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Ventricular fibrillation: evolution of the multiple-wavelet hypothesis

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Every heartbeat is preceded by an electrical wave of excitation that rapidly propagates through the cardiac muscle, triggering mechanical contractions of cardiac myocytes. Abnormal propagation of this wave causes severe cardiac arrhythmias. The most dangerous of these is ventricular fibrillation, the leading cause of sudden death in the industrialized world. It is well established that ventricular fibrillation is a result of turbulent propagation of the electrical excitation wave. However, despite more than a century of investigation, the precise mechanism of its initiation and maintenance remains largely unknown. Novel experimental tools for the visualization of the excitation wave as well as advanced three-dimensional computer models of the heart, which have become available in recent years, have intensified attempts to solve the puzzle of ventricular fibrillation. These efforts have revealed significantly different manifestations of ventricular fibrillation, suggesting that multiple mechanisms are responsible for this arrhythmia. Several new hypotheses have been put forward recently that deviate considerably from Moe's standard hypothesis of fibrillation, which has dominated the field for almost four decades. One of the hypotheses that has been most actively discussed is the spiral-breakup (also called the restitution) hypothesis. This hypothesis may lead to a breakthrough in our understanding of the factors that cause this deadly arrhythmia and provide a constructive approach to the development of efficient antifibrillatory drugs.

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1. Moe's multiple-wavelet hypothesis

For almost four decades now, the dominating hypothesis about the mechanism of ventricular fibrillation (VF) has been Moe's multiple-wavelet hypothesis (Moe *et al.* 1964). Moe constructed the multiple-wavelet hypothesis on the basis of computer simulations of a two-dimensional array of coupled excitable elements (cellular automata) with randomly distributed refractory periods. According to Moe, fibrillation occurs as a result of the heterogeneity of cardiac tissue in the refractory period. It is initiated by a train of external stimuli with extremely short coupling intervals of almost the same length as the minimal refractory period of myocardial cells. At such short intervals, cells with refractory periods exceeding the stimulation period do not have enough time to recover and fail to respond. This results in fragmentation of the excitation waves and formation of multiple wavelets. The latter wander randomly through

the myocardium, forming non-sustained re-entry loops. Occasionally, wavelets disappear when they collide with another wavelet or with the boundary. They can also break up, producing daughter wavelets after they encounter refractory cells. Moe's simulations showed that such irregular activity can be self-sustaining if the size of the tissue and the number of wavelets are sufficiently large.

Moe's hypothesis was put on a solid theoretical basis by Krinsky (1966). In his seminal work, scarcely known in Western literature, Krinsky studied a class of cellular automata models similar to those of Moe. He derived the necessary conditions for self-sustaining activity in this class of models and demonstrated the existence of a critical mass of fibrillation and its dependence on the extent of tissue heterogeneity. Krinsky's findings also showed that increased heterogeneity in refractory periods may have opposite effects on the initiation and maintenance of fibrillation. If the heterogeneity is large, fragmentation of the wavefronts and initiation of re-entry occur more readily. However, at the same time, the re-entry circuits become less stable. This may affect the persistence of fibrillation and in some cases lead to a paradoxical outcome: increased heterogeneity possibly resulting in the termination of self-sustained fibrillation.

Moe's hypothesis successfully explained experimental phenomena such as the persistence of fibrillation after the elimination of the initial triggering and the existence of a critical mass (for a review, see Allessie (1995)). However, as Moe clearly realized, his hypothesis lacked specific quantitative predictions that could be tested experimentally. To correct this deficiency, numerous attempts have been undertaken to characterize the spatial distribution of refractory periods in normal and diseased myocardium, as well as to determine the relationship between this distribution and the incidence of VF (for reviews, see Janse (1998) and Antzelevitch *et al.* (1999)). These studies have revealed convincing evidence of a positive correlation between increased heterogeneity in refractory periods and fibrillation. However, these studies suffer from a major technical limitation: the intrinsic complexity of the experimental protocol for measuring the refractory period prevents such measurements from being made at a large number of points. Therefore, they do not prove that heterogeneity in refractory periods is indeed a necessary condition for both the initiation and maintenance of VF.

