

ORIGINAL ARTICLE

Assessment of cardiovascular reactivity by fractal and recurrence quantification analysis of heart rate and pulse transit time

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Methods used for the assessment of cardiovascular reactivity are flawed by nonlinear dynamics of the cardiovascular responses to stimuli. In an attempt to address this issue, we utilized a short postural challenge, recorded beat-to-beat heart rate (HR) and pulse transit time (PTT), assessed the data by fractal and recurrence quantification analysis, and processed the obtained variables by multivariate statistics. A 10-min supine phase of the head-up tilt test was followed by recording 600 cardiac cycles on tilt, that is, 5–10 min. Three groups of patients were studied, each including 20 subjects matched for age and gender— healthy subjects, patients with essential hypertension (HT), and patients with chronic fatigue syndrome (CFS). The latter group was studied on account of the well-known dysautonomia of CFS patients, which served as contrast against the cardiovascular reactivity of the healthy

population. A total of 52 variables of the HR and PTT were determined in each subject. The multivariate model identified the best predictors for the assessment of reactivity of healthy subjects vs CFS. Based on these predictors, the ‘Fractal & Recurrence Analysis-based Score’ (FRAS) was calculated: $FRAS = 76.2 + 0.04 \cdot HR\text{-supine-DET} - 12.9 \cdot HR\text{-tilt-R/L} - 0.31 \cdot HR\text{-tilt-s.d.} - 19.27 \cdot PTT\text{-tilt-R/L} - 9.42 \cdot PTT\text{-tilt-WAVE}$. The median values and IQR of FRAS in the groups were: healthy = -1.85 (IQR 1.89), hypertensives = +0.52 (IQR 5.78), and CFS = -24.2 (5.34) (HT vs healthy subjects: $P = 0.0036$; HT vs CFS: $P < 0.0001$). Since the FRAS differed significantly between the three groups, it appears likely that the FRAS may recognize phenotypes of cardiovascular reactivity.

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Introduction

Cardiovascular reactivity is defined as the change in blood pressure (BP), heart rate (HR), or other haemodynamic parameters in response to physical or mental stimuli.¹ Various methods are employed for the study of cardiovascular reactivity. At 24 h ambulatory monitoring measures short- and long-term variabilities in BP and HR. In the laboratory, the cardiovascular reactivity is studied under psychological, cold pressor, or postural challenge, lower-body negative pressure, physical exercise, and combined mental and physical challenges.^{2–4} The aim of these efforts is to measure BP and HR changes under various conditions, and compare them to

baseline values. For this purpose, attention has to be paid not only to average values of BP and HR but also to fluctuations of the measurements around the average levels. The standard deviation supplies data on the signal dispersion around the mean, but does not provide information on the patterns that characterize the variability of the signal over a period of time. This has led to the development of other methods for the evaluation of cardiovascular variability, among which spectral analysis has been widely used.⁴ Spectral analysis allows the overall variance of the signal to be split into its various frequency components. 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.⁵ In fact, autonomic cardiovascular modulation is characterized by a high degree of nonlinearity between external stimuli and cardiovascular response.⁴ Other methods have been proposed in an attempt to address the issue of nonlinear dynamics of the cardiovascular responses.

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These include fractal analysis,^{6,7} recurrence quantification analysis,^{8,9} and multivariate models that consider the relation between two or more cardiovascular signals.¹⁰ It has been suggested that joint quantification of BP and HR fluctuations, and utilization of non-Euclidean mathematic analysis may provide more reliable information on cardiovascular reactivity.⁴

In the present study, we developed a method for assessment of the cardiovascular reactivity in application of the above principles. The correlations between the fluctuations of two cardiovascular parameters were assessed, and usage was made both of common statistical methods, fractal analysis and recurrence quantification analysis. A multivariate discriminant model assessed the best predictors to identify the cardiovascular reactivity pattern observed in healthy persons, and other reactivity patterns that occur in certain disease states. 'Reactivity phenotypes' were recognized.

