Effects of stress on heart rate complexity—A comparison between short-term and chronic stress

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ABSTRACT

This study examined chronic and short-term stress effects on heart rate variability (HRV), comparing time, frequency and phase domain (complexity) measures in 50 healthy adults. The hassles frequency subscale of the combined hassles and uplifts scale (CHUS) was used to measure chronic stress. Short-term stressor reactivity was assessed with a speech task. HRV measures were determined via surface electrocardiogram (ECG). Because respiration rate decreased during the speech task ($p < .001$), this study assessed the influence of respiration rate changes on the effects of interest. A series of repeated-measures analyses of covariance (ANCOVA) with Bonferroni adjustment revealed that short-term stress decreased HR D2 (calculated via the pointwise correlation dimension PD2) ($p < .001$), but increased HR mean ($p < .001$), standard deviation of R–R (SD_{RR}) intervals ($p < .001$), low (LF) ($p < .001$) and high frequency band power (HF) ($p = .009$). Respiratory sinus arrhythmia (RSA) and LF/HF ratio did not change under short-term stress. Partial correlation adjusting for respiration rate showed that HR D2 was associated with chronic stress ($r = -.35$, $p = .019$). Differential effects of chronic and short-term stress were observed on several HRV measures. HR D2 decreased under both stress conditions reflecting lowered functionality of the cardiac pacemaker. The results confirm the importance of complexity metrics in modern stress research on HRV.

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1. Introduction

For millennia we have understood that heart rate (HR) responds to stress. Two recent developments allow one to examine measures of this linkage more precisely. The first development differentiates between chronic stress exposure and responses to short-term stressors, i.e., reactivity. The second development deals with different ways of characterizing the fundamental properties of the HR itself and different ways of measuring its variability. This study examines how short-term stressors and long-term stress exposure relate to measures of HR and HR variability (HRV).

Exposure to chronic stress is a good predictor of cardiovascular disease. Ongoing troubles and the failure to resolve negative emotional states such as anger and anxiety generate imbalance between the sympathetic (SNS) and the parasympathetic nervous system (PNS), the two branches of the autonomic nervous system

(ANS). An increase in the sympathetic-to-parasympathetic ratio (SPR) is now being linked to increased cardiovascular morbidity and mortality (Piccirillo et al., 1997; Gorman and Sloan, 2000; Rozanski and Kubzansky, 2005).

There are two major approaches how chronic psychosocial stress can be conceptualized in research on HRV. One is based on the measurement of major life events and assumes that experiencing major events such as divorce or death of a loved one requires adjustment that leads to psychological and/or physical symptoms (Selye, 1956; Moss, 1973). The other approach focuses on measures of minor incidents and hassles (e.g., argument with partner); that approach suggests that minor events are more common than major events and, thus, may be more salient for the individual at a single point in time (Kanner et al., 1981; DeLongis et al., 1982; Weinberger et al., 1987).

Research on HRV has generally focused on acute, laboratory stressors as opposed to chronic stress. Assessment of the impact of acute stress on HRV has been done utilizing cognitive (e.g., mental arithmetic), psychomotor (e.g., mirror tracing), or physical (e.g., cold pressor) challenges. Moreover, as standard laboratory stressors do not always engage subjects' affective response, social interaction stressors such as public speaking tasks are often

applied to provide a more appropriate social context in which negative emotions might be elicited (Waldstein et al., 1998).

Continuous changes in sympathetic and parasympathetic neural impulses exhibit alterations in HR and cause oscillation of the R–R interval around its mean value (HRV). Increasingly refined calculations have been developed to measure HRV. One of the more global and simple measures of HRV is the standard deviation of the mean R–R interval (SD_{RR}) (Berntson et al., 1997). When healthy subjects are acutely stressed, HR increases and SD_{RR} decreases transiently (De Geus et al., 1990; Boutcher and Stocker, 1996). Chronically stressed individuals, on the other hand, show decreased HR (Furlan et al., 2000; Lucini et al., 2005). Respiration has a strong influence on HR changes and is commonly included as a covariate in statistical analysis of the relation between stress and HRV changes (Berntson et al., 1997). Respiratory sinus arrhythmia (RSA) is the HRV in synchrony with respiration and represents the difference between the longest and the shortest heart period within the respiratory cycle (Berntson et al., 1997). RSA is known as an index of cardiac parasympathetic activity and usually decreases under acute psychological stress (Task force of ESC and NAPE, 1996; Houtveen et al., 2002). However, despite their value in estimating overall HRV or components of HRV related to respiration, these "time domain" measures have only limited application in cases requiring a more precise parsing of HRV pattern (Berntson et al., 1997).

"Frequency domain" methods such as spectral analysis and autoregressive techniques are applied to analyze an R–R interval time series on the basis of its frequency distribution. It is proposed that the instantaneous balance between sympathetic and para-sympathetic activities can be captured by the ratio between low frequency band power (LF, 0.05–0.15 Hz) and high frequency band power (HF, >0.15 Hz); the latter represents primarily respiratory components. This ratio of LF/HF is sometimes referred to as a measure of "sympathovagal balance" (Pagani et al., 1986; Malliani et al., 1991; Task force of ESC and NAPE, 1996). Studies on healthy individuals show that acute stress increases LF/HF and decreases HF, suggesting activation of the SNS as well as withdrawal of PNS activity under stress (Pagani et al., 1997). However, data are far from being unequivocal that the LF/HF ratio represents a relative sympathetic modulation (Eckberg, 1997). Moreover, a major proportion of HRV occurs over a large frequency span showing broad, noise-like, irregular variability (Kobayashi and Musha, 1982). Such evidence supports critics who argue that the proposed rigid scheme of the frequency bands cannot cope with the complex and variable interactions between the different rhythms (Koepchen, 1991; Grasso et al., 1997; Lambertz and Langhorst, 1998; Cammann and Michel, 2002; Perlitz et al., 2004).

The interactions between multiple autonomic influences (e.g., PNS, SNS, hormones, preload, and afterload) causes the output from the cardiac pacemaker to fluctuate in an apparently random, i.e., chaotic manner (Denton et al., 1990). Moreover, under normal conditions, the HR generating system tends to be homeokinetic (rather than homeostatic), i.e., it fluctuates between a set of metastable states or attractors (Lipsitz and Goldberger, 1992; Lipsitz, 1995). Such structural and functional diversity of the sinus node leads to a large repertoire of responses and enables the heart to switch from one state to another quickly, perhaps a needed requirement for adaptation to external and internal challenges of everyday life (Goldberger et al., 2002). In this respect, a stronger regularity and decreased responsiveness of the cardiac pacemaker to changing circumstances may be associated with increased risk of disease (Pincus, 1994).

In recent years, a third class of HRV measures, the "phase domain" methods, has been developed in order to grasp the complex properties of the HR dynamics. These measures are derived from chaos theory and non-linear system theory and differ from the conventional HRV methods because they are not designed to assess the magnitude of variability but rather the quality, scaling, and correlation properties of the HR dynamics (Beckers et al., 2006). No strict definition of complexity exists (Kanters et al., 1997), and although irregularity and unpredict-ability are important characteristics, they alone are not sufficient to comprehensively describe complexity. The most widely applied complexity measure of HRV is the approximate entropy (ApEntr). The ApEntr measures the amount of information needed to predict the future state of a system thus providing an index of randomness or unpredictability of a system (Pincus, 1991). The higher the ApEntr, the smaller the likelihood that runs of patterns which are close remain close on the next incremental compar-isons (Mäkikallio et al., 1996). A decrease in HR ApEntr has been found to be predictive of ventricular and atrial fibrillation and to correlate with the risk of sudden infant death syndrome (Pincus, 2001). A second measure, the largest Lyapunov exponent (LLE), captures the dynamical properties of the system orbiting within the attractor (Elbert et al., 1994). The LLE quantifies the sensitivity of a system to initial conditions, which manifests itself graphically as adjacent trajectories that diverge widely from their initial close position. A positive LLE indicates sensitive dependence on initial conditions and thus loss of predictability (Ruelle, 1979). Patients with major depression and no heart disease have a significantly decreased LLE which may be related to the higher risk of cardiovascular mortality in this group (Yeragani et al., 2002).

A third measure, the correlation dimension D2, focuses on the system's geometric (static) structure (Elbert et al., 1994). The D2 gives information about the number of independent functional components necessary to describe the underlying system and the degree of non-linear coupling between these components (Grass-berger and Procaccia, 1983). The higher the D2 is, the more degrees of freedom of a system and, therefore, the greater the range of possible adaptive responses. However, as the D2 cannot be validly applied to non-stationary data which are typical for long epochs of biological data (e.g., ECG, electroencephalogram, EEG) the point-wise correlation dimension (PD2) is often alternatively used (Skinner et al., 1991, 1993). The PD2 is based on the presumption that the variability of a time series is determined and patterned. It provides a series of "point" dimensions irrespective of whether the system is stochastic or deterministic or is stationary in time (Nahshoni et al., 2004). Skinner et al. (1993) found in high-risk cardiac patients that PD2 reduction preceded lethal arrhythmias by hours, but was not reduced in high-risk controls having only non-sustained ventricular tachycardia. However, when the SD_{RR} was used to characterize HRV, no difference was detected between the two groups.

As yet, only a few studies have investigated the impact of acute stressors on various HR complexity measures in healthy indivi-duals. Anishchenko et al. (2001) showed in healthy young subjects that short-term psychological stress was associated with both decreases and increases in HR complexity (i.e., normalized entropy) regardless of the type of stressor (i.e., noise exposure, mental arithmetic, arithmetic against noise, and examination stress). Moreover, Hagerman et al. (1996) demonstrated in ten healthy individuals (33–51 years of age) that the dominant LLE of HR significantly decreased during exercise stress. Finally, other authors showed decreases in the fractal dimension of HR after subjects had been stressed by prolonged exercise (Nakamura et al., 1993) and orthostatic hypotension (i.e., head-up tilt and lower body negative pressure) (Butler et al., 1994). To date, no study has investigated the influence of chronic psychosocial stress on HR complexity.

In this study, we applied a dimensional complexity measure, i.e., the D2, calculated via the PD2, on HR time series and compared it with time and frequency based measures under two stress conditions: when healthy subjects report chronic stress and in response to an acute, psychologically challenging speech task stressor. This study assessed the influence of respiration rate on the associations between stress exposure (acute, chronic) and HR and HRV measures. We hypothesized that acute stress is associated with HR increases whereas chronic stress is related to HR decreases. Furthermore, we hypothesized that acute and chronic stresses are both associated with decreases in HRV, HF, RSA and D2, and with increases in LF/HF.

2. Methods

2.1. Subjects

Fifty subjects were recruited through advertisements and referral in this protocol, which was approved by the University of California, San Diego (UCSD) Institutional Review Board. Of the fifty subjects included in this study, 22 were men and 28 were women, 37 were Caucasian Americans and 13 were African Americans. Participants were between 25 and 39 years old (mean 30.32 ± 4.73) and had a body mass index (BMI) between 18 and 29 (mean 23.44 ± 2.65) with an ideal body weight between 78 and 126% (mean $101\% \pm 0.11$) as determined by Metropolitan standards. All subjects were normotensive and had blood pressures (BP) less than 140/90 mmHg based on the average of three seated BP measurements. History and physical examination verified that they were healthy subjects without illnesses that might affect ANS activity. No subject was regularly taking prescription medication and none had a history of current drug or alcohol abuse.

2.2. Combined hassles and uplifts scale

To assess chronic stress prior to stress testing we administered the combines hassles and uplift scale (CHUS, Lazarus and Folkman, 1989). We selected the hassles frequency subscale as our primary measure of this construct. This 53-item subscale determines perceived number of events over the past month. The CHUS has been shown to have good reliability and validity, predicting mood and somatic health outcomes (DeLongis et al., 1982; Zarski, 1984) as well as being somewhat related to positive and negative affect (Kanner et al., 1981).

2.3. Speech task

Cardiovascular reactivity testing was used to perturb the heart and ANS. The subjects were admitted to the General Clinical Research Center of the UCSD Medical Center the night prior to testing. Reactivity testing was performed the next morning at 9:00 a.m., following a light non-caffeine-containing breakfast. Subjects were brought to the testing laboratory, instrumented, and then allowed to sit quietly for 30 min for habituation to the instrumentation and testing environment. A 3-min baseline was determined at the end of the habituation period. After this baseline period, the subjects were given instructions for a speaking task. This task involved preparing and presenting a speech in response to one of two situations (accused of shoplifting and automobile dealer not honoring a warranty). These situations were randomly presented to the subjects. Subjects were told that this speech would be videotaped and rated by experts on poise and articulation. The video camera was displayed prominently during the procedure. Subjects were given 3 min to prepare their speech and told that the speech should cover certain points. Immediately after the preparation period, subjects spoke for 3 min. If subjects stopped talking before the end of the period, they were reminded to continue the talk by reiterating or summarizing the main points. This speech stressor has been used extensively in our laboratory and other laboratories and elicits reliable changes in the measured parameters (i.e., Nelesen et al., 1996; Hurwitz et al., 1993; Llabre et al., 1993; Bagget et al., 1996; Light et al., 1999).

2.4. Heart rate variability

Time series of the R–R interval and the HR were determined from the electrocardiogram (ECG, model 78352C; Hewlett-Packard; Andover, MA) in a lead I configuration. Respiration rate was determined by chest movement with bands wrapped around the chest and with strain wiring that went to the transducer in ECG monitor. The signals of ECG and chest movement were relayed to an analog-to-digital converter (DT2801; Data Translation; Marlboro, MA), sampling at 1 kHz per channel. Data were collected in 3-min epochs using Global Lab software (Data Translation). The review and calculation were performed using a computer program developed at University of Miami, Behavioral Medicine Research Center (Han et al., 1991; Nagel et al., 1993). This program calculated the time domain measures of HRV, i.e., the mean and the SD_{RR} as well as respiration-related (RSA) and non-respiration-related (NRSA) components of HRV. It also performed the frequency domain analyses to estimate spectral analysis of HRV. Spectral power analyses were applied on R–R interval time series to obtain HF power (>0.15 Hz) and LF power (0.05–0.15 Hz). In addition, the ratio of LF/HF components was determined.

Because the RSA is correlated with the respiration, while the NRSA is not, the two components can be separated by an adaptive filtering system. For this purpose, the instantaneous HR time series, as well as respiration, were subsampled at a 4 Hz frequency. Details of the calculation have been reported previously (Han et al., 1991; Nagel et al., 1993). In summary, adaptive filtering is a time-domain measure that permits the temporal tracking of changes in HRV. The reliability of this technique is very high and has many advantages: (1) it is free of the susceptibility for violation of stationary assumptions to which the spectral analytic frequency domain methods are subjected; (2) it extracts the variance in HR that is corresponding with the ongoing respiratory signal, and thus it is not necessary to a priori define the spectral bandwidth associated with respiration; and (3) it contains the ability to separate signal components of the HR correlated or uncorrelated with respiration.

A technician who was blinded to the subjects performed scoring of HRV and impedance cardiograph.

2.5. Estimation of the correlation dimension (D2) via calculating the pointwise correlation dimension (PD2) of the time series

The so-called correlation dimension D2 (Grassberger and Procaccia, 1983) is used to estimate the dimensional complexity or the number of the degrees of freedom of a time series. It is calculated after embedding the time series into the phase space, i.e., the time series is used to reconstruct an adequate representation of the dynamic system in the phase space. A phase space is defined as an ideal, mathematical space with one point for every possible state of the system, having as many dimensions as there are degrees of freedom in the system (Nicolis and Prigogine, 1989). In non-stationary systems, the number of coupled variables at each time-point is variable, which means that the system's trajectory occupies more or less phase space. The more phase space is occupied by the system, the higher is the dimensional complexity (Vandenhouten, 1998; Kowalik, 2003). A fast and simple method of phase space reconstruction is given by Takens (1981), which is used in the present publication.

According to Takens theorem, it is possible to construct a phase space trajectory of a system from a single scalar time series of the observable quantity $\xi_i (i = 0, \ldots, N)$ by composition of vectors with so-called delay coordinates:

$$x_i := \{\xi(i), \xi(i+\tau), \xi(i+2\tau), \ldots, \xi(i+(m-1)\tau)\} \in \mathbb{R}^m$$

with the embedding dimension $m = 2n + 1$ (with n being the degrees of freedom of the system) and the delay τ for $N \to \infty$ in the substitute phase space ($\mathbb{R}^m$) that is dynamically and topologically equivalent to the trajectory in the original phase space. In practice, infinite time series (with $N \to \infty$) are not available. Therefore, in every experimental situation the so-called embedding parameters m and τ have to be selected carefully in order to obtain an optimal reconstruction from a finite time series. In this publication, the delay τ is determined as the position of the first minimum of the first derivative of the autocorrelation function of the signal:

$$\frac{d(R_{\xi\xi}(t))}{dt}$$

which has been shown to be a good choice for the general representation of an attractor in the phase space of delay coordinates (Vandenhouten, 1998). Detailed descriptions of the embedding process and the selection of τ are given elsewhere (Lambertz et al., 2000; Vandenhouten, 1998).

The correlation dimension D2 can estimate the dimension of the trajectory in the substitute phase space, gained by the embedding of the time series. From the theoretical point of view, this is only useful if the trajectory has stationary states within the phase space. If a system changes its behavior, i.e., passing phase transitions, its trajectory can consist of combined tortuous attractors. In such situations D2 only can be usefully calculated as the mean of the different degrees of dimension in the course of time.

In order to solve the problem with non-stationary time series Skinner and co-workers (Skinner et al., 1991, 1993) developed the method of PD2. Estimating the global dimension of a time series by calculating the mean of the PD2 is done much faster than calculating it by the D2 algorithm (Skinner et al., 1998; Kowalik, 2003). In the present publication the PD2s were calculated using the Dataplore® software[1] (Vandenhouten et al., 1999) in which the algorithm is realized according to Skinner and co-workers by the formula:

$$D2(i) := \frac{d}{d[\log r]} \log \left(\frac{1}{N-1} \sum_{j=0, j \neq i}^{N-1} \theta(r - ||\hat{x}i - \hat{x}j||) \right)$$

Here r denotes the radius of a phase space neighbourhood around x. x_i and x_j are the phase space coordinates, delayed by τ (as mentioned above in the description of the

Table 1
Effect of speech task stress on heart rate and various measures of heart rate variability. Mean (±S.D.) baseline and speech task of heart rate and various measures of heart rate variability. Repeated-measures ANCOVA considering the influence of respiration rate change was used to assess the effect of speech task (F value and degrees of freedom).

	Baseline	Speech task	F (1, 45)
HR (beats/min)	74.2 ± 9.46	87.4 ± 15.32	44.259***
HR variability (SD$_{RR}$)	33.2 ± 23.83	96.0 ± 86.64	16.047***
RSA (beats/s^2)	3.3 ± 2.5	3.6 ± 2.1	0.569
LF (ms^2/Hz)	8.0 ± 5.93	19.7 ± 15.65	15.237***
HF (ms^2/Hz)	6.9 ± 4.89	15.8 ± 17.83	7.54**
LF/HF	1.5 ± 1.11	1.8 ± 1.20	0.863
D2	3.5 ± 0.27	3.2 ± 0.33	32.935***

Abbreviations: SD$_{RR}$, standard deviation of the mean R–R interval; RSA, respiratory sinus arrhythmia; LF, low frequency band power; HF, high frequency band power; D2, correlation dimension; HR, heart rate.
** $p \leq .01$ (two-tailed).
*** $p \leq .001$ (two-tailed).

phase space reconstruction). N is the length of the time series and θ is the Heaviside function, given by

$$\theta(x) = \begin{cases} 0 & if \quad x < 0 \\ 1 & if \quad x \geq 0 \end{cases}$$

For the embedding of the time series, the program needs the declaration of the values of τ and the range m_{min} to m_{max} in which the embedding dimension m is varied automatically by the algorithm during the calculation of the PD2.

The D2 values needed for further statistical comparison and evaluations in the present publication were calculated as the mean from the resulting PD2 time series ($D2 = \overline{PD2} = \overline{D2(i)}$).

2.6. Statistical analyses

Values are expressed as means ± standard deviation. This study used a natural logarithm transformation to normalize distributions of the HRV indices (LF, HF and LF/HF). Analysis of variance (ANOVA) was applied to test the effect of speech task on measures of HR and HRV. In addition, analysis of covariance (ANCOVA) for repeated measures was used to assess whether variance in respiration rate change can account for the effects of interest. Post hoc comparisons applied the Bonferroni test, a correction for the number of comparisons. The effect of speech task on respiration rate was tested via paired t test. Partial correlation was used to assess the influence of baseline respiration rate on the relationship between chronic hassles frequency and baseline measures of HR and HRV. The relationships between baseline data of HR, SD$_{RR}$, RSA, LF power, HF power, LF/HF, D2, and respiration rate were analyzed using Pearson correlation coefficients. Results were considered statistically significant when they met the $p \leq .05$ criterion; all tests were two-tailed. All statistical analyses were done using SPSS 15.0 for Windows.

3. Results

During speech task stress, mean respiration rate decreased significantly from 0.24 ± 0.07 Hz baseline to 0.19 ± 0.06 Hz (T = 3.89, d.f. = 46, $p < .001$). In Table 1, levels of the different HR indices are presented for baseline and speech task. Repeated-measures ANOVA showed that HR mean (F = 44.200, d.f. = 1, 46, $p < .001$), SD$_{RR}$

Table 2
Correlation between chronic stress and heart rate and various measures of heart rate variability. Partial correlation coefficients (n = 50) between chronic hassles frequency and baseline HR indices adjusted for baseline respiration rate.

	Chronic hassles frequency
HR (beats/min)	r = .06
HR variability (SD$_{RR}$)	r = .14
RSA (beats/s^2)	r = .11
LF (ms^2/Hz)	r = .10
HF (ms^2/Hz)	r = −.10
LF/HF	r = .17
D2	r = −.35*

Abbreviations: BL, baseline; HR, heart rate; SD$_{RR}$, standard deviation of the mean R–R interval; RSA, respiratory sinus arrhythmia; LF, low frequency band power; HF, high frequency band power; D2, correlation dimension.
* $p < .05$ (two-tailed).

(F = 23.584, d.f. = 1, 46, $p < .001$), LF power (F = 24.565, d.f. = 1, 46, $p < .001$), and HF power (F = 12.967, d.f. = 1, 46, $p = .001$) increased significantly in response to the speech task, whereas D2 decreased significantly from baseline to the stressor (F = 49.145, d.f. = 1, 46, $p < .001$). Both RSA (F = 1.96, d.f. = 1, 46, $p = .660$) and LF/HF (F = 1.587, d.f. = 1, 46, $p = .214$) remained unchanged. Moreover, repeated-measures ANCOVA showed that respiration rate was not accounting for these effects (Table 1): HR mean (F = 44.259, d.f. = 1, 45, $p < .001$); SD$_{RR}$ (F = 16.047, d.f. = 1, 45, $p < .001$); LF power (F = 15.237, d.f. = 1, 45, $p < .001$); HF power (F = 7.54, d.f. = 1, 45, $p = .009$); D2 (F = 32.935, d.f. = 1, 45, $p < .001$); RSA (F = 0.569, d.f. = 1, 45, $p = .455$); LF/HF (F = 0.863, d.f. = 1, 45, $p = .358$).

Pearson correlation showed that baseline respiration rate was not significantly associated with chronic hassle frequency (r = .001, $p = .994$). Table 2 shows the partial correlation coefficients between chronic hassles frequency and baseline HR indices adjusted for baseline respiration rate. The only baseline HR measure that was significantly correlated with chronic hassles frequency was D2 (r = −.352, $p = .019$). There was no significant correlation between chronic hassles frequency and baseline respiration rate. Moreover, chronic hassles severity correlated significantly neither with any of the baseline measures of HR and HRV adjusted for baseline respiration rate nor with respiration rate (data not shown).

Table 3 shows the Pearson correlation coefficients among the baseline HR indices and between respiration rate and baseline HR indices. HR at baseline did not correlate significantly with any of the dynamic HR indices. SD$_{RR}$ at baseline was significantly positively correlated with RSA, LF and HF band power, and was significantly negatively correlated with D2. RSA, LF and HF band power correlated significantly positively. D2 showed significantly negative correlations with SD$_{RR}$, LF band power, and the LF/HF. Baseline respiration rate was significantly negatively correlated with LF band power.

Table 3
Correlation among all indices under study. Pearson correlation coefficients (n = 50) among all baseline heart rate values and between baseline heart rate values and respiration rate.

	HR (beats/min)	HR variability (SD$_{RR}$)	RSA (beats/s^2)	LF (ms^2/Hz)	HF (ms^2/Hz)	LF/HF	D2
HR variability (SD$_{RR}$)	r = −.121						
RSA (ms^2)	r = −.147	r = .517***					
LF (ms^2/Hz)	r = .048	r = .446***	r = .036				
HF (ms^2/Hz)	r = −.101	r = .605***	r = .699***	r = .431**			
LF/HF	r = .119	r = −.108	r = −.436**	r = .524***	r = −.410**		
D2	r = −.013	r = −.504***	r = −.044	r = −.528***	r = −.150	r = −.342*	
Respiration rate (Hz)	r = .046	r = −.154	r = −.194	r = −.320*	r = −.260	r = −.022	r = .279

Abbreviations: BL, baseline; HR, heart rate; SD$_{RR}$, standard deviation of the mean R–R interval; RSA, respiratory sinus arrhythmia; LF, low frequency band power; HF, high frequency band power; D2, correlation dimension.
* $p \leq .05$ (two-tailed).
** $p \leq .01$ (two-tailed).
*** $p \leq .001$ (two-tailed).

4. Discussion

HR contains an enormous amount of information, and diverse measures of HR offer distinctly different parts of this information. Until recently, complexity analysis was very difficult to do. While it is now feasible, it is still a new and relatively unfamiliar technique because of precise time-locked acquisition of signals and complex mathematics. In this study, we compared one type of HR complexity measure, the D2 (calculated via PD2) with time domain measures (i.e., SD_{RR}, RSA) and frequency domain measures (i.e., LF, HF and LF/HF) of HRV under short-term and chronic stress. We found that under acute stress HR complexity measure D2 decreased, whereas SD_{RR}, LF, and HF increased (RSA and LF/HF remained unchanged, respiration rate decreased). In addition, we found that HR D2 was the only HRV measure which significantly correlated with chronic stress (i.e., HR complexity decrease). Respiration rate showed no influence on the reported associations between stress and the various measures of HR and HRV.

