Irregularity test for very short electrocardiogram (ECG) signals as a method for predicting a successful defibrillation in patients with ventricular fibrillation

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A significant proportion of patients with ventricular fibrillation (VF) can only be defibrillated after a period of chest compressions and ventilation before the defibrillation attempt. In these patients, unsuccessful defibrillations increase the duration of heart arrest and reduce the possibility of a successful resuscitation, which could be avoided if a reliable prediction for the success of defibrillation could be made. A new method is presented for estimating the irregularity in very short electrocardiographic (ECG) recordings that enables the prediction of a successful defibrillation in patients with VF. This method is based on a recently developed determinism test for very short time series. A slight modification shows that the method can be used to determine relative differences in irregularity of the studied signals. In particular, ECG recordings of VF from patients who could be successfully defibrillated are characterized by a higher level of irregularity, indicating a chaotic nature of the dynamics of the heart, which is in agreement with previous studies on long ECG recordings showing that cardiac chaos was prevalent in healthy heart, whereas in severe congestive heart failure, a decrease in the chaotic behavior was observed. (Translational Research 2007;149:145–151)

Abbreviations: ECG = electrocardiogram; FFT = fast Fourier transform; HRV = heart rate variability; VF = ventricular fibrillation.

Current guidelines of advanced life support require immediate attempt of defibrillation of ventricular fibrillation (VF). With increasing duration of the VF, the success of immediate electrical defibrillation decreases.[1] Consequently, some patients with VF have a better probability of return of spontaneous circulation if defibrillation was attempted after a period of chest compressions.[2] Unsuccessful defibrillation attempts are harmful because they prolong the ischemic time and cause electrical injury to the heart.[3] A method that would predict the success of electrical defibrillation would increase the success of cardiopulmonary resuscitation.

Electrocardiogram (ECG) monitoring is universally available during advanced life support. Different parameters of VF signals have been tested for the prediction of success of defibrillation, including amplitude, frequency, bispectral analysis, amplitude spectrum area, wavelets, nonlinear dynamics, N(α) histograms, and combinations of these parameters.[4]

It has been believed for decades that VF is a random (or stochastic) waveform. Most recent studies have suggested that VF is indeed a complex, nonlinear pattern formed by drifting spiral waves of electrical activ-

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ity, which travel across the myocardium, and their subsequent breakdown.[5,6]

It is well known that a dynamical system must have at least 3 properties to be designated as being chaotic. First, the system must be deterministic (ie, not random). Second, it must have sensitive dependence on initial conditions, which means that no matter how close together are 2 initial starting points, if you wait long enough, the solution of these 2 starting points will be largely different. Finally, a chaotic system must have an attractor. Using complex correlation statistics, Kaplan and Cohen have argued that the VF waveform seems to fall down on this final criterion.[7] They suggested that the VF waveform exhibits characteristics similar to a nonchaotic random signal. Some recent papers dispute these findings.[8] Yu et al[9] used a complex mathematical algorithm to show that early VF signals contain 80–90% determinism.

If VF waveforms are amenable to mathematical description in this fashion, the implications are twofold.[10] First, if the VF waveform can be described, then its behavior can be predicted. With knowledge of the mathematical description of VF, a chaos control strategy could be used to restore a diseased cardiac rhythm to normal.[11] Via the application of small judiciously chosen stimuli at a predetermined point of the VF waveform delivered by a so-called smart pacemaker, the waveform could be changed and even abolished. Defibrillation might no longer involve hundreds of Joules but instead a much smaller, focused energy. However, problems exist with this approach. The behavior of a chaotic VF waveform can only be predicted if initial conditions are known very accurately. Although this constraint makes prediction of the VF waveform theoretically possible, the undertaking remains infeasible in practice. Second, computer capacities required to describe the waveform in such a way are prodigious and cannot be warranted by the currently available technology. Thus, by the time the waveform has been analyzed, the window for intervention would be long gone.

