Scale-Independent Measures and Pathologic Cardiac Dynamics

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We study several *scale-independent* measures of cardiac interbeat interval dynamics defined through the application of the wavelet transform. We test their performance in detecting heart disease using a database consisting of records of interbeat intervals for a group of healthy individuals and subjects with congestive heart failure. We find that *scale-independent* measures effectively distinguish healthy from pathologic behavior and propose a new two-variable scale-independent measure that could be clinically useful. We compare the performance of a recently proposed scale-dependent measure and find that the results depend on the database analyzed and on the analyzing wavelet. [S0031-9007(98)07110-5]

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The regulation of the cardiac rhythm is a highly complex process [1,2]. Such complexity manifests itself through the nonstationarity and nonlinearity of interbeat interval sequences. The study of the statistical properties of these interbeat interval sequences has attracted the attention of researchers in a wide range of fields [3–10]. The goal of many of these studies is to uncover statistical quantities that (i) will enable the identification of the mechanism (or class of mechanisms) responsible for the scaling properties of the fluctuations in the cardiac rhythm, and (ii) will provide means of diagnosis and prognosis of heart disease.

Here we study the effectiveness of scale-independent measures—the exponents characterizing the scaling of the partition function of the wavelet coefficients of the heartbeat records with the wavelet scale a—in distinguishing healthy cardiac dynamics from interbeat interval dynamics in congestive heart failure. We compare the performance of these *scale-independent* measures with the performance of a *scale-dependent* measure [8]. Some pathological conditions may alter the statistical characteristics of cardiac dynamics at a specific scale or range of scales [10]. In such cases, scale-dependent measures may be fruitfully used by selecting the adequate temporal scale. However, we show that if not properly selected, *scale-dependent* measures may reflect characteristics specific to the subject or to the method of analysis instead of universal, subject-independent characteristics.

The nonstationary character of interbeat interval records for healthy or sick subjects requires the application of methods that can appropriately treat such nonstationarities. Recent studies show that the wavelet transform [11–16] can remove effects due to nonstationarities present in physiological time series [7–10,12–16]. The coefficients of the discrete wavelet transform are defined as

$$W_a(n) \equiv a^{-1} \sum_{i=1}^{M} t_i \psi((i - n)/a). \qquad (1)$$

Here t_i is the interval between beats i and $i + 1$, ψ is the generating wavelet, a is the scale of the wavelet, M is the number of points in the time series, and n is the beat for which the coefficient is calculated. For a fractal signal, the sum Z_q of the qth moments of the coefficients of the wavelet transform scale as [15–17]

$$Z_q(a) \equiv \sum_i |W_a(i)|^q \sim a^{\tau(q)}, \qquad (2)$$

where the sum is only over the maxima of $|W_a|$. In analogy with what occurs in scale-free physical systems, in which phenomena described at a coarse-grained level by the same mechanisms are characterized by the same scaling exponents, we assume that the scale-independent measures, $\tau(q)$, depend only on the underlying mechanisms of heart rate regulation. Hence, the exponents $\tau(q)$ should take roughly the same values for healthy individuals [19]. On the other hand, we expect major changes in the mechanisms of heart rate regulation due to pathological conditions, such as congestive heart failure, to lead to changes in the values of the exponents (see Fig. 1). These assumptions are supported by previous studies [6] and by our findings.

We analyze a standard database containing 24 h records of interbeat intervals (corresponding to approximately 10^5 beats) for 18 healthy subjects and 12 heart failure subjects [9]. As the analyzing wavelet, we use the third derivative of the Gaussian [15,16,18]. Nocturnal records are likely to be less affected by the influence of different activity levels, and there is evidence that some statistical properties are different for diurnal and nocturnal sequences of healthy subjects [7,10]. Hence, we analyze the nocturnal fraction of each of the records—corresponding to the 6 h from midnight to 6 a.m., or approximately 20 000 beats—instead of the mixture of diurnal and nocturnal records [8]. To further test the performance of the methods studied, we divide every record into subrecords of length 5000 beats ($N = 75$ healthy subrecords, and $N = 48$ heart failure subrecords).

