Ventricular fibrillation frequency from implanted cardioverter defibrillator devices

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Aims

The dominant frequency (DF) of ventricular fibrillation (VF) provides a measure of cycle length that may relate to the underlying complexity of the arrhythmia. Dominant frequency analysis may therefore provide insights into VF mechanisms, and potentially guide future therapies. Dominant frequency analysis can be undertaken on stored electrograms (EGMs) from implanted cardioverter defibrillator devices (ICDs). Demonstration of the reproducibility of the DF during separate VF events is necessary before using this tool.

Methods and results

We identified 82 patients receiving a Medtronic ICD who had two episodes of VF induced during ICD testing. We extracted EGMs recorded during both episodes and determined DF using the fast Fourier transform. The mean DF for the population was 4.7 ± 0.6 Hz, corresponding to a cycle length of 213 ms. First and second episodes of VF were very highly correlated (interclass correlation = 0.87, P < 0.01) demonstrating that DF was highly reproducible. The 18 patients on Class III agents had a significantly lower DF than the remaining 63 (4.4 ± 0.4 vs. 4.8 ± 0.6 Hz, P < 0.01, n = 18). However, the DF of patients with ischaemic heart disease (n = 34) did not differ when compared with dilated cardiomyopathy patients (n = 25) (4.7 ± 0.6 vs. 4.6 ± 0.4 Hz, P = 0.3).

Conclusion

The DF of short intervals of induced VF is highly reproducible and is sensitive to pharmacological interventions that extend effective refractory period. Such estimates of DF may therefore have clinical utility and in patients with ICDs provide a means of investigating mechanisms underlying the initiation and early phases of VF.

Keywords

Ventricular fibrillation • Dominant frequency • Implantable cardioverter defibrillator

Introduction

Although ventricular fibrillation (VF) has historically been regarded as a random process, recent works show that there is in fact a high degree of order in the electrical activity that occurs during this rhythm disturbance.¹–⁴ This insight has led to numerous attempts to characterize the spatiotemporal organization of VF, motivated by the view that this may improve our understanding of the factors that initiate and sustain fibrillation.²,³,⁵,⁶ Such studies have produced important clinical outcomes demonstrating, for instance, that identifiable characteristics of electrical activity in VF are associated with the probability of transthoracic defibrillation success.⁷,⁸

Frequency analysis has been used widely as a descriptor of VF. The principal peak in the electrogram (EGM) amplitude spectrum—dominant frequency (DF)—has been used to identify possible sites of origin of VF.¹ The DF has also been related to the complexity of the wave patterns that occur during VF as demonstrated in clinical, laboratory, and computer modelling scenarios.²–¹⁴ The frequency of VF has been well characterized in animal hearts, but to a lesser extent in human hearts.²,⁵,⁶ The data on human VF have been limited to relatively small studies using defibrillator rhythm recordings or data recorded at the time of cardiac surgery.³,¹² Ventricular fibrillation appears to be more organized in human hearts than in animal hearts, which may have important implications particularly when modelling or applying animal data to human VF.²–⁴,¹³,¹⁵

With the evolution of the implantable cardioverter defibrillator (ICD), collection of data during VF episodes now provides a unique opportunity to study the initiation of VF and the early phases of the event in a wide patient population.¹⁶ Electrograms, heart rate, and
additional discriminator criteria are retrieved from devices for clinical purposes, but other data not routinely used for the device diagnostic algorithms can also be accessed from ICDs. Although EGM data available from ICDs are limited in terms of amplitude or morphology by the inherent design requirements of these devices, representative frequency data are available. We and others17 have used such data to characterize VF behaviour.

Before attempts can be made to exploit this approach in a clinically relevant setting, there are a number of basic questions that need to be answered. The most important of these is whether DF measurements from ICD EGMs are reproducible. A previous study carried out more than 10 years ago with a small patient group reported that repeated events had only fair to good reproducibility.18 The objective of our study was to determine the reproducibility of DF estimated from ICD EGMs recorded with current generation devices in a larger and more representative sample of patients.

Methods
We identified patients who underwent ICD implantation at Auckland and Wellington Hospitals from January 2001 until December 2006 who received Medtronic devices (Gem, InSync, Maximo, and Marquis). Two episodes of VF were induced during device testing with either T wave shock delivered after a standardized drive train, followed by a shock (most commonly of 1.1 J) synchronized to the nadir of the T wave or 50 Hz burst stimulation. Repeat induction occurred at an interval of at least 5 min of normal rhythm and stable haemodynamic state after termination of the initial VF event. Only patients who had two episodes of VF induced with the same method were included in the study. The only episodes analysed were VF as defined by the operator during testing based on the surface ECG morphology with ventricular tachycardia being excluded. All device testing was performed under general anaesthesia.

The EGM was recorded as a bipolar signal between the tip and the ring (12 mm) of the right ventricular lead. These signals were exported using the software provided by the manufacturer, and analysed using custom-written LabVIEW® (National Instruments Inc., Austin, TX, USA) applications. Demographic data were extracted from each patient’s clinical records. The study was approved by the regional ethics committee under the provisions for observational research.

Data analysis
For each VF event, we determined the DF as follows. The EGM, sampled at either 64 or 128 Hz depending on the model of ICD, was transformed using a Hanning window, a fast Fourier transform was performed and the power spectrum was estimated. The DF was defined as the frequency between 0.5 and 20 Hz with most power. The episodes varied in length from 3 to 5.5 s. The episode length was determined by the individual detection and charge times for the device and did not vary within the two tests. This resulted in a mean frequency resolution of $0.19 \pm 0.065$ Hz. Examples of EGM signals and the derived power spectra for one subject are given in Figure 1. Owing to the autogain feature of the ICD systems, measures based on EGM amplitude were not analysed.

Statistical analysis
All parametric values are given as mean ± SD. We compared the first induced episode of VF with the second using intra-class correlation (ICC). An ICC of 0.75–1 indicating excellent correlation; 0.4–0.75, fair to good correlation; and <0.4, poor correlation.

Figure 1 EGMs recorded from one patient during induced VF, test (episode 1) and retest (episode 2). Corresponding power spectra are given in the inset figures.
Comparison of means was performed by two-sample Student’s t-test. Correlations were examined using Pearson’s correlation. Statistical significance was considered when the two-sided P-value was <0.05. Analyses were performed using SPSS v16.

Results

We identified 82 patients who met the inclusion criteria. Patient demographics are given in Table 1. The majority of patients received their ICD for secondary prevention (71%). Mean age was 57 years (range 8–79) and 72% were male. A total of 34 patients had coronary artery disease, 25 had dilated cardiomyopathy (DCM), with other causes being less common. Mean left ventricular ejection fraction was 37% and 57 years (range 8–79) and 72% were male. A total of 34 patients were on Class III anti-arrhythmic agents (14 on amiodarone and 4 on sotalol).

Table 1 Patient population characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56.9 ± 16.2 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 59</td>
</tr>
<tr>
<td></td>
<td>Female 23</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>34 (41)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>25 (30)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular dysplasia</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Idiopathic VT</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (6)</td>
</tr>
<tr>
<td>LVEF %, mean, SD</td>
<td>37 ± 13.7</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>24 (29)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>58 (71)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
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<tr>
<td>Diabetes</td>
<td>27 (33)</td>
</tr>
<tr>
<td>Previous history of AF</td>
<td>23 (28)</td>
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<tr>
<td>Therapy at implantation</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>57 (70)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>41 (50)</td>
</tr>
<tr>
<td>Class III agents</td>
<td>18 (22)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>14 (17)</td>
</tr>
<tr>
<td>Diuretic treatment</td>
<td>27 (33)</td>
</tr>
</tbody>
</table>

Ventricular fibrillation frequency characteristics

The DF for test 1 was 4.73 ± 0.61 Hz (corresponding to a cycle length of 213 ms) with 25th and 75th quartiles of 4.25 and 5.03 Hz, respectively (235 and 199 ms cycle lengths). The corresponding DF histogram is given in Figure 2A. For test 2, DF was 4.72 ± 0.65 and the 25th and 75th quartiles were 4.15 and 5.03 Hz, respectively (for DF histogram, see Figure 2B). Both distributions exhibit positive skew and kurtosis. However, a Kolmogorov–Smirnov test demonstrates that neither differs significantly from a normal distribution (P = 0.3 and 0.6 for tests 1 and 2, respectively).

The ICC between the DF from the first and the second test was 0.87 (P < 0.01), demonstrating a very strong correlation. Consistent with this, the difference in DF between first and second episodes of VF (Figure 2C) was not significantly different from zero (0.01 ± 0.26 Hz, P > 0.5, n = 82).

Differences within patient groups

We examined the effect of specific diseases or medication on the frequency of VF. Patients taking Class III agents at the time of testing had lower DF (4.4 ± 0.4 vs. 4.8 ± 0.6 Hz, P < 0.01, n = 18). However, the DF of patients with ischaemic heart disease (n = 34) did not differ from those with DCM (n = 25) (4.7 ± 0.6 vs. 4.6 ± 0.4 Hz, P = 0.3). There was no difference in DF between other patient groups or drug therapies nor was any relationship seen between DF and age as demonstrated by correlation coefficient (R = 0.032) for the linear regression between these variables.