2. A single-source hypothesis

The development of advanced methods for visualizing the activation process in the heart—such as multi-electrode and, more recently, optical mapping methods—as well as the availability of novel numerical methods for data analysis have led to a number of studies that quantify the excitation patterns on the surface of the heart during VF (Gray *et al.* 1995, 1998; Witkowsky *et al.* 1998). These studies show that the activation patterns during VF can differ significantly from those predicted by the multiple-wavelet hypothesis. The main difference is the small number of the wavelets and their short lifespan. As has been shown by Gray *et al.* (1995), in extreme cases VF can be produced by a single meandering wavelet or, to use contemporary terminology, by a hypermeandering spiral wave. Gray *et al.* (1998) estimated that, on average, the total number of coexisting spiral waves during fibrillation is as low as 1–2 for rabbits, 5 for sheep and 15 for humans (assuming the same spiral wave density per unit area). Moreover, the majority of spiral waves (80% for rabbits and 84% for sheep) last for

a shorter time than one rotation cycle, i.e. they do not form complete re-entry loops. Similar results (a small number of wavelets and a high incidence of incomplete re-entry circuits) were obtained by Rogers *et al.* (1999), who used completely different techniques (multiple-electrode versus optical mapping).

The small number of surface wavelets and their short lifespan may indicate that VF is maintained not by multiple wavelets wandering around but by some rather stable rapid sources of excitation located intramurally. Due to the high frequency of the sources, the generated waves break, producing complex activation patterns characteristic of fibrillation. The possibility of such fibrillation, also called induced fibrillation or fibrillatory propagation, was considered earlier in relation to atrial fibrillation (Jalife *et al.* 1998; Moe & Abildskov 1959) and has been demonstrated recently in the human heart. Specifically, it has been shown that a source of atrial fibrillation can be identified and removed by an ablation procedure which terminates the fibrillation (Jais *et al.* 1997).

Recently, strong experimental evidence has been produced revealing that VF, at least in some cases, can also be regarded as 'induced' fibrillation (Zaitsev *et al.* 2000). The authors induced VF in a slab of ventricular myocardium and found that surface patterns of excitation were similar to those recorded in the whole heart during VF. These authors also studied the distribution of excitation frequencies on the epicardial and endocardial surfaces during VF. The major finding from this study was that the typical frequency map appeared to be unexpectedly simple and organized. It consisted of a few relatively large domains (averaging 1.1 cm^2 in area) with uniform frequency within each domain. The ratios of frequencies in adjacent domains were often close to 1:2, 3:4 or 4:5 as a result of an intermittent Wenckebach-like propagation block at the boundaries between domains. The domains persisted for many excitation cycles. These data suggest that the high-frequency intramural source drives the fibrillation and that the complex patterns are secondary processes due to the interaction of waves from this source with the heterogeneities of the medium. The authors hypothesize that such a source is likely to be a stable scroll wave (a three-dimensional analogue of a spiral wave) concealed inside the ventricular wall. Such a concealed source may result from scroll alignment along the myocardial fibres (Berenfeld & Pertsov 1999).

3. Spiral-breakup and restitution hypothesis

Exponential growth in computational power and the increasing availability of computers in recent decades have significantly extended the possibilities for computer modelling of excitation propagation in the heart. Studies of cardiac propagation in cellular automata models have been superseded by studies in so-called ionic models of cardiac tissue, which describe in a much more accurate way interactions between adjacent cells and transmembrane ionic currents. The first attempts to use such models to simulate functional re-entry (also referred to as rotor or spiral wave re-entry) in large two-dimensional cell layers led to the following unexpected discovery. Immediately after initiation, a single spiral wave becomes fragmented into a complex pattern of activation reminiscent of fibrillation. An example of such a computation is shown in figure 1. The computation starts with one rotating spiral wave (figure 1*a*). After several rotations, the spiral wave breaks in the vicinity of the core (figure 1*b*), producing a daughter wavelet. The latter curls, attempting to form