Despite the problems with the VF waveform analysis, studying the dynamical properties of VF ECG signals seems to be promising. Several examples exist of successfully established links between some heart diseases and changes in dynamic properties of the corresponding ECG signals. It has been shown that cardiac chaos is prevalent in a healthy heart, whereas in severe congestive heart failure, a decrease in the chaotic behavior is observed that could be a physiological marker of congestive heart failure and a possible prognostic sign of death caused by progressive heart failure and sudden cardiac death.[12,13]

To analyze a time series successfully, the latter usually has to be of sufficient length, typically comprising several thousand points or more. To develop a practical decision-making system for assisting the electrical defibrillation of VF, an efficient analysis of short ECG signals is needed that must be employed (and finished) at the beginning of ECG monitoring, just before the defibrillation is carried out. In practice, only a few seconds are available for both the acquisition and the analysis of the signal.

This study shows that VF signals, recorded only a couple of seconds before defibrillation, can be efficiently analyzed to recognize dynamic differences between signals, which are obtained from successfully and unsuccessfully defibrillated patients. Degrees of irregularity in signals are compared by using a modified method, which was recently proposed for testing the determinism in very short time series[14] to show that a higher level of irregularity in the VF signals is associated with a higher defibrillation success.

The paper is organized as follows. First, methods and devices used for the collection of data are presented. The time series analysis method is presented next, whereas the results are presented in a comparative way in the subsequent section. At the end, advantages and limitations of the proposed analysis are discussed.

DATA

Patients. Overall, 120 recordings of VF from patients with primary out-of-hospital cardiac arrest, which occurred between April 2001 and December 2003, were retrospectively evaluated in a blinded fashion. Only patients with VF as the initial ECG rhythm were included. Cardiopulmonary resuscitation and defibrillation were performed in the out-of-hospital setting by the medical emergency service, and all patients were treated in accordance with advance cardiac life support recommendations.[15] In particular, the first 3 monophasic defibrillations were performed at an energy setting of 200J, 200J, and 360J. Subsequent defibrillations had energies of 360J. No data are available regarding the pharmacological treatment of the study group.

The study was approved by the National Committee for Ethics at the Ministry of Health. Informed consent was not required.

Signal recording. A monophasic defibrillator (LifePak 12; Medtronic, Redmond, Wash) was used for defibrillations and simultaneous online ECG recordings. The self-adhesive ECG/defibrillation electrodes were attached on the patient's skin to conform with a standard lead II. The ECG data were stored in a digitized form (sampling rate 256 Hz, with 8-bit resolution).

Defibrillation was regarded as successful when VF was converted to a supraventricular rhythm (heart rate > 60/min and QRS duration < 0.12 s) for at least 30 s without any ongoing cardiopulmonary resuscitation or QRS > 0.12 s and palpable pulse. Evaluation of success or failure of defibrillation attempts was performed before determination of other features of ECG data.

Up to 3-s-long periods of VF signal just before defibrillation have been analyzed to eliminate potential noise caused by chest compressions.

METHODS

A method proposed recently by Binder et al[14] was employed that exploits statistical properties of the growth of small separations between trajectories in the phase space. As a result of a unique and novel statistical analysis, the method requires only a very small number of input points, and thus, it seems appropriate for the analysis of short ECG recordings. As the method is fast, it can be appropriate to characterize different states of heart malfunctioning in continuous real time, thus aiding human-based decisions regarding further treatment of patients.

The method exploits the expression $d(t) \approx d_0 e^{\lambda t}$, which describes the temporal evolution of small separations in the phase space. Whereas for a deterministic system, either regular or chaotic, this expression holds, whereby λ is related to the largest Lyapunov exponent, a random system will have d independent of d_0. This fact, which inspired Binder et al[14] to propose a determinism test for a short time series, can be summarized as follows. For a series of n points, generate all possible $n(n - 1)/2$ distances d_0 between distinct points in the phase space, reconstructed from the time series with the embedding dimension m and delay τ. Next, evolve all initial distances forward in time for a fixed number of time steps i and calculate resulting distances. Finally, plot the graph d_i versus d_0, whereby different values of d_0 should be averaged over small bins to annihilate statistical fluctuations. If the binned d_i versus d_0 dependence, for small, can be fitted well by a line with a positive slope and near-zero intercept, the origin of the studied time series is likely to be deterministic, whereas independent d_i with respect to different d_0 are a sure sign of random origin. Figure 1 features the analysis of a short VF ECG recording and a time series of uniformly distributed random numbers. Obviously, the VF recording possesses clear markers of determinism, whereas the random numbers yield unrelated d_i and d_0.

