Identifying sudden cardiac death risk and specifying its occurrence time by analyzing electrocardiograms in natural time

P. A. Varotsos,[a] N. V. Sarlis, E. S. Skordas, and M. S. Lazaridou
Solid State Section and Solid Earth Physics Institute, Physics Department, University of Athens, Panepistimiopolis, Zografos, 157 84 Athens, Greece

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Sudden cardiac death (SCD) is a frequent cause of death and may occur even if the electrocardiogram seems to be similar to that of a healthy individual. A method which not only identifies the risk but also provides an estimate of the time of an impending cardiac arrest is proposed. Analyzing 159 electrocardiograms in natural time, the authors find that the key quantity is the entropy change under time reversal. After it becomes maximum at the scale of 13 heartbeats, ventricular fibrillation starts within ~3 h in 16 out of 18 SCDs. The method also distinguishes congestive heart failure patients from SCD. © *2007 American Institute of Physics*.
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The healthy heart beats irregularly. Initial studies showed that, in healthy subjects, heart-rate fluctuation displays $1/f$ noise and fractal dynamics with long-range correlation, e.g., Ref. 1. Later, e.g., Refs. 2 and 3, even higher complexity was reported, which breaks down in illness.[4–8]

Physiological time series most likely[9,10] contain stochastic and deterministic components. Since entropy is a concept equally applicable to deterministic as well as stochastic processes, its use is preferred[9] here in the electrocardiogram (ECG) analysis. Our approach differs essentially from that of other authors, because the entropy we employ is defined[11] in an entirely different time domain, i.e., the natural time domain. This has already been shown[11,12] to provide a useful tool to distinguish similar looking signals that are emitted from systems of different dynamics.

The natural time χ is introduced[13,14] by ascribing to the m th pulse of an electric signal consisting of N pulses, the value $\chi_m=m/N$, and the analysis is made in terms of the couple (χ_m,Q_m), where Q_m denotes the duration of the m th pulse. For example, Fig. 1 shows how the RR (beat-to-beat) interval time series can be read in natural time. The entropy S in the natural time domain is defined[11] as $S=\langle\chi\ln\chi\rangle-\langle\chi\rangle\ln\langle\chi\rangle$, where $\langle f(\chi)\rangle\equiv\Sigma_{m=1}^{N}p_m f(\chi_m)$ and $p_m=Q_m/\Sigma_{n=1}^{N}Q_n$. It is *dynamic* entropy depending on the *sequential* order of pulses.[9] The entropy obtained upon considering[15] the time reversal T, i.e., $Tp_m=p_{N-m+1}$, is labeled by S_- (Figs. 1(c) and 1(d) show how the reading of Figs. 1(a) and 1(b) becomes under time reversal). It was found[15] that, in general, S_- is different from S, and hence S shows the breaking of the time-reversal symmetry. The difference S-S_- will be hereafter labeled ΔS; this will also have a subscript (ΔS_i) meaning that the calculation is made (for each S and S_-) at a scale i (=number of successive pulses). We shall show below that ΔS_i, *if* calculated at proper scales, is probably the key measure that may identify the impending sudden cardiac risk as well as provide an estimate of the time of its occurrence. Sudden cardiac death remains a major cause of death in industrialized countries.[16–18]

The data analyzed in natural time are 159 long-lasting (from several hours to around 24 h) ECG recordings, which come from databases,[19] containing (i) 72 healthy subjects (H), (ii) 44 patients with congestive heart failure (CHF), (iii) 25 subjects with atrial fibrillation (AF), and (iv) 18 individuals who suffered sudden cardiac death (SCD) (see Appendix 1 of Ref. 20). The results presented here refer to the RR intervals (see Fig. 1), i.e., $Q_m=\mathrm{RR}_m$, as well as to the NN intervals, i.e., $Q_m=\mathrm{NN}_m$. The latter are intervals between consecutive *normal* beats, while intervals between pairs of normal beats surrounding an ectopic beat are discarded.

In our procedure, a window of length i is sliding, each time by one pulse, through the whole time series. The entropies S and S_-, and therefrom their difference ΔS_i, are calculated each time. Thus, we form a new time series consisting of successive ΔS_i values (see Appendix 2 of Ref. 20). The standard deviation of these values is denoted by $\sigma[\Delta S_i]$. Upon shuffling the Q_m randomly (thus destroying any information hidden in the *ordering* of the heartbeats[9,21]), the ΔS_i values turn to a sequence of different values labeled $\Delta S_i^{\mathrm{shuf}}$ whose standard deviation is designated by $\sigma[\Delta S_i^{\mathrm{shuf}}]$ (its theoretical estimation is given in Appendix 3 of Ref. 20). The measure $N_i\equiv\sigma[\Delta S_i^{\mathrm{shuf}}]/\sigma[\Delta S_i]$, which quantifies the extent to which the ordering of the heartbeats contributes to the ΔS_i values (being unity for a *random* process), is also computed.

