

Specific Patterns of Premature Beats Tend to Initiate Ventricular Tachyarrhythmias in Human Patients

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Abstract

Introduction. Previously, we demonstrated that certain patterns of abnormal rapid beats, notably "short-long-short-short" (SLSS) patterns, tend to produce action potential block in computer models, and tend to initiate VF in in vivo canine experiments, consistent with our theory based on electrical restitution. Here we present evidence that these same patterns often precede VF in human ECG recordings. Methods. Thirty-four ECG recordings from just prior to and during tachyarrhythmic events were obtained from ICDs implanted in several human patients. The distributions of the first four abnormal RR intervals prior to arrhythmia onset were fit to single-gaussian and dual-gaussian distributions. Results. Dual-gaussian distributions were obtained for the second and third abnormal beats, while single gaussian distributions were obtained for the first and fourth. These distributions are consistent with the tendency of the SLSS pattern of premature beats, as well as SLLS and SSSS patterns, to precede the tachyarrhythmic event, as described by our computer model. Conclusions. The results provide further evidence that electrical restitution theory, the basis for both our theory and computer model, although imperfect, is sufficient to both predict and understand the manner in which premature beats initiate VF. This understanding may, in the future, lead to new methods for preventing VF, through the imposition of stimuli designed to avoid the dangerous premature beat patterns described in this study.

1. Introduction

An understanding of the mechanisms responsible for the initiation of rapid, abnormal cardiac rhythms is potentially very important, because it could lead to the development of therapies, both electrical and pharmaceutical, that could prevent these dangerous rhythms before they have a chance to start. Yet, these mechanisms are poorly understood. One target of study, when it appears, is the pattern of premature

beats that often precedes the onset of these rapid rhythms.

Our group has been studying these premature beats from both experimental and theoretical perspectives. In 2003, Fox et al [1] employed a coupled maps computer model to show that certain patterns of premature beats, most commonly a short-long-short-short (SLSS) pattern, tended to cause action potential block on cardiac fibers. Block in fiber systems such as this one is thought to be linked to the triggering tachyarrhythmias in the actual heart. Otani [2] developed a theory that explained this pattern of stimulus intervals, and extended the diagnostics of the coupled maps model so that its predictions could be visualized in 4D "interval-length" space. We then used this version of the model during *in vivo* canine experiments to generate predictions while the experiments were being performed [3]. Specifically, the action potential duration (APD) restitution function measured in each animal was inputted into the model, which then yielded predictions of which types of premature intervals should cause action potential block. When the model predicted SLSS patterns were most likely to produce block, we found that this pattern was also most likely to induce ventricular fibrillation (VF) in that animal. Less commonly, the model predicted that an SLLS pattern was mostly likely to produce block. In this case, we found that this same interval pattern tended to induce VF, while the SLSS pattern did not.

In the present study, we are attempting to determine whether SLSS, SLLS and other types of premature beat patterns are also related to the onset of VF in humans. If true, the study would provide evidence that the mechanism described by Otani [2] is operative, thus giving us new clues about what happens in the first stages of VF induction.

2. Methods

Electrocardiograms (ECGs) from seventy-one (71) episodes of tachyarrhythmia and ventricular fibrillation (VF) in human patients were obtained from 34 case numbers taken from the MADIT II trial [4]. Patients in this trial

