Fractal Mechanisms and Heart Rate Dynamics

Long-range Correlations and Their Breakdown With Disease

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Abstract: Under healthy conditions, the normal cardiac (sinus) interbeat interval fluctuates in a complex manner. Quantitative analysis using techniques adapted from statistical physics reveals the presence of long-range power-law correlations extending over thousands of heartbeats. This scale-invariant (fractal) behavior suggests that the regulatory system generating these fluctuations is operating far from equilibrium. In contrast, it is found that for subjects at high risk of sudden death (eg, congestive heart failure patients), these long-range correlations break down. Application of fractal scaling analysis and related techniques provides new approaches to assessing cardiac risk and forecasting sudden cardiac death, as well as motivating development of novel physiologic models of systems that appear to be heterodynamic rather than homeostatic. **Key words:** cardiac interbeat interval, fluctuation, sudden cardiac death, fractal scaling analysis.

Scale-invariant properties in biologic systems have received much attention recently.[1,2] The absence of characteristic length (or time) scales may confer important biologic advantages related to adaptability of response.[2,3] We present here some recent progress in applying scale-invariant (fractal) analysis to interbeat interval time series. We will concentrate on the concept of long-range (power-law) correlations, which is a consequence of the scaling properties. We will also emphasize the difficulties of analyzing heartbeat time series, which arise mainly from their nonstationarity and sometimes short data length.

A system is said to exhibit long-range correlations when some physical properties of the system are correlated at different times (or positions) and the corresponding correlation function decays much slower than exponentially as a function of time or distance. In physics and mathematics, long-range correlations typically refer to a power-law decay of the correlation function.[4] The mechanism for generating such long-range correlations is not always obvious. Usually, long-range correlations are a result of the collective behavior of a complex system (under unique conditions), with the multiple components interacting through "local" (short-range) interactions. A well-studied example in statistical physics is a

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system at or near its critical point—such as the critical point of liquid-gas transition,[5] for which the interactions among the molecules are quite short range, being essentially nearest-neighbor only. In this case, the origin for generating long-range correlations is the balance between two competitive mechanisms—order (interaction between molecules) and disorder (thermal fluctuations)—over all scales.

Human Heartbeat Dynamics

Clinicians often describe the normal activity of the heart as "regular sinus rhythm." But, in fact, cardiac interbeat intervals normally fluctuate in a complex, apparently erratic manner[2,6] (Fig. 1). This highly irregular behavior has recently motivated researchers[7,8] to apply time-series analysis that derive from statistical physics, especially methods for the study of critical phenomena where fluctuations at all length (time) scales occur. These studies show that under healthy conditions, interbeat interval time series exhibit long-range power-law correlations reminiscent of physical systems near a critical point.[5,9] Furthermore, certain disease states may be accompanied by alterations in this scale-invariant (fractal) correlation property. We explore here the potential utility of such scaling alterations in the detection of pathologic states.

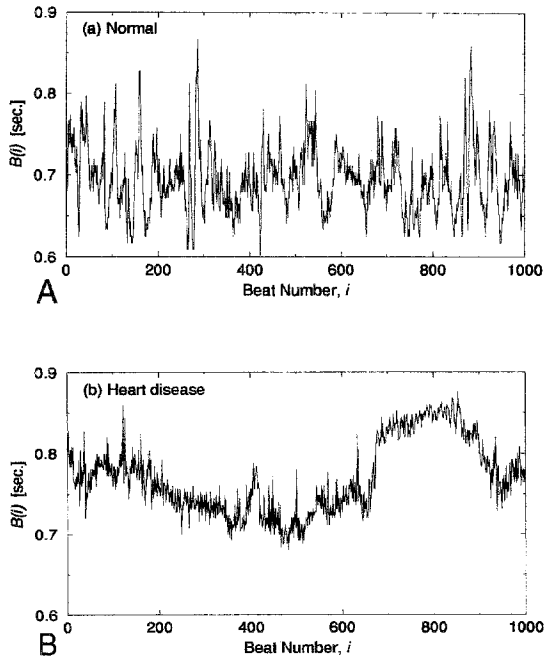

Fig. 1. The interbeat interval time series B(i) of 1,000 beats for (A) a healthy subject and (B) a patient with severe cardiac disease (dilated cardiomyopathy). The healthy heartbeat time series shows more complex fluctuations compared to the diseased heart rate fluctuation pattern.

