Ventricular fibrillation: one spiral or many?

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Ventricular fibrillation is the major cause of sudden cardiac death, the leading cause of death in the industrialized world; however, the mechanisms for its onset are not well understood. To further understand the dynamics of fibrillation at and near its onset, we compared spatial and temporal variability of mean inter-activation intervals in a stable canine model for ventricular fibrillation. Temporal variability was very small, suggesting that the relevant physiological parameters remained constant during our experiments. Spatial variability was usually significantly larger and appeared incompatible with the dynamics of a single, meandering spiral wave. This confirmed recent results that a single spiral wave cannot generate ventricular fibrillation. Thus the onset of fibrillation is a multistage process, with spiral-wave breakdown providing a crucial step in the quasi-periodic route to fibrillation.

Keywords: fibrillation; meandering; spiral wave; spatial variability

1. INTRODUCTION

Ventricular fibrillation is the major cause of sudden cardiac death, the leading cause of death in the industrialized world. Cardiac electrical activity in fibrillation is apparently highly disordered; however, Damle *et al.* (1992) and Bayly *et al.* (1993) found strong evidence for local spatial organization, leading the way for extensive further investigations. More recently, Gray *et al.* (1995), Panfilov & Hogeweg (1995) and Winfree (1995) considered the question of whether fibrillation could be generated by a single, meandering spiral wave. This question was answered in the past year by Gray *et al.* (1998) and Witkowski *et al.* (1998), who demonstrated the existence of multiple spirals in an extensive investigation of order in fibrillation.

The above evidence strongly suggests that the onset of ventricular fibrillation is a multistage process involving the breakdown of a single spiral wave. Rational drug design might aim to prevent the onset of ventricular fibrillation (which usually results in sudden cardiac death) by stopping any stage in its onset. Additional information about spatial organization in fibrillation might eventually lead to a better understanding of its onset, and thus potentially to improvements in drug design and implantable pacemakers/defibrillators.

We sought to quantify spatial and temporal variability at and near the onset of ventricular fibrillation, by analysing variability among electrograms recorded at different sites during the same episode of fibrillation in a stable canine model. We found little temporal variability,

confirming the temporal stability of our model, as well as significant spatial variability. This indicates that the intrinsic local dynamics of fibrillation is determined by relatively stable physiological parameters in our model. As we shall show below, the amount of spatial variability appears incompatible with the dynamics of a single, meandering spiral wave, providing quantitative evidence that a single spiral wave cannot generate ventricular fibrillation, in agreement with results of Gray *et al.* (1998) and Witkowski *et al.* (1998).

Finally, Garfinkel *et al.* (1997) developed a dynamical framework for the onset of ventricular fibrillation, namely the quasi-periodic route to chaos (Ruelle & Takens 1971). The dynamics of a single, meandering spiral wave contains two of the three frequencies required for this route to fibrillation. As we shall discuss below, additional spiral waves, or any other significant anisotropy or interaction may provide the third required frequency.

2. MATERIALS AND METHODS

Surface electrograms were obtained from a stable canine model of ventricular fibrillation (Nwasokwa 1987; Nwasokwa & Bodenheimer 1991; Hastings *et al.* 1996; Garfinkel *et al.* 1997) as follows. An intact canine heart was excised and cross-perfused by connecting its blood vessels to a second dog to maintain haemodynamic stability. This preparation maintained the perfusion and temperature of the excised heart at conditions similar to those at the onset of fibrillation. Ventricular fibrillation was induced in the excised heart with a 60-Hz pulse. Unipolar electrograms were obtained from the epicardial ventricular surface.

These electrograms $V(t)$ were recorded beginning several seconds after the apparent onset of fibrillation, and then

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Table 1. *Mean interactivation intervals from approximately simultaneous surface electrograms in a stable canine model of ventricular fibrillation*(Data is shown as mean $\pm$ s.d., in ms.)

