Electrical Turbulence in Three-Dimensional Heart Muscle

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Rotors or vortex action potentials with a diameter of about 1 centimeter and a rotation period of about 0.1 second occur in normal myocardium just before transition to fibrillation, a disorderly pattern of action potential propagation. Numerical models and corresponding mathematical analysis have recently suggested candidate mechanisms, all two-dimensional, for this transition from periodic electrical activity to something resembling turbulence. However, comparably recent experiments unanimously show that rotors, and the spiral waves they radiate, remain stably periodic in two-dimensional myocardium. This seeming paradox suggests a transition mediated through disorderly dynamics of the electrical vortex in three dimensions, as a "vortex filament."

The electrophysiologist's equations for the ionic mechanism of excitation and its electronic spread in normal cell membranes has three solutions (*1–3*): One is quiescence at the resting potential; one is the familiar action potential translating with a characteristic rectilinear speed; and one (only in two- and three-dimensional media) is a vortex of characteristic size and angular velocity called the rotor. The rotor's electrocardiographic signature is the short-period tachycardia that immediately precedes fibrillation (*4, 5*).

Sudden cardiac death takes a thousand lives daily in the United States alone, accounting for about 1 death in 10 (*6, 7*). Most such incidents involve ventricular fibrillation, a spatially and temporally complicated mode of myocardial activation that precludes adequate pumping of blood to the brain. Most also involve diseased hearts; however, some involve ostensibly healthy hearts, anatomically normal without prior evidence of irregularities in the electrical activation of contraction (*6, 7*). The unexpected, apparently spontaneous lethal occurrence of ventricular fibrillation thus does not depend on detectable abnormalities (though its incidence may be enhanced by abnormalities).

Irregularities in Heart Muscle

The practical focus of cardiologists is necessarily abnormal myocardium. In the design and interpretation of experiments in which fibrillation is induced in diseased hearts, the dominant emphasis is on random dispersion of membrane properties, that is, discontinuous inhomogeneities in the affected tissue. This paradigm was crystallized with overwhelming persuasiveness 30 years ago by the first major use of numerical experiments to model atrial myocardium (the thin-walled upper chambers of the heart). The best ideas of that time were brilliantly incorporated in a coarsely discretized caricature of the essentially two-dimensional atrial myocardium. It demonstrated that without conspicuous random nonuniformities of local refractory duration, vortex action potentials remain periodic and cannot degenerate into a turbulence resembling atrial fibrillation (*8*).

From this historic model there has grown an experimental literature in which similar ideas are imputed to the much finer grained and essentially three-dimensional myocardium of the ventricles (the lower, massive pumping chambers). The extent of diverse nonuniformities are measured, correlated with the electrical shock strength needed to induce fibrillation, and altered pharmaceutically. The essential finding is that on the pertinent scale of 1 to 2 cm such irregularities are quantitatively slight in healthy tissue, but can be greatly increased by ischemia and infarction, and that the electrical thresholds for fibrillation decline substantially after such damage (*9*).

Turbulence in Excitable Media

It remains perplexing that normal healthy ventricles are comparably subject to fibrillation not unlike that of diseased tissue. It also turns out that the original inference (from numerical models) that spontaneous breakup of spiral waves requires inhomogeneities was not correct. Such models employ a rule (a restitution curve) for the duration of the depolarized phase of the action potential as a function of the interval since prior repolarization. The rule used 30 years ago is no longer regarded as very realistic (*10*). When the original model is rerun with this rule replaced by contemporary refinements, spiral waves become unstable even when all of the electrophysiological parameters are as uniform as they can be in a coarsely discrete caricature (*11–13*). If this numerical model is completely replaced by a detailed ionic model of the ventricular cell membrane based on electrophysiological measurements gathered during the 12 years after the introduction of the original model (*14*) and if its 2-mm chunks of isopotential tissue are replaced by cells almost as small as real myocardial fibers, then its spiral waves degenerate into dramatic turbulence even in the perfectly uniform and continuous case (*15, 16*).

This might be a deficiency of the numerical membrane model, in particular, its unrealistically steep restitution curve. But simpler numerical models have since been constructed that also exhibit rotor-catalyzed turbulence through other principles of uniform nonlinear dynamics (*17–19*). The putatively indispensable role of physiological irregularities in the catalysis of fibrillation in normal ventricles was never proved and now seems uncertain, given the demonstrated reality of rotors in normal myocardium (*4*) and the demonstration of rotor-catalyzed turbulence in numerical models (*11–13, 15–19*).

