Multiresolution Wavelet Analysis of Heartbeat Intervals Discriminates Healthy Patients from Those with Cardiac Pathology

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We applied multiresolution wavelet analysis to the sequence of times between human heartbeats (R-R intervals) and have found a scale window, between 16 and 32 heartbeat intervals, over which the widths of the R-R wavelet coefficients fall into disjoint sets for normal and heart-failure patients. This has enabled us to correctly classify every patient in a standard data set as belonging either to the heart-failure or normal group with 100% accuracy, thereby providing a *clinically* significant measure of the presence of heart failure from the R-R intervals alone. Comparison is made with previous approaches, which have provided only *statistically* significant measures. [S0031-9007(97)05278-2]

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Multiresolution wavelet analysis [1–5] has proved to be a useful technique for analyzing signals at multiple scales, even in the presence of nonstationarities which often obscure such signals [6,7]. The sequence of times between human heartbeats (R-R intervals) is a prototype of a nonstationary time series that carries information about the state of cardiovascular health of the patient [8,9].

By projecting this sequence into a wavelet space, a new set of variables is obtained, whose statistics allow us, for the first time, to correctly classify every patient in a standard data set as either heart-failure or normal, with 100% accuracy. It is clear from our results that the R-R intervals alone suffice as a measure for the presence of heart failure; the full electrocardiogram is not required. This remarkable result arises from the ability of multiresolution analysis to simultaneously and compactly monitor multiple time scales and thereby to expose a hitherto unknown scale window (between 16 and 32 heartbeat intervals) over which the widths of the R-R wavelet coefficients fall into disjoint sets for normal and heart-failure patients. The emergence of this particular scale window should help shed light on the underlying dynamics of cardiovascular function [9]. Previous approaches [10–12], even those that have made use of wavelets [13], have been successful only in providing a *statistically* significant measure, rather than the *clinically* significant one we have developed. The analysis method we have used is applicable to a wide variety of nonstationary physical and biological signals, regardless of whether the underlying fluctuations have stochastic origins or arise from nonlinear dynamical processes.

The series of intervals between adjacent heartbeats τ_i [known as R-R or interbeat intervals in cardiology; see Figs. 1(a) and 1(b)] is thought to result from a complex superposition of multiple physiological processes at their respective characteristic time scales [9]. The object of this Letter is to demonstrate that is is possible, without any *a priori* knowledge of the physiological time scales or underlying heart dynamics, to determine a range of scales over which a statistic of the wavelet coefficients permits each heart-failure and normal patient to be correctly categorized.

Scale-dependent statistics are constructed by transforming the discrete-time sequence of R-R intervals $s = \{\tau_i\}$ [14] into a space of wavelet coefficients. One can think of the transformed signal in terms of a landscape over a two-dimensional plane whose axes are interbeat-interval number i and scale m [see Fig. 1(c)]. Smaller scales correspond to more rapid variations and therefore to higher frequencies. The height is the value of the corresponding wavelet coefficient. With such a three-dimensional construct it is possible to trace the behavior at different scales as the heartbeat sequence proceeds. Technically the coefficients are obtained by carrying out a discrete wavelet transform (DWT) [1,4]

$$W_{m,n}^{\mathrm{wav}}(s) = 2^{-m/2} \sum_{i=0}^{M-1} \tau_i \psi(2^{-m} i - n) , \qquad (1)$$

where the scale variable m and the translation variable n are non-negative integers, and M represents the total number of R-R intervals analyzed. The discrete wavelet transform is evaluated at the points (m, n) in the scale–interval-number plane.

We have carried out this transformation using a broad range of orthonormal, compactly supported analyzing wavelets. We present results for both Daubechies 10-tap and Haar wavelets; similar results were obtained using other wavelets. Orthogonality in the DWT provides that the information represented at a certain scale m is disjoint from the information at other scales. Because certain wavelets ψ have vanishing moments, polynomial trends in the signal are automatically eliminated in the process of wavelet transformation [6,7,15]. This is salutatory in the case of the heartbeat time series, as is evident from the trends apparent in Fig. 1(b), which are eliminated by the wavelet transformation shown in Fig. 1(d).

