Patterns of cardiovascular reactivity in disease diagnosis

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Summary

Background: Aberrations of cardiovascular reactivity (CVR), an expression of autonomic function, occur in a number of clinical conditions, but lack specificity for a particular disorder. Recently, a CVR pattern particular to chronic fatigue syndrome was observed.

Aim: To assess whether specific CVR patterns can be described for other clinical conditions.

Methods: Six groups of patients, matched for age and gender, were evaluated with a shortened head-up tilt test: patients with chronic fatigue syndrome (CFS) (n = 20), non-CFS fatigue (F) (n = 15), neurally-mediated syncope (SY) (n = 21), familial Mediterranean fever (FMF) (n = 17), psoriatic arthritis (PSOR) (n = 19) and healthy subjects (H) (n = 20). A 10-min supine phase was followed by recording 600 cardiac cycles on tilt (5–10 min). Beat-to-beat heart rate (HR) and pulse transit time (PTT) were measured. Results were analysed using conventional statistics, recurrence plot analysis and fractal analysis.

Results: Multivariate analysis evaluated independent predictors of the CVR in each patient group vs. all other groups. Based on these predictors, equations were determined for a linear discriminant score (DS) for each group. The best sensitivities and specificities of the DS, consistent with disease-related phenotypes of CVR, were noted in the following groups: CFS, 90.0% and 60%; SY, 93.3% and 62.5%; FMF, 90.1% and 75.4%, respectively.

Discussion: Pathological disturbances may alter cardiovascular reactivity. Our data support the existence of disease-related CVR phenotypes, with implications for pathogenesis and differential diagnosis.

Introduction

Numerous control mechanisms regulate and integrate the functions of the cardiovascular system in order to supply blood to specific body areas according to need.1,2 When homeostasis is challenged, a reproducible cardiovascular reactivity (CVR) pattern is elicited, i.e. a change in blood pressure, heart rate or other haemodynamic parameters.3

The BP and HR responses to postural challenge can be used as one index of cardiovascular autonomic activity, if there is no evidence of organic heart disease, venous insufficiency or hypovolaemia.4 For this purpose, the head-up tilt test is used. During head-up tilt, there is a large gravitational shift of blood away from the chest to the capacitance system below the diaphragm, resulting in a rapid decrease in stroke volume. Compensatory vasoconstriction of the resistance and the capacitance vessels is the key factor in the maintenance of arterial BP in upright posture. The haemodynamic response to head-up tilt is characterized by a slight decrease in systolic BP by 6.5 mmHg (range −19 to +11), increase in diastolic BP by 5.6 mmHg.
charts was done by outside investigators who at least 2 weeks prior to the study. Analysis of ambulatory and had taken no medications for arthritis, and healthy subjects. The subjects' ages ranged from 20 to 40 years. All were fully analyzed for cardiovascular reactivity (CVR) pattern in patients with chronic fatigue syndrome. Classical outcome measures of the head-up tilt test are vasodepressor reaction, cardioinhibitory reaction, orthostatic hypotension and the postural tachycardia syndrome. None of these reaction patterns has been strictly associated with one particular nosological entity, i.e. because of lack of sensitivity and specificity, their presence is not predictive of a specific clinical diagnosis. Fluctuations in HR (heart rate variability) also reflect autonomic nervous system function but results of their measurement, too, are not specific for a particular clinical entity. The claimed specificity of low-frequency powers as markers of sympathetic tone and of high-frequency powers as markers of vagal tone is highly debated.

The origin of the present study lies a few years back, in the unexpected finding of a specific cardiovascular reactivity (CVR) pattern in patients with chronic fatigue syndrome. This observation was validated in four studies using different methodologies. The present work was designed to investigate whether disease-specific CVR patterns are associated with disorders other than chronic fatigue syndrome. Numerous factors modulate the response to baroreflex activation, including neurohumoral influences and vasoactive substances, which may, in varying combinations, shape the configuration of CVR. We supposed that disorders with a dysautonomic background, such as neurally mediated syncope, might display discrete CVR patterns. Previous studies in rheumatic disorders suggested that dysautonomia is present in these disorders. Because of our interest in these rheumatic disorders, we evaluated the possibility that a specific CVR pattern might be operative in patients with familial Mediterranean fever, or with psoriatic arthritis.

Methods

The committee for human investigation at our hospital approved the study. Patients were primarily referred for evaluation by head-up tilt test for one of the following indications: assessment of CFS, evaluation of unexplained syncope, and appraisal of occult dysautonomia in rheumatic disorders. Six groups of subjects were matched for age and gender: CFS, non-CFS fatigue, neurally mediated syncope, familial Mediterranean fever, psoriatic arthritis, and healthy subjects. The subjects' ages ranged from 20 to 40 years. All were fully ambulatory and had taken no medications for at least 2 weeks prior to the study. Analysis of charts was done by outside investigators who were unaware of the study design. Some of these patients had been included in previous studies of autonomic dysfunction. In this study, the stored data from tilt tests was reanalysed using different dependent measures and statistical methodology.

Patient groups

CFS patients (CFS): 20 consecutive patients referred from a CFS clinic for evaluation by head-up tilt test. All met the Centers of Disease Control and Prevention definition criteria of CFS, i.e. clinically evaluated, medically unexplained fatigue of at least 6 months duration, that is of new onset, not a result of ongoing exertion, not substantially alleviated by rest, and substantially reduces previous levels of activity. The diagnosis of CFS was based on patient history and exclusion of other diagnosable medical or psychiatric illness. The subjects' mean age was 30.8 (SD 16.1) years, and 65% were women. The median duration of illness was 17.1 months (range 7 months to 4 years).

Patients with non-CFS chronic fatigue (F): 15 subjects referred from a CFS clinic. Similarly to the CFS patients, they complained of fatigue of new onset, not a 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. Their mean age was 31.9 (SD 9.7) years and 66.6% were women. The median duration of illness was 7 months (range 3–13 months).

Patients with neurally-mediated syncope (SY): 21 subjects referred for head-up tilt test to evaluate syncope of unknown cause. All had two or more syncopal or presyncopal spells during the previous 3 months. Their mean age was 29.3 (SD 18.2) years and 66.6% were women. The study patients met the recommended criteria of the European Society of Cardiology for neurally-mediated syncope. To be included in this study, a positive response to tilt table testing was required.

Patients with familial Mediterranean fever (FMF): 17 subjects who fulfilled the criteria for the diagnosis of FMF, and whose last attack of FMF remitted at least 7 days prior to the head-up tilt test. Their mean age was 34.1 years (SD 12.3) and 64.7% were women.

Patients with psoriatic arthritis (PSOR): 19 subjects fulfilling the diagnostic criteria for psoriatic arthritis. Their mean age was 31 years (SD 5.8) and 63.2% were women.

Healthy subjects (H): 20 physicians and paramedics working on the medical ward, who...
volunteered to participate in the study. Subjects were eligible if they did not report persistent fatigue or syncope during the preceding 12 months, and had normal findings on physical examination, routine laboratory tests, chest X-rays, and electrocardiogram. Their mean age was 28.5 years (SD 7.9) and 60% were women.

We excluded patients with somatic, neurological or psychiatric co-morbidities, women receiving oral contraceptives or hormone replacement therapy, and subjects presenting an ectopic atrial rhythm during the head-up tilt test. By excluding from the study patients with evidence of organic heart disease, venous insufficiency or hypovolaemia, the CVR could be used as an index of autonomic nervous activity. Each experimental group of patients was compared with the combined pool of all other patients. Thus, the analysis was tailored to recognize the reactivity of each particular disorder from a spectrum of different CVRs and not merely from the reactivity of healthy persons.

