clinical features of advanced disease were defined in the study protocol as evidence of varices, ascites, or systolic blood pressure (SBP), history of encephalopathy, or history of decompenstation episode. FIS, Fatigue Impact Scale; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; NS, not significant. AMA, antimitochondrial antibody.

Cardiac MRS

Cardiac high-energy phosphate metabolism was subsequently assessed in representative subgroups of the PBC patients and normal control subjects using 31P MRS within 2 wk of the impedance assessment. Data were collected via a 3T Intera Achieva scanner (Philips, Best, Netherlands) with a 10-cm diameter 31P surface coil (Pulseteq) for transmission/reception of signal. Subjects were placed in a prone position and moved into the magnet so their heart was at magnet isocenter. Localizing images were collected by using the in-built body coil to confirm location of the heart. Shimming was performed via a cardiac-triggered, breath-held field map (30). A slice-selective, cardiac-gated one-dimensional chemical shift imaging sequence was used with a 7-cm slice-selective pulse-applied foot head to eliminate contamination from the liver, with spatial presaturation of lateral skeletal muscle to avoid spectral contamination. We used 16 coronal phase-encoding steps, yielding spectra from 10-mm slices (TR = heart rate, 192 averages at the center of k-space with cosine-squared acquisition weighting, ~20-min acquisition time). Spectral locations were overlaid onto an anatomical image, and the first spectrum arising entirely beyond the chest wall was selected. Quantification of PCr, the γ resonance of adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (DPG) was performed by using the AMARES time domain fit routine in the jMRUI processing software (Vandamme). After fitting, the ATP peak area was corrected for blood contamination by 1/6 of the amplitude of the combined 2,3-DPG peak (3), and the ratios of PCr to ATP (PCr/ATP ratios) were calculated and corrected for saturation, with T1 values of cardiac PCr and ATP taken from the literature (34). Flip angle correction was made by using

Indicators of preload. End-diastolic index (EDI) is defined as end-diastolic volume per body surface area.

All parameters were assessed initially at rest in the supine position over 10 min (phase 1) and, subsequently, during 40 min of passive head-up tilting (HUT; phase 2), a standard approach undertaken to stimulate the normal cardiovascular response to orthostasis. All parameters were measured continuously on a beat-to-beat basis, and mean values during the phases were used in the analysis. Variability of all parameters was also assessed. The HUT test was terminated at the patient’s request or when symptoms developed during the test that required termination of the assessment. In all groups only subjects who completed both resting and HUT phases of the study were included in the analysis of the hemodynamic and cardiovascular responses to orthostasis.
a gadolinium-doped 20 mM phenyl phosphonic acid phantom at the
center of the coil and a calibration dataset (2,5).

Cardiac Magnetic Resonance Cine Imaging

Cardiac magnetic resonance cine imaging was acquired in a sepa-
rate session in the patients undergoing cardiac MRS to assess cardiac
morphology and systolic and diastolic function. A dedicated six-
channel cardiac coil (Philips) was used with the subjects in a supine
position and ECG gating (Philips vectorcardiogram, VCG system).
A stack of balanced steady-state free precession images was obtained in
the short axis view covering the entire left ventricle (field of view =
350 mm, TR/TE = 3.7/1.9 ms, turbo factor 17, flip angle 40°, slice
thickness 8 mm, 0 mm gap, 14 slices, 25 phases, resolution 1.37 mm,
temporal duration ~40 ms per phase, dependent on heart rate). Image
analysis was performed by using the cardiac analysis package of the
ViewForum workstation (Philips). Manual tracing of the epicardial
and endocardial borders was performed on the short axis slices at
end-systole and end-diastole. The contours were reviewed by viewing
the cine data with the contours attached. The basal slice selected for
analysis for end-diastole and for end-systole occurred when at least
50% of the blood volume was surrounded by the myocardium (10).
The apical slice was defined as the last slice showing intracavity blood
pool. Papillary muscles were included in calculations of mass and
excluded from calculations of volume. The interventricular septum
was included as part of the left ventricle. Left ventricular mass,
ejection fraction, and end-systolic and end-diastolic volumes were
calculated. Myocardial mass was determined by multiplying the tissue
volume by 1.05 g/cm³ (specific density of myocardium). The body
surface area was estimated from the subjects’ weight and height
according to the formula of Dubois and Dubois (4), and this was used
to standardize the measurements for subject size.

