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Circadian variation of human ventricular fibrillation dominant frequency

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ABSTRACT

Aim: Circadian variation in human ventricular fibrillation (VF) dominant frequency is unknown. If present this would provide evidence of physiological influence on VF. The objective was to quantify the circadian variation in human VF dominant frequency.

Methods: Eight-lead Holter ECG recordings were obtained from a patient with VF who was supported by a bi-ventricular assist device. Recordings of up to 24 h duration were obtained on 6 days with an average interval between recordings of 7 days. Dominant frequency and amplitude were obtained using spectral analysis and assessed for i) circadian, ii) inter-recording and iii) inter-lead differences.

Results: There was a significant circadian variation in amplitude (night: 0.027±0.004 mV Hz vs day: 0.044±0.006 mV Hz, p < 0.0001) but not dominant frequency (night: 7.85±0.62 Hz vs day: 7.93±0.54 Hz, p > 0.05). There were significant differences between recordings in dominant frequency which ranged from 6.80±0.29 Hz to 8.36±0.38 Hz (p < 0.0001) and dominant frequency spectral amplitude which ranged from 0.033±0.014 mV Hz to 0.043±0.017 mV Hz (p < 0.0001). Histograms of dominant frequencies in leads exhibited strikingly different distributions, particularly in V2 that was characterised by a bimodal distribution, while the other leads were characterised by predominantly unimodal distributions.

Conclusion: VF dominant frequency spectral amplitude exhibits circadian variability. These results provide evidence for modulation of VF, probably induced by changes in posture and physical activity.

Keywords: Ventricular fibrillation, dominant frequency, circadian variability
1. Introduction

The cardiovascular system exhibits circadian variability that is thought to promote a healthy balance between the sleep/wake cycle (1). For example, impaired circadian patterns in blood pressure and heart rate have prognostic significance (2,3). The autonomic nervous system plays a key role in mediating this cycle (4). On one hand, circadian variability is an essential characteristic of a healthy cardiovascular system, yet it also seems to provide a window of opportunity for adverse cardiovascular events at certain times of the cycle. Particularly, incidence of sudden cardiac death increases in the morning (5), as does onset of ventricular arrhythmias (6-9). These increases probably relate to the circadian pattern of myocardial infarction (10). It has been suggested that circadian changes in cardiac electrophysiological properties, for example, ventricular refractoriness that shortens during the morning, also contributes to the circadian cycle of arrhythmogenicity (11). Additionally, Vendetti et al (12) demonstrated in patients with implantable cardioverter-defibrillators significantly increased defibrillation threshold during the morning and increased numbers of failed defibrillation attempts in the morning compared to other periods of the day. The study did not present data for defibrillation thresholds or failures at night. Defibrillation success has been associated with lower VF dominant frequency and larger ECG waveform amplitude (13-15). Hence, diurnal variations in these parameters might help to explain the observed diurnal patterns of defibrillation success.

The aim of our study was to assess circadian variability in human VF dominant frequency and amplitude. Dominant frequency is an important parameter related to the frequency of underlying re-entrant circuits or triggers that sustain the arrhythmia (16, 17). The dominant frequency spectral amplitude is a measure of the power contained in the ECG at the dominant frequency. We have already reported the spatial and temporal variability in
dominant frequency in short duration ECG recordings of human VF (18). However, due to the difficulty of obtaining recordings of sufficient duration, the circadian variation of dominant frequency is unknown.

2. Methods

2.1. Patient characteristics

The patient was a 29 year old female admitted to the Freeman Hospital with cardiogenic shock due to viral myocarditis. A Berlin Heart Biventricular Assist Device was implanted, and the patient underwent heart transplantation three months later, though subsequently died in the early post-operative period. Histological examination of the explanted heart revealed appearances of a fibro-inflammatory cardiomyopathy in keeping with post-acute lymphocytic myocarditis though with no morphological features as to the aetiology. There was serological evidence of a recent adenoviral infection at the time of presentation. Shortly after implantation of the ventricular assist device the patient developed sustained VF. The patient was not prescribed any cardiac medication or anti-arrhythmics. There were no significant serum electrolyte abnormalities. Despite the VF the patient recovered well on biventricular support, enough to allow home visits. The settings of the device (rate, systolic and diastolic pressures) were kept constant throughout the assist device support period. The cause of death after transplantation was primary graft failure. Informed consent and ethical approval were obtained to conduct this study.