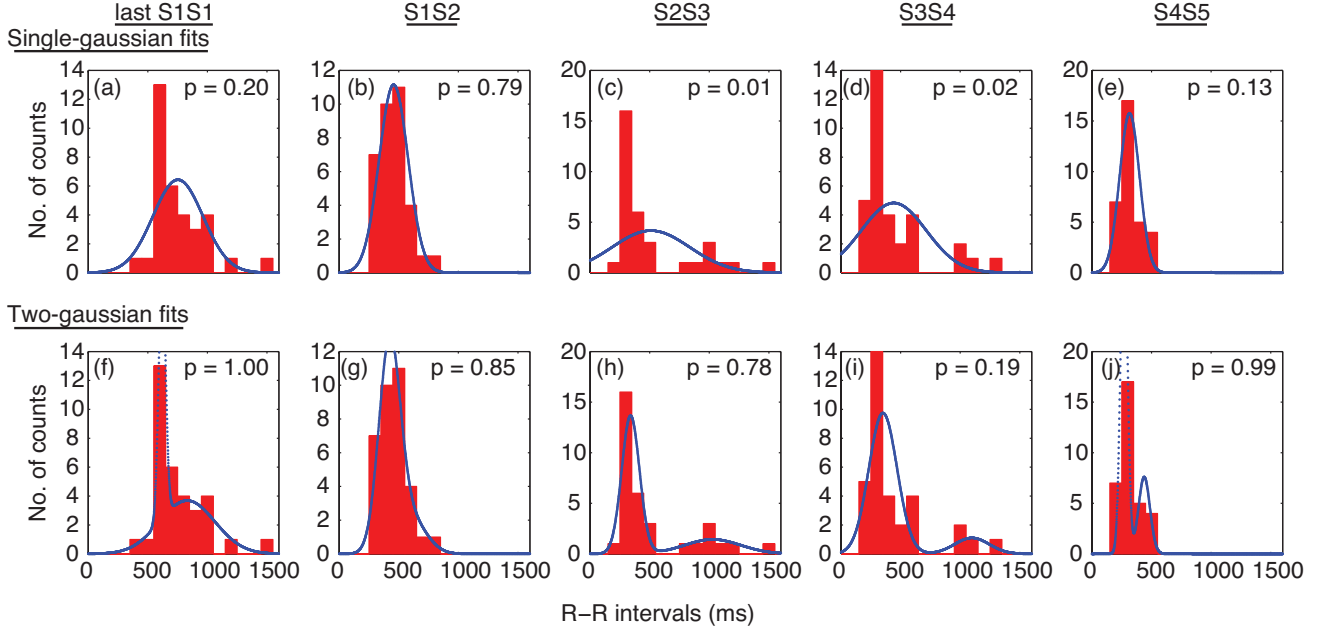


Figure 1. ICD inter-beat interval histograms (in red) for the last S1S1 interval, and the S1S2, S2S3, S3S4, and S4S5 intervals. Upper panels (in blue): the best fit of a single gaussian distribution to the ICD data. Lower panels (in blue): the best fit of a two-gaussian distribution to the ICD data. The computed p -value appearing in each plot is a measure of the goodness of fit of each distribution appear above each plot. The smaller p is, the worse the fit. We choose $p < 0.05$ as the criterion to reject the corresponding distribution as a fit to the experimental data.

had had a previous myocardial infarction and presented with an ejection fraction of 30% or less. A number of these episodes had to be eliminated for various reasons, leaving 34 ECGs from 32 different case numbers. RR intervals of the abnormal beats immediately preceding VF were measured manually. In each of the 34 records, we defined the last normal RR interval preceding the onset of tachyarrhythmia as the “last S1S1” interval, and then defined the next interval (i.e., the first premature RR interval) as the “S1S2” interval. Intervals immediately following the S1S2 interval were then defined, in sequence, as the S2S3, S3S4 and S4S5 intervals.

When each of these interval families (i.e., the S1S2 family of intervals, the S2S3 family of intervals, etc.) was plotted as a histogram (Fig. 1), the presence of one or more “bumps” in the distribution of intervals was immediately apparent. Specifically, for both the S2S3 and S3S4 intervals (Figs. 1(c) and (d) respectively), there appear to be two populations: very short intervals on the order of 350 ms, and very long intervals, around 1000 ms, with very little in between. The other interval distributions measured (Figs. 1(a), (b) and (e)) did not exhibit the double-bump feature.

