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Mechanisms of Cardiac Fibrillation

Many mechanisms have been proposed to explain ventricular fibrillation, which is the precursor to sudden cardiac death, the leading cause of death in the industrialized world (*1*). A recent hypothesis discussed by Arthur T. Winfree (*2*) involves three-dimensional (3D) rotors of electrical activity that become unstable when the heart thickness exceeds some critical value. Winfree (*2*, p. 1006) states, "Several pinned rotors would collectively resemble fibrillation in the . . . electrocardiogram, and individual epicardial electrodes would still reveal their individual local periodicities." Although attractive, such an idea remains speculative. Even the most sophisticated systems record extracellular potentials from only a limited number of sites (*3*), making the demonstration of multiple rotors during fibrillation difficult. Moreover, to our knowledge, experimental data are not available as yet showing more than two simultaneous rotors activating the ventricles at various frequencies and resulting in fibrillation. We have used voltage-sensitive probes and high-resolution video imaging to record electrical wave propagation on the surface of the isolated rabbit heart during ventricular fibrillation (*4*). Here we present direct experimental evidence that even a single rapidly moving rotor can give rise to electrocardiographic patterns that resemble fibrillation.

In three episodes of fibrillation, video "movies" of the transmembrane potential signal from the ventricular surface demonstrated a single rapidly moving rotor associated with turbulent electrical activity as recorded by an electrocardiogram (ECG) (Fig. 1A). Specifically, as the rotor (top panel) drifted along complex trajectories on the heart surface (middle), the ECG displayed irregular periodicity and morphology (bottom). To complement our experimental studies of surface data, we conducted computer simulations incorporating more realistic 3D heart geometry (*5*). With the appropriate model parameters we observed a rotor moving rapidly through the heart that was similar to our experimental recordings (Fig. 1). These irregular ECGs and their corresponding narrow-banded frequency spectra (Fig. 2, A and B), for both the experiments and simulations, are consistent with previous data obtained during fibrillation (*6*). Furthermore, the width of these frequency spectra can be related to the frequency of rotation of the rotor, the speed of its motion, and the wave speed through the Doppler phenomenon according to the following relationship:

$$1/(1 + v_{s,max}/v) < f'/f_s < /(1 - v_{s,max}/v) \quad (1)$$

where $v_{s,max}$ is the maximum speed of the rotor, v is the wave speed, and f'/f_s is the observed frequency normalized to the frequency of the rotor. In the experimental episode presented in Fig. 1A, the ratio $v_{s,max}/v$ was 0.39, and for the simulation (Fig. 1B) $v_{s,max}/v$ was 0.37; the dotted lines in Fig. 2 depict the range of frequencies predicted by the use of Eq. 1. Also, the ratio of periods ahead and behind moving rotors, calculated with the use of recordings from the heart surface, also showed excellent agreement with those predicted by the Doppler effect (Fig. 2C). In contrast to Winfree's hypothesis, the activity at individual sites was irregular with narrow-banded spectra similar to those for the ECGs. Our results suggest that it is the speed of the rotor(s), not their number,

