

Abnormal Impedance Cardiography Predicts Symptom Severity in Chronic Fatigue Syndrome

ARNOLD PECKERMAN, PHD; JOHN J. LAMANCA, PHD; KRISTINA A. DAHL, MD; RAHUL CHEMITIGANTI, MD; BUSHRA QUREISHI, MD; BENJAMIN H. NATELSON, MD

ABSTRACT: *Background:* Findings indicative of a problem with circulation have been reported in patients with chronic fatigue syndrome (CFS). We examined this possibility by measuring the patient's cardiac output and assessing its relation to presenting symptoms. *Methods:* Impedance cardiography and symptom data were collected from 38 patients with CFS grouped into cases with severe (n = 18) and less severe (n = 20) illness and compared with those from 27 matched, sedentary control subjects. *Results:* The patients with severe CFS had significantly lower stroke volume and cardiac output than the controls and less ill patients. Postexertional fatigue and flu-like symptoms of infection differentiated

the patients with severe CFS from those with less severe CFS (88.5% concordance) and were predictive ($R^2 = 0.46$, $P < 0.0002$) of lower cardiac output. In contrast, neuropsychiatric symptoms showed no specific association with cardiac output. *Conclusions:* These results provide a preliminary indication of reduced circulation in patients with severe CFS. Further research is needed to confirm this finding and to define its clinical implications and pathogenetic mechanisms. **KEY INDEXING TERMS:** Chronic fatigue syndrome; Cardiac output; Impedance cardiography. [*Am J Med Sci* 2003;326(2):55–60.]

Chronic fatigue syndrome (CFS) is a clinically defined illness of unknown etiology. Minimal criteria for receiving the diagnosis are unremitting disabling fatigue accompanied by several other neuropsychological, rheumatological, and influenza-like symptoms.¹ Patients frequently report an infection as a precipitating event. However, efforts to find infectious or immunological causes for this illness have not been successful.² In the meantime, accumulating evidence points to a possible problem with circulation in CFS. The reported findings included autonomic dysfunction,^{3–5} lower plasma volume and/or red cell mass,^{6–8} and abnormalities in neurohormonal systems of circulatory control.^{9,10} Although abnormalities in single systems may be insufficient to cause a circu-

latory dysfunction, cumulatively they could produce significant deficiencies in organ blood flow and symptoms. Supporting this possibility, a magnetic resonance spectroscopy study indicated that patients with CFS may have reduced blood flow in exercising muscles,¹¹ and another study using nuclear imaging found evidence of postexercise reduction in brain blood flow in CFS.¹²

Based on this evidence, we hypothesized that patients with CFS have reduced cardiac output. The present study tested this hypothesis using noninvasive impedance cardiography.¹³ Early analyses of preliminary data indicated, however, that reduction in cardiac output was characteristic of the patients most severely afflicted with CFS, rather than all patients with CFS. For this report, therefore, patients with CFS were stratified into groups with severe or less severe CFS using criteria described previously.^{15,16} Another objective for this study was to identify whether there are relationships between low cardiac output and specific CFS symptoms, which would be critical for future, more targeted studies of circulatory involvement in CFS.

Methods

Participants. Thirty-eight patients with CFS and 27 control subjects participated in the study. The subjects were recruited

From the CFS Cooperative Research Center, Department of Neurosciences, University of Medicine and Dentistry of New Jersey, Newark, New Jersey, and VA Medical Center, East Orange, New Jersey.

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Current affiliation for JLL: The Heart Failure Center, Division of Circulatory Physiology, NY Presbyterian Hospital, New York, New York.

Correspondence: Arnold Peckerman, Ph.D., VA Medical Center, War-Related Illness and Injury Study Center (WRIISC) (129), 385 Tremont Ave., East Orange, NJ 07018 (E-mail: apeckerm@njneuromed.org).

