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commentary

Chronic fatigue syndrome: illness severity, sedentary lifestyle, blood volume and evidence of diminished cardiac function

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ABSTRACT

The study examined whether deficits in cardiac output and blood volume in a CFS (chronic fatigue syndrome) cohort were present and linked to illness severity and sedentary lifestyle. Follow-up analyses assessed whether differences in cardiac output levels between CFS and control groups were corrected by controlling for cardiac contractility and TBV (total blood volume). The 146 participants were subdivided into two CFS groups based on symptom severity data, severe ($n = 30$) and non-severe ($n = 26$), and two healthy non-CFS control groups based on physical activity, sedentary ($n = 58$) and non-sedentary ($n = 32$). Controls were matched to CFS participants using age, gender, ethnicity and body mass. Echocardiographic measures indicated that the severe CFS participants had 10.2% lower cardiac volume (i.e. stroke index and end-diastolic volume) and 25.1% lower contractility (velocity of circumferential shortening corrected by heart rate) than the control groups. Dual tag blood volume assessments indicated that the CFS groups had lower TBV, PV (plasma volume) and RBCV (red blood cell volume) than control groups. Of the CFS subjects with a TBV deficit (i.e. $\geqslant 8\%$ below ideal levels), the mean $\pm$ S.D. percentage deficit in TBV, PV and RBCV were -15.4 ± 4.0, -13.2 ± 5.0 and $-19.1 \pm 6.3\%$ respectively. Lower cardiac volume levels in CFS were substantially corrected by controlling for prevailing TBV deficits, but were not affected by controlling for cardiac contractility levels. Analyses indicated that the TBV deficit explained 91–94% of the group differences in cardiac volume indices. Group differences in cardiac structure were offsetting and, hence, no differences emerged for left ventricular mass index. Therefore the findings indicate that lower cardiac volume levels, displayed primarily by subjects with severe CFS, were not linked to diminished cardiac contractility levels, but were probably a consequence of a co-morbid hypovolaemic condition. Further study is needed to address the extent to which the cardiac and blood volume alterations in CFS have physiological and clinical significance.

Key words: anaemia, cardiac output, chronic fatigue syndrome, deconditioning, echocardiography, hypovolaemia.

Abbreviations: *A*, peak late filling velocity; BMI, body mass index; BP, blood pressure; BSA, body surface area; CFS, chronic fatigue syndrome; CI, cardiac index; CO, cardiac output; *E*, peak early filling velocity; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HHV-6, human herpesvirus-6; HR, heart rate; IVSWTd, interventricular septal wall thickness; LV, left ventricular; LVID, LV internal dimension; LVIDd, LVID at diastole; LVIDs, LVID at systole; LVLd, LV length at diastole; LVLs, LV length at systole; LVMI, LV mass index; LVPWT, LV posterior wall thickness; LVPWTd, LV posterior wall thickness at diastole; MARCH, Markers Assessing Risk for Cardiovascular Health; MIAEPO, Miami Epoetin Alpha Clinical Trial; PV, plasma volume; PVB19, human parvovirus B19; RBCV, red blood cell volume; SBP, systolic BP; SI, stroke index; SV, stroke volume; SVR, systemic vascular resistance; TBV, total blood volume; Vcf_c, velocity of circumferential shortening corrected by HR; $\dot{V}O_{2max}$, maximal oxygen consumption.

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INTRODUCTION

The severe debilitating fatigue of CFS (chronic fatigue syndrome) is commonly accompanied by a cluster of symptoms that suggest an underlying chronic or episodic cardiovascular and autonomic dysfunction [1]. Previous studies have shown that, when compared with healthy control subjects, CFS patients have postural tachycardia and orthostatic intolerance predisposing to pre-syncopal symptoms and a precipitous fall in BP (blood pressure) [2–6]. In addition, some studies have reported that CFS subjects have an exaggerated SBP (systolic BP) decrease during the Valsalva manoeuvre, vascular supersensitivity to infused noradrenaline (norepinephrine) and diminished respiratory sinus arrhythmia, suggesting abnormalities in autonomic mediation of cardiovascular functioning [7–9].

Previously, two studies using impedance cardiography to evaluate cardiovascular function have compared CFS patients with sedentary non-CFS controls [10,11]. In the initial study, no differences were found in BP during supine rest, but the CFS cohort had a more diminished SV (stroke volume) than controls [10]. In a subsequent study by this laboratory, cardiac performance was evaluated as a function of CFS illness severity. Relative to the non-severe CFS and sedentary-control subjects, severely affected CFS patients had lower SV and CO (cardiac output) [11]. These results underscore the value of considering CFS illness severity, a study design modification that has been suggested but rarely implemented in this literature [12,13].

Only two previous studies have used an echocardiographic examination of cardiac structure and function to compare CFS with non-CFS subjects [14,15]. One study showed that CFS subjects did not differ from controls in SV, but had a more diminished LVID [LV (left ventricular) internal dimension]), thinner LVPWT (LV posterior wall thickness) and less LV mass [14]. More recently, others have reported that CFS patients had a greater prevalence of small heart syndrome, defined via a chest roentgenogram as a cardiothoracic ratio $\leqslant 42\%$; 61 % of CFS subjects compared with 24 % of control subjects had small heart syndrome [15]. These CFS patients also had a shorter LVID, and more diminished stroke and cardiac index values. Notably, others have indicated that subjects with small heart syndrome may also have similar symptomatology as those with CFS, such as prolonged post-exertional weakness and fatigue, and orthostatic syncope [16].