Our analysis in this study is based on the beat-to-beat heart rate fluctuations of digitized electrocardiograms recorded with an ambulatory (Holter) monitor. The time series obtained by plotting the sequential intervals between beat i and beat i + 1, denoted by B(i), typically reveals a complex type of variability (Fig. 1). The mechanism underlying such fluctuations appears to be related primarily to countervailing neuroautonomic inputs. Parasympathetic stimulation decreases the firing rate of pacemaker cells in the heart's sinus node. Sympathetic stimulation has the opposite effect. The nonlinear interaction (competition) between the two branches of the autonomic nervous system is the postulated mechanism for the type of erratic heart rate variability recorded in healthy subjects.[6,10]

An immediate problem facing researchers applying time-series analysis to interbeat interval data is that the heartbeat time series is often highly nonstationary. Several approaches can be taken to reduce these nonstationary effects. We will discuss one particular method and its physiologic implications.

Detrended Fluctuation Analysis

To describe quantitatively the properties of normal interbeat fluctuations, we can first examine the moments of their distribution such as mean value, variance, etc. However, these measurements contain no information about the dynamics, that is, the sequential ordering of data points. The correlation function is a natural statistical measurement that does reveal some important properties of the dynamics. We will introduce a useful analysis to quantify the correlation properties of the interbeat time series. The method is derived from the concept of self-similar processes.

The concept of self-similar processes was first proposed by Kolmogorov[11] in theoretical physics and later introduced into mathematics through the influential work of Mandelbrot on fractals.[12] An object is self-similar if its subset can be rescaled to resemble (statistically) the original object. A scaling exponent (also called the *self-similarity parameter*) can be defined by this rescaling process. A stationary time series with long-range correlations can be integrated, that is, form an accumulated sum, to form a self-similar process. Therefore, measurement of the self-similarity scaling exponent of the integrated series can tell us the long-range correlation properties of the original time series. Hurst analysis[4] and root-mean-square analysis of random walks[13] are both based on this concept.

As discussed above, an immediate problem facing researchers in applying time-series analysis to heartbeat data is that the interbeat time series are often highly nonstationary. An important question is whether this heterogeneous structure arises trivially from external and intrinsic perturbations that drive the system away from a homeostatic "set point." An important alternative hypothesis is that such fluctuations are, at least in part, due to the underlying dynamics of the system. If

this hypothesis is correct, that is, neurophysiologic control systems behave like dynamical systems that are far from equilibrium, such long-range correlations are consequences of the underlying control mechanisms and their properties in the signals should be very robust with respect to other varying trends in the data. The key problem is how to decompose subtle fluctuations with long-range correlations from other nonstationary trends.

To this end, we introduced a modified root-mean-square analysis of a random walk—termed *detrended fluctuation analysis* (DFA)*[14]—to the analysis of heartbeat data. The advantages of DFA over conventional methods are that it permits the detection of long-range correlations embedded in a seemingly nonstationary time series and also avoids the spurious detection of apparent long-range correlations that are an artifact of nonstationarity. This method has been tested on control time series that consist of long-range correlations with superposition of a nonstationary external trend. It has also been successfully applied to detect long-range correlations in highly heterogeneous DNA sequences.[14–16]

To illustrate the algorithm of DFA, we use the interbeat time series shown in Figure 1A as an example. Briefly, the interbeat interval time series (of total length N) is first integrated, $y(k) = \sum_{i=1}^{k}[B(i) - B_{ave}]$, where B(i) is the ith interbeat interval and B_{ave} is the average interbeat interval. Next, the integrated time series is divided into boxes of equal length, n. In each box of length n, a least-squares line was fit to the data (representing the trend in that box) (Fig. 2). The y coordinate of the straight line segments is denoted by $y_n(k)$. Next, we detrend the integrated time series, y(k), by subtracting the local trend, $y_n(k)$, in each box. For a given box size n, the characteristic size of fluctuation for this integrated and detrended time series is calculated by

$$F(n) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}[y(k) - y_n(k)]^2} \quad (1)$$