To examine possible diastolic dysfunction, blood pool volumes
were calculated across all phases to look for the characteristic two-
phase expansion of the blood pool. The papillary muscles were
included in this determination. The left ventricular volume measure-
ments (25 per cardiac cycle) were plotted against time. The data were
then smoothed by using a piecewise cubic spline algorithm and
oversampled into 256 data points to create a volume-vs.-time curve.
The rate of change of blood pool volume was determined by taking
the first derivative of this curve over the entire cardiac cycle. End-
systole and end-diastole were defined as the times of lowest and
greatest volumes, respectively. The time point halfway between end-
systole and end-diastole was defined as the diastolic midpoint.

Five indexes of left ventricular diastolic function were determined
from the cine magnetic resonance data in each subject (14): 1) peak
early filling rate (defined as the maximum value of the first derivative
between end-systole and the diastolic midpoint); 2) peak late filling
rate (i.e., the maximum value of the first derivative between the
midpoint and end-diastole); 3) the early-to-late ratio (i.e., the peak
early rate divided by the peak late rate); 4) the time to peak early
filling (i.e., the time interval between end-systole and peak early
filling); and 5) the early filling percentage (i.e., the volume increase
from end-systole to the midpoint divided by the stroke volume ×
100). These five indexes were determined for each subject as well as
normalizing the early filling rate for end-diastolic volume.

Fatigue Assessment

Severity of fatigue was assessed in all subjects by use of the
Fatigue Impact Scale (FIS), a generic fatigue measure that has been
validated for use in all the subject groups studied (29). Assessment
was performed at the same time of day in all participants as per our
standard approach to fatigue assessment in PBC. 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.
The 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.
Individual scores are summed to provide a total score, with higher
scores indicating worse fatigue.

Statistical Analysis

Analysis was performed blinded to the status of patients and
control subjects. Where variables were normally distributed, data are
presented as mean and standard deviation and comparisons were
drawn between groups using the Student’s t-test. Where variables
were not normally distributed, data are presented as median and range
and comparisons are drawn by Mann-Whitney tests. Correlation analyses
and logistic regressions were performed by using the GraphPad Prism
package (http://www.graphpad.com/prism/Prism.htm). Pearson correla-
tion was performed when variables were parametric and Spearman Rank
when variables were nonparametric. Bonferroni correction for multiple
testing was applied. A value of $P < 0.05$ was considered a statistically
significant result.

RESULTS

Cardiovascular Responses to Standing Assessed by
Impedance Cardiography

Details of the ICG findings in response to standing are shown in Table 2. No subjects had a prolonged QTc. BPC patients as a group exhibited impairment in the capacity of the left ventricle to respond appropriately to orthostasis. Under normal conditions the LVET (the mechanical systole time) shortens as patients undergo the cardiac stimulus of passive
tilting from the supine to the vertical position (HUT). BPC patients showed a significant reduction in this shortening (compared
with the age-, sex-, and fatigue status-matched normal
control group), indicating a reduced cardiac physiological
response to orthostatic stress (Fig. 1A). This was independent
of changes in heart rate (data not shown). This effect was PBC
specific since patients with PSC exhibited normal shortening of
LVET in response to orthostasis (Fig. 1A). Supine, pretilting
absolute LVET was similar in PBC patients and normal
subjects (Fig. 1B) whereas LVET posttilt (i.e., in response to
orthostasis) was significantly prolonged in PBC patients
compared with control subjects (Fig. 1C). No significant difference
was seen between the nonfatigued and fatigued PBC patients
with regard to degree of LVET shortening in response to
orthostasis (Fig. 1D).

