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Chronic fatigue syndrome and impaired peripheral pulse characteristics on orthostasis—a new potential diagnostic biomarker

John Allen[1], **Alan Murray**[1], **Costanzo Di Maria**[1] **and Julia L Newton**[2,3]

[1] Microvascular Diagnostics, Regional Medical Physics Department, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK
[2] UK NIHR Biomedical Research Centre in Ageing and Age-Related Diseases, Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne NE2 4HH, UK

E-mail: julia.newton@ncl.ac.uk

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Abstract

Autonomic nervous system dysfunction is frequently reported in chronic fatigue syndrome (CFS) with orthostatic intolerance, a common symptom that can be objectively assessed. The frequent finding of autonomic dysfunction and symptoms on standing has the potential to provide a diagnostic biomarker in chronic fatigue. In this study we explored the clinical value of non-invasive optical multi-site photoplethysmography (PPG) technology to assess cardiovascular responses to standing. Multi-site PPG pulses were collected from tissue pads of the ears, fingers and toes of 14 patients with CFS and 14 age-matched sedentary subjects using a measurement protocol of a 10 min baseline (subject supine) followed by 3 min of tilting on a tilt table (head-up to 70°). Percentage change in pulse timing (pulse transit time, PTTf) and pulse amplitude (AMP) at each site were calculated using beat-to-beat pulse wave analysis. A significant reduction in the overall pulse timing response to controlled standing was found for the CFS group (using summed absolute percentage change in PTTf for ear, finger and toe sites, median change of 26% for CFS and 37% for control with $p = 0.002$). There were no significant differences between subject groups for the AMP measure at any site. Changes in AMP with tilt were, however, weakly significantly and negatively correlated with fatigue severity ($p < 0.05$). Receiver operating characteristic (ROC) analysis of timing measures produced an area under the curve of 0.81. Experimental linear discriminant classification analysis comparing both timing and amplitude measures produced an overall diagnostic accuracy of 82%. Pulse wave abnormalities have been observed in CFS and represent a

[3] Author to whom any correspondence should be addressed.

potential objective measure to help differentiate between CFS patients and healthy controls.

Keywords: autonomic dysfunction, microvascular, orthostasis, photoplethysmography, pulse wave analysis, tilt

Introduction

Chronic fatigue syndrome (CFS) is a debilitating condition that can affect all age groups and leads to significant impairment of quality of life (Fernandez *et al* 2009, CFS/ME Working Group 2009, Prins *et al* 2006, National Institute for Health and Clinical Excellence 2010). Despite this, the pathophysiology of CFS is not understood, although a number of reports suggest that abnormalities of autonomic nervous system function occur frequently and that orthostatic intolerance is a common symptom that can be objectively assessed (Newton *et al* 2007, Freeman and Komaroff 1997, Pagani and Lucini 1999, Naschitz *et al* 2004, Schondorf and Freeman 1999). One of the current difficulties in recognizing CFS has been the lack of a suitable diagnostic biomarker. The frequent finding of autonomic dysfunction and symptoms on standing has the potential to provide such a biomarker. Photoplethysmography (PPG) is a technique that utilizes an optical transducer, often infrared, which produces a signal associated with change in the volume of red blood cells in the peripheral microvascular bed with each pressure pulse initiated by the heart (Allen and Murray 2000). The main peripheral sites where the PPG pulse signal can be obtained are the tissue pads of the ears, fingers and toes where there is a high degree of superficial vasculature. The characteristics of the PPG pulse signal are body site specific and there are differences in timing (pulse transit time) and amplitude over time (Zheng *et al* 2008). By studying the pulses obtained simultaneously (multi-site PPG) from six peripheral sites (i.e. right and left ears, fingers and toes), the right–left characteristics also allow important information about the peripheral circulation. PPG is a simple measurement technique that allows real time assessment, and can lead to a global measure making it a powerful clinical investigation tool. In this study we investigated for the first time novel multi-site pulse wave parameters obtained from across the body in response to standing as a potential biomarker in CFS. The ultimate aim of the study was to allow us to improve our understanding of the underlying physiological abnormalities that arise in CFS, with a view to informing future diagnostic tools and treatments.