without preselection through community announcements and referrals. An initial diagnosis was established using the 1994 Centers for Disease Control and Prevention (CDC) case definition for CFS.¹ It requires 6 or more months of unexplained fatigue, substantial reduction in activities relative to premorbid levels, and 4 or more symptoms from a specified list that includes postexertional fatigue, sore throat, tender lymph nodes, impaired memory or concentration, muscle or multijoint pain, new headaches, and unrefreshing sleep. As part of their evaluation, all patients were further classified as severe or less severe cases using the criteria reported previously.^{15,16} Briefly, to meet the criteria for severe CFS, the patient had to satisfy the more stringent 1988 CDC case definition of CFS,¹⁷ which requires >50% reduction in activities and 7 or more of the symptoms listed in the case definition. In addition, at least 7 of those symptoms had to be rated as "substantial" or worse in severity in the month before intake. Patients with less severe CFS could have fulfilled the 1988 or 1994 case definition but did not meet our severity requirement. Of the 38 patients, 18 met the criteria for severe CFS, and 20 had less severe CFS. The control subjects were persons of sedentary lifestyle, defined as nonparticipation in regular (>1 time/week) exercise. Subjects with medical conditions known to affect cardiovascular regulation or taking drugs with sympathomimetic or blocking activity, including tricyclic antidepressants, were excluded from the study. None of the control subjects was taking any medication other than birth control pills. Nineteen patients with CFS (9 with severe CFS) were on medications at the time of the study. The most common medications were selective serotonin reuptake inhibitors and atypical antidepressants (7 patients) and a thyroid (synthroid) medication (4 patients). Review of medication patterns found no apparent differences between the severe and less severe CFS groups. The local institutional review board approved the study protocol, and all subjects signed the informed consent forms.

Questionnaire Assessments. Levels of fatigue on the day of the study were measured using the Activation-Deactivation Adjective Check List (AD ACL) energy scores,¹⁸ and assessment of depressive symptoms was made with the Beck Depression Inventory (BDI).¹⁹ The AD ACL energy ratings were obtained both before and after the testing, and the difference between them was used as a measure of fatigue induced by testing.

Design and Measurements. Testing was conducted in a quiet, temperature-controlled room between 11:00 AM and 1:00 PM. The subject was instructed to have breakfast but not to consume anything with caffeine for 4 hours before presenting for the study. The study protocol that provided data for this report consisted of a 10-minute period of supine rest, followed by a 5-minute period of quiet standing. Impedance cardiogram was recorded with a University of Miami impedance cardiograph (model R03)²⁰ using methods described in previous publications.^{21,22} Impedance cardiograms were computer-scored and edited without awareness of the subject group status to provide measures of stroke volume and prejection period. Heart rate was measured from the electrocardiograph. The means of 2 30-second data samples recorded during the last 2 minutes of the supine and standing periods were used in analyses. Mean arterial pressure was recorded in synchrony with impedance cardiography using a Dinamap (Model 1846 SX) blood pressure monitor.

Statistical Analysis. The effects of illness were examined in analyses of variance for repeated measures that compared the severe CFS, less severe CFS, and control groups on measurements taken in the supine and standing postures, followed, as indicated, by post hoc analyses of simple effects and interactions. Symptom patterns descriptive of the severe CFS and their relationships with cardiac output were explored, respectively, with stepwise logistic²³ and multiple regression²⁴ analyses, using $P < 0.05$ criteria for entry and removal. All data are reported as means \pm SD unless indicated otherwise. P values < 0.05 were accepted as statistically significant in all analyses.

Table 1. Descriptive Characteristics (mean \pm SD) of the Study Samples

Variable	Severe CFS (N = 18)	Less Severe CFS (N = 20)	Control (N = 27)
Gender (W/M)	16/2	12/8	19/8
Age (years)	40 \pm 8	39 \pm 10	38 \pm 8
Education (years)	17 \pm 3	16 \pm 3	15 \pm 2
Height (cm)	165 \pm 7	170 \pm 10	166 \pm 9
BMI (kg/m ²)	27 \pm 8	25 \pm 7	26 \pm 5
BDI total score	11 \pm 6*	13 \pm 8*	1 \pm 2
AD ACL energy score	5 \pm 5*	6 \pm 4*	16 \pm 6

* $P < 0.0001$ relative to control subjects.

BMI, body mass index; BDI, Beck Depression Inventory; AD ACL, Activation-Deactivation Adjective Check List.