Table 2. Impedance cardiographic parameter response to standing

<table>
<thead>
<tr>
<th>Change in Response to Standing</th>
<th>Controls</th>
<th>Low-Fatigue PBC</th>
<th>High-Fatigue PBC</th>
<th>PSC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>$-0.7 \pm 0.8$</td>
<td>$-1.1 \pm 0.7$</td>
<td>$-0.4 \pm 0.7$</td>
<td>$-1.1 \pm 1.3$</td>
<td>0.15</td>
</tr>
<tr>
<td>End-diastolic index</td>
<td>$-11.7 \pm 11.5$</td>
<td>$-16.9 \pm 8.6$</td>
<td>$-6.8 \pm 8.2$</td>
<td>$-17.4 \pm 12.5$</td>
<td>0.14</td>
</tr>
<tr>
<td>Left ventricular ejection time</td>
<td>$36.3 \pm 15.0$</td>
<td>$22.3 \pm 16.4$</td>
<td>$25.1 \pm 15.1$</td>
<td>$34.2 \pm 19.0$</td>
<td>0.13</td>
</tr>
<tr>
<td>Heart rate</td>
<td>$12.6 \pm 6.4$</td>
<td>$8.2 \pm 6.4$</td>
<td>$8.2 \pm 4.2$</td>
<td>$13.2 \pm 11.3$</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Values are means ± SD.
To further explore left ventricular function in PBC patients, we examined cardiac muscle bioenergetics in 15 of the PBC patients (8 fatigued and 7 nonfatigued, groups representative of the whole study group in terms of age and disease severity) and 8 of the normal control subjects by cardiac MRS. PBC patients exhibited significantly lower cardiac muscle PCr/ATP ratio (a recognized measure of cardiac muscle bioenergetic integrity) compared with control subjects (Fig. 2). No significant association between PCr/ATP ratio and patient age was seen in either PBC patients or normal control subjects (data not shown). Previous studies have identified a value for PCr/ATP ratio of 1.6 as being of clinical relevance, with, in dilated cardiomyopathy patients, values of less than 1.6 being associated with significantly increased risk of cardiac mortality (26). PCr/ATP values of <1.6 were absent from the normal control subjects but present in 6/15 (40%) of PBC patients (P < 0.05). Analysis of the cine imaging to quantify cardiac structure and function demonstrated no significant difference in any measure of left ventricular morphology between the control subjects and PBC patients. None of the study subjects were found to have occult valvular heart disease. The functional measures of early and late filling rates, the ratio of the two rates and the time to midpoint were all found to be normal (Table 3 and 4). All cardiac parameters in both subject groups were found to be within the previously reported normal range for females of this age group (22).

**Structural and Functional Cardiac Function Assessed by Magnetic Resonance**

In the normal subjects a close inverse correlation was seen between cardiac bioenergetic function as denoted by PCr/ATP ratio on MRS assessment and LVET assessed by ICG (Fig. 3A), implying the possibility that limitation in myocardial energetics is compensated for by reduction in LVET shortening to maintain normal function (all the normal subjects had normal ejection fractions and cardiac output). In PBC patients, in