Unfortunately, no direct comparisons with sedentary non-CFS controls were conducted in either of those studies. Controlling for physical activity is essential because CFS patients are mostly sedentary [17], and, with more prolonged illness duration and severity, deconditioning can result in cardiac atrophy, and substantially diminished cardiac contractility and haemodynamic performance [17–19]. In addition, disease chronicity is often associated with anaemia, idiopathic hypovolaemia and dehydration, which can predispose to orthostatic syncopal susceptibility and other autonomic and circulatory deficits [20,21]. Indeed, when direct blood volume measurements were performed, subnormal PV (plasma volume) and RBCV (red blood cell volume) have been observed in 53 and 84 % respectively, of the severely affected CFS patients, and 63 % of these patients had low TBV (total blood volume) [22]. Thus it cannot be concluded with certainty that the CFS cardiac structure and function abnormalities reported previously were not a consequence of deconditioning due to sedentary lifestyle or abnormalities in blood volume, cardiac contractility or other underlying pathophysiology.

Therefore the present study compared CFS with non-CFS participants on cardiac structure and function, while controlling for illness severity, sedentary lifestyle, blood volume, cardiac contractility and relevant demographic and anthropometric factors. Hence the study design evaluated outcomes among four groups: two CFS groups subdivided on illness severity (severe and non-severe) and two healthy non-CFS control groups subdivided on physical activity (sedentary and non-sedentary). Furthermore, to reduce error variance due to sampling bias, non-CFS participants were matched for age, gender, ethnicity and BMI (body mass index) of the CFS participants.

MATERIALS AND METHODS

Participants

A total of 146 men and women contributed data from two different studies: MIAEPO (Miami Epoetin Alpha Clinical Trial) and MARCH (Markers Assessing Risk for Cardiovascular Health). Both studies received approval from the University of Miami Institutional Review Board for human subjects research and followed institutional guidelines. All subjects provided written informed consent. MIAEPO was a double-blind placebo-controlled limited cross-over study with the primary objective to examine the impact of epoetin α pharmacotherapy on RBCV, autonomic function and orthostatic susceptibility in CFS. Subjects were recruited through physician referral and media reports, and relevant information was provided via an internet questionnaire. Of these subjects, 475 were phone-screened and 166 potentially eligible participants were invited to a screening session. Of the 166 participants who were screened, 104 were CFS-diagnosed patients and 62 were sedentary non-CFS control subjects. Of the 104 CFS subjects, 35 voluntarily withdrew prior to completing baseline assessments, 13 did not meet study eligibility criteria, and 56 completed baseline assessments. Of the 62 control subjects, 25 did not meet

study eligibility criteria, 13 voluntarily withdrew, and 24 completed the baseline assessments. Therefore, from the MIAEPO study, 56 CFS persons and 24 non-CFS persons participated in the present study.

Study-eligible MIAEPO subjects: (i) were aged 18–55 years; (ii) if CFS, provided supporting documentation of their physician diagnosis; (iii) had no history of major systemic disorders or any medical illness that met CFS exclusionary criteria as per 1994 CDC guidelines [12]; (iv) were not anaemic at study entry, using standard blood chemistry diagnostics (a MIAEPO study objective was to identify CFS subjects who had no anaemia using standard blood chemistry diagnostic tests, but upon assessment with blood volume testing using radioactively labelled red blood cells had low RBCV; non-CFS persons enrolled in the MIAEPO study were excluded if they had low TBV, defined as $\geqslant 8\,\%$ below ideal an TBV [23]), (v) had no history of current or past major depressive disorder with melancholic or psychotic features, bipolar disorder of any type, psychotic episode, anorexia or bulimia nervosa; (vi) had no history of panic disorder within 6 months of study entry; (vii) had no history of illicit drug or alcohol abuse or dependency within 2 years before the onset of CFS symptomatology and no history of drug or alcohol abuse or dependency within 6 months of study entry; (viii) were not being treated in the 3 months preceding study entry with medication having a cardiovascular, metabolic, autonomic, immune or endocrine effect; (ix) had no previously diagnosed primary sleep disorder and were using hypnotic agents to induce sleep <3 times/week; (x) presented no ECG arrhythmias associated with tachycardia, bradycardia (<50 beats/min), heart block or myocardial infarction; (xi) were not pregnant and had no intention of becoming pregnant; and (xii) if CFS, were willing to participate in a 7-month clinical trial including receiving subcutaneous self-injections of epoetin α or placebo.

The MARCH study was designed to assess biobehavioural factors and subclinical cardiovascular disease risk [24]. MARCH subjects were recruited from Miami-Dade and Broward counties of Florida via newspaper advertising. From the 338 participants who completed the protocol, 37 healthy sedentary non-CFS subjects and 32 healthy non-sedentary non-CFS subjects were selected for inclusion in the control groups. Sedentary and non-sedentary control subjects from the MARCH studies were selected using a matching procedure based on age, gender, race and BMI of the CFS participants. Specifically, MARCH subjects qualified for inclusion if the range of age and BMI were within 18–54 years and 17–35.6 kg/m^2 respectively. Control subjects were reduced in number to maintain comparable group proportions as that of the CFS cohort, i.e. women (75 %), black race (4 %) and BMI $\geqslant 25$ kg/m^2 (41 %).

MARCH study subjects were aged 18 to 55 years, and were healthy based on physical examination, medical history, fasting blood chemistry analysis and 12-lead ECG [24]. Otherwise, the eligibility criteria were similar to the MIAEPO study, with the following exceptions. MARCH subjects were excluded for: (i) use of birth control pills; and (ii) psychiatric conditions based on self-report or history of psychiatric medication use. These subjects were not evaluated for and thus not excluded for primary sleep disorder, use of hypnotic agents or low TBV.