2.2. Data recording and dominant frequency analysis

Eight-lead Holter ECG (H12+, Mortara, Italy) recordings were obtained from the patient on six separate days. The first recording (day 1) was obtained 26 days after implantation of the assist device. The mean interval between recordings was 7 days (range 5 to 10). Five recordings were 24 hours duration and one was limited to 18 hours due to patient request.
No recordings were available at VF onset and VF did not terminate. ECGs were recorded at a sample rate of 1000 Hz and stored on computer for subsequent processing and analysis. ECGs were filtered using a 6th order Butterworth filter with pass band of 0.5 to 30 Hz to minimise baseline and movement artefact while preserving the fibrillation signal. Spectral analysis using the Fast Fourier Transform was applied to contiguous 1-minute segments of the ECG recordings, and dominant frequency and amplitude were determined for each segment. Spectra were visually inspected to see if they exhibited harmonic peaks sometimes observed in highly organised ventricular arrhythmias that might have hindered the detection of the dominant spectral peak but there was none. Herein dominant frequency refers to the frequency with the largest spectral amplitude measured in Hz and amplitude refers to the amplitude of the spectrum at the dominant frequency measured in mV Hz. Amplitude is an indirect measure of the power of signal components at different frequencies. Frequency resolution of the spectra was 0.015 Hz. Signal processing and analysis was carried out using Matlab R2009b (The Mathworks Inc, USA). Differences in dominant frequency and amplitude were quantified i) between day and night, ii) between recordings, and iii) between ECG leads.

2.3. Statistical analysis

Circadian variation in dominant frequency and amplitude were assessed by comparing differences in mean day (08:00 to 00:00, comprising morning: 08:00 to 12:00, and afternoon/evening: 12:00 to 00:00) and night (00:00 to 08:00) values using the Wilcoxon rank sum test. Differences between recordings and leads were assessed by Kruskal-Wallis test. A p value less than 0.05 was used to indicate statistical significance. Summary values are shown as mean±sd unless otherwise stated. Statistical analysis was carried out using Matlab Statistical Toolbox R2009b.
3. Results

3.1 Spectral parameters

Figure 1, left panel, shows the minute-by-minute dominant frequency and amplitude for each recording. The right panel shows histograms of dominant frequency for each recording. The most notable observations were that i) there was clear circadian variation in amplitude, and ii) dominant frequency changed between recordings.

3.2. Circadian differences in spectral parameters

Figure 2 summarises the mean day and night dominant frequency and amplitude for each recording. Amplitude was significantly reduced at night compared to day (0.027±0.004 vs 0.044±0.006 mV Hz, p < 0.0001). This indicated that the amplitude during the day is on average 1.63 (0.044/0.027) times that at night. In a sub-analysis of morning and afternoon/evening values, there was a significant reduction in amplitude from morning to afternoon/evening (0.055±0.011 vs 0.041±0.006 mV Hz, p < 0.01) and a further significant reduction from afternoon/evening to night (0.041±0.006 vs 0.027±0.004 mV Hz, p < 0.003). However, dominant frequency did not change significantly from night to day (7.85±0.62 vs 7.93±0.54 Hz, p > 0.05). To illustrate the circadian variation of the ECG figure 3 illustrates representative sections of day and night ECGs of 10 s duration alongside their associated spectra. Both ECG and spectral amplitude are clearly increased in the day compared to night.

3.3. Differences between recordings

Figure 4 summarises dominant frequency and amplitude from recordings on different days. There were significant differences in both dominant frequency (p < 0.0001) and amplitude (p < 0.0001). Dominant frequency ranged from 6.80±0.29 Hz on day 1 to 8.36±0.38 Hz on
day 22. Amplitude ranged from 0.033±0.014 mV Hz on day 22 to 0.043±0.017 mV Hz on day 36.

3.4. Differences between leads

Figure 5 shows histograms of dominant frequency from each lead. The histogram distributions were not equal for all leads. Particularly V2 for all recordings exhibited a bimodal distribution whereas the other leads predominantly exhibited a unimodal distribution. Table 1 describes the similarity of distributions between leads by quantifying the percentage overlap (area under the curves) in the distributions. Values are average for the six recordings. V2 distributions exhibited the least similarity with the other lead histograms with approximately 50% overlap. Figure 6 compares by lead the dominant frequencies with the greatest histogram count for each recording. For V2 the dominant frequencies with the greatest histogram count for each peak in the bimodal histogram distribution were identified as indicated by the two boxplots in figure 6. There were significant differences between leads for the lowest V2 dominant frequency (p < 0.02) but no significant difference for the highest V2 dominant frequency (p > 0.05).

