Differences in the characteristics of induced and spontaneous episodes of ventricular fibrillation

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Aims The degree of organization of ventricular fibrillation (VF) can be examined in terms of the regularity of the electrical activity within the ventricle. Using electrograms (EGMs) stored within implanted cardioverter defibrillators (ICDs), we examined the hypothesis that the degree of organization, or regularity, was different if the VF was induced by electrical stimulation as opposed to occurring clinically due to ischemia or scar.

Methods and results We compared the statistical characteristics of EGMs recorded by ICDs during spontaneous episodes with those induced during device testing in the laboratory in nine subjects. Regularity of the VF EGM signals was quantified using autocorrelation, Shannon entropy (derived from cycle to cycle activation complexes), and Kolmogorov entropy (derived from eight second long episodes of VF). All three measurements showed a statistically greater degree of regularity for induced VF than in spontaneous episodes.

Conclusion Analysis of VF EGMs using these techniques is novel and robust, providing a new way for assessing electrical organization during VF. The clinical significance and utility of differences in VF waveform regularity is unclear at this stage.

KEYWORDS
Implanted cardioverter defibrillator; Ventricular fibrillation

Introduction
Ventricular fibrillation (VF) is the major cause of sudden cardiac death. Although VF has historically been regarded as a random process,¹ recent studies have demonstrated that there are local spatio-temporal correlations which suggest that this is not necessarily the case.² The belief that VF may be deterministic in nature has driven attempts to characterize VF waveforms, particularly from the surface ECG, in the hope that this may guide therapeutic interventions.³,⁴ In addition features of VF have also been analysed using electrograms (EGMs) obtained in experimental models of VF⁵,⁶ and during implanted cardioverter defibrillator (ICD) testing.⁷,⁸ This work suggests that the characteristics of VF may differ according to the mode of induction⁶ and may be related to the maintainance⁷ or probability of recurrence⁸ of arrhythmia.

A number of different methods have been used to quantify and detect patterns or order in VF waveforms. These range from relatively simple time domain measures, such as cycle length (CL),⁸ to far more complex measures based upon non-linear dynamics.⁹ Information ‘entropy’ provides a means of estimating the information content in apparently random signals. Entropy analysis quantifies the extent to which that dataset is random (high level of entropy) or regular (low level of entropy) regardless of data units or value ranges,¹⁰ and this provides a potentially powerful approach to characterizing VF waveforms.

We hypothesize that the regularity of spontaneously occurring episodes of VF (due to scarring, ischaemia, or repolarization disorders) and induced episodes (recorded during ICD testing) are distinct. In this study, we have tested this hypothesis by comparing the entropy of spontaneous and induced VF EGM signals.

If the organization of VF differs significantly in these situations, this may have implications for the determination of defibrillation thresholds, and also for the interpretations of studies designed to understand the mechanics of VF.

Methods
We identified ICD patients who had received device therapy for episodes within the programmed VF zone over a 36-month period. Each episode was graded clinically as either VF or fast VT, and only VF episodes were included in the study.

We extracted the stored EGM data from the clinical event and then paired this with the VF EGM data recorded in the laboratory during device testing at implantation. Device testing was performed during implantation under general anaesthesia. VF was induced by delivery of a shock at the nadir of the T-wave following a pacing train of eight stimuli at a CL of 400 ms. The institution’s device testing protocol required two successful terminations of induced VF.

The local Ethics Committee approved the study.

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Data analysis
Cycle length and CL variability, autocorrelation functions, Shannon entropy (SH) and Kolmogorov entropy (KH) were estimated from recorded EGM signals for each VF incident. The temporal resolution of the EGM signals was 10 ms. Absolute measures of EGM amplitude could not be obtained due to the autoamplifier feature of the ICD.

Conventional time series analysis
For each episode of VF, we determined the position of each peak within the signal, and calculated mean and standard deviation of cycle length defined as the peak to peak interval. Only EGM signals with >30 cycles were included in the subsequent analysis.

Autocorrelation of electrogarms
Autocorrelation functions for individual episodes of VF were constructed by creating a duplicate of the EGM time series and incrementally shifting it in time with respect to the starting point of the original time series. The correlation between the two series was then calculated for shifts in time of up to 2000 ms. For statistical comparison of autocorrelation values between spontaneous and induced events the r-value of the first peak in the autocorrelation function was extracted for each EGM.