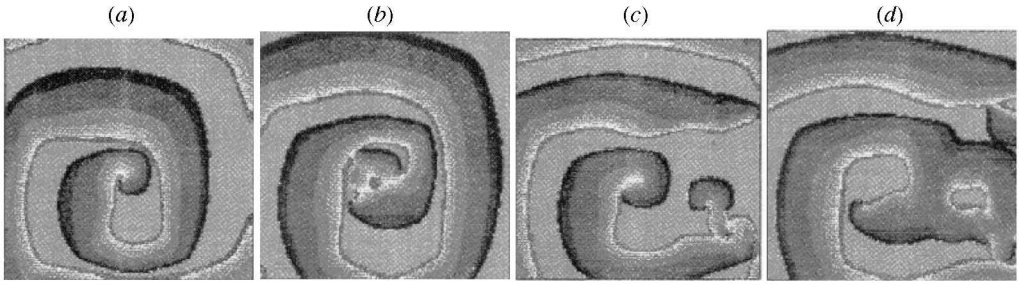

Figure 1. Spiral breakup in a Noble (1962) model of cardiac tissue. Reproduced from Panfilov & Holden (1990) with permission from Elsevier Science. Sequential snapshots of potential distribution: (*a*) $t = 1720$ ms; (*b*) $t = 1880$ ms; (*c*) $t = 2920$ ms; (*d*) $t = 3080$ ms. Potentials are coded in equal 10 mV steps, from −85 mV (dark) to +5 mV (white).

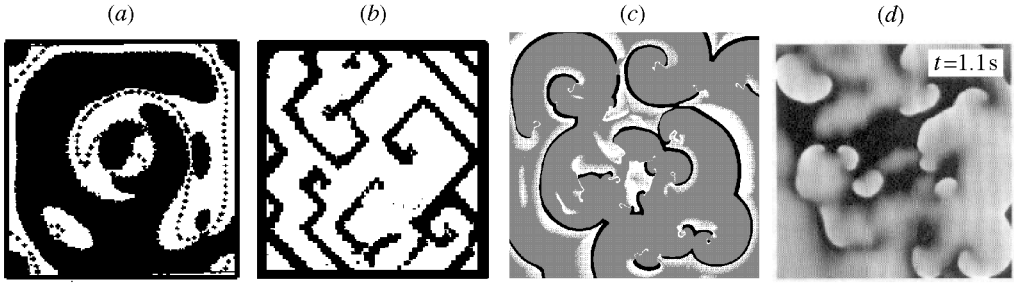

Figure 2. Patterns of excitation after several rotations of a spiral wave in (*a*) a λ–ω model (reproduced with permission from Kuramoto & Koga (1981)), (*b*) a cellular automata model (reproduced with permission from Ito & Glass (1991)), (*c*) a modified FitzHugh–Nagumo model (reproduced from Panfilov & Hogeweg (1993) with permission from Elsevier Science) and (*d*) an ionic model of cardiac tissue (reproduced with permission from Qu *et al.* (1999)).

another spiral. Eventually, however, it also breaks, producing further fragmentation and complicating the activation pattern (figure 1*c*). The region of chaotic behaviour gradually extends to the whole medium, leading, ultimately, to a complex pattern that comprises many wavelets of various sizes (figure 1*d*). The dynamics of this process qualitatively reproduces the experimentally observed transition from ventricular tachycardia to VF. This pattern is similar to the fibrillation described by Moe but with one important difference: it occurs in homogeneous cardiac tissue. This phenomenon has been termed 'spiral breakup' (the 'restitution' hypothesis) and has become the basis for an alternative to Moe's multiple-wavelet hypothesis.