Methods

All participants gave informed consent and our institution's committee for human research approved the study. All patients were fully ambulatory at the time of the study. The patients were not taking medications for at least 2 weeks before the study. Technicians carrying out the HUTT did not know of the intention to compare between the groups. Data of earlier studies, which utilized somewhat different equations, were revised, expanded and processed according to the latest equation. In phase I of the study, cardiovascular reactivity measures were determined in a control group of healthy subjects, and differentiated from abnormally exaggerated reactivity observed in a group of patients with CFS. The latter were selected because they display an exaggerated cardiovascular reactivity. Based on the measurements obtained in study phase I, an equation was established to express numerically an individual's cardiovascular reactivity over a wide range of possible reactivities. In study phase II, the equation was applied to calculate the cardiovascular reactivity of hypertensive patients.

Patients

The study sample consisted of patients referred to the Syncope Clinic of Bnai-Zion Medical Center between January 2001 and January 2002. The subjects' ages ranged from 18 to 40 years, and both patients and controls were fully ambulatory. Subjects were not taking medications for at least 4 weeks prior to the study, including sleeping pills, tranquilizers, or antidepressants. Excluded from the study were patients with any somatic, neurological, or psychiatric comorbidities, as well as women receiving oral contraceptives or hormone replacement

therapy. Three groups were studied, each including 20 subjects, matched for age and gender.

Patients with recently diagnosed arterial hypertension, who were not until now given antihypertensive medication, participated in this study. They presented mild to moderate essential hypertension according to criteria of the Sixth Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure.¹¹ Their average age was 27.7 years (s.d. 12.1) and 55% were women. Their average body mass index was 25.6 kg/m² (s.d. 1.1). No patient had diabetes mellitus or angina pectoris. Two patients were actual smokers; one stopped smoking 6 years earlier. The average level of the LDL cholesterol in this group was 135 mg/Dl (s.d. 22.1) and the HDL cholesterol was 40.3 mg/Dl (s.d. 6.5).

Healthy control subjects were eligible if they did not report persistent fatigue and had normal findings on physical examination, routine laboratory tests, chest X-rays, and electrocardiogram. Their average age was 29.4 years (s.d. 8.1) and 60% were women. Their average body mass index was 23.1 kg/m² (s.d. 0.8). Patients with the chronic fatigue syndrome (CFS) were selected out of 27 consecutive subjects referred from a CFS clinic for evaluation with the HUTT. They met the Centers of Disease Control and Prevention definition criteria of CFS.¹² The patients' average age was 29.2 years (s.d. 15.5) and 65% were women. Their average body mass index was 22.9 kg/m² (s.d. 1.3).

The protocol of the tilt test and PTT recordings were based on the 10-min supine –30 min head-up tilt test as previously described.¹³ Testing was conducted from 8:00 to 11:00 am 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 within 6 h of the examination. Intake of food products and medications with sympathomimetic activity prior to the study were 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 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 to 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 semiopen position, with the palm turned downward and fixed with adhesive strips, taking care not to apply pressure to the PPG transducer.¹⁴ The electrocardiogram (ECG) and PPG were recorded on a Datex-Engstrom Cardiocap™ II instrument (Datex Instrumentation Corporation, Helsinki, Finland), connected to the Biopac MP 100 data acquisition system (Biopac, Santa Barbara, CA, USA). The PTT was automatically computed on the 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 samples per second provided 1/500 Hz resolution for the HR and PTT measurements. Measurements were acquisitioned in the supine position over a 10-min period. The table was then gently tilted head-up to an angle of 70° and the acquisition continued for a total of 600 cardiac cycles (usually 5–10 min), according to a method previously described.¹⁵

Data processing

The RR intervals on ECG recordings and the corresponding PTT values were automatically computed with the AcqKnowledge software. Four sets of values were obtained, each comprising approximately 600 measurements—the time series of HR values supine and similar time series of PTT supine, HR tilt, and PTT tilt measurements. Later, the measurements were reviewed and edited. For this purpose, the computer program signalled HR values less than 45 bpm or in excess of 110 bpm, and PTT values less than 0.2 s or longer than 0.4 s. For each of the aberrant measurements, the investigator decided whether or not it was likely to be authentic in the context of 30–40 contiguous measurements. PTT measurements less than 0.2 s were considered to be artefacts, based on our experience that such values

occurred only upon movement of the transducer. PTT values greater than 0.4 s were considered to be artefacts when occurring alone or as couples, but when clustering in series of three or more spikes the occurrence was considered to be authentic. Suspicious HR values were deleted together with the concomitant PTT measurements, and suspicious PTT values were deleted together with the concomitant HR measurements. After editing, the data were advanced to mathematical analysis.