Our findings of reduced HR D2 in response to stress are in line with studies of the relationship between acute physical stress and HR complexity (Nakamura et al., 1993; Butler et al., 1994; Hagerman et al., 1996). Moreover, our findings partly confirm the Anishchenko et al. (2001) study in which a group of healthy students subjected to various kinds of psychological stress (i.e., noise exposure, mental arithmetic, arithmetic against noise, and examination stress) could be divided into two subgroups of HR complexity (i.e., normalized entropy) reactors: those with a decrease in HR complexity and those with an increase in HR complexity. Thus, this study's findings of a loss of HR D2 in response to stress are consistent with results from other studies in this research area.

What does decreased HR D2 under acute stress tell us about the underlying physiology and possible consequences of stress-mediated HRV changes? Under normal conditions, the HR generating system fluctuates between a set of metastable states or attractors ready to adapt to internal or external challenges of an ever-changing environment (Lipsitz and Goldberger, 1992; Lipsitz, 1995). The higher the HR D2, the more degrees of freedom of the cardiac pacemaker (Kresh and Izrailtyan, 1998) and, therefore, the greater range of possible adaptive responses. In our study of 50 young healthy subjects, HR D2 decreased significantly from 3.5 to 3.2 under acute stress (Table 1). This change towards more stable and periodic behavior of the HR under stress may be associated with stronger regularity, decoupling of multimodal integrated networks and deactivation of control-loops within the cardiovascular system (Pincus, 1994; Nahshoni et al., 1998, 2004). Thus, the reduction in HR complexity during stressful conditions may represent a lower adaptability and fitness of the cardiac pacemaker and a functional restriction of the participating cardiovascular elements.

The complex phenomena of HR control may represent activities of the SNS, PNS and renin-angiotensin system as well as other feedback systems, e.g., PNS/SNS feedback loop (Osaka et al., 1993). Systems may contribute differentially to HR complexity. Predominance of the SNS feedback loop is accompanied by attenuation of HR dimensionality (Elbert et al., 1994), whereas transition to a higher HRV dimension was shown to be associated with PNS accentuation (Vaughn et al., 1995). This is supported by the observation that the restoration of functional order patterning in the transplanted heart during the donor-host assimilation process can be ascribed to a long-term progressive rise from low dimensional (dimension ~1 after 2 years) sympathetic to high dimensional (dimension ~3 after 8 years) parasympathetic dominance (Kresh and Izrailtyan, 1998). In addition, pharmacological trials show that parasympathetic withdrawal through atropine is associated with a decrease in HR complexity, whereas sympathetic withdrawal through propanolol either fails to alter HR complexity or increases it (Osaka et al., 1993; Yamamoto and Hughson, 1994; Yamamoto et al., 1995; Hagerman et al., 1996). Thus, one could speculate that the decrease of HR D2 in our study in response to short-term stress is due to a "sympathovagal" imbalance characterized by a decrease in PNS activity and a (relative) increase in sympathetic tone.

However, our conclusion from non-linear mathematics is only partly supported by the other findings of this study on linear characteristics of the R–R interval time series. There was a significant increase in HR and LF power when subjects were acutely stressed, suggesting a rise in SNS activity. On the other hand, this study showed an increase in SD_{RR} and HF power under short-term stress without concurrent rise in LF/HF, reflecting an increase in PNS activity (Akselrod et al., 1981). The short-term stressor is at the limit of the stationarity assumption; thus the spectral measures might not pick up the changes appropriately. RSA, often used as an index of cardiac parasympathetic activity, however, did not change under short-term stress.

Discrepancies between non-linear and linear findings on HRV have been shown in other studies (e.g., Hagerman et al., 1996; Yeragani et al., 2002) and may be attributable to shortcomings of the linear methods. It was shown that HRV especially in the range of LF- and HF-bands is the result of complex non-linear interactions of different central and peripheral physiological oscillators (Langhorst et al., 1984; Lambertz and Langhorst, 1998; Lambertz et al., 2000). Involved in these non-linear interactions are at least three important rhythms: (1) the respiratory rhythm (originating in the respiratory oscillator neurons of the brainstem), (2) rhythms of vessels (originating in their smooth muscles), and (3) the reticular rhythm (originating in the brainstem reticular formation; frequency range: ~0.15 Hz ± 0.03 Hz). The frequencies of these rhythms and their coupling strength change in the course of time depending on the momentary activation level (e.g., relaxation vs. stress) of the organism (Perlitz et al., 2004). Coupling phenomena of the rhythms extensively exceed their own basic frequency bands because harmonics and subharmonics of each of them are widely involved, and different types of frequency- and phase couplings of the interacting rhythms can be observed (Lambertz and Langhorst, 1998; Lambertz et al., 2000; Perlitz et al., 2004). The interacting rhythms influence the processing of baroreceptor input at their relay neurons in the NTS. Thereby, baroreceptor feedback underlies these complex rhythmical changes causing non-linear rhythmical effects on HR, HRV, blood pressure, respiration and – via ascending activation – on higher brain functions (Lambertz et al., 2000; Perlitz et al., 2004).

Although spectral analyses of HRV are useful for a variety of physiological stresses, HRV changes during mental stress tests such as a speech task should be interpreted with caution as the respiratory changes produced by speech markedly alter variability and the spectral component of the RR interval time series without necessarily involving respective changes in autonomic activation (Brown et al., 1993; Hoshikawa and Yamamoto, 1997; Bernardi et al., 2000; Beda et al., 2007). Beda et al. (2007) showed that for the tasks involving speech, the respiratory pattern is far from being sinusoidal (short inspiration and longer expiration) and is highly erratic. This pattern is associated with markedly broadband characteristics in HR power spectrum, and with considerable power present in both the LF and HF bands. Moreover, Bernardi et al. (2000) demonstrated that free talking and, in particular, doing stressful mental arithmetics aloud were associated with a slowing in respiratory rate and a relative reduction in ventilation, with a concomitant shift of respiratory power into the LF band, decrease in RR interval mean, and increase in SD_{RR}. Such evidence on the influence of speech-related respiratory patterns on linear HRV measures could explain why in our study speech task stress

was associated with increases and not with decreases in SD_{RR} and HF power, independently of changes in parasympathetic modulation of HR.

In our study, speech task stress was associated with a decrease in respiration rate which may have been due to the vocal nature of the stress task (Bernardi et al., 2000). Moreover, the observed change in respiration frequency did not interfere with the associations between speech task stressor and the diverse measures of HR and HRV. This observation runs counter to the assumption that speech task-related respiration could have been due to the discrepancies between non-linear and linear findings on HRV in our study. However, given the high variability and complexity of the respiratory patterns during speech (Beda et al., 2007), it is possible that additional indices associated with the speech task which were not assessed in this study (e.g., respiratory depth, central respiratory drive and metabolic demand) may have influenced the stress-mediated HRV changes and masked or accentuated the relative contribution of SNS and PNS to these changes.

Regarding HR D2 and its relationship to stress, it might be that the vocal nature of the speech task did not influence the non-linear HRV changes to the same extent as the linear HRV changes. Kanters et al. (1997) showed that HR D2 and the non-linear predictability of HR remained unchanged during forced respiration.