**Fig. 1.** A: shortening in the left ventricular ejection time (LVET) in primary biliary cirrhosis (PBC) patients compared with age- and sex-matched normal (Norm) control subjects. PBC patients exhibit a significant lower shortening response than control subjects, indicating reduced cardiac physiological response to the stress of head-up tilt (HUT). B: the abnormality in PBC patients was exclusively in the response to HUT as absolute LVET at rest in the supine position is normal in PBC patients. C: absolute LVET following tilt was, in contrast, significantly abnormal in PBC patients. D: LVET shortening following tilting was identical in age- and sex-matched PBC patients with high and low levels of fatigue. PSC, primary sclerosing cholangitis.
subjects and PBC patients. Within the PBC group, however, significant differences were compensated for by other mechanisms to preserve cardiac output. This finding suggests that any specific myocardial functional abnormality in PBC is not shown. This suggests that afterload characteristics are normal (or at least maintained) in PBC. The fatigue-specific cardiac output effects in PBC were solely a result of stroke volume change since fatigue asso-
ciated was seen with change in stroke volume on standing (Fig. 4B). A significant overall correlation was also seen between absolute level of fatigue severity in PBC and fall in cardiac output upon orthostasis (Fig. 4C).

Cardiac output is determined by heart rate and stroke volume. The fatigue-specific cardiac output effects in PBC were solely a result of stroke volume change since fatigue association was seen with change in stroke volume on standing (Fig. 5, A and B) but not heart rate change (Fig. 5, C and D). Stroke volume change differences associated with fatigue appeared, in turn, to result entirely from changes in preload characteristics. EDI fall on orthostasis showed a strong fatigue association (Fig. 6, A and B). Furthermore, degree of fall in EDI showed a strong direct correlation with fall in cardiac output on standing for the PBC patient group (Fig. 6C). In contrast to preload characteristics no association was seen between changes in afterload characteristics (total peripheral resistance index) on standing and fatigue severity in PBC (data not shown). This suggests that afterload characteristics are normal (or at least maintained) in PBC.

**DISCUSSION**

In this study we have demonstrated, using two complementary modalities, a distinct pattern of functional cardiovascular

---

**Table 3. Subject characteristics and left ventricle morphology and systolic function parameters for the magnetic resonance studies**

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 8)</th>
<th>PBC (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>75.1 ± 10.9</td>
<td>67.9 ± 11.9</td>
</tr>
<tr>
<td>Height, m</td>
<td>162 ± 6</td>
<td>161 ± 6</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.80 ± 0.15</td>
<td>1.71 ± 0.15</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67.6 ± 10.9</td>
<td>69.1 ± 6.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>130.5 ± 29.4</td>
<td>122.6 ± 18.3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>84.7 ± 11.8</td>
<td>76.4 ± 7.9</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>5.0 ± 0.5</td>
<td>4.8 ± 0.9</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>65.6 ± 4.6</td>
<td>65.5 ± 3.5</td>
</tr>
<tr>
<td>LV EDV, ml</td>
<td>118.4 ± 13.0</td>
<td>116.1 ± 21.1</td>
</tr>
<tr>
<td>LV ESV, ml</td>
<td>40.6 ± 6.3</td>
<td>40.4 ± 9.8</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>77.8 ± 11.0</td>
<td>75.7 ± 12.5</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>92.0 ± 6.9</td>
<td>90.6 ± 8.1</td>
</tr>
<tr>
<td>LV EDV index, ml/m²</td>
<td>67.2 ± 6.3</td>
<td>67.9 ± 9.4</td>
</tr>
<tr>
<td>LV ESV index, ml/m²</td>
<td>23.1 ± 3.7</td>
<td>23.7 ± 5.1</td>
</tr>
<tr>
<td>Stroke volume index, ml/m²</td>
<td>44.1 ± 5.3</td>
<td>44.3 ± 4.8</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>52.2 ± 1.6</td>
<td>53.3 ± 4.0</td>
</tr>
</tbody>
</table>

The suffix “index” denotes values normalised for subject size estimated from the subject’s weight and height according to the formula of Dubois and Dubois (4). LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume.