We first present the results for the determination of the occurrence time of the impending cardiac arrest that are ob-

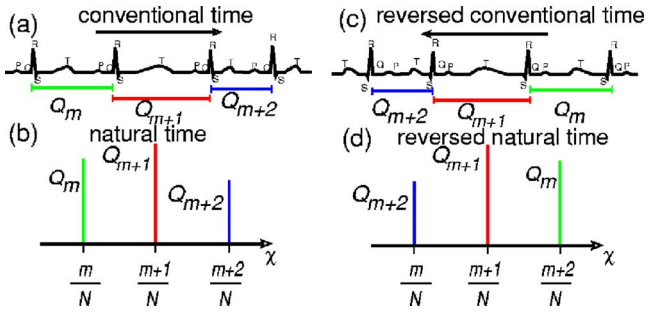

FIG. 1. (Color online) (a) Schematic diagram (not in scale) of a four heartbeat excerpt of an ECG in the usual (conventional) time domain. The durations Q_m, Q_{m+1}, and Q_{m+2} of the three RR intervals are shown. (b) The RR interval time series of (a) read in natural time; the vertical bars are *equally* spaced, *appropriately* separated, i.e., by a distance $1/N$ (where $N=i$ denotes the window length, see also Appendix 2 of Ref. 20), but the length of each bar denotes the duration of the corresponding RR interval marked in (a). This differs essentially from the plot of the Q_m vs the index m. In (c) and (d), we depict (a) and (b), respectively, but under time reversal.

[a]Electronic mail: pvaro@otenet.gr

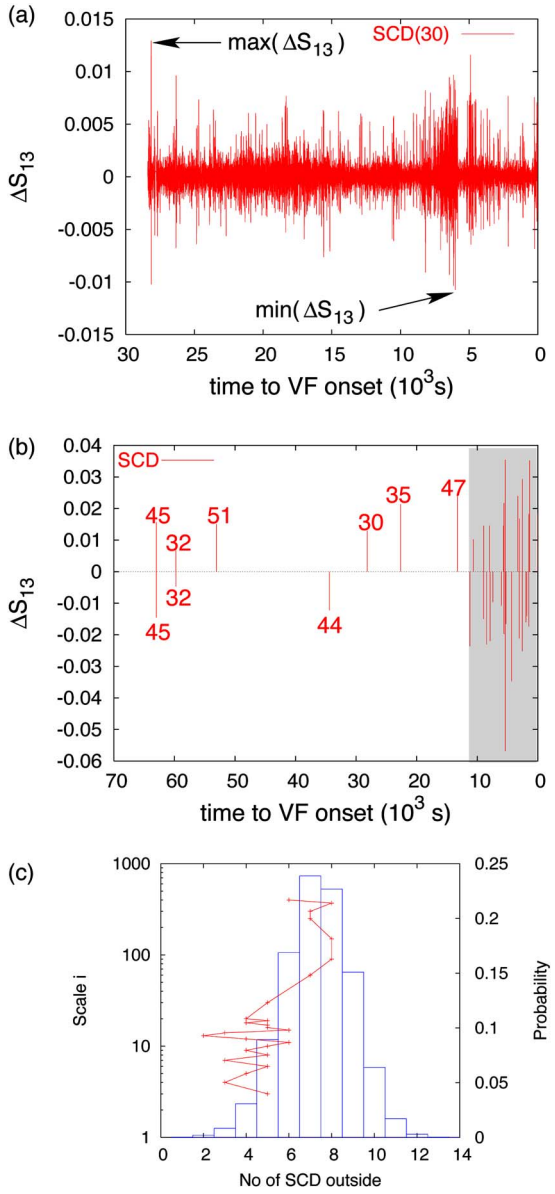

FIG. 2. (Color online) Results from the analysis of the RR time series: (a) plot of the quantity ΔS_{13} vs the time to the VF onset for one SCD, i.e., 30. The quantities max(ΔS_{13}) and min(ΔS_{13}) are shown by arrows. (b) For each of the 18 SCDs (each bar corresponds to each individual), we plot the max(ΔS_{13}) value—in the upper part (i.e., positive ΔS_{13} axis)—and the value min(ΔS_{13})—in the lower part (i.e., negative ΔS_{13} axis)—vs the time it appears *before* the VF onset. The shaded part indicates the last 3 h before the VF onset. (c) The red curve shows the number of SCD that violates both conditions $T_{\max} \leqslant 3$ h and $T_{\min} \leqslant 3$ h as a function of scale i. The probability to achieve by chance the relevant number of SCD is drawn by blue bars (right vertical scale).

