Mechanisms underlying ventricular tachycardia and its transition to ventricular fibrillation in the structurally normal heart

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Abstract

Reentrant ventricular tachycardia (VT) is the most common sustained arrhythmia leading to ventricular fibrillation (VF). However, despite more than a century of research, the mechanism(s) of the conversion from reentrant VT to VF have not been elucidated. Based on their different electrocardiographic appearance, reentrant VT and VF have traditionally been thought of as resulting from two widely different mechanisms. Whereas VT is seen as a rapid but well organized process whereby the excitation wave rotates about a single well-defined circuit, fibrillation has been described as turbulent cardiac electrical activity, resulting from the random and aperiodic propagation of multiple independent wavelets throughout the cardiac muscle. Recently, the application of concepts derived from the theory of non-linear dynamics to the problem of wave propagation in the heart and the advent of modern high-resolution mapping techniques, have led some investigators to view VT and VF in terms of a single mechanism, whereby the self-organization of electrical waves forms ‘rotors’ that give rise to rapidly rotating spiral waves and results in either VT or VF, depending on the frequency of rotation and on the interaction of wave fronts with the cardiac muscle. As such, monomorphic VT is thought to result from a stationary rotor, whose frequency of rotation is within a range that allows 1:1 excitation of both ventricles. On the other hand, VF is thought to result from either a single rapidly drifting rotor, or a stationary rotor whose frequency of excitation is exceedingly high, thus resulting in multiple areas of intermittent block and giving rise to complex patterns of propagation with both deterministic and stochastic components. This article reviews the prevailing theories for the maintenance of VF, and discusses recently proposed mechanisms underlying transitions between VT and VF. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Ventricular fibrillation (VF) and reentrant ventricular tachycardia (VT) are the leading immediate causes of sudden cardiac death in the industrialized world and continue to be a major public health concern. They account for nearly 300,000 fatalities annually in the United States alone [1,2]. Yet, despite more than a century of research, we still do not fully understand their electrophysiologic mechanism(s), and have not been able to elucidate the manner in which VT converts into VF, or vice versa. The purpose of this article is to review the literature on the prevailing mechanisms of the maintenance of VT and of VF in structurally normal hearts, as well as possible mechanisms underlying the transition from VT to VF. This knowledge should pave the way for new insights into therapy and prevention of these complex arrhythmias. It should be noted that this review does not address issues relating to ischemia. For a discussion of the role of ischemia in modulation of activity in the heart the reader is referred to the Refs. [3–5].

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2. Reentrant ventricular tachycardia

Although focal or non-reentrant mechanisms do play a role in arrhythmogenesis [6], today reentry is believed to be the major mechanism underlying most lethal cardiac arrhythmias. It is thus widely accepted that sustained reentrant VT is one of the most common precursors of VF and sudden cardiac death in patients with organic cardiac lesions. Earlier experimental studies attempting to elucidate the electrophysiologic mechanisms of VT were mostly carried out during the acute or subacute phases of coronary occlusion simulating myocardial infarction [7–11]. In those studies, ventricular excitation was usually mapped using multiple electrodes, and the role of reentry occurring around the ischemic-nonischemic border zone (an anatomical obstacle) or in anisotropic myocardium, was emphasized as the cause of repetitive responses preceding ventricular fibrillation. To date, sustained VT occurring in patients without structural cardiac diseases, so-called idiopathic VT, has attracted little attention. Except for a handful of studies in small groups of patients with no apparent structural heart disease (see Peeters et al. [12] for review), most work on idiopathic VT has been done in patients manifesting the long QT syndrome, or those showing a QRS pattern of right bundle branch block and left axis deviation [13–16]. Such paucity of information may have resulted, at least in part, from the lack of an adequate experimental model of idiopathic monomorphic VT (MVT).

Recent experimental studies using optical mapping of ventricular excitation in non-ischemic isolated cardiac tissue preparations, as well as computer simulations, have suggested that MVT is probably caused by stationary ‘rotors’ giving rise to vortex-like reentrant activity, whereas non-stationary reentry may be responsible for polymorphic VT and VF [17–22]. Even in these studies, however, it was difficult to produce MVT in the whole heart. Sustained MVT occurred in a very small number of Langendorff-perfused rabbit heart preparations [19]. However, stationary vortex-like activity was demonstrated in thin pieces of ventricular muscle superfused in a tissue bath [18,22]. In such cases, the activity was demonstrated to be anchored to a small area of heterogeneity in the tissue (e.g., a small artery or region of connective tissue).

Earlier, Watanabe and Uchida [23] reported successful induction of sustained VT in isolated rabbit hearts after rapid ventricular stimulation in the presence of verapamil. This arrhythmia was characterized by rapid rate, monomorphic pattern, and occasional transition to different QRS morphologies (pleomorphism). Although initial mapping studies utilizing 18 closely-spaced bipolar electrodes attached to the epicardial surface of both ventricles, as well as entrainment of the tachycardia by rapid pacing suggested reentry as the most likely mechanism (Watanabe and Uchida, personal communication), more detailed analyses of the ventricular excitation process were deemed mandatory in order to (i) establish the reentrant nature of this arrhythmia and (ii) elucidate the mechanism causing transitions to different QRS morphologies.

3. Mechanisms of VF maintenance

Traditionally, maintenance of fibrillation is thought to be the result of random phenomena. This notion stems from Moe’s postulate that fibrillation is the result of the total disorganization of activity arising from randomly wandering wave fronts, ever changing in direction and number [24–26]. This idea culminated in the multiple wavelet hypothesis, in which randomness in temporal and spatial distribution of membrane properties plays a role [25]. Although Moe’s original multiple wavelet hypothesis was intended to provide a basis for atrial fibrillation, later experimental studies assumed that a similar mechanism was also applicable to VF [27–29]. However, today there is ample evidence in the literature that suggests that wave propagation in the heart during VF is not entirely random. A summary of the studies that have documented ‘organization’ during VF follows.

In 1981 Ideler and colleagues [30] documented that ventricular activation during the transition to VF arose near the border of the ischemic-reperfused region of the dog heart and was organized as it passed across the non-ischemic tissue, but the body surface ECG appeared disorganized as judged by the variable spacing between successive coexistent activation fronts. Other techniques, such as spectral correlation and coherence analysis [31,32], as well as non-linear dynamics approaches have also been used to study VF organization [32]. Ropella et al. [31] measured the coherence spectrum of bipolar electrograms in patients with normal and abnormal rhythms and determined that fibrillatory rhythms exhibited significantly less coherence than non-fibrillatory events. Nevertheless, they documented a certain degree of coherence even during VF. Another attempt to measure spatio-temporal correlations during VF was carried out by Damle et al. [33] who used vector mapping to analyze epicardial activation directions in an attempt to detect and quantify underlying organization at adjacent sites in the heart and during different cycles of VF. Moreover, they developed a linear regression model and showed a predictable relation between activation at adjacent regions during a given beat of VF suggesting that the activation of the myocardium proceeds as a wave front rather than as a random localized event, thus providing strong evidence for the presence of spatio-temporal organization during VF [33].

Garfinkel et al. [34] used non-linear dynamics theory to study fibrillation in a computer model and in thin sheets of canine and human ventricular tissue. They found that fibrillation arose through a quasiperiodic stage of period and amplitude modulation; thus they concluded that fibrillation is a form of spatio-temporal chaos. More recently,
Bayly et al. [35] explored several techniques to quantify spatial organization during VF. In this regard they used epicardial electrograms recorded from pig hearts using rectangular arrays of unipolar extracellular electrodes and concluded that VF is neither ‘low-dimensional chaos’ nor ‘random’ behavior, but rather a high dimensional response with a degree of spatial coherence [35].

Recently, the development of an analytical technique by Gray et al. [36] which markedly reduces the amount of data required to depict the complex patterns of fibrillation, has enabled investigators to study the detailed dynamics of wavelets and rotors, including their initiation, life span, and termination. Using a fluorescent potentiometric dye and video imaging, Gray et al. recorded the dynamics of transmembrane potentials from a large region of the heart and determined that transmembrane signals at many sites exhibit a strong periodic component. With this analysis, each site could be represented by its phase around an attractor. Using spatial phase maps at each instant in time, Gray et al. revealed the ‘sources’ of fibrillation in the form of topological defects, or phase singularities [37] around which spiral waves rotated. Thus, they were able to demonstrate that a substantial amount of spatial and temporal organization underlies cardiac fibrillation in the whole heart [36].

In addition, work from our laboratory [38] and others [39,40] demonstrated organization during VF in the form of sequences of wave propagation that activated the ventricles in a spatially and temporally similar manner over time. Moreover, Chen et al. [38] in the isolated Langendorff-perfused rabbit heart demonstrated that the frequency of the spatially and temporally periodic activity in the optical movies corresponded to the dominant peak in both the global bipolar electrogram and the optical pseudo-ECG. Those data suggested that the sources of the periodic activity were the dominant sources that maintained VF. Moreover, the quantification of wavelets revealed that during VF the multiple wavelets, which are present on the epicardial surface, result from wavebreaks and do not appear to be responsible for the maintenance of VF.

### 3.1. Rotors and VF

About three decades ago, a new idea emerged based on theoretical [41] and experimental [42] findings, which demonstrated that the heart could sustain electrical activity that rotated about a functional obstacle. These ‘rotors’ were thought to be the major organizing centers of fibrillation. Since then, much work has focused on rotors as the underlying mechanism for VF in the heart. However, two schools of thought have emerged. On one hand, many recently proposed mechanisms for fibrillation have focused on transience and instability of rotors [43,44]. Over the past two decades, substantial experimental [27,44–47] and theoretical work [43,48] has accumulated suggesting that ‘turbulence’ in VF is associated with breakup of a single spiral wave or a pair of counter-rotating spiral waves into a multispiral disordered state. However, alternative explanations for the breakup of the rotor in the three-dimensional myocardium have been proposed.

One such mechanism, referred to as the restitution hypothesis, suggests that the breakup of the rotor into a multispiral state ensues when the oscillations of the action potential duration (APD) are of sufficiently large amplitude to cause block of conduction along the wave front [48–50]. This idea builds on previous work demonstrating that the slope of the electrical restitution relation determines certain dynamical behavior that may be appropriate to the development of ventricular fibrillation [51]. In particular, if the slope of the action potential restitution curve, in which duration of the action potential is plotted against the preceding diastolic interval, is >1, then APD alternans is possible [51]. The initiation of APD alternans has been proposed to be the first step in period-doubling sequences that culminate in complex behavior [52–54]. Subsequently, this process would result in the destabilization of the wave fronts and the formation of a multispiral state [44]. Another mechanism for breakup focuses on the fact that propagation within the three-dimensional myocardium is highly anisotropic due the intramural rotation of the fibers, thus producing twisting and instability of the organizing center (filament), which results in its multiplication following repeated collisions with boundaries in the heart [43].

Work from our laboratory has also focused on rotors as the primary engines of fibrillation [18,20,22]. However, in contrast to the breakup mechanism of VF, it is proposed that VF is a problem of self-organization of non-linear electrical waves with both deterministic and stochastic components [19,21,36,55]. This has lent further support to the hypothesis that there is both spatial and temporal organization during VF in the structurally normal heart, although there is a wide spectrum of behavior during fibrillation. On the one hand, it has been demonstrated that a single drifting rotor can give rise to a complex pattern of excitation that is reminiscent of VF [20]. On the other, it has been suggested that VF is the result of a high frequency stable source and the complex patterns of activation are the result of the fragmentation of emanating electrical activity from that source, i.e. fibrillatory conduction [56,57]. In the following sections, these two extremes are examined.