Results

Baseline Characteristics. The control and CFS groups had similar demographic and anthropometric characteristics (Table 1). Symptoms of depression on the BDI were higher and the AD ACL energy scores were lower in the patients with CFS than in control subjects, but there were no significant differences between the severe and less severe CFS groups (Table 1). The mean severity ratings for the 10 symptoms (0–5 scale) were greater in the severe than in the less severe CFS group (3.0 \pm 0.9 versus 1.9 \pm 0.6, $P < 0.0001$). However, the reported percentage reductions in activities from premorbid levels were not significantly different (62 \pm 18 versus 57 \pm 19%, respectively, $P > 0.40$).

CFS Severity And Hemodynamic Function. Figure 1 displays mean arterial pressure, heart rate, and stroke volume in the supine and standing positions in the CFS and control groups. The patients with severe CFS had lower supine stroke volume than the control and less severe CFS groups (Figure

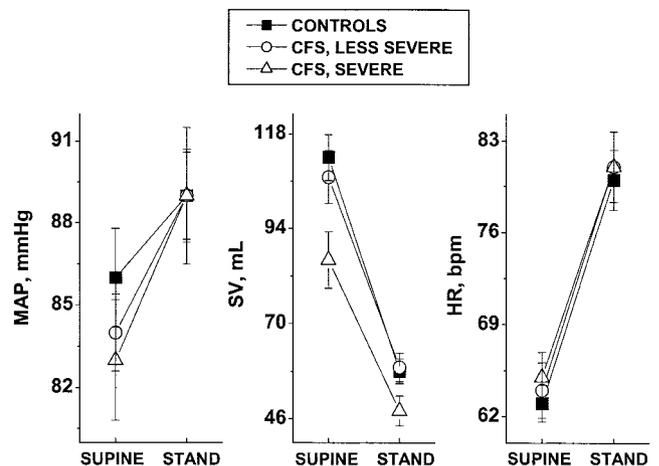


Figure 1. Mean (\pm SE) supine and standing mean arterial pressure (MAP), stroke volume (SV), and heart rate (HR) in the CFS and control groups.

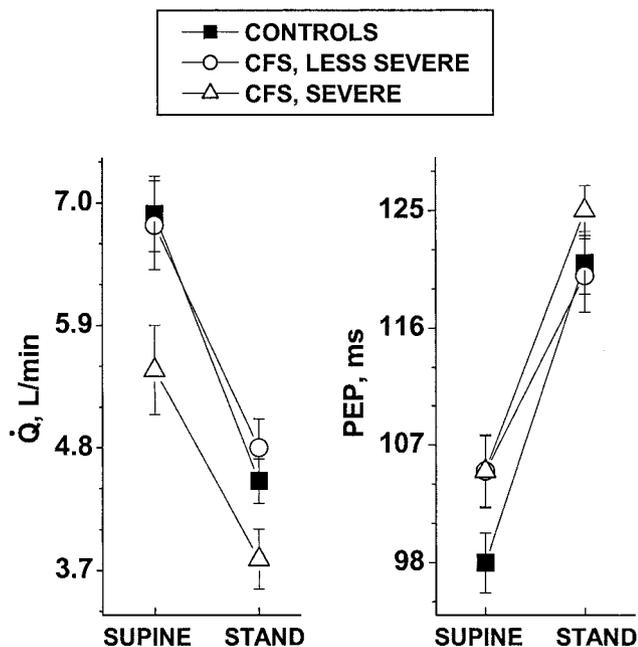


Figure 2. Mean (\pm SE) supine and standing cardiac output (\dot{Q}) and preinjection period (PEP) in the CFS and control groups.