Protocol
The protocol of the tilt test and pulse transit time (PTT) recordings has been described in detail elsewhere. Testing was conducted from 0800 to 1100 h, in a quiet environment, and at a constant room temperature of 22–25°C. The patients maintained a regular meal schedule, but were restricted from smoking and caffeine ingestion 6 h prior to the examination. Intake of food products and medications with sympathomimetic activity prior to the study was prohibited. The patient 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 (Baumanometer standby model 0661–0250 mercury column sphygmomanometer) 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, and 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 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 photoplethysmograph transducer. The electrocardiogram and photoplethysmogram were recorded on a Datex-Engstrom Cardiocap II instrument (Datex Instrumentation Corporation), connected to the Biopac MP 100 data acquisition system (Biopac). The PTT was automatically computed using AcqKnowledge software, and the tracings were continuously displayed on the computer screen. The computer program identified the PTT 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 PTT 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 measurement continued for a total of 600 cardiac cycles (usually 5–10 min).

Measurements were reviewed and edited to eliminate ectopic ventricular beats and lasting arrhythmia, as well as artifacts. For testing purposes, the computer program marked HR values < 45 bpm or in > 110 bpm and PTT values < 0.2 s or > 0.4 s. Extreme values in heart rate within the context of 30–40 contiguous measurements, when reviewed by experienced clinicians blinded to the patient source of data, were considered not plausible. PTT measurements < 0.2 s were considered to be artifacts, based on our experience that such values occur only upon movement of the transducer. PTT values > 0.4 s were considered artifactual when occurring alone or as couples, but authentic in clusters of five or more spikes. Suspect HR values were deleted together with the concomitant PTT measurements, and suspect PTT values were deleted together with the concomitant HR measurements. After editing, the data was advanced to mathematical analysis.

Analysis
HR and PTT measurements in the supine and tilt phases were processed separately by three mathematical methods, general statistics, recurrence plot analysis and fractal analysis, thus combining the power of Euclidian and non-Euclidian mathematics.

General statistics
The mean, standard deviation, minimum, maximum, variance, skew, and kurtosis were calculated. Correlations between variables were calculated, thus identifying related parameters: the correlation coefficients between systolic and diastolic BP, between systolic BP and HR, and between diastolic BP and HR; average of standard deviations between pairs of successive systolic BP measurements; average of standard deviations between pairs of successive diastolic BP measurements; and average of standard deviations between pairs of successive HR measurements.
**Fractal analysis**

For fractal analysis, time series of 500–600 consecutive edited measurements, either HR or PTT, were loaded into the Benoit Version 1.3 analyser (Trusoft International). Time curves were constructed. The fractal dimension of the time curve (FD) was calculated with the aid of four different methods: R/S, roughness-length, variogram, and wavelets analysis. Typical tracings are shown in Figure 1. When observing the fractal scaling line, a fractal window is noticed along the middle and right section of the axis. Within this window, the linear fit is unmistakable, having most points close to the axis. Along the fractal scaling line, the fractal behaviour (on the right) and the non-fractal behaviour (on the left) alternate, as often seen in biological systems.

**Recurrence quantitative analysis**

In our study, we used the Visual Recurrence Analysis computer program, version 4.2, developed by Eugene Kononov in 1999. Technically, this method expands a one-dimensional time series into a higher dimensional space. This is done by using a ‘delayed coordinate embedding’, which creates a phase space portrait (recurrence plot) of the system. To start recurrence quantitative analysis calculations, 500–600 consecutive edited HR or PTT measurements were loaded into the computer program. The embedding dimension, time delay and false nearest neighbour were determined. On this basis, the recurrence quantitative analysis variables were computed: recurrence, determinism, ratio, entropy, maxline, trend, and spatio-temporal entropy. Recurrence quantifies the percentage of the plot occupied by recurrent points. Determinism is the percentage of recurrent points that appear in sequence, forming diagonal line structures in the distance matrix. Entropy measures the richness of deterministic structuring of the series. Trend is the regression coefficient of the relationship between time and amount of recurrence. Typical tracings are shown in Figure 2.

To summarize, four data sets were obtained in each patient, both HR and PTT in supine and tilt positions, together comprising the variables of CVR.