### 3.2. Drifting vortices and VF

Gray et al. [19,20] studied the applicability of spiral wave theory to VF. They used high-resolution video imaging of a voltage sensitive fluorescent dye in the structurally normal isolated Langendorff-perfused rabbit heart, and demonstrated the presence of a drifting rotor on the epicardial surface of the heart. Simultaneous recording of a volume-conducted ECG and fluorescence imaging demonstrated that the single rapidly moving rotor was...
associated with turbulent polymorphic electrical activity, which was indistinguishable from VF. It was assumed that rotors were the two-dimensional epicardial representation of a three-dimensional scroll wave. In addition, computer simulations, incorporating a realistic three-dimensional heart geometry and appropriate model parameters, demonstrated the ability to form a rapidly drifting rotor similar to that observed in the experiments [20]. Frequency analysis of the irregular ECGs for both the experiments and simulations demonstrated spectra that were consistent with previously published data [58,59]. Furthermore, they showed, through the Doppler relationship, that the width of the frequency spectrum can be related to the rotation frequency of the rotor, the speed of its motion, and the wave speed [20].

3.3. Fibrillatory conduction

As discussed above, Gray et al. [20] have demonstrated unequivocally that, in the rabbit heart, even a single drifting rotor can produce an ECG that is indistinguishable from VF. However, it has been demonstrated also that in other hearts a more complex spatio-temporal organization may prevail. This has lead Jalife and colleagues [56,57] to suggest that some forms of fibrillation depend on the uninterrupted periodic activity of discrete reentrant circuits. The faster rotors act as dominant frequency sources that maintain the overall activity. The rapidly succeeding wave fronts emanating from these sources propagate throughout the ventricles and interact with tissue heterogeneities, both functional and anatomical, leading to fragmentation and wavelet formation [56]. The newly formed wavelets may undergo decremental conduction or they may be annihilated by collision with another wavelet or a boundary, and still others may form new sustained rotors. Thus, the result would be fibrillatory conduction or the frequency-dependent fragmentation of wave fronts, emanating from high frequency reentrant circuits, into multiple independent wavelets [38,57].

Zaitsev et al. [60] using spectral analysis of optical epicardial and endocardial signals from sheep ventricular slabs have provided additional evidence suggesting that fibrillatory conduction may be the underlying mechanism of VF. These authors [60] present data showing that the dominant frequencies (DFs) of excitation (i.e. peak with maximal power) do not change continuously on the ventricular surfaces of slabs. Rather, the frequencies are constant over regions termed domains; moreover, there are only a small number of discrete domains found on the ventricular surfaces. They also demonstrated that the DFs of excitation in the adjacent domains were often 1/2, 3/4, or 4/5 ratios of the fastest DF domain and this was suggested to be the result of intermittent Wenckebach-like conduction blocks at the boundaries between domains [60]. Thus, they concluded that, in their model, VF may be the result of a sustained high frequency three-dimensional intramural scroll wave, which creates a highly complex pattern of activation when wave fronts emanating from it fragment as the result of interaction with the heterogeneities present in the cardiac tissue [60].

More recently, we presented new evidence in the isolated Langendorff-perfused guinea pig heart that strongly supports the hypothesis that fibrillatory conduction from a stable high frequency reentrant source is the underlying mechanism of VF [61]. Optical recordings of potentiometric dye fluorescence from the epicardial ventricular surface were obtained along with a volume-conducted ‘global’ ECG. Spectral analysis of optical signals (pixel by pixel) was performed and the DF from each pixel was used to generate a DF map, which revealed that DFs were distributed throughout the ventricles in clearly demarcated domains. The highest frequency domains were always found on the anterior wall of the LV. Moreover, optical data showed wavebreaks and conduction blocks in the periphery of the high frequency domains. Thus, the results demonstrated that in the isolated guinea pig heart, a high frequency reentrant source that remains stationary in the LV is the mechanism that sustains VF.

4. Mechanisms of transition from VT to VF and vice versa

Today it is generally believed that regardless of the initiating event, vortex-like reentrant activity may in fact underlie both reentrant ventricular tachycardias and fibrillation [19,22,57,62]. In the following sections, the prevailing mechanisms that are believed to be involved in the transformation of these arrhythmias will be discussed with the focus on rotors as agents that determine the arrhythmia manifestation. Nevertheless, it should be noted, that other factors such as intercellular coupling may also play a role in the dynamics of the arrhythmias. However, for that discussion the reader is referred to Uchiyama et al. [63].

