Ventricular response in atrial fibrillation: random or deterministic?

KENNETH M. STEIN, JEFF WALDEN, NEAL LIPPMAN, AND BRUCE B. LERMAN

Division of Cardiology, Department of Medicine, New York Hospital-Cornell Medical Center, New York, New York 10021; and Division of Cardiology, Department of Medicine, University of Connecticut, Farmington, Connecticut 06030

Stein, Kenneth M., J. Jeff Walden, Neal Lippman, and Bruce B. Lerman. Ventricular response in atrial fibrillation: random or deterministic? Am. J. Physiol. 277 (Heart Circ. Physiol. 46): H452–H458, 1999.—The ventricular response in atrial fibrillation is often described as “chaotic,” but this has not been demonstrated in the strict mathematical sense. A defining feature of chaotic systems is sensitivity on initial conditions: similar sequences evolve similarly in the short term but then diverge exponentially. We developed a nonlinear predictive forecasting algorithm to search for predictability and sensitivity on initial conditions in the ventricular response during atrial fibrillation. The algorithm was tested for simulated R-R intervals from a linear oscillator with and without superimposed white noise, a chaotic signal (the logistic map) with and without superimposed white noise, and a pseudorandom signal and was then applied to R-R intervals from 16 chronic atrial fibrillation patients. Short-term predictability was demonstrated for the linear oscillators, without loss of predictive ability farther into the future. The chaotic system demonstrated high short-term predictability that declined rapidly further into the future. The pseudorandom signal was unpredictable. The ventricular response in atrial fibrillation was weakly predictable (statistically significant predictability in 8 of 16 patients), without sensitive dependence on initial conditions. Although the R-R interval sequence is not completely unpredictable, a low-dimensional chaotic attractor does not govern the irregular ventricular response during atrial fibrillation.

METHODS

Nonlinear predictive forecasting. The behavior of every nonrandom (deterministic) system, no matter how complex, can be considered to occur within a “phase space,” which can be represented by a Cartesian coordinate system with one axis for each of the variables necessary to completely describe the state of the system at any given time. For most biologic systems, the nature of these variables, or even their number, is unknown. However, a topological equivalent of phase space is known to exist. The future behavior of a system may be predicted from empirical data using the technique of “lags” (26). With the use of this technique, an embedding dimension (E) is chosen and the points that constitute a phase space are represented as the vectors

\[
\mathbf{X}_n = (R_{R_n}, R_{R_{n-L}}, R_{R_{n-2L}}, \ldots, R_{R_{n-(E-1)L}})
\]

where \(R_{R_n}\) is the n-th R-R interval in the time series and L is the lag, a positive integer. As proposed by Sugihara and May (25), the future behavior of a system may be predicted (“forecasted”) by observing other sufficiently similar trajectories in phase space. Importantly, and in distinct from other methods of forecasting such as autoregressive modeling, this scheme does not require any assumptions about the underlying mathematical relationships of the system other than the initial assumption that the system is deterministic (or, more
precisely, that its behavior can be described within a phase space of finite dimension).

The nonlinear predictive forecasting algorithm therefore consists of the following steps. 1) The technique of lags is used to reconstruct 8 different phase spaces with embedding dimensions from 3 to 10. 2) For each R-R interval in the time series (RR\textsubscript{i}), the three nearest neighbors in each phase space, determined using the Cartesian distance metric
\[ d_{ij} = \sqrt{(X_i - X_j)^2} \]
are chosen from every other point (RR\textsubscript{j}) in the same time series. The predicted next R-R interval (RR\textsubscript{i+1}) is determined as the average of the R-R intervals that follow (RR\textsubscript{i+1}) the three nearest neighbors (each weighted by the inverse of its \(d_{ij}\)). 3) The Pearson correlation coefficient (r) between predicted and actual R-R intervals is computed for all intervals in the time series for each of the eight phase spaces. 4) The phase space with the embedding dimension yielding the highest correlation coefficient is determined. Within that embedding dimension, the 3 nearest neighbors of each R-R interval trajectory in phase space are used to predict the evolution of that trajectory from 1 to 10 steps into the future using a method analogous to that described in the second step. For a system of dimension n, and for a sufficiently large data set, the correlation coefficient should be approximately the same for all embedding dimensions >n. Therefore, the embedding dimension giving the maximum correlation coefficient does not strictly correspond to the dimension of the system but suffices for the practical purpose of nonlinear prediction. 5) For each distance into the future, the correlation coefficient between predicted and actual R-R intervals is computed for all intervals in the time series.