**Computing the discriminant score (DS)**

The overall goal of discriminant analysis is to predict group membership from a set of predictor variables. Specifically, it aims to investigate differences between groups, determine the most efficient way to distinguish between groups, and to determine variables which do not contribute to group distinctions. Multivariate analysis was conducted on all variables of CVR, thereby evaluating independent variables for the assessment of the CVR in each patient group versus all other groups. Based on the regression coefficients (slopes and intercepts) of these predictors, a linear discriminant score (DS) was computed for each subject. The best cut-off was established between the DS of a specific disorder versus the DS in all other groups. Thus, equations were derived to calculate the DS in each group.

**Identifying disease-related CVR phenotypes**

There are no established criteria for defining disease-related phenotypes of CVR. For the purpose of this study, we required that three conditions be present to define a CVR phenotype: (i) an equation expressing the CVR of the study group from control populations; (ii) a heterogenous comparison control population, at least three times the size of the study group, and including patients with a clinical resemblance or a common pathophysiological background with the study group, as well as healthy subjects, (iii) a DS cut-off for the CVR at least 90% specific and 50% sensitive. By these standards, in a study group of 20 subjects and a control group of 100 subjects, there will be at least 10 true positive and no more than 10 false positive cases. Better results are expected if the sensitivity and specificity of the DS exceed the minimal acceptable values.

In each group of patients, an equation was computed to find the DS, which expresses the CVR in that particular group. Cut-off values of each DS were set at >90% specificity and >50% sensitivity. For each patient group, when a CVR pattern met the above conditions, especially DS limits, a ‘phenotype’ was defined.

**Results**

I. Assessment of discriminant scores which express the CVR in each patient group

**CFS vs. controls**

Multivariate analysis identified the best predictors for the assessment of CFS vs. the combined pool of control to be: (A) tilt-HR-determinism by recurrence quantitative analysis ($p=0.0005$), (B) supine-HR-roughness-length by fractal analysis ($p<0.0001$), (C) supine-HR-R/S by fractal analysis ($p<0.0001$) and (D) tilt-PTT-wavelets by recurrence quantitative analysis ($p=0.0002$). Based on the regression coefficients (slopes and intercepts) of these
Figure 1. Steps in processing the recurrence plot. A Time series of the heart rate recorded in a patient with chronic fatigue syndrome during the supine phase of the head-up tilt test (heart rate values are shown on the y-axis and time on the x-axis). B Visual recurrence plot. C Deterministic points (on the y-axis vs. epoch numbers on the x-axis). D Recurrence points (on the y-axis vs. epoch numbers on the x-axis).
predictors, a linear DS was computed and called DS-CFS.

\[
\text{DS-CFS} = -10.52 + (A \times 0.11) + (B \times 18.49) + (C \times -14.08) + (D \times 0.006262)
\]

The DS-CFS cut-off > 0.05 differentiated CFS from all other patients with 90.0% specificity and 60% sensitivity. Hence, a phenotypic CVR was recognized in the majority of the CFS patients.

**Non-CFS fatigue vs. controls**

The best predictors for distinguishing patients belonging to group F (non-CFS fatigue) from all other patients were: (E) tilt-HR-entropy-average by recurrence quantitative analysis \((p=0.002)\), (F) supine-PTT-minimal value by general statistics \((p=0.01)\), (G) tilt-HR-R/S by fractal analysis \((p=0.0001)\) and (H) tilt-HR-recurrence-average by recurrence quantitative analysis \((p=0.0001)\).

\[
\text{DS-F} = 7.92 + (E \times -4.71) + (F \times 13.12) + (G \times -6.83) + (H \times 0.78)
\]

The DS-F cut-off > 0.27 differentiated patients with non-CFS fatigue from all other patients with 93.3% specificity and 40% sensitivity. These data are not consistent with the proposed criteria of a discrete CVR phenotype.

**Neurally-mediated syncope vs. controls**

The best predictors for the assessment of patients belonging to this group vs. all other patients were: (I) supine-HR-kurtosis by general statistics \((p<0.0001)\), (J) supine-HR-variance by general statistics \((p=0.0001)\), (K) supine-PTT-standard deviation by general statistics \((p<0.0001)\), (L) tilt-PTT-ratio by recurrence quantitative analysis \((p<0.0001)\) and (M) tilt-PTT-standard deviation by general statistics \((p<0.0001)\).

\[
\text{DS-SY} = -13.37 + (I \times 0.00010) + (J \times 0.074) + (K \times 61.91) + (L \times 8.13) + (M \times 7.20)
\]

The DS-SY cut-off > -0.7 differentiated patients with neurally-mediated syncope from all other patients with 93.3% specificity and 62.5% sensitivity. Hence, a phenotypic CVR was recognized in a majority of the patients with neurally-mediated syncope.

**FMF vs. controls**

The best predictors for the assessment of patients belonging to this group versus all other patients were: (N) supine-PTT-kurtosis by general statistics \((p<0.0001)\), (O) tilt-HR minimum by general statistics \((p=0.0002)\), (P) tilt-HR-variance by general statistics \((p=0.0001)\), (Q) tilt-HR-R/S by fractal analysis \((p=0.0024)\), (R) tilt-HR-average by general...
statistics, and (S) tilt-PTT-trend by recurrence quantitative analysis \((p<0.0001)\).

\[
DS_{-\text{FMF}} = -33.56 + (N \times 0.032) + (O \times 0.13) \\
+ (P \times 0.024) + (Q \times 11.21) \\
+ (R \times 14.77) + (S \times 0.018)
\]

The DS-FMF cut-off \(> -0.27\) differentiated FMF from all other patients with 90.1\% specificity and 76.4\% sensitivity. These data are consistent with a phenotypic CVR in the majority of the FMF patients.

**Psoriatic arthritis vs. controls**

Only one variable was significantly associated with psoriatic arthritis when compared to the common pool of all other patients: (T) supine-HR-standard deviation by general statistics \((p = 0.02)\).

\[
DS_{-\text{PSOR}} = 1.1931557 + (T \times -0.2901153)
\]

The DS-PSOR cut-off \(> -0.01\) differentiated PSOR from all other patients with 90\% specificity, but only 26.3\% sensitivity. Thus the data are not consistent with the proposed criteria of a discrete CVR phenotype.

**Healthy subjects vs. controls**

The best predictors for the assessment of healthy subjects versus all other patients were (U) supine-HR-average by general statistics \((p = 0.003)\) and (V) tilt-PTT-R/S by fractal analysis \((p = 0.0043)\).

\[
DS_{-\text{H}} = 29.73 + (U \times -0.059) + (V \times -14.73)
\]

The DS-H cut-off > 0.25 differentiated healthy subjects from all others with 96.5\% specificity, but only 33.3\% sensitivity. These data are not consistent with the proposed criteria of a discrete CVR phenotype.

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>DS cut-off</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFS</td>
<td>&gt;0.05</td>
<td>90.0</td>
<td>60</td>
</tr>
<tr>
<td>F</td>
<td>&gt;0.27</td>
<td>93.5</td>
<td>40</td>
</tr>
<tr>
<td>SY</td>
<td>&gt;-0.22</td>
<td>93.3</td>
<td>62.5</td>
</tr>
<tr>
<td>FMF</td>
<td>&gt;0.14</td>
<td>90.1</td>
<td>75.4</td>
</tr>
<tr>
<td>PSOR</td>
<td>&gt;0.51</td>
<td>90.1</td>
<td>26.3</td>
</tr>
<tr>
<td>H</td>
<td>&gt;0.89</td>
<td>96.5</td>
<td>33.3</td>
</tr>
</tbody>
</table>

CFS, chronic fatigue syndrome; F, non-CFS fatigue; SY, neurally-mediated syncope; FMF, familial Mediterranean fever; PSOR, psoriatic arthropathy; H, healthy subjects.