4.1. Wavelength and arrhythmias — the leading circle concept

One proposed mechanism for the interconversion of VT to VF implicates the action potential duration and/or the effective refractory period and is based on the leading-circle concept [42], in which the length of the circuit is determined by the electrophysiological rather than anatomical properties of the medium as originally described by Mines [64]. In fact, here, the length of the circuit is equal to the wavelength of circulating impulse, the product of the action potential duration (APD) and the conduction velocity (CV), and is subject to change by modification of either the APD or the CV. Moreover, the revolution time is proportional to the refractory period of the tissue [42]. Thus, based on the insights provided by the leading circle model, it is believed that the most efficacious means of
preventing and/or terminating cardiac tachyarrhythmias is by the prolongation of the action potential duration/refractoriness [65].

There are numerous reports in the literature that support this position. For example, Andersen et al. [66] used dofetilide, a selective cardiac potassium channel blocker, to study the incidence of ischemia induced VF in closed-chest pigs. In a randomized, blinded, and placebo controlled study performed in 32 pigs it was found that during a 2-h ischemic period, VF occurred in 38% of dofetilide treated pigs and in 81% of the placebo treated pigs, thus suggesting that prolongation of the refractory period decreased the incidence of VF. In another study involving dofetilide, Bashir et al. [67] determined that in patients with sustained ventricular tachycardia inducible by programmed electrical stimulation dofetilide suppressed or slowed VT. More recently, Dorian and Newman [68] demonstrated that tetracilam, an investigational antiarrhythmic drug which blocks the transient outward current, \( I_{to} \), and the delayed rectifier current, \( I_{K} \), increased magnitude-squared coherence, a measure of spatial organization, cycle length, and temporal regularity of VF. Similarly Qi et al. [69] used azimilide, a complete \( I_{K} \) blocker (i.e. it blocks both \( I_{K} \alpha \) and \( I_{K} \beta \)) in open-chest anesthetized dogs to show that the magnitude squared coherence increased in a dose dependent manner; moreover, the arrhythmia cycle length increased. These studies seem to suggest that in fact by modifying the refractoriness of the myocardium it is possible to alter the arrhythmia dynamics.

However, recent data suggest that wavelength/refractoriness is not the best parameter on which predictions about changes in behavior of an arrhythmia can be made. For example, Watanabe and Uchida [23] and Watanabe et al. [70] have reported that rapid ventricular stimulation in isolated rabbit hearts in the presence of verapamil, a calcium channel blocker, resulted in the induction of sustained monomorphic ventricular tachycardia (MVT). The induction of MVT rather than fibrillation despite a reduction of effective refractory period (ERP) by verapamil seemed paradoxical, suggesting that parameters other than tissue refractoriness may play a role.

4.2. Drift and anchoring of rotors

Another mechanism proposed for the transformation of VT to VF is based on the theory of spiral waves in excitable media and on experiments using high resolution optical mapping in isolated two-dimensional ventricular preparations and whole heart, as well as computer simulations [19,22,62]. Such studies have suggested that the behavior of the core of the reentrant circuit plays an important role in determining the ECG manifestation of the arrhythmia. In fact, it has been demonstrated that a stationary position of the core produces a monomorphic pattern of excitation, i.e. VT. In contrast, a drifting core, i.e. a core whose position demonstrates beat-to-beat changes, leads to an irregular pattern of activation [62]. Davidenko et al. [18,62] proposed that when the core drifts in one direction, it produces a Doppler shift in the excitation period in such a way that two coexisting frequencies can be observed, one ahead and one behind the drifting core. Under this condition, the activation frequency behind the core is always slower than the frequency ahead of the core. Simulated ECGs obtained during reentrant activity showed that, in the presence of a unidirectional drifting rotor, there is an undulating pattern, i.e. waxing and waning, whereby the axis of the depolarization complex demonstrates a gradual torsion much like torsades de pointes [22]. However, when the core drifts at higher speed and in many directions then the ECG pattern is more complicated and resembles VF [19,19,22,62]. Thus, in this manner the dynamics of the rotor can determine the arrhythmia manifestation.

