Title: Reduced Heart Rate Variability and Baroreflex Sensitivity in Primary Biliary Cirrhosis

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Abbreviations: Heart rate variability (HRV), baroreflex sensitivity (BRS), low frequency (LF), high frequency (HF), very low frequency (VLF), Primary biliary cirrhosis (PBC).

Abstract

Standardized mortality ratio for primary biliary cirrhosis (PBC) is 2.87. Even after accounting for liver and cancer-related deaths there is an unexplained excess mortality associated with PBC. We have assessed heart rate variability (HRV) and baroreflex sensitivity (BRS) risk factors associated with cardiovascular mortality, in 57 PBC patients and age and sex-matched normal controls.

Methods:

HRV and BRS was measured non-invasively in subjects and controls. Beat to beat RR interval and 'Portapres' blood pressure data were processed using power spectral analysis. Power was calculated in very low (VLF), low (LF) and high frequency (HF) bands according to international guidelines. BRS (alpha) was computed using cross-spectrum analysis. Patients also underwent fatigue severity assessment using a measure validated for use in PBC.

Results:

PBC patients had significantly lower total HRV compared to controls (p=0.02), with the reduction occurring predominantly in the low frequency domain (p=0.03). BRS was also significantly reduced compared to controls (p=0.02). There were no significant differences in HRV or BRS between cirrhotic and non-cirrhotic patients. Within the PBC patient group HRV was significantly lower in fatigued than in non-fatigued patients (p<0.05).

Conclusion:

Abnormalities of HRV and BRS in PBC are not specific to advanced disease but are associated with fatigue severity. Abnormalities could be associated with increased risk of sudden cardiac death, potentially contributing to the excess mortality seen in PBC.

Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease with a probable autoimmune aetiology. The disease is characterized by destruction of the small intra-hepatic bile ducts. Loss of bile ducts leads to the clinical features of cholestasis. The disease is typically progressive, with a proportion of patients going on to develop cirrhosis (1). Although the risk and rate of progression to cirrhosis differ markedly between individual patients a proportion of PBC patients will develop life-threatening liver complications. The mortality from such complications is reflected in the standardized mortality ratio (SMR) of 2.87 over long-term follow-up reported recently for our comprehensive cohort of PBC prevalent between 1987 and 1994 (2).

It is striking, however, that non-liver factors also contribute significantly to the excess mortality associated with PBC. Indeed, in our cohort study the SMR excluding all liver deaths remained significantly elevated at 1.73. This raises the important question as to what non-liver pathologies contribute to the elevated mortality rate seen in PBC. Interest has naturally focused on the two most significant sources of mortality in the general population, namely malignant and cardiovascular disease. In respect of the first of these possibilities, a comprehensive study performed in the same patient population as that demonstrating elevated non-liver mortality has suggested that there is no significantly increased risk of malignant disease in PBC (3) other than an increased risk of hepato-cellular carcinoma seen predominantly in male patients with advanced disease, but which, given the female predominant demographics of the disease, is not sufficient to skew overall mortality (4).

The data regarding the question of cardiovascular risk in PBC are, in contrast, more complex with robust prospective studies notably lacking. The hyper-cholesterolaemia of cholestasis typically seen in PBC patients does not appear to hold the same implications for cardiovascular risk as elevated cholesterol levels do in non-cholestatic patients (5,6,7). This notwithstanding, recent data have suggested an increased cardiovascular risk in some

subgroups of PBC patients (8). Furthermore, our group has recently demonstrated, in a follow-up study of a geographically-defined PBC patient cohort (9) that fatigue is associated with an increased prevalence of sudden cardiac death (10).

Reductions in both heart rate variability (HRV) and baroreflex sensitivity (BRS) (non-invasive tools used to assess autonomic function) are independently associated with an increased risk of sudden cardiac death in the general population (11,12,13,14). Both correlate well with established markers of autonomic dysfunction (15) and abnormalities are also associated with mild changes in standard batteries of autonomic function tests, providing an indication of early autonomic dysfunction which is itself an indicator of poor prognosis (16). In this study we therefore set out to characterise the extent to which HRV and BRS are reduced in PBC potentially contributing to cardiac risk, and to examine, given the apparent links between fatigue and sudden cardiac death risk, associations between HRV and BRS reduction and fatigue severity in this disease.