### Table 2

<table>
<thead>
<tr>
<th>DS</th>
<th>CFS ((n = 20))</th>
<th>F ((n = 15))</th>
<th>SY ((n = 15))</th>
<th>FMF ((n = 17))</th>
<th>PSOR ((n = 19))</th>
<th>H ((n = 20))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFS</td>
<td>60</td>
<td>13.2</td>
<td>20</td>
<td>0</td>
<td>10.5</td>
<td>15</td>
</tr>
<tr>
<td>F</td>
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<td>40</td>
<td>20</td>
<td>5.8</td>
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<tr>
<td>SY</td>
<td>5</td>
<td>6.6</td>
<td>73.3</td>
<td>5.8</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>FMF</td>
<td>5</td>
<td>13.2</td>
<td>13.2</td>
<td>76.4</td>
<td>5.2</td>
<td>15</td>
</tr>
<tr>
<td>PSOR</td>
<td>10</td>
<td>13.2</td>
<td>6.6</td>
<td>11.7</td>
<td>26.3</td>
<td>10</td>
</tr>
<tr>
<td>H</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>5.8</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>None</td>
<td>30</td>
<td>13.2</td>
<td>26.6</td>
<td>11.7</td>
<td>57.9</td>
<td>35</td>
</tr>
<tr>
<td>Several</td>
<td>10</td>
<td>20</td>
<td>33.3</td>
<td>17.6</td>
<td>5.2</td>
<td>15</td>
</tr>
</tbody>
</table>

DS, discriminant score; CFS, chronic fatigue syndrome; F, non-CFS fatigue; SY, neurally-mediated syncope; FMF, familial Mediterranean fever; PSOR, psoriatic arthropathy; H, healthy subjects.

**II. Frequency distribution of various CVR patterns within each patient group**

In addition to the group-specific DS, other CVR patterns were met by some subjects. For example, of the CFS patients, 60\% met the DS-CFS cut-off, 5\% the DS-F, DS-SY or DS-FMF, 10\% the DS-PSOR, 10\% met two or more DSs, and 30\% did not match a defined reactivity. In the group of patients with FMF, 76.4\% met the DS-FMF cut-off, 5.8\% the DS-PSOR or DS-H, 11.7\% the DS-F, 17.6\% matched two DSs, and 11.7\% did not match a defined reactivity pattern. The spectrum of reactivity patterns noted within groups is shown in Table 2 and Figures 3 and 4.

**III. Disease-related CVR phenotypes**

In the groups of CFS, neurally-mediated syncope and FMF patients, the proposed criteria for disease-related CVR phenotypes were met. In the groups of non-CFS fatigue patients, psoriatic arthritis and...
healthy subjects, there was low sensitivity of the DS, thus proposed criteria for disease-related CVR phenotypes were not satisfied.

Discussion

In the present study, disease-related, distinct cardiovascular reactivity patterns were discerned in different patient groups. Phenotypes of CVR were recognized in the CFS, neurally-mediated syncope and FMF groups.

Previous studies have defined a variety of patterns of abnormal CVRs on postural challenge, including postural hypotension, postural hypertension, supine hypertension with postural hypotension, postural tachycardia syndrome, and vasovagal reactions. None of the above stereotypic cardiovascular responses has been strictly associated with any nosological entity. However, we did discern disease-related, distinct CVR patterns in the present study. The differences between classical methods of assessment for CVR and the current method may account for the disparity in findings.

The method for assessment of the CVR in this study is based on four principles: (i) postural challenge; (ii) beat-to-beat acquisition of data; (iii) data processing by applying regular statistics, fractal analysis and recurrence quantitative analysis; and (iv) discriminant analysis to discern predictors of the particular CVR in one study group versus the CVR in a large heterogenous comparison group. Each mathematical method supplied a different dimension for the analysis of the time series. For example, the equation for computing the DS in patients with chronic fatigue syndrome includes three fractal

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**Figure 3.** Cardiovascular reactivity patterns in chronic fatigue syndrome (CFS). A dot indicates a patient who met the cut-off for the indicated discriminant score (DS). Cut-offs met by CFS patients were: 60% DS-CFS, 5% DS-F, DS-SY or DS-FMF, 10% DS-PSOR, 10% matched two patterns, and 30% did not have a defined reactivity pattern. CFS, chronic fatigue syndrome; F, non-CFS fatigue; SY, neurally-mediated syncope; FMF, familial Mediterranean fever; PSOR, psoriatic arthropathy; H, healthy subjects.