As it is well known that densely sampled ECG recordings possess clear signs of deterministic origin,[16] and thus a yes/no determinism assessment is unlikely to have useful discriminative power with respect to defibrillation success, the above method is exploited in a new way. In particular, the focus is on the slope k of the line that approximates the linear dependency of the d_i on d_0 for small d_0. Importantly, it is noted that the slope of the line can be directly linked with the complexity of oscillations. A slope of $k > 1$ indicates that initial distances between nearby points in the reconstructed phase space diverge as time progresses, which can be observed as an indicator of chaotic behavior. As decrease of cardiac chaos is a well-known companion of several heart malfunctions,[17] it is expected that resistant VF is characterized by smaller than the less-resistant VF.

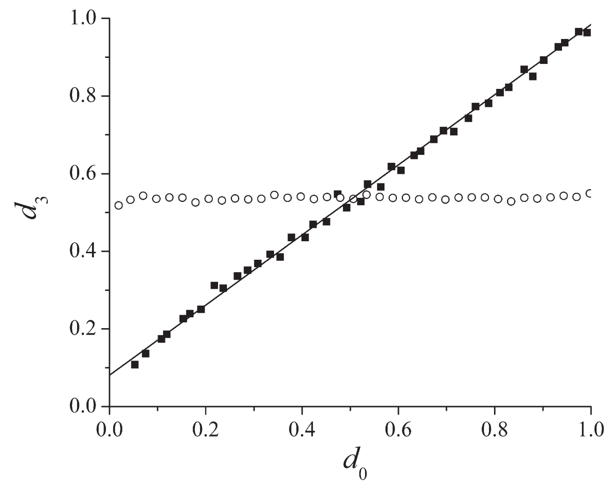

Fig 1. Application of the method on a short human ECG recording (filled squares) and uniformly distributed random numbers (open circles). Each set occupies 600 data points and was analyzed by using the parameters $m = 5$, $\tau = 1$, and $i = 3$. It is evident that the squares can be approximated well by a line of slope $k = 0.91$ and near-zero intercept of the abscissa at 0.081, which confirms the deterministic origin of the ECG recording. On the other hand, the crossed circles are evenly spread across the x axis and are thus independent of d_0, which confirms the stochastic origin of uniformly distributed random numbers. Results are virtually independent of the parameters m, τ, and i, as already reported in Binder et al.[14]

Thus, k is declared as the main quantity to distinguish between different states of the examined heart disease.

Overall, 120 ECG recordings of VF were analyzed, each occupying $n = 600$ data points sampled by $dt = 0.004$, all belonging to individuals suffering from primary cardiac arrest. Overall. 50% of patients' defibrillations resulted in nonshockable rhythm associated with palpable pulse, whereas in the other half, defibrillation was not successful, resulting in persistent VF or asystole. The aim is to distinguish between these 2 groups to minimize "hands-off" time to deliver unsuccessful defibrillation. To do so, the above method is employed in a blinded fashion, meaning that the method is universally applied to all recordings and after that the success of the method is compared with the success of the defibrillation. The calculations are carried out for $m = 5$, $\tau = 3$, and $i = 3$, whereas the cut-off for small d_0 is set to 1% of the maximal recorded initial distance between distinct points in the phase space. As all possible pairs of distinct points are considered for the analysis, the method is fairly robust against variations of the embedding parameters m and τ, as well as the number of forward integration steps i.[14] As ECG recordings were previously found to originate from high-dimensional systems,[17] $m = 5$, which represents the best compromise between a fast execution of the algorithm and an authentic phase space reconstruction, is used. Before performing the analysis, all samples are rescaled to unit variance to eliminate artificial results caused by amplitude variations in ECG recordings, which might be caused by extrinsic factors not relevant for this analysis. It was found, however, that the results below remain virtually identical also without the amplitude rescaling of

