Cardiovascular Reactivity in Fibromyalgia: Evidence for Pathogenic Heterogeneity

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ABSTRACT. Objective. To evaluate disease-specific cardiovascular reactivity patterns in patients with fibromyalgia (FM) using a recently described method called fractal and recurrence analysis score (FRAS).

Methods. The study group included 30 women with FM, average age 46.7 years (SD 7.03). An age matched group of 30 women with other rheumatic disorders or having a dysautonomic background [chronic fatigue syndrome (CFS), non-CFS fatigue, neurally mediated syncope, and psoriatic arthritis (PsA)] served as controls. Subjects were evaluated with a head-up tilt test with beat-to-beat recording of the heart rate (HR) and pulse transit time. A 10-minute supine phase was followed by 600 cardiac cycles recorded on tilt. Data were processed by recurrence plot and fractal analysis. Variables acting as independent predictors of the cardiovascular reactivity were identified in FM patients versus controls.

Results. No statistically significant differences were found between the groups by univariate analysis comparing 92 variables of cardiovascular reactivity in FM patients compared to controls.

Conclusion. Study of cardiovascular reactivity utilizing a head-up tilt test and processing the data using the FRAS method did not reveal a specific FM-associated abnormality. Our data confirm studies that utilized other methodologies and reached similar conclusions. Patients with FM represent a heterogeneous group with respect to their pattern of cardiovascular reactivity. (J Rheumatol 2005; 32:335–9)

Key Indexing Terms: FIBROMYALGIA DYSAUTONOMIA CARDIOVASCULAR REACTIVITY FRAC TAL ANALYSIS

Fibromyalgia (FM) is a clinical syndrome characterized by widespread pain and abnormal sensitivity on palpation of specific tender points.\(^1,2\) In addition, patients with FM frequently experience fatigue, sleep disorder, headache, anxiety, and a spectrum of chronic dysfunctional illnesses. The pathogenesis of FM has been elusive, made difficult by the absence of distinctive biochemical or histological abnormalities. The very concept of FM has been challenged with suggestions that it represents an inappropriate extraction from the epidemiological continuum of subjective discomfort. Skeptics express concern about the subjective nature of chronic pain, the lack of a gold standard laboratory test, and absence of a clear pathogenic mechanism by which to define FM clearly.\(^3,4\) If a characteristic feature could be identified that demarcates this group from the rest of the population, it would provide significant support for FM as a distinct entity.\(^5\) Such evidence may be obtained from the study of the autonomic nervous system, which has been widely reported to be aberrant in FM.\(^6-11\)

In the clinical setting, autonomic nervous system activity is assessed by surrogate methods, chiefly cardiovascular reactivity (CVR). The fast response of blood pressure (BP) and heart rate (HR) to acute stimuli is under autonomic nervous control. Therefore, BP and HR measurements during orthostatic challenge on head-up tilt testing (HUTT) can be used as one measure of cardiovascular autonomic activity, providing there is no evidence of organic heart disease, venous insufficiency, or hypovolemia.\(^12\) Classical pathological reactions to HUTT include vasodepressor reaction, cardioinhibitory reaction, orthostatic hypotension, and postural tachycardia syndrome. In studies utilizing these outcome measures, evidence for abnormal CVR was found in up to 60% of patients with FM.\(^13\) However, these aberrations of CVR are considered nonspecific since the same reactions occur in a large variety of conditions associated with autonomic dysfunction.\(^14\)

Methods used for assessment of CVR are flawed by the nonlinear dynamics of cardiovascular responses to stimuli.
A proposed approach for addressing this difficulty has been suggested by the simultaneous quantification of BP and HR fluctuations, with application of non-Euclidian mathematical analysis. Recently, we developed a method to assess CVR applying the above principles: correlations between BP and HR fluctuations were assessed utilizing both common statistical and fractal analysis. The data were evaluated via multivariate analysis to identify independent variables with ability to act as predictors in the definition of CVR in the FM group versus comparison groups. Based on these predictors, an equation was formulated to calculate a linear discriminant score for the patient group. This variable was called the fractal and recurrence analysis-based score (FRAS). By applying this methodology, a specific disease-related CVR pattern has been described in patients with chronic fatigue syndrome (CFS), familial Mediterranean fever (FMF), and neurally mediated syncope. We applied the FRAS technique to search for a disease-specific distinct CVR pattern in patients with FM.

