Nonlinear properties of cardiac rhythm abnormalities

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Many physical processes have distributions of times between events that have non-normalizable, power law probability density functions (PDF's). The moments of such distributions are not defined. We found that the PDF's of the times between events of ventricular tachyarrhythmia (rapid heart rate) and premature ventricular contractions have a power law form indicative of a non-normalizable distribution, and that the timing between these events cannot be meaningfully characterized by the mean frequency of such events. The Hurst analysis showed that there were self-similar correlations in the data. These results indicate that the physical processes that disrupt the normal rhythm of the heart produce a fractal pattern in the timing between these events. It also suggests that the mean and the variance of the frequency of these events may not be good measures to assess the status of patients with these arrhythmias and determine the effectiveness of therapeutic procedures.

I. INTRODUCTION

A. Nonclassical properties of physical systems

Classical measures of the arithmetic mean and variance are the most used statistical measures. It is not always fully appreciated that the usefulness of these measures depends on the properties of the data satisfying certain assumptions. If the data do not match these assumptions, then the results of the analysis may not be meaningful. The basic assumption of these classical statistical measures is that the probability density function (PDF) is integrable and that its second moment is finite. When this is the case, as it is for such classical PDF's as the Gaussian and Poisson distributions, then the moments are defined and have finite values. In such cases, as more data are analyzed, the moments of these samples approach finite, limiting, values that we identify as the mean and the variance of the population. A physical process that generates a structure with a characteristic scale can be meaningfully characterized by the mean value $\langle t \rangle$ of the data. Correlations within the data will typically have an exponential form proportional to $\exp(-t/\langle t \rangle)$.

However, many physical processes generate self-similar structures that extend over a large range of scales [1–4]. These data cannot be meaningfully characterized by a single mean value. The PDF will have a non-normalizable, power law form proportional to t^{-a}. That is, the integral

$$\int_0^\infty t^{-a} dt \tag{1}$$

is not finite, and therefore the distribution is not normalizable. The integral $\int_0^\infty t t^{-a} dt$, will approach 0 or ∞, and therefore the mean is not defined. As more data are included in the analysis, or the resolution is changed, the means of the samples will not approach a finite limit. Either the increasing number of small values included will drive the mean toward zero, or the few large values included will drive the mean towards infinity. Similarly, the correlations within the data will typically have a power law form proportional to t^{-a} that cannot be characterized by a single characteristic scale. The correlations extend over a large range of scales.

If the properties of the experimental data to be analyzed do not match the assumptions of the tools used, then the result produced from the analysis may not be meaningful, and can be misleading and spurious. Moreover, the results of the analysis will not be able to lead us toward an understanding of the physical mechanism that generated the data.

Some biomedical systems also exhibit self-similarity in spatial structures or temporal processes [5,6]. We will show below that the times between events that disrupt the normal rhythm of the heart have statistical properties that do not match the assumptions of the classical statistical measures, and thus such data cannot be meaningfully characterized by the arithmetic mean or variance. This may have important consequences for analyzing and interpreting patient data, and determining the physical mechanisms that generate these events.

B. Heart rhythm abnormalities

Sudden cardiac death is the single most common cause of death in the United States. It almost always arises from abnormalities in the rhythm of the heart. The heart normally contracts in an organized way that pushes blood out of the

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ventricles. When this spatial-temporal organization is lost in ventricular tachyarrhythmias, such as ventricular fibrillation, blood is not pumped, and death occurs in a few minutes. There is much interest in determining a measure of heart function that presages the onset of ventricular fibrillation, so that the timely use of drugs or electrical stimulation could be used to prevent sudden cardiac death.

Almost all the previous nonlinear studies of heart arrhythmias analyzed the time intervals between heartbeats, called the *R-R* intervals [7–11,27]. In this paper, rather than utilizing the *R-R* intervals, we analyzed the times between events that disrupt the normal rhythm of the heart. The timing of the events that we analyzed were (1) episodes of ventricular tachyarrhythmia (rapid heart rate), and (2) premature ventricular contractions. Here we present, for the first time to our knowledge, the PDF and Hurst analysis of the times between these arrhythmic events.

1. Ventricular tachyarrhythmia (v-tach)

Ventricular tachyarrhythmias occur when the main chambers of the heart, the ventricles, beat at such rapid rates that the pumping function of the heart is severly compromised or completely ineffectual. It is now possible to implant cardioverter defibrillators in the body that detect v-tach, and then generate a strong enough electrical shock to restart the heart into a normal rhythm. These devices can store v-tach event times in memory over years of followup, and output them when interrogated with a radio frequency transceiver. Here we present an analysis of the times between v-tach recorded from 30 patients with these implanted devices.