Two-Dimensional Ventricular Muscle

Clarification of electrical dynamics in diseased or damaged tissue requires quantitative characterization of such damage. The tissues used in most in vitro experiments are surely damaged to some extent, but this is seldom quantifiable. Some seem more susceptible to fibrillation and some less so or even completely insusceptible, even when excitability seems normal and many inhomogeneities are evident (*4, 5, 20*). Different kinds of damage need to be distinguished before the electrical behavior of abnormal tissues can be related to quantifiable principles. Theorists have also been hamstrung by the lack of a dependably quantitative numerical model of the normal membrane [this difficulty may have been removed recently (*21*)].

Meanwhile, a surprise lurks in a collection of experiments (*3–5, 20, 22–28*) potentially showing fibrillation in ventricular preparations dimensionally similar to those postulated in almost all numerical models, that is, two-dimensional. None did show fibrillation, although most or all supported reentrant action potentials (rotors and the activation fronts they emit) at periods almost as short as prefibrillatory tachycardia. In order of publication: Canine thin right ventricular free wall did not support fibrillation when the thicker left ventricles were chemically depolarized by KCl (*22*); without KCl, epicardium surviving over an infarct in canine left ventricle supported a reentrant electrical vortex (rotor) indefi-

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nitely (*23*) but would not fibrillate; with endocardium frozen rather than infarcted, to circumvent possible alteration of electrophysiological properties, rabbit hearts sustained in Langendorf apparatus showed the same phenomena (*24, 25*); a thin slice of sheep epicardium sustained in vitro supported rotors indefinitely but could not be induced to fibrillate (*4, 20*); the rabbit result was confirmed and related to anisotropic fiber orientation (*26*), and the canine result was confirmed and shown to change at an intermediate thickness of the surviving epicardium (*27*); and canine epicardial slices behaved much like sheep slices in vitro (*5, 28*). In short, the mechanism of transition from tachycardia to fibrillation, normally spontaneous in thicker ventricular walls (*3, 27, 29–31*), seems lacking in all of the two-dimensional preparations that were not deliberately made abnormal by ischemia or pharmaceuticals (*7*). In such tissues, enhanced inhomogeneity may even stabilize a rotor: Just as in chemically excitable media (*32–34*), it becomes pinned on local irregularities (an improbable event in three dimensions) and adopts a longer period, which is thereby less prone to instigate transition to fibrillation (*5*).

Conceivably, all of these experiments with thinned myocardium should be rejected on the grounds that the electrical properties of their cell membranes and intercellular connections were not quantitatively shown to be normal in all respects and might have been altered to inhibit fibrillation. For example, the rotor's period is often longer in thinned preparations compared with those in the intact heart [for example, in the dog, compare (*5, 23, 27*) with (*29–31*)], the restitution curve might be uniformly flattened in some preparations, or there might be more inhomogeneities suitable to stabilize rotors by pinning (*5*). Alternatively, taking the evidence at face value, one must infer that fibrillation in normal ventricular myocardium depends on its substantial thickness (*11, 35, 36*).

Fibrillation in Three Dimensions

The most recent of these experiments (*27*) tests this inference in the same format used in chemically excitable media: A thickness threshold is sought at which complex and changing short-period wave behavior abruptly becomes disciplined to simple drifting spiral waves of slightly longer period (*37, 38*). Such a threshold was indeed found in canine ventricles and bears the same relation to rotor period: The threshold is about $1/\pi$ times the distance a spiral wave propagates during one rotation period. The reason is simple, at least in the better-understood chemical media: This distance is the nominal diameter of the rotor, the source of the reentrant activation front. In three dimensions, this source is not, as in two dimensions, a small elliptical disk [about 3 mm by 3 or 10 mm in anisotropic myocardium, depending on orientation (*2, 4, 5, 20*)] but a filament like somewhat flattened spaghetti. Such vortex filaments were predicted (*38–41*) and observed (*30, 31*) in normal dog myocardium, extending upright from endocardium to epicardium. In tissue thick enough to admit such a filament lying on its side, its opportunities to snake about, fragment, and close in rings are suddenly unlimited (*11, 35–38*).