Since the important information regarding the dynamics is contained in the value of the exponents from the power

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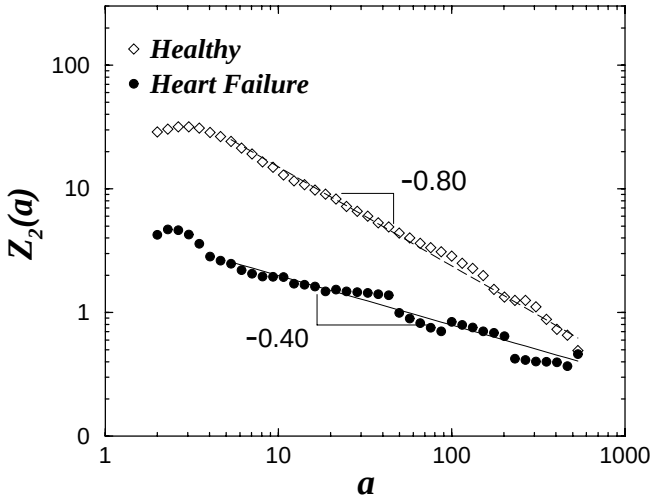

FIG. 1. Log-log plot of the dependence of $Z_2(a)$ on scale a for a healthy individual and a subject with congestive heart failure. Good power law scaling is observed for scales $a > 5$. Note that the exponent $\tau(q = 2)$ of the power law is significantly different for the two cases: $\tau(q = 2) = -0.80 \pm 0.05$ for the healthy record, and $\tau(q = 2) = -0.40 \pm 0.05$ for the congestive heart failure record. The results obtained for $Z_2(a)$ are consistent with results obtained in Ref. [6] through a detrended fluctuation analysis (DFA). The exponent α of the DFA is equal to $[\tau(q = 2) + 3]/2$ [6]. Our independent estimates of $\alpha \approx 1.1$ for healthy records and $\alpha \approx 1.3$ for congestive heart failure are in agreement with the results of [6].

law scaling of Z_q, we calculate the exponents from least squares fits of the empirical data. We find that the best separation between the healthy and heart failure groups is obtained for $q = 2$ and 5. Table I shows the average value of the exponents for the healthy and heart failure groups. We perform a Student's t-test and verify that the differences between the mean values are statistically significant [20]. Figure 2a shows the values of the exponents for each of the subrecords in the database [9]. The robust degree of separation between the two groups suggests that our results might have a potential clinical application (see also Ref. [21] for further applications of scale-independent measures).

We quantify the performance of the different methods using two measures. First, we consider for the two groups of subrecords the ratio η

$$\eta \equiv \frac{(\mu_{\rm H} - \mu_{\rm CHF})^2}{\sigma_{\rm H}^2 + \sigma_{\rm CHF}^2}, \tag{3}$$

where $\mu_{\rm H}$ and $\mu_{\rm CHF}$ are the means of the scaling exponents of, respectively, healthy and congestive heart failure cases, and $\sigma_{\rm H}$ and $\sigma_{\rm CHF}$ are the respective standard deviations. For a good separation between the values of the measure for the two cases—difference in means much larger than standard deviations—$\eta \gg 1$. Next, we consider the "statistical distance" from the means of the "boundary" that minimizes incorrect classification for both groups [22]

$$d^2 = \left(\frac{\mu_{\rm H} - \frac{\sigma_{\rm H} * \mu_{\rm CHF} + \sigma_{\rm CHF} * \mu_{\rm H}}{\sigma_{\rm H} + \sigma_{\rm CHF}}}{\sigma_{\rm H}} \right)^2. \tag{4}$$

Table II shows the values of η and d^2 for the methods considered. The best discrimination is obtained for $\tau(q = 2)$.