MATERIALS AND METHODS

Patients and controls. Participants gave informed consent and our institution’s committee for human research approved the study. The study sample consisted of patients referred to the Syncope Clinic of Bnai-Zion Medical Center between January 2001 and September 2003. Patients and controls were primarily referred for evaluation by HUTT for one of the following indications: volunteering for this study, evaluation of unexplained syncope, or appraisal of occult dysautonomia. All patients and controls were fully ambulatory and took no medications for at least one week before the study. Patients with any significant somatic, neurological, or psychiatric comorbidities as well as women receiving oral contraceptives or hormone replacement therapy were excluded from the study. Specifically, those with evidence of organic heart disease, venous insufficiency, or hypovolemia were not included. The study group included 30 women with FM. An age matched group of 30 women with other rheumatic disorders or having a dysautonomic background served as controls.

Statistical design. A sample size of about 25 subjects in each group was calculated to have a power of at least 75% to detect a difference of 0.75 SD between the mean of the 2 groups, at 5% one-tailed level of significance. This effect size was based on studies that showed significance between groups in some of the variables.

Patient assessment. For assessment of fatigue related symptoms, the Chalder fatigue severity scale was utilized. This is a self-report instrument in which subjects are asked to rate the extent to which fatigue has caused problems for them in relation to example statements. The questionnaire comprises 11 items, each quantified on a scale of 0 to 3. Thus, the maximum Chalder score is 33. In our institution, healthy subjects had fatigue scores in the range 0 to 6 (data not presented). The simple Chalder scale provided data comparable to more complex and time consuming fatigue impact questionnaires and is an acceptable substitute.

The FM group (n = 30) included consecutive female patients referred from a rheumatology clinic. Their average age was 46.7 (SD 7.03) years. Patients with FM met the criteria of the American College of Rheumatology (ACR) for FM. The mean number of tender points was 14.7/18. All patients had normal sedimentation rate, creatine kinase, and thyroid stimulating hormone levels and there was no evidence of any comitant inflammatory rheumatic disorder. Patients who met the formal criteria of the Centers for Disease Control and Prevention (CDC) for definition of CFS were excluded from the FM group; non-CDC defined fatigue patients were included.

The comparison group (n = 30) was a heterogeneous population, including subjects with either a rheumatic disorder or having a dysautonomic background, matched for age and sex with FM patients. This group included patients with CFS, non-CFS fatigue, neurally mediated syncope, and PsA. Their average age was 46.9 (SD 10.2) years.

Patients with CFS (n = 7) met the CDC criteria with clinically evaluated, medically unexplained fatigue of at least 6 months’ duration of new onset, not a result of ongoing exertion, not substantially alleviated by rest, and causing a substantial reduction in previous levels of activity. In addition they satisfied the requirement of 4 or more of the following symptoms: subjective memory impairment, tender lymph nodes, muscle pain, joint pain, headache, unrefreshing sleep, and postexertional malaise (more than 24 h). Exclusion criteria comprised active, unresolved or suspected disease, melancholic or bipolar depression, psychotic disorders, dementia, anorexia or bulimia nervosa, FM, alcohol or other substance misuse, and severe obesity.

Patients with non-CFS chronic fatigue (n = 7) were consecutive subjects referred from a CFS clinic. Similar to the CFS patients, they complained of new onset fatigue not the result of ongoing exertion, not substantially alleviated by rest, associated with substantial reduction in previous levels of activity, and lasting 3 months or more, but they did not otherwise meet the definition criteria of CFS. FM patients were excluded from this group.

Patients with neurally mediated syncope (n = 7) were consecutive subjects referred for HUTT for evaluation of syncope of unknown cause. The diagnosis of neurally mediated syncope was eventually established. All subjects had 2 or more syncopal or presyncopal episodes during the previous 3 months. Patients with PsA (n = 9) fulfilled criteria for PsA, but did not meet ACR criteria for FM.

Average Chalder scores were 17.21 (SD 6.9) for FM, 18.2 (SD 6.1) for CFS, 17.7 (SD 7.5) for non-CFS fatigue, 5.3 (SD 2.4) for neurally mediated syncope, and 6.8 (SD 2.8) for patients with PsA.

All patients completed the full duration of the short tilt test. Technicians carrying out the HUTT did not know of the intention to compare groups.