In numerical experiments with uniformly anisotropic and perfectly continuous and homogeneous three-dimensional excitable media loosely based on ionic models of the cell membrane, such vortex filaments spontaneously lash about unless confined to a layer thinner than about a rotor diameter (*42*). Apart from reasonably steady rotation, any regularities in their motion remain to be discovered; superficially, it is chaotic or turbulent even though the medium is continuous and perfectly uniform. The interval histogram peaks asymmetrically at intervals somewhat shorter than rotations of the two-dimensional spiral wave, as in ventricular fibrillation but more sharply (*43, 44*). Snapshots of the voltage patterns look more complicated than epicardial maps during monomorphic tachycardia, but probably less complicated than some maps during fibrillation (*45, 46*). I think of such computations as illustrating a possible mechanism of transition from the orderly vortex filaments observed in thick myocardium (*29, 30*) toward whatever confused condition underlies fibrillation, not necessarily involving coherent vortices at all except as ancestral short-period instigators. Pursuit of such hints will require statistical measures capable of distinguishing one kind of turbulence from another and clean data on the local time series and spatial patterns of tachycardia and fibrillation in normal ventricles (*44–46*).

This putative thickness threshold of about one rotor diameter (3 to 10 mm, depending on fiber orientation) complements the known area threshold for creating and sustaining a rotor (3 mm by 3 or 10 mm perpendicular to thickness, depending on fiber orientation). Together, they constitute a compact critical volume of 3 mm by 3 mm by 10 mm (about 0.1 g of tissue) beyond which reentrant tachycardia (monomorphic or polymorphic) can spontaneously become more complex (fibrillation). Given an area sufficient for an intramural vortex filament to snake around freely, perhaps three diameters in every intramural direction, we have a critical mass of several grams for fully developed fibrillation, not out of line with familiar experience.

The Influence of Ventricular Wall Thickness

An alternative interpretation of the crucial role of tissue thickness stems from the observation (*27*) that rotors in situ have a longer period in thinner (and more epicardial) layers. This might be the result of pinning, electrical conduction effects penetrating a space constant (1 mm) from each boundary, an epi-endo gradient of tissue properties, or all of these. Fibrillation is induced by repetitive activation only at periods shorter than about 110 ms in healthy canine myocardium (*10, 47, 48*). If rotors provide such stimuli only in tissue at least a few millimeters thick, this would contribute to a disorderly outcome. Periods this short do not seem to be required, but it is conceivable that electrical stimulation at 120-ms intervals might show that the key to rotor stability in thin preparations is simply that thinning somehow lengthens their period. It would also be useful to repeat all experiments mentioned above to leave endo- rather than epicardium intact while measuring restitution curves, to test the interpretation that thickness per se is crucial.

Another possible contributor to this ostensible thickness effect arises from the conspicuous rotation of fiber orientation from epicardium to endocardium, typically by about 150° regardless of thickness (*49*). It has been suggested that twist renders vortex filaments unstable (*50*). If this were true and all other things were equal, thicker myocardium, bearing less twist per unit distance, would be less liable to such instabilities. The fact is otherwise: The generally thinner right ventricular free wall may be capable of supporting spiral waves stably (*22*), but the thicker left wall always degenerates to fibrillation (*3, 22, 29–31*). Perhaps other things are not equal. The question should be answered by data on a diagram such as Fig. 1.

Such a diagram suggests a way to experimentally determine whether just the rotating anisotropy or just the thickness, or some combination of the two, determines vortex filament instability. Each left or right ventricular wall is characterized vertically by its average rate of rotation (degrees per millimeter) and horizontally by thickness (millimeters). Regions above about 150° per millimeter in the right wall or 50° per millimeter in the left wall are inaccessible to experiment because such thin walls belong to species with ventricular area insufficient to support a rotor anyway. Taking every mammal's heart wall, whether left or right, to twist its fiber direction on average about 150° from epicardium to endocardium (and through the septal wall), all hearts would lie on the indicated hyperbola. Plots for a given specimen's left wall would lie lower than and to the right of the values for its right

wall. The substantial variations of thickness from place to place in one specimen may largely lie along the iso–total-rotation hyperbola, but there are also regional variations of total rotation, so the "hyperbola" might be broader than shown. This plane is shaded into regions of rotor stability (clear) and instability (gray), segregated by a boundary to be determined by experiment. If only the rotation rate needs to exceed some threshold, then only very thick heart walls will stably support rotors. If only thickness is critical, then only very thin heart walls will stably support rotors; I drew the boundary to indicate such. The original right-left contrast [one lying on each side of the border (*22*)] does not answer whether the border runs vertically, horizontally, or diagonally. The left-thinning experiment (*27*) crosses the putative boundary near a thickness of 3 mm in canine myocardium with about 13° per millimeter of rotation, proving that the boundary is not strictly horizontal, that is, instability is not determined exclusively by rotation. A second thinning experiment on an initially thicker left wall, thus with less rotation of anisotropy, would reveal whether the boundary is nearly vertical (dominated by thickness and barely affected by fiber rotation) or substantially tilted (if fiber rotation plays some important role in the mechanism of instability).