Our findings on the association between chronic stress (i.e., frequency of hassles in the past month) and various HRV measures further support the assumption that D2 expresses properties not captured by the orthodox linear methods of HRV analysis (Nahshoni et al., 1998). HR D2 was the only variable which was significantly correlated with chronic stress (Table 2). In addition, HR D2 was negatively correlated with many of the linear measures of HRV which, for the most part, were positively correlated with each other (Table 3).

The finding of a decreased HR D2 in association with chronic stress has clinical relevance, as cardiovascular disease is associated with decreased HR complexity (Lipsitz, 2004). More irregular HRV may reflect the greater ability of HR to return to baseline condition after it has been perturbed (Yamamoto et al., 1995). In addition, HRV reflects not only respiratory influences but also regulatory influences on HR, e.g., when blood pressure is changed (Hoshikawa and Yamamoto, 1997). Thus, chronically reduced HR complexity due to stress may be associated with a chronic failure of the HR to return to baseline condition after perturbation and a chronically reduced ability to respond with HR reduction when blood pressure is increased. In this respect, chronically stressed people behave like aged people. There is evidence that healthy aging is associated with a decline in the complexity of sinus rhythm HR dynamics (Lipsitz, 1995), due to structural factors (e.g., loss of sinoatrial pacemaker cells) and functional changes (e.g., altered coupling between these components) (Lipsitz and Goldberger, 1992). It may be that chronic stress, like chronic depression (Yeragani et al., 2002), aggravates this normal ANS aging process.

This study has some limitations. We only assessed the influence of respiratory frequency on the relation between stress and linear and non-linear measures of HRV because of the nature of the respiratory signal processing applied in this study. Future studies may also wish to examine the interesting question whether the relation between stress and HR D2 is influenced by respiratory D2. The current study did not assess the influence of respiratory indices other than respiratory frequency (such as respiratory depth and central respiratory drive) on the effects of interest. In further studies one could consider the metabolic demand of speaking by applying a control speech task, in which individuals speak for the same amount of time, but on an emotionally neutral topic without the stress of subsequent evaluation. Our findings cannot be generalized to acute stressors

other than the speech task or to complexity measures other than D2. Hassles frequency correlated negatively with HR D2; but hassles severity did not correlate with any HRV measure. This could be because subjective reports of severity generally show weaker correlation with physiological data than do self-reports of event frequency (Herbert and Cohen, 1993). Other approaches to chronic and acute stressors, which deal more adequately with the personal meaning of stress (e.g., Brown and Harris, 1989; Schubert et al., 2003), could be more appropriate.

Further studies could apply larger sample size and a "toolkit" of various non-linear metrics to probe different stress-related aspects of HR complexity (Goldberger et al., 2002). Such investigations could be accomplished on healthy individuals as well as on patients suffering from various pathophysiologic conditions characterized, for example, by imbalance of autonomic innervation (e.g., obesity and post-traumatic stress disorder).

In conclusion, there is increasing recognition that quantification and interpretation of HRV in adaptation to external challenges depend on an adequate appreciation of both linear as well as non-linear characteristics. This study compared the influences of short-term and chronic stress on various time, frequency, and phase domain measures of HRV and showed that only HR D2 correlated consistently (negatively) with both types of stressors. These findings provide further evidence that stress-induced change in cardiac pacemaker functioning is more irregular than can be revealed by applying conventional linear measures of HR.

References

Akselrod, S., Gordon, D., Ubel, F.A., Shannon, D.C., Berger, A.C., Cohen, R.J., 1981. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 213, 220–222.

Anishchenko, V.S., Igosheva, N.B., Pavlov, A.N., Khovanov, A., Yakusheva, T.A., 2001. Comparative analysis of methods for classifying the cardiovascular system's states under stress. Critical Reviews™ in Biomedical Engineering 29, 462–481.

Bagget, H.L., Saab, P.G., Carver, C.S., 1996. Appraisal, coping, task performance, and cardiovascular responses during the evaluated speaking task. Personality and Social Psychology Bulletin 22, 483–494.

Beckers, F., Verheyden, B., Aubert, A.E., 2006. Aging and nonlinear heart rate control in a healthy population. American Journal of Physiology-Heart and Circulatory Physiology 290 (December 22), H2560–H2570 (Epub 2005).

Beda, A., Jandre, F.C., Phillips, D.I., Giannella-Neto, A., Simpson, D.M., 2007. Heart-rate and blood-pressure variability during psychophysiological tasks involving speech: influence of respiration. Psychophysiology 44 (July 20), 767–778 (Epub 2007).

Bernardi, L., Wdowczyk-Szulc, J., Valenti, C., Castoldi, S., Passino, C., Spadacini, G., Sleight, P., 2000. Effects of controlled breathing, mental activity and mental stress with or without verbalization on heart rate variability. Journal of the American College of Cardiology 35, 1462–1469.

Berntson, G.G., Bigger Jr., J.T., Eckberg, D.L., Grossman, P., Kaufmann, P.G., Malik, M., Nagaraja, H.N., Porges, S.W., Saul, J.P., Stone, P.H., van der Molen, M.W., 1997. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 34, 623–648.

Boutcher, S.H., Stocker, D., 1996. Cardiovascular response of young and older males to mental challenge. Journals of Gerontology Series B: Psychological Sciences and Social Sciences 51, P261–267.

Brown, T.E., Beightol, L.A., Koh, J., Eckberg, D.L., 1993. Important influence of respiration on human R–R interval power spectra is largely ignored. Journal of Applied Physiology 75, 2310–2317.

Brown, G.W., Harris, T.O., 1989. Life Events and Illness. Guilford Press, New York.

Butler, G.C., Yamamoto, Y., Hughson, R.L., 1994. Fractal nature of short-term systolic BP and HR variability during lower body negative pressure. American Journal of Physiology 267 (1 Pt. 2), R26–33.

De Geus, E.J., van Doornen, L.J., de Visser, D.C., Orlebeke, J.F., 1990. Existing and training induced differences in aerobic fitness: their relationship to physiological response patterns during different types of stress. Psychophysiology 27, 457–478.

DeLongis, A., Coyne, J.C., Dakof, G., Folkman, S., Lazarus, R.S., 1982. Relationship of daily hassles, uplifts, and major life events to health status. Health Psychology 1, 119–136.

Denton, T.A., Diamond, G.A., Helfant, R.H., Khan, S., Karagueuzian, H., 1990. Fascinating rhythm: a primer on chaos theory and its application to cardiology. American Heart Journal 120, 1419–1440.

Eckberg, D.L., 1997. Sympathovagal balance: a critical appraisal. Circulation 96, 3224–3232.

Elbert, T., Ray, W.J., Kowalik, Z.J., Skinner, J.E., Graf, K.E., Birbaumer, N., 1994. Chaos and physiology: deterministic chaos in excitable cell assemblies. Physiological Reviews 74, 1–47.