Methods

Participants

All measurements were undertaken in a temperature-controlled measurement facility at Freeman Hospital (normothermic temperature 23 $\pm$ 1 °C). All patient measurements were made by a trained operator blinded to the fatigue status and were performed at approximately the same time of day. Blood pressure was measured with the subject in the supine position at rest using a sphygmomanometer. All subjects were asked to refrain from smoking or caffeine for 3 h prior to their assessment.

Subjects were recruited via the local CFS Clinical Service. All fulfilled the Fukuda diagnostic criteria for CFS (Fukuda *et al* 1994) and none was taking medications that could potentially interfere with assessment. Controls were recruited via notices in the hospital and

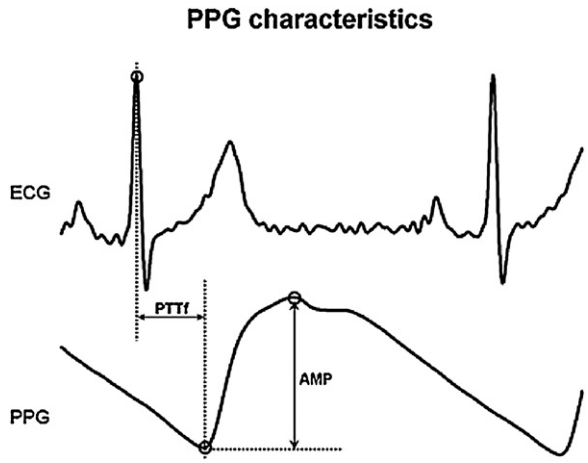

Figure 1. Extracted PPG pulse amplitude (AMP) and timing (PTTf) characteristics, with cardiac timing reference ECG added.

were sedentary and matched for age, sex and body mass index (BMI). All subjects completed an assessment of fatigue severity, the gold standard Fatigue Impact Scale (FIS) (Fisk *et al* 1994). Ethical permission was secured for this project and all participants provided written informed consent.

PPG pulse wave characteristics in response to a controlled orthostatic tilt manoeuvre

Multi-site PPG was used to examine the changes in pulse wave characteristics in response to a controlled orthostatic tilt test manoeuvre (Parry *et al* 2009). PPG is a non-invasive optical technique which can easily detect clear pulse waveforms at peripheral body sites, i.e. the ear lobe, index finger pad, great toe pad. In a healthy subject a clear PPG response to a change in body position is expected compared to a marked reduced change in patients with autonomic dysfunction, such as in patients with diabetes (Allen 2007). In this study we investigated the changes in multi-site beat-to-beat PPG pulse amplitude and timing changes with controlled orthostasis induced by head up tilt challenge at the ear, finger and toe sites.

Multi-site PPG pulse measurement technology has been described in detail elsewhere (Allen and Murray 2000, Zheng *et al* 2008). In this study we acquired pulses simultaneously from the right and left ear lobes, index finger and great toe sites. Multi-site PPG pulses were recorded to computer for 15 min at a sampling rate of 2 kHz. A single lead ECG was also recorded to provide a cardiac timing reference (figure 1). The tilt protocol comprised a 10 min resting baseline measurement followed by a 70° controlled head up tilt for 3 min before returning to the horizontal level. This angle of tilt is a standard used in the Falls and Syncope Assessment Service within our hospital centre (Parry *et al* 2009). A tilt table (type: CNS Systems, Model 2900) was used, which allowed controlled tilting to be achieved in less than 20 s.

Pulses were analysed off-line using Matlab software (Mathworks Inc.) to provide beat-to-beat multi-site pulse transit time (to foot of pulse, PTTf) and foot-to-peak amplitudes (AMP) of the pulsatile 'ac' PPG signal for the full period, and to analyse the changes with tilt (Allen 2007). The median pulse parameters were calculated for the baseline period over 400 s, and for the tilt period for the last 100 s at the 70° tilt angle for each body measurement

