Rotors and Turbulence in Ventricular Fibrillation—Role of Inward Rectifier Potassium Channels

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Ventricular fibrillation (VF) is by far the most important immediate cause of sudden cardiac death (SCD). Every year, VF is responsible for an estimated 300,000 deaths annually in the US alone. Owing to its highly complex electrocardiographic (ECG) appearance, VF is commonly thought of as an exceptionally complex and disorganized cardiac activation in which electrical waves propagate through the ventricles chaotically and unpredictably. In fact, during VF the ventricular activation sequence is profoundly abnormal; electrical wave fronts do not follow the usual paths. The heart rate accelerates to the extreme, and the electrical waves assume a complex vortex-like behavior that looks a lot like eddy formation and turbulence in water. Such turmoil renders the heart unable to pump blood. Thus, the blood pressure drops and immediate loss of consciousness follows. Unfortunately, despite many years of research and speculation, the mechanism underlying VF continues to be a matter of speculation and debate.

Over the last several years, evidence has accumulated supporting the idea that, while VF is indeed complex, it is in fact deterministic, quantifiable, and, in theory, mechanistically understandable. In this regard, it seems reasonable to suggest that achieving a comprehensive knowledge of VF mechanisms will require a clear familiarity with the underlying bases of cardiac excitation and its frequency dependence, in which cardiac ion channels play important roles. More specifically, it is the author's contention that advances in VF understanding will require thorough quantitative knowledge of the ionic mechanisms of the extremely complex phenomena that underlie the initiation and maintenance of VF, including wave break and rotor formation, rotor stabilization, and spiral wave behavior. In this article, the most salient aspects related to the dynamics of VF are briefly reviewed, as well as current knowledge, however incomplete, of the role played by inward rectifying potassium channels in the mechanisms of VF initiation and maintenance.

Functional Re-entry and Spiral Waves

Theoretical and experimental studies that began to appear in the relevant literature more than 60 years ago have established that the heart can sustain electrical activity that rotates about a functional obstacle. In this regard, the experimental work of Allessie and collaborators in the 1970s that gave birth to the so-called ‘leading circle’ concept was an essential initial step toward our current understanding of the phenomenon of functional re-entry in cardiac tissue: that is, re-entry without the involvement of an anatomical obstacle (see Figures 1A and 1B). At about the same time, work conducted by Soviet scientists using the Belousov-Zhabotinski reaction and its numerical counterparts led to the idea that 2D spiral autowaves (see Figure 1C) could be a possible mechanism of cardiac arrhythmias. Subsequently, the notion of spiral autowaves was brilliantly expanded into the third dimension (see Figure 1D) by the late Arthur T. Winfree, who in fact coined the term ‘rotor’ to signify the actual vortex that generates the spiral (scroll) wave activity, and led to the virtual abandonment of the use of the term ‘leading circle.’ Thereafter, much work has focused on rotors as the underlying mechanism of ventricular tachycardia and VF.

Rotors and Their Break-up

Life-threatening, complex cardiac tachyarrhythmias can be due to the activity of a re-entrant electrical source, i.e. a rotor of characteristic size and angular velocity from which spiral waves radiate at a high frequency. The basic components of the rotor are a curved wave front, a curved wave tail, and a core around which the wave front and tail rotate (see Figure 1C). The rotor may drift and travel along complex paths or may be completely stationary with spiral waves emanating from it and propagating through the ventricles. The waves may undergo a variety of behaviors; for example, they may be highly stable and spiral periodically around their generating rotor to activate the ventricles at extremely high frequencies, or they may undergo break-up in the rotor’s periphery and result in fibrillatory conduction, the net result being complex spatial and temporal patterns of ventricular activation. In other words, the behavior of the rotor, and that of the waves generated by it, may be reflected on ECG as monomorphic or polymorphic ventricular tachycardias, or even VF.

