

## **Understanding the Mechanism and Targeting the Localised Treatment of Complex Heart Rhythm Disturbances**

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There are currently intractable problems in the study and treatment of heart rhythm disturbances (a field referred to as Cardiac Electrophysiology (EP)). The most complex of the heart rhythm disturbances lead to apparently random electrical activation of the heart muscle, known as fibrillation - both atrial fibrillation (AF), the commonest cardiac arrhythmia and ventricular fibrillation (VF) responsible for sudden arrhythmic death. The need for better treatment strategies for AF and VF currently challenge the limits of our understanding.

Localised destruction of myocardium (ablation) remains the mainstay of curative arrhythmia management. This clinical field evolved from the need to ablate specific points of either the origin of a focal arrhythmia (arising from a focal cluster of electrically unstable cells) or a site of interruption of the pathway of an abnormal electrical circuit, by heating the target with the tips of wires passed into the heart. Although these techniques have evolved with the emergence of curative procedures for atrial fibrillation and a renewed focus on ventricular arrhythmias and sudden arrhythmic death, the development of ablative and other treatments for the more complex arrhythmias is limited by incomplete understanding, interpretation and prediction of the electrophysiological behaviour of the myocardium. Better understanding of these complex arrhythmic myocardial substrates is needed for the development of better medical treatment, targeting and delivery for the growing number of patients with generalised myocardial disease who are prone to suffer these complex arrhythmic conditions.

The electrogram, recorded from electrodes in contact with myocardium, is the basic form in which clinical EP data are acquired and is the signature of electrical activation at each location, representing interaction of local cellular activation and local anatomy and their spatiotemporal distribution throughout the myocardium. At present, electrograms are categorised for clinical purposes by largely binary descriptors – simple or complex, early or late, high or low amplitude, etc, with very little insight into the wealth of information contained in the signal itself. Rudimentary mathematical approaches such as dominant frequency analysis have been applied to local electrogram signals and by this and associated techniques, we and others have provided insight that is of very limited clinical utility.

Clinical tools including sophisticated electrospatial mapping systems that can accurately log electrograms in 3-dimensional space, coupled with high resolution imaging of the heart to get accurate anatomical and architectural information about the myocardium, are providing enormous quantities of high-resolution data, and better insight is essential for deriving simpler and less invasive approaches to risk assessment, diagnosis and treatment of myocardial electromechanical dysfunction in general, and specifically the major clinical challenge of the growing population with complex arrhythmia.

An experienced clinical electrophysiologist performing a clinical EP study and ablation does so with an empirically-based model of cardiac EP behavior in mind. The clinician applies his integrated visually-acquired information and underlying knowledge of the arrhythmia mechanism to predict that ablation at a particular position will produce the expected response. The complexity of fibrillatory activation ultimately requires real-time

interpretation of whatever information is available clinically – such as spatially distributed electrogram and high resolution anatomical and architectural data, to determine sites of interest for targeting ablation, and this is the current clinical challenge in this field.

(1) The key mathematical question for me is, "How does the speed of the leading and trailing edge of an electrocardial wave depend on its curvature, its profile (width and shape), the local substrate geometry and the local conductance?" A sub-question for which simple models may more readily provide the answer would be, "How does the curvature of the wave front interact with curvature of the local substrate geometry and the local conductance?"

Even for FitzHugh-Nagumo it would be great to have a formula that expresses the speeds of the front-front and back-front as functionals of the wave shape and establishes the conditions for stable propagation. Even a variational statement about this question would be illuminating I believe. Then comes the issue of boundary conditions, spatial inhomogeneity and how they affect the spatial-temporal timing of wave interactions and how these effects may show up in electrogram data.

(2) Another broad important traditional question was reviewed in the latest issue of Chaos by our friend, