Of all the cardiac arrhythmias seen in clinical practice, atrial fibrillation (AF) and ventricular tachycardia/fibrillation (VT/VF) are among the leading causes of morbidity and mortality in the developed world. AF is the most common sustained arrhythmia and is associated with an increased risk of stroke, heart failure, dementia, and death.1–3 In developed nations overall prevalence of AF is 0.9% and the number of people affected is projected to more than double over the next 2 decades.3,4 VT/VF is the most important immediate cause of sudden cardiac death (SCD). Incidence of SCD is estimated to be 4 to 5 million cases per year worldwide.5,6 Thus arrhythmias and SCD are among the most significant manifestations of cardiovascular diseases worldwide, but their underlying mechanisms remain elusive. Arrhythmogenic substrates may be established by ischemia, infarction, heart failure and genetic mutations, all of which may cause inflammation, extracellular matrix remodeling, interstitial fibrosis, fatty infiltration, and changes in the 3-dimensional cellular architecture of the working myocardium.7,8 Over the last 17 years, the study of the molecular genetic basis of monogenic cardiac rhythm disorders, together with characterization of functional expression and biophysical properties of mutant channels from patients with inheritable ion channel diseases, has significantly advanced our understanding of the molecular basis of cardiac arrhythmias.9 Yet, this clearly has not been sufficient. Despite such advances, predictable prevention of AF or VF is currently not possible and the development of effective antiarrhythmic pharmacological agents has been extremely difficult.

Not all questions related to arrhythmia mechanisms are directly answerable by reductionist experiments such as DNA sequencing or patch clamping. There is a hierarchy of questions whose levels are determined by the generality of the answers sought. Thus the question of what a mutation in an ion channel protein (eg, Kir2.1) does to a certain manifestation of cardiac electrical activity (eg, the inward rectifier potassium current) belongs to a relatively low level in the hierarchy of pathophysiological questions, because it deals with a narrowly restricted phenomenon. An experimenter might formulate and answer to that question precisely, and yet have only a vague, intuitive appreciation of its higher, more general implications, such as the consequences that the ion channel mutation may have on the propagation of the normal cardiac impulse in the 3-dimensional heart, or on the self-organization of that impulse into the dangerous 3-dimensional scroll waves that control the dynamics of cardiac fibrillation. Experience has demonstrated that these difficult questions require technologies and approaches that are possible thanks to the availability of advanced computational methods. During the last 20 years, such methods have made it conceivable to generate geometrically accurate numeric models that incorporate precise information about local cellular electrical activity, as well as highly sophisticated electrode and optical mapping systems that allow detailed analyses of the dynamics of cardiac electric wave propagation in 1, 2, and 3 dimensions in the normal and the disease heart.10–13

Computational approaches have been used for many years as valuable tools to aid in research aiming at understanding...
the mechanisms that underlie normal and abnormal rhythms of the heart, from the molecular (ion channel) and cellular, to the whole heart. Numerous advances in spatial-temporal imaging, computer simulations, molecular and genetic techniques have allowed investigation into the manner in which the electric impulse is initiated and propagated and about the dynamics of reentry. Just as importantly, together, computationally based experiments and models are leading the way in helping us to unravel the structural, ionic, molecular, and genetic mechanisms underlying the most dangerous arrhythmias. We have now reached a stage in our use of computational technology where we can integrate many different layers of the biology of cardiac electrical behavior and investigate how, individually and collectively, they contribute to the generation and maintenance of arrhythmias. With such efforts, we may be able to improve patient outcomes through the development of better designed and targeted treatments and preventative measures for cardiac arrhythmias. Therefore, the Editors of *Circulation Research* have invited 3 groups of scientists who have contributed to the field of computational cardiac electrophysiology to write a set of review articles, and to provide comprehensive overviews of current knowledge in their chosen topics, all of which are relevant to this thematic series.

**The 3-Dimensional Cardiac Structure as a Substrate for Arrhythmias**

Undoubtedly, achieving a clear understanding of how an electric wave propagates through the complex 3-dimensional structure in the normal heart at the tissue scale and at the level of intact atria and ventricles is a daunting objective, but it is needed because it will likely provide and important resource. Cardiac impulse propagation is an emerging property which manifests itself when physico-chemical systems in the heart are organized in particular ways, and requires detailed knowledge of a wide variety of factors at multiple levels of integration, from the molecule to the organ level. In the first article of this series, Dr Bruce Smaill and his collaborators at the University of Auckland present a comprehensive overview of how, combined with detailed data from in vivo and in vitro experiments, biophysically-based high-level computational methods may provide valuable insight into 3-dimensional electrical impulse propagation in the heart. They illustrate by example how an integrated approach makes it possible to dissect key factors that determine the spread of electrical activation at multiple spatial scales more effectively than can be achieved by experiments in vivo or in vitro alone. They demonstrate also how appropriate quantitative descriptions of cell activation, cell-to-cell communication, impulse propagation between cells, tissue geometry, and myocyte architecture are necessary to model the 3-dimensional spread of electrical activation in the heart. In other words, the particular emphasis of this article is on essential aspects of structure and function at each of the above levels and on the extent to which these can be simulated in current computer models. They also delineate how this approach is being extended to analyze the formation of triggers for reentry and the substrates that sustain arrhythmia in heart disease. The take home message of the article by Smaill et al is that generating structure-based computer models that incorporate accurate information about local cellular electrical activity is a worthwhile exercise because it could provide a powerful tool for investigating the bases of complex arrhythmia. In particular, this highly sophisticated approach offers considerable promise for future understanding of the mechanisms responsible for arrhythmias in structural heart disease and the effects of structural remodeling on AF and VT/VF.