4. Discussion

This is the first study to quantify circadian variations in human VF dominant frequency and amplitude. VF is typically sustained for seconds rather than hours so there has been a paucity of data of sufficient duration to allow assessment of circadian variations of VF dominant frequency. Patients developing VF who are supported by ventricular assist devices provide a novel model that facilitates the study of human VF over much longer periods, typically weeks or months, than any other model. Using this model we have collected a unique dataset and quantified the circadian pattern of VF spectral characteristics repeatedly in the same patient over several weeks. The obvious difference
of this model to normal VF is that the assist device ensures the heart remains continuously perfused. This is not a restriction in our study because we were interested in the circadian pattern of VF rather than the effects of ischaemia. We have demonstrated a circadian pattern that was characterised by significant reductions in VF amplitude at night. Postural changes are the most plausible explanation for this circadian pattern, particularly since day-time amplitudes exhibited large variability reflecting the relatively active state of this patient whereas night-time amplitudes, when the patient would be expected to be sedentary, were relatively constant. However, autonomic influences may also contribute to the circadian pattern of VF. As discussed in the introduction, the effect of the autonomic nervous system on a range of cardiac parameters is well established. Circadian changes in atrial fibrillation dominant frequency have been reported with significantly reduced cycle length (increased dominant frequency) during daytime, but not in patients with already short cycle lengths (18). In our study dominant frequency of VF did not change significantly from day to night suggesting there is no autonomic influence on VF dominant frequency. Defibrillation success has been related to organisation of VF (13, 14). It is interesting that in our patient VF was more organised, as suggested by increased waveform amplitude, in the morning, when previous studies have indicated that defibrillation success is lowest (12). Although there was no circadian pattern of VF dominant frequency, there were significant inter-recording and inter-lead differences in dominant frequency. This is the second case of long-term VF data from our group and the results confirm our previously published data which revealed significant inter-recording and inter-lead differences in dominant frequency (19). Inter-lead differences in dominant frequency probably reflect spatial differences in underlying activation patterns that have been shown in invasive human studies (20). Day-to-day variability in dominant frequency might arise due to changes in the cardiac electrophysiological properties due to progression of disease.
5. Conclusion

In this novel model of human VF sustained over several weeks we have shown a circadian pattern of VF amplitude but not dominant frequency. These results provide evidence for modulation of VF, probably induced by changes in posture and physical activity.

Conflict of interest statement

All authors have no disclosures relevant to this manuscript.

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References


Figure legends

Figure 1  Left panel: Dominant frequency (DF) and amplitude (Amp) across each recording. Median dominant frequency is shown in red and the range across leads in blue. Amplitude (mV Hz) was scaled by times 50 and is shown in black. Right panel: Histograms of dominant frequency for each of the recordings.

Figure 2 Comparisons of night and day dominant frequency (DF) and amplitude (Amp.). There were no significant differences for dominant frequency (p > 0.05) but amplitude was significantly increased during the day (p < 0.0001).

Figure 3. Examples of ECG leads and corresponding spectra from night and day. For both night and day each row shows an ECG lead of 10 s duration and the power spectrum calculated from a 1 minute interval of ECG containing the illustrated ECG section.

Figure 4. Boxplots of dominant frequency (DF) and amplitude (Amp.) at each recording. There were significant differences between recordings of both dominant frequency and amplitude. Box represents the interquartile range (IQR: q3-q1) of data and median is shown as a line. Whiskers represent points within q1 – 1.5 x IQR and q3 + 1.5 x IQR.

Figure 5. Histograms of dominant frequency for each lead and recording.

Figure 6. Boxplot of dominant frequency for each lead. The dominant frequency with the maximum count for each recording was used to construct the boxplot for each lead. Two boxplots for V2 represent the bimodal distribution of the histogram.
Table 1. Similarity of lead dominant frequency distributions shown in figure 5.

<table>
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<tr>
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<th>I</th>
<th>II</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
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Values are the average percentage overlap of area under the curves of lead dominant frequency histograms over the six recordings. The distributions for lead V2 (bold) had least similarity to the distributions of the other leads.