Impaired blood pressure variability in chronic fatigue syndrome—a potential biomarker

J. FRITH¹,², P. ZALEWSKI³, J. J. KLAWE³, J. PAIRMAN¹,², A. BITNER³, M. TAFIL-KLAWE⁴ and J. L. NEWTON¹,²

From the ¹UK NIHR Biomedical Research Centre in Ageing, Newcastle, UK, ²Institute for Ageing and Health, Newcastle University, Newcastle, UK and ³Department of Hygiene and Epidemiology and ⁴Department of Physiology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

Address correspondence to Professor J. L. Newton, Institute for Ageing and Health, Medical School, Framlington Place, Newcastle-upon-Tyne, NE2 4HH, UK. email: julia.newton@nuth.nhs.uk

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Summary

Introduction: Autonomic dysfunction is common in chronic fatigue syndrome (CFS). This study set out to derive an autonomic biomarker using a comprehensive assessment of heart rate and blood pressure variability.

Methods: Heart rate and non-invasive continuous blood pressure measurements (task force monitor) at rest and on standing were performed in CFS (Fukuda n=68) and matched controls (n=68) to derive high frequency (HF; parasympathetic) and low frequency (LF; sympathetic) heart rate variability (HRV), systolic (SBPV) and diastolic (DBPV) blood pressure variability. Variables of significance were combined using receiver operator curves to explore the diagnostic utility of parameters particularly at rest.

Results: At rest, LF-HRV (sympathetic) was significantly increased in CFS compared to controls, while parasympathetic markers were significantly reduced (P=0.006). Total DBP spectral power was increased (P=0.0003) across all domains, with a shift towards sympathetic and away from parasympathetic SBPV (P=0.05). On standing, overall SBPV response was significantly reduced with reductions in both sympathetic and parasympathetic components of SBPV (all P<0.0001). Change in LF-DBP and relative balance of LF/HF DBP on standing differed between CFS and controls (P<0.0001). Using the 85% sensitivity levels, we determined a threshold for three chosen resting BPV parameters of LF DBP >3.185, rest HF DBP >0.86, rest total DBP >7.05. Achieving all of these differentiated between CFS and controls with 77% sensitivity and 53% specificity.

Conclusion: This study has shown that there are objectively measured abnormalities of blood pressure variability in CFS and that these abnormalities have the potential to be a bedside diagnostic tool.

Introduction

Chronic fatigue syndrome (CFS) affects at least 0.2–0.4% of the population; it is debilitating and life changing. Despite this, there are currently no diagnostic tools beyond symptom recognition and no curative treatments. Studies have confirmed that both subjectively assessed symptoms and objective measurement of autonomic nervous system (ANS) function are reported in ~90% of those with CFS,¹–⁴ underlining the potential for...
autonomic parameters to provide a potential bedside diagnostic biomarker and therapeutic target.

In CFS, studies have shown that response of the autonomic nervous system to the physiological stress of standing is abnormal. However, whether CFS is a dysautonomia remains controversial with the majority of studies failing to confirm the presence of autonomic abnormalities at rest, suggesting that CFS is a physiological disorder of orthostasis. Further studies have shown that blood pressure measured over 24 h is low in CFS with spectral indices of blood pressure variability (BPV) being significantly lower in CFS compared to controls, differences which in one study disappeared on assuming the upright position.

Spectral analysis of beat-to-beat heart rate and blood pressure are increasingly recognized as sensitive assessments of cardiovascular regulation that have the potential to be clinical diagnostic and prognostic markers. Heart rate (HR) and BPV allows simple bedside measurement of the balance between the parasympathetic and sympathetic nervous systems in a non-invasive manner, and in addition BPV is an important marker of sympathetic vasomotor tone.

A number of studies have reported the potential for physiological measurements particularly in response to standing to be a potential biomarker. In this study, we aimed to build on this important work and determine whether we could derive an autonomic biomarker at rest using a comprehensive assessment of HR and BPV in a well-characterized cohort of patients with CFS compared to appropriately matched controls.