Rotors and Ventricular Fibrillation in the Human Heart

During VF, there may be a wide spectrum of rotor behaviors. Under appropriate conditions, even in the structurally normal heart of small animals, rotors may be long-lasting and result in a high degree of spatial and temporal organization. Consequently, the question may be raised as to whether the same applies to the ventricles of larger animals such as dogs.
pigs, and, of course, humans. Recent studies suggest that even in large hearts such as that of the pig, the dynamics of wave propagation during VF are not as complex as might occur if the mechanism were spiral break-up, which occurs in the hearts such as that of the pig, the dynamics of wave propagation during VF. In fact, Rogers et al. were unable to rule out the possibility that mother rotors located in unmapped regions in their swine heart experiments maintained the fibrillatory activity. Additionally, a study has proposed that the mother rotor and the multiple wavelets are both mechanisms of VF in the human heart. Yet another study, in which the epicardium of the human left ventricle was mapped, concluded that there is significant organization of human VF.

The results described in the previous paragraph are consistent with the data of Thomas et al., who investigated the way in which activation is established in the absence of a ring-like anatomical obstacle. Successful re-entry occurs when wavelength (dark blue) is smaller than path length and allows for a fully excitable gap (light blue). B. Leading circle re-entry around a functional obstacle. Partially excitable gap allows wave front to 'bite' its wave tail of refractoriness. C. 2D spiral wave rotates around an unexcited but excitable core in a neonatal rat ventricular myocyte monolayer. D. Diagrammatic representation of a 3D scroll wave.

**Potassium Channels and Cardiac Excitation**

In the heart, potassium currents are diverse in that their individual properties depend not only on the membrane potential and their dissimilar activation and recovery kinetics, but also on the activation frequency. Diffusion of potassium ions through the cell membrane as the so-called inward rectifier potassium current ($I_{K1}$) maintains the resting membrane potential in all cardiac cells. In most mammals, upon action potential (AP) depolarization (phase 0) the transient outward current ($I_{to}$), is rapidly activated to mediate the initial phase of repolarization (phase 1) followed by rapid inactivation. The more slowly activating delayed rectifier currents ($I_{K2}$ and $I_{K4}$) contribute to the slow repolarization that characterizes the AP plateau (phase 2). During the terminal phase of repolarization (phase 3), $I_{K1}$ again predominates, rapidly restoring the membrane potential to resting values (phase 4). During tachyarrhythmias, probably all potassium currents involved in cardiac repolarization participate to various degrees in helping to establish the dynamics of cardiac excitation and propagation. Attention will be focused here only on $I_{K1}$.

$I_{K1}$ Controls Ventricular Fibrillation Frequency

$I_{K1}$ flows through membrane channels formed by members of the strong inward rectifier (Kir2.x) sub-family of proteins. Inward rectifier potassium channels are part of a large family of membrane-spanning proteins that have a conserved GYG sequence. Each protein spans the membrane twice, with both N and C termini being intracellular. Four homomeric or heteromeric subunits may form a channel. These channels are termed inward rectifiers because their permeability to potassium is greater in the inward than in the outward directions. Rectification is due to a voltage-dependent blockade of the channel by penetration of positively charged molecules such as polyamines (PA) and magnesium ($Mg^{2+}$) from the intracellular space into the pore. Spermine and spermidine are the most potent PA blockers of $I_{K1}$. At voltages positive to the resting membrane potential, PAs and $Mg^{2+}$ are drawn to the pore. They block it, reducing the outflow of potassium ions and resulting in a smaller outward current relative to the inward component. In the heart, the strong inward rectifier channels are formed by tetramers of Kir2.x proteins. Of the Kir2.x subfamily members, the Kir2.1 subunit is a key carrier of $I_{K1}$. In the ventricles, the highly non-linear current/voltage relationship of $I_{K1}$ allows it to act as a stabilizer of the resting membrane potential. The role of $I_{K1}$ is also apparent during depolarization and the late phase of repolarization of the AP. Increasing the density of $I_{K1}$ causes action potential duration (APD) abbreviation. Decreasing its density has the reciprocal effect.