The first computational observation of spiral wave breakup was reported in 1981 (Kuramoto & Koga 1981) in a model (the so-called λ–ω system) that was quite different from the models of cardiac tissue. This report remained unnoticed for almost a decade until the phenomenon was rediscovered at the beginning of the 1990s in ionic models of cardiac tissue (Courtemanche & Winfree 1991; Panfilov & Holden 1990, 1991; Winfree 1989) and in cellular automata models of excitable media (Gerhard *et al.* 1990; Ito & Glass 1991). Figure 2 illustrates spiral breakup in different models. Although the models differ significantly, the main pattern of excitation during breakup is similar in all cases. The wavelets occur as a result of the spiral wave's fragmentation close to its core.

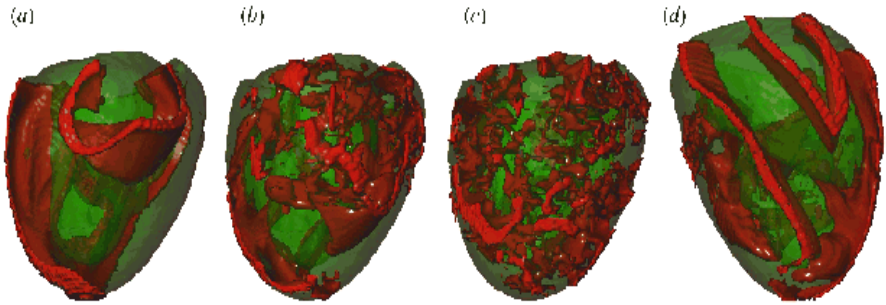

Figure 3. Spiral breakup in an anatomical model of the heart. Three-dimensional view of the excitation front is shown at the following times after spiral initiation: (*a*) $t = 500$ ms; (*b*) $t = 1000$ ms; (*c*) $t = 2500$ ms; (*d*) $t = 1000$ ms (rear view). Reproduced with permission from Panfilov (1997).

Spiral breakup develops only if the medium is sufficiently large (Courtemanche & Winfree 1991; Karma 1994). If this critical condition is not met, the following two scenarios are possible. The spiral does not break up and remains stable for an infinitely long time. Alternatively, the spiral breaks up, but the wavelets are unable to maintain fibrillation. Eventually, they collide with the boundaries of the tissue and vanish. It should be noted, however, that the values for the critical size predicted by the two-dimensional models are large. For a square domain, the critical size is estimated to be larger than two wavelengths of re-entry (Panfilov 1997), which does not look realistic from an experimental point of view.

A possible cause of these discrepancies is the three-dimensional nature of fibrillation. Interestingly, spiral (scroll) breakup occurs more readily in three dimensions than in two dimensions (Panfilov & Hogeweg 1995, 1996). The critical mass for fibrillation in a cube was found to be about one wavelength (the size of one side). It was also shown that for certain parameter values, the breakup occurs only in three dimensions, but not at all in two dimensions.

The breakup was also modelled in an anatomical model of the heart (Panfilov 1997). This model is based on extensive experimental measurements of the heart structure (Hunter *et al.* 1997) and includes realistic ventricular geometries and tissue anisotropy. Figure 3 shows the development of turbulence in this model. Just as in two-dimensional and three-dimensional cases, breakup starts with a single scroll wave (figure 3*a*), which, after several rotations, breaks close to its core (figure 3*b*). In the early stages of breakup (figure 3*d*), the regions with regular propagation can still be identified. Over time, the regions with chaotic behaviour gradually expand and eventually spread over the whole heart (figure 3*c*). For spiral wave breakup to develop into sustained fibrillation, the size of the heart (as measured from top to bottom) has to be greater than the wavelength of the spiral wave, which in this model is 40 mm (Panfilov 1999*a*,*b*).