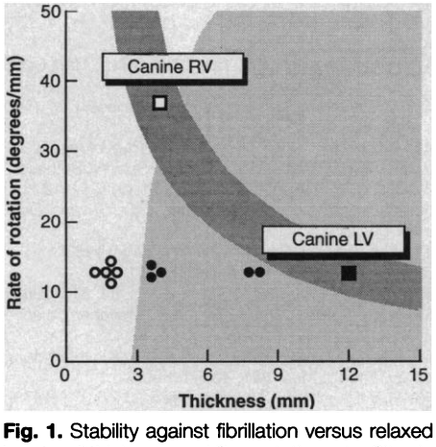

Fig. 1. Stability against fibrillation versus relaxed heart wall thickness and fiber rotation rate. Sites in normal left (LV) and right (RV) ventricular walls are characterized vertically by average rate of fiber rotation and horizontally by thickness near a hyperbola averaging 150° total rotation. In those with sufficient thickness to get away from dominating boundaries or sufficient rotation rate, or some combination, vortex filaments may go unstable (lightly shaded area). Pertinent supplementation of the original right-left contrast (*22*) (squares) has appeared thus far in only one experiment (*27*) (circles). Hollow symbols retained stable tachycardia, and filled symbols fibrillated. A few more experiments on ventricular walls of various thicknesses would help to resolve the direction of the putative border, here guessed to be essentially vertical (independent of rotation) at a thickness close to the transverse rotor diameter.

Normal Physiology and Rotors

It is important to remember that the electrical properties and especially the cellular and tissue architecture of the atria differ starkly from those of the ventricles. The atria are thin and conspicuously inhomogeneous with large holes and gaps between bundles of excitable fibers. Their short-period arrhythmias and fibrillation may differ in mechanism from those in the ventricles; certainly no great thickness is prerequisite to fibrillation in the atria. Atrial arrhythmias are not lethal because they do not spoil ventricular synchrony. However, drifting rotors in the ventricles, especially if decaying to fibrillation, forebode immediate mortality. It would not be surprising, therefore, if the chief characteristics of rotors and the fragments of spiral waves that surround them, now so well understood in chemical and numerical excitable media, play a role in the phylogenetic scaling of ventricular physiology. If, as the limited present evidence suggests (*3*), the rotor is the same in the ventricular myocardium of any mammalian species, then it becomes interesting to plot the coordinated values of body weight, heart weight, ventricular surface area, and wall thickness against the minimum safely sustainable sinus rhythm interval over species ranging from mouse to whale. Figure 2 presents a beginning, spanning a narrower range of body weight, eclectically gathered from eutherians and marsupials. Mammals are represented by rats (third datum from the left, the third hollow circle), guinea pigs (fourth datum, the first gray circle), and man (the last black circle). A simple trend emerges. The elliptical region covers laboratory data on rotors ranging from nominal diameter of 1 cm (longitudinal direction) and period of 100 ms to 2 cm and 200 ms. Rotors thus turn out to lie on the phylogenetic trend line near the transition from normal hearts (hollow circles) that spontaneously defibrillate (unless chemically modified or ischemic, of course) to normal hearts (black circles) capable of failure by sustained fibrillation. It seems that ventricles cannot stably beat faster than the rotor period unless they are too small to accommodate a rotor. Individuals susceptible to death by ventricular fibrillation (black circles) have sufficient ventricular surface dimensions to accommodate a rotor pair (1 to 2 cm in longitudinal fiber direction) and have a wall thickness sufficient to accommodate a vortex filament of one rotor diameter [transverse to fibers, with anisotropically reduced electrical scale, about (1 cm)/3 = 3 to 4 mm].

In all of the experiments cited here, the stimulus used to instigate rotors (and thus fibrillation if they decay) was an electrical shock, a single dc pulse of millisecond duration. This is because only in that case is the theory of instigating rotors by the "pinwheel experiment" simple (*2*, *39*–*41*, *51*) and quantifiable (*2*). The stimulus in cases of sudden cardiac death is seldom anything of the sort. It has been suggested (*51*, *52*) that unfortunately timed phasic activity in vagal or sympathetic innervation or both may play a role analogous to electric shock; thus far it has only been shown that this can indeed induce rotors in the atrium (*53*) and that the ventricles are innervated in classically unforeseen ways (*54*). Another candidate is transient myocardial ischemia due to vascular spasm. The quantitative theory of the ventricular fibrillation threshold in terms of rotor induction by a single dc shock (*2*) still remains unable to account for the many-fold lower threshold toward closely-spaced multiple shocks (*47*, *48*).