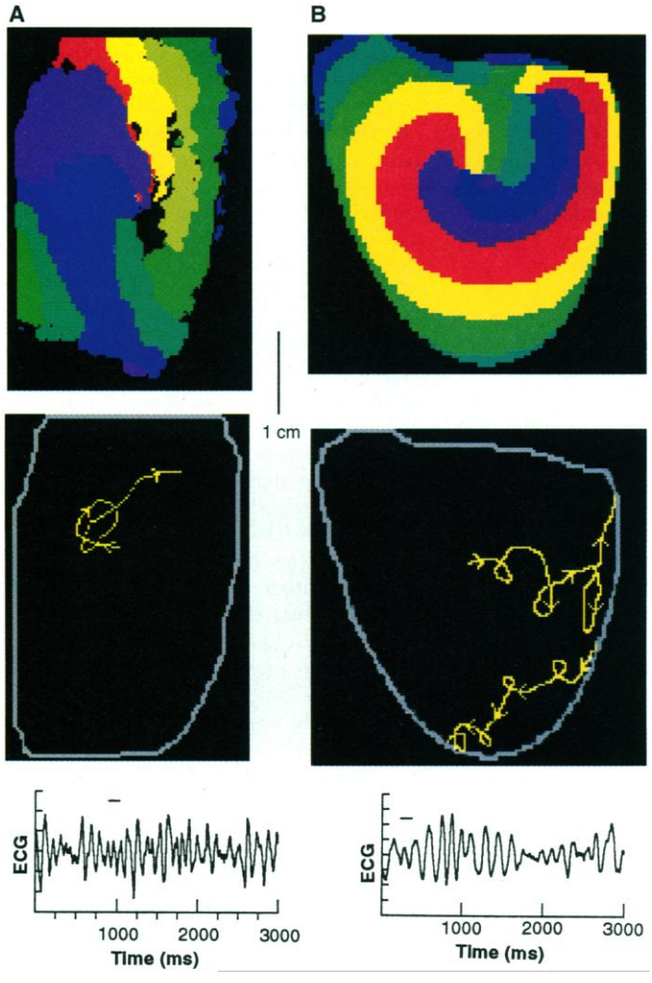

Fig. 1. Rapidly moving rotors. (**A**) Experiment. (**B**) Simulation. Isochrone maps of the surface activity displayed rotors as shown in the top panels. Each isochrone map was computed from one cycle of rotation as denoted by the horizontal bar in the bottom panel (red denotes earliest and purple latest time of activation). Portions of the paths of the organizing centers (cores) of the nonstationary rotors are depicted in the middle panels. Trajectories of the rotor cores were calculated from the surface recordings using time-space plots (*4*). Speed of the rotor cores ranged from zero to approximately 40% of the wave speed. These rapidly moving cores resulted in irregular electrocardiograms that are characteristic of fibrillation as shown in the bottom two graphs.

that gives rise to the irregular ECGs characteristic of fibrillation. We also performed a simulation in which we placed seven stationary rotors in the heart that resulted in a regular, periodic ECG unlike fibrillation.

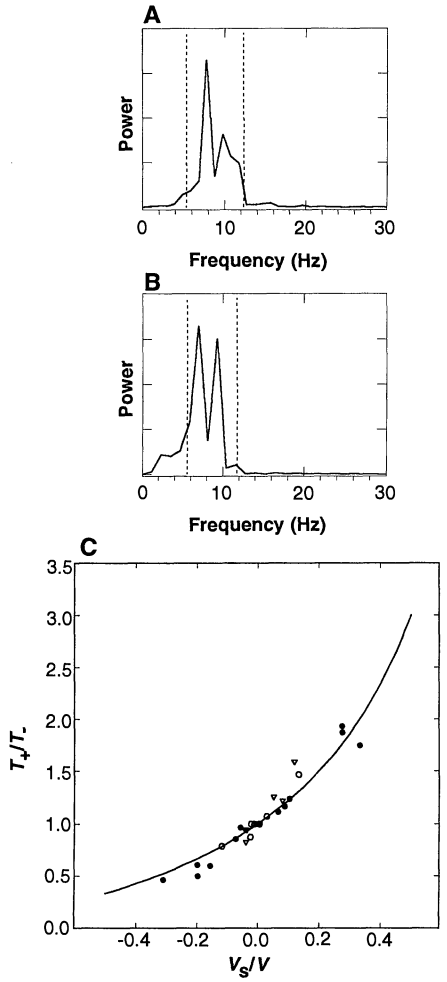

Fig. 2. Theory compared with experiment. Frequency spectra corresponding to the ECGs in Fig. 1 are displayed in panels (**A**) experiment, and (**B**) simulation. Values of $v_{s,max}$ and v were calculated from the surface recordings with the use of time-space plots (*4*). These values, in conjunction with Doppler theory (Eq. 1) predict the widths of the narrow-band frequency spectra (predicted ranges marked by dotted lines). In Langendorff-perfused hearts (n = 6), the conduction velocity during reentry (v) was calculated in both the longitudinal (44 ± 4 cm/s) and transverse (21 ± 2 cm/s) ventricular epicardial fiber directions; these values compare favorably with other published data (*7*). For the experiment shown in Fig. 1A, the frequency of rotation of the rotor (f_s = 7.5 Hz) was calculated as the inverse of the average cycle length from two sites for 15 beats. Units of power are arbitrary. (**C**) Instantaneous relationship of the ratio of activation periods ahead (T_-) and behind (T_+) the moving rotors to the dimensionless quantity v_s/v for both the animal experiments (open symbols: circles are transverse direction; triangles are longitudinal direction) and the simulations (filled symbols). Solid line indicates the theoretical prediction from Eq. 1 giving $T_+/T_- = (1 + v_s/v)/(1 - v_s/v)$. Points are well fit by the theoretical curve ($P < 0.05$, n = 25).