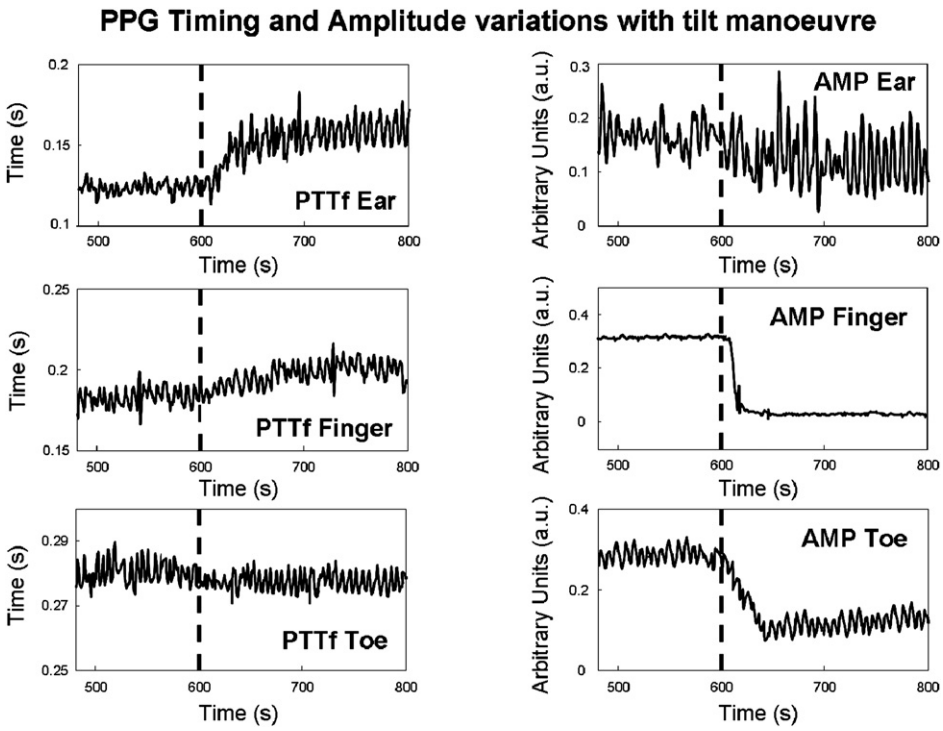

Figure 2. Beat-to-beat changes in PPG 'ac' pulse measures (AMP and PTTf), and their changes just pre- and post-tilt for the ear, finger and toe measurement sites. The ear site shows the greatest relative change with posture change.

site (figure 2). Median analysis was employed to minimize the effect of outliers in beat-to-beat data from noise/movement artefact. The percentage changes in pulse timing (PTTf) and amplitude (AMP) values with tilt were calculated using the following formula:

$$\text{Change in pulse measure}(\%) = [(\text{Tilt value} - \text{Baseline value})/\text{Baseline value}] * 100.$$

There is bilateral similarity in peripheral pulse characteristics in subjects without vascular disease, i.e. the right side should be highly similar to the left side in timing and amplitude and their changes (Allen and Murray 2000). The right and left side % change values were therefore averaged for each body measurement site, i.e. for ear lobes, index fingers and great toes.

Statistical analysis

Summary statistics were calculated and assessed using Minitab. Median values of beat-to-beat data within subjects were used to help minimize the effect of outliers due to noise, and parametric (mean, standard deviation) value used to express group baseline and changes with tilt. The changes with tilt between groups were compared using Student's *t*-test. Receiver operating characteristic (ROC) analysis was performed with SPSS software. Contingency tables were produced to summarize group classifications, with diagnostic accuracy (A), sensitivity (Se), specificity (Sp), negative predictive value (NPV) and positive predictive value (PPV) calculated. Cluster analysis was performed on selected well performing measures, and optimal linear separation of groups was estimated.

Table 1. A clinical summary for CFS and healthy control group subjects. Mean (standard deviation) values are shown.

	Controls	CFS	*p*-value	
Age (years)	42 (14)	50 (14)	0.19	*t*-test
Body mass index (kg m^{-2})	26.0 (4.9)	25.0 (3.0)	0.58	*t*-test
Resting SBP (mmHg)	127 (13)	122 (22)	0.5	*t*-test

Table 2. Baseline values for PTTf and AMP using averaged right and left ear, finger and toe sites.

		Ears		Fingers		Toes	
		CFS	Controls	CFS	Controls	CFS	Controls
PTTf	Mean (s)	0.132	0.130	0.186	0.186	0.289	0.309
	SD (s)	0.013	0.013	0.015	0.013	0.033	0.041
	CFS vs Controls (*p*-value)	*0.594*		*0.904*		*0.152*	
AMP	Mean (au)	0.031	0.083	0.464	0.424	0.146	0.224
	SD (au)	0.018	0.067	0.230	0.165	0.111	0.146
	CFS vs Controls (*p*-value)	*0.010*		*0.602*		*0.123*	

Results

Subjects

A total of 14 subjects with CFS and 14 healthy control subjects were studied (table 1), with no significant differences between the number of males/females in the two groups ($p = 0.11$, χ^2 test), and with no significant differences in age ($p = 0.19$, *t*-test). All subjects were Caucasian. There were no excluded subjects in this pilot study.