This computation is repeated over all time scales (box sizes) to provide a relationship between F(n) and the box size n (ie, the number of beats in a box). Typically, F(n) will increase with box size n. A linear relationship on a double log graph indicates the presence of scaling, that is, the integrated and detrended time series is a self-similar process. In other words, fluctuations in small boxes are similar to fluctuations in bigger boxes in a power-law fashion. The slope of the line relating log F(n) to log n determines the scaling exponent (self-similarity parameter), alpha. For a process where the value at one interbeat interval is completely uncorrelated from any previous values (eg, white noise), the integrated value, y(k), corresponds to a random walk and therefore alpha = 0.5.[13] If there are only short-term correlations, the initial slope may be different from 0.5, but alpha will approach 0.5 for large window sizes. An alpha greater than 0.5 and less than or equal to 1.0 indicates persistent long-range power-law correlations, while 0 < alpha < 0.5 indicates antipersistent power-law correlations[15]; alpha = 1 corresponds to 1/f noise. For alpha greater than 1, correlations exist but cease to be of a power-law form; alpha = 1.5 indicates brown noise, the integration of white noise. The alpha exponent can also be viewed as an indicator that describes the "roughness" of the original time series: the larger the value of alpha, the smoother the time series. In this context, 1/f noise can be interpreted as a compromise or balance between the complete unpredictability of white noise (very rough landscape) and the much smoother landscape of Brownian noise.[17]

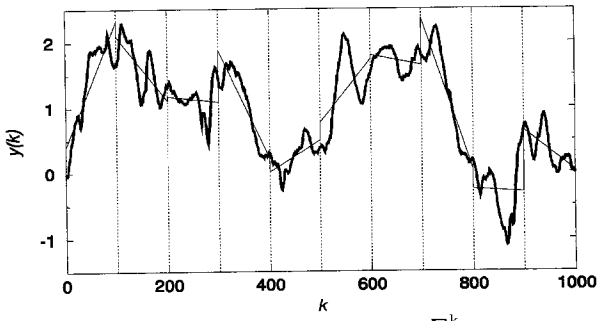

Fig. 2. The integrated time series: $y(k) = \sum_{i=1}^{k}[B(i) - B_{ave}]$, where B(i) is the interbeat interval shown in Figure 1(A). The vertical dotted lines indicate the box of size n = 100; the solid straight line segments indicate the trend estimated in each box by a linear least-squares fit.

Figure 3 compares the DFA analysis of representative 24-hour interbeat interval time series of a healthy subject and a patient with congestive heart failure. Notice that

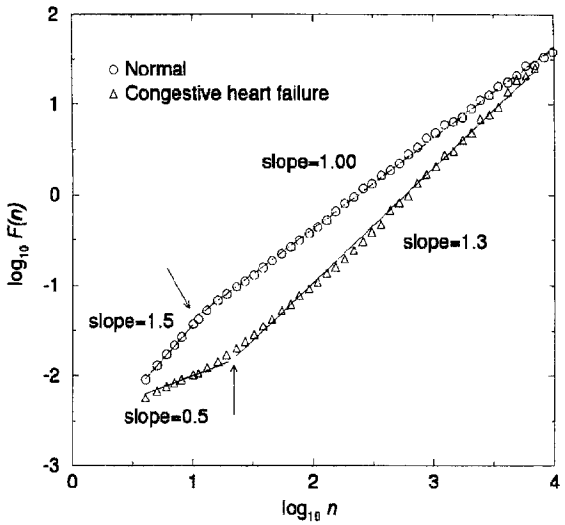

Fig. 3. Plot of log F(n) versus log n for two very long interbeat interval time series (approximately 24 hours). The circles represent a healthy subject and the triangles represent a subject with congestive heart failure. Arrows indicate crossover points in scaling.