The fibrillation we observed most likely was not a result of the 3D effects proposed by Winfree (*2*). According to him, a critical thickness of one rotor diameter (3 to 4 mm) is required for fully developed fibrillation: "vortex filaments spontaneously lash about unless confined to a layer thinner than about a rotor diameter" (*2*, p. 1004). Yet, in our rabbit heart experiments, single rotors drifted freely on the surface of the right ventricle with a thickness (0.8 mm) that is usually less than one core diameter. Also, there is considerable evidence that the signals we recorded from the surface of the rabbit heart represented the activity throughout the entire wall (*7*), thus resulting in a straight vortex filament. Moreover, we performed computer simulations that demonstrated that a rotor with a straight filament gives rise to fibrillatory patterns if the rotor moves rapidly (greater than approximately 30% of the wave speed).

In summary, we present data demonstrating that a single rapidly moving rotor gives rise to ECG patterns of activity indistinguishable from fibrillation. Although not all episodes of fibrillation we observed were due to a single rotor, we present evidence suggesting a mechanism for fibrillation that does not require a critical thickness or many rotors for fibrillation to occur. Furthermore, our data demonstrate that the Doppler phenomenon provides a robust explanation for the narrow-banded frequency spectra characteristic of fibrillation that has perplexed investigators for many years.

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Winfree (*1*) points out that numerical models of turbulence based on the phenomenon of 2D spiral breakup cannot be candidate mechanisms for ventricular fibrillation in normal heart because experiments show that rotors remain stable in 2D [see example in (*2*)].

Recently we studied 3D turbulence in excitable media induced by the effect of spiral breakup (*3*). We found that the 3D turbulence differs from 2D turbulence in two important ways: in 3D it existed in a wider range of parameters, and it became persistent in media of smaller spatial size. These differences could explain the paradox pointed out by Winfree.

We found that turbulence in 3D in our model (*4*) existed in a range of parameters $\varepsilon_1^{-1} \geq 54$ while turbulence in 2D exists for $\varepsilon_1^{-1} \geq 58$. In our model, therefore, there is at least a 7.5% range of parameter values in which we can have turbulence in 3D but normal rotation of a spiral wave in 2D. This finding can provide the following explanation for the paradox that fibrillation in normal heart can be induced in thick 3D preparations, but has not been observed in 2D slices of cardiac tissue (*1*). If the cardiac tissue is in a range of parameters which supports turbulence in 3Ds only, then we will find no breakup in 2D preparations but we will find turbulence in thick slices of cardiac tissue.

In the case of one such computation (Fig. 1), the spiral wave remains stable in 2D (Fig. 1A), but breaks into turbulence in 3D (Fig. 1B). Increasing numerical noise by a two- and threefold increasing of the space integration step does not result in any breakups in 2D at $\varepsilon_1^{-1} = 54$.

In our model, this range of parameters where turbulence exists in 3D and does not

exist in 2D is quite narrow. However, we expect that in more realistic ionic models of cardiac tissue (5, 6) the range could be much wider. Our hypothesis is that the scroll wave in 3D has more complicated dynamics because of the meandering of the curved filament, which, together with 2D pulse instabilities, cause local distortions. In our computations we see such distortions of the circular filament before it breaks up. Therefore, in the media with pronounced meandering of spiral waves, we can expect larger distortions of the filament and thus larger differences in the range of parameters in which 2D and 3D turbulence exist. In our model, the meandering pattern has a characteristic size of 10 mm (scaled for the wavelength of 45 mm). However, it has been shown that ionic models of cardiac tissue demonstrate strong meandering of spiral waves, with the size of the pattern of 20 to 30 mm (6, 7). We therefore expect that in such models and in real cardiac tissue there could be a large range of parameters where turbulence exists in 3D only.