Differences in pulse between controls and CFS at baseline

The range of baseline values for PTTf and AMP are given in table 2. There were significant differences between subject groups at baseline for the ear site pulse amplitude AMP measure ($p = 0.010$). There were no differences at the fingers and toes for AMP and none at any measurement site for PTTf.

Differences in pulse between controls and CFS whilst subjects tilted

At tilt the pattern was similar to baseline with significant differences found between subject groups at the ear site for the pulse amplitude AMP measure only ($p = 0.014$).

Relative changes in pulse transit time from baseline in response to orthostasis

The relative changes in PTTf from baseline to tilt position are summarized in figure 3(a). At individual sites the change was statistically significant for the ear site only ($p = 0.005$).

A composite tilt PTTf response score was then formed for each subject, using the summed absolute percentage changes in PTTf from segmental levels of ear, finger and toe (each level calculated using the average of right and left sides) and was significantly lower in the CFS group compared to controls ($p = 0.002$) (figure 3(b)).

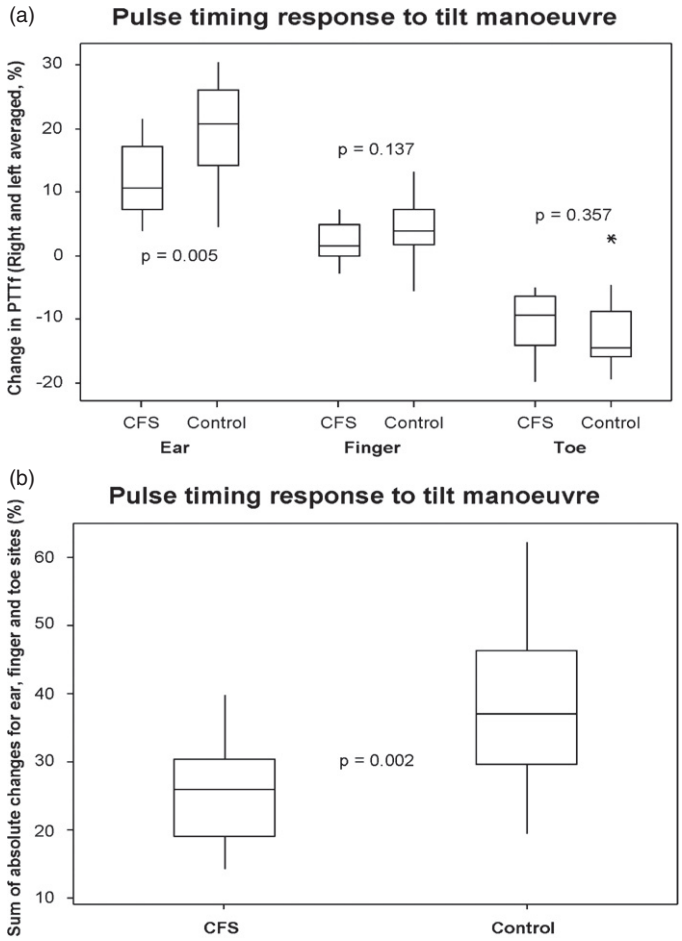

Figure 3. (a) Percentage change in pulse PTTf timing measure with tilt using the average of the right and left sides at ears, fingers and toes. (b) Percentage change in composite PTTf measure with tilt. * represents an outlier value.

Relative changes in pulse amplitude from baseline in response to orthostasis

There were no significant differences for amplitude changes between control and CFS groups at individual body sites and also no significant difference for the composite tilt AMP response score. ROC analysis was not performed for AMP because of equivalence in this measure between the groups.

Relationship between pulse measures and Fatigue Impact Score (FIS)

A significant negative association was found in the patient group between fatigue severity (using FIS) and the relative change in ear pulse amplitude with tilt ($p < 0.05$) (figure 4), with regression line of $\textit{Change in AMP} = 23.1 - 0.46^{*}\text{FIS}$. No significant relationship was found between FIS and the baseline amplitude measures or between FIS and the change in finger or toe amplitude measures with tilt. There was no clear relationship found between FIS and any of the baseline or tilt PTTf timing measures.