CFS group assignment by illness severity

The present study examined outcomes as a function of illness severity (severe and non-severe) as defined previously [25]. In brief, to be classified as severely ill CFS subjects had to report that they had seven or more of ten CFS symptoms (symptoms included post-exertional fatigue, unrefreshing sleep, general weakness, memory or concentration impairments, muscle aches/pain, joint pain, headache, fever chills, sore throat and tender lymph nodes), and at least seven of these symptoms had to persist for $\geqslant 6$ months and be rated as moderate or severe either currently or in the past [11,25].

Control group assignment by sedentary lifestyle

For control subjects, assignment to control groups was based upon sedentary lifestyle indexed by physical activity. Physical activity in energy expenditure was derived using the Paffenbarger Physical Activity Questionnaire [26] and the compendium of energy expenditure ratings for physical activities [27]. Sedentary status was defined as an average energy expenditure $\leqslant 1500$ kcal/week (where 1 kcal ≈ 4.184 kJ), whereas non-sedentary status was designated as expending $\geqslant 2200$ kcal/week (cf. [28]).

Procedures

In both MIAEPO and MARCH studies, the objective of the screening session was to confirm that study eligibility criteria were met. In this session, family and personal medical history, and a physical examination were then conducted. All subjects underwent a 12-lead ECG and seated casual BP procedures. Standard comprehensive blood chemistries, pregnancy screening and urine toxicology [i.e. alcohol, barbiturates, benzodiazepines, cannabinoids, LSD (lysergic acid diethylamide), PCP (phencyclidine), THC (Δ^9-tetrahydrocannabinol), morphine and amphetamines] were performed. In the MIAEPO study, additional blood assays were performed including CBC (complete blood count), iron, TIBC (total iron binding capacity), ferritin and liver function chemistries, creatinine, BUN (blood urea nitrogen), sedimentation rate, creatine kinase, thyroid-stimulating hormone, serum folate, vitamin B12, rheumatoid factor and antinuclear antibody testing. Participants completed the structured clinical diagnostic interview [29], and a battery

of questionnaires to provide a subjective assessment of CFS symptomatology and severity of illness, chronic and current fatigue, vitality, psychological regulation, and quality of life. This information was used along with that from the participant's physician, the physical examination and comprehensive blood chemistries to confirm a CFS diagnosis [12]. Following the screening session, the MIAEPO study consisted of three pre-treatment sessions, including procedures to measure blood volume, an echocardiography examination of cardiac structure and function, and a graded exercise fitness test. In the MARCH study, following the screening session, two baseline assessment sessions were administered, which included an identical echocardiography evaluation [24].

Blood volume test

Used since the 1960s, the dual tag test is the gold standard method for obtaining blood volumes [30]. Blood volume procedures were performed in the Radiology Department, Division of Nuclear Medicine at Jackson Memorial Hospital, Miami, FL, U.S.A.. Using the recommendations of the International Council for Standardization in Hematology, this procedure included the ^{51}Cr labelling of red blood cells to measure RBCV, and the ^{125}I labelling of serum albumin to measure PV [31]. Blood samples were collected 10, 20 and 30 min after labelled blood re-injection and were assayed. Volumes were calculated from the known dosage administered and the radioactivity concentration measured in the blood. An extensive description of these methods is described elsewhere [32]. {Owing to temporary federal withdrawal of ^{125}I, PV was directly measured in 18 study participants using the BVA-100 semi-automated system (Daxor) designed for measuring plasma ^{131}I-labelled human serum albumin. The device directs the scintillation detector and derives PV from measurements of plasma radioactivity, employing single-use kits of 10 μCi of ^{131}I-albumin injectate, a matching standard in a pre-measured aliquot, and a patient blank. To correct for albumin transudation, the device extrapolates to time 0 using five serial samples taken every 6 min from 12 to 36 min post-injection. This method has been validated against the gold standard dual tag method with an average PV difference of 3.3 % between methods [32]}. TBV was calculated by summing RBCV and PV; volumes were corrected by body weight. Whole-body haematocrit was derived from the RBCV/TBV ratio. The percentage deviation from predicted PV, RBCV and TBV values were derived from ideal body weight and blood volume data controlling for age, gender, weight and height, as described previously [23].

Resting seated and supine BP

Causal sphygmomanometric BP in the seated position was obtained every 3 min, and the average of the second and third measurements was computed. In addition, resting BP measurements in the supine position were obtained using an oscillometric device (Dinamap 1846SXP; Critikon) just prior to the echocardiographic examination. SVR (systemic vascular resistance) was derived by dividing the MAP (mean arterial pressure)/CO ratio by 16.67 [33].

Cardiac function and structure

Both studies employed two-dimensional and M-mode echocardiograms recorded in the left lateral decubitus position using a cardiac phased-array ultrasound imaging system (SONOS 5500; Philips Medical Systems). The images were quantified by readers blinded to the clinical data using a Nova-Microsonic ImageVue workstation, according to the recommendations of the American Society of Echocardiography [34]. Inter- and intra-scorer measurement reliabilities were high ($r_s > 0.90$; coefficients of variation, $< 7\%$), as described previously [24]. From five cardiac cycles, averages were computed for measures of cardiac structure and function. Measures of cardiac function included: ESV and EDV (end-systolic and end-diastolic volumes respectively, SV, SI (stroke index), EF (ejection fraction), HR (heart rate), CO and CI (cardiac index). Cardiac contractility was indexed using Vcf_c (velocity of circumferential shortening corrected by HR). Cardiac compliance was assessed using E (peak early filling velocity), A (peak late filling velocity) and the E/A ratio. Structural measurements included LVLd and LVLs (LV length at diastole and systole respectively), LVIDd and LVIDs (LVID at diastole and systole respectively), cardiac wall thicknesses at diastole [LVPWTd (LV posterior wall thickness at diastole) and IVSWTd (interventricular septal wall thickness)], and LVMI (LV mass index), using the formula described by de Simone et al. [35].

Aerobic capacity

In the MIAEPO study, a graded exercise test was used to obtain aerobic capacity, indexed by body-weight-adjusted $\dot{V}O_{2max}$ (maximal oxygen consumption; $\dot{V}O_{2max}$/kg). The direct assessment of $\dot{V}O_{2max}$ was obtained immediately upon exercise termination. The test consisted of a supervised symptom-limited maximum exercise test performed using a fully automated electronically braked cycle ergometer and open-circuit spirometry (Vmax 29c Cardiopulmonary Exercise Testing Instrument; SensorMedics).

Statistical analyses

Using SPSS (version 16.0), data screening included an examination of descriptive statistics, variable distributions and an evaluation of departures from normality. Because subject recruitment, selection or attrition may have resulted in group heterogeneity, analyses examined group differences for potential covariates: gender, age, ethnicity, BMI, BSA (body surface area), income and education. Any variables found to differ among the groups were included as covariates in all analyses. Using ANCOVA

Table 1 Subject demographic and physical characteristics of the CFS and control groups, subdivided by illness severity and physical activity criteria

Values are means (S.E.M.). *Values obtained from 27, 24, 49, and 25 subjects respectively. Race is coded as white (non-Hispanic white and Hispanic white) or black (African-American and Caribbean-American). Values for BMI, BSA and aerobic capacity are adjusted based on the covariates age and education. Group effect *P* level, post-hoc comparisons in parentheses are significant. Group numbers are: 1, severe CFS group; 2, non-severe CFS group; 3, sedentary control group; 4, non-sedentary control group. n.s., not significant.

Measurement	Severe CFS ($n = 30$)	Non-severe CFS ($n = 26$)	Sedentary control ($n = 58$)	Non-sedentary control ($n = 32$)	Group effect *P* level among the four groups
Gender (% women)	86.7	61.5	74.1	68.8	n.s.
Race (% white)	96.7	96.2	96.6	96.9	n.s.
Overweight/obese (BMI $\geqslant$ 25 kg/m^2) (%)	33.3	50.0	41.4	40.6	n.s.
Age (years)	43.9 (1.5)	39.2 (1.6)	38.2 (1.3)	36.8 (1.4)	$P < 0.01$ (1 > 2, 3 and 4)
Total family income ($k)*	38.1 (3.0)	35.0 (4.0)	16.5 (2.1)	20.3 (2.9)	$P < 0.001$ (1 and 2 > 3 and 4)
Education (years)	15.7 (0.5)	15.0 (0.5)	13.5 (0.4)	14.1 (0.6)	$P < 0.01$ (1 > 3 and 4; 2 > 3)
BMI (kg/m^2)	24.5 (0.7)	25.8 (0.9)	25.4 (0.6)	25.4 (0.7)	n.s.
BSA (m^2)	1.7 (0.03)	1.8 (0.05)	1.7 (0.03)	1.8 (0.03)	n.s.
Aerobic capacity					
Observed $\dot{V}o_{2max}$ (ml · kg^{-1} of body weight · min^{-1})	20.7 (1.1)	19.7 (1.0)	18.9 (1.1)	—	n.s.
Predicted $\dot{V}o_{2max}$ (ml · kg^{-1} of body weight · min^{-1})	27.8 (1.0)	30.0 (1.4)	26.3 (1.5)	—	n.s.
Difference from predicted $\dot{V}o_{2max}$ (%)	−25.1 (3.2)	−32.7 (2.9)	−25.7 (3.3)	—	n.s.

(analysis of covariance), outcome measures were analysed for group differences (i.e. severe CFS compared with non-severe CFS compared with sedentary control compared with non-sedentary control). An effect reflecting CFS status was indicated by a difference between the CFS and non-CFS groups. An effect reflecting sedentary lifestyle was reflected by a difference between the non-sedentary control group and the three other sedentary groups. For significant group effects ($P = 0.05$), post-hoc pairwise comparisons were conducted using Fisher's LSD (least significant difference) test.

RESULTS

Participant characteristics

From the MIAEPO study, 56 CFS (42 women and 14 men) and 24 sedentary non-CFS control (19 women and five 5 men) participants met the study eligibility criteria and completed pre-treatment assessments. Owing to technical reasons, blood volume measures were not obtained for three MIAEPO sedentary control subjects. From the MARCH study, 200 sedentary and 84 non-sedentary persons available based upon physical activity criteria. Of these subjects, 34 sedentary and 32 non-sedentary control subjects were selected based on matching criteria. Table 1 shows the subject demographic and physical characteristics of the four groups, as subdivided by illness severity and physical activity grouping criteria. Of the parameters used for group matching, no significant group differences emerged for group composition based on gender, race or the proportion overweight or obese. Neither BMI nor BSA differed significantly among the groups. However, group differences were found for age [$F(3, 142) = 4.0$, $P < 0.01$], wherein the severe CFS group was older than the other groups ($P < 0.05$). In addition, group differences were found for income and education [$F(3, 121) = 14.6$, $P < 0.001$; $F(3, 142) = 4.2$, $P < 0.009$ respectively]; although the CFS groups did not differ in income and education, they had higher incomes than the control groups ($P < 0.003$), and attained more years of education than the sedentary control group ($P < 0.04$). Therefore age and education were included as covariates in subsequent analyses, but due to the extent of missing data (14 %) and similar pattern of group differences, income was not controlled analytically. The respective mean ± S.D. physical activity level expended by the sedentary and non-sedentary control subjects was 550.9 ± 460.9 and 3878.2 ± 2089.7 kcal/week. As can be seen in Table 1, the observed aerobic capacity and the difference from the predicted aerobic capacity did not differ significantly among all three of the sedentary groups. For these groups, the adjusted mean ± S.D. aerobic capacity was well below the predicted value (−27.3 ± 16.4 %), indicating substantial deconditioning.

