Noise Effects on the Complex Patterns of Abnormal Heartbeats

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Patients at high risk for sudden death often exhibit complex heart rhythms in which abnormal heartbeats are interspersed with normal heartbeats. We analyze such a complex rhythm in a single patient over a 12-h period and show that the rhythm can be described by a theoretical model consisting of two interacting oscillators with stochastic elements. By varying the magnitude of the noise, we show that for an intermediate level of noise, the model gives best agreement with key statistical features of the dynamics.

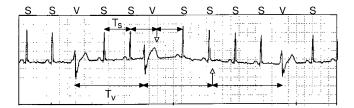
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Individuals with frequent abnormal heartbeats (Fig. 1) may be at high risk for sudden cardiac death [1]. Such abnormal heart rhythms often have a random appearance. Attempts have been made to analyze these rhythms by inspecting short data strips [2,3] and matching them beat by beat to various models [3-6]. Other approaches [7,8]characterize statistical properties in longer records of up to several hours. However, the mechanisms underlying these abnormal rhythms and their changes over long periods of time remain elusive. Here we show that a theoretical model consisting of two coupled oscillators [3-7] describes the observed patterns of abnormal heartbeats in one clinical case provided we introduce noise to the periods of the oscillators. This approach may generalize to the analysis of the underlying mechanism of a large number of records with complex patterns of abnormal heartbeats.

We consider a continuous 12-h segment of the ambulatory electrocardiographic record of an individual with heart failure and frequent abnormal heartbeats (Fig. 1). The normal sinus heartbeats, S-beats, arise from activity in the sinus node, the normal pacemaker of the heart. The time intervals between the normal beats appear to be periodic in this short tracing, but they do fluctuate during the 12-h period. The abnormal ventricular beats, V-beats, arise in the lower chambers of the heart, the ventricles. Although the timing between the V-beats appears to be irregular, the histogram of the interventricular time intervals, the time intervals between consecutive V-beats, consists of equidistant peaks implying that the interventricular time intervals are multiples of a fixed number (Fig. 1). This result is consistent with the possibility that the heart rhythm arises from a competition between two oscillators: the normal sinus oscillator, and an abnormal ventricular oscillator with periods T_S and T_V , respectively. Such rhythms are called parasystolic.

After each S-beat or V-beat, there is a time period, called the refractory time θ , during which all other heartbeats are blocked. Because in our case $\theta/T_S \ge 1/2$, all V-beats will block the following S-beat [9].

The finite width of the peaks in Fig. 1 indicates the presence of either noise on the timing of the V-beats or coupling between the S- and the V-beats, or both. To estimate the amount of noise or type of coupling we first compare the data to the predictions of the pure parasystolic model, i.e., with no noise and no coupling. To describe the pure parasystolic mechanism we introduce the phase ϕ_i of the ith ventricular beat in the sinus cycle, i.e., the time interval between the ith ventricular beat and the previous sinus beat normalized by T_S [3–6]. Successive values of



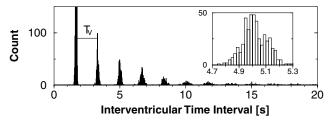


FIG. 1. Upper panel: Electrocardiogram over 6.6 s of a patient with heart failure. Sinus (S) and ventricular (V) beats differ in morphology. S-beats are separated by an interval T_S . The time interval between the S-beats with an intervening V-beat is approximately $2T_S$, implying that an S-beat has been blocked (downward white arrow). The interventricular time interval T_V , determined from the histogram in the lower panel, is also indicated and is consistent with a blocked V-beat (upward white arrow). Lower panel: The histogram of the time intervals between consecutive abnormal V-beats for the 12-h record from which the segment in the upper panel was extracted ($\approx 80\,000$ beats with $\approx 5000\,V$ -beats). The time interval between the peaks is 1.67 s ($\approx 3T_S$). The inset is an enlargement of the peak at 5 s. The sampling rate of the underlying electrocardiographic time series is 128 Hz.

 ϕ_i are determined by iterating the difference equation:

$$\phi_{i+1} = (\phi_i + T_V/T_S) \mod 1,$$
 (1)

where a ventricular beat is expressed if $\phi_{i+1} > \theta/T_S$. For a fixed irrational ratio T_V/T_S (incommensurate periods), the phase of the V-oscillator with respect to the S-oscillator will, for sufficiently long times, be equally distributed in the interval [0,1]. Interestingly, the sequence of the number of intervening S-beats between consecutive V-beats, called the NIB sequence, consists of only three different values (NIB-triplets). The values of these NIB-triplets change with T_V/T_S and θ/T_S [10]. Examples are shown in Fig. 2a. These NIB-triplets are sensitive to noise and coupling.