Entropy analysis
For each peak to peak EGM, we converted the signal from time to phase, so that the regularity being measured was not of the peak to peak times, but rather the activation pattern. We then resampled the signal at 10\(^8\) intervals using cubic spline interpolation (see Figure 1). At each of the 36 sample points, the distribution of points across complexes was plotted in a 30-bin histogram, with maximum and minimum values defined by the maximum and minimum voltages across the 30 complexes. From the bin occupancy of each histogram, SH was then calculated as:

\[ SH = \sum_{b=1}^{N} P_b \log(P_b) \]

where \( P \) is actual histogram bin probability, \( b \) the bin number, and \( N \) the number of histogram bins. The median value across the 36 points of the complexes was then used as a measure of ‘regularity’ or ‘randomness’. If all complexes were identical, then all voltages would fall into a single histogram bin and give \( SH = 0 \). While if the complexes were completely different, then each voltage would occupy a different histogram bin and give \( SH > 0 \). Thus lower \( SH \) indicates higher degrees of regularity. For each VF episode, the median value of the 36 SH values across the complexes was calculated. Previous studies have demonstrated that \( SH \) is statistically robust at detecting regularity when applied to time series of as few as 50 data points, considerably less than that used in the present study.

Kolmogorov entropy is an alternative, but related, method for determination of the regularity within the signals. KH characterizes the degree of regularity in the entire signal, in contrast to SH which we have applied on a cycle-by-cycle basis. In a system with a high degree of order, the activity of the system will repeat itself over time, whereas in a disordered or random system, the activity will not be repeated. In KH, activity is looked at in terms of the rate at which the trajectories (changes in voltage from one point to another) diverge within a given phase space (the phase space being a plot of voltage at one point in time vs. the voltage at one or more other points in time).

To calculate KH we used the Grassberger and Procaccia algorithm. First, the correlation integral, which measures the spatial correlation between the various states of a system in its phase space, is determined. The integral curves are calculated by plotting the trajectory occurring between points separated by a given time delay (determined by the zero crossings of the autocorrelation function), and then determining this distance between all pairs of points within this phase space. The cumulative distribution of these distances is determined for a given integral length. This process is repeated over multiple embedding dimensions of phase space (m), for which this study ranged from two to six. By calculating the slope of the plots of cumulative distribution vs. integral length and plotting this relationship we can determine, at higher embeddings, the point at which these curves converge toward a common value, and this gives an estimate of KH. The integral curves of a periodic process (which is totally regular) will converge towards zero, while in more irregular processes KH will have a higher value. The utility of KH to detect regularity in short time series, and time series with a small number of data points, such as used in this study has previously been demonstrated.

Statistical analysis
For all subjects, there were two induced VF events, and we selected the most irregular value obtained from these for each subject. Four patients had more than one spontaneous event, and for those subjects, we selected the most regular spontaneous event measurements. In this way, we attempted to minimize any difference that may exist in the regularity between spontaneous and induced episodes. Paired data for each subject were analysed using the Wilcoxon-signed rank test. A P-value <0.05 was viewed as statistically significant. Statistical tests were performed using SPSS 11.0.

Results
Clinical information on the patient group
From a cohort of ~150 ICD patients at our local hospital, we identified 12 ICD patients who received device therapy for spontaneous VF events, all with ICD leads placed at the RV apex. Three patients were excluded because their ICD had not recorded sufficient EGM data for one or both of the spontaneous and induced events due to the rapidity of device detection and treatment delivery. This left nine patients

![Figure 1](https://academic.oup.com/europace/article-abstract/9/11/1054/478870/1054)
for whom we had paired datasets of spontaneous and induced VF events. Patient characteristics are given in Table 1. Spontaneous and induced EGM signals for one patient are shown in Figure 2.

Cycle length and cycle length variability

The mean cycle length for spontaneous events was significantly shorter (160 ± 28 ms) than for induced events (183 ± 17 ms, P = 0.03, Wilcoxon-signed rank test), but there was no significant difference in the mean standard deviation of cycle length between the two types of events (65 ± 14 ms for spontaneous events and 67 ± 25 ms for induced events).

Autocorrelation

Autocorrelation plots are shown in Figure 3 for the two EGM signals given in Figure 2. In both autocorrelation plots, there is a rapid decline in autocorrelation, with recurrent peaks at time delays equal to the mean cycle length. The rapid decline of the autocorrelation function towards zero indicates that the characteristics of the signal tend towards randomness, although the peaks at the mean cycle length indicate a periodic activation of the region of cardiac tissue surrounding the right ventricular (RV) apex lead. In the example shown in Figure 2, the rate of decline was greater for the spontaneous episodes. This was confirmed statistically using the correlation value of the first peak which for eight of the nine subjects was higher in the induced than the spontaneous episode, (Figures 2 and 3, P = 0.04, Wilcoxon-signed rank test), indicating that the induced time series was more regular than the spontaneous time series.

Entropy measurements

Median SH values were higher, indicating a lower degree of regularity, in the spontaneous episodes than in the induced events in eight of the nine subjects (Figure 4, P = 0.04, Wilcoxon-signed rank test). Likewise KH measurements were higher in the spontaneous events in eight of the nine subjects (Figure 4, P = 0.04, Wilcoxon-signed rank test).

For all three measures (autocorrelation, SH, and KH), the spontaneous VF episodes were less regular than the induced episodes in eight of the nine subjects. For all three measures in one patient with dilated cardiomyopathy (DCM), the spontaneous event was more regular than the induced event.