Measurement of CVR. The protocol of the tilt test and pulse transit time recordings has been described. Testing was conducted from 8:00 to 11:00 AM in a quiet environment at a constant room temperature of 22–25°C. Subjects maintained a regular meal schedule but were prohibited from smoking and caffeine ingestion for 6 h before examination. The subjects lay in a supine position on the tilt table, secured to the table at the chest, hips, and knees with adhesive girdles. The cuff of the BP recording device was attached to the left arm, which was supported at heart level at all times during the study. The right forearm and hand were supported by a cast suspended with a sling around the patient’s neck. The fingers pointed to the mid-axillary line at the level of the fourth intercostal space. The photoelectric sensor of the photoplethysmograph (PPG) was placed on the distal phalanx of the second or third finger. The hand was held in a relaxed semi-open position, with the palm turned downward and fixed with adhesive strips, taking care not to apply pressure to the PPG transducer. The electrocardiogram (ECG) and PPG were recorded on a Datex-Engstrom Cardiocap™ II instrument (Datex Instrumentation Corp., Helsinki, Finland), connected to the Biopac MP 100 data acquisition system (Biopac, Santa Barbara, CA, USA). The pulse transit time was automatically computed on the AcqKnowledge software (Biopac), and tracings were continuously displayed on the computer screen. The computer program identified the pulse transit time as the time interval between the peak of the electrocardiographic R wave and the peak of the pressure wave at the finger, as measured by the pulse plethysmograph. A sample rate of 500 data points per second provided 1/500 Hz resolution for the HR and pulse transit time measurements. Measurements were taken in the supine position over a 10-min period. The table was then gently tilted head-up to an angle of 70° and measurements continued for a total of 600 cardiac cycles (usually 5 to 10 min). The RR intervals on ECG recordings and the corresponding pulse transit values were automatically computed with the AcqKnowledge software. Four sets of values were obtained, each comprising approximately
600 measurements: HR supine, pulse transit time supine, HR tilt, and pulse transit time tilt.

Data editing. Measurements were reviewed and edited to screen out artifacts. For this purpose, the computer program marked HR values < 45 bpm or > 110 bpm and pulse transit time values < 0.2 s or > 0.4 s. For each of these aberrant measurements the investigator, blinded to the patient, decided whether or not the value was likely, in the context of 30–40 contiguous measurements. Pulse transit measurements < 0.2 s were considered to be artifacts, based on our experience that such values occur only upon movement of the transducer. Pulse transit values > 0.4 s were labeled artifacts when occurring alone or as couples, but were considered authentic and were accepted when occurring in clusters of 5 or more spikes. Suspect HR values were deleted together with the concomitant pulse transit times, and suspect pulse transit values were deleted together with the concomitant HR measurements. After editing, data were advanced to mathematical analysis.

Mathematical data processing. HR and pulse transit time measurements in the supine and tilt phases were processed separately by 3 mathematical methods: general statistics, fractal analysis, and recurrence plot analysis as described. The average, standard deviation, minimum, maximum, variance, skewness, and kurtosis were calculated. For fractal analysis, time series of 500–600 consecutive edited measurements, either HR or pulse transit times, were loaded into the Benoit Version 1.3 analyzer (Trusoft International, St. Petersburg, FL, USA). Time curves were constructed. The fractal dimension of the time curve (FD) was calculated with the aid of 4 different methods: R/S, roughness-length, variogram, and wavelets analysis. Recurrence quantitative analysis (RQA) was performed with the visual recurrence analysis computer program (version 4.2; developed by E. Kononov, 1999). The RQA variables computed were the recurrence, determinism, ratio, entropy, maxline, trend, and spatio-temporal entropy. Thus, 4 data sets were obtained from each patient including HR and pulse transit times in supine and tilt positions, together comprising the CVR variables (23 × 4 = 92 variables).

Computing the discriminant score. Multivariate analysis was conducted to find those variables that might function as independent predictors for the assessment of cardiovascular activity at rest and CVR on postural challenge in the FM group as distinct from the comparison group. Based on the regression coefficients (slopes and intercepts) of these predictors, an equation was derived to calculate the linear discriminant score.

Statistical analysis. The variables were tested for normality using the Kolmogorov-Smirnov test. For normally distributed variables, comparison between FM and control patients was performed using Student’s t test for independent groups. Nonparametric variables were compared using the Mann-Whitney U test. Two-tailed p values of 0.05 or less were considered statistically significant.

RESULTS
Univariate analysis, comparing 92 variables in the FM compared to the non-FM group, revealed no significant difference in any variable. This is illustrated in Figure 1, comparing average supine HR values as well as average tilt HR values in FM and control subjects. Figure 2 shows fractal dimensions of the HR during the supine and tilt phases of the HUTT in FM and control subjects. Similar values of the fractal dimensions were found in patients and controls.