1, $P < 0.03$). All 3 groups had a significant decline in stroke volume during standing ($P < 0.0001$). However, the decline in the severe CFS group was smaller, resulting in narrowing of differences in the standing position between the severe CFS and the control group (simple group \times posture interaction, $P < 0.02$). There were no significant group differences in mean arterial pressure and heart rate, which increased during standing in all groups ($P < 0.0001$, Figure 1). As a result, cardiac output was significantly lower in the severe CFS group, both in the supine and standing positions (Figure 2, $P < 0.03$). Essentially identical results were obtained on cardiographic data expressed as index values (the mean 2-posture cardiac index values 3.2 ± 0.9 , 3.2 ± 0.8 , and 2.6 ± 0.5 L/m², for control, less severe, and severe CFS groups, respectively). Both CFS groups had an increased pre-ejection period in the supine but not in the standing position (interaction $P < 0.05$, Figure 2). Analyses of pre-ejection period values adjusted for heart rate produced identical results and are not reported. To explore the extent to which these results may have been influenced by medications, the above analyses were repeated separately in the medicated and unmedicated subsets of patients with CFS. In the unmedicated group, the supine and standing stroke volume and cardiac output were lower in the severe ($n = 9$) than in less severe CFS ($n = 10$) patients (88 ± 29 and 47 ± 13 versus 119 ± 34 and 64 ± 21 mL, and 5.2 ± 1.2 and 3.6 ± 0.5 versus 7.3 ± 2.2 and 5.0 ± 1.6 L/min, $P < 0.04$ and 0.02 , respectively), whereas in the medi-

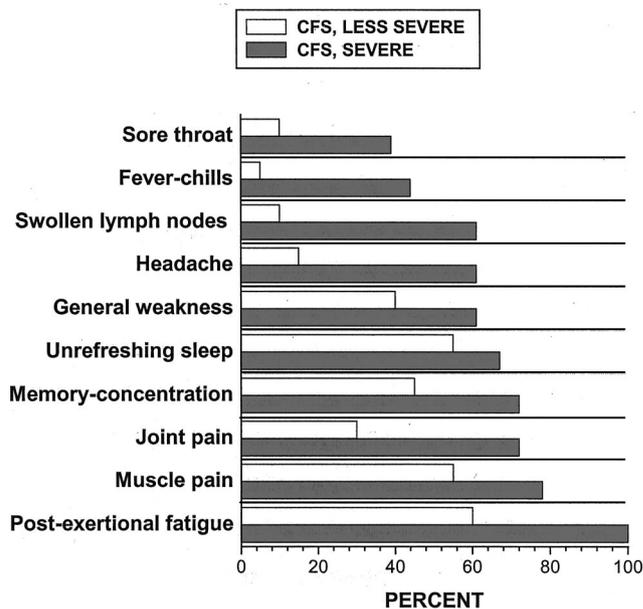


Figure 3. Percentages of patients with severity ratings ≥ 3 (0–5 scale) for the 10 symptoms listed in the 1988 case definition (see Methods). The severe CFS group had greater percentages ($P < 0.05$) for all symptoms except for muscle pain, memory-concentration, unrefreshing sleep, and general weakness.

cated group, there was only a trend (85 ± 10 and 49 ± 9 versus 94 ± 20 and 54 ± 12 mL, and 5.8 ± 0.9 and 4.1 ± 0.5 versus 6.3 ± 1.7 and 4.6 ± 1.1 L/min, $P > 0.17$ and 0.23). The medicated patients also had somewhat higher supine and standing mean arterial pressure (86 ± 9 and 91 ± 9 versus 82 ± 6 and 87 ± 9 mm Hg, $P < 0.07$) and heart rate (68 ± 8 and 85 ± 11 versus 62 ± 9 and 77 ± 11 beats/min, $P < 0.03$) than the unmedicated group.

Symptom Profile in Severe CFS. As used for the purposes of case definition, all qualifying symptoms are given equal weight (see Methods). It is possible, however, that some symptoms might be more characteristic of the severe CFS than others. To examine this possibility, additional analyses were performed to determine whether patients with severe or less severe CFS could be reliably discriminated on the basis of their symptom patterns. Figure 3 depicts symptom profiles of the 2 patient groups. The patients with severe CFS rated their symptoms of postexertional fatigue, flu-like infection (sore throat, fever-chills, and swollen lymph nodes), and headaches as substantial or worse significantly more often than the patients with less severe CFS. In fact, the mean severity ratings (0–5 scale) for sore throat and fever-chills in the less severe CFS group were not significantly different from those in the control group (0.7 ± 1.0 and 0.9 ± 1.0 versus 0.2 ± 0.4 and 0.2 ± 0.6 , respectively, $P > 0.05$). In a stepwise logistic regression, severity ratings for postexertional fatigue and sore throat

emerged as significant predictors of the group status (odds ratios, 2.3 and 3.9; 95% confidence intervals, 1.0–5.1 and 1.5–10.0; $P < 0.05$ and 0.005, respectively), providing correct identification for 88.5% of the patients.