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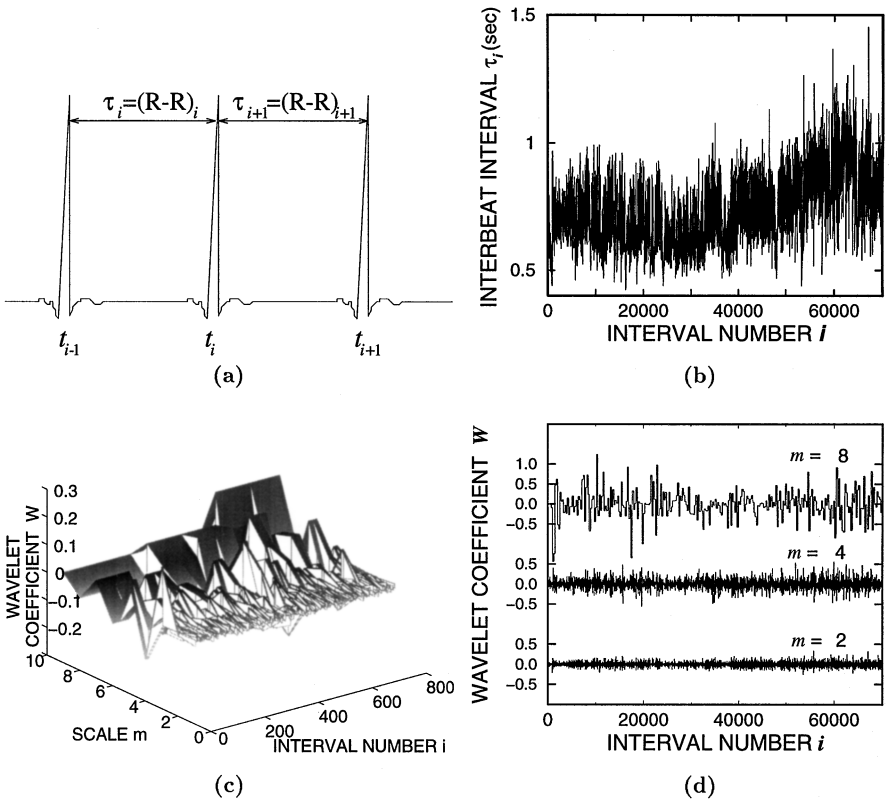

FIG. 1. (a) Schematic diagram of an electrocardiogram segment, showing the beat occurrence times t_i and the interbeat (R-R) intervals τ_i. (b) Series of interbeat intervals τ_i versus interval number i for a typical normal patient (data set 16 265). (Adjacent values of the interbeat interval are connected by straight lines to facilitate viewing.) Substantial trends are evident. (c) 3D representation of the wavelet coefficient W as a function of scale ($1 \leq m \leq 10$) and interval number i (n has been rescaled to i), over a portion of the data set, using a Daubechies 10-tap analyzing wavelet. (d) Wavelet coefficient at three scales ($m = 2$, 4, and 8) for the data set illustrated in (b). The trends in the original interbeat-interval time series are removed by the wavelet transformation.

Since the signal s fluctuates in time, so too does the sequence of wavelet coefficients at any given scale, though its mean is zero [1]. A natural measure for this variability is the wavelet-coefficient standard deviation, as a function of scale:

$$\sigma_{\mathrm{wav}}(m) = \left[\frac{1}{N-1} \sum_{n=0}^{N-1} [W_{m,n}^{\mathrm{wav}}(s) - \langle W_{m,n}^{\mathrm{wav}}(s) \rangle]^2 \right]^{\frac{1}{2}}, \tag{2}$$

where N is the number of wavelet coefficients at a given scale m [$N = \mathrm{int}(M/2^m)$]. The principal results of this paper are displayed in Fig. 2, where σ_{wav} is plotted vs scale ($1 \leq m \leq 10$) for all 27 patients (open and solid circles) [14], using the Haar wavelet (left) and the Daubechies 10-tap wavelet (right). The wavelet coefficients for heart-failure patients evidently exhibit substantially lower variability than those for normal patients at intermediate scales. Indeed at scales 4 and 5, corresponding to 2^4–$2^5 = 16$–32 heartbeat intervals, σ_{wav} serves to completely separate the two classes of patients for both types of wavelets (white regions), thereby providing a clinically significant measure [16,17] of the presence of heart failure with 100% sensitivity at 100% specificity (such that all normals are so identified). One can do no better. Though it has been previously shown that complete separation can be achieved using heart*rate* analysis [17,18], this is the first instance that we know of in which the *R-R intervals* can be used as a definitive determinant of the presence of a heart disorder in an individual patient. Both at smaller, and at larger scales, there are multiple overlaps of the heart failures and the normals, though the measure certainly remains statistically significant over all scales shown. Similar results are obtained for other analyzing wavelets.

The results indicate that healthy patients exhibit greater fluctuations than those afflicted with heart failure over a time scale of 16–32 heartbeat intervals (roughly 0.2–0.5 min). This also appears to apply for sudden cardiac death (SCD) as illustrated by the open squares in Fig. 2. It is tempting to ascribe the physiological origin of this window to baroreflex modulations of the sympathetic or parasympathetic tone, which lie in the range 0.04–0.09 Hz (0.2–0.5 min), but we do not believe that this is a correct association. Rather, we expect that this window likely has its origin in the intrinsic behavior of the heart itself. It will be important to carry out a thorough study in which our multiresolution wavelet-analysis technique is applied to the R-R intervals from transplanted hearts to carefully assess the role that the autonomic system might play in heartrate variability.