The algorithm can be used to test for the hallmark of chaotic systems: sensitive dependence on initial conditions. In linear systems, nearby trajectories tend to remain nearby, and therefore these systems are equally predictable in the far future as well as in the near future. Random sequences, in contrast, are equally unpredictable in both the near future and far future. In chaotic systems, however, nearby trajectories tend to diverge exponentially. Therefore, they are predictable in the near future but not the far future. For example, the weather is easily predictable 5 min into the future, moderately predictable 5 h into the future, and virtually unpredictable 5 days into the future. By computing the (Pearson) correlations between values predicted from 1 to 10 steps into the future using the nonlinear predictive forecasting algorithm, we can therefore gain insight into whether the system behaves more like a linear system, a random system, or a chaotic system.

Simulated R-R intervals. We tested the above algorithm by applying it to computer-generated sequences of simulated R-R intervals (test sets) of varying lengths (50–2,000 intervals) and with varying amounts of added noise to assess the impact of sequence length and measurement error on the performance of the algorithm. The following test sets were created. 1) A linear oscillator was constructed (chosen to simulate the dominant low- and high-frequency oscillations in human heart period during sinus rhythm)

\[
X(t) = 800 + 100 \sin \left( \frac{2\pi t}{25} \right) + 100 \sin \left( \frac{2\pi t}{5} \right)
\]

2) A linear oscillator with a high signal-to-noise ratio was constructed [using a computerized pseudorandom number (Rand) generator]

\[
X(t) = 800 + 100 \sin \left( \frac{2\pi t}{25} \right) + 100 \sin \left( \frac{2\pi t}{5} \right) + \text{Rand}(-25, +25)
\]

3) A linear oscillator with a low signal-to-noise ratio was constructed

\[
X(t) = 800 + 50 \sin \left( \frac{2\pi t}{25} \right) + 50 \sin \left( \frac{2\pi t}{5} \right) + \text{Rand}(-100, +100)
\]

4) A chaotic system was constructed using the logistic map, a known chaotic system. This system is iteratively determined according to the equations

\[
Y(t) = \lambda (Y_{t-1})(1 - Y_{t-1})
\]

\[\lambda = 4\]

\[
X(t) = 600 + 400Y(t)
\]

5) A chaotic system with a high signal-to-noise ratio was constructed by adding uniformly random numbers scaled over the interval (−25, +25) to the values X(t) from the logistic map in test set 4. 6) A chaotic system with a low signal-to-noise ratio was constructed by adding uniformly random numbers scaled over the interval (−100, +100) to the values X(t) from the logistic map. 7) Finally, a random system consisting of uniformly random numbers scaled over the interval (600, 1,000) was constructed.

Atrial fibrillation. In 16 patients with chronic atrial fibrillation, 24-h ambulatory electrocardiographic recordings of bipolar leads CM\textsubscript{1} and CM\textsubscript{2} were obtained using a standard reel-to-reel Holter monitoring system (Del Mar Avionics, Irvine, CA) and scanned by a computer-based system (Marquette Laser XP; Marquette Electronics, Milwaukee, WI) with total visual verification and correction of beat morphology and timing by one of the authors. The results were digitized at 128 Hz, yielding an approximate temporal resolution of 8 ms. After scanning was completed, the first series of ≤2,000 consecutive R-R intervals without intervening ventricular ectopic beats or artifact was extracted for each patient and downloaded to a personal computer for application of the identical algorithm used for the test sets.

Statistical and power spectral analysis. The significance of the observed Pearson correlation coefficients was determined using a standard two-tailed t-test. A P value <0.01 was taken as indicating that a correlation was significantly different from zero (i.e., was significantly predictable). For data sets of 1,600–2,000 beats this criterion for weak but significant predictability approximately corresponds to a correlation coefficient >0.06. Grouped comparisons of continuous variables were made via the t-test. Grouped comparisons of dichotomous variables were made via Fisher’s exact test. For these purposes a P value <0.05 was required to reject the null hypothesis. Power spectra were computed for raw heart period data using a 1,024-point fast Fourier transform algorithm with a Tukey-Hamming window (11 point).