The data are from 28 patients with Telectronics 4210 or CPI PRx cardioverter defibrillators, 17 of whom were implanted at the Medical College of Virginia and McGuire Veterans Administration Medical Center, Richmond, VA, and 11 at the Sentara Norfolk General Hospital, Norfolk, VA. Additional data were obtained from two patients with CPI PRxII cardioverter defibrillators from a clinical database (Guidant CPI Inc, St. Paul, MN). The analysis of arrhythmic events has typically been based on Holter monitors that record data over only a 24-h period. The data from the cardioverter defibrillators are unique in that they consist of the detection of all the v-tach events in each patient, which covers a total time period of two years for the patient who has had the cardioverter defibrillator for the longest time.

2. Premature ventricular contractions (PVC's)

Another rhythm abnormality occurs when premature ventricular contractions interrupt the regular pattern. The frequency of PVC's on Holter monitors can identify patients at risk for more serious arrhythmias and a supression of these abnormal beats has been used to direct medical therapy of arrhythmias. Data from the heart can be recorded over a 24-h period by a Holter monitor worn by a patient. A Rozzin Holter PC system was used to analyze the recordings from six patients to detect PVC's and determine the time between events.

Previous studies of PVC's have been based almost exclusively on classical linear statistical measures. Recently, two studies determined the fractal dimension of these events embedded along a one-dimensional time axes [12,13]. Neither of these studies determined the statistical distribution of those interevent times or the correlations between the interevent times. The results presented here are, to our knowledge, the first PDF's and self-similar correlation analysis of the times between PVC events.

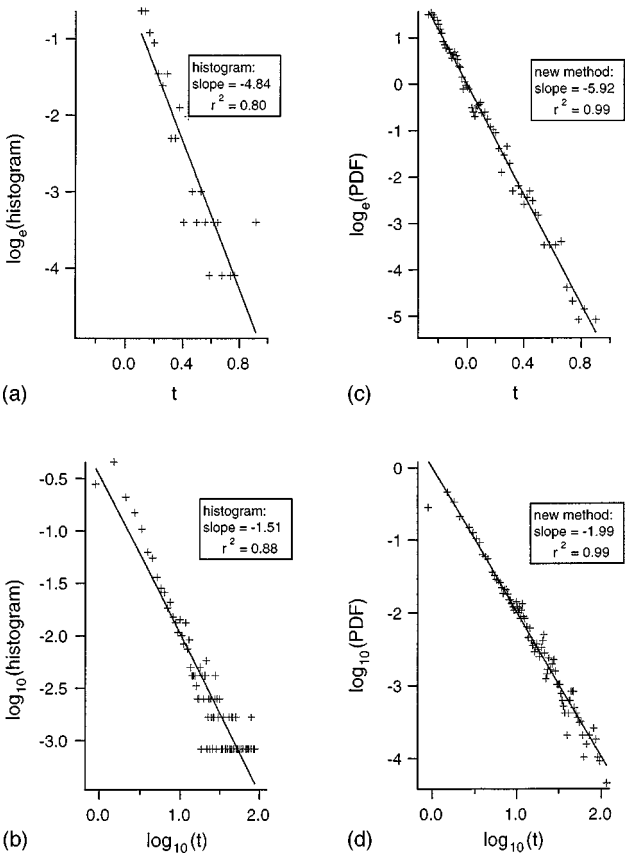

FIG. 1. (a)–(d) Comparison between the standard histogram method and our multihistogram method used to determine the probability density function (PDF). The PDF's were determined for two different simulated processes with 2000 interevent times. The first one has an exponential distribution $\exp(-kt)$, where $k=6.0$, and the second one has a power law distribution $t^{-\alpha}$, where $\alpha=2.0$. The fit of the functional forms is characterized by the correlation coefficient r, with higher values of r indicating a better fit. In both cases the functional form and the parameter estimation is significantly better using our method.

II. ANALYSIS

First, we analyzed the PDF's of the times between v-tach and PVC's. The power law form of those PDF's suggested that the mean and variance are not a meaningful measure of these data, which was confirmed by a direct computation of those moments. Finally, we found evidence of self-similar, long term, correlations in the interevent times.