It is useful to tease apart the roles played by the *magnitudes* τ_i of the interbeat intervals and their *ordering* in achieving this complete separation. The effects of the former also reside in the randomly reordered (shuffled) sequence of R-R intervals; however information about the ordering is removed in this surrogate data set [17]. We therefore calculate the standard deviation $\sigma_{\mathrm{wav}}^{\mathrm{shuf}}$ for all 27 heartbeat time series after shuffling the R-R intervals. [The first 70 000 interbeat intervals were selected for analysis after the entire data sets (see [14] and Table I in Ref. [17]) were shuffled.] The results are shown in Fig. 3(a). It is clear that the two classes of patients are no

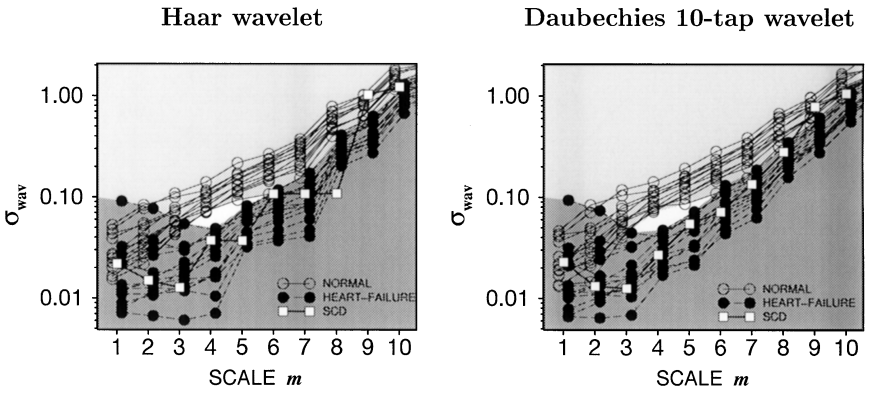

FIG. 2. Wavelet-coefficient standard deviation σ_{wav} versus scale m for the standard 27 data-set collection [14], using the Haar wavelet (left) and the Daubechies 10-tap wavelet (right). Complete separation of the two groups is achieved at scales 4 and 5, corresponding to 2^4–2^5 heartbeat intervals. Results for an SCD patient (white squares), using the same number of interbeat intervals, also exhibit low variability. The outcome is similar for both analyzing wavelets.

longer completely separated; three heart-failure patients fall among the normals at all scales, yielding a sensitivity of 80% at a specificity of 100%. Comparison with Fig. 3(b) shows that the shuffled-wavelet result is essentially identical to that obtained by using the standard deviation σ_{int} of the interbeat intervals obtained from these data sets, a measure that has long been used in cardiology [19,20]. The concurrence in sensitivity displayed in Figs. 3(a) and 3(b) is not accidental; the shuffled interbeat intervals essentially comprise a renewal process so that the IIH contains all of the available information. All dependencies among intervals, and therefore long-term correlations, are removed from the shuffled surrogate data [17], leaving behind only short-term information. Indeed, for the Haar analyzing wavelet, $\sigma_{\mathrm{wav}}(m = 0)$ (in the absence or in the presence of shuffling) is analytically identical to σ_{int}.

The ordering of the interbeat intervals gives rise to scaling behavior, as is evident from a comparison of Figs. 2 and 3(a). For normal patients (open circles, solid lines) the straight-line behavior in Fig. 2 indicates that approximate scaling is maintained across all scales whereas for heart-failure patients (filled circles, dashed lines) the relatively flat nature of the curves in the region $m \leq 3$ indicates that σ_{wav} is essentially scale independent in this region.

The distinction can be examined quantitatively by calculating the average scaling exponents α [21] in the two ranges ($1 \leq m \leq 3$ and $3 \leq m \leq 10$), for both classes of data. For the 12 normal patients, the value of α is quite insensitive to the range over which it is estimated; it is nearly the same in the two subregions (1.40 ± 0.37 and 1.22 ± 0.11, respectively). For the 15 heart-failure patients, on the other hand, the average scaling exponent estimated in the region $1 \leq m \leq 3$ (0.26 ± 0.60) is dramatically lower than the value 1.57 ± 0.17 estimated in the region $3 \leq m \leq 10$. Over the range of larger scales, the values of the scaling exponents α provided by our wavelet measure are in good accord with typical values δ provided by the interval-based periodogram at low frequencies (see Table I in Ref. [17]), as expected. We conclude that scaling persists across a broader range for normal patients than it does for heart failures, as is visually evident in Fig. 2.