**Figure 4.** Cardiovascular reactivity patterns in FMF patients. A dot indicates a patient who met the cut-off for the indicated discriminant score (DS). Cut-offs met by FMF patients were: 76.4% DS-FMF, 5.8% DS-PSOR or DS-H, 11.7% DS-F, 17.6% matched two phenotypes, and 11.7% did not have a defined reactivity pattern. CFS, chronic fatigue syndrome; F, non-CFS fatigue; SY, neurally-mediated syncope; FMF, familial Mediterranean fever; PSOR, psoriatic arthropathy; H, healthy subjects.
variability. Similarly to fractal measures, recurrence quantitative analysis and four variables of general statistics.

Fractal measurements differ from measurements used in regular Euclidean geometry. FD represents a ‘self-similarity’ in dynamic behaviour over multiple scales of time. The FD can be seen as the minimum number of underlying variables that are required to explain the signal as it is. The lower the dimension is, the simpler is the signal. Recurrence quantification analysis is a relatively new analytical tool for the study of nonlinear dynamic systems, originally developed by Eckmann, Kamphorst and Ruelle as a purely graphical tool to analyse dynamic processes. It can graphically detect hidden patterns and structural changes in data, and reveal similarities across the time series under study. According to classical concepts of physiology, healthy systems are self-regulated to reduce variability and maintain physiological constancy. Contrary to the predictions of homeostasis, however, even under resting conditions the normal human heartbeat and a variety of other systems fluctuate in a complex manner. Studies of fractal dynamics in physiology suggest that maintaining constancy is not the goal of physiological control. In contrast, in subjects at high risk of sudden death, including those with heart failure, fractal organization breaks down. Fractal analysis may assist the assessment of cardiac risk and forecast sudden cardiac death. Healthy ageing is associated with R-R interval dynamics showing higher regularity and altered fractal scaling consistent with a loss of complex variability. Similarly to fractal measures, recurrence plots provide better understanding of physiological processes, when used to describe the nonlinear dynamics between left ventricle and arterial system, determine the presence of organization of the atrial activation processes during atrial fibrillation, and in assessment of heart failure, where a decrease in chaos may be indicative of congestive heart failure.

In our study, results obtained by different methods of fractal analysis were not overlapping. The fractal dimension calculated according to one method was often an independent predictor of CVR, while the fractal dimensions calculated by other methods were not. The ‘lack of self-consistency’ of different methods of fractal analysis in our study is remarkable, and can be expected to occur in a self-affine (repetitively similar but not identical) fractal system. A fractal system may be self-similar (repetitively identical along the scale) or self-affine. In assessing self-similar structures, different methods of fractal analysis converge, yielding almost identical fractal dimensions. In assessing self-affine patterns, as frequently encountered in biology, each method of fractal analysis may reflect a different aspect of the dynamic pattern. Thus, applying various methods for fractal analysis may provide complementary information.

The use of discriminant analysis enabled us to discern predictors for particular CVR patterns in each individual study group vs. comparison groups. In the definition of CVR phenotypes, we proposed that the DS cut-off of the CVR must be at least 90% specific and 50% sensitive. Designation of the control group affects the specificity, and from our prior experience, the use of a large and heterogeneous control population is important to address the requirement for specificity. In the present study, each patient group was compared with the combined pool of other patients (including subgroups of patients who may resemble the study patients, in addition to healthy subjects), so that discriminant analysis might recognize a disease-specific CVR pattern. Thus, the analysis was tailored to recognize the reactivity of each particular disorder from a spectrum of different CVRs, and not merely from the reactivity of healthy subjects.