Discussion

Our study has demonstrated that DF of VF is highly reproducible for successive inductions of VF during device testing. Dominant frequency did not differ between patients with underlying ischaemic heart disease when compared with DCM, but was significantly reduced by Class III agents. Our study confirms the feasibility of using interrogated ICD data for further investigation into VF characteristics. Implanted cardioverter defibrillator devices are now routinely used in patients with a wide range of cardiac pathologies that are associated with sudden death due to rhythm disturbance. Ventricular fibrillation data collected by these devices are available from clinical events and also at initial implant testing. This provides an exciting opportunity to investigate the mechanisms that give rise to VF in large and well-specified patient groups. Before this can be fully exploited, it is necessary to identify the most appropriate methods of analysis and to establish the reproducibility of the techniques employed.

Frequency analysis and, in particular, DF have been widely used to characterize spatiotemporal features of fibrillation. Dominant frequency is a measure of the cycle length of VF, and it may also be predictive of defibrillation threshold. The focus of this study was to assess the reproducibility of DF estimates.
Test–retest data acquired at the time of ICD implantation were used for this purpose.

We found that DF was highly consistent for induced VF episodes in a test and re-test scenario. This is at variance with the results of the only previous comparable study, which used similar methods and patient populations. Taneja et al. quantified a greater range of measures of the VF frequency distribution than in this study and reported that repeated events have only fair to good reproducibility. However, the statistical power of their study was constrained by the use of relatively short data lengths (3 s) across a much smaller patient group ($n = 24$).

Anti-arrhythmic drugs can modulate fibrillation frequency and also influence the spatial complexity of VF through their effects on conduction velocity, refractoriness, and wavelength. There is some evidence that chronic cardio-selective beta-blockade decreases initial fibrillation frequency, presumably because it reduces the effects of sympathetic activation and circulating catecholamines on wavelength. It has been established that amiodarone and sotalol reduce the frequency and complexity of VF and this has been attributed to action potential lengthening as a result of potassium channel blockade. In this study, we have confirmed that these Class III anti-arrhythmic agents reduce DF, but could demonstrate no significant effect of beta-blockade.

We found no difference in DF between patients with ischaemic heart disease and non-ischaemic DCM. We had presumed that the increased dimension of dilated hearts would have reduced DF. The lack of difference is probably a result of overlap between these patient groups as evidenced by the overall low ejection fraction. In addition, factors other than underlying substrate may well play a significant role here in determining DF. To clarify these issues, considerably larger patient groups would need to be studied.

The mean DF observed in this study was ~4.7 Hz, which lies towards the lower end of the range reported for human VF. Clayton et al. demonstrated that DF increases during the period immediately after initiation of VF and, in general, higher fibrillation frequencies are associated with recording durations that would enable DF to plateau at a maximum value. For instance, Nanthakumar et al. reported a DF of 5.8 ± 1.8 Hz for patients undergoing bypass surgery, where VF was sustained for 2 min. Triggers initiating VF have previously been examined in a subset of MADIT II patients using data from clinical events treated by an ICD. Our study shows that it is possible to quantify key features of VF throughout the entire epoch. This may unlock an important store of information about human VF and the mechanisms that initiate and sustain it. Given the reproducibility of DF of VF, it would also be reasonable to explore clinical correlates with this measure. In particular, this approach could be applied in large population-based studies furthering our insights into VF among different disease groups.

**Limitations of the study**

There are inherent limitations in analysing VF using data from ICD testing. The duration of the VF epochs acquired was typically around 5 s, which reduced the resolution of the power spectrum to a mean of 0.19 Hz. The non-uniform recording time may also contribute to variability in DF estimates, since the frequency of fibrillation increases initially. However, variation in episode length has no impact on the main finding of this study that the DF of short intervals of induced VF is highly reproducible, because it is the same for both of the tests carried out in each patient. Although the automatic gain control used in ICDs may introduce low-frequency artefacts in the EGMs recorded, any modulation of frequency components occurs substantially below the range of dominant frequencies observed in this study. Ventricular fibrillation exhibits complex spatiotemporal variation and as a result, power spectra and DF may vary with different recording locations and lead systems. Implanted cardioverter defibrillator devices record bipolar EGMs from pace/sense or tip to coil electrodes in the right ventricle. Although this has the advantage of standardization of measurement site and lead system, the extent to which we can generalize VF behaviour from measurements...
made in a small region of the heart remains uncertain. Finally, it should be noted that the arrhythmias acquired in ICD testing are induced events and we have previously reported that induced and spontaneous VF events have distinct characteristics.17

Conclusion
The DF of short intervals of induced VF is highly reproducible and is sensitive to pharmacological interventions that extend effective refractory period. Such estimates of DF may therefore have clinical utility and in patients with ICDs provide a means of investigating mechanisms underlying the initiation of VF.

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Conflict of interest: none declared.

References