**Rotors and the Mechanism of Cardiac Fibrillation**

As discussed above, AF and VT/VF are by far the most significant cardiac arrhythmias faced by the physician. Owing to their highly complex electrocardiographic appearance, both AF and VF are commonly thought of as being the result of exceptionally complex and disorganized cardiac activation, in which electrical waves propagate through the atria or ventricles chaotically and unpredictably. In fact, during fibrillation the electrical activation sequence is profoundly abnormal; electrical wave fronts do not follow the usual paths. The atrial or ventricular rates accelerate to the extreme and 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. Nevertheless, emerging evidence now clearly supports a major role for rotors as the drivers of cardiac fibrillation in animal models and in humans. Drs Sandeep Pandit and José Jalife from the University of Michigan review current knowledge on the role of cardiac electrical rotors and their accompanying spiral waves in the mechanism of fibrillation. After a brief historical overview regarding reentry, they then discuss the basic concepts and terminologies pertaining to rotors and their initiation. The reader is introduced to the intrinsic dynamic properties of the rotors and of the spiral waves they generate, including their dependence on phase singularities and wavefront curvature, and to the implications of rotor dynamics for the spatio-temporal organization of fibrillation, independent of the species being studied. They then illustrate how analyzing the complex spatiotemporal patterns seen during fibrillation on the surface of the heart can be greatly simplified by the method of phase mapping, which helps in identifying and quantitating phase singularities. They also review the most relevant work demonstrating how the use of dominant frequency maps can help in localizing the high-frequency rotors that maintain fibrillation. Thereafter, they present an update on the ionic mechanisms of rotors and spiral waves in the last 2 decades, and the significance of such mechanisms for drug therapy. The article concludes by looking at recent evidence strongly suggesting that rotors are critical in sustaining both atrial and ventricular fibrillation (AF, VF) in the human heart, which may have critical implications for treatment with radiofrequency ablation.
Noninvasive Imaging of Cardiac Electrophysiology

In the third and final article of this series, Dr Yoram Rudy, from the University of Washington in St Louis, reviews for us recent advances using a modern, computationally based, noninvasive imaging modality (electrocardiographic imaging, ECGI) for the diagnosis and guided therapy of cardiac arrhythmias. ECGI brings electrocardiography to an unprecedented level of sophistication, one that was almost impossible to imagine 25 years ago. It clearly exemplifies the power of computational approaches in cardiac electrophysiology. It combines recordings of 224 body-surface electrocardiograms and a thoracic CT scan to reconstruct potentials, electrograms, and isochrones (activation sequences) on the human heart surface. As demonstrated by excellent examples used in Dr Rudy’s review article, ECGI enables the reconstruction from the body surface of the epicardial activation and repolarization of the heart during normal sinus rhythm, as well as during pacing of an atrium or ventricle, and enables accurate diagnosis of a wide variety of focal and reentrant arrhythmias. Through the development of detailed mathematical models of cardiac cells and tissue, Dr Rudy and his team investigate the mechanisms and consequences of genetically-inherited cardiac arrhythmias, impaired cell-to-cell communication, and abnormal spread of the cardiac impulse in the diseased heart (eg, myocardial infarction). As discussed in Dr Rudy’s review, ECGI imaging has been tested and evaluated extensively with excellent results in experimental setups and in patients with various heart conditions, including comparisons with catheter mapping and multi-electrode mapping directly from the heart during open-heart surgery. Currently, Dr Rudy is using ECGI to study mechanisms of various cardiac arrhythmias (eg, atrial fibrillation, ventricular tachycardia) in patients and to guide therapeutic interventions and the technique is now being used by other laboratories. In his review article, Dr Rudy demonstrates how an integrated approach of electrical propagation mechanisms at all levels of the cardiac system helps us gain novel insights into life-threatening cardiac arrhythmias, in such a way as to improve diagnostics and leading to successful strategies for prevention and treatment of such arrhythmias.

Altogether, this thematic review series provides an overview on the cutting-edge technology and science that is currently generating some of the most germane information on the cutting edge technology and science that is currently generating some of the most germane information on the mechanisms, diagnosis, and treatment of the most complex and dangerous cardiac arrhythmias seen in clinical practice.

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References


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