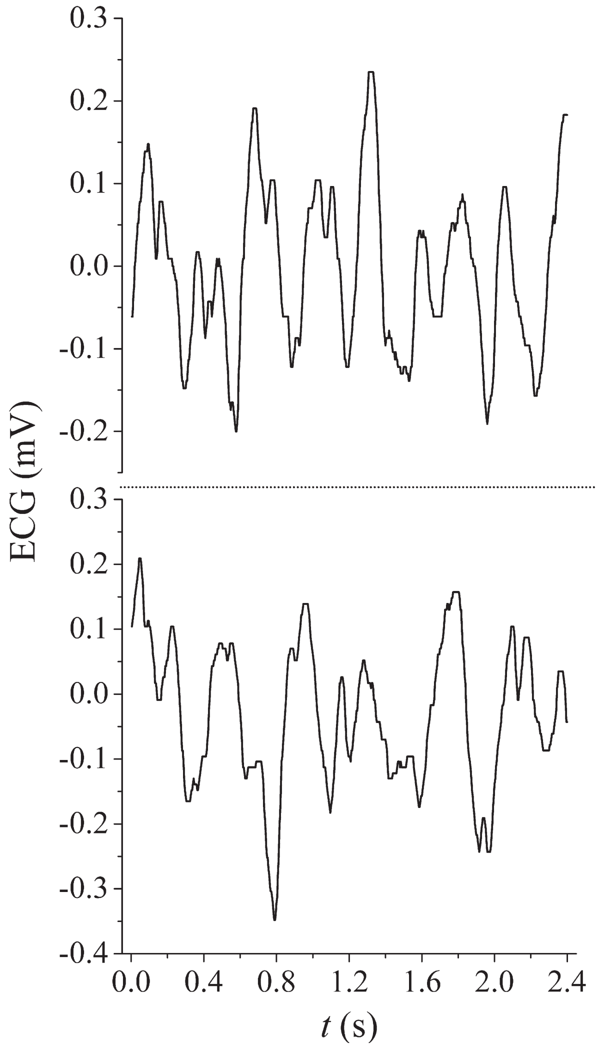

Fig 2. Application of the method on an ECG recording belonging to a successfully defibrillated patient (upper panel) and on a trace of an unsuccessfully defibrillated individual (lower panel). Each set occupies 600 data points and was analyzed by using the same parameters as in Fig 1. Although visual inspection reveals no significant differences between the 2 traces, the upper recording is characterized by $k = 2.24$, whereas the lower trace has $k = 0.55$. The dynamical complexity of ECG activity is clearly diminished by the subsequently unsuccessfully defibrillated patient.

individual samples, which is not at all surprising because d_i and d_0 are always compared relatively with one another.

The research was conducted according to the principles of the Declaration of Helsinki, first adopted in June 1964, and amended last in Edinburgh, Scotland at the 52nd World Medical Association General Assembly, October 2000.

RESULTS

First, 2 temporal traces of VF ECG recordings were presented. The upper panel of Fig 2 shows a recording of a subsequently successfully defibrillated patient, whereas the lower panel features an unsuccessfully defibrillated patient. Although the visual inspection of both traces hardly reveals any significant differences between them, the above-outlined method discloses a fascinating fact. In particular, whereas the trace in the upper panel of Fig 2 is characterized by $k = 2.24$, the lower recoding has $k = 0.55$, which clearly suggests that patients who were subsequently unsuccessfully defibrillated have a substantially lower dynamical complexity of ECG activity than successfully defibrillated individuals. Importantly, the inability of inferring this information from the temporal traces solely by visual inspection stresses the potential usefulness as well as the necessity for the application of this proposed method.