Numerical modelling allows one to count the number of sources which organize VF during spiral breakup. The main idea was to represent scroll waves by their 'singular filaments' (Winfree & Strogatz 1984). In an electrophysiological context the filament is simply the organizing centre around which a three-dimensional scroll rotates. Figure 4*a* shows that even one scroll wave (one filament) can produce quite a complex pattern of excitation in the heart. Figure 4*b* shows a surface pattern of excitation during spiral breakup and figure 4*c* shows filaments found from this pattern

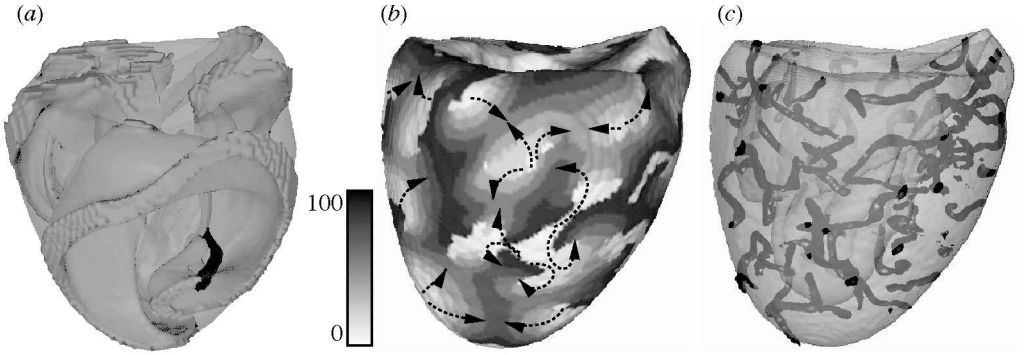

Figure 4. (*a*) Three-dimensional view of the excitation pattern generated by a single scroll wave located within the wall of the left ventricle. The depolarized region in the heart is depicted in grey, the filament of the scroll wave in black. Reproduced with permission from Panfilov (1999*b*). (*b*) The activation map on the surface of the heart during electrical turbulence due to the process of spiral breakup. The coding of the activation time in milliseconds is shown by a legend bar. The size of the heart is 94 mm. (*c*) Filaments of sources of excitation that organize the pattern of excitation in figure 4*b*. Reproduced with permission from Panfilov (1999*a*).

of excitation. We see a large number of filaments (about 50) in the 94 mm heart. By comparing these figures, we can find a correspondence between the individual filaments and the surface dynamics. The centre of a rotor corresponds to the site where a filament intersects the surface. Apparently, however, some filaments are hidden inside the wall and do not intersect the surface. Although such filaments are invisible from the surface, they may play an important role in the dynamics of the patterns of excitation because all the filaments interact. The average number of filaments estimated for the 94 mm heart was 38 ± 4.85 (Panfilov 1999*a*). This number decreases rapidly with decreasing heart size: for the 51 mm heart the number of filaments was only 10.4 ± 2.2. Thus, the smaller the heart, the simpler the activation patterns.

4. Alternans and mechanism of spiral breakup

Although the precise mechanism of spiral breakup is still unknown, there is considerable evidence that it is closely connected with so-called alternans instability. Alternans instability usually develops at high stimulation rates and manifests itself as rate-dependent alternations in the action potential duration (APD) (short–long–short–long, etc.). The phenomenon of APD alternans has been known since the beginning of the last century (Mines 1913) and has been studied intensively in connection with the stability of re-entry in a one-dimensional ring of tissue (Courtemanche *et al.* 1996; Frame & Simson 1988).