A. PDF (probability density function)

Estimation of the PDF's of heart rhythm abnormalities is a difficult task, because the interevent times are distributed over many time scales. The times between v-tach events extended from 20 s (the resolution time of the cardioverter defibrillators) to 493 days in this patient group. The PDF can be determined from the histogram of interevent times. However, the result will depend on the size of the bins used. Narrow bins will be good estimators at short times but poor

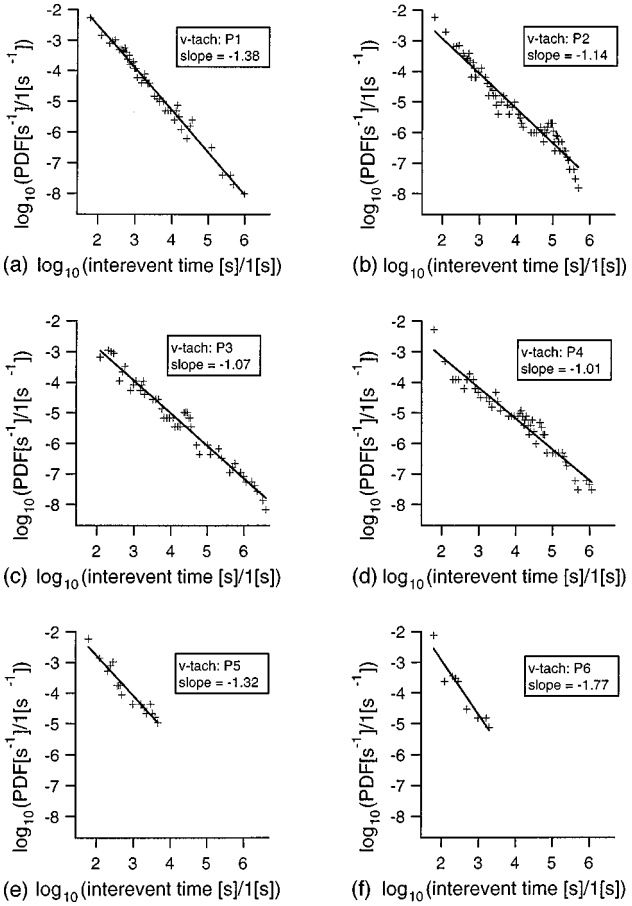

FIG. 2. (a)–(f) PDF of v-tach interevent times are plotted for six different patients who had the most recorded events. The numbers of interevent times for these patients are 156, 196, 55, 100, 71, and 103, respectively. The straight lines on these log-log plots indicate that these PDF's have a power law form.

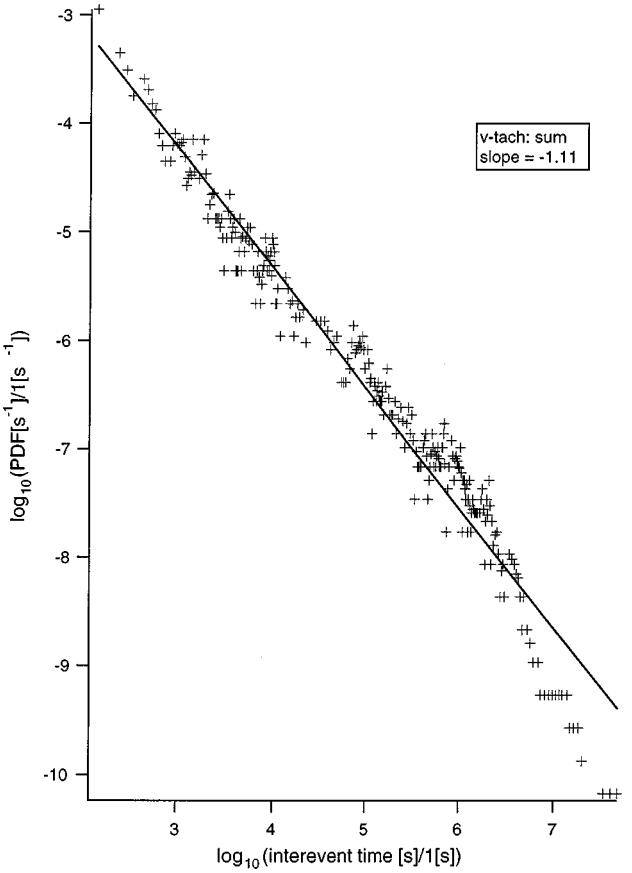

FIG. 3. PDF of v-tach interevent times from all 30 patients are plotted on a log-log scale. The total number of interevent times is 1131. The PDF of the combined data also has a power law distribution of interevent times.

ones at long times, and vice versa for wide bins. We used a multihistogram method to improve the accuracy of the estimation of the PDF. We computed histograms of different bin sizes, evaluated the PDF from each histogram, and then combined those values to form the completed PDF. The algorithm is described in Appendix A. We found that this procedure is fast and accurate in determining single exponential, multiple exponential, and nonexponential (power law) distributions from both test and experimental data [14,15]. A comparison of single exponential and power law PDF's determined from histograms of a fixed bin size and from this procedure is shown in Fig. 1.

PDF's of the times t between events of v-tach for six patients, recorded from their cardioverter defibrillators, are shown in Fig. 2. The number of interevent times ranged from 55 to 196 per patient. The straight lines on the log-log plots indicate that these PDF's are a power law proportional to t^{-a} where $1.01<a<1.77$. There were not enough events from the other 24 patients to accurately determine the PDF's for each patient individually. The PDF determined from the times between events combined from all 30 patients is shown in Fig. 3. The total number of interevent times was 1131. Even though these patients have different underlying types of heart disease and are receiving different medical therapies, the PDF of the combined events also has the same coherent power law form with $a=1.11\pm0.06$ over five decades in time. This may indicate some essential property of heart function that transcends the specific mechanisms of different disease processes. Figure 3 also shows a downward deviation from a power law form at interevent times greater than 20 days. This may indicate that the physiological mechanisms that produce the longer interevent times are different from those that produce the shorter intervent times.

PDF's of the times between events of PVC's for six patients are shown in Fig. 4. The number of interevent times ranged from 573 to 11 590 per patient. The straight lines on the log-log plots also indicate that these PDF's are power laws proportional to t^{-a}, where $1.32<a<2.41$. The PDF's from these six patients are shown together in Fig. 5. The power law form of the PDF's extend over three decades in time. The difference in the three-decade range of the PVC data, compared to the five-decade range of the v-tach data, may be due to the fact that the PVC data are from Holter recordings that are limited to a 24-h span, which is much less than the two-year duration of v-tach data available from the implanted cardioverter defibrillators.

The overall form of the PDF's of the PVC's is a power law over a wide range of interevent times. However, there are also second order deviations from this form. As shown in Fig. 4, the PDF's from all six patients deviate from a power law at short interevent times in a way that is characteristic of the more complex form $(C+t)^{-a}$ This may indicate that

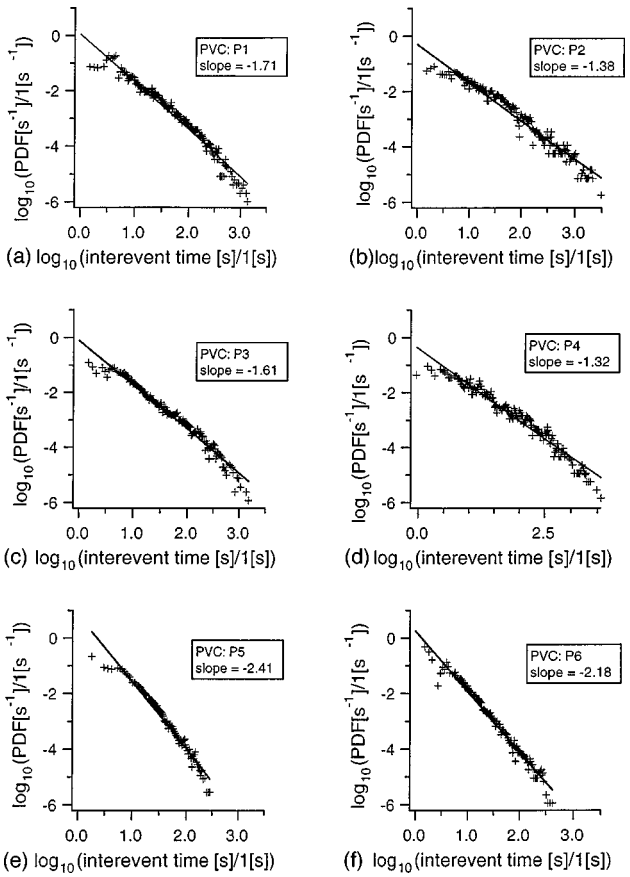

FIG. 4. (a)–(f) PDF of PVC interevent times are ploted for six different patients. The numbers of interevent times for these patients are 3152, 896, 2705, 573, 9192, and 11 590, respectively. The straight lines on these log-log plots indicate that these PDF's have a power law form.

there is a limiting physiological process that produces a natural time scale C at short times. Also, the PDF's from some patients are slightly curved rather than linear. Such curves are characteristic of a stretched exponential form $\exp)-Bt^b$) that approaches a power law as b approaches 0[14]. Thus, these slightly curved PDF's may represent stretched exponential forms that are close to power laws. This power law form of the PDF's indicates that there is a very broad range of the times between both v-tach and PVC events which cannot be meaningfully characterized by the classical statistical measures of the mean and the variance.