Subjects and Methods

Subjects

PBC study subjects were prospectively recruited through the local patient support group. All subjects had previously identified themselves as being willing to participate in clinical studies in PBC. Recruitment was thus performed in a blinded fashion with regard to cardiovascular disease status and the presence of other cardiovascular risk factors. All patient participants had definite or probable PBC as defined using standard diagnostic criteria (all 3 of, and 2 out of 3 of cholestatic serum liver biochemistry, serum anti-mitochondrial antibody at a titre of >1:40 and compatible/diagnostic liver histology). Standard clinical information was collected on all PBC patients together with symptom assessment using the Fatigue Impact Score (FIS) previously validated for use in PBC (17,18). In each subject details of treatments and personal and family history of cerebrovascular and cardiovascular disease were also recorded, together with data regarding established cardio-vascular risk factors including smoking history and waist/hip ratio (19,20).

All PBC patients were individually matched by age and sex to population controls selected by two routes. Those over the age of 65 were recruited from the Newcastle Healthy Ageing Project, a cohort of older patients randomly selected from one GP register in the North East of England. Those under 65 were recruited via notices placed in the hospital. As was the case with the PBC patients controls were neither positively nor negatively selected on the basis of previous cardiac history.

The study had ethical approval from the Local Research Ethical Committee.

Cardio-Vascular Assessment

All PBC patients and case-matched normal controls underwent the same cardiac risk factor assessment protocol which took place at the same time of day in all cases. Participants were asked to refrain from drinking caffeinated drinks or smoking on the morning on the

assessment. All subjects had a 12 lead electrocardiogram, height, weight, waist and hip circumference measured.

HRV and BRS were calculated from beat to beat surface ECG RR intervals and phasic systolic blood pressure (SBP) using digital photoplethysmography ('Portapres', Amsterdam). The electrocardiogram (ECG) was recorded using standard limb leads I or II to obtain a clear signal. Both signals were captured to computer over a 5 minute period whilst subjects lay supine (using LabVIEW data acquisition card type DAQ-1200, National Instruments, Newbury). Non-sinus beats were removed semi-automatically and corrected using interpolation of preceeding beats (21). Power spectral analysis was calculated using Fast Fourier Transform based techniques giving total power (<0.40Hz), and power in the very low (VLF) (<0.04), low (LF)(0.04-0.15Hz) and high (HF) (0.15-0.40Hz) frequency bands according to international guidelines (22). Sympatho-vagal balance was examined by low frequency: high frequency ratio. Baroreflex sensitivity (alpha, BRS) was calculated using the cross spectral density in frequency bands (alpha LF, alpha HF) (23).

Statistical Analysis

Comparisons between PBC patients and normal controls were performed using Mann Whitney U Test. For comparisons between PBC subgroups the Kruskall-Wallis test was used. All statistical tests were performed using the Graphpad Prism statistics package. Significance was set at $p < 0.05$.

Results

Subject Group Characterisation

57 PBC patients and matched controls were studied. All subjects were female and ages were identical in the two groups indicating effective matching. None of the PBC patients or normal controls had a 12 lead ECG suggestive of ischaemic heart disease. No patients or controls had a history of myocardial infarction or had required investigation and/or treatment of symptoms potentially of cardiac origin. 10 of the total PBC group had previously undergone liver transplantation. Of the remaining 47 PBC patients 12 (26%) were known to have cirrhosis and 27(57%) were known to be pre-cirrhotic (based on most recent liver biopsy carried out for clinical reasons, no liver biopsies were performed specifically for this study). The remaining 8 (17%) subjects had not undergone histological assessment and were excluded from stage-related subgroup analysis.

The mean FIS for the total PBC group was 35 ± 32. Fifteen (26%) of the non-transplanted PBC subjects had an FIS higher than 80 (> 2x median FIS for a geographically defined PBC cohort[18]) and were defined, for the purposes of the study, as the 'high fatigue' group. 15 (26%) non-transplanted PBC patients had FIS below 28 (< median FIS for normal controls in the previous study and were defined as the 'low-fatigue' group.

The mean waist/hip ratio of the total PBC population was 0.82 ± 0.07 with 36/57 (70%) of the group having waist/hip ratios over 0.8 which is itself an independent predictor of cardiovascular morbidity (19,20). There were no significant differences between the ages of the PBC subgroups (transplanted v non-transplanted, early stage v advanced stage, fatigued v non-fatigued).