Furlan, R., Barbic, F., Piazza, S., Tinelli, M., Seghizzi, P., Malliani, A., 2000. Modifications of cardiac autonomic profile associated with a shift schedule of work. Circulation 102, 1912–1916.

Goldberger, A.L., Peng, C.K., Lipsitz, L.A., 2002. What is physiologic complexity and how does it change with aging and disease? Neurobiology of Aging 23, 23–26.

Gorman, J.M., Sloan, R.P., 2000. Heart rate variability in depressive and anxiety disorders. American Heart Journal 140 (Suppl. 4), 77–83.

Grassberger, P., Procaccia, I., 1983. Measuring the strangeness of strange attractors. Physica D9, 189–208.

Grasso, R., Schena, F., Gulli, G., Cevese, A., 1997. Does low-frequency variability of heart period reflect a specific parasympathetic mechanism? Journal of the Autonomic Nervous System 63, 30–38.

Hagerman, I., Berglund, M., Lorin, M., Nowak, J., Sylven, C., 1996. Chaos-related deterministic regulation of heart rate variability in time- and frequency domains: effects of autonomic blockade and exercise. Cardiovascular Research 31, 410–418.

Han, K., Nagel, J.H., Hurwitz, B.E., Schneiderman, N., 1991. Decomposition of heart rate variability by adaptive filtering for estimation of cardiac vagal tone. In: Nagel, J.H., Smith, W.M. (Eds.), Bioelectric Phenomena, Electrocardiography, Electromagnetic Interactions, Neuromuscular Systems, vol. 12IEEE Publishing Services, New York, pp. 660–661 (No. 2).

Herbert, T.B., Cohen, S., 1993. Stress and immunity in humans: a meta-analytic review. Psychosomatic Medicine 55, 364–379.

Hoshikawa, Y., Yamamoto, Y., 1997. Effects of Stroop color-word conflict test on the autonomic nervous system responses. American Journal of Physiology 272 (3 Pt. 2), H1113–H1121.

Houtveen, J.H., Rietveld, S., de Geus, E.J., 2002. Contribution of tonic vagal modulation of heart rate, central respiratory drive, respiratory depth, and respiratory frequency to respiratory sinus arrhythmia during mental stress and physical exercise. Psychophysiology 39, 427–436.

Hurwitz, B.E., Nelesen, R.A., Saab, P.G., Nagel, J.H., Spitzer, S.B., Gellman, M.D., McCabe, P.M., Phillips, D.J., Schneiderman, N., 1993. Differential patterns of dynamic cardiovascular regulation as a function of task. Biological Psychology 36, 75–95.

Kanner, A.D., Coyne, J.C., Schaefer, C., Lazarus, R.S., 1981. Comparison of two modes of stress measurement: daily hassles and uplifts versus major life events. Journal of Behavioral Medicine 4, 1–39.

Kanters, J.K., Hojgaard, M.V., Agner, E., Holstein-Rathlou, N.H., 1997. Influence of forced respiration on nonlinear dynamics in heart rate variability. American Journal of Physiology 272 (4 Pt. 2), R1149–1154.

Kobayashi, M., Musha, T., 1982. 1/f fluctuation of heartbeat period. IEEE Transactions on Biomedical Engineering 29, 456–457.

Koepchen, H.P., 1991. Physiology of rhythms and control systems: an integrative approach. In: Haken, H., Koepchen, H.P. (Eds.), Springer Series in Synergetics. Rhythms in Physiological Systems, vol. 55. Springer–Verlag, Berlin, Heidelberg, pp. 3–20.

Kowalik, Z.J., 2003. Biomedizinische Zeitreihen und Nichtlineare Dynamik. LIT Verlag, Münster, Hamburg, London.

Kresh, J.Y., Izrailtyan, I., 1998. Evolution in functional complexity of heart rate dynamics: a measure of cardiac allograft adaptability. American Journal of Physiology 275 (3 Pt. 2), R720–727.

Lambertz, M., Langhorst, P., 1998. Simultaneous changes of rhythmic organization in brainstem neurons, respiration, cardiovascular system and EEG between 0.05 Hz and 0.5 Hz. Journal of the Autonomic Nervous System 68, 58–77.

Lambertz, M., Vandenhouten, R., Grebe, R., Langhorst, P., 2000. Phase transitions in the common brainstem and related systems investigated by nonstationary time series analysis. Journal of the Autonomic Nervous System 78, 141–157.

Langhorst, P., Schulz, G., Lambertz, M., 1984. Oscillating neuronal network of the "common brainstem system". In: Miyakawa, K., Koepchen, H.P., Polosa, C. (Eds.), Mechanisms of Blood Pressure Waves. Japan Science Society Press/ Springer Verlag, Tokyo/Berlin, pp. 257–275.

Lazarus, R.S., Folkman, S., 1989. Hassles and Uplifts Scales: Manual (Research Edition). Palo Alto, CA.

Light, K.C., Girdler, S.S., Sherwood, A., Bragdon, E.E., Brownley, K.A., West, S.G., Hinderliter, A.L., 1999. High stress responsivity predicts later blood pressure only in combination with positive family history and high life stress. Hypertension 33, 1458–1464.

Lipsitz, L.A., 1995. Age-related changes in the "complexity" of cardiovascular dynamics: a potential marker of vulnerability to disease. Chaos 5, 102–109.

Lipsitz, L.A., 2004. Physiological complexity, aging, and the path to frailty. Science of Aging Knowledge Environment 2004, pe16.

Lipsitz, L.A., Goldberger, A.L., 1992. Loss of 'complexity' and aging. Potential applications of fractals and chaos theory to senescence. The Journal of the American Medical Association 267, 1806–1809.

Llabre, M.M., Saab, P.G., Hurwitz, B.E., Schneiderman, N., Frame, C.A., Spitzer, S., Phillips, D., 1993. The stability of cardiovascular parameters under different behavioral challenges: one-year follow-up. International Journal of Psychophysiology 14, 241–248.

Lucini, D., Di Fede, G., Parati, G., Pagani, M., 2005. Impact of chronic psychosocial stress on autonomic cardiovascular regulation in otherwise healthy subjects. Hypertension 46 (October 3), 1201–1206 (Epub 2005).

Mäkikallio, T.H., Seppanen, T., Niemela, M., Airaksinen, K.E., Tulppo, M., Huikuri, H.V., 1996. Abnormalities in beat to beat complexity of heart rate dynamics in patients with a previous myocardial infarction. Journal of the American College of Cardiology 28, 1005–1011.

Malliani, A., Pagani, M., Lombardi, F., Cerutti, S., 1991. Cardiovascular neural regulation explored in the frequency domain. Circulation 84, 482–492.

Moss, G.E., 1973. Illness, Immunity and Social Interactions: The Dynamics of Biosocial Resonation. John Wiley and Sons, New York.