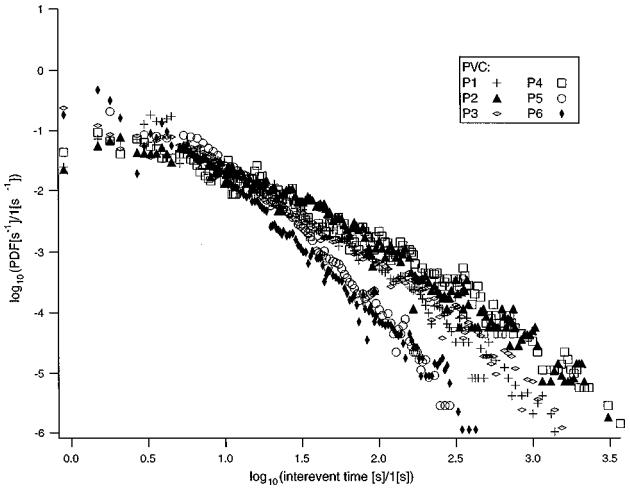

FIG. 5. PDF of PVC interevent times from all six patients are plotted on a log-log scale. There are noticable differences between the slopes of the PDF's from different patients.

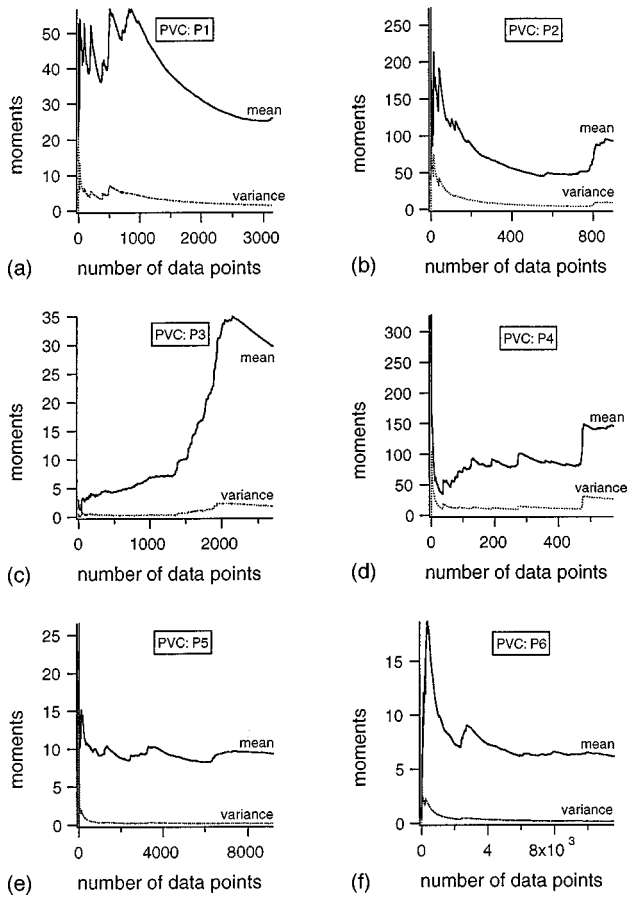

FIG. 6. (a)–(f) The sample means and sample variances of the PVC interevent times are plotted as a function of data length. The changes in those values indicate that the sample means do not necessarily converge to limiting values.

B. Mean and variance

The classical analysis assumes that the sample means and variances will approach finite limiting values that we identify with the population mean and variance. The power law form that we found for the PDF's suggested that this would not be the case for the timing of these rhythm abnormalities. To test this conjecture, we determined the mean and the variance of the times between PVC events over different amounts of data, starting with two interevent times and finishing with all the interevent times in a given set. The results are presented in Fig. 6, which shows that the means and the variances do not always approach stable, limiting values, as suggested by the power law form of the PDF's. There were not enough data to perform a similar analysis on the times between events of v-tach.

Thus the mean rate of the PVC or v-tach events that occur over some finite interval does not describe the data appropriately, and could lead to an invalid assessment of a patient's clinical condition. This is an important finding because many