The mechanism of APD alternans is governed by the slope of the APD restitution curve (Courtemanche *et al.* 1996; Guevara *et al.* 1984; Nolasco & Dahlen 1968). This curve relates the APD to the diastolic interval (DI), which is the time that has elapsed between the end of the preceding action potential and the start of the next one (see figure 5*a*). There is a simple criterion for governing the onset of the alternans: alternans occurs if, at the pacing frequency, the slope of the restitution curve is greater than one. This criterion can be understood from figure 5*b*, which

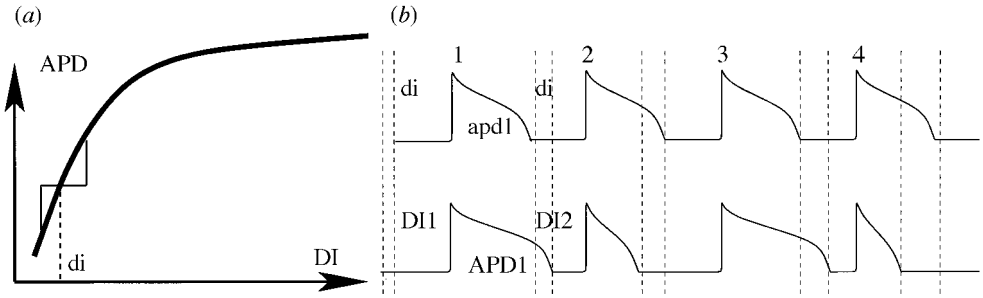

Figure 5. (*a*) Schematic of the APD restitution curve. The thick solid line is the restitution curve, the thin solid line shows deviations of DI and the corresponding deviations of APD around point di. (*b*) Schematic of a periodic stimulation (the upper panel) and of the instability growth (the lower panel). Further explanations are in the text.

shows the response of cardiac tissue to rapid pacing with a period corresponding to a steep part of the restitution curve (the slope is more than one). Because a slope that is more than one means that a small change in di results in a larger change in apd, a small difference between di and DI1 (the lower panel) results in a larger difference between apd1 and APD1, which, in turn, results in a larger difference between di and DI2, etc., leading to instability.

Indications that APD alternans may be related to spiral wave breakup were obtained by Panfilov & Hogeweg (1993). The authors showed that the forcing of one-dimensional tissue at a period of a spiral wave did indeed cause oscillations in APD. The first numerical examples demonstrating that such oscillations can cause breakup were obtained by Karma (1993, 1994). In his simulations he used a simplified FitzHugh–Nagumo model with two dynamic variables. By varying parameters of the model, he gradually reduced the period of spiral rotation until alternans occurred and its amplitude started to increase. When oscillations of APD had become sufficiently large, he observed the breakup of the spiral. Similar results were obtained later using more detailed ionic models of cardiac tissue (Qu *et al.* 1999).

Until recently, however, there was no experimental evidence to support the spiral-breakup hypothesis. Data on restitution properties of myocardium indicated that the slopes of the restitution curve were consistently less than one (see, for example, Elharrar & Surawicz 1983). The situation changed dramatically after Koller *et al.* (1998) demonstrated steep restitution curves with a maximum slope greater than one in dog myocardium. According to the authors, previous failures to observe such slopes can be attributed partly to the fact that the restitution was measured at quite a long period of stimulation (usually 500 or 300 ms). Koller *et al.* (1998) developed a new approach (the dynamic restitution protocol), which enabled measurements to be made for short cycle lengths (100–300 ms) and during VF.

Additional support for the restitution hypothesis has been obtained from studies by Riccio *et al.* (1999) and Garfinkel *et al.* (2000) who demonstrated that certain drugs can flatten the restitution curve and also prevent the occurrence of VF. Riccio *et al.* (1999) have shown that diacetyl monoxime and verapamil significantly reduce the slope of the restitution curve. These drugs not only prevented VF but also converted the existing VF into a regular periodic activity. Similar results were obtained by Garfinkel *et al.* (2000) with another drug, bretylium. Garfinkel *et al.* (2000) also mapped the electrical activity in the tissue. They showed that bretylium converts

multiple irregular wavelets into stationary spiral waves. Riccio *et al.* (1999) found that another anti-arrhythmic drug, procainamide, which did not reduce the slope of the restitution curve, neither prevented the induction of VF nor regularized VF. The experiments by Riccio *et al.* (1999) also provide a plausible explanation as to why the breakup mechanism was never observed in early optical mapping studies. These studies used diacetyl monoxime and verapamil as electromechanical uncouplers to prevent mechanical artefacts. The fact that these drugs also flatten the restitution curve makes spiral wave breakup less likely.