Group classifications

Table 2 shows the CFS characteristics and reported CFS symptom prevalence of the CFS groups. Relative to the non-severe group, the severe CFS subjects reported a 'moderate' or 'severe' intensity for about twice as many CFS-related symptoms. Of the ten CFS symptoms, more than 80 % of the severe group reported experiencing all of the symptoms, except sore throat and tender lymph

Table 2 Characteristics and symptoms of the CFS groups, subdivided by reported illness severity

Values are means (S.E.M.) unless otherwise noted. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with non-severe CFS subjects.

Measurement	Severe CFS ($n = 30$)	Non-severe CFS ($n = 26$)
CFS-related characteristics		
Time since CFS diagnosis (years)	6.6 (0.9)	5.3 (0.9)
Age of fatigue onset (years)	34.5 (1.7)	31.4 (1.6)
Fatigue duration (years)	8.9 (1.0)	7.8 (0.9)
Moderate or severe CFS symptoms (n)	8.5 (0.2)***	4.2 (0.3)
Prevalence of CFS-related symptoms (% of subjects endorsing the CFS symptoms as 'moderate' or 'severe' intensity')		
Post-exertional fatigue	100.0 (5.5)	88.5 (4.5)
Unrefreshing sleep	100.0 (5.5)*	80.8 (4.1)
General weakness	96.7 (5.3)**	65.4 (3.3)
Impaired memory or concentration	96.7 (5.3)**	65.4 (3.3)
Muscle aches/pain	93.3 (5.1)***	46.2 (2.4)
Joint pain	86.7 (4.8)***	19.2 (1.0)
Headaches	83.3 (4.6)***	19.2 (1.0)
Feverish/chills	83.3 (4.6)***	7.7 (0.4)
Sore throat	56.7 (3.1)***	11.5 (0.6)
Tender lymph nodes	53.3 (2.9)**	15.4 (0.8)

nodes, which were reported by only approximately half of these subjects; of the non-severe group, 80 % or more subjects reported experiencing only two symptoms with 'moderate' or 'severe' intensity, post-exertional fatigue and unrefreshing sleep. The prevalence of reported 'moderate' or 'severe' autonomic and cardiovascular-related symptomatology (i.e. chest pain, racing heart, blurred vision, nausea, dizziness after standing and night sweats) that persisted for 6 or more months either currently or in the past was 16.1, 23.2, 30.4, 35.7, 55.4 and 55.4 % respectively. No group differences were found in time since CFS diagnosis, age of fatigue onset or fatigue duration.

Cardiac function, SVR and BP

Table 3 shows the adjusted group means $\pm$ S.E.M for cardiovascular outcomes. A comparison of BPs indicated no group differences in seated or supine levels. A trend towards significant group differences in SVR [$F(3, 140) = 2.1$, $P = 0.10$] was due to more SVR elevation in the severe CFS subjects than controls ($P < 0.04$). In addition, analyses yielded a significant difference in CI among the groups [$F(3, 140) = 3.3$, $P < 0.03$]. Both the severe and non-severe CFS groups had a more diminished CI level than the control groups ($P < 0.04$). The lower CI in the CFS groups was not due to HR differences among groups. Instead, a significant group difference in SI among the groups [$F(3, 140) = 3.2$, $P < 0.03$] was due to a lower SI in the severe CFS group than both of the control groups ($P < 0.03$). In contrast, the non-severe CFS and control groups did not differ in SI, but an inspection of group means suggested that the diminished CI in the non-severe CFS subjects was due to a combination of lower SI and HR (see Table 3). Similar findings were observed for group differences in EDV, wherein the severe CFS group tended to have a lower EDV than all of the other groups [$F(3, 140) = 2.5$, $P = 0.065$]. No differences were found among groups in ESV.

Further analyses showed, relative to the control groups, that the CFS groups had more diminished cardiac contractility, indexed by Vcf_c [$F(3, 140) = 16.2$, $P < 0.001$]. In contrast, no group differences were found for cardiac compliance, indexed by the E/A ratio. When analyses controlled for cardiac contractility, the group differences in cardiac volume levels (i.e. CI, SI and EDV) remained significant ($P < 0.04$). Thus the diminished cardiac volume level, which was more apparent in the severe than non-severe CFS subjects, does not appear to be a consequence of a depression in contractility.

Cardiac structure

No group differences in LVLs were found, although the severe CFS group tended to have shorter LVLd than the control groups [$F(3, 140) = 2.3$, $P = 0.09$]. Both CFS groups and the sedentary control subjects had significantly shorter LVIDd and LVIDs than the non-sedentary control subjects [$F(3, 140) = 8.7$, $P < 0.001$; and $F(3,140) = 5.6$, $P < 0.002$ respectively]. In contrast, greater cardiac wall thickness was observed in the CFS groups [IVSWTd: $F(3, 140) = 7.4$, $P < 0.001$; LVPWTd: $F(3, 140) = 5.8$, $P < 0.002$]; specifically, both CFS groups had significantly greater IVSWTd and LVPWTd than the non-sedentary control subjects ($P < 0.02$). However, in terms of their impact on LVMI, the alterations in cardiac

Table 3 Cardiac function and structure in the CFS and control groups, adjusted for age and education

Values are means (S.E.M.). Group effect *P* level, post-hoc comparisons in parentheses are significant. Group numbers are: 1, severe CFS group; 2, non-severe CFS group; 3, sedentary control group; 4, non-sedentary control group. circ/s, circumferences/s; DBP, diastolic BP; n.s., not significant; pru, peripheral resistance units.