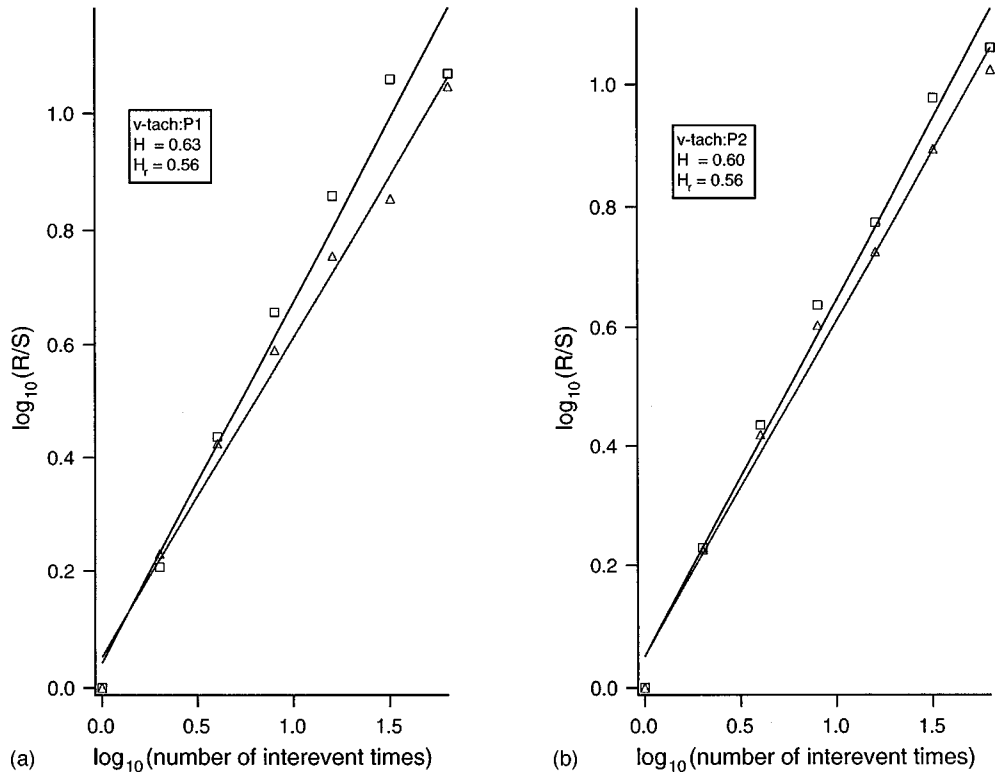

FIG. 7. (a) and (b) Hurst analysis of the v-tach interevent times. The analysis was performed for each data set (squares) and its surrogate (triangles). The higher values of the Hurst exponent (H), in comparison with the surrogate data set (H_r), indicate that there are significant persistent correlations.

medical doctors use such measures to assess the status of a patient.

C. Hurst rescaled range (R/S)

Self-similar, long term correlations in the interevent times can be evaluated by methods based on fractal concepts [16]. These methods can meaningfully analyze data with non-normalizable PDF's that have the power law form of a Levy stable distribution. The moments of such a PDF do not exist because they do not approach finite, nonzero values in the limit as more data are analyzed. For example, in a fractal time series there are larger deviations from the mean as more values of the time series are included. Thus the dispersion increases as more values of the time series are included. The dispersion determined over only one number of values is therefore not an appropriate measure of the statistical properties of such a time series. The appropriate measure is to determine how the dispersion depends on the number of values analyzed.

The Hurst exponent is the slope of the plot of the log (dispersion) vs log (number of values analyzed). When $0<H<0.5$, the self-similar correlations at all time scales are antipersistent; that is, increases at any one time are more likely to be followed by decreases over all later time scales. When $H=0.5$, the self-similar correlations are uncorrelated. When $0.5<H<1$, the self-similar correlations at all time scales are persistent; that is, increases at any one time are more likely to be followed by increases over all later time scales. For a time series $X(t)$ embedded in the space $(X(t),t)$ the fractal dimension $D=2-H$. The value of H has proved a meaningful way to characterize self-similar correlations in physical and biomedical systems [5,6,17–19].

H can be determined directly by determining how the dispersion depends on the number of values analyzed. This can be evaluated by using the relative dispersion (standard deviation and mean), Fano factor (variance and mean), mean squared deviation, or the Hurst rescaled range (running sum minus the average, divided by the standard deviation) [20]. H can also be determined from the PDF of the intervals formed by the time series values crossing a threshold [21] and from a wavelet analysis [22,23]. There are minor differences in the statistical and systematic errors in these methods [5,24–26]. For these studies, we used the classical Hurst rescaled range analysis described in Appendix B.

We determined the rescaled range R/S as a function of the number, M, of data values. The straight lines on the plots of $\log(R/S)$ versus $\log(M)$, shown in Figs. 7 and 8, indicate the presence of self-similar correlations in the times between events of v-tach and PVC's. Since the slope $H>0.5$, these correlations were persistent, rather than antipersistent. We determined the statistical significance of values of H by comparing them with values of H computed from surrogates formed by randomizing the data to remove those correlations. The values of H from 20 surrogates generated from the values of each original data set in random order were determined. If there are N surrogates, the probability p that the value of H from the data is greatest of all these values is equal to $1/N+1$. We could thus determine the probability that the higher value of H from the data is statistically significantly different from the H of the surrogates.