Nagel, J.H., Han, K., Hurwitz, B.E., Schneiderman, N., 1993. Assessment and diagnostic applications of heart rate variability. Biomedical Engineering-Applications, Basis and Communications 5, 147–158.

Nahshoni, E., Adler, E., Laniado, S., Keren, G., 1998. Fractal organization of the pointwise correlation dimension of the heart rate. Medical Hypotheses 51, 367–376.

Nahshoni, E., Aizenberg, D., Sigler, M., Strasberg, B., Zalsman, G., Imbar, S., Adler, E., Weizman, A., 2004. Heart rate variability increases in elderly depressed patients who respond to electroconvulsive therapy. Journal of Psychosomatic Research 56, 89–94.

Nakamura, Y., Yamamoto, Y., Muraoka, I., 1993. Autonomic control of heart rate during physical exercise and fractal dimension of heart rate variability. Journal of Applied Physiology 74, 875–881.

Nelesen, R.A., Dimsdale, J.E., Mills, P.J., Clausen, J.L., Ziegler, M.G., Ancoli-Israel, S., 1996. Altered cardiac contractility in sleep apnea. Sleep 19, 139–144.

Nicolis, G., Prigogine, I., 1989. Exploring Complexity. W.H. Freeman and Co. Ltd., San Francisco.

Osaka, M., Saitoh, H., Atarashi, H., Hayakawa, H., 1993. Correlation dimension of heart rate variability: a new index of human autonomic function. Frontiers of Medical and Biological Engineering 5, 289–300.

Pagani, M., Lombardi, F., Guazzetti, S., Rimordi, O., Furlan, R., Pizzinelli, P., Sandrone, G., Malfatto, G., Dell'Orto, S., Piccaluga, E., 1986. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circulation Research 59, 178–193.

Pagani, M., Montano, N., Porta, A., Malliani, A., Abboud, F.M., Birkett, C., Somers, V.K., 1997. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. Circulation 95, 1441–1448.

Perlitz, V., Lambertz, M., Cotuk, B., Grebe, R., Vandenhouten, R., Flatten, G., Petzold, E.R., Schmid-Schönbein, H., Langhorst, P., 2004. Cardiovascular rhythms in the 0.15 Hz band: common origin of identical phenomena in man and dog in the reticular formation of the brain stem? Pflügers Archiv – European Journal of Physiology 448, 579–591.

Piccirillo, G., Elvira, S., Bucca, C., Viola, E., Cacciafesta, M., Marigliano, V., 1997. Abnormal passive head-up tilt test in subjects with symptoms of anxiety power spectral analysis study of heart rate and blood pressure. International Journal of Cardiology 60, 121–131.

Pincus, S.M., 1991. Approximate entropy as a measure of system complexity. In: Proceedings of the National Academy of Sciences of the United States of America, vol. 88. pp. 2297–2301.

Pincus, S.M., 1994. Greater signal regularity may indicate increased system isolation. Mathematical Biosciences 122, 161–181.

Pincus, S.M., 2001. Assessing serial irregularity and its implications for health. Annals of the New York Academy of Sciences 954, 245–267.

Rozanski, A., Kubzansky, L.D., 2005. Psychologic functioning and physical health: a paradigm of flexibility. Psychosomatic Medicine 67 (Suppl. 1), S47–53.

Ruelle, D., 1979. Analyticity properties of the characteristic exponents of random matrix products. Advances in Mathematics 32, 68–80.

Schubert, C., Lampe, A., Geser, W., Noisternig, B., Fuchs, D., König, P., Chamson, E., Schüßler, G., 2003. Daily psychosocial stressors and cyclic response patterns in urine cortisol and neopterin in a patient with systemic lupus erythematosus. Psychoneuroendocrinology 28, 459–473.

Selye, H., 1956. The Stress of Life. McGraw-Hill, New York.

Skinner, J.E., Carpeggiani, C., Landisman, C.E., Fulton, K.W., 1991. The correlation-dimension of heartbeat intervals is reduced in conscious pigs by myocardial ischemia. Circulation Research 68, 966–976.

Skinner, J.E., Pratt, M., Vybiral, T., 1993. A reduction in the correlation dimension of heartbeat intervals precedes imminent ventricular fibrillation in human subjects. American Heart Journal 125, 731–743.

Skinner, J.E., Zebrowski, J.J., Kowalik, Z.J., 1998. New algorithms for analysis of heart rate variability: low-dimensional chaos predicts lethal arrhythmias. In: Kantz, H., Kurths, J., Mayer-Kress, G. (Eds.), Nonlinear Analysis of Physiological Data. Springer–Verlag, Berlin, Heidelberg, New York, pp. 129–166.

Takens, F., 1981. Detecting strange attractors in turbulence. In: Rand, D., Young, L.S. (Eds.), Dynamical Systems and Turbulence Vol. 898 of Lecture Notes in Mathematics. Springer–Verlag, Berlin, pp. 366–381.

Task force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 93, 1043–1065.

Vandenhouten, R., 1998. Analyse instationärer Zeitreihen komplexer Systeme und Anwendungen in der Physiologie. Dissertation, Shaker, RWTH Aachen.

Vandenhouten, R., Rasche, M., Parotat, E., Lenz, A., Fluck, M., 1999. Dataplore, a Professional Environment for Time Series and Signal Analysis

(Manual). ixellence GmbH Bahnhofstrasse, Halle VII, 15745 Wildau, Germany.

Vaughn, B.V., Quint, S.R., Messenheimer, J.A., Robertson, K.R., 1995. Heart period variability in sleep. Electroencephalography and Clinical Neurophysiology 94, 155–162.

Waldstein, S.R., Neumann, S.A., Burns, H.O., Maier, K.J., 1998. Role-played inter-personal interaction: ecological validity and cardiovascular reactivity. Annals of Behavioral Medicine 20, 302–309.

Weinberger, M., Hiner, S.L., Tierney, W.M., 1987. In support of hassles as a measure of stress in predicting health outcomes. Journal of Behavioral Medicine 10, 19–31.

Yamamoto, Y., Hughson, R.L., 1994. On the fractal nature of heart rate variability in humans: effects of data length and beta-adrenergic blockade. American Journal of Physiology 266 (1 Pt. 2), R40–49.

Yamamoto, Y., Nakamura, Y., Sato, H., Yamamoto, M., Kato, K., Hughson, R.L., 1995. On the fractal nature of heart rate variability in humans: effects of vagal blockade. American Journal of Physiology 269 (4 Pt. 2), R830–837.

Yeragani, V.K., Rao, K.A., Smitha, M.R., Pohl, R.B., Balon, R., Srinivasan, K., 2002. Diminished chaos of heart rate time series in patients with major depression. Biological Psychiatry 51, 733–744.

Zarski, J.J., 1984. Hassles and health: a replication. Health Psychology 3, 243–251.