Methods

Subjects

Consecutive subjects with CFS (Fukuda Criteria) who had attended the Northern Regional CFS Clinical service were invited for assessment in the autonomic laboratory. Each CFS patient was matched for age and sex to a sedentary control, recruited via notices placed within the hospital. Both patients and controls were excluded if taking any medication that could influence assessment of haemodynamic (e.g. β-blockers, calcium antagonists and antidepressants) if diabetic or with renal or hepatic disease. Subjects were excluded if not in sinus rhythm, unable to stand or unable to attend the autonomic laboratory for assessment.

Assessment of haemodynamic responses

Apparatus

All CFS patients (n=68) and matched controls (n=68) underwent formal autonomic assessment in the Cardiovascular Laboratory; all measurements were performed with a dedicated high-tech device—task force monitor (TFM, CNSSystems, Medizintechnik, Graz, Austria). The main area of TFM application is as an automated and computed beat-to-beat analysis of heart rate [electrocardiogram (ECG)] oscillometric and non-invasive continuous blood pressure measurements (oscBP, contBP). On the basis of these biological signals source, haemodynamic and autonomic parameters are calculated. The TFM facilitates continuous (beat-to-beat), reliable and reproducible measurements of all parameters. Basic statistics (mean, median, minimum, maximum and SD) of all parameters were calculated automatically for defined periods.

Protocol of autonomic assessment

All subjects were instructed to refrain from smoking, caffeine, alcohol ingestion and intensive physical activity on the day of investigation and ate a light breakfast only. All investigations were performed at the same time of day and took place in a neutral ambient temperature, quiet room.

In all cases, TFM measurements were performed during 10 min of supine rest (Phase 1) and subsequently brought to standing at 70° by tilt table; patients then stood quietly for 40 min (Phase 2). At the end of this time, the tilt table was returned to the supine position and measurement was continued for a further 10 min. The test was terminated early at the patient’s request, if syncopal or pre-syncopal symptoms were reproduced, or if systolic blood pressure dropped below 80 mmHg for longer than 3 min.

Assessment of HR and BPV

All cardiovascular assessments were carried out with continuous heart rate and beat-to-beat blood pressure measurement implemented in TFM. The integrity of the autonomic nervous system was assessed using a three-channel ECG and continuous blood pressure monitoring (contBP—with periodically cross-checked oscillometric BP measurements). TFM automatically provides a power spectral analysis for HRV and BPV. HRV and BPV spectral analyses are conducted using the adaptive autoregressive model (AAR) proposed by Bianchi et al. In addition to total power spectral density (PSD), three frequency bands are calculated with TFM: VLF, LF
and HF, but only two of these were taken account of as there were short-term autonomic regulations of HR and BP, i.e. LF 0.05–0.17 Hz (low-frequency band) and HF 0.17–0.4 Hz (high-frequency band) in absolute values, and both frequencies were also calculated in normalized units (LFnu-RRI, HFnu-RRI for HRV and LFnu-sBP, HFnu-sBP, LFnu-dBP and HFnu-dBP for SBPV and DBPV). Using only HRV bands when considering autonomic regulation has some limitations; therefore, TFM also provides spectral analysis of BPV, a more reliable tool for sympathetic and parasympathetic autoregulation assessment. For that purpose bands, LFnu-RRI, LF-RRI, LF-sBP, LFnu-sBP, LF-dBP and LFnu-dBP are referred to as sympathetic modulation of sino-atrial (SA) node and vasomotor function. While HF-RRI and HFnu-RRI bands refer to parasympathetic modulation of cardiovascular activity. Cardiovascular disturbances of the autonomic circulatory regulation cause alternations in spectra and proportion of frequencies in the total spectrum power. Parameters, such as PSD, LF and HF are quantitative indicators of autonomic regulation, and the ratio between LF and HF band represents the sympatho-vagal balance.25–27

Due to the characteristic of the AAR model, which may produce outliers when analyzing R-wave to R-wave, all HR beat-to-beat data was filtered using Grubbs’ test for outliers elimination. This method of filtering is well-documented and has a strong mathematical background.28

Statistical analysis

Parametric variables are presented as mean and standard deviation and comparisons drawn between groups using the Student’s t-test and proportions by Fisher’s exact test, where non-parametric data are presented as median and range and comparisons drawn using Mann–Whitney tests. Correlation analyses were obtained using ‘Prism-Graphpad’ (http://www.graphpad.com/prism/Prism.htm). P < 0.05 was considered a statistically significant result. Variables were analysed using IBM SPSS statistics version-19 and receiver operator curves to derive characteristics with 85% sensitivity thresholds, which were then combined in order to define the best potential biomarker.