---

**Table 4. Diastolic function parameters**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>PBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early filling rate, ml/s</td>
<td>360.7 ± 69.5</td>
<td>351.2 ± 90.9</td>
</tr>
<tr>
<td>Late filling rate, ml/s</td>
<td>208.0 ± 53.7</td>
<td>211.2 ± 54.2</td>
</tr>
<tr>
<td>Early-to-late ratio</td>
<td>1.9 ± 0.6</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>Time to peak flow rate, ms</td>
<td>128.4 ± 14.3</td>
<td>137.6 ± 22.2</td>
</tr>
<tr>
<td>Early filling percentage, %</td>
<td>71.9 ± 5.7</td>
<td>70.0 ± 4.7</td>
</tr>
<tr>
<td>Early filling rate/end-diastolic volume, s⁻¹</td>
<td>3.1 ± 0.5</td>
<td>3.0 ± 0.7</td>
</tr>
</tbody>
</table>

---

Fig. 2. A: 2 representative cardiac $^{31}$P spectra from PBC patient (i) and a normal control subject (ii). The assignment of the peaks for phosphocreatine (PCr), adenosine triphosphate (ATP), phosphodiester (PDE), and the combined signals from 2,3-diphosphoglycerate (2,3-DPG) and inorganic phosphate (Pi) are identified. B: PCr-to-αATP ratio for myocardial tissue in control subjects and PBC patients.
changes in PBC. These changes take two forms, one of which represents an underlying generic abnormality of myocardial energetic function (demonstrated by cardiac MRS), the second being a peripheral vasculature functional change (shown by noninvasive ICG), which appears to dictate the extent to which the individual can cope with the underlying abnormality. This pattern appears to relate to autonomic function/dysfunction and to play a role in the expression of fatigue.

PBC patients as a group have an abnormality in their left ventricular function manifested as a failure to demonstrate the normal shortening in the LVET seen when undergoing the cardiovascular stimulus of moving from the supine to upright position. The abnormality in PBC patients is entirely associated with their cardiovascular physiological response to prolonged standing, standardized by using HUT, since supine LVETs are normal in PBC patients. This effect appears to be specific to PBC as PSC patients with, if anything, a greater degree of cholestasis, showed normal physiological shortening of LVET in response to standing.

We have previously demonstrated abnormalities in peripheral muscle bioenergetic function in PBC using MRS (7). These changes were characterized by an overreliance on anaerobic pathways of energy generation, with overutilization of the lactic dehydrogenase pathway and excess muscle acidosis. In designing the present study we speculated that were cardiac muscle subject to the same effect, and were the same underlying process (which at present remains unclear) to also occur in cardiac muscle, this might contribute to a generic process of myocardial dysfunction. We therefore applied phosphorus

---

**Fig. 3.** Correlation between the LVET following tilting assessed by impedance cardiography and the cardiac muscle PCr-to-ATP ratio (PCr/ATP ratio) as assessed by magnetic resonance spectroscopy in normal control subjects (A) and PBC patients (B). The vertical solid line denotes a PCr/ATP ratio of 1.6, a previously identified cutoff value suggestive of increased mortality risk in patients with dilated cardiomyopathy. The horizontal broken line denotes the mean resting supine LVET for normal control subjects.

---

**Fig. 4.** A: change in cardiac output (CO) on tilting in normal control subjects, all PBC patients, and PSC patients. Normal control subjects exhibit the predicted fall in cardiac output following tilting. PBC patients as a group and PSC patients exhibit a normal cardiac output fall following tilting. B: change in cardiac output on tilting in age- and sex-matched groups of PBC patients with low (LF) and high (HF) fatigue levels; **P < 0.01 vs. high-fatigue PBC. The “normal” drop in cardiac output on tilting seen in the PBC patient group as a whole therefore masks an exaggeration of the cardiac output fall in low-fatigue PBC patients and diminution of the effect in high-fatigue patients. C: change in cardiac output on tilting correlated with fatigue severity in a mixed PBC patient cohort. FIS, Fatigue Impact Scale.
MRS approaches to heart muscle, demonstrating significantly reduced PCr/ATP ratio (a recognized measure of cardiac muscle bioenergetic function) in PBC patients compared with normal control subjects. This finding, which mirrors those seen in a number of functional cardiac diseases, including left ventricular failure and Friedrich’s ataxia (26–30), represents a failure of normal energy-generation processes. The energetic changes observed in heart muscle are akin to those seen previously in peripheral muscle, giving rise to the intriguing possibility that metabolic abnormalities in tissues, and therefore the functional sequelae of PBC, are multisystem in their expression. A significant proportion of PBC patients had a PCr/ATP ratio of less than 1.6, a cutoff value previously identified as indicating significant risk of cardiac mortality in the context of dilated cardiomyopathy (26). If this value were to retain its significance of risk prediction in the PBC population, it might go someway to explaining any excess nonliver mortality seen in PBC patients. Interestingly, structural magnetic resonance of the hearts of PBC patients revealed no anatomical abnormalities. This may explain why less sophisticated, nonfunctional forms of cardiac imaging in PBC have previously failed to demonstrate any abnormality.