The role of $I_{K1}$ in rotor behavior has been investigated in both computer simulations and experiments. In the guinea pig heart, VF is manifested by a stable high-frequency rotor that is sustained and anchored in the left ventricle (LV). This causes the frequency of activation of the LV (panel B, 32Hz) to be higher than that of the right ventricle (RV, 14Hz). The anchoring of the rotor in the LV and the subsequent regional difference in frequency between the LV and RV have been attributed to differences in IK1 density between the two chambers. As shown in Figure 2, incorporation of the characteristics demonstrated for $I_{K1}$ in the LV and RV into a computer-based ionic model of the cardiac ventricular myocytes reproduced a stable rotor with a rotation frequency of 35Hz in the region with larger $I_{K1}$. Fibrillatory conduction characterized the region of the model with right ventricular $I_{K1}$. Further experimentation explored the effect of $I_{K1}$ blockade on the dynamics of VF in this model. Barium ($Ba^{2+}$) was used at relatively low concentrations (1–50µM) to selectively block $I_{K1}$ in the isolated, Langendorff-perfused guinea pig heart. The major finding was that $Ba^{2+}$ perfusion resulted in a dose-dependent decrease in the frequency of re-entry. At 50µM, $Ba^{2+}$ perfusion terminated VF. It was also shown that $Ba^{2+}$ caused a proportional
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Figure 2: Role of \(I_{K1}\) Density in Ventricular Fibrillation Dynamics in a 2D Model (6x6cm\(^2\)) of the Guinea Pig Ventricles Consisting of >200,000 Excitable Elements (‘Cells’)

The simulated left ventricle (LV, center) is surrounded by the right ventricle (RV, periphery). Top: phase map of ventricular fibrillation (VF) maintained by a stable rotor in the LV, with fibrillatory conduction to RV. Red square shows the perimeter of the LV model (area 2x2cm\(^2\)). As illustrated by the inset on the right, each color represents a different phase of the action potential in each cell. Bottom: current-voltage (IV) relations of \(I_{K1}\) used for LV (left) and RV (right). Note larger \(I_{K1}\) density in LV. Broken curve is \(I_{K1}\) with nominal density. For further explanation see text and reference 13.

decrease in the density of \(I_{K1}\) in isolated myocytes. Those experiments indicated that \(I_{K1}\) affected the stability and duration of re-entry.

From the Molecule to the Organ

A more recent study provided the first demonstration at the molecular level of the role played by \(I_{K1}\) in the control of the stability and frequency of rotors and of VF. Cardiac-specific upregulation of \(I_{K1}\) in a transgenic mouse heart accelerated the final phase of AP repolarization, which significantly shortened the APD and the QT interval.\(^\text{14}\) During re-entry, this translates into a shorter wavelength and relative membrane hyperpolarization, both of which contribute to greater sodium (Na) channel availability during the excitable gap and thus to increased excitability ahead of the rotating wave front. In addition, \(I_{K1}\) overexpression augments the voltage gradient established between resting cells in the core and the active cells in its immediate surroundings. These effects help to enhance the electrotonic currents that flow continuously between resting and active cells, which further contributes not only to hasten the repolarization of the active cells but also to reduce the propagation velocity near the core.\(^\text{20,27}\) The end result is a steeper rise in the local conduction velocity (CV) as a function of the distance from the core and a faster, more stable rotor in transgenic compared with wild-type hearts. Further, during re-entry in the \(I_{K1}\) overexpressing hearts, the unexcited cells at the center of the core provide a larger than normal outward conductance, which decreases the likelihood of being excited by the depolarizing influence of their immediate, actively depolarized neighbors (sink-to-source mismatch), helping to reduce core size and meandering and to stabilize the rotor.

Taken together, experimental data in isolated guinea pig and transgenic mouse hearts as well as computer simulations strongly argue that \(I_{K1}\) is a stabilizer of re-entry because of its ability to shorten APD and reduce CV near the center of rotation.\(^\text{14,20,27}\) Increased \(I_{K1}\) should prevent wavefront tail interactions and thus prevent rotor destabilization and break-up.\(^\text{14,20,27}\) In this regard, \(I_{K1}\) is an important current during functional re-entry because it mediates the electrotonic interactions between the unexcited core and its immediate surroundings.\(^\text{14,20,27}\) As such, the interplay between \(I_{K1}\) and the rapid sodium inward current (INa) is a major factor in the control of cardiac excitability and therefore the stability and frequency of re-entry\(^\text{25}\) and VF.