In media of slightly graded excitability, a rotor typically glides at speeds as high as a few percent of the activation front propagation speed, thus possibly as fast as 1 cm/s in myocardium. It may then vanish when it encounters a boundary (for example, the atrio-ventricular ring or the epi- or endocardial surface) or a rotor turning in the

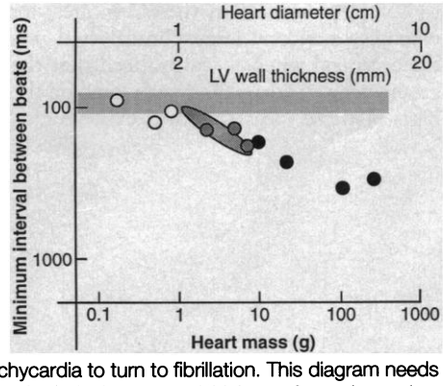

Fig. 2. Homeotherm maximum heart rates (*56*) versus relaxed geometry (*57*) across a 2000-fold range of body weights. The shaded horizontal bar supposes that the 75- to 110-ms range of activation intervals found (*47*) to induce fibrillation in dogs applies to all mammals and eutherians. Hearts commonly exposed to sinus excitation at such short intervals (hollow circles) turn out to be safely too small to accommodate rotors. The elliptical region nominally spans 1 cm at 100 ms to 2 cm at 200 ms; no evidence yet suggests that rotor properties depend on heart size. Larger hearts (filled circles) are large enough two dimensionally to sustain rotors, and their walls are not too thin to accommodate the rotor three dimensionally: A thickness of 3 to 4 mm transverse to fibers allows tachycardia to turn to fibrillation. This diagram needs more exact information on stability of fibrillation, ranges of ventricular area and thickness for each species, species-specific information on rotor size and period to establish the universal pertinence of the measurements in dogs, and more species covering a wider range of heart size.

opposite direction, or it may become pinned on a local inhomogeneity, thereafter continuing to spin with some longer period characteristic of that snag, as in monomorphic reentrant tachycardia (*5*, *35*).

The electrocardiogram of two such separately pinned rotors would qualitatively resemble torsade de pointes, a polymorphic reentrant tachycardia responsible for syncope (fainting) in patients with uncommonly prolonged systole. It has a strikingly regular period with an amplitude that waxes and wanes as in a beat note. Several pinned rotors would collectively resemble fibrillation in the electrical summation of a body-surface electrocardiogram, and epicardial electrodes or catheter electrodes would still reveal their individual local periodicities. A single gliding rotor activates myocardium at a range of Doppler-shifted periods, so their summation in the electrocardiogram waxes and wanes and extinguishes abruptly when glide terminates at a boundary such as the atrio-ventricular ring, as is familiar clinically (*5*). However, the typical period of torsade oscillations barely overlaps that of freely drifting rotors in normal myocardium: Torsade is generally slower. This indicates at least some additional essential factor in this syndrome, perhaps a slowing of activation and recovery throughout the diseased myocardium (*11*, *35*). Interpretation of this arrhythmia in terms of a rotor in perfectly normal three-dimensional myocardium would entail the expectation of prompt decay to fibrillation, which is not uniformly observed. I conjecture that the longer period has something to do with the rotor's enhanced stability.

Medical Pertinence

Medical applications require a quantitative understanding of ventricular fibrillation in order to improve implanted defibrillators, identify populations at particular risk, and avoid fibrillation onset. Dependence on ideas from three decades ago has not yet led to complete success in these ventures; for example, a recent large clinical trial was discontinued when it was noticed that the group given the drug therapy favored on the basis of those ideas (*55*) was experiencing three times as many deaths as the untreated matched control group. By redirecting attention from fibrillation in indescribably abnormal myocardium to merely the mechanism of fibrillation onset in quantifiably normal myocardium, we find alternative mechanisms logically indicated for experimental test. Although such a restricted focus seems unlikely to reveal panaceas, it does highlight testable predictions. Incomprehensible sudden death, although predominantly afflicting individuals whose hearts are already abnormal, could turn out to be a recognizable modification of understandable fibrillation in normal hearts and in the electrophysiologist's descriptive equations for the ionic mechanism and electronic spread of action potentials in idealized uniform media.

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58. I thank W. Calder for direction to physiological scaling data. This paper was written during sabbatical leave from the University of Arizona with financial support from the U.S. National Science Foundation (Computational Biology).