Three mathematical methods were applied: general statistics, recurrence plot analysis, and fractal analysis.

Recurrence quantitative analysis (RQA)

Recurrence plot analysis is a relatively new technique for the qualitative assessment of time series.^{8,9} 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. In our study, we utilized the Visual Recurrence Analysis computer program version 4.2 developed by Eugene Kononov, 1999. To start RQA calculations, 500–600 consecutive edited HR or PTT measurements were loaded in the computer program. The embedding dimension, time delay and false nearest neighbour were determined. On this basis, the RQA variables were computed: recurrence, determinism, ratio, entropy, maxline, trend, and spatiotemporal entropy. Figure 1 illustrates the recurrence plot of the HR in a healthy subject. Besides the global impression given by the

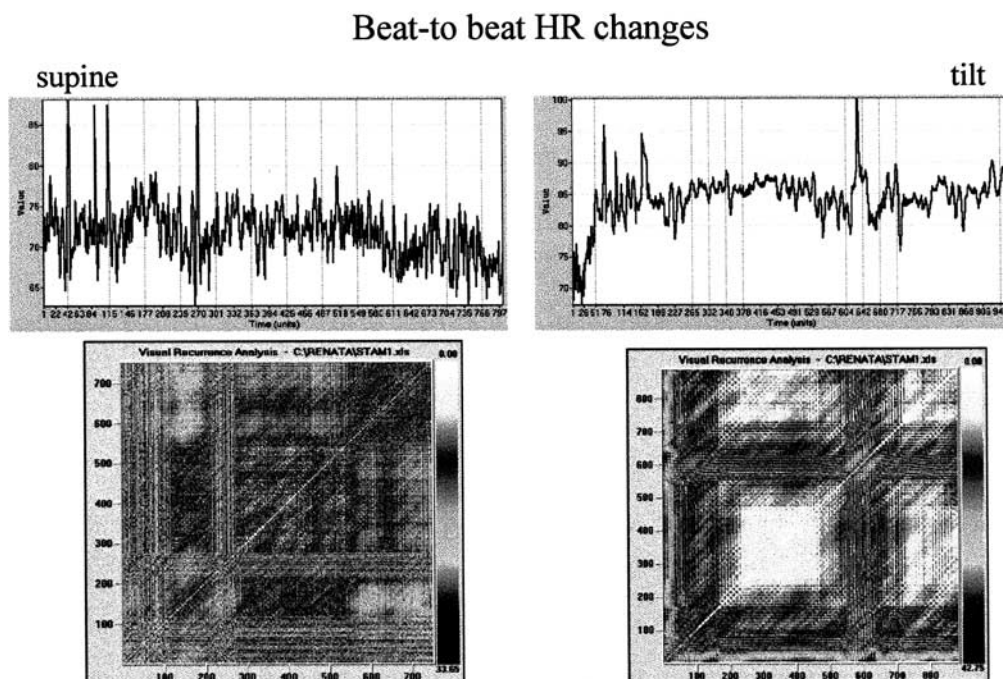


Figure 1 Recurrence plot analysis of the time series of the HR during the supine and tilt phases in a healthy subject.

Recurrence quantitative analysis of the HR on tilt

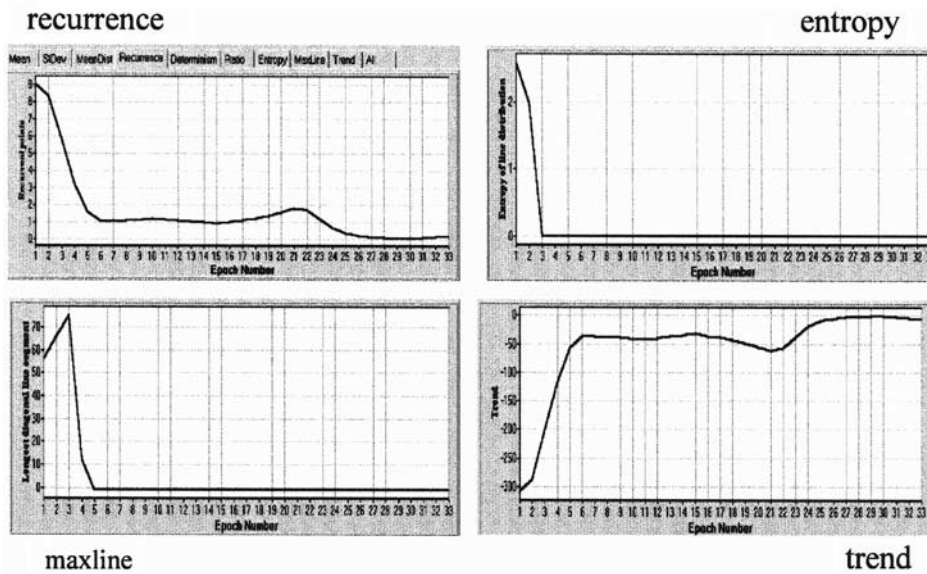


Figure 2 Quantitative analysis of the time series of the HR displaying the trend, determinism, recurrence, and entropy of time distribution.

appearance of the recurrent plot, quantitative descriptors were developed and are included in the RQA method. These are recurrence, determinism, ratio, entropy, maxline, trend, and spatiotemporal 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 relation between time and the amount of recurrence (Figure 2).

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 analyzer (Trusoft Int'l, Inc., 1999, St Petersburg, FL, USA). 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 3.

On collecting all computed variables derived by analysis of time series measurements, 13 variables were obtained. By summarizing the four data sets in each patient, including HR and PTT in supine and tilt positions, a total of 52 variables of cardiovascular reactivity were obtained. Means and s.d.'s of all 52 cardiovascular reactivity variables were calculated and comparisons between the data of CFS patients and controls were performed. A multivariate analysis was conducted, evaluating independent predictors of CFS. Based on the regression

coefficients (slopes and intercept) of these predictors, a linear discriminant score was computed for each subject. This discriminant score was called 'Fractal & Recurrence Analysis-based Score' (FRAS). The best cut-off between the FRAS of healthy subjects and CFS was established.

In phase II of the study, the FRAS was determined in patients with arterial hypertension. Finally, the FRAS values in the different groups were compared.

Statistical analysis

Mann–Whitney U test was used for univariate analysis. For multivariate analysis, forward stepwise logistic regression analysis was applied. A two-tailed P -value of 0.05 or less was accepted as statistically significant. The predictive characteristics of FRAS (sensitivity, specificity, and total accuracy) were calculated from the logistic model, using regression coefficients of the relevant independent variables (predictors). Receiver characteristic curve analysis (ROC) was built using Wilcoxon's method for detecting the best cut-off point of the FRAS. The FRAS in the five groups were compared using the Kruskal–Wallis ANOVA followed by a corrected Mann–Whitney multiple comparison test.

Results

On univariate analysis, 13 variables showed significant differences between CFS and controls. These included six fractal parameters, five RQA

Beat-to beat PTT changes

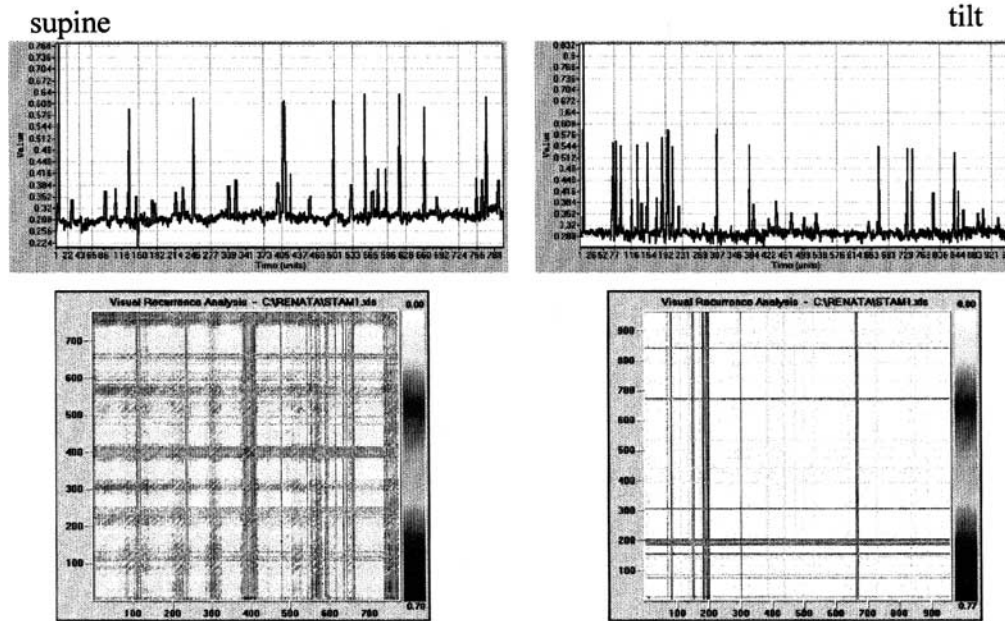


Figure 3 Recurrence plot analysis of the time series of the PTT during the supine and tilt phases.