Discussion

In this study, the regularity of the EGM waveforms during spontaneous VF events were compared with those induced during device testing. We found that the spontaneous events were less regular than the induced episodes. The significance of this difference is not clear.

Device testing at implantation serves to ensure that the ICD can detect VF adequately and can then terminate tachycardia episodes. However, device testing protocols are not well standardized, with different inductions being used, and varying methods of determining defibrillation thresholds. A study examining the effect of mode of induction of VF on cycle length variation reported that differing modes of induction resulted in VF episodes with differing levels of organization. They observed that VF induced by either T-wave shock or AC current showed greater levels of organization over the first 5–10 s of VF than VF induced by non-shock methods. However, it was not determined whether these differences altered defibrillation threshold or affected the capacity of the device to sense VF. Moreover, differences between induced and spontaneously occurring events.

Table 1 Patient demographics

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean 58 (min 24, max 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>7 male, 2 female</td>
</tr>
<tr>
<td>Indications for device</td>
<td>4 IHD, 3 LQTS, 2 DCM</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>9</td>
</tr>
<tr>
<td>LVEF</td>
<td>Mean 36% (min 30, max 60)</td>
</tr>
</tbody>
</table>

Figure 2 Representative EGMs from one subject showing a VF event that was induced in the laboratory during device testing and a spontaneous event.

Figure 3 Autocorrelation function plots shown for the two EGM signals given in Figure 2. The first peak after zero was used for statistical comparison of induced and spontaneous events.
VF were not investigated. The authors suggested that this required investigation, and the studies examining the mechanism of VF should analyse mode of induction. In our study all inductions used a standardized pacing train, followed by a T-wave shock. The spontaneous events occurred in the absence of any clinical evidence of ischaemia.

To our knowledge, this is the first study to compare entropy assessments from paired data of induced and spontaneous VF events. A previous study has compared spontaneous and induced episodes of VT from far-field ICD EGMs, and found that induced episodes had a shorter cycle length and distinct waveform morphologies when compared with spontaneous events. In the current study, we found a higher level of regularity in the induced events compared with the spontaneous events. This implies a greater degree of spatio-temporal organization during induced events. Although there is considerable interest in the analysis of the level of organization of VF, a single underlying mechanism for the arrhythmia has not been established. If, however, we accept a multiple wandering wavelet model for VF, then greater regularity would be associated with a lower number of wavelets, as complexity is generated at the zones in which wavelets interact. A previous study of induced VF EGMs during device testing suggested that greater regularity was associated with an increased probability that the event would terminate spontaneously rather than require shock treatment, and the authors speculated that this may relate to the way in which propagating wavefronts interact with inexcitable objects to influence local activation coherence.

The differences between spontaneous and induced events reported in this study should be interpreted with a degree of caution. We have made no attempt to relate our measures of regularity to any clinical endpoint. The induced events occurred with the patients under general anaesthetic, and differences in regularity of VF may relate to this altered neuro-vegetative state. In addition, the size of the study is small, and a larger dataset would obviously allow for a greater degree of confidence in the differences detected. There are also intrinsic limitations in the use of the device stored EGM signal. The temporal resolution is lower than is ideal from a research point of view, and the automatic gain control means that VF amplitude cannot be analysed. In addition, the speed with which modern ICDs detect and treat VF is such that only short time series were available for analysis, and ideally measures of regularity would be applied to longer segments of data.

It is also not clear how the signal recorded from the apex of the RV relates to activity throughout the whole ventricle, and future studies are planned to investigate this. Kim et al. previously used KH to examine the dynamics of VF in isolated perfused swine hearts. They reported that measurements from one point within the ventricle were sensitive to reductions in tissue mass at remote sites within the ventricle, and argued that this measure accurately reflected ventricular dynamics. In contrast, Luo et al. measured bipolar EGMs from the posterior left ventricle (LV) and from an oesophageal electrode and compared these signals with RV signals during device testing. They found significant differences in spatial organization when comparing LV and RV EGMs, which may imply that regularity measurements may be very sensitive to the site of measurement. It is also unclear what effect inducing VF using the ICD electrode has on the regularity of the complexes recorded at the same site.

We have observed significant differences in the regularity of EGM signals during spontaneous and induced episodes of...
VF. That there are differences between these events should not be surprising, but has not been previously demonstrated. Although the clinical significance of these differences is unclear, induced VF is distinct from spontaneously occurring VF. This may have significance for device testing, as the induced event being sensed and treated is at least in some ways different from a clinical event. There may also be implications for defibrillation thresholds, although this is yet to be established. Our study does not imply that we should change current practice, but raises questions about what we are actually testing in the laboratory at the time of implant. Furthermore, studies seeking to understand mechanisms of VF that utilize electrical induction of VF may be examining a different phenomenon than VF from ischemia or scar.

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References