The restitution hypothesis, if proved, provides a new paradigm for screening new anti-arrhythmic drugs, based on measurements of the slope of the restitution curve. It is interesting that the importance of the slope of the restitution curve in the development of instabilities of propagation was recognized as early as 1990 (Lewis & Guevara 1990), i.e. even before the spiral-wave breakup was discovered in cardiac models. Lewis & Guevara (1990) also proposed that the steepness of the restitution curve could be used as a criterion for screening anti-arrhythmic drugs. However, at that time, due to the lack of experimental data showing steep slopes of the restitution curve, this idea was not seriously considered. After the recent theoretical and experimental findings by Koller *et al.* (1998), Qu *et al.* (1999), Riccio *et al.* (1999) and Garfinkel *et al.* (2000), the restitution hypothesis has made a powerful comeback. Recent major failures of clinical antifibrillatory drug tests have revealed the need for new screening principles. The restitution hypothesis is a good candidate for this.

It should be noted, however, that the original formulation of the restitution hypothesis may require revision. It may not be sufficient to have a slope greater than one for the spiral breakup to occur. In a careful analysis of the breakup mechanism in the Luo & Rudy (1991) model, Qu *et al.* (1999) found several cases in which the restitution curve was steeper than one but with no breakup occurring. A similar result for the FitzHugh–Nagumo model was obtained in Karma (1994). From these studies, it was concluded that for the breakup to occur, it is important to have quite a substantial range of diastolic intervals over which the APD restitution slope is steeper than one. However, it is not yet known how wide this range should be and what the exact conditions are. The restitution hypothesis has not yet provided an explanation for the origin of the initial spiral wave. It should be noted that the triggering of fibrillation has not been fully explained by the multiple-wavelet hypothesis either.

5. Concluding remarks

In this short review we have discussed three of the most popular new hypotheses of VF that have emerged recently in the wake of the significant technological advances in experimental and computational methods and that have generated an enormous amount of new information about this arrhythmia. These hypotheses do not constitute the whole range of mechanisms that has been proposed. For instance, several alternative mechanisms of spiral breakup have been discovered in computer simulations, none of which requires a steep restitution curve (Baer & Eiswirth 1993; Chudin *et al.* 1999; Fenton *et al.* 1999). Biktashev *et al.* (1994) have proposed a three-dimensional mechanism in which breakup can occur due to negative filament tension. The possibility of breakup due to rotational anisotropy of myocardium was shown in Panfilov & Keener (1995) and Fenton & Karma (1998). Another type of

three-dimensional instability produced by smooth heterogeneity (gradient) has been described in Panfilov *et al.* (1984), Pertsov *et al.* (1990*b*), Panfilov & Keener (1993) and Mironov *et al.* (1996). It has been hypothesized that such instability may develop at the border between normal and ischaemic tissue and may be responsible for VF during acute ischaemia (Pertsov & Jalife 1995). Cabo *et al.* (1996) demonstrated experimentally in sheep epicardium that fibrillation-like activation patterns can be produced by the vortex-shedding phenomena (Agladze *et al.* 1991; Panfilov & Pertsov 1982; Pertsov *et al.* 1990*a*).

Which of the proposed mechanisms is relevant? Perhaps there is no unique answer to this frequently asked and seemingly very straightforward question. The latter proposal is based on the assumption that fibrillation is one phenomenon and therefore should have a unique explanation. However, the more we learn about VF, the clearer it becomes that this may not be the case. VF may have not only different manifestations and different degrees of complexity, but also different mechanisms. Therefore, there is unlikely to be only one magic drug capable of preventing the innumerable manifestations of VF.

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