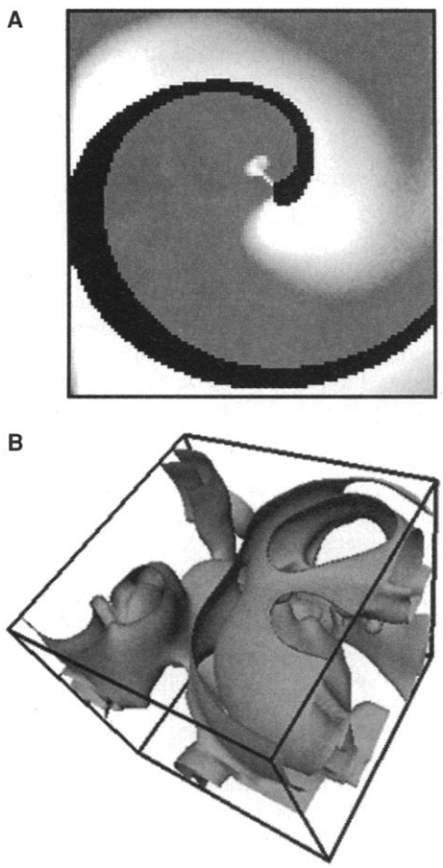

Fig. 1. Spiral wave in 2D and turbulence in 3D at $\varepsilon_1^{-1} = 54$. Computations using FitzHugh-Nagumo–type equations: $\partial e/\partial t = \nabla^2 e - f(e) - g$; $\partial g/\partial t = \varepsilon(e, g)(ke - g)$ with $f(e) = C_1 * e$ when $e < e_1$; $f(e) = -C_2 * e + a$ when $e_1 \le e \le e_2$; $f(e) = C_3 * (e - 1)$ when $e > e_2$, and $\varepsilon(e, g) = \varepsilon_1$ when $e < e_2$; $\varepsilon(e, g) = \varepsilon_2$ when $e > e_2$, and $\varepsilon(e, g) = \varepsilon_3$ when $e < e_1$ and $g < g1$. The parameters determining the shape of the function $f(e)$ are $e_1 = 0.0026$, $e_2 = 0.837$, $C_1 = 20$, $C_2 = 3$, $C_3 = 15$, $a = 0.06$ and $k = 3$. (**A**) 2D spiral wave after 70 rotations in the medium of 120*120 elements. Black area represents the excited state of the tissue ($e > 0.6$), dark gray indicates the region where $g > 1.8$ (close to the absolute refractory state) and intermediate shading from dark gray to white shows different levels of g, $0 < g < 1.8$ (estimate of the relative refractory period). (**B**) 3D turbulence that has developed in the medium of 120*120*120 elements. Gray surface depicts the excited region of the tissue ($e > 0.6$).

The persistence of turbulence depends on the spatial size of the excitable medium (6, 8). If the size of the tissue in 2D is less than some critical size, then the breaking or meandering spirals eventually disappear at the boundaries of the excitable medium. We compared the lifetimes of turbulent regimes in 2D and 3D. To study this we initiated spiral waves in 2D using four different types of initial conditions. In these initial conditions we varied the length of the break, its location, and the initial recovery of the medium. We computed the maximum of observed lifetime. We also initiated scroll waves with a curved filament in 3D and computed their lifetimes in media of different sizes (Fig. 2). (If activity persisted longer than 100 cycles we considered the lifetime as infinite.) We see (Fig. 2) that turbulence in 3D becomes persistent in much smaller media [size = 1.15 wavelength (λ)] than does turbulence in 2D (size = 2.46λ).

We also did computations in 3D excitable medium of the shape of parallelepiped with the fixed thickness of 0.6λ. We found that in this case 3D turbulence becomes persistent in the box with dimensions of 0.6λ × 1.5λ × 1.5λ. This gives approximately the same value for the volume of excitable medium necessary to support the turbulence as for the case of a cubic box (Fig. 2).