RESULTS

Test sets. As long as a minimum of 100 intervals was specified, short-term predictability was demonstrated for the system of linear oscillators with no loss of predictive ability farther into the future even in the presence of a large amount of noise (low signal-to-noise ratio) (Fig. 1). For the case of 50 points, short-term predictability was paradoxically improved by the addition of noise; this may relate to boundary and/or aliasing effects specific to sampling 50 points of the function sin(2πt/25) + sin(2πt/5). In contrast, although the chaotic system demonstrated high short-term predictability, the correlation between predicted
and actual intervals declined rapidly with attempts to forecast further into the future. The chaotic signal was distinctive with as few as 50 intervals to analyze in the presence of a high signal-to-noise ratio, although not in the presence of a low signal-to-noise ratio (Fig. 2). As expected, the pseudorandom signal was not predictable.

Atrial fibrillation. The group of 16 patients with chronic atrial fibrillation included 9 males and 7 females with a mean age of 57 ± 12 yr. Of the 16 patients, 6 had no underlying cardiovascular disease, 5 had significant valvular heart disease (mitral regurgitation or mixed rheumatic valvular disease), 1 had an ischemic cardiomyopathy, and 3 had hypertension. Two patients had mitral valve prolapse without significant mitral regurgitation (including 1 patient with coexisting hypertension). Also, 12 of 15 patients were being treated with digoxin, 4 of 15 were on β-blockers, 3 of 15 were on calcium-channel blockers, and 4 of 15 were on antiarrhythmic drug therapy (2 on procainamide, 1 on amiodarone, and 1 on propafenone). One patient’s medications could not be ascertained with certainty. No patient had clinical evidence of digitalis intoxication. During the recording period, the mean R-R interval...
was 804 ± 186 ms (range: 539–1,090 ms). The average standard deviation of the R-R interval was 178 ± 48 ms (range: 118–254 ms). In contrast, for the uniform random signal tested, the mean was 797 and the standard deviation was 143.

The best embedding dimension for prediction one beat into the future (future = 1) ranged from 3 to 10 (mean: 5.9 ± 2.7). As shown in Fig. 3 there was no characteristic "best" embedding dimension for the group as a whole. With the use of each individual patient's best embedding dimension, the ventricular response in atrial fibrillation was only weakly predictable at all time scales and there was no evidence of sensitive dependence on initial conditions (Fig. 4).

However, in 8 of 16 patients, the R-R interval series was significantly (albeit weakly) predictable as evidenced by a correlation coefficient significantly different from zero (Fig. 5). These patients were not significantly different from their counterparts in age, gender, presence of structural heart disease, medications, mean R-R interval, standard deviation of the R-R interval, number of beats analyzed, or best embedding dimension (all P > 0.10). For two individual patients, the ventricular response was moderately predictable (r values of 0.37 and 0.56, respectively, at future = 1) but did not show evidence of sensitive dependence on initial conditions. Although the significance is uncertain, electrocardiograms (ECG) from these patients demonstrated notably "coarse" fibrillatory activity (Fig. 6). Power spectral analysis revealed broad-band power spectra for all patients. The power spectrum for the patient with the highest degree of nonlinear predictability is shown in Fig. 7.

DISCUSSION

The principal findings of the present study are 1) that a nonlinear forecasting algorithm can feasibly be applied to R-R interval data sets and, as evidenced by the performance when applied to computer-generated test sets, can reliably discriminate linear, chaotic, and random types of behavior; 2) that the ventricular response in atrial fibrillation does not appear to represent chaos in the strict mathematical sense of a deterministic aperiodic system; and 3) that, in a significant number of patients, the beat-to-beat ventricular response in atrial fibrillation is not wholly unpredictable.

Nonlinear forecasting. The results in the test sets demonstrate that nonlinear forecasting is a practical approach for qualitatively analyzing the dynamics of a complex system such as that generating the R-R interval data stream. Nonlinear forecasting was initially proposed by Sugihara and May (25) for application to biologic time-series data. The primary advantage of this approach versus linear forecasting systems (e.g., power spectral analysis or autoregressive modeling) is that it does not require any assumptions about the underlying mathematics of the system beyond the
hypothesis that the system is deterministic (i.e., predictable).