Measurement	Severe CFS ($n = 30$)	Non-severe CFS ($n = 26$)	Sedentary control ($n = 58$)	Non-sedentary control ($n = 32$)	Group effect *P* level among the four groups
BP					
Seated SBP (mmHg)	108.57 (2.30)	109.68 (2.64)	110.35 (1.49)	112.03 (2.00)	n.s
Seated DBP (mmHg)	71.10 (1.99)	71.70 (1.76)	73.65 (1.18)	73.48 (1.51)	n.s
Supine SBP (mmHg)	106.53 (1.50)	108.24 (2.24)	109.02 (1.66)	107.53 (2.39)	n.s.
Supine DBP (mmHg)	65.21 (1.40)	66.22 (1.71)	65.07 (1.15)	65.53 (1.61)	n.s.
Vascular resistance					
SVR (pru)	1.03 (0.03)	0.99 (0.04)	0.93 (0.02)	0.92 (0.04)	$P < 0.10$ (1 > 3 and 4)
Cardiac function					
CO (litres/min)	4.71 (0.18)	5.12 (0.25)	5.31 (0.14)	5.46 (0.21)	$P < 0.10$ (1<3 and 4)
CI (litres · min^{-1} · m^{-2})	2.75 (0.11)	2.76 (0.09)	3.05 (0.06)	3.08 (0.13)	$P < 0.05$ (1 and 2 < 3 and 4)
HR (beats/min)	71.70 (1.85)	67.73 (1.74)	72.77 (1.22)	70.03 (1.44)	n.s.
SV (ml)	66.01 (2.22)	75.88 (3.30)	73.51 (1.85)	78.10 (2.74)	$P < 0.05$ (1 < 2, 3 and4)
SI (ml/m^2)	38.50 (1.32)	41.02 (1.22)	42.23 (0.70)	43.96 (1.57)	$P < 0.05$ (1 < 3 and 4)
EDV (ml)	108.25 (3.13)	120.85 (4.82)	119.16 (2.92)	122.97 (4.01)	$P < 0.10$ (1 < 2, 3 and 4)
ESV (ml)	42.24 (1.39)	44.96 (1.93)	45.65 (1.25)	44.87 (1.99)	n.s.
Cardiac contractility					
Vcf_c (circ/s)	0.68 (0.03)	0.75 (0.03)	0.89 (0.02)	0.94 (0.03)	$P < 0.001$ (1 and 2 < 3 and 4)
Cardiac compliance					
E (cm/s)	80.98 (2.78)	77.04 (2.38)	77.80 (1.55)	75.94 (2.15)	n.s.
A (cm/s)	63.36 (2.37)	56.76 (2.32)	60.15 (1.87)	56.25 (2.08)	n.s.
E/*A* ratio	1.34 (0.07)	1.39 (0.05)	1.35 (0.04)	1.39 (0.05)	n.s.
Cardiac structure					
LVLd (cm)	7.95 (0.10)	8.14 (0.12)	8.31 (0.08)	8.27 (0.11)	$P < 0.10$ (1 < 3 and 4)
LVLs (cm)	6.28 (0.09)	6.35 (0.11)	6.42 (0.09)	6.17 (0.11)	n.s.
LVIDd (cm)	3.92 (0.07)	4.09 (0.09)	4.14 (0.06)	4.47 (0.06)	$P < 0.001$ (1, 2 and 3 < 4; 1 < 3)
LVIDs (cm)	2.82 (0.07)	2.84 (0.07)	2.88 (0.05)	3.15 (0.05)	$P < 0.01$ (1,2 and 3 < 4)
IVSWTd (cm)	0.92 (0.02)	0.97 (0.02)	0.88 (0.02)	0.84 (0.01)	$P < 0.001$ (1 and 2 > 4; 2 > 3)
LVPWTd (cm)	0.93 (0.02)	0.97 (0.02)	0.90 (0.02)	0.86 (0.01)	$P < 0.01$ (1 and 2 > 4; 2 > 3)
LVMI (g/m^2)	29.02 (1.26)	30.77 (1.36)	30.67 (1.02)	30.81 (1.10)	n.s.

wall thickening and cavity dimensions were offsetting. Hence analyses indicated no group differences in LVMI.

Blood volume and cardiac function differences

Table 4 shows the adjusted mean ± S.E.M. values for blood volume measurements derived for the CFS groups and the sedentary controls. Analyses indicated that significant group differences emerged for the percentage difference from ideal blood volume for TBV, PV and RBCV [$F(2, 72) = 14.8$, $P < 0.001$; $F(2, 72) = 13.0$, $P < 0.001$; and $F(2, 72) = 8.1$, $P < 0.002$ respectively]. For each blood volume measurement, the severe CFS group had greater deficits than the non-severe CFS group, which in turn had greater deficits than the sedentary control group ($P < 0.05$). The proportion of subjects per group that had TBV, PV and RBCV deficits is shown in Table 4. Of the CFS subjects with a TBV deficit ⩾8% below ideal levels, the mean ± S.D. percentage deficit in TBV, PV and RBCV was −15.4 ± 4.0% (range, −8.9 to −25.6%), −13.2 ± 5.0% (range, −6.9 to −29.3%) and −19.1 ± 6.3% (range, −7.2 to −36.5%) respectively.