We next ask if we can improve discrimination by using multivariate measures. Figure 3 shows a scatter plot in the phase space $(\tau(q = 2),\ \tau(q = 5))$ for the subrecords in the database. Clear separation between healthy and heart failure subjects is apparent. An estimate of the performance of the two-variable measure leads to $\eta = 4.19$ [23], which is the highest value of the four methods discussed here (Table I).

Next we compare the performance of our scale-independent method with the scale-dependent measure of Ref. [8], which appears to perfectly classify every subject in an older version ($N = 27$ subjects) of the standard database [9] as either belonging to a healthy group or to a heart failure group. Reference [8] studies the variance of the coefficients of the wavelet transform

$$\sigma_{\rm wav}^2(a) \equiv \frac{a}{M} \sum_{j=1}^{M/a} [\tilde{W}_a(j) - \langle \tilde{W}_a(j) \rangle]^2. \tag{5}$$

Here $\langle \cdots \rangle$ represents a time average, and $W_a(j) \equiv a^{1/2} W(ja)$ [24]. The variance $\sigma_{\rm wav}^2$ is related to the partition function Z_2. Note that (i) there is no normalization by the number of coefficients taken in the calculation of the partition function Z_2 [15,16], and (ii) the average value of the coefficients of the wavelet transform $\langle \tilde{W}_a(j) \rangle$ is approximately zero, so we can write

$$\sigma_{\rm wav}^2(a) \sim a^2 Z_2(a). \tag{6}$$

From (6) it follows that

$$\sigma_{\rm wav}^2(a) \sim a^{\gamma}, \tag{7}$$

with $\gamma = 2 + \tau(q = 2)$.

Reference [8] reports that the values of $\sigma_{\rm wav}^2$ separate into two nonoverlapping groups for a limited range of scales, 16–32 beats. Figure 2d shows the values of $-\log \sigma_{\rm wav}^2(a = 24)$ for all the subrecords in the database [9], and we note that the claim of Ref. [8] does not hold. Furthermore, comparison of the values of η (Table II suggests that the scale-independent methods presented

TABLE I. Average and standard error of our estimates of the exponents $\tau(q = 2)$, $\tau(q = 5)$, and γ, and of the scale-dependent measure $-\log \sigma_{\rm wav}^2(a = 24)$ for the healthy ($N = 75$ datasets) and heart failure ($N = 48$ datasets) groups in nocturnal conditions for subrecords 5000 beats long. A Student's t-test indicates that the differences in the means for healthy vs heart failure for a given measure are significant to the $p < 10^{-8}$ level [20].

	Healthy	Heart failure
$\tau(q = 2)$	-0.71 ± 0.01	-0.36 ± 0.03
$\tau(q = 5)$	-0.45 ± 0.03	-0.09 ± 0.04
γ	1.37 ± 0.02	1.76 ± 0.03
$-\log \sigma_{\rm wav}^2(a = 24)$	1.59 ± 0.03	2.15 ± 0.05