Ethical permission

Ethical permission was from the Newcastle and North Tyneside Local Research Ethics Committee. All patients and controls provided written informed consent.

Results

Autonomic data was available from 68 CFS patients who were matched case by case to 68 sedentary community controls. The CFS patients were of comparable age to the controls (mean ± SD age (years) 46.6 ± 12.1 vs. controls 47.9 ± 13.4; P= 0.6), and there were equal numbers of males in both groups 25 (38%).

Comparison between CFS patients and matched controls in autonomic responses at rest

As has been shown in previous studies, HRV markers of sympathetic function were significantly increased in the CFS group compared to controls, particularly LF-nuRRI, while parasympathetic markers were significantly reduced (Figure 1a and b). Although the total power was not significantly different between the CFS and control groups, there was a clear shift in the sympathovagal balance with the LF/HF ratio being increased in the CFS group (Figure 1c).

There were striking differences between the groups at rest in DBPV (Figure 2) with a clear increase in total diastolic BP power, which was a generalized increase across all domains.

There were no significant differences in individual SBPV at rest (data not shown), although there was a small but significant shift, at rest, in the balance towards sympathetic and away from parasympathetic SBPV (Figure 3).

Comparison between CFS patients and matched controls in autonomic responses on standing

There were significant changes in the SBPV response to standing with reduced responses in overall SBPV on standing (Figure 4a), which was associated with reductions in both sympathetic and parasympathetic components of SBPV (Figure 4b and c) but with a shift more towards parasympathetic on standing (Figure 4d). Change in LF-nuDBP and relative balance of LF/HF-DBP on standing was different between CFS and controls (Figure 5).

Derivation of a potential autonomic biomarker

All variables also underwent ROC analysis. Those parameters that showed a significant relationship on ROC analysis are shown in Figure 6. We then choose those resting variables that performed well on ROC in order to ensure that any potential
Figure 1. HRV at rest. (a) LF-nu RRI (sympathetic) is significantly increased while (b) HF-nu RRI (parasympathetic) is reduced and the (c) sympathetic–vagal balance is significantly increased.

Figure 2. DBPV at rest. (a) Total DBP PSD is significantly higher at rest in CFS; this is due to an increase in both (b) LF DBPV and (c) HF DBPV.
A biomarker would have greater clinical utility. Using the 85% sensitivity levels, we determined a threshold for three chosen resting BPV parameters and incorporated these into models. The specific thresholds chosen were LF dBP > 3.185, rest HF dBP > 0.86, rest PSD dBP > 7.05. The sensitivity, specificity, positive and negative predictive values for each combination of ROC significant variables are shown in Table 1. Achieving all these threshold values differentiated between CFS and controls with 77% sensitivity and 53% specificity.

**Discussion**

This study has shown for the first time in a well-characterized cohort of patients with CFS that there are objectively measured abnormalities of BPV and that these abnormalities have the potential to be a bedside diagnostic tool in CFS.

Previous studies have explored the potential for autonomic variables to be a diagnostic marker, but the utility of these has been limited due to their complexity and the need for dynamic testing. In our

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**Figure 3.** The balance between LF and HF SBPV at rest is significantly increased in CFS compared to controls.

**Figure 4.** Change in SBPV on standing. (a) Total PSD SBPV responses significantly less well on standing in CFS compared to controls; this comprises reductions in both LF SBPV (b) and HF SBPV (c), although the balance is significantly reduced (d).