*Computer software of the DFA algorithm is available upon request; contact C.-K. Peng (e-mail: peng@chaos.bih.harvard.edu).

for large time scales (asymptotic behavior), the healthy subject interbeat interval time series shows almost perfect power-law scaling over two decades ($20 \leq n \leq 10{,}000$) with alpha = 1 (ie, 1/f noise), while for the pathologic data set alpha $\cong$ 1.3 (closer to Brownian noise). This result is consistent with our previous finding that there is a significant difference in the long-range scaling behavior between healthy and diseased states.[7,8]

Normal vs Pathologic Time Series

To test for statistical significance using the DFA method, we reanalyzed cardiac interbeat data from two different groups of subjects reported in our previous work.[7] 12 healthy adults without clinical evidence of heart disease (age range, 29–64 years; mean, 44 years) and 15 adults with severe heart failure† (age range, 22–71 years; mean, 56 years). Data from each subject consisted of approximately 24 hours of electrocardiographic recording. Data from the patients with heart failure due to severe left ventricular dysfunction are likely to be particularly informative in analyzing correlations under pathologic conditions since these individuals have abnormalities in both the sympathetic and parasympathetic control mechanisms[18] that regulate beat-to-beat variability. Previous studies have demonstrated marked changes in short-range heart rate dynamics in heart failure compared to healthy function, including the emergence of intermittent relatively low-frequency (approximately 1 cycle/min) heart rate oscillations associated with the well-recognized syndrome of periodic (Cheyne-Stokes) respiration, an abnormal breathing pattern often associated with low cardiac output.[18]

We observed the following scaling exponents‡ (for time scales $10^2 \sim 10^4$ beats) for the group of healthy cardiac interbeat interval time series (mean value ± SD): alpha = 1.00 ± 0.11. This result is consistent with previous reports of 1/f fluctuations in healthy heart rates (by spectral analysis).[3,19] The pathologic group shows a significant ($P < .01$ by Student's t-test) deviation from normal of the long-range correlation exponent. For the group of heart failure subjects, we find that alpha = 1.24 ± 0.22. Of interest, some of the heart failure subjects show an alpha exponent very close to 1.5 (Brownian noise), indicating random walk-like fluctuations, also consistent with our previous findings in this group. The group-averaged exponent alpha is less than 1.5 for the heart failure patients, suggesting that pathologic dynamics may only transiently operate in the random walk regime or may only approach this extreme state as a limiting case. We obtained similar results when we divided the time series into three consecutive subsets (of approximately 8 hours each) and repeated the above analysis. Therefore, our findings are not simply attributable to different levels of daily activities.

Crossover Phenomena

Although this asymptotic scaling exponent may serve as a useful index for selected diagnostic purposes, a drawback is that very long data sets are required (at least 24 hours) for statistically robust results. For practical purposes, clinical investigators are often interested in the possibility of using substantially shorter time series. In this regard, we note that for short time scales, there is an apparent crossover exhibited for the scaling behavior of both data sets (arrows in Fig. 3). For the healthy subject, the alpha exponent estimated from the very small n (< 10 beats) is larger than that calculated from the large n (> 10 beats). This is probably due to the fact that on very short time scales (up to 10 beats), the physiologic interbeat interval fluctuation is dominated by the relatively smooth heartbeat oscillation associated with respiration, thus giving rise to a large alpha value. For longer scales, the interbeat fluctuation, reflecting the intrinsic dynamics of a complex system, approaches that of 1/f behavior as previously noted. In contrast, the pathologic data set shows a very different crossover pattern (Fig. 3). For very short time scales, the fluctuation is quite random (close to white noise, alpha $\approx$ 0.5). As the time scale becomes larger, the fluctuation becomes smoother (asymptotically approaching Brownian noise, alpha $\approx$ 1.5). These findings are consistent with our previous report of altered correlation properties under pathologic conditions.[7,8]

Clinical Application: Preliminary Results

The above observation of a differential crossover pattern for healthy versus pathologic data motivated us to extract two parameters from each data set by fitting the scaling exponent alpha over two different time scales: one short, one long. To be more precise, for each data, set we calculated an exponent alpha_1 by making a least-squares fit of log F(n) versus log n for $4 \leq n \leq 16$. Similarly, an exponent alpha_2 was obtained from $16 \leq n \leq 64$. Since these two exponents are not extracted from the asymptotic region, relatively short data sets are sufficient, thereby making this technique applicable to "real world" clinical data.