Heart Rate Variability and Baroreflex sensitivity

Power spectral analysis (PSA) of HRV produces power bands, or spectra, which vary according to the tone of modulating autonomic activity. Specific frequency ranges in a short-term recording (5 minutes) produce high and low frequency power bands. The high

frequency band is influenced by cardiac parasympathetic tone. The low frequency band is influenced by both sympathetic activity and parasympathetic activity (22).

The non-transplanted PBC patient group had significantly lower HRV than age and sex matched controls in total power (TP, fig 1, table 1) and in all frequency bands other than HF. The reduction in TP was predominantly due to a reduction in LF HRV. Significant reduction in mean RR interval was also seen in the non-transplanted PBC patients. BRS (alphaLF) was also significantly lower in the non-transplanted PBC group compared to age and sex matched controls (fig 2). Within the non-transplanted PBC patient group no significant difference was seen between cirrhotic and pre-cirrhotic patients with regard to either HRV or BRS (table 1). Strikingly, both HRV and BRS remained low in the post-transplant PBC patients (Table 1).

The "high fatigue" PBC group (FIS >80) had significantly lower total HRV compared to the "low-fatigue" group (FIS<28) (p<0.05). This fatigue effect was predominantly due to a significant reduction in the VLF component (p=0.01) (fig 3).

Discussion

Reduced heart rate variability and baroreflex sensitivity are recognized as risk factors for cardiovascular mortality in general, and sudden cardiac death in particular. A recent study (uncontrolled for the presence of fatigue) has shown that HRV over 24 hours is reduced in PBC patients (24). In the current study we have shown significantly lower HRV and BRS in a large group of PBC patients compared to age and sex matched controls. The finding, in both the current study and the Hungarian series, of high frequencies of parameters of dysautonomia which have previously been associated with increased cardiovascular risk may start to explain the increased non-liver attributable mortality seen in PBC. Further support for the hypothesis that those with PBC may be at increased risk of cardiovascular disease comes from the finding of an elevated waist/hip ratio above 0.8 which is also recognized as conveying increased cardiovascular risk (19,20) and the earlier observations, made in two case control studies, that PBC patients are significantly more likely to be cigarette smokers than controls (9,10).

The findings of this study add to what is already a complex literature regarding cardiac risk in PBC. A key early study concluded that PBC patients did not have an increased risk of ischaemic heart disease (5). In fact, the study demonstrated an odds ratio of 1.7 for cardiac death in PBC (a figure strikingly similar to our value for unexplained excess mortality in PBC (2)) which only failed to reach statistical significance because of the study size. Moreover, the study design adopted (over 70% of the patients had advanced liver disease with over 40% of patients dying during follow-up of largely liver reasons) may have, in crude terms, largely excluded patients likely to survive from their liver disease long enough to experience any cardiac morbidity. A more recent study, which addressed risk of ischaemic heart disease events as well as cardiac death, showed a similar non-significant increase in cardiac event risk in PBC patients (odds ratio 2.2) (8). Indeed, the increased risk of cardiac events in some patient groups reached statistical significance. It is also worth emphasizing that previous studies of cardiac disease risk in PBC have focused largely on ischaemic heart disease

manifestations rather than sudden cardiac death. Reduced HRV and BRS are associated, in particular, with increased risk of sudden cardiac death as opposed to ischaemic heart disease. It may therefore be the case that earlier studies of cardiac risk in PBC have focused on the manifestation of cardiac mortality less relevant to PBC patients. This may help to further explain the apparent contradictions between the current and previous studies. Our current observations certainly suggest that the established view, that PBC patients have a normal if not lowered risk of cardiac disease should be reconsidered.

The reduction in HRV demonstrated here in PBC patients is predominantly in the low frequency power domain which suggests that the impairment involves both sympathetic as well as parasympathetic abnormalities. Further studies are warranted to examine autonomic function in those with PBC in order to clarify the precise autonomic abnormalities. Previous studies have shown reduced BRS (25,26) and HRV (27) in small heterogenous groups of cirrhotic patients compared to healthy controls. These studies concluded that the abnormalities of HRV and BRS were stage related, suggesting that any cardiovascular risk is restricted to those with severer forms of the disease. Our current study, in which we included patients with a wide range of disease stages (55% having pre-cirrhotic disease), underlines that this is not the case and that those with earlier stages of disease are also at risk. Furthermore, in the current study we have shown that transplanted patients retain lowered heart rate variability which may have implications for post-transplant survival.