Table 1 Fractal & Recurrence Analysis-based Scores (FRAS) in hypertensive and other patient groups

Group (n=20)	FRAS (avg)	FRAS (s.d.)	FRAS (relative s.d.)	P-value ^a
HT	0.71	3.39	4.75	
Healthy	-1.83	1.44	-0.81	0.036
CFS	-23.77	3.65	-0.15	<0.0001

^aHypertensives compared to other groups.

parameters, and two parameters derived from summary statistic analysis.

The multivariate model identified the best predictors for the assessment of CFS vs mixed control patients to be (1) HR on tilt, - fractal dimension by roughness-length analysis (HR-tilt-R/L), (2) PTT on tilt, - fractal dimension by roughness-length analysis (PTT-tilt-R/L), (3) HR supine, - determinism on recurrence quantification analysis (HR-supine-DET), (4) PTT on tilt, - fractal dimension by wavelets analysis (PTT-tilt-WAVE), and (5) HR on tilt standard deviation (HR-tilt-s.d.). Based on the regression coefficients (slopes and intercept) of these predictors, a linear discriminant score was computed for each subject. This discriminant score was called FRAS:

$$\text{FRAS} = 76.2 + 0.04 * \text{HR-supine-DET} - 12.9 * \text{HR-tilt-R/L} - 0.31 * \text{HR-tilt-s.d.} - 19.27 * \text{PTT-tilt-R/L} - 9.42 * \text{PTT-tilt-WAVE}.$$

With the aid of Equation (1), FRAS values were calculated in the three patient groups (Table 1 and

Figure 4). Comparison of FRAS values in hypertensive patients and in the other groups showed significant differences: hypertensive vs healthy, $P=0.0036$; hypertensive vs CFS, $P<0.0001$. The range of reactivities was narrow both in healthy individuals (FRAS relative s.d. = -0.81) and CFS patients (FRAS relative s.d. = -0.15), but ample in hypertensives (FRAS relative s.d. = 4.75). The median values and IQR of FRAS in the groups were: healthy = -1.85 (IQR 1.89), hypertensives = +0.52 (IQR 5.78), and CFS = -24.2 (5.34) (see Figure 5).

Discussion

The proposed FRAS of this study conferred numerical expression to the cardiovascular reactivity during postural challenge. The FRAS differed significantly between the groups. Within each group, the range of reactivity was narrow in healthy subjects and in CFS patients, but wide in hypertensives.

The method we propose differs from methods applied in other studies in that we utilized a short tilt phase, recorded the PTT, and processed the obtained measurements with the aid of Euclidean and non-Euclidean mathematics. Each mathematical method supplied a different dimension for the analysis of the data series: among five independent predictors of the FRAS, three were fractal dimensions, one belonged to recurrence quantification, and another to standard statistics.

Two PTT variables were independent predictors of the FRAS. This demonstrates the relevance of