Of the cardiac volume (CI, SI and EDV) and contractility (Vcf_c) variables found previously to differ among CFS and sedentary control groups, the three-group comparisons similarly indicated a greater cardiac function decrement in the severe CFS subjects than the other groups ($P < 0.06$, 0.05, 0.02, and 0.03 respectively). Then, as shown in Table 5, after controlling for the percentage difference from ideal TBV, analyses indicated that these group differences were no longer significant for CI, SI and EDV ($P = 0.33$, 0.62 and 0.40 respectively), whereas the severe CFS subjects continued to have less contractility than the controls ($P < 0.02$). Notably, regression analyses indicated that the TBV deficits

Table 4 Blood volume measurements in the CFS groups and sedentary control group, adjusted for age and education

Values are means (S.E.M.). Group effect *P* level, post-hoc comparisons in parentheses are significant. Group numbers are: 1, severe CFS group; 2, non-severe CFS group; 3, sedentary control group. n.s., not significant.

Measurement	Severe CFS ($n = 30$)	Non-severe CFS ($n = 26$)	Sedentary control ($n = 21$)	Group effect *P* level among the three groups
TBV (ml/kg)	57.31 (1.69)	61.04 (1.77)	63.08 (2.03)	$P < 0.10$ ($1 < 3$)
PV (ml/kg)	37.16 (1.10)	38.80 (1.15)	40.99 (1.32)	n.s.
RBCV (ml/kg)	20.15 (0.78)	22.24 (0.82)	22.09 (0.94)	n.s.
Difference from ideal TBV (%)	−9.71 (2.00)	−2.15 (2.10)	8.09 (2.41)	$P < 0.001$ ($1 < 2 < 3$)
Difference from ideal PV (%)	−7.60 (2.35)	−0.14 (2.47)	12.08 (2.83)	$P < 0.01$ ($1 < 2 < 3$)
Difference from ideal RBCV (%)	−13.26 (2.29)	−5.82 (2.40)	1.57 (2.75)	$P < 0.01$ ($1 < 2 < 3$)
Below normal TBV (%)	63.3	26.9	0.0	
Below normal PV (%)	56.7	34.6	4.8	
Below normal RBCV (%)	70.0	46.2	23.8	

Table 5 Cardiac function measurements in the CFS and sedentary control groups, adjusting for the difference from ideal TBV, in addition to age and education

Values are means (S.E.M.). Group effect *P* level, post-hoc comparisons in parentheses are significant. Group numbers are: 1, severe CFS group; 2, non-severe CFS group; 3, sedentary control group. circ/s, circumferences/s; n.s., not significant.

Measurement	Severe CFS ($n = 30$)	Non-severe CFS ($n = 26$)	Sedentary control ($n = 21$)	Group effect *P* level among the three groups
CO (litres/min)	4.94 (0.21)	5.16 (0.21)	5.11 (0.27)	n.s.
CI (litres·min^{-1} · m^{-2})	2.77 (0.10)	2.77 (0.10)	3.00 (0.13)	n.s.
SV (ml)	70.11 (2.59)	76.08 (2.49)	69.44 (3.21)	n.s.
SI (ml/m^2)	39.37 (1.23)	41.00 (1.18)	40.87 (1.52)	n.s.
EDV (ml)	113.52 (3.85)	120.87 (3.70)	117.53 (4.76)	n.s.
Vcf_c (circ/s)	0.82 (0.02)	0.86 (0.02)	0.91 (0.03)	$P < 0.10$ ($1 < 3$)

explained 73.2, 91.7, 94.0 and 26.6 % respectively, of the group differences in CI, SI, EDV and Vcf_c. Thus the TBV deficits substantially accounted for the group differences in cardiac volume measures.

DISCUSSION

The major findings of the present study were that, relative to healthy non-CFS subjects, patients with CFS and more substantially those classified with severe CFS had (i) lower CI, which replicated previous reports [11,15], due to a decrement in SI of approx. 10.2 %; (ii) a cardiac contractility deficit of approx. 25.1 %; and (iii) a TBV deficit of approx. 15.4 %. When cardiac contractility was controlled, the lack of a significant correction in cardiac volume measurements (CI, SI and EDV) indicated that these CFS functional differences were unlikely to be related to contractility. Similarly, the finding that the sedentary control subjects did not have a decrement in cardiac volume level suggests that the lower cardiac volume level in the CFS subjects was not likely to be due to deconditioning. This conclusion is supported by the observation that the CFS groups had a similar aerobic capacity deficit compared with the sedentary control group. Moreover, the aerobic capacity deficit did not correlate significantly with the decrement in cardiac volume in these subjects. Notably, the observed group differences for indices of cardiac volume were nullified by analytically controlling for prevailing TBV deficits; the TBV deficit accounted for 91–94 % of the group differences in cardiac volume. Therefore it is probable that the decrement in cardiac volume in CFS subjects is secondary to a hypovolaemic condition, rather than due to a primary cardiac functional abnormality. However, without the demonstration that blood volume treatment provides a resolution of the cardiac abnormalities, such a conclusion cannot be made with certainty.

The decrement in cardiac volume level in CFS subjects was of a relatively moderate magnitude and CI levels remained within nominal ranges for these patients. Nevertheless, a functional deficit in the observed magnitude may have physiological relevance under conditions of physical and mental challenge. There are numerous studies indicating that, during head-up tilting, CFS patients relative to their non-CFS counterparts have haemodynamic dysfunction, often reflected by excessive tachycardia and susceptibility to hypotensive collapse, as well as pre-syncopal and syncopal events [2–6]. However, it should be noted that in the present study the decrement in cardiac volume level did not manifest differences in aerobic

capacity in CFS subjects relative to non-CFS sedentary controls. A previous study reported that, compared with healthy controls, a small cohort of CFS patients had heightened vasomotor sensitivity to sympathetic stimulation, requiring an approx. 10-fold less noradrenaline infusion to induce a 50% peripheral venoconstriction increase [9]. Hence, in subjects with CFS, altered adrenoceptor, post-receptor vascular or other mechanisms may be acting to compensate for prevailing cardiac functional limitations.