The uniform distribution of the phases of the V-beats allows us to derive the fraction of V-beats which are observed at a particular T_S . The total number of S-beats and V-beats, N, during a time interval T is given by $N = T/T_S$. The total number of observed and blocked V-beats in T is T/T_V . Out of these a fraction of $(T_S - \theta)/T_S$

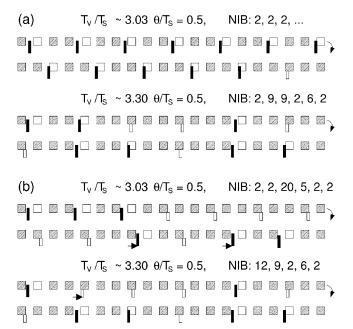


FIG. 2. Generation of NIB-triplets for $\theta/T_S = 0.5$ and two different values of T_V/T_S . The boxes are the S-beats with their refractory times. Empty boxes are blocked beats, and dashed boxes are expressed beats. The expressed V-beats are symbolized by black bars, the blocked ones by empty bars. S-beats after each expressed abnormal beat are blocked since $\theta/T_S \ge 0.5$. (a) Deterministic model without coupling. In the upper panel, the ratio of the periods $T_V/T_S \approx 3$. The phase of the V-beat with respect to the S-beats is therefore changing slowly, and the NIB is 2 for several periods until it is blocked for several periods. For $T_V/T_S \approx 3.3$ the NIB-triplet 2, 6, 9 is generated. (b) Model with coupling and noise. Coupling shifts the V-beats into the refractory time for $T_V/T_S \approx 3$. For $T_V/T_S \approx 3.3$ the coupling has minimal effects. The addition of noise (arrows) changes the NIB sequences by moving some V-beats into or out of the refractory time. For $T_V/T_S \approx 3$, this combines two consecutive appearances of NIB = 2 into NIB = 5 (8, 11,...). For $T_V/T_S = 3.3$, combinations of NIB = 2 with the other two values, 6 or 9, generates NIB = 9 or 12.

occurs outside of the refractory period and is observed. Call n_V , the number of observed V-beats in the time interval T. It follows that $n_V = (T_S - \theta)/T_S \times T/T_V$, and consequently

$$n_V/N = (T_S - \theta)/T_V. (2)$$

Perturbation of the timing of the V-beats by Gaussian noise does not affect this distribution, but it is sensitive to any coupling between the two oscillators.

To compare the properties of the unperturbed model to the clinical data, we iterate Eq. (1) using typical parameter values for the patient under consideration, and plot, first, histograms showing the NIB values for three sets of parameters in Fig. 3a, and, second, the fraction of V-beats from Eq. (2) in Fig. 4a. The corresponding plots for the clinical data are shown in Figs. 3b and 4a. Since the value of T_S fluctuates during the record, we combine the data from different times of the day during which T_S falls in a fixed 10 ms range. Figure 3b shows the histograms of NIB values for three different values of T_S . For $T_S = 0.61$ s $(T_V/T_S < 3)$ and $T_S = 0.51$ s $(T_V/T_S > 3)$, we find the same NIB-triplets as in the deterministic model (Fig. 3a). However, additional peaks in the data (Fig. 3b) contradict the "rule" of only three NIB values in the purely deterministic model. Furthermore, for $T_S = 0.55 \text{ s} (T_V/T_S \approx 3)$, fewer beats with NIB = 2 are present in the data, and new NIB values appear largely corresponding to the sequence $5, 8, 11, \ldots = 3n - 1$, where $n \ge 2$ is an integer [11]. These discrepancies can be explained in part by the effects of noise on the timing of the V-beats (Fig. 2b). Figure 4a shows in detail that, for $T_V/T_S \approx 3$, the clinical data contain many fewer V-beats than expected. This suggests that, for $T_V/T_S \approx 3$, coupling between the two oscillators phase locks the V-beats within the refractory time of the S-beats. The distribution of the phases (not shown) for $T_V/T_S \approx 3$ is indeed peaked near the refractory time.