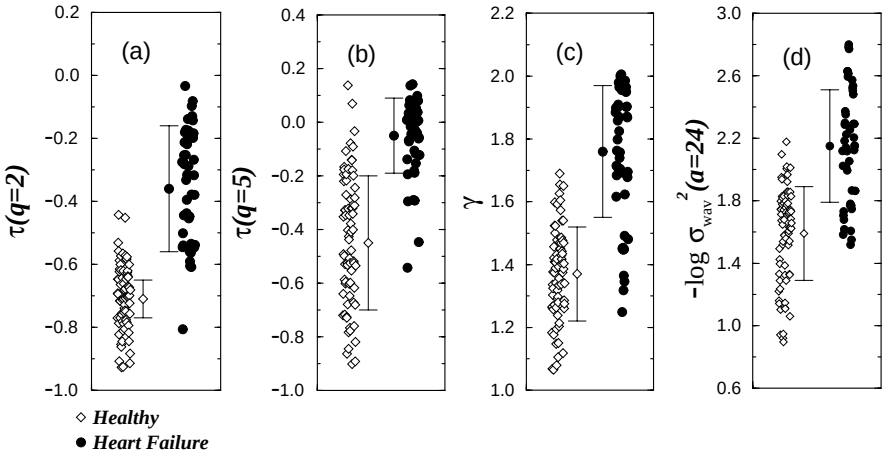

FIG. 2. (a) Exponent $\tau(q = 2)$ calculated from the nocturnal subrecords in the standard database 9 by least squares fits to a linear dependence of $\log Z_2$ on $\log a$. (b) Exponent $\tau(q = 5)$ calculated from the nocturnal subrecords in the database by least squares fits to a linear dependence of $\log Z_5$ on $\log a$. (c) Exponent γ calculated from the nocturnal subrecords in the database by least squares fits to a linear dependence of σ^2_{wav} on $\log a$. All estimates of the exponents were obtained from fits to scales $a > 8$. (d) Values of $-\log \sigma^2_{\mathrm{wav}}(a = 24)$ for the nocturnal subrecords in the database. We also show in the figures the average values and standard deviations of the exponents for the two groups (Table I). Table II compares the performance of the different methods.

here provide better discrimination of healthy from heart failure than the scale-dependent method of Ref. [8].

Finally, we test the two crucial assumptions of the method of Ref. [8] by asking the questions: Does the range of scales where good discrimination is found depend on (i) the *particular* group of subjects considered and (ii) on the analyzing wavelet? To test (i), we study the night-time records in the database with the Haar wavelet (used in [8]). As shown in Fig. 4a, we find that there is *no* range of scales for which there is absolute separation between the two groups. To test (ii), we study the same records but use the third derivative of the Gaussian as the analyzing wavelet (Fig. 4b). It is clear that there is *no* single scale for which the healthy and heart failure groups are clearly separated. These results suggest that the method reported in Ref. [8] is sensitive to aspects that are *particular* to a training set of subjects and to a particular analyzing wavelet.

The ambiguity regarding the appropriate range of scales for which discrimination between healthy and pathological groups is optimized highlights an important problem with such an analysis: The values of σ^2_{wav} or Z_q at particular scales are importantly influenced by factors that are *particular* to each individual rather than with "*universal*" scaling behavior due to the dynamics of cardiac rhythm regulation. On the other hand, the results of Figs. 2 and 3 suggest that measures which probe universal aspects of the dynamics of heart beat regulation can perform well without the ambiguity of such scale-dependent measures based on nonuniversal aspects of the dynamics. Moreover, since scale-independent measures—the exponents—do not require a specific range of scales to be set, we might expect

TABLE II. Comparison of the performance of the different one-variable measures discussed in the text. The larger the value of η or d^2 the better the discrimination provided by the method; see Eqs.(3) and (4).

	Group	μ	σ	η	d^2
$\tau(q = 2)$	Healthy	−0.71	0.06		
	Heart failure	−0.36	0.20	2.81	1.81
$\tau(q = 5)$	Healthy	−0.45	0.25		
	Heart failure	−0.05	0.14	1.95	1.05
γ	Healthy	1.37	0.15		
	Heart failure	1.76	0.21	2.28	1.17
$-\log \sigma^2_{\mathrm{wav}}(a = 24)$	Healthy	1.59	0.30		
	Heart failure	2.15	0.36	1.43	0.72