Fractal dimension of the HR by different methods

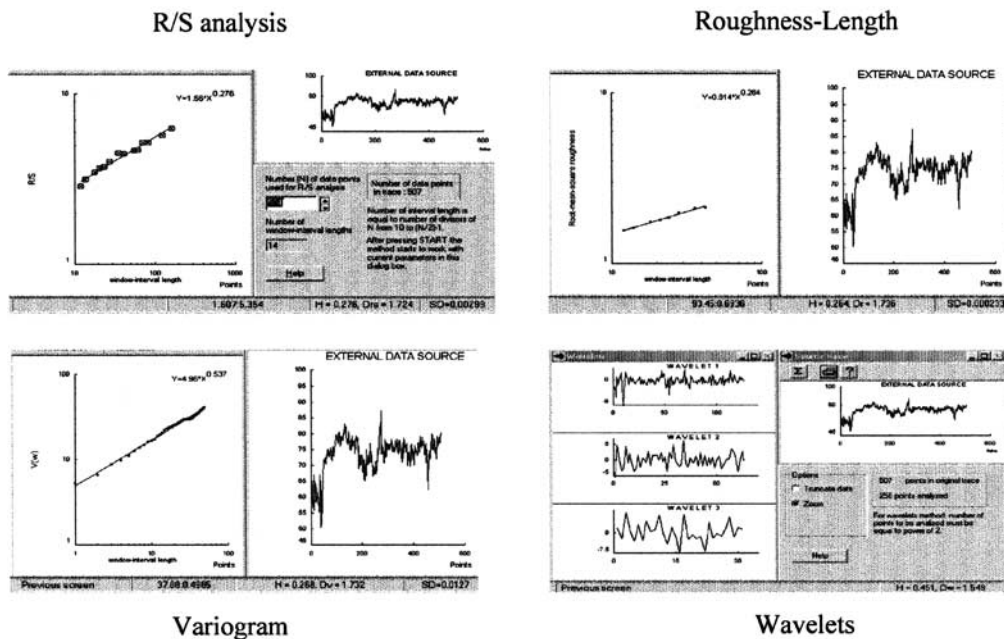


Figure 4 Fractal analysis of the HR time series during tilt using four different methods: R/S, roughness-length, variogram, and wavelets analysis.

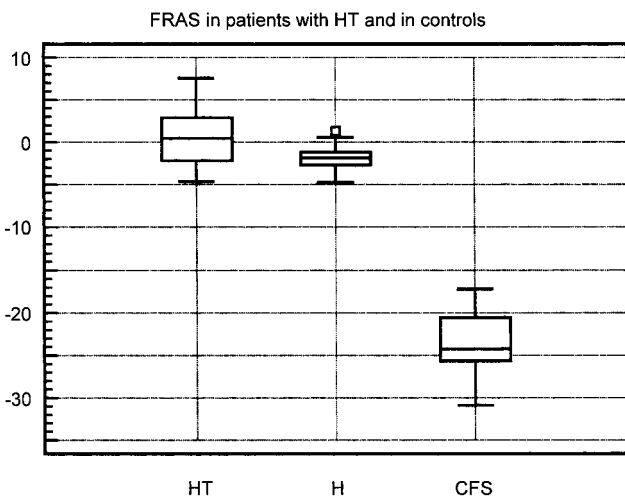


Figure 5 FRAS values in the three patient groups. HT = arterial hypertension, CFS = chronic fatigue syndrome. The boxes contain 50% of the values falling between the 25th and 75th percentiles, the horizontal line within the box represents the median value, and the 'whiskers' are the lines that extend from the box to the highest and lowest values, excluding the outliers.

PTT measurements for cardiovascular reactivity. However, the pathophysiological mechanisms connecting the PTT to cardiovascular reactivity are not fully understood. It is possible that the BP controls both the reactivity and the PTT. Indeed, the pulse wave velocity correlates with the BP.^{16,17} However, the connection between BP and PTT is weak, and the accuracy of the PTT as a surrogate measure of BP

has been contested.^{18,19} A second factor that may link the PTT to cardiovascular reactivity is the isometric contraction time. In using the electrocardiographic R wave as a starting point for PTT measurement, it is not only the pulse wave velocity that is measured in the PTT, but also the delay between the occurrence of the R wave and the opening of the aortic valve, that is, the isometric contraction time. Conditions that affect the duration of the isometric contraction time, such as ventricular stroke volume, inotropic influences, and HR,^{17,20} may affect the PTT. These conditions are also known to influence the cardiovascular reactivity. Third, the degree of stiffness of the large arteries affects both the cardiovascular reactivity and the pulse wave velocity,^{21–24} consequently influencing the PTT.

Computer-assisted image analysis was utilized to calculate the FD of the time curves. Fractal measurements differ from measurements used in regular Euclidean geometry.^{25,26} 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, the simpler the signal. In our results, the FD provided three out of five independent predictors utilized to compute the FRAS. Another relatively new analytical tool for the study of nonlinear dynamic systems utilized in this study is RQA. RQA was originally developed by Eckmann *et al*⁸ as a purely graphical tool to analyse dynamic processes.⁸ With RQA, one can graphically detect hidden patterns and structural changes in

data and perceive similarities across the time series under study. Recently, RQA has been applied to the study of nonlinear dynamics of HR variability.^{10,27} In the present investigation, the RQA of the HR provided one of five variables indispensable to compute the FRAS.