According to theory of excitable media, drift may be the result of spatial gradients in parameters such as refractory period [71], fiber orientation [22], or in a bounded medium as the result of interaction of the rotor with a border [72]. It is well known that in the healthy myocardium there are non-uniformities in refractoriness, excitability, and fiber orientation, which allow for spiral drift. However, it should be noted that spiral drift may be short lived since spirals may spontaneously terminate or they may anchor to regions of low excitability or small discontinuities (e.g. patches of fibrosis, or small vessels) [22].

4.3. Core size as a determinant of arrhythmia dynamics

We have shown that the size and dynamics of the core around which reentrant waves rotate [57] may be important determinants of arrhythmia manifestation. In fact, following the studies of Watanabe and Uchida [23] and Watanabe et al. [70], we used verapamil as a tool in optical mapping experiments to demonstrate that functional reentrant circuits are the underlying mechanism of both VF and MVT in the structurally normal isolated heart. Indeed, during verapamil perfusion, there was a reduction in the dominant frequency of VF, despite a reduction in the ERP, and concomitantly a significant increase in the core area of transiently appearing rotors. The data showed that the reduction in frequency during verapamil perfusion was the consequence of the pivoting point of the rotor traveling a longer distance to complete a rotation, which led to an increase in its period and a slowing in the rate of VF and eventual conversion to VT. Thus, we concluded that the frequency of the source determines whether the overall manifestation is disorganized fibrillation or organized tachycardia. VF results when the rotation frequency increases to such an extent that the cardiac tissue is unable to keep up with the source, thus resulting in the breakup of activity in the tissue surrounding the well-organized source. However, if the source frequency is sufficiently
slow, then the emanating wave will not break up in which case VT rather than VF may be observed.

4.4. Spiral breakup

Recently, several studies have suggested that the manifestation of the arrhythmia (i.e. VF or VT) was determined by the restitution property of the cardiac action potential [44,47]. In accordance with this idea, Riccio et al. [44] identified drugs (verapamil and diacetyl monoxime) that reduced the slope of the restitution relation and tested whether such drugs prevented the initiation of VF. Moreover, they sought to determine whether it was possible to convert VF into a more periodic rhythm (e.g. ventricular tachycardia). They demonstrated that in fact verapamil and diacetyl monoxime reduced the slope of the restitution relation and prevented the induction of VF, or converted the existing VF into a periodic rhythm [44]. Thus, they concluded that the slope of the restitution relation is an important determinant of VF [44]. More recently, Garfinkel et al. [47] also suggested that the slope of the restitution relation is important for the genesis of unstable wave propagation that results in wave breaks and VF. They studied the action of bretylium, a class III antiarrhythmic agent [73], and determined that it flattened the restitution relation, prevented wave breaks, prevented the induction of VF and converted VF into a periodic rhythm [47]. Thus, these studies seem to suggest that the dynamic behavior of VF may depend on the restitution of the cardiac action potential.

However, during spiral wave reentry, there is significant APD abbreviation around the spiral core [74]. Recent simulations suggest that such a reduction in APD may be due to the electrotonic influence exerted by the core of the spiral and the activation of the inward current, $I_{K1}$ [74]. Furthermore, simulations suggest that such an action potential duration abbreviation can occur over a distance up to 1.5 cm [75]. In this regard, it is unclear whether APD restitution plays any role in stability. If it does, which APD is important? Near the core or far away from the core? Consequently, more research is needed to determine whether it is the restitution of the cardiac AP or the dynamics of the core of the vortex that determines the manifestation of the arrhythmia.