The results for all patients, separated in groups A and B with respect to the success of defibrillation, are presented in Fig 3 for different numbers of data points used for the analysis. Irrespective of the number of used data points, ECG recordings of VF that could be successfully defibrillated (group A) are characterized by substantially larger values of k than the recordings belonging to the group of VF that could not be successfully defibrillated (group B). In particular, the average k of all subjects included in the study, obtained when all available 600 data points were used for the analysis (lower right panel of Fig 3), equals $\bar{k} = 1.31 \pm 0.31$ for group A and $\bar{k} = 0.93 \pm 0.27$ for group B, the number after $\pm$ being the standard deviation of the mean value for both groups. To test whether the difference between $\bar{k}$ for the 2 groups is statistically significant, an ANOVA model was applied. These types of models are normally used to compare the difference between the mean values of 2 or more groups or categories. Based on the results of the ANOVA analysis, the difference between the 2 mean values was found to be statistically significant at $p = 0.0001$. What is remarkable is that these convincing results were obtained out of 2.4-s-long ECG recordings. Even more strikingly, it is noted that only 100-data-point-long ECG recordings suffice to discriminate both groups of patients, although the discriminative power of the method increases substantially as longer signals are used for the analysis (compare results in different panels of Fig 3).

It seems that the method can discriminate between VF patients who were and who were not successfully defibrillated. As the method is fast, it can be implemented in real time, thus assisting in finding the optimal treatment at any given time.

To strengthen the results and eliminate the possibility of chance, surrogates were generated for each of the studied ECG recordings. By using the surrogates, a determination could be made regarding whether the

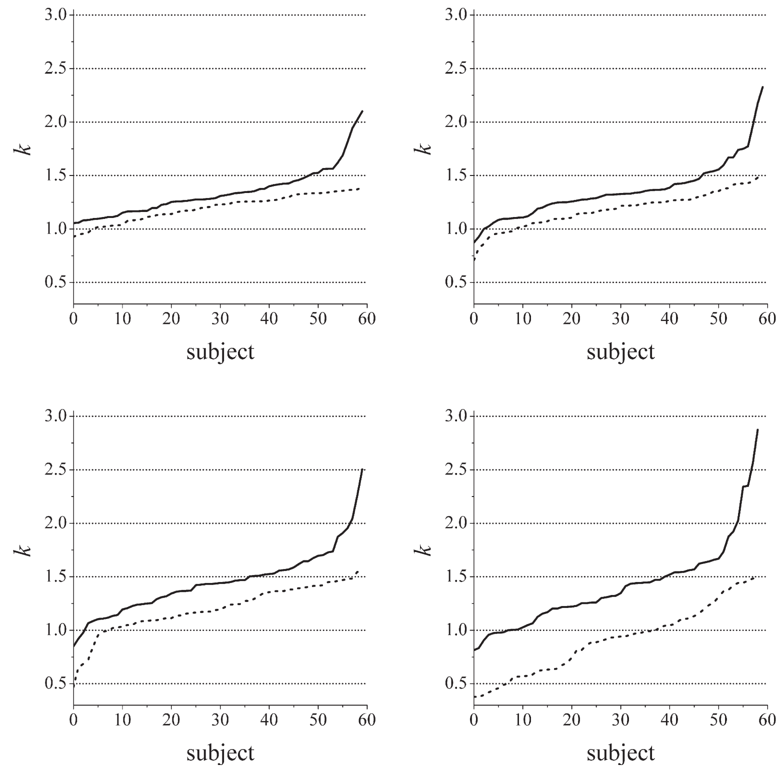

Fig 3. Distribution of k's in an ascending order from left to right for VF patients that were successfully defibrillated (group A, solid line) and patients that were not successfully defibrillated (group B, dashed line). Presented panels show results obtained by analyzing 100 (upper left panel)-, 200 (upper right panel)-, 300 (lower left panel)-, and 600 (lower right panel)-point-long ECG recordings.