**Figure 5.** Change in the sympathetic–vagal (LF/HF) balance of DBPV on standing is significantly reduced compared to controls.
model, we chose to include only measures obtained at rest in order to enhance clinical applicability. As a result, we believe our model has comparable validity but advantages of utility. In order to optimize our model as a clinical tool, we acknowledge the need to further validate it in a new population and to explore its utility perhaps in combination with other putative diagnostic markers.

Other studies have confirmed the presence of abnormalities of HRV and BPV in CFS, but the use of varying techniques for collection, e.g. during sleep, at rest and in response to dynamic testing, has made comparison between studies difficult.\textsuperscript{9–14} Our finding of changes in SBPV and DBPV in the CFS group is interesting and may point towards the underlying pathogenesis of this disease particularly in light of the predominance of DBPV abnormalities, implying an abnormality of the heart in rest rather than when contracting. We, and others, have recently shown that the hearts of those with CFS have subtle impaired contractility particularly in response to the stress of standing.\textsuperscript{8,30–34} Our group has also shown that CFS patients have lower blood pressure overall suggesting that the impaired cardiac pump may be leading to reduced output and blood pressure, which leads to reduced perfusion of downstream organs and symptoms as a consequence.

In our study, we have demonstrated a significant increase in sympathetic autonomic nervous system activity, with both HRV and BPV. LF-sBP is

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure6.png}
\caption{ROC analysis of variables at rest from which the 85\% thresholds have been derived. The variables at rest have greater validity than those in response to standing, and hence these parameters were incorporated into the biomarker model.}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{lllll}
\hline
Over threshold & Sensitivity & Specificity & PPV & NPV \\
\hline
A alone & 82 & 34 & 57 & 64 \\
B alone & 82 & 40 & 59 & 68 \\
C alone & 83 & 31 & 56 & 64 \\
A and B & 77 & 47 & 60 & 67 \\
A or B & 91 & 26 & 56 & 75 \\
A, B or C & 91 & 19 & 54 & 68 \\
A, B and C & 77 & 53 & 63 & 69 \\
More than 2 of & 84 & 34 & 57 & 68 \\
A, B or C & & & & \\
\hline
\end{tabular}
\caption{Defining the utility of diastolic blood pressure variability at rest as a potential diagnostic tool in CFS}
\end{table}

Note. Using the 85\% thresholds from ROC analysis for parameters where A = rest LF dBP >3.185, B = rest HF dBP >0.86, C = rest PSD dBP >7.05.

PPV, positive predictive value; NPV, negative predictive value.

All values are shown as percentages.
considered a stronger marker of sympathetic activity at rest than LF-RRI, and we believe that our findings add further evidence to the case for CFS being a disorder of sympathetic overactivity. We would suggest that our results suggest that CFS subjects may have been suffering from a pathological sympathetic activity over a period of time that has lead to their autonomic effectors (heart and blood vessels) becoming resistant to a physiological sympathetic stimulation. The implications of this are great for patients as in other diseases, changes in heart rate and BPV have been associated with increased morbidity and mortality.\textsuperscript{35} Furthermore, our findings would fit with other models of CFS pathogenesis such as the central sensitization model and could suggest that the autonomic abnormalities characteristic of CFS are a secondary phenomena or a marker of another physiological abnormality.\textsuperscript{36} Studies are needed to explore the underlying pathogenesis of autonomic dysfunction in CFS.

Our study is cross-sectional in nature and includes only subjects attending one specialist centre, and we believe our findings require reproduction in other centres in a prospectively recruited cohort and using the autonomic parameters identified in this study in combination with other variables in order to increase the sensitivity and specificity to differentiate between CFS patients and controls. We also believe that an important next step will be to explore whether these, and other potential biomarkers, are stable over time and whether when examined in other fatigue-associated diseases, they prove to be CFS-specific biomarkers or generic fatigue biomarkers.

Furthermore, we believe that our study highlights the potential value of non-invasive autonomic parameters as clinical diagnostic biomarkers in this disease where currently diagnosis is based entirely upon subjective categorization of the symptoms experienced by patients.

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