5. Implications for the clinic

Traditionally, VF was believed to be the result of a large number of wandering wavelets [25–27]. However, the evidence discussed here suggests that electrical wave propagation in the heart during VF is not random. Recent advances in mapping techniques have made it possible to show that in some hearts, e.g. rabbit, even a single drifting scroll can give rise to an ECG that is indistinguishable from VF [21,36]. Yet, in other hearts a more complex pattern of spatial and temporal organization usually prevails [36]. It is possible that both VT and VF in these hearts result from self-organization of waves into a small number (e.g. one to three) of stationary vortices. In the case of monomorphic VT the vortices would be stationary and their frequency of rotation would be within a range that allows 1:1 excitation of both ventricles. In the case of VF, either a single rapidly drifting rotor, or one or more stationary rotors whose frequency of excitation is exceedingly high, would result in multiple areas of intermittent block and wave front fragmentation, and would give rise to complex patterns of propagation with both deterministic and stochastic components [56]. It is thus reasonable to speculate that the knowledge that rotors and vortex-like reentry is a common mechanism for VT and VF in structurally normal hearts of guinea pigs, rabbits and sheep, may pave the way for a better understanding of the mechanisms of these arrhythmias in the normal, as well as in the diseased human heart. It seems feasible that self-organization in the case of the larger human heart occurs in the form of a relatively small number of drifting rotors that interact with each other giving rise to complex spatiotemporal patterns, resulting in the formation of multiple short-lived phase singularities with variable dynamics. So, why is this important? Perhaps, the immediate practical application involves using this knowledge in our efforts to reduce the energy of the electric field required to terminate fibrillation. Indeed, recent modeling and experimental work has focused on the study of how electrical shocks of high energy affect the dynamics of vortices, including their initiation and termination. For example, there is evidence to suggest that the timing of the shock and the position of the vortex with respect to the electrode applying the shock play crucial roles in defibrillation [76].

Another application of this new knowledge is in the area of new antiarrhythmic drug design. As discussed above, recent results from our laboratory [61] demonstrate that, in the isolated guinea pig heart, sustained VF is maintained by a stationary, high frequency rotor that is consistently present in the left ventricular anterior free wall, and by the complex, spatially distributed fragmentation of wave fronts emanating from that rotor. This results, at least in part, from the presence of spatially distributed gradients in the density of inward rectifier current ($I_{K1}$), with the left ventricular myocytes showing significantly weaker inward going rectification than the right ventricular myocytes. As a result, sharply demarcated LV-to-RV gradients of excitation frequency are the hallmark of VF in these hearts. Consequently, in theory, any agent that can increase the degree of inward going rectification should provide the desired effect. Increasing rectification would cause a voltage-dependent decrease in the $I_{K1}$ conductance without affecting the resting potential. Thus, at relatively low concentrations, this hypothetical agent would reduce the frequency of rotation and convert VF into VT. This in itself would be therapeutic since it would allow defibrillation at
a lower level of energy than that required for VF. At higher doses, the hypothetical $I_{K1}$ modifier would also increase the action potential duration in a similar manner to that of class III antiarrhythmic agents. However, since $I_{K1}$ has been implicated in controlling the APD near the core of a rotor [74], an agent that can increase the rectification of $I_{K1}$ may be more efficacious in terminating complex reentrant arrhythmias than any class III agent.

6. Conclusions

Based on their different ECG manifestations, VF and VT have traditionally been thought of as resulting from two widely different mechanisms. As such, fibrillation was believed to be the product of turbulent cardiac electrical activity, arising from the random and aperiodic propagation of multiple independent wavelets throughout the heart. In contrast, VT was seen as a rapid but well organized process whereby the excitation wave rotated about a single well-defined circuit. However, the recent application of concepts derived from the theory of non-linear dynamics to the problem of wave propagation in the heart and the advent of modern mapping techniques, have led to the suggestion that in fact there is a single mechanism underlying both VF and VT. According to this new view, the self-organization of electrical waves forms ‘rotors’ that give rise to rapidly rotating spiral waves and result in either VT or VF, depending on the frequency of rotation as well as the interaction of wave fronts with the cardiac muscle. Thus, monomorphic VT is thought to result from a rotor, whose frequency of rotation is within a range that allows 1:1 excitation of both ventricles. In contrast, VF is thought to result from either a single rapidly drifting rotor, or a stationary rotor whose frequency of excitation is exceedingly high, thus resulting in multiple areas of intermittent block and giving rise to complex patterns of propagation with both deterministic and stochastic components.

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