irregularity of the measured data could be attributed to the innate system dynamics or whether it is rather a consequence of random inputs, measurement inaccuracies, or fluctuations of system parameters during data acquisition. In the simplest case, if the ECG recordings would be independent random numbers, any random shuffle (without repetition) of the series would yield exactly the same results as the original dataset. A more stringent test, which is employed below, can distinguish between deterministic recordings and such recordings that originate from a stationary Gaussian linear process that has been distorted by a monotonic, instantaneous, time-independent measurement function f. To achieve such an effect, the surrogates are generated so that the original power spectrum and the empirical distribution of the series, caused by the function f, are preserved.[18] More precisely, the original dataset is shuffled and the fast Fourier transform (FFT) is applied. The amplitudes of the FFT are rescaled in accordance with the FFT amplitudes obtained from the original series. This rescaling enforces the correct spectrum but usually modifies the distribution of the resulting series, which is obtained by the inverse FFT. Therefore, rescaling is performed by using the ranks of the resulting series and the sorted copy of the original data. As a result of this rescaling, however, the power spectrum is again modified, and thus, the procedure has to be repeated until a given accuracy is reached.[19]

Figure 4 features the same analysis as Fig 3; only this time the surrogates of all available data points instead of the original recordings were used. It is evident that now both groups of patients show virtually identical distributions of k's. Moreover, the average slope in both groups is near zero, which is in accordance with the results presented in Fig 1 for the uniformly distributed random numbers. The surrogates are indeed random series, only in that they have identical distribution functions as their deterministic counterparts, which confirms that statistical difference of distributions of k's reported in Fig 3 must be attributed to the decrease of complexity of the cardiac rhythm, which is more pronounced in patients with VF resistant to defibrillation.

DISCUSSION

The results of this study show that very short (only 2.4-s-long) VF recordings can be efficiently exploited for predicting the success of defibrillation. A compar-

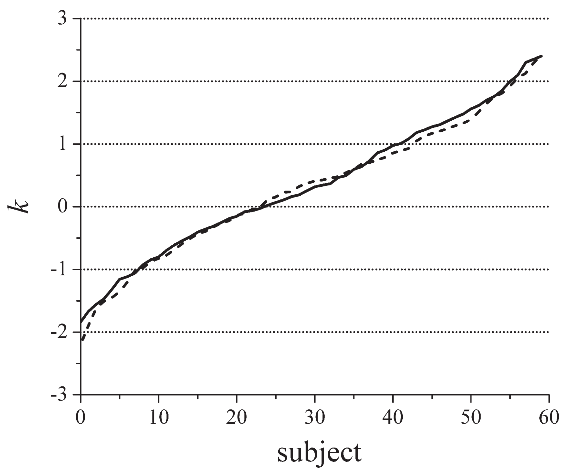

Fig 4. Distribution of k's in an ascending order from left to right for subjects belonging to group A (solid line) and group B (dashed line). The analysis has been performed on the surrogates of the full, 2.4-s-long, original ECG recordings used in the lower right panel of Fig 3.

ative analysis was carried out for the 2 groups of patients with different success of defibrillation, and it showed that a higher level of irregularity in the VF signals is associated with a higher defibrillation success, which may have clinical applications and lead to the development of a decision-making software that will provide results in real time.

Several previous studies have also indicated that changes in dynamics of ECG signals appear before VF attacks. For example, Skinner et al[17] showed that an imminent VF in human subjects is characterized by a reduction in the correlation dimension of heartbeat intervals that precedes the VF. Results published in Skinner et al[17] lend support to this study because they show that changes in deterministic dynamical properties of ECG signals before VF can indeed be observed.