Fatigue is a particularly debilitating symptom in patients with PBC, the underlying aetiology of which remains elusive (17,18,28,29). In the current study fatigued patients had greater impairment of heart rate variability than non-fatigued patients, particularly related to the very low frequency (VLF) component of HRV. This finding raises interesting possibilities that may shed light upon potential abnormalities that may contribute to fatigue pathogenesis in PBC. The origin of the VLF domain is unclear but it has been implicated in thermoregulation and neuro-humoral abnormalities (22). In animal models it has been suggested that abnormalities of central serotoninergic neurotransmission may play a role in

the fatigue associated with liver disease (30). Examining HRV and BRS in other liver diseases associated with fatigue, such as Hepatitis C, may help determine whether the effects seen are directly related to the liver disease itself.

Our group has recently demonstrated a relationship between degree of deposition of the heavy metal manganese in the globus pallidus of patients with PBC and fatigue severity (but not disease stage) (28). Reduced heart rate variability has been recognised in manganese alloy workers (31), and epidemiological studies suggest that fatigue is a common symptom in those exposed to manganese (32,33). If there is indeed a link between our previous findings regarding the association between manganese deposition and fatigue severity (but not disease severity), and the current observation of an association between decreased heart rate variability (a predictor of cardiac risk) and fatigue severity (but not disease severity) it may help explain the paradox that although symptom severity does not correlate with histological and biochemical disease severity (18,29) overall survival is decreased in symptomatic patients (34,35,36).

This study raises important questions about the potential degree of cardiac risk experienced by PBC patients, as well as the role the factors determining such risk play in the symptomatic manifestations of the disease. Prospective studies are required to determine, in particular, the true degree of cardiac risk in PBC patients and how these risk factors interact with other recognized risk factors for cardiovascular morbidity and mortality. Further studies will determine which interventions may be appropriate and effective in reducing this risk.

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Figure legends

Figure 1: Heart rate variability (HRV) in the untransplanted PBC group compared to age and sex matched controls (p=0.03).

Figure 2: Baroreflex sensitivity (BRS) in the untransplanted PBC group compared to age and sex matched controls (p=0.02).

Figure 3: Heart rate variability (HRV) in fatigued PBC subjects (FIS >80) compared to that in the un-fatigued (FIS <28) subjects a) Total HRV (p<0.05) b) very low frequency (p=0.01

Table 1: Heart rate variability in PBC subjects and age and sex matched controls.

		Normals	Total PBC	PBC without transplant	Transplanted	Cirrhotic	Precirrhotic
	N	57	57	47	10	12	27
Heart rate variability	Mean RR	936 (889-980) β	864 (845-913)	875 (839-913)β	853 (794-994)	888 (816-960)	846 (800-881)
	Total HRV	665 (826-1466)+γμ	416 (466-1072)+	444 (473-1202)γ	364 (209-688)	512 (-70-2584)	415 (341-613)
	VLF	255 (263-502)# δ	137 (196-376)#	137 (191-400)δ	126 (56-430)	167 (118-610)	127 (112-228)
	LF	221 (307-551)>ε	154 (147-474)>	159 (152-547) ε	107 (79-179)	134 (-218-1351)	152 (134-276)
	HF	118 (162-487)∞	92 (91-254) ∞	92 (94-291)	82 (47-106)	97 (-45-697)	80 (74-131)
Baroreflex sensitivity	αLF	7.9 (7.1-11.2)≈η	5.1 (5.0-7.2) ≈	5.3 (5.0-7.5) η	5.2 (4.0-6.6)	5.9 (4.0-9.7)	5.6 (4.2-7.6)
	αHF	8.8 (8.1-12.4) αλ	5.6 (5.3-7.6) α	5.7 (5.3-8.0)λ	3.9 (2.6-7.8)	5 (3.6-8.7)	5.3 (4.5-8.1)

Unless indicated all values are expressed as median (95% CI). All symbols indicate statistically significant differences between values ($p<0.05$)

Heart rate variability (HRV), Low frequency (LF), High frequency (HF), Very low frequency (VLF)