dog, episode, site	first 250 intervals	second 250 intervals	first 500 intervals	second 500 intervals
D1, E1, A	145.4 $\pm$ 35.6	150.2 $\pm$ 39.9	147.8 $\pm$ 37.9	149.8 $\pm$ 40.9
D1, E1, B	127.6 $\pm$ 27.2	127.8 $\pm$ 27.0	127.7 $\pm$ 27.1	130.0 $\pm$ 26.5
D1, E1, C	130.4 $\pm$ 20.8	128.7 $\pm$ 21.3	129.6 $\pm$ 21.1	132.6 $\pm$ 23.8
D2, E1, A	74.9 $\pm$ 27.9	72.7 $\pm$ 26.9	73.8 $\pm$ 27.4	78.1 $\pm$ 28.2
D2, E1, B	111.8 $\pm$ 29.6	111.5 $\pm$ 31.1	111.7 $\pm$ 30.3	111.4 $\pm$ 29.5
D2, E2, A	110.7 $\pm$ 28.9	112.2 $\pm$ 28.1	111.4 $\pm$ 28.5	113.3 $\pm$ 27.5
D2, E2, B	107.9 $\pm$ 25.0	108.9 $\pm$ 28.6	108.4 $\pm$ 26.8	108.7 $\pm$ 33.9
D2, E2, C	110.8 $\pm$ 37.2	109.5 $\pm$ 37.7	110.1 $\pm$ 37.4	108.5 $\pm$ 36.4
D3, E1, A	91.8 $\pm$ 24.3	92.0 $\pm$ 24.1	91.9 $\pm$ 24.1	92.4 $\pm$ 24.3
D3, E1, B	92.9 $\pm$ 21.8	95.4 $\pm$ 22.7	94.1 $\pm$ 22.3	93.9 $\pm$ 22.3
D3, E2, A	127.8 $\pm$ 33.8	139.1 $\pm$ 36.6	133.5 $\pm$ 35.6	128.1 $\pm$ 33.3
D3, E2, B	128.8 $\pm$ 34.8	132.7 $\pm$ 36.5	130.7 $\pm$ 35.7	129.6 $\pm$ 33.2
D3, E2, C	135.7 $\pm$ 39.1	142.3 $\pm$ 42.7	139.0 $\pm$ 41.0	139.3 $\pm$ 44.9
D4, E1, A	117.5 $\pm$ 24.4	118.6 $\pm$ 24.3	118.1 $\pm$ 24.3	114.7 $\pm$ 28.5
D4, E1, B	122.5 $\pm$ 38.4	130.0 $\pm$ 39.2	126.3 $\pm$ 38.9	114.4 $\pm$ 29.5
D4, E2, A	127.8 $\pm$ 32.9	137.8 $\pm$ 36.7	132.8 $\pm$ 34.3	129.1 $\pm$ 33.8
D4, E2, B	130.5 $\pm$ 35.8	133.9 $\pm$ 37.7	132.2 $\pm$ 36.8	132.2 $\pm$ 33.3
D4, E2, C	139.2 $\pm$ 40.5	144.4 $\pm$ 46.0	141.8 $\pm$ 42.7	145.3 $\pm$ 45.9

analysed offline to identify activation times to an accuracy of 1 ms from peaks in dV/dt (upstroke velocity), subject to a refractory period of 30 ms (Garfinkel *et al.* 1997). This analysis yielded series of interactivation intervals ('intervals') between activation peaks, which may be regarded as time-series indexed by the interval number. Eighteen relatively long interval series (at least 1000 intervals) were obtained from multiple, approximately synchronized recordings from seven distinct episodes of ventricular fibrillation: three episodes with recordings at two sites each, and four episodes with recordings at three sites each. For each such episode, variability among interval series from different sites (spatial variability) was compared with variability between segments of each interval series (temporal variability), using standard analysis of variance (ANOVA) techniques.

3. RESULTS

In most cases, we found large differences between the average interactivation interval at different sites in the same episode of ventricular fibrillation. For example, in series of 500 interactivation intervals from three sites in canine 1, episode 1, large differences (15%, $p < 0.001$, ANOVA) were found between the average intervals at site A and that at sites B and C. Other episodes frequently displayed similarly large differences among average interactivation intervals at different sites (see table 1).

In contrast, no significant differences were found between 250-interval segments of these series and in interactions between recordings and segments. The ANOVA results are summarized in the table 2.

In comparisons between the first and second 250-interval segments of interval series, significant inter-

actions with site were observed in two episodes. Significant differences between segments were found in two out of the remaining five episodes. Four of these five episodes, as well as the two with interactions, displayed significant differences among sites. Similarly, in comparisons between the first and second 500-interval segments, significant interactions were also observed in two episodes. One of the remaining five episodes showed significant differences between the segments; all seven episodes showed significant differences among sites.

In summary, interactivation intervals at different sites in a single episode of ventricular fibrillation frequently display large and highly significant differences in duration, sustained over 1000 intervals or approximately 2 min (average difference, 13%; range, 2–46%).