We applied this quantitative fluctuation analysis to the two different groups of subjects mentioned above to measure the two scaling exponents alpha_1 and alpha_2. All data set records were divided into multiple subsets (each with n = 8,192 beats ~ 2 hours) and the two exponents were calculated for each subset. For healthy subjects, we find the following exponents (mean value ± SD) for the cardiac interbeat interval time series: alpha_1 = 1.201 ±

†Electrocardiographic recordings of Holter monitor tapes were processed both manually and in a fully automated manner using our computerized beat recognition algorithm (Aristotle). Abnormal beats were deleted from each data set. The deletion has practically no effect on the DFA analysis since less than 1% of total beats were removed. Patients in the heart failure group were receiving conventional medical therapy prior to receiving an investigational cardiotonic drug.[20]

‡Typical regression fit shows excellent linearity of the double log graph (indicated by correlation coefficient $r > .97$) for both groups; however, usually, data from healthy subjects show even better linearity on log-log plots than data from subjects with heart disease.

0.178 and $alpha_2$ = 0.998 ± 0.124. For the group of congestive heart failure subjects, we find that $alpha_1$ = 0.803 ± 0.259 and $alpha_2$ = 1.125 ± 0.216, both significantly ($P < .0001$ for both $alpha_1$ and $alpha_2$) different from normal. Furthermore, we show in Figure 4 that fairly good discrimination between these two groups can be achieved by using these two scaling exponents. We note that not all subjects in our preliminary study show an obvious crossover in their scaling behavior. Only 8 of 12 healthy subjects exhibited this crossover, while 11 of 15 pathologic subjects exhibited a reverse crossover. However, the two scaling exponents ($alpha_1$ and $alpha_2$) measured from relatively short data sets can still be potentially useful indicators to distinguish normal from pathologic time series.

To test the effect of data length on these calculations, we repeated the same DFA measurements for longer data sets (n = 16,384) and also for shorter data sets (n = 4,096). As expected, the results for shorter data sets are less reliable (more overlap between two groups) due to anticipated statistical error related to the finite sample size.[21] On the other hand, longer data sets result in little improvement for the distinction between groups. Therefore, the data length of 8,192 seems to be a statistically reasonable choice.§

Furthermore, we note that data from normal interbeat interval time series are tightly clustered, suggesting that there may exist a universal scaling behavior for physiologic interbeat time series. In contrast, the pathologic data show more variation, a finding that may be related to different clinical conditions and varying severities of the pathologic states.

Forecasting Clinical Outcomes: Survival Rate Assessment

Based on the hypothesis that there is a region of scaling behavior (Fig. 4) over which normal (healthy) cardiac control operates, we have recently found another promising application of DFA in analyzing data sets from the Framingham Heart Study, which was a prospective, population-based study.[22] The primary group of interest was individuals with congestive heart failure; 28 congestive heart failure cases and 41 sex- and age-matched healthy control cases were analyzed by our scaling analysis. Briefly, using Holter monitor data (approximately 2 hours) from each subject of the Framingham Study, we assigned an index (range from 0 to 1) to each individual by estimating the probability that this particular heartbeat time series was operating in the appropriate region in Figure 4 (normal vs pathologic). Note that the data

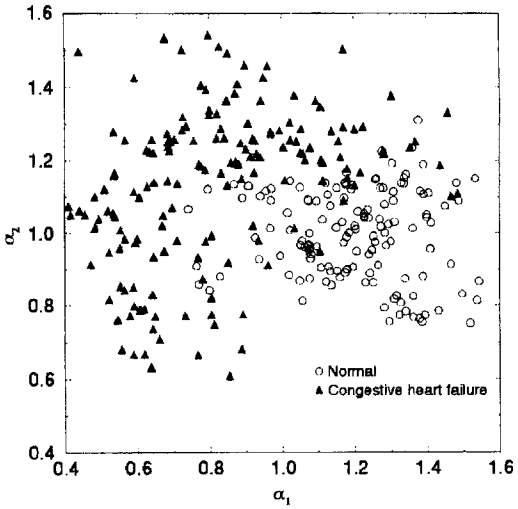

Fig. 4. Scatterplot of scaling exponents $alpha_1$ versus $alpha_2$ for the healthy subjects (circles) and subjects with congestive heart failure (triangles). The alphas were calculated from interbeat interval data sets with a length of 8,192 beats. Longer data set records were divided into multiple data sets (each with 8,192 beats). Note good separation between the healthy and heart-disease subjects, with clustering of points in two distinct "clouds."