DISCUSSION
Cardiovascular reactivity in FM was studied utilizing a head-up tilt test and processing data with the FRAS method. Study of the CVR did not identify a specific FM-associated abnormality.

The capability to tailor autonomic testing to a specific clinical entity emerged in studies of patients with CFS. Initially, CVR in CFS was assessed utilizing the usual outcome measures: vasodepressor reaction, cardioinhibitory reaction, orthostatic hypotension, and postural tachycardia syndrome. By these measures, evidence for abnormal CVR was found in one-half of patients with CFS. However, increased lability of BP and HR was noted in all subjects on head-up tilt, but no appropriate measure to express these findings was available. A study was undertaken to define objective and precise parameters of hemodynamic instability on postural challenge. A new method was proposed...
involving computation of BP and HR changes during HUTT, followed by processing of the data by fractal analysis methods. The degree of BP and HR instability was then used for comparison between CFS and control groups. This method confers numerical expression to the degree of BP and HR unsteadiness, i.e., the hemodynamic instability score. Subsequent studies confirmed that there is a particular CVR pattern in CFS that differs from dysautonomia in other disorders. To support this observation, a second technique for assessment of CVR was proposed, FRAS. Beat-to-beat HR and pulse transit time were measured. A 10-min supine phase of the HUTT was followed by recording 600 cardiac cycles on tilt, i.e., 5 to 10 min. The short tilt period was well tolerated and the existence of a specific CVR in patients with the CFS was confirmed. In addition to CFS, we applied the FRAS method to assess CVR in patients with neurally mediated syncope and patients with FMF.

In studies of CVR, the following principles have emerged in assessment of disease-specific patterns of reactivity. First, beat-to-beat analysis of HR and pulse transit times have provided better results than HR and BP measurements at 5-min interval for assessment of CVR. Second, selection of a clinically homogenous test group and a large, heterogenous comparison group is essential for identifying a disease-related CVR pattern. By including a variety of clinical disorders, the controls represent a large range of CVR patterns. In addition, the analytic power of the proposed method is challenged by including disorders that resemble each other clinically (in this study by comparing CVR in FM with CVR in CFS, non-CFS fatigue, and neurally mediated syncope) as well as unrelated neural disorders (FMF in this study). Third, in the definition of disease-specific CVR patterns, a 90% specificity for the discriminant score was required, and a sensitivity greater than 50%. Disease-specific CVR patterns have been identified in CFS, neurally mediated syncope, and FMF. In each, high sensitivity and specificity of the CVR pattern was observed separating each from the CVR pattern of the others. In this study of CVR we did not observe a specific FM-associated abnormality. The observed differences between the groups were very small in most variables, therefore insufficient power is not the reason for lack of significance.

The mechanisms putatively involved in disease-related CVR patterns may be speculated upon. The conventional understanding that CVR is merely the result of arterial baroreflexes is simplistic and no longer tenable. Indeed, numerous factors modulate the response to baroreflex activation apart from strength of the activating stimulus. These include the set-point of the reflex, neuronal input from the hypothalamus, cortical centers and brainstem centers, the responsiveness of cardiovascular receptors and structures, interactions of aortocarotid with chemoreflex arcs, and modulatory influences of neurohumoral and vasoactive substances. Serotonin, adenosine, and opioids are additional triggers of the Betzold-Jarisch reflex; peripheral sympathetic afferents are directly activated by circulating mediators; and higher nervous centers modulate the cardiovascular reflexes. Disease-specific CVR patterns may be explained by the existence of unique permutations in the cardiovascular, neuroendocrine, and paracrine changes present in certain disorders.

In applying FRAS to the study of CVR patterns in healthy subjects, no specific CVR pattern was observed. We speculate that CVR in healthy individuals is heterogeneous, not modulated by a specific pathologic mechanism into uniformity. This study conducted in patients with FM did not uncover a specific CVR pattern. Our data are in agreement with results of prior studies in our laboratory concerning CVR in patients with FM and our findings appear to be consistent with the concept that FM is a common symptomatic framework, rather than a separate disease entity, and therefore patients’ CVR patterns are accordingly heterogenous.

The pathogenesis of FM remains elusive. Support for FM as a distinct entity was suggested from studies of HR variability and norepinephrine-evoked pain in FM. Yet the specificity of the latter 2 tests has yet to be elucidated. Our study based on FRAS does not support the definition of FM in terms of autonomic nervous activity.

REFERENCES