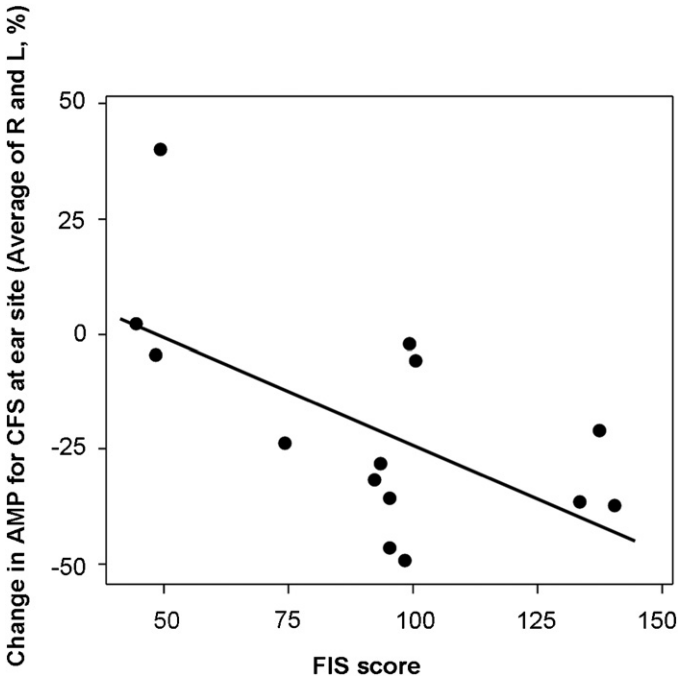

Figure 4. Association between FIS and change in amplitude AMP with tilt for the 14 CFS patients (regression line is *Change in AMP* $= 23.5 - 0.5^{*}$FIS, $p < 0.05$).

Table 3. Contingency tables from graphical cluster analysis and used for diagnostic accuracy calculations for selected pulse measure sets A and B.

(a) Chosen set A. Pulse PTTf baseline versus change in PTTf on tilt, ear site alone.

	Predicted controls	Predicted CFS
Actual controls	10	4
Actual CFS	2	12

(b) Chosen set B. Pulse AMP baseline versus composite summed absolute change in PTTf of ear, finger and toe sites on tilt.

	Predicted controls	Predicted CFS
Actual controls	9	5
Actual CFS	0	14

Pilot assessment of diagnostic classification accuracy

ROC analysis calculated the area under the curve as 0.81 (specificity Sp = 64% and sensitivity Se = 86%) (figure 5(a)) for (a) PTTf change at ear site with tilt. It was also 0.81 (Sp = 79% and Se = 79%) for (b) the summed PTTf change with tilt (figure 5(b))

Improved classification results were obtained by using the simple cluster analyses for two selected sets of pulse timing and/or amplitude measures. Firstly (referred to as measure set A), baseline ear PTTf was compared with change in ear PTTf on tilt (scatter plot, figure 6(a)). Here, a linear discrimination line was added to demonstrate the estimated optimal separation of the two subject groups. From this cluster analysis approach a contingency table (table 3(a)) gave classification parameters of A (79%), Se (86%), Sp (71%), NPV (83%) and PPV (75%). Secondly (measure set B), baseline ear pulse amplitude was compared with absolute summed

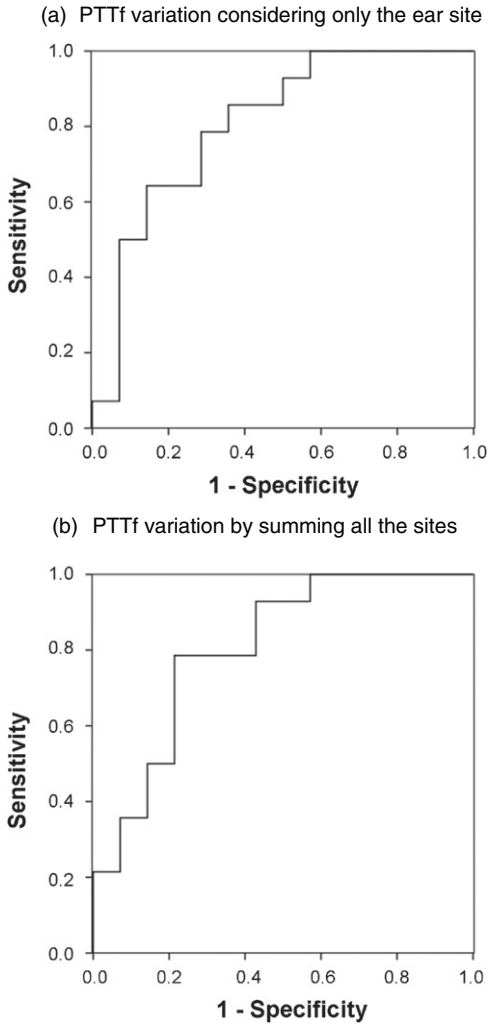

Figure 5. ROC analysis for pulse measure set A with change in pulse PTTf timing measure at the ear with tilt having an area under the curve = 0.81 (standard error 0.09) with accuracy optimized for sensitivity of 86% and specificity of 64% (at cut-off of 18%), and for pulse measure set B with composite summed pulse PTTf timing change for ear, finger and toe sites having an area under the curve = 0.81 (0.08) and with accuracy optimized to give sensitivity of 79% and specificity of 79% (at cut-off of 30%).

PTTf timing change on tilt (table 3(b)) (scatter plot, figure 6(b)), with accuracy and sensitivity increasing (A (82%), Se (100%), Sp (64%), NPV (100%) and PPV (74%)).

Discussion and summary

This study has confirmed that there are pulse wave abnormalities at rest and in response to orthostasis in the debilitating disease CFS that have the potential to be utilized as a bedside diagnostic marker to help identify which subjects might benefit from further clinical and objective assessment. This study is novel in that we have utilized state-of-the-art multi-site PPG technology to assess cardiovascular responses to controlled tilt.

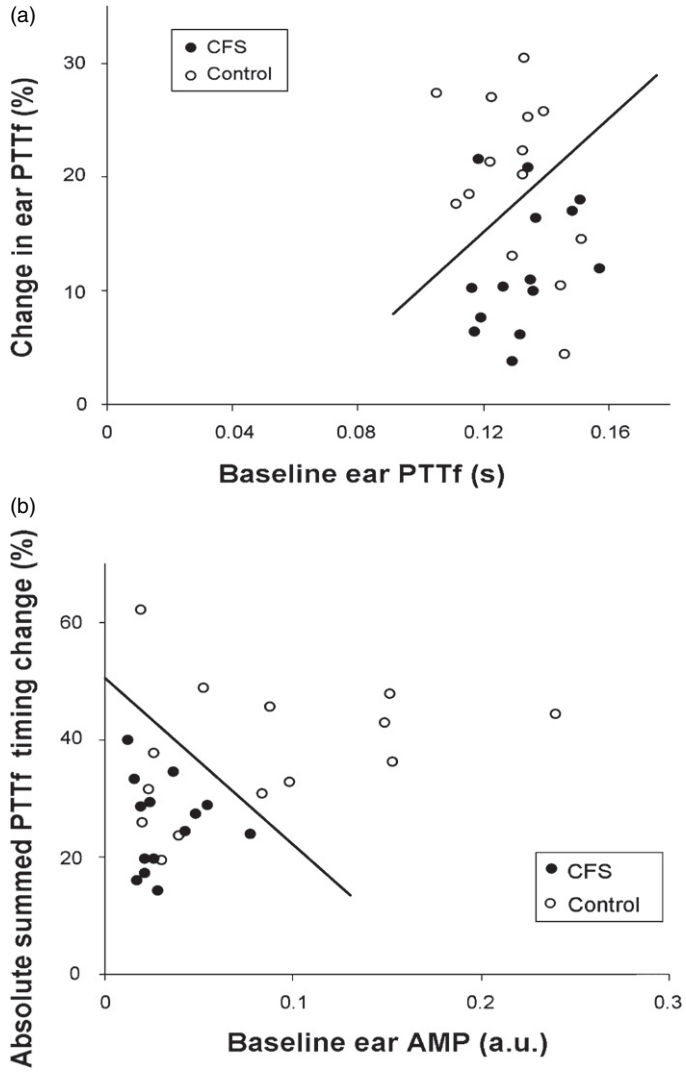

Figure 6. (a), (b) Cluster analysis plots each with a superimposed estimated linear discrimination line separating groups for pulse measure sets A and B, respectively.