Cardiac Output and Symptoms of CFS. The next set of analyses examined whether there might be specific relationships between the self-reported symptoms and cardiac output. In the stepwise multiple regression analysis of patients with CFS as a group, lower cardiac output (the mean of supine and standing values) was associated with greater severity ratings for postexertional fatigue and fever-chills, and lower ratings for a problem with memory and concentration (standardized regression coefficients, -0.66 , -0.38 , and 0.45 , $P < 0.0001$, 0.008 , and 0.006 , respectively). No other symptom met the $P < 0.05$ criterion for entry in the stepwise procedure. Partial regression plots illustrating those results for the 2 negative predictor variables are shown in Figure 4. The proportion of variance in the mean cardiac output values explained by the linear combination of the 3 symptoms ($R^2 = 0.46$, $P < 0.0002$) was more than twice the amount of variance in cardiac output explainable by the CFS severity status ($R^2 = 0.19$, $P < 0.007$). This comparison illustrated the degree to which low levels of cardiac output in the patients with CFS were specifically related to the symptoms characteristic of severe CFS. As a specific example of the relationship between postexertional fatigue and cardiac output, increases in tiredness after the testing, as measured by changes in the AD ACL energy scores, tended to be greater in patients with lower cardiac output ($r = 0.47$, $P < 0.006$).

Discussion

These results provide initial evidence of reduced cardiac output in severe CFS. They suggest that in some patients with CFS, blood pressure is maintained at the cost of restricted flow, possibly resulting in a low flow circulatory state.²⁵ Thus, there might be periods in daily activities when demands for blood flow are not adequately met, compromising metabolic processes in at least some vascular compartments. If confirmed, this finding would signify that some cases of CFS might be explained and potentially treated as low circulation problems.

Several deficiencies capable of affecting cardiac output have been reported in CFS, including lower blood volume,⁶ impaired venous regulation,⁷ and changes in autonomic,²⁶ endocrine,¹⁰ and cardiac function.²⁷ Also, some percentage of patients presenting with symptoms of CFS may in fact have covert heart disease.²⁸ The abnormalities causing a reduction in cardiac output in CFS thus may be dispersed over multiple systems, and changes in any 1 of them may be subtle and difficult to detect. The

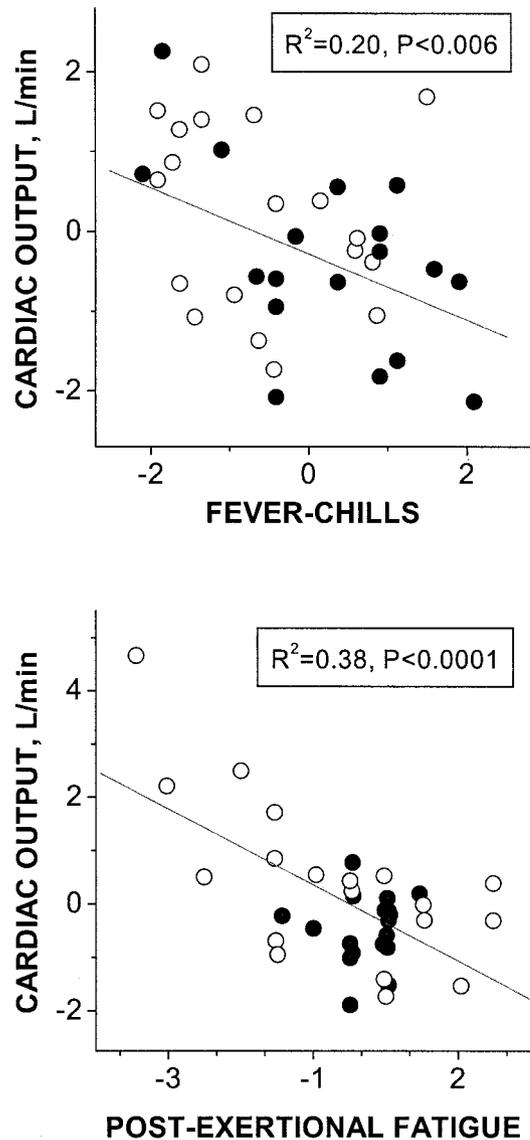


Figure 4. Partial regression plots showing the relationships between cardiac output and its predictors, residualized with respect to 2 other significant predictors in the multiple regression analysis. For illustration purposes, subjects with severe CFS are identified by filled symbols.