Although no group differences in cardiac mass were observed, the CFS and sedentary control groups had a smaller LV chamber size than the non-sedentary control group; this finding appears to support the previous suggestion of small heart syndrome in CFS [15]. That the present finding arose in the sedentary groups suggests a common aetiology. The established linkage between deconditioning and cardiac atrophy, including myocardial wall thinning, supports this possibility [36,37]. However, this interpretation may not be valid because poorer aerobic capacity was not significantly associated with a smaller LV chamber size in these study participants. In contrast, the cardiac wall thickness findings did indicate CFS status differences; cardiac wall thicknesses were greater in the CFS compared with the control groups. Although resting BP was not elevated in the CFS subjects, there was a trend towards greater SVR in the severe CFS subjects, which may have played a role in stimulating the observed cardiac wall thickening. Alternatively, given that CFS onset is often linked with recent infection and CFS patients tend to have an elevated prevalence of bacterial and/or viral infections [38,39], one possible source of the wall thickness differences may be infection. HHV-6 (human herpesvirus-6), PVB19 (human parvovirus B19) and combined PVB19/HHV-6 are frequently found in cardiac biopsies from patients with viral myocarditis [40,41]. In addition, some evidence suggests that these viruses may trigger and perpetuate fatigue syndromes in non-CFS and CFS patients [39,42]. However, we are not aware of any reported cases of viral myocarditis in CFS patients.

The present findings of RBCV deficit in CFS are comparable with a previous study of severely affected CFS patients [22]. However, the present results extend this deficit to non-severely affected CFS subjects. In addition, the CFS subjects in the present study had a deficit in PBV as well. Notably, approx. two-thirds of the severe CFS group had a below-normal TBV, a prevalence that was 2-fold greater than the non-severe CFS subjects (see Table 4). In addition, the magnitude of TBV deficit was quite substantial, extending up to 6 S.D. below normal in some subjects. Although a number of fluid volume regulation factors could induce an independent PV decrement, it is common for a primary reduction in RBCV to result in a corresponding PV decline [43]. An RBCV deficiency suggests the presence of an associated anaemic condition; however, CDC (Centers for Disease Control and Prevention) diagnostic criteria dictate that the presence of anaemia is exclusionary for a CFS diagnosis [12]. The CFS cohort in the present study did not have blood chemistry abnormalities that would warrant such a diagnosis. Thus the elevated prevalence of low RBCV suggests that the CFS subjects may have an anaemia type that goes undetected by standard haematological evaluations. Normochromic normocytic anaemia is one such condition that is defined by a low RBCV, despite the presence of normal levels of haematocrit, haemoglobin and serum ferritin, and red blood cell count, size and shape [44]. This anaemia type is common in chronic systemic disorders, such as heart disease, renal failure, endocrine insufficiency, hepatic disease, gastrointestinal malabsorption, rheumatological conditions, chronic infections and cancer, disorders that are exclusionary for a CFS diagnosis [20]. Thus CFS may be another chronic condition that results in hypoproliferative anaemia. Current research suggests that normochromic normocytic anaemia may arise from a chronic inflammatory process that interferes with renal erythropoietin production or signalling and by inhibiting bone marrow red blood cell production [46]. Although a chronic inflammatory condition accompanying CFS has been hypothesized [47,48], such findings are inconsistent and not yet confirmed [49].

The primary limitation of the present study was its cross-sectional nature, wherein a determination of causal relationships is not possible. However, no previous studies of men and women with CFS have evaluated, using state-of-the-art methods, cardiac structure and function in the context of blood volume, while controlling for CFS illness severity and sedentary lifestyle. Notably, subjects were rigorously classified according to current international CFS criteria, and were carefully evaluated and excluded for confounding variables such as medication use, and co-morbid systemic and psychiatric conditions. Hence subjects were not deliberately recruited with prevailing autonomic and cardiovascular symptoms. Indeed, the prevalence of such symptoms in the CFS cohort at study entry was comparable with that reported by other CFS studies [2,7,50,51]. Despite stringent matching procedures, which successfully controlled for numerous factors, the CFS cohort was older and more educated than the control subjects, necessitating statistical correction. The classification of illness severity was a study strength and, as expected, yielded a group of severely affected subjects manifesting a greater prevalence of CFS-related symptoms than their non-severe CFS counterparts. In addition, another strength was the design control for sedentary lifestyle. It was presumed that the CFS study participants were sedentary and that the sedentary control group would provide an appropriate comparison. However, self-reported physical activity levels were not ascertained in the CFS subjects. A related

study limitation was that the duration of a sedentary lifestyle was not known for the sedentary control subjects. Thus it remains possible that those with CFS may have been physically inactive for a longer duration and consequently the observed CFS status differences may be due to some related process. Despite these shortcomings, the lack of a difference in aerobic capacity between the CFS groups and the sedentary control group suggests that they were well-matched on this factor.

In conclusion, the present findings suggest that the observed decrement in CFS cardiac volume level may be a consequence of a co-morbid hypovolaemic condition, secondary to normochromic normocytic anaemia. Given these findings, it may be prudent in the clinical setting to perform a direct examination of blood volume status in CFS patients and consider treatment for those with abnormal levels. A blood volume deficit may impact adversely on oxygen delivery and nutrient supply, impair haemodynamic regulation, and contribute to the exacerbation of fatigue and other CFS symptomatology [52,53]. Future research should consider the patho-aetiological basis of hypovolaemia in CFS, and the extent to which this condition may impact physiological function and other aspects of clinical significance.

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