In the normal control group the PCr/ATP ratio showed a strong inverse correlation with the LVET seen in response to orthostasis. Given that all the normal control subjects had normal cardiac function, and PCr/ATP ratios within the normal range, this suggests that prolongation of the LVET following the challenge of tilting represents a homeostatic response to lower levels of cardiac energetic function. In simple terms prolongation of the ejection time could be regarded as a compensatory mechanism for slight reductions in the capacity of the left ventricle to “push.” Intriguingly, extrapolation of the regression line for the relationship between LVET following tilting and PCr/ATP ratio results in it meeting the intersection of the previously identified risk cutoff for PCr/ATP ratio of 1.6 and the mean supine LVET in normal subjects. It is logical that the upper limit of LVET posttill (i.e., the maximum degree of prolongation possible to compensate for impairment in energetic function) would be at a value equivalent to the supine value, i.e., no shortening. Theoretically, beyond this time compensation cannot occur and decompensation might result. Given that this occurs at a value of 1.6 for PCr/ATP ratio, this may provide a mechanistic explanation for the significance of this cutoff value (which to date has only been identified empirically through an association with increased mortality risk in relevant populations). In PBC patients, many of whom have PCr/ATP ratios significantly lower than 1.6, the normal relationship between LVET following tilting and PCr/ATP ratio is lost.
ratio is absent. The PBC patients are, therefore, unable to compensate in the normal physiological manner for their cardiac muscle bioenergetic abnormality. This effect appears, however, to be unrelated to fatigue since all the features of LVET prolongation and PCr/ATP ratio were unrelated to fatigue severity. This element of the study suggests, therefore, that there is a generic, mild, functional abnormality of cardiac muscle in people with PBC to which patients have variably successful adaptive responses.

Cardiovascular function abnormality in PBC patients was not restricted to presumed myocardial changes. Complex changes were also seen in cardiac output in response to the physiological stressor of prolonged standing following the challenge of head-up tilt. In normal subjects tilting is associated with a significant drop in cardiac output associated with decreased venous return to the heart. In the group of low-fatigued PBC patients, fully matched to the normal control subjects with regard to age, sex, and fatigue severity, this normal drop in cardiac output in response to standing was seen. In an age- and sex-matched group of high-fatigue patients, however, this drop in cardiac output was significantly reduced. This effect appeared to be due to stroke volume changes (the normal drop in stroke volume seen following tilting was increased in the fatigued but not the nonfatigued group, the level of this effect showing a significant correlation with fatigue severity). This finding would be in keeping with previous literature examining ICG responses to standing in patients with chronic fatigue syndrome, in which changes in cardiac output have also been demonstrated (26).