There were only enough data from two patients to perform the Hurst analysis on the times between v-tach. In both

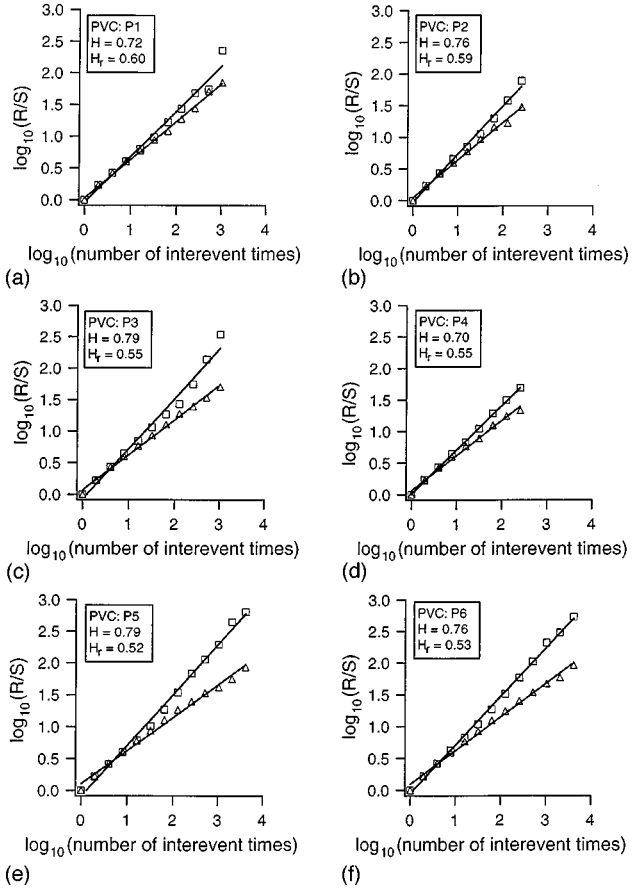

FIG. 8. (a)–(f) Hurst analysis of the PVC interevent times. The analysis was performed for each data set (squares) and its surrogate (triangles). The higher values of the Hurst exponent (H), in comparison with the surrogate data set (H_r), indicate that there are significant persistent correlations.

cases, the correlations were persistent with values of H equal to 0.60 ± 0.02 and 0.63 ± 0.04. For the first patient, the values of H of three of the 20 surrogates were larger than the H of the data, indicating that the H of the data was not different from the H of the uncorrelated surrogates at the 0.05 level of statistical significance. For the second patient, all of the values of H from 20 surrogates were less than the value of H from the data, indicating that the $H=0.63$ of the data was statistically significant with $p<0.05$. Therefore, there appear to be weak persistent correlations in the times between v-tach that are on the borderline of statistical significance.

For the times between PVC's, $0.70<H<0.79$, in all six patients, the values of H from all 20 surrogates generated from each patient were less than the H of the patient data, demonstrating that these persistent correlations were statistically significant, $p<0.05$. Therefore, there are strong persistent correlations in the times between PVC's that are statistically significant. The weaker correlations in the v-tach data as compared to the PVC data may reflect the fact that the v-tach data have fewer events, or that there are different functional mechanisms that generate v-tach and PVC's.

III. CONCLUSIONS

Previous statistical analysis of heart data has concentrated on a study of the time between consecutive heartbeats. Here we presented an analysis of the timing of events that disrupt the rhythm of the heart. To our knowledge, this is the first PDF and Hurst analysis of the times between episodes of ventricular tachyarrhythmia (v-tach) which were recorded by implanted cardioverter defibrillators over periods up to two years, and is a detailed analysis of the times between episodes of premature ventricular contractions (PVC's) which were recorded by Holter monitors over periods of 24 h. We found that there are fractal patterns in the timing of these events common to both these abnormalities.

The power law form of the PDF's of the times between v-tach, over five orders in time, and PVC's, over three orders in time, indicated that the statistics of these events were best described by non-normalizable distributions. Data from such distributions cannot be meaningfully characterized by a mean and a variance. In fact, we showed that the mean and the variance of the number of PVC's per unit time did not always reach stable, limiting values as the amount of data analyzed was increased. These results suggest that the mean frequency of v-tach or PVC events will not necessarily provide good clinical measures to assess the state of patients with heart disease or to evaluate the effectiveness of therapies in treating their disease. The fractal nature of the timing between these events was also evident in the existence of long-range, self-similar, persistent correlations, with Hurst exponent $H>0.5$, that extended over all time scales.