These observations lead us to consider a heart-failure index determined by the difference of these scaling exponents: $\Delta = \alpha(3 \leq m \leq 10) - \alpha(1 \leq m \leq 3)$. Evaluating Δ for each patient we find that two heart failures fall among the normals, corresponding to a sensitivity of 87% at a specificity of 100%. Thus considering only the scaling information in σ_{wav}, while ignoring the magnitude differences for normals and heart failures associated with short-term information [as illustrated in Fig. 3(a)], fails to give rise to complete separation.

Over the years, using this same collection of data, a number of measures based on scaling have been evaluated for their accuracy in discriminating between normal and heart-failure patients. Peng *et al.* [10] examined the correlation properties of the heartbeat-interval increments $I_i = \{\tau_{i+1} - \tau_i\}$, and obtained the exponent of the associated power-law spectrum, which they denoted as β. It was shown subsequently [17] that this measure is

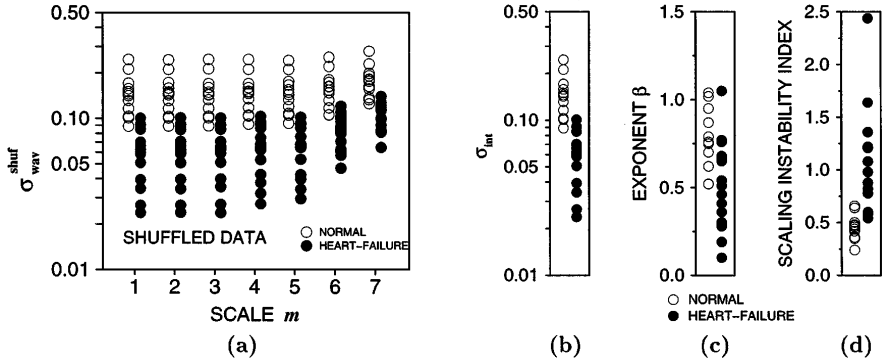

FIG. 3. (a) Wavelet-coefficient standard deviation $\sigma^{\mathrm{shuf}}_{\mathrm{wav}}$ versus scale m for the standard 27 data-set collection [14] after random reordering of the R-R intervals (shuffling), using a Daubechies 10-tap wavelet. (b) Standard deviation of the interbeat intervals σ_{int} for the 27 data sets. (c) Exponent β of the heartbeat-interval increment-process spectrum for all 27 original (nonshuffled) data sets. (d) The scaling instability index for 25 of the original 27 data sets.

isomorphic to the exponent δ of the interval-based spectrum at low frequencies and therefore reveals only long-term correlations. We have calculated β for all 27 data sets and present the results in Fig. 3(c). This measure results in seven heart failures among the normals, yielding a sensitivity of 53% at 100% specificity, so that it is not very successful in discriminating the two classes of patients. The interbeat-interval standard deviation σ_{int} shown in Fig. 3(b) (sensitivity of 80% at 100% specificity) performs significantly better. In a subsequent paper, Peng and collaborators [11] constructed a "detrended fluctuation measure" which turns out to yield approximately 80% sensitivity at 100% specificity for the 27 data sets. Most recently, this same group introduced a so-called "scaling instability index" [12], which achieved a sensitivity of 71% at 100% specificity for the 25 (of the same 27) data sets that they reported, as shown in Fig. 3(d). The performance of both of these latter measures is therefore comparable to that achievable with the interbeat-interval standard deviation measure σ_{int} introduced by Wolf *et al.* in 1978 [19]. As far as we are aware, no group has been able to successfully separate this standard collection of data with 100% sensitivity at 100% specificity using scaling measures alone.

We conclude that our multiresolution approach succeeds not only because it eliminates trends in a mathematically acceptable way, but also because it crisply reveals a range of scales over which heart-failure patients differ from normals, both in short- and long-term heartbeat behavior. In contrast, interbeat-interval measures reflect only short-term behavior, whereas scaling measures reflect only long-term behavior.

Finally we note that it will be important to evaluate the performance of our wavelet-based measure for other heart-failure and SCD data sets, and for other cardiac disorders, as well as for data segments of shorter lengths.

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[21] The scaling exponent α is computed from an individual wavelet-coefficient standard-deviation curve (as shown in Fig. 2) by calculating the slope of its square (rendering it a variance so that it corresponds to other standard scaling-exponent measures) on a base-10 log-log plot. Thus $\alpha = d[\log_{10}\sigma^2_{\text{wav}}(m)]/d(\log_{10} 2^m) = (2/\log_{10} 2)d[\log_{10}\sigma_{\text{wav}}(m)]/dm$.