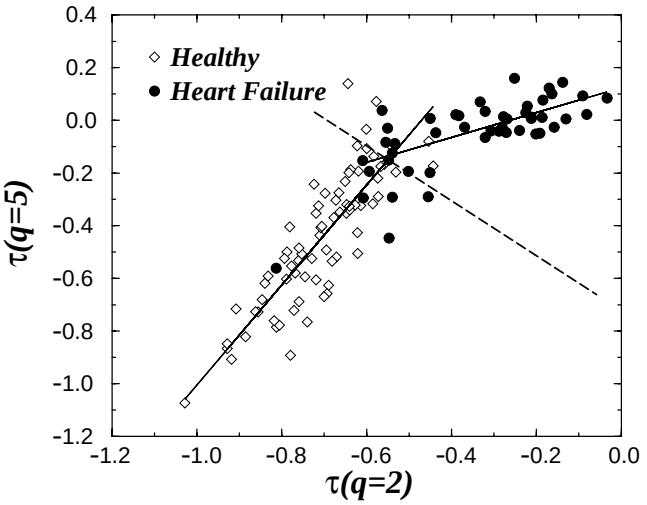

FIG. 3. Two-variable measure for detection of healthy and heart failure subrecords. We define a two-dimensional space to characterize the interbeat interval subrecords of individuals. The coordinates of this space are $\tau(q = 2)$ and $\tau(q = 5)$. The continuous lines shown quantify the linear correlations between the values of $\tau(q = 2)$ and $\tau(q = 5)$ for the two groups. The dashed line, which bisects the two linear fits, provides good separation between healthy and heart failure subrecords.

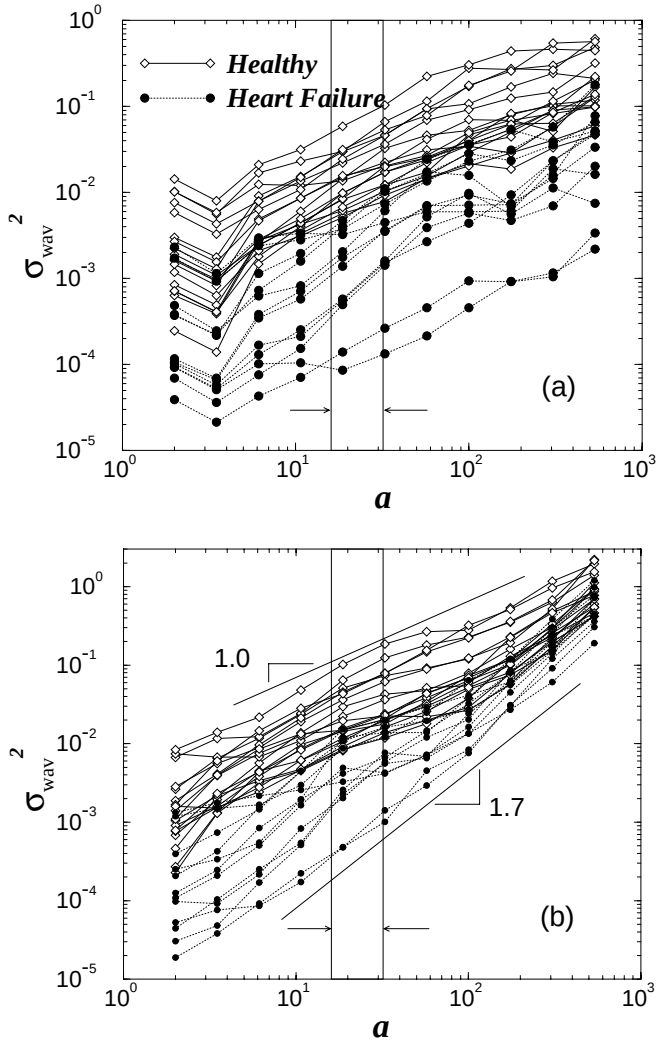

FIG. 4. (a) Test of the results of Ref. [8] for the database [9], using the Haar wavelet. The arrows indicate the range of scales identified in [8] as providing "100% accuracy" in separating the healthy and heart failure groups. However, we find overlap between healthy and heart failure groups when the database is expanded to include more subjects. (b) Log-log plot of $\sigma^2_{\rm wav}$ vs scale a for the same subjects, using the third derivative of the Gaussian as the analyzing wavelet. It is visually apparent that the data are approximately linear in the log-log plot with different exponents for the healthy and heart failure groups. On the other hand, contrary to Ref. [8], we find no scale for which a clear separation between the two groups is visible.

them to continue to perform well on new "out of sample" records [21].

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[24] The coefficients of the wavelet transform are calculated with spacing that increases linearly with scale a.