Phenotypes of CVR, uniform reactivity patterns which are both specific and prevalent within the disease group, were recognized in chronic fatigue syndrome, neurally-mediated syncope and familial Mediterranean fever. By contrast, the CVR in healthy subjects was remarkably variable, confirming data from the literature. The mechanisms involved in disease-related cardiovascular reactivity patterns are incompletely understood. The conventional understanding that cardiovascular reactivity is merely the result of arterial baroreflexes is simplistic and no longer tenable. Indeed, numerous factors modulate the response to baroreflex activation besides the strength of the activating stimulus. These include the set point of the reflex, neuronal input from hypothalamus, cortical centres, brainstem centres, the responsiveness of cardiovascular receptors and structures, interactions of aortocarotid with chemoreflex arcs, and the modulatory influences of neuro-humoral and vasoactive substances. Thus, serotonin, adenosine and opioids are additional triggers of the Betzold-Jarisch reflex, peripheral sympathetic afferents are directly activated by circulating mediators, and higher nervous centres modulate the cardiovascular reflexes. Disease-specific CVR patterns may be explained by the interplay between cardiovascular and neuro-endocrine and paracrine changes associated with certain disorders. We are just beginning to learn about CVR phenotypes, and
empirical observation is presently in advance of our understanding.

There are limitations to the applicability of the method proposed in this study. Though the short tilt test is well tolerated by patients, processing the FRAS is time-consuming (average 3 h, with data cross-checked by two independent observers). The number of subjects included in this paper is relatively small in relation to their subdivisions within subgroups. There is need to evaluate prospectively the different discriminant scores in larger patient groups so as to extend the investigation from the ‘training’ groups of the present study to ‘test’ groups in future studies. Confirmatory data as to the presence of a specific CVR pattern in CFS were obtained by applying the methodology of the ‘haemodynamic instability score’.8–11 The presence of a specific CVR pattern in patients with familial Mediterranean fever has been confirmed in a subsequent study including 35 patients with this disorder (Naschitz et al., unpublished data).

So far, reproducibility of the FRAS was assessed in a group of 12 CFS patients, by repeating the examination for a second or third time at two to four-week intervals. In all instances, classification using the DS-CFS > 0.05 was correct, and thus reproducible (Naschitz et al., personal communication). The specific CVR phenotype in CFS has also been found to be reproducible when assessed with the ‘haemodynamic instability score’. Two-to-five examinations were performed in each subject at 1–2 week intervals, for a total of 35 examinations in the 14 patients. The patients were correctly classified by the HIS cut-off in all instances.10 Reproducibility of the DS-FMF and DS-SY remains to be assessed in future studies.

The R-wave gated digital photoplethysmography used by us for assessment of the PTT, records a peripheral volume pulse and not a pressure pulse.39 Continuous BP monitoring of larger arteries might have produced different data.

The importance of recognizing disease-specific CVR phenotypes, in addition to providing a better understanding of the physiology and pathophysiology of the cardiovascular system, may consist in offering supporting data for the diagnosis of certain disorders. Recognizing the CFS reactivity phenotype in the present study and in five cross-sectional studies, which made usage of different measurement techniques but were based on similar principles of analysis, has been found useful in supporting the clinical diagnosis of CFS.8–12 Furthermore, CVR phenotype may provide an objective criterion to monitor the course of dysautonomia in CFS under treatment.40 The clinical implications of finding a CVR phenotype in FMF have not been explored. Potentially, identifying the FMF phenotype by tilt test in an atypical patient can strengthen the diagnosis of FMF in the appropriate clinical context, much as the finding of certain DNA mutations strongly favours the diagnosis of FMF without providing definitive proof.41 Pathological disturbances may shape cardiovascular reactivity. The familiar head-up tilt test can expose vasovagal reaction, postural tachycardia syndrome, or orthostatic hypotension, but these syndromes are not specific to a particular disease entity. Techniques such as the FRAS seem to be able to reveal previously hidden CVR phenotypes. Additional work is needed to determine the applicability of this methodology in the identification of CVR phenotypes, and its importance for clinical practice.

References