4. HOW MANY SPIRALS?

It appears unlikely that a single, possibly meandering spiral wave can generate the significantly different sequences of interactivation intervals at different sites observed during the same episode of ventricular fibrillation, especially in the frequent absence of similar temporal differences. (This discussion also applies to scroll waves in three dimensions.) For example, during the 2-min period in which 1001 activations occurred at site B in canine 1, episode 1, only 867 activations occurred at site A, a 16% difference. Even if the active zone of a particular spiral wave were very narrow (a conduction velocity of 10 cm s^{-1} and an action potential duration of 40–50 ms would yield a 4-mm wide active zone), there is not room for many activation fronts between two sites in

Table 2. Analysis of variance of interactivation-interval series, showing significance (*p*-value) for selected factors

canine	1	2		3		4	
episode	1	1	2	1	2	1	2
number of sites	3	2	3	2	3	2	3
factor							
time: 1st 250 vs 2nd 250 intervals	n.s.	n.s.	0.025	n.s.	0.001	0.025	0.005
space: among sites during 1st 500 intervals	0.001	0.001	0.001	n.s.	0.005	0.001	0.001
interaction between time and space during 1st 500 intervals	n.s.	n.s.	0.025	n.s.	n.s.	0.05	n.s.
time: 1st 500 vs 2nd 500 intervals	0.05	n.s.	n.s.	n.s.	n.s.	0.001	n.s.
space: among sites during 1st 1000 intervals	0.001	0.001	0.05	0.001	0.05	0.001	0.001
interaction between time and space during 1st 1000 intervals	n.s.	0.05	n.s.	n.s.	n.s.	0.001	n.s.

a canine ventricle. Hence, for a single, meandering spiral wave to generate 867 activations at one site and 1001 activations at another in the absence of an intermittent conduction block, the trajectory of the centre must wind repeatedly around one or both of the sites, a total of at least 134 times during the 2-min period of observation. However such a stable, rapid meander also appears implausible, as it would require sustained rotational motion of the centre at half the highest velocity observed in both animal models and computer simulations (Gray *et al.* 1995).

Moreover, meandering spiral waves in the ventricle appear likely to degenerate to spatio-temporal chaos via a quasi-periodic transition (Garfinkel *et al.* 1997). The resulting dynamics may contain several transiently stable spirals, as implied by our results. The quasi-periodic route to chaos requires three independent frequencies (Ruelle & Takens 1971). The natural frequency of a single spiral wave provides one frequency. The onset of meandering is a Hopf bifurcation that introduces a second frequency into the dynamics (Karma 1990; Skinner & Swinney 1991; Barkley 1992; Hakim & Karma 1997). The third required frequency can arise in several ways: (i) electrical activity wrapping around the ventricle, introducing a time-scale on the order of 1 s (the ventricular circumference of 12–15 cm divided by the conduction velocity of 10–20 cm s⁻¹); (ii) spatial anisotropy causing variations of the order of 10% in conduction velocity (Fenton & Karma, 1998), and thus introducing roughly the same time-scale (the order of ten interactivation intervals); or (iii) other electrical activity in the heart, for example, intermittently conducted sinus waves or other spiral waves. The presence of this third frequency may yield a quasi-periodic transition to chaos. This transition cannot in general yield a persistent,

chaotically meandering spiral because meandering spirals and scroll waves (their three-dimensional analogues) are generally unstable in anisotropic 3D tissue, as implied by Fenton & Karma (1998). Note, however, that significant interaction in several episodes may be associated with a single, meandering spiral wave.

Our results are thus consistent with the observation of Garfinkel *et al.* (1997) that a fibrillating ventricle appears to be a spatially extended, chaotic system, the dynamics of which cannot be readily explained by a single, meandering spiral wave. Limitations to this argument will be described below. This result further confirms the results of Gray *et al.* (1998) and Witkowski *et al.* (1998) on the existence of multiple spirals during fibrillation.

Finally, the relative stability of mean interactivation intervals at any site (compared with variability between sites) suggests that the physiological parameters that determined the mean interactivation interval remained stable for the duration of our recordings. Our data on spatial variability are therefore probably representative of the early stages of fibrillation when there is little significant ischemia, and may therefore lead to further information about its onset. However, a different model would clearly be needed to study changes in cardiac dynamics due to ischemia.

(a) Limitations

1. There may be alternative explanations for the frequently observed large differences in numbers of activations at different sites; for example, an intermittent conduction block might prevent activations generated near one site from reaching another site. However, a structural conduction block is very unlikely in our model for ventricular fibrillation, as fibrillation was induced in apparently healthy hearts by 60-Hz electricity and recordings were made far from the valvular ring. Because a functional intermittent conduction block involves refractory behaviour following stimulation from a second source, such as a second spiral wave, the existence of a sustained, functional intermittent conduction block would imply the existence of at least two self-sustaining re-entrant sources.
2. Meandering spiral waves have been seen to show three or more frequencies, without any chaos (Plesser & Muller 1995). However, Garfinkel *et al.* (1997) provided significant additional evidence for chaos from their analysis of lag plots and power spectra of interval series.
3. Spiral waves can meander chaotically (Diks *et al.* 1995); however, breakup of such waves in anisotropic heart tissue also appears likely, as implied by Fenton & Karma (1998).

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