In contrast to cardiac output, no fatigue-related difference in heart rate change on standing was seen in the PBC patients. To explore the mechanism of this effect we went on to examine aspects relating to both preload and afterload on the heart. Whereas afterload parameters were normal (or at least maintained) in PBC, with no fatigue association, aspects of the physiology of preload showed a similar pattern of abnormality in PBC with a strong fatigue association. In particular, EDI showed an increased drop following tilting in fatigued but not nonfatigued PBC patients. In all assessments of cardiac output, its constituent components, and pre- and afterload aspects of cardiac function the PSC patient group behaved in the same way as normal control subjects. These findings, and the strong association between EDI and cardiac output drop seen in response to orthostasis, suggest that it is abnormalities in preload regulation that underpin the fatigue-associated cardiac output response associations seen in PBC. It is likely that this is a physiological compensatory response, which may be a normal homeostatic response, to ensure “upstream” maintenance of cerebral perfusion (preserve cerebral function at all costs) at a “downstream” cost that we believe arises either as a result of, or secondary to, the autonomic dysfunction pattern that we and others have described as a frequent occurrence in PBC patients. Autonomic dysfunction, through changes in either capillary or vasomotor function in peripheral tissues (33), could accelerate cardiac return in response to the physiological stress of standing through an increase in preload, stroke volume, and therefore cardiac output relative to non-autonomic-dysfunction subjects.

This study has a number of limitations. Although MRS is considered an appropriate technique for studying cardiac metabolism in vivo, in some hands, it is considered to have reduced reproducibility. Our local data, however, demonstrate reproducibilities of 15% in PCr/ATP ratios, allowing us to be confident that the effects observed in the PBC population are genuine. Furthermore, ICG as a noninvasive technique has

Fig. 6. A: change in end-diastolic index (EDI, a marker of preload) on tilting in normal control subjects and age- and sex-matched groups of PBC patients with low and high fatigue levels and PSC. *P < 0.05 vs. high-fatigue PBC. **P < 0.01 vs. high-fatigue PBC. ***P < 0.005 vs. high-fatigue PBC. Normal control subjects exhibit the predicted fall in EDI following tilting. Significant differences are seen between the high- and low-fatigue PBC patients with regard to EDI change on tilting. PSC patients mirror low-fatigue PBC patients. B: change in EDI on tilting correlates with fatigue severity in PBC. C: degree of change in cardiac output on standing in PBC correlates strongly with degree of change in EDI, suggesting that it is preload characteristics that determine the cardiac output changes associating with fatigue in PBC.
potential for variability and may underestimate cardiac output. Further studies are needed to confirm our findings. The systemic circulation in patients with cirrhosis is known to be hyperdynamic with associated cardiovascular abnormalities such as increased cardiac output, heart rate, and reduced peripheral resistance (18, 19). It could be argued that the findings of our present study represent a manifestation of cirrhotic cardiomyopathy. It is important, however, to note that the patients included in this study all had early stage liver disease and none were cirrhotic. It may be, therefore, that the assumption that cardiomyopathy is associated with advanced disease needs to be revisited in light of our studies’ findings. Finally, a cross-sectional study of this type cannot determine the significance of the identified abnormalities in terms of cardiac risk and outcome. Future longitudinal studies of fully phenotyped patients will be necessary to address this question.

The findings of this study go some significant way to explaining the previous pattern of symptoms described in PBC. On the basis of our findings we have concluded that there is a generic tendency to altered myocardial function in PBC that does not typically appear to be symptomatic in terms of “classical” myocardial dysfunction symptoms. Patients have a variable degree of autonomic “dysfunction” that may in actual fact represent a compensatory mechanism to increase cardiac return to mitigate the effects of altered myocardial function. The effects of autonomic dysfunction in this model would be to alter perfusion patterns in tissues, potentially reducing muscle perfusion and contributing to peripheral mechanisms of fatigue. We believe that this study provides novel insights into the complexity of cardiovascular function and autonomic dysfunction and may open new avenues to both the investigation and the treatment of this disease.

GRANTS
This research was funded by the Medical Research Council.

DISCLOSURES
No conflicts of interest are declared by the author(s).

REFERENCES