Distinct cardiovascular reactivity patterns

The FRAS differs between the groups of healthy persons, hypertensives, and CFS patients. Within each group, the range of the FRAS values (illustrated by the relative s.d.) was narrow in the healthy and CFS groups, supporting the uniform pattern of the cardiovascular reactivity in each of these populations. The range of FRAS was wide in the group of hypertensive patients, suggesting that this group is heterogeneous. Heterogeneity suggests that various pathophysiological mechanisms may be involved in the cardiovascular reactivities among individuals with essential hypertension.

The ability of the FRAS to identify distinct reactivity patterns is analogous to another method described by us, the haemodynamic instability score (HIS). The HIS assesses cardiovascular reactivity by utilizing a standardized postural challenge, serial recording of the HR and BP, fractal analysis, and multivariate discriminant assessment of the variables. Both methods are geared towards identifying the reactivity of CFS patients. In contrast to the FRAS, the HIS applies a 30-min long tilt and measurements are taken at 5-min intervals. Both the HIS and the FRAS methods differentiated between the characteristic cardiovascular reactivities of healthy subjects, hypertensives, and patients with CFS. The HIS distinguished CFS from healthy subjects with 97% sensitivity and 97% specificity. The HIS also discerned the particular reactivity of CFS patients from the cardiovascular reactivities of other patient groups, which may confound the diagnosis of CFS, such as patients with fibromyalgia, non-CFS fatigue, and neurogenic syncope.^{28–30} The HIS identified a distinctive cardiovascular reactivity in patients with essential hypertension.⁷ Thus, the correlation of results obtained by both the FRAS and the HIS methods supports the authenticity of reactivity phenotypes.

Limitations

There are limitations to the applicability of the FRAS. First, the test is demanding for technicians, although it is patient-friendly. Second, only small groups of patients have been studied; the study populations were homogenous and, as such, are not representative of the population at large. Third, comparison of the FRAS with other tests of cardiovascular reactivity, in particular baroreflex sensitivity and HR variability, remains to be performed.

Perspectives

By utilizing a passive challenge, the head-up tilt test is not restricted by cultural constraints and is applicable to a wide range of populations. The short tilt phase utilized for data acquisition is in general well tolerated, with the possible exception of patients with autonomic failure. This represents an important advantage by comparison to the long tilt necessary for assessment of the HIS. There are many accessible and reasonably priced computer programs that can perform a fractal analysis and RQA.

The practical application of the FRAS as a diagnostic test is supported by previous studies that utilized the HIS for the diagnosis of CFS. In these studies, which comprised 70 patients with CFS, 73 patients with non-CFS chronic fatigue, and 41 patients with fibromyalgia, the sensitivity of the HIS for the diagnosis of CFS was 91.4% and the overall specificity was 85.1%.^{28–30} The high sensitivity and specificity of the HIS for CFS improves on the moderate sensitivity and poor specificity of classical autonomic testing for CFS.^{31–33} Based on these data, it appears that the HIS can reinforce the clinician's diagnosis by providing objective criteria to the assessment of CFS, which, until now, could only be subjectively inferred. The main limitation of the HIS is the frequent 'HIS dropouts' who are unable to complete the full HUTT because of syncope or near syncope. The FRAS may overcome this problem. If the high sensitivity and specificity of the FRAS for the diagnosis of CFS is confirmed in larger studies, it could become the method of choice in supporting the clinical suspicion of CFS.

Knowledge of a gamut of reactivity phenotypes may advance our understanding of the pathophysiology of circulatory disorders, in particular in hypotensive disorders, postural intolerance without hypotension, and arterial hypertension. It may become possible to classify the latter disorders into subtypes, based on their specific reactivity phenotypes. Tailoring of drug treatment according to patients' cardiovascular reactivities may be beneficial.

We are only at the beginning stages of investigating how the FRAS can be utilized to examine cardiovascular reactivity. Further studies are needed in order to determine the applicability of the FRAS to the identification of characteristic phenotypes and their importance in clinical practice.

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