On the basis of Figs. 3a, 3b, and 4, we propose that the pattern of V-beats in the data may be described by a stochastic difference equation [12]

$$\phi_{i+1} = \left(\phi_i + \frac{T_V}{T_S} + \frac{f(\phi_i, T_S, T_V)}{T_S} + \frac{\eta}{T_S}\right) \mod 1, (3)$$

where η is a Gaussian random variable distributed around 0, and $f(\phi_i, T_S, T_V)$ gives the change of T_V due to the coupling of the S-beats to the V-beats [2,4,13].

Each of the S-beats that may appear between consecutive (expressed or blocked) V-beats iteratively changes the position of the next V-beat depending on the timing of the S-beats (phase resetting). These changes add up to $f(\phi_i, T_S, T_V)$ [14]. The phase resetting curve [15] in Fig. 4b leads, for $T_V/T_S \approx 3$, to a fixed point in Eq. (3), such that the V-beats always fall in the refractory period of the S-beat and thus are always blocked. However, the noise term leads to a dispersion of the phases of the V-oscillator such that some of the V-beats are expressed. Thus, both the coupling and the stochastic term interact to generate

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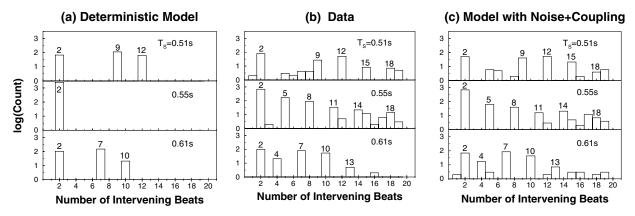
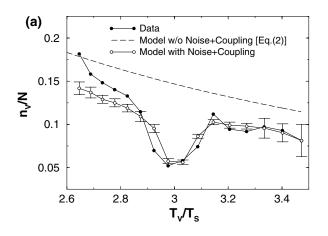


FIG. 3. Histograms of the number of intervening beats (NIB) on a logarithmic scale for $T_S=0.51$, 0.55, and 0.61 s, from top to bottom. For $T_V=1.67$ s, the corresponding ratios of the periods are $T_V/T_S=3.27$, 3.03, and 2.73. In the middle panel the count for NIB = 2 is 2465 in (a), 677 in (b), and 686 in (c). (a) Simulation of the deterministic model with constant T_S , $T_V=1.67$ s. The average S-beat interval T_S varies from 0.47 to 0.64 s based on the data set we study. For each histogram, the number of S-beats corresponds to the number of S-beats in the data with the same average T_S . (b) NIB histogram for the data. The value for T_S at each V-beat is the average S-beat interval in a window of 20 beats centered at the V-beat. All V-beats in this window are replaced by the corresponding blocked S-beats which are placed in the middle of the two neighboring S-beats. The histogram of the NIB values is computed from all sequences of the record that have the same mean T_S . For $T_S=0.55$ s ($T_V/T_S=3.03$), we find NIB values 2, 5, 8, 11, ..., $T_S=0.55$ s ($T_S=0.55$) and noise. Instead of a constant $T_S=0.55$ we use the S-beat intervals of the data, and we add to $T_S=0.55$ s because of the coupling.

the dynamics. The effects of the coupling and the noise for $T_V/T_S \neq 3$ are represented schematically in Fig. 2b. Figure 3c shows how the distributions of the NIB val-



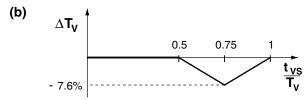


FIG. 4. (a) The fraction n_V/N plotted against the ratio T_V/T_S . The theoretical curve given by Eq. (2), with θ as in Fig. 3a, is reproduced by the model without coupling, and remains unchanged when noise is added. The data deviate from this curve at the ratio $T_V/T_S=3$, where we find less than half of the predicted V-beats. The model with coupling and noise reproduces this behavior. (b) The coupling between the two oscillators. The change ΔT_V of the period of the V-oscillator as a function of the ratio of the time t_{VS} between the last V-beat and an S-beat, and T_V . The coupling shortens the intrinsic T_{V_0} to the apparent T_V .

ues change when both coupling and noise are included in the simulation. The model now reproduces quantitatively the data. For $T_S \approx 0.55$ s ($T_V/T_S \approx 3$) the number of the V-beats is reduced by the coupling, and the NIB sequence 2,5,8,..., is generated by the noise. As a consequence of the noise moving the V-beats randomly in and out of the refractory time, the blocking mechanism gives rise to a discrete Poisson process leading to an approximately exponential falloff of the peak heights of the occurrences of the NIB values 2,5,8 [6,16]. Finally, the model gives an accurate estimate of the fraction of V-beats as a function of T_S shown in Fig. 4a.