To demonstrate this statistically, we first used the expectation-maximization (EM) statistical algorithm to compute both the single-gaussian and two-gaussian distri-

butions that best fit our last-S1S1, S1S2, S2S3, S3S4 and S4S5 intervals from the 34 ECGs. Specifically, the EM method was allowed to converge on optimized values for μ_j , σ_j and a_j in distributions of the form

$$f(x) = \sum_{j=1}^N \frac{a_j}{\sqrt{2\pi}\sigma_j} \exp\left(-\frac{(x-\mu_j)^2}{2\sigma_j^2}\right), \quad (1)$$

where μ_j , σ_j and a_j are the mean, standard deviation and relative area of the j th normal distribution, and the a_j 's are constrained to sum to 1 for both $N = 1$ and $N = 2$. The single-gaussian and two-gaussian distributions we obtained appear as the blue curves in the top and bottom rows, respectively, of Fig. 1. Histograms of the experimental data are duplicated in the plots in the bottom row to facilitate comparison.

We note that it is always possible to improve the fit by increasing the number of normal distributions N in the sum. Yet, if N is too large, the added bumps just correspond to noise and not any physical property. Thus, to determine the optimal value of N , we instead we proceeded as follows: We first defined the quantity,

$$R_D = \frac{2}{n} \sum_{i=1}^n |F_D(x_i) - F(x_i)| \quad (2)$$

Table 1. Mean, standard deviation, and relative areas of the gaussian distribution(s) that make up the distributions deemed to fit the ICD beat intervals, as determined from the p -values obtained for best-fit one- and two-gaussian distributions. These parameters we calculated using the EM algorithm.

	Mean(ms)	Std. Dev.(ms)	Rel. Area	Mean(ms)	Std. Dev.(ms)	Rel. Area
Last-S1S1 intervals	753	211	1.00			
S1S2 intervals	457	122	1.00			
S2S3 intervals	340	75	0.75	1028	235	0.25
S3S4 intervals	352	119	0.88	1098	145	0.12
S4S5intervals	316	84	1.00			

where

$$F(x) = \int_{-\infty}^x f(x')dx' \quad (3)$$

is the cumulative distribution function of the distribution $f(x)$ we are testing, and

$$F_D(x_i) = (i - 0.5)/n, \quad i = 1, \dots, n \quad (4)$$

is an effective cumulative distribution for our ICD dataset of intervals x_i : $D = \{x_i | i = 1, \dots, n\}$, with n in this case being 34. Defined in this way, R_D is smaller when the fit of $f(x)$ to the experimental data is better. To assess how good a given value for R_D is, we calculated the equivalent quantity, R_{T_j} , for 1000 datasets T_j , $j = 1, \dots, 1000$, each created using the probability distribution $f(x)$. We then calculated the quantity p , defined as the percentage of the 1000 datasets we created that are fitted by $f(x)$ more poorly than our experimental dataset, using the inequality $R_{T_j} > R_D$ as our criterion. We then say that $f(x)$ is not a good fit to the experimental data if $p < 0.05$. The motivation for this criterion is that, if more than 95% of the datasets we created using, say, the single-gaussian distribution are better fits for the distribution than our experimental dataset, then the chances are less than 5% that our experimental dataset could have been created by this single-gaussian distribution and still fit this badly. Thus, the single-gaussian distribution can be rejected as an explanation for the data we obtained, and we can move on to the two-gaussian distribution, and so on.

3. Results

The p -values for each of the intervals families for both the one- and two-gaussian distributions using this method are shown in each of the panels of Fig. 1, while Table 1 shows the optimal distribution parameters obtained from the EM method. Examination of the p -values shows that the single-gaussian distributions calculated for the last-S1S1, S1S2 and S4S5 intervals are reasonable fits for the ICD data for those beat intervals, since $p > 0.05$ for those distributions (Figs. 1(a), (b) and (e)). However, the S2S3 and S3S4 intervals are not a good match for their computed

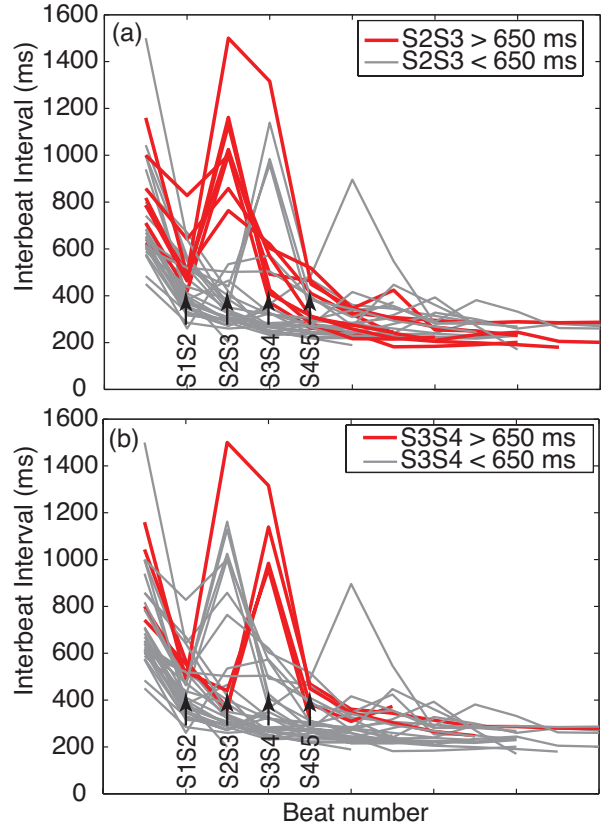


Figure 2. Beat intervals for the 34 ECG records with (a) the 8 records with S2S3 intervals > 650 ms, and (b) the 4 records with S3S4 intervals > 650 ms marked in red.

best-fit, single-gaussian distributions ($p < 0.05$, Figs. 1(c) and (d)). For those two beat intervals, we see that two-gaussian distributions are a good fit ($p > 0.05$, Figs. 1(h) and (i)), confirming what we found upon casual observation. The means of the two gaussian peaks calculated from EM algorithm, are around 350 and 1000 ms, as expected, as shown in Table 1.

Examination of the eight ECG records whose S2S3 interval is in the population centered around 1028 ms shows

that for all but one of them, all the other intervals following the last S1S1 interval are short, as illustrated in Fig. 2(a). Thus, starting with the S1S2 interval, the pattern observed is SLSS..., where S refers to “short” intervals roughly in the 300–600 ms range, while L indicates intervals >700 ms. Similarly, all but one of the four ECG records whose S3S4 interval is in the “long-interval” population has the interval pattern SSLSS. This one exceptional pattern is the same in both cases and has pattern SLLS.

4. Discussion

These patterns are in general agreement with our previous *in vivo* canine experiments, in which various patterns of premature stimuli were introduced [3, 5]. In these experiments, both SLSS and, less commonly, SLLS patterns of premature stimuli led to the onset of VF. Patterns that started with SS also often to lead to VF, although the effects of subsequent premature stimuli (e.g., SSLSS) were not specifically studied. One significant difference is that the long interval in the canine experiments was only 40–60 ms longer than the short intervals, whereas in our human data they were 700 ms longer.

Our results of our study also largely agree with other, earlier studies. In the Locati study [6], the presence of a short-long-short (SLS) pattern preceding the onset of torsade de points was verified through use of the t-test on consecutive intervals. We also find that most of the patterns of premature beats that end in VF start off as a series of short premature beats, which may either precede or be part of the beginning of the tachyarrhythmia. Another study that finds the SLS pattern preceding tachyarrhythmia is Anthony et al [7]. They find that this pattern is less common than arrhythmias that start with a single premature beat. This is also consistent with our findings—there are many more traces that show up as gray in both panels of Fig. 2 (22 of 34—65%. not counting one rogue gray trace having a long S5S6 interval) which correspond to series of only short intervals preceding tachyarrhythmia onset.

We have yet to make a direct comparison of our results from this human ECG study with our coupled maps model. Previously, however, we have found that monotonically increasing electrical restitution functions, as suggested by the dependency of the QTc diagnostic on the RR interval, tend to point to SLSS as well as series of short intervals as the patterns of intervals that are most likely to lead to action potential block. This tendency holds even when the slope of the restitution function is positive but much less than one. The set of beat intervals resulting in block is considerably smaller in this case, but still quite significant as a group. Modifications of this tendency due to short-term

cardiac memory or hysteresis have also yet to be considered, but are currently under investigation.

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