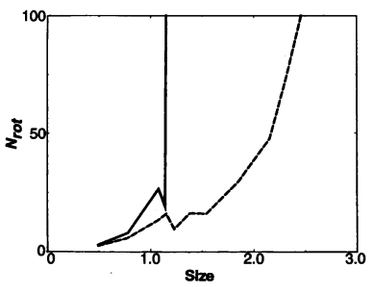

Fig. 2. Maximum observed lifetime of the turbulent regime in 2D excitable medium (dashed line) and in 3D excitable medium (solid line) in relation to size of the excitable medium (in arbitrary units). Lifetime N_{rot} is measured as the number of rotation cycles, the size of the medium is measured in terms of the average wavelength of a 2D spiral wave at these parameter values. (Because the spiral wave is not stable, we used average values.) Computations at $\varepsilon_1^{-1} = 75$ were made in square domains in 2D and cubic domains in 3D.

The difference in the size of the excitable medium necessary to support turbulence in 2D and in 3D can be also important for understanding the differences in results of experiments in 2D and 3D preparations. This is because the wavelength of a spiral wave in myocardium is of the order of 30 to 60 mm (*1*), which is comparable to the size of the ventricles of the canine or human heart. Many 2D experiments were performed on preparations of relatively small spatial size (about 20 mm by 20 mm). Our results show that, in order to obtain sustained breakup in 2D, one should either use larger preparations or decrease the wavelength of rotor in excitable tissue by application of drugs, for example.

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Response: A decade ago it seemed that to decipher the dynamics of ventricular fibrillation would necessarily entail the recognition of different kinds of fibrillation (*1*). Gray *et al.* proffer a new kind.

My article (*2*) pointed to a disconcerting experimental fact: In all known preparations of *normal healthy* ventricular myocardium, the vortex mode of action potential ("rotor") seems stable unless the tissue is more than 3 to 4 mm thick. Within this 3- to 4-mm gray zone (Fig. 1), unaltered natural hearts also acquire susceptibility to fibrillation. Something about thickness facilitates rotor instabilities, resulting in spatiotemporal electrical instability. Half-a-dozen distinguishable possibilities have been discussed in these comments and by me (*3*). One of the two possibilities that I have recently emphasized (*2*, *4*) implicates a threshold thickness suggestively close to the observed 3 to 4 mm. The seven groups of experiments I reviewed (*2*) did not show spatiotemporal complexity of propagation in normal healthy ventricular myocardium thinner than 3 to 4 mm. This raises questions about fibrillation models based on rotors and their 2D instabilities, some of which are now well developed theoretically.

Gray *et al.* present a model to restore a strictly 2D option by settling for temporal disorder without requiring the normally ex-

pected spatial disorder described by others (5). Temporal disorder alone is sufficient under the clinician's classical criterion of fibrillation: a high-frequency aperiodic ECG signal. Rotor motion gives rise to substantially Doppler-shifted intervals of excitation fore and aft (6). Such motion ("drift and meander") was expected in myocardial rotors (7) and, at the speeds familiar in diverse excitable media including myocardium, was expected to impress the ECG like a polymorphic tachycardia (8). Gray *et al.* confirmed this in myocardium (9) and argued that, should the rotor move still faster, the ECG would look still less periodic, even "completely irregular" (10). This might be the complicated "hyper-meander" recently described in simple electrophysiological models (11).

The demonstration referred to in the comment by Gray *et al.* (12) uses a 7- to 10-gram heart of a rabbit weighing 2 kg. The bulk of its wall should be about 3 mm thick, in the gray zone (Fig. 1); the 0.8-mm thickness mentioned by Gray *et al.* applies only to the right ventricular free wall, but their reported observations involved the 3-mm–thick left wall, as well. Gray *et al.* (12) cooled the heart until electrical instabilities arose spontaneously. These unexplained instabilities satisfy the clinician's temporal criterion without the familiar spatial fragmentation of activation fronts [the spatio-temporal criterion intended in my article (2)]. This new mechanism may be the simplest kind of "fibrillation." Its independence from 3D processes is not yet certain from video observations limited to the 2D surface (12). If the mechanism is indeed 2D, it might be developed into a counter-example to my inferences (2) about electrophysiologically normal ventricular myocardium. This would require a similar, but more difficult experiment using such tissue. The preparation used (9, 10, 12) is said to be only "structurally" normal. Is it electrically normal? Diverse mechanisms of fibrillation have long been reported in diversely damaged tissues, even in thin atrial myocardium. Would the results of this experiment be nearly the same if the rabbit's heart were nourished with blood in situ rather than with salt solutions in vitro, in the absence of (i) ultraviolet light, (ii) the membrane-bound photosensitizing dye di-4-ANEPPS and its DMSO vehicle, (iii) the excitation-contraction uncoupler diacetyl monoxime, and (iv) at normal 38°C (rather than cooled so much as to elicit spontaneous electrical instabilities)? Is such abnormality essential for this rotor's uniquely rapid motion? Sustained travel at the reported speed of Mach 0.39 (relative to action potential speed under the same conditions) is a new