Our study using novel methodology has confirmed that there were significant differences between the CFS patient group and matched controls at baseline for the ear site pulse amplitude AMP measure. Ear pulse measurements are a relatively new measurement site with recent studies suggesting that ear pulse plethysmography waveform measurements may be a potential diagnostic tool to detect clinically significant hypovolemia before the onset of cardiovascular decompensation (McGrath 2011). Our finding of abnormalities of ear pulse waveform in this group with CFS together with studies suggesting that CFS may be associated with a 'small heart syndrome' (Miwa and Fujita 2008, Hollingsworth *et al* 2010) and/or a depleted blood volume (Hurwitz *et al* 2010, Miwa and Fujita 2009, Streeten and Bell 1998) would suggest that the non-invasive technology used in this study may have the potential to detect vascular volume abnormalities at the bedside in patients with CFS.

Previous studies have indicated that pulse width of ear plethysmographic measurements are particularly sensitive to changes in systemic vascular resistance providing valuable evidence with respect to changes in peripheral vascular tone (Awad *et al* 2007). This small preliminary study which included only a small number of subjects did not however consider the impact of change of posture upon measurements and our finding of reductions in pulse transit time on orthostasis in CFS compared to matched controls, particularly at the ears and when summed over all from head to foot, would point to this being a technique that may provide insights into the mechanisms that underpin the pathogenesis of CFS.

It is interesting that the predominant abnormalities of pulse wave form found in this study were at the ear. Studies suggest that the ear is relatively immune to vasoconstrictive challenges which make ear plethysmographic waveforms a suitable monitor for central haemodynamic changes with ear plethysmographic width having been shown to have a good correlation with cardiac output (Awad *et al* 2006). Previous studies have found reduced cardiac output in CFS compared to controls (Hollingsworth *et al* 2010, Peckerman *et al* 2003, LaManca *et al* 1999) which may explain the findings from this study. Another potential explanation is that our finding of reduced PTTf at the ears could be linked to impaired cerebral autoregulation and that this response is abnormal in response to the stress of standing. Studies have suggested that impaired cerebral autoregulation is found in those with positional orthostatic tachycardia syndrome (Ocon *et al* 2009). Our previous studies have confirmed that there is considerable overlap between CFS and postural orthostatic tachycardia syndrome (Hoad *et al* 2008) and it may be that cerebral auto-regulation abnormalities account for some of the orthostatic symptoms described by these patients.

Our finding of a relationship between increasing fatigue assessed using the FIS and a reduced change in AMP suggests that this abnormality is associated with symptom severity. Although we cannot suggest causation, we believe that this finding requires further evaluation in larger numbers of well characterized patients in order to determine whether this association is of physiological significance and plays a role in the pathogenesis or perpetuation of symptoms in CFS. Further studies beyond this initial pilot should also consider test repeatability, the link between pulse measures and heart rate and blood pressure with tilt, further cluster analysis which is automated to exploit the full information within the multi-site PPG measurements, and to include other fatigue related patients to act as further controls.

We believe that this study highlights the potential for multi-site PPG assessments to form a diagnostic biomarker in CFS. The abnormalities that we have found in this study make physiological sense in terms of the existing literature in CFS and the ROC curve analysis confirms the utility of this bedside objective measure to differentiate between CFS patients and controls. This pilot study emphasizes the need to test the use of PPG technology in a further well characterized CFS population.

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References

Allen J 2007 Photoplethysmography and its application in clinical physiological measurement *Physiol. Meas.* **28** R1–39

Allen J and Murray A 2000 Similarity in bilateral photoplethysmographic peripheral pulse wave characteristics at the ears, thumbs and toes *Physiol. Meas.* **21** 369–77

Awad A A, Haddadin A S, Tantawy H, Badr T M, Stout R G, Silverman D G and Shelley K H 2007 The relationship between the photoplethysmographic waveform and systemic vascular resistance *J. Clin. Monit. Comput.* **21** 365–72

Awad A A, Stout R G, Ghobashy M A, Rezkanna H A, Silverman D and Shelley K H 2006 Analysis of ear pulse waveform *J. Clin. Monit. Comput.* **20** 175–84

CFS/ME Working Group 2009 A report of the CFS/ME Working Group (Available at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4064840 last accessed on 20 February 2010)