studied in Figure 4 are treated as a representative training set. (None of the Framingham Heart Study subjects are included in this training set.) The question we posed was: What is the utility of this new fractal index? In particular, does this measure add independent information to conventional measures? In comparison with 10 other time and frequency measures, we found that the DFA index carries prognostic information about mortality not extractable from these traditional methods of heart rate variability analysis.[22]

Conclusion

Our finding of nontrivial long-range correlations in healthy heart rate dynamics is consistent with the observation of long-range correlations in other biologic systems that do not have a characteristic scale of time or length.[2,23–28] Such behavior may be adaptive for at least two reasons. (1) The long-range correlations serve as an organizing principle for highly complex, nonlinear processes that generate fluctuations on a wide range of time scales. (2) The lack of a characteristic scale helps prevent excessive mode-locking that would restrict the functional responsiveness of the organism. Support for these related conjectures is provided by observations from severe diseased states, such as heart failure, where the breakdown of long-range correlations is often accompanied by the emergence of a dominant frequency mode (eg, the Cheyne-Stokes frequency). Analogous transitions to highly periodic regimes have been observed in a wide range of other disease states including certain malignancies, sudden cardiac death, epilepsy, and fetal distress syndromes.[3]

§We also tested these calculations by varying the fitting range for $alpha_2$. We find that the results are very similar when we measure $alpha_2$ from 16 beats to 128 beats; however, when we move the upper fitting range for $alpha_2$ from 128 beats to 256 beats or more, the pathologic data sets show larger variation of $alpha_2$, leading to less obvious separation from normal subjects. This is partly due to the fact that, for finite length data sets, the calculation error of F(n) increases with n.[21] Therefore, scaling exponents obtained over larger values of n will have greater uncertainty.

The complete breakdown of normal long-range (fractal) correlations in the cardiovascular system could theoretically lead to three possible diseased states: (1) random walk (brown noise), (2) highly periodic behavior, or (3) completely uncorrelated behavior (white noise). Cases 1 and 2 both indicate only trivial long-range correlations of the types observed in severe heart failure. Case 3 may correspond to certain cardiac arrhythmias such as fibrillation. More subtle or intermittent degradation of long-range correlation properties may provide an early warning of incipient pathology. Finally, we note that the long-range correlations present in the healthy heartbeat and gait indicate that the neuroautonomic and central nervous control mechanisms actually drive the system away from a single steady state. Therefore, the classic theory of homeostasis, according to which stable physiologic processes seek to maintain constancy,[29] should be extended to account for this dynamic, far from equilibrium, behavior of these heterodynamic systems.

Acknowledgments

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Nonlinear Forecasting and the Dynamics of Cardiac Rhythm

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Abstract: Since the initial development of the electrocardiogram, cardiologists have made dramatic advances in the description and understanding of cardiac arrhythmias. Despite these successes, the analysis of cardiac rhythm has remained largely descriptive. Recently, the principles of nonlinear dynamics, or chaos theory, have been applied to the quantitative analysis of cardiac rhythm in a variety of diverse situations. In chaos theory, three types of signals can be defined: periodic signals, which repeat themselves over some finite time interval, chaotic signals, which, while deterministic, demonstrate complex behavior and do not repeat themselves, and random signals, which are unpredictable and nondeterministic. The technique of nonlinear forecasting defines trajectories in a suitably defined phase space and uses the future evolution of trajectories that are close to each other over short distances to make predictions for times further into the future. The ability to reliably predict the future evolution of the trajectories derived from any signal is an important characteristic of the underlying dynamics of the signal and can therefore used to determine those dynamics. The foundation of nonlinear forecasting is reviewed, and an algorithm is described that can be used to determine the underlying dynamics of a signal and has been applied to the analysis of R-R interval data. **Key words:** nonlinear dyamics, chaos theory, trajectories, periodic signals, chaotic signals, random signals.

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The development of the string galvanometer by Willem Einthoven (for which he received the 1924 Nobel Prize for Medicine[1,2]) ushered in the era of modern cardiology. However, despite the advances made in the last century in our understanding of cardiac arrhythmias, the analysis of cardiac rhythm has remained largely descriptive. For example, while beat-to-beat variations in sinus cycle length (sinus arrhythmia) in normal subjects has long been recognized, it is only relatively recently that heart rate variability anal-