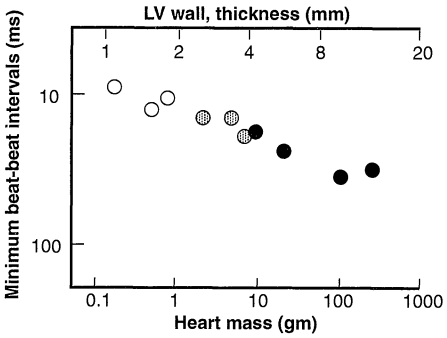

Fig. 1. Homeotherm maximum heart rates in relation to ventricular wall thickness, extracted from figure 2 (2). Small normal hearts (○) do not support fibrillation. Larger hearts (●) do. Hearts in the transitional gray (◍) zone with a thickness of 3 to 4 mm differ, or the outcome depends on criteria for "fibrillation."

achievement, amounting to perhaps 50 cm in a few seconds within the confines of a 2- to 3-cm-thick heart; can it occur under the normal physiological conditions of interest?

I am grateful to Gray *et al.* for skewering my recent side-remark (2) that in the 2D case a collection of *several* rotors would most plausibly underlie an ECG impression of temporal irregularity. This new example restores my former more naïve faith that a single rotor could also do the job, at least under special conditions (13).

Two principal lessons are underscored by this valuable contribution: (i) Normal myocardium activated by a single pinned rotor presents as "monomorphic tachycardia" through the ECG (3, 4, 13); if that rotor exhibits drift or simple meander, we get "polymorphic tachycardia," that is, *torsades de pointes* (3, 8–10), and if it exhibits hyper-meander or something faster and still less regular than seen elsewhere, then it presents the clinician's "fibrillation" (12), but without the spatial breakup observed in familiar epicardial maps of fibrillation (5). (ii) It is time to give separate names to distinct contexts, mechanisms, and criteria for "fibrillation" (1).

Panfilov and Hogeweg stress that whereas thin layers of otherwise normal ventricular myocardium as much as 4 to 5 cm in diameter seem not to support fibrillation (2), yet larger areas might. The first glimpse of ephemeral "fibrillation" induced by rotors in a detailed ionic model of myocardium needed a 10-cm 2D arena (14). Less detailed (and possibly more realistic) models have since obtained persisting electrical turbulence inside half that diameter (15). It is encouraging to learn that in one such model smaller areas suffice if they are also thicker.

A medium thickness of 0.6 λ, as Panfilov and Hogeweg would require, might correspond to a ventricular wall no more than 1 cm thick. This approaches realistic values for laboratory animals and humans. At the moment, laboratory results indicate a wall thickness exceeding 0.5 cm is necessary for rotors to induce spatiotemporal fibrillation. Thus theory and experiment are now converging.

With regard to the 54:58 gap between parameter values in these numerical experiments, I am more inclined to accept Panfilov and Hogeweg's projection of future behavior in more realistic models than to stress the relevance of such a fine distinction in present-day models.

The unexpected experimental result that some thickness is required for rotors to catalyze fibrillation in normal ventricular muscle has not been observed in the thin atrial muscle (2, 4). Atrial fibrillation is common, yet relative to any animal's ventricles, rotor wavelengths are at least as long in the (smaller) atria (16). This contrast presumably reflects a greater heterogeneity of atrial tissues, as first demonstrated in models 30 years ago (17).

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