tained from the time evolution of ΔS_i deduced from the RR time series. In Fig. 2(a), we give as an example the time series of ΔS_{13}, for one SCD, i.e., the one labeled 30. In the horizontal axis, the time is measured from the ventricular fibrillation (VF) onset. The time of the VF initiation for each SCD (except the individual 49 who paced with no VF) is given.[19] VF initiation remains one of the leading immediate causes of sudden cardiac death.[22] The maximum and the minimum values of ΔS_{13} will be labeled max(ΔS_{13}) and min(ΔS_{13}), respectively. The times of their appearances are designated $T_{\max}$ and $T_{\min}$, respectively. An inspection of Fig. 2(a) in conjunction with Table 1 of Ref. 20 reveals that $T_{\max} \approx 28\,150$ s and $T_{\min} \approx 6000$ s (before the VF onset). The corresponding values for all the other SCDs studied are also given in the same table, which presents the extrema of ΔS_{13} along with the time of their appearance. These values, which are depicted in Fig. 2(b), reveal that interestingly in the vast majority of SCD (i.e., in all 18 SCDs except the individuals 32 and 45, the latter having a history of ventricular ectopy), they are smaller than around 3 h. In other words, *only* for two individuals (i.e., 32 and 45) out of 18, *both* $T_{\max}$ and $T_{\min}$ are larger than around 3 h. The results for a variety of other length scales are summarized in Fig. 2(c), where we plot in red the number of SCD that violates both conditions, i.e., $T_{\max} \leqslant 3$ h and $T_{\min} \leqslant 3$ h, at various scales. The probability to have such a result by chance is also shown in the right vertical scale. This probability has been found by Monte Carlo calculation, in which the observation times for both extrema, i.e., $T_{\min}$ and $T_{\max}$, were assumed to be uniformly distributed within the total duration T_{total} of the record for each individual (see Table 1 of Ref. 20). We observe that for small scales ($i < 30$), the observed number of SCD differs significantly from the one expected by chance. Especially, the probability to find by chance the result obtained at $i = 13$ is smaller than 0.2%. In other words, an optimum length scale (i.e., $i = 13$ heartbeats) exists, at which the magnitude of ΔS_i maximizes (in 16 out of 18 cases) ≈ 3 h (at the most) before the VF onset, thus signaling the imminent risk.

Since many SCD experience arrhythmia (consisting of one or more types including premature ventricular contractions (PVCs), AF, and nonsustained tachycardia), it has been confirmed (through a direct inspection of the ECG) that the extreme values of ΔS_{13} in Fig. 2(b) mainly come from trains of occurrences of PVCs. We emphasize, however, that beyond the PVCs, the method of ΔS_i captures *additional* elements of cardiac dynamics that distinguish SCD from other individuals as it will now be discussed.

In Fig. 3(a), we plot N_3(NN) versus $\sigma[\Delta S_7]$(NN) deduced from the NN time series of all individuals except for the 25 AFs (since for the latter, relevant NN annotations were not available). This figure reveals the major importance of the N_3(NN) in two respects. First, the vast majority of SCD (i.e., 14 out of 18, lying in the shaded region) exhibit N_3(NN) values that are *smaller* than the minimum N_3(NN) value, labeled $H_{\min}$, computed among the H investigated [this is plotted with a horizontal green line]. Second, the vast majority of CHF have N_3(NN) values *larger* than $H_{\min}$, thus allowing in principle a distinction between CHF and SCD.

In Fig. 3(b), we plot N_3(RR) versus $\sigma[\Delta S_7]$(RR) deduced from the RR time series, respectively. This figure shows that the distinction between CHF and SCD achieved in Fig. 3(a) is now lost. This is understood in the context that frequent PVCs influence the RR time series (but *not* the NN) of both CHF and SCD. A closer inspection of Fig. 3(b), however, reveals two important points. First, almost all SCDs (i.e., except 32) exhibit N_3(RR) values that are smaller (hence high complexity breaks down) than the minimum value $H_{\min}$ computed in H, thus emphasizing again the importance of the scale $i = 3$. Second, the shaded region that contains the vast majority of AF (18 out of 25) lies to the right of the maximum value of $\sigma[\Delta S_7]$(RR) observed in H, labeled $H_{\max}$ (the right most vertical green line). Four out of the five SCDs (i.e., except 47) located in this region also suffered from atrial fibrillation; thus this shaded region seems to separate AF from the others.