In order to estimate the magnitude of the noise, we calculate the cross correlation between the numbers of occurrences of each NIB value in the model and the clinical data [17]. Figure 5 shows the correlation as a function of the

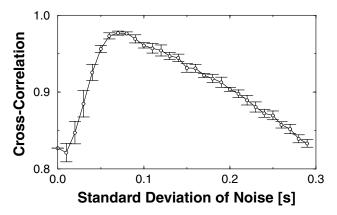


FIG. 5. The cross correlation between data and model as a function of the noise level. We cross correlate the histograms in Figs. 3b and 3c for all values of T_S from 0.48–0.62 s in steps of 0.01 s [17].

068104-3 068104-3

standard deviation σ of the noise. The correlation function has a maximum at $\sigma \approx 0.07$ s. This value of σ also best reproduces the broadness of the peaks in the distribution of the interventricular time intervals (Fig. 1). Further, the model reproduces the asymmetrical form of the peaks in the histogram (inset of Fig. 1). In the simulation, the coupling splits the peaks into two subpeaks giving them an asymmetrical appearance (not shown).

In this work we analyzed the patterns of abnormal heartbeats in a 12-h record from a single patient and proposed that the dynamics results from a combination of deterministic and stochastic mechanisms. Quantitative comparison between predictions of the model and the clinical data shows best agreement for an optimal level of noise in the model.

Our approach is in contrast to standard approaches [1] in which crude measures, such as the average numbers of abnormal heart beats per unit time, are used for clinical assessment. We believe that distinctive dynamics are associated with different mechanisms, and hence different therapeutic strategies. Thus, the detailed program of analysis applied to one clinical record in this Letter is essential to better classify cardiac arrhythmias based on the underlying mechanisms and resulting dynamics.

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- mated as the minimal time interval between an *S*-beat and the following *V*-beat. Analysis (not given here) shows that the refractory time is weakly dependent on T_S . We assume $\theta = 0.29T_S + 0.15$ s, where T_S varies from 0.5 to 0.62 s. The refractory time after the *V*-beats cannot (and need not) be estimated since here the following *S*-beats are always blocked.
- [10] For the purely deterministic model, the NIB sequences can be shown to follow three "rules" [3,5]: (i) there are at most three different values for the NIB; (ii) the sum of the two smaller ones is the largest NIB value minus one, implying that (iii) one of the NIB values must be odd. The θ/T_S , T_V/T_S -parameter space can be completely partitioned into regions of these triplets [5]. The problem is related to the gaps and steps problem in number theory: G. A. Hedlund, Am. J. Math. **66**, 605 (1944); N. B. Slater, Proc. Cambridge Philos. Soc. **63**, 1115 (1967).
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- [14] Each *S*-beat between two consecutive *V*-beats changes the time interval between the *V*-beats. The time interval t_{VS}^n between a *V*-beat with the phase ϕ_i and the *n*th *S*-beat is $(n-\phi_i)T_S$, $n=1,\ldots,n_{\max}$, where the *S*-beat with n=1 is blocked if the *V*-beat was expressed. The period T_{Vn} including the effects of all *S*-beats up to the *n*th is found by iterating: $T_{Vn} = T_{Vn-1} + \Delta T_V(n-\phi_i)T_S/T_{Vn-1}$, where $\Delta T_V(x)$ is given by Fig. 4b and $T_{V_0} = 1.76$ s, the intrinsic period of the *V*-beats. In Eq. (3), we then have $f(\phi_i, T_S, T_V) = T_{Vn_{\max}} T_V$. The number n_{\max} of *S*-beats between consecutive *V*-beats, expressed or blocked, is the smallest integer number such that $(n_{\max} \phi_i)T_S \leq T_{Vn_{\max}}$. In our particular case, n_{\max} may be 3 or 4.
- [15] Some other coupling curves are possible and yield similar agreement with the data. The coupling curves with best fit to our data all had a flat or positive first part $(T_V/T_S \le 0.5)$ and a negative second part $(T_V/T_S \ge 0.5)$. This form is similar to physiologically motivated phase resetting curves [2,4]. A direct derivation of the phase resetting curve from the data is difficult since every two V-beats are separated by at least two S-beats.
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