Fernandez A A *et al* 2009 Chronic fatigue syndrome: aetiology, diagnosis and treatment *BMC Psychiatry* **9** S1–11

Fisk J D, Ritvo P G, Ross L, Haase D A, Marrie T J and Schlech W F 1994 Measuring the functional impact of fatigue: initial validation of the fatigue impact scale *Clin. Infect. Dis.* **18** S79–83

Freeman R and Komaroff A L 1997 Does the chronic fatigue syndrome involve the autonomic nervous system? *Am. J. Med.* **102** 357–64

Fukuda K *et al* 1994 The chronic fatigue syndrome—a comprehensive approach to its definition and study *Ann. Int. Med.* **121** 953–9

Hoad A, Spickett G, Elliott J and Newton J 2008 Postural orthostatic tachycardia syndrome is an under-recognized condition in chronic fatigue syndrome *Q. J. Med.* **101** 961–5

Hollingsworth K G, Jones D E J, Taylor R, Blamire A M and Newton J L 2010 Impaired cardiovascular response to standing in Chronic Fatigue Syndrome *Eur. J. Clin. Invest.* **40** 608–15

Hurwitz B E, Coryell V T, Parker M, Martin P, LaPerriere A, Klimas N G, Sfakianakis G N and Bilsker M S 2010 Chronic fatigue syndrome: illness severity, sedentary lifestyle, blood volume and evidence of diminished cardiac function *Clin. Sci.* **18** 125–35

LaManca J J, Peckerman A, Walker J, Kesil W, Cook S, Taylor A and Natelson B H 1999 Cardiovascular response during head-up tilt in chronic fatigue syndrome *Clin. Physiol.* **19** 111–20

McGrath S P 2011 Pulse oximeter plethysmographic waveform changes in awake, spontaneously breathing, hypovolemic volunteers *Anaesthesia and Analgesia* **112** 368–74

Miwa K and Fujita M 2008 Small heart syndrome in patients with chronic fatigue syndrome *Clin. Cardiol.* **31** 328–33

Miwa K and Fujita M 2009 Cardiac function fluctuates during exacerbation and remission in young adults with chronic fatigue syndrome and 'small heart' *J. Cardiol.* **54** 29–35

Naschitz J E, Yeshurun D and Rosner I 2004 Dysautonomia in chronic fatigue syndrome: facts, hypotheses, implications *Med. Hypotheses* **62** 203–6

National Institute for Health and Clinical Excellence 2010 Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy); diagnosis and management of CFS/ME in adults and children (Available at http://guidance.nice.org.uk/CG53 last accessed on 18 January 2010)

Newton J L, Okonkwo O, Sutcliffe K, Seth A, Shin J and Jones D E J 2007 Symptoms of autonomic dysfunction in chronic fatigue syndrome *Q. J. Med.* **100** 519–26

Ocon A J, Medow M S, Taneja I, Clarke D and Stewart J M 2009 Decreased upright cerebral blood flow and cerebral autoregulation in normocapnic postural tachycardia syndrome *Am. J. Physiol. Heart Circ. Physiol.* **297** H664–73

Pagani M and Lucini D 1999 Chronic fatigue syndrome: a hypothesis focusing on the autonomic nervous system *Clin. Sci.* **96** 117–25

Parry S W, Reeve P, Lawson J, Shaw F E, Davison J, Norton M, Frearson R, Kerr S and Newton J L 2009 The Newcastle Protocols 2008: an update on head-up tilt table testing and the management of vasovagal syncope and related disorders *Heart* **95** 416–20

Peckerman A *et al* 2003 Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome *Am. J. Med. Sci.* **326** 55–60

Prins J B, van der Meer J W M and Bleijenberg G 2006 Chronic fatigue syndrome *Lancet* **367** 346–55

Schondorf R and Freeman R 1999 The importance of orthostatic intolerance in the chronic fatigue syndrome *Am. J. Med. Sci.* **317** 117–23

Streeten D H and Bell D S 1998 Circulating blood volume in chronic fatigue syndrome *J. Chronic Fatigue Syndr.* **4** 3–11

Zheng J, Hu S, Xin S and Crabtree V 2008 Effect of postural changes on lower limb blood volume, detected with non-invasive photoplethysmography *J. Med. Eng. Technol.* **32** 358–64