It is important to note that densely sampled continuous ECG recordings were used. In previous studies, analyzing heart rate variability (HRV), long-term ECG signals were often reduced to sequences of interbeat intervals. However, a fundamental difference exists between the "full" ECG signals and the sequences of interbeat intervals because of the loss of information. No clear evidence exists for the presence of determinism in series of interbeat intervals, which does not mean that determinism in the underlying system is altogether absent, but that potential determinism in the HRV is too complex to be accessible through interbeat intervals alone.[20]

An advantage of the current method is that it allows rescaling of the ECG signals and herewith minimizes undesired effects related to noninherent amplitude variations. In previous studies, it has been recognized that the amplitude and frequency of VF signals can provide estimates of myocardial energy metabolism, which can be used to predict the likelihood of successful defibrillation.[21,22] However, the actual power of methods using VF amplitudes as a measure for the defibrillation success is constrained by a large intersubject variability that stems in part from variable electrode size and placement, impedance of the electrode–skin interface, chest configuration, and vectorial change of the ECG waveform.[23] Therefore, the analysis of the rescaled ECG signals is much more universal and reliable.

The most important advantage of this approach, however, is the ability to test irregularity in extremely short (only a couple of seconds long) VF recordings. As fast analyses of ECG signals hold the promise of achieving actual clinical use, several previous studies have also tried to develop methods for analyzing a short time series in the shortest possible time. For analyzing the dynamical properties of ECG recordings of patients with congestive heart failure, for example, a special nonlinear systems identification technique has been developed to analyze cardiac chaos and its relation to HRV.[12,24] The method can detect nonlinear dynamics in a short, noisy time series.[25] However, it is optimal for a time series consisting of 1000 points or more. Presently, even 100 data points suffice to separate both groups of patients (see upper left panel of Fig 3). Although the discriminative power of this method increases with longer recordings, the latter definitely need not to consist of more than 600 data points to obtain statistically relevant results. Some problems limiting the use of the method reported in[25] are also related to an absolute relevance of models generated by the method, which concerns the core of the algorithm based on iteratively generating a family of polynomial autoregressive models.[12]

This method gives a quantitative estimation of the irregularity of very short VF signals. As pointed out, a slope of $k > 1$ indicates a complex chaotic behavior. The results in Fig 3 show that the average k of all subjects included in the study equals $\bar{k} = 1.31 \pm 0.31$ for successfuly defibrillated patients and $\bar{k} = 0.93 \pm 0.27$ for unsuccessfully defibrillated patients, which indicates a higher irregularity or complexity in signals obtained from individuals that could be defibrillated successfully. These results are in agreement with previous analyses of ECG recordings of patients with congestive heart failure, emphasizing that chaotic ECG signals characterize a healthy heart, whereas a decrease in the complexity could be an indicator of congestive heart failure.[12,13] To further strengthen the success of this method, it would be nice to identify some correlations between the results and other known heart failure data specific for a particular patient or study group. Unfortunately, however, data on preexistent heart failures was not available for these patients, which could potentially influence the VF signal. However, because even severe heart dysfunctions can occur without any warning symptoms, it is argued that, at least in general, it is very difficult to estimate correlations between known heart diseases and VF signals.

In the context of other recent studies, it should be pointed out that further developments of successful methods for analyzing VF ECG signals might be expected by combining several existing methods. In a recent study, a combination of median frequency, peak power frequency, spectral flatness, and frequency band-limited energy of the power spectral density in VF signals before 868 defibrillations in 156 patients with out-of-hospital cardiac arrest was studied.[26] They generated different secondary decorrelated feature sets from the 4 original spectral features using the principal component analysis. To ensure reliability, the available data were split into a training set and a test set. If the advice of the highest performing classifier has been followed, which corresponded to the combination of 2 secondary features, 42% of unsuccessful defibrillations would have been avoided, whereas 8% of successful defibrillations would have not been given. It is questionable, however, whether this prediction would be powerful enough to improve survival of the patients with primary heart arrest. According to the authors, the low specificity and positive predictive value indicate that other features should also be added. One candidate might be the irregularity test presented in this article.

In conclusion, a higher degree of irregularity is detected in VF ECGs of patients that are more prone to be successfully defibrillated. By applying the described method for the analysis of very short ECG signals, results can be obtained in real time, which gives additional power to the presented algorithm and will hopefully promote it to actual clinical use.

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