These results indicate that the physical process that disrupts the functioning of the heart produces a fractal pattern in time. Bassingthwaighte, Liebovitch, and West (Ref. [5]) reviewed different physical mechanisms that produce such characteristics. Properly characterizing the statistical properties in these data, which can be done in terms of the slope of the power law PDF and the self-similar correlations of the Hurst exponent, is a necessary first step toward developing a physical theory of the mechanisms that generate these life-threatening arrhythmic events.

ACKNOWLEDGMENTS

We thank Richard N. Fogoros, M.D. (Allegheny General Hospital, Pittsburgh, PA) and Hugh G. Calkins, M.D. (Johns Hopkins University Hospital, Baltimore, MD) for each contributing data on one of their PRxII patients. This work was supported in part by NIH Grant No. EY06234.

APPENDIX A: EFFICIENT ALGORITHM TO DETERMINE THE PDF

To determine the PDF, we computed histograms of different bin sizes, evaluated the PDF from each histogram, and then combined those values to form the completed PDF. $N(k)$ is the number of interevent times, t, in the range $(k-1)\Delta t<t\leqslant k\Delta t$. The PDF at $t=(k-\frac{1}{2})\Delta t$ is equal to $N(k)/(\Delta t N_T)$ where N_T is the total number of interevent times. From each histogram we included, in the PDF, the values computed from the second bin, $k=2$, and continuing for bins $k>2$, stopping at the first bin, $k=k_{\max}$, that contains no interevent times or at $k=20$, whichever comes first. We excluded from the PDF the value computed from the first bin, $k=1$, because it includes all the times unresolved at resolution Δt. We also excluded from the PDF the values

computed from the bins $k>k_{\max}$ or $k>20$ because the interevent times in these bins are too sparse to give good estimates of the PDF. We used histograms of different bin size Δt. The size of the smallest bin $\Delta t_{\min}$ was determined by using the method of trial and error to find the smallest bin size for which there are interevent times in the first four bins. Then the procedure described above was used to compute values of the PDF from that histogram. The next histogram was formed with bin size $2\Delta t_{\min}$, and the values of the PDF were computed. This procedure was iterated so that each subsequent histogram had a bin size double the size of the previous histogram. This was continued until the first time that there are no interevent times in the second, third, or fourth bins. The complete PDF determined in this way extended over the greatest range possible because it had values computed from small bins at short times, as well as from large bins at long times. It also included more values at times that can be computed from overlapping bin sizes. This produces an effective weighting of the PDF, because more values are generated at interevent times that have more events. We found empirically that this weighting provides reliable least squares fits of PDF functions because time intervals with more events, where the PDF is thus more accurate, are weighted more in the fit. We have found that this procedure is accurate and robust in determining PDF's of different forms, such as single exponential, multiple exponential, and power laws.

APPENDIX B: HURST RESCALED RANGE (R/S) ANALYSIS

The range R is the difference between the maximum and minimum of the deviation from the mean of the running sum of the interevent times over a given number of interevent times. The rescaled range R/S, is the range R divided by the standard deviation S. We determined how R/S depended on the number of interevent times. This was done by partitioning the total set of N_T interevent times into consecutive segments of M values. The mean, $\langle x\rangle_{n,M}$, and standard deviation, $S_{n,M}$, of the interevent times $x(i)$ in the nth segment were

$$\langle x\rangle_{n,M}=\frac{1}{M}\sum_{i=(n-1)M+1}^{nM}x(i), \tag{B1}$$

$$S_{n,M}=\left[\frac{1}{M}\sum_{i=(n-1)M+1}^{nM}(x(i)-\langle x\rangle_{n,M})^2\right]^{1/2}. \tag{B2}$$

For i in the range $(n-1)M+1\leq i\leq nM$, we then computed

$$Y_{n,M}(i)=\sum_{k=(n-1)M+1}^{i}(x(k)-\langle x\rangle_{n,M}), \tag{B3}$$

found the range

$$R_{n,M}=\max(Y_{n,M}(i))-\min(Y_{n,M}(i)), \tag{B4}$$

computed the rescaled range $(R/S)_{n,M}$ of that segment,

$$(R/S)_{n,M}=\frac{R_{n,M}}{S_{n,M}}, \tag{B5}$$

and averaged the rescaled ranges computed from the segments,

$$(R/S)_M=\left(\frac{1}{N(M)}\right)\sum_{n=1}^{N(M)}(R/S)_{n,M}, \tag{B6}$$

where $N(M)=N_T/M$.

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