Other methods that can be used to look for evidence of chaotic behavior include estimation of the dimension of the attractor for the system to be analyzed (a measure of complexity/aperiodicity) (8) and estimation of the largest Lyapunov exponent of the system (a measure of sensitive dependence on initial conditions). In theory, nonlinear forecasting has an advantage over the former approach in that it is less dependent on very long data streams for accurate interpretation (27) and an advantage over the latter approach in that it is more robust and less dependent on initial assumptions about the behavior of the system.

Predictability of atrial fibrillation. This is the first analysis to discover evidence of significant (although weak) predictability in the beat-to-beat changes in the ventricular response in atrial fibrillation in some patients. Subtle ordering has previously been demonstrated in atrial activation during atrial fibrillation (7, 17). Significant positive or negative correlations between successive ventricular beats during atrial fibrillation have been described in some human subjects (15) as well as in some animal models (14). However, most analyses have not demonstrated any systematic order to the ventricular response during atrial fibrillation in humans, and most authorities describe the pulse in atrial fibrillation as random (1, 6, 12, 29). It is possible that these results differed from ours because the analytic approach (autoregression) depends on an assumption of strict linearity. The signals that we observed were most compatible with a weak linear system superimposed on a very noisy background (cf. Figs. 1 and 4). There was no evidence of sensitive dependence on initial conditions, and our results are therefore not compatible with the notion that the ventricular response in atrial fibrillation might represent a form of low-dimensional chaos.

Although the present analysis shows weak predictability in the ventricular response during atrial fibrillation, it does not permit us to identify the physiological causes of that predictability in these patients. However, van den Berg and colleagues (28) have previously demonstrated a moderate correlation between heart rate variability in atrial fibrillation and systemic vagal tone. These observations might explain the analogy between the prognostic utility of measures of heart rate

Fig. 6. A 12-lead electrocardiogram from the patient whose ventricular response demonstrated the greatest degree of predictability. Notably "coarse" fibrillatory activity is present.

Fig. 7. Power spectral analysis of heart period data from the patient whose ventricular response demonstrated the greatest degree of predictability. Spectrum is "broad band," with no discrete high-frequency peaks.
variability in atrial fibrillation and the same measures in sinus rhythm (20, 21). It is possible that the weak predictability demonstrated in the present study represents the effect of cyclic oscillations in parasympathetic and/or sympathetic tone at the level of the atrioventricular node, superimposed on the effectively random sequence of impulses reaching the distal node due to concealed penetration of multiple wave fronts (13) engaging the perinodal atrium from different directions (11, 24). It should be noted that the R-R interval power spectra did not reveal narrow peaks within ranges characteristic of parasympathetic or sympathetic oscillations, but it is possible that this may represent an intrinsic limitation of Fourier analysis in such a “noisy” system. The two patients with the highest degrees of predictability had coarse atrial fibrillation on the surface ECG, but the physiological significance of this observation is uncertain.

Limitations. It is possible that analysis of longer recordings would have yielded better predictability because, for a short time series, “nearest” neighbors in phase space are not necessarily “near” neighbors. We chose a recording length of ~2,000 intervals to maximize stationarity of the underlying system. Likewise, it is possible that analysis of embedding dimensions >10 would have yielded better predictability. However, there was no evidence suggesting this, and the results would not, in any event, reflect low-dimensional chaos. Similarly, using the three nearest neighbors for prediction was an empirical choice; others have proposed using the single nearest neighbor for prediction (16). However, although this may have had some quantitative effect, it is unlikely that it would qualitatively affect our results. Finally, to study patients with stable chronic atrial fibrillation, it was necessary to accept patients undergoing treatment with a variety of medications including digoxin, β-blockers, calcium-channel blockers, and antiarrhythmic drugs. Although we observed no important differences accorded to the use of any of these agents, the possibility that subtle drug effects may have altered the results cannot be fully excluded.

In summary, despite the above considerations, the present data demonstrate the potential of nonlinear predictive forecasting as a tool for qualitative analysis of dynamic systems and demonstrate that atrial fibrillation is not a chaotic rhythm. Furthermore, although the pathophysiological significance is not clear, the technique reveals the existence of a subset of patients with atrial fibrillation whose R-R interval sequence is not entirely unpredictable.

REFERENCES