present data, however, do suggest certain interpretations regarding the causes of reduced cardiac output in the patients with severe CFS. Notably, the reduction in stroke volume in these patients was more clearly seen when they were in the supine position and tended to improve during standing, indicating worsened cardiac performance under conditions of augmented preload. Improvements in cardiac performance in cardiac patients in the upright position have been reported,²⁹ indicating positive effects of preload reduction on left ventricular function of the diseased heart. An increased pre-ejection period in the supine position, when sympathetic

activity is dormant, and its normalization during standing, when it is increased, may also indicate a problem with contractility or diastolic function, either of which could affect stroke volume. Although this pattern is consistent with cardiac dysfunction, a number of other circulatory, neurogenic, and endocrinologic abnormalities could explain the present findings. Cardiac output is dependent on fluid status. The subjects in this study were not fasting, so they should not have been dehydrated, although it is possible. Reduced supine cardiac output was also reported in association with low blood volume in patients with symptoms of orthostatic intolerance.³⁰ Hypovolemia is frequently associated with postural tachycardia.³¹ The patients with CFS in this study had standing heart rate increases similar to those of the control subjects. However, the lack of heart rate differences does not preclude the possibility that those patients were not moderately hypovolemic.³² Reduction in cardiac output in patients with CFS could also be the effect of deconditioning. However, this seems unlikely, because there seem to be no significant differences in physical fitness between patients with CFS and sedentary control subjects.³³ Furthermore, if deconditioning were the cause, the patients with severe CFS would be expected to report greater reduction in activities, which was not the finding of this study.

Secondary analyses relating cardiac output to specific symptoms found that postexertional fatigue and symptoms in the infectious category were the most characteristic complaints in the patients with severe CFS, and severity of those symptoms was associated with a lower cardiac output. In contrast, the prevalence of cognitive symptoms was not markedly higher in the severe CFS group, and ratings of cognitive impairment were not predictive of reduced cardiac output. This suggested that problems outside of circulation produce cognitive deficits in CFS. One limitation of the present results is that they were based on self-reported symptoms and would need to be replicated using objective behavioral and physiological measurements.

Although the reduction in cardiac output in CFS is not likely to fall within the range that would be considered abnormal, this should not detract from its physiological significance. Even marginal reduction in cardiac output can result in selective underperfusion during activities that increase demand for blood flow. More targeted studies will be needed to clarify the mechanisms of associations between reduced cardiac output and postexertional and infectious symptoms in CFS, as well as the role reduced circulation might play in symptom exacerbation under other conditions that strain the capacity for autoregulation, such as quiet standing or excessive heat. Inquiries should also be directed at conditions that may not be overtly expressed in symptoms of CFS, such as the possibility of underperfusion in the

kidneys and the gut, as the organs in which the initial conservation of cardiac output takes place.

The present results need to be considered in light of limitations of impedance cardiography. With this method, stroke volume is computed using an empirically derived formula based on changes in transthoracic bioelectrical impedance that occur as a function of pulsatile blood flow.¹³ However, understanding of determinants of transthoracic impedance remains incomplete, and it is known to be affected by many factors, including body habitus, adiposity, and cardiac status.³⁴ Although suitable for monitoring of an individual patient,³⁵ the between-group comparisons assume identity in relevant physical characteristics that may not always be warranted. Given the levels of uncertainty still existing in impedance cardiography, the study findings would need to be confirmed using other cardiography methods. Another limitation of this study is that many of our patients were on medications, including selective serotonin reuptake inhibitors, which may have influenced our results.³⁶ Analyses comparing the medicated and unmedicated patients were consistent with this possibility, but they also indicated that our findings of lower cardiac output were not the effect of medications.

In summary, this study provides a preliminary indication of reduced cardiac output in some patients with CFS and suggests means for their identification using a set of clinical criteria. This finding opens a promising new avenue in research in CFS as an illness with the potential for circulatory insufficiency.

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