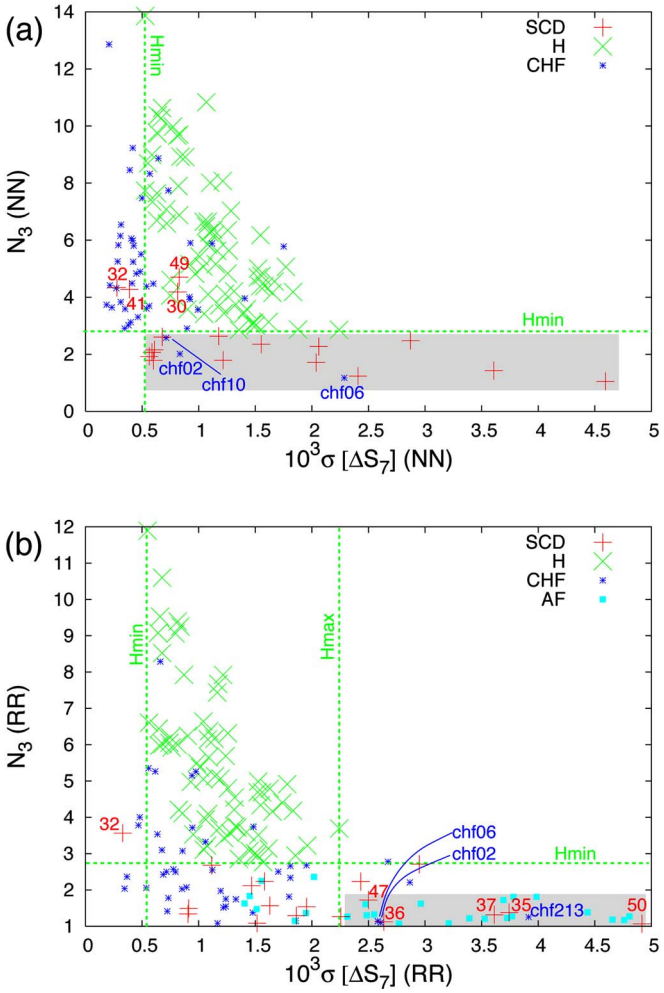

FIG. 3. (Color online) Quantity N_3 vs $\sigma[\Delta S_7]$ for (a) the NN and (b) the RR time series. The green horizontal line corresponds to the minimum N_3 value computed in H.

In order to understand the physical origin of the present findings, we resort to the neural influences on cardiovascular variability. Let us consider that, physiologically, the origin of the complex dynamics of heart rate has been attributed to antagonistic activity of the two branches of the autonomic nervous system, i.e., the parasympathetic and the sympathetic nervous systems, respectively, decreasing and increasing heart rate.[1,5,23,24] Their net result is what seems to be actually captured by ΔS_i, as shown in Appendix 4 of Ref. 20. A variety of research has now established[25] two clear frequency bands in heart rate and blood pressure with autonomic involvement: (i) a higher frequency (HF) band, which lies in[26,27] the range of 0.15–0.40 Hz and is[5] "indicative of the presence of respiratory modulation of the heart rate" or reflects[27] "modulation of vagal activity, primarily by breathing" and (ii) a lower frequency (LF) band from 0.04 to 0.15 Hz (i.e., at around 0.1 Hz), which is usually described as corresponding to[26] "the process of slow regulation of blood pressure and heart rate" or that[27] "it reflects modulation of sympathetic or parasympathetic activity by baroflex mechanisms" due to[5] "the emergence of a limit cycle caused by the vascular sympathetic delay" (its exact explanation, however, is still strongly debated[28]). The aforementioned scale $i=13$ [see ΔS_{13} in Fig. 2(b)] corresponds to the LF band, while the scale $i=3$ (see N_3 in Fig. 3) to the HF band. Thus, the magnitude of ΔS_i, when calculated for length scales corresponding to the HF and LF bands, quantifies the extent to which the processes, modulation of vagal activity primarily by breathing and the slow regulation of blood pressure and heart rate, are "disorganized," respectively.

In summary, the entropy change ΔS_i under time reversal, at the scale $i=3$ heart beats, identifies the sudden cardiac death risk and distinguishes SCD from truly healthy individuals as well as from those with the life-threatening congestive heart failure. Furthermore, in those classified as SCD, the measured ΔS_i at the scale $i=13$ heartbeats provides an estimate of the occurrence time of the impending VF onset.

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[20]See EPAPS Document No. E-APPLAB-91-062732 for additional information on the ECG data and theoretical aspects. This document can be reached via a direct link in the online article's HTML reference section or via the EPAPS homepage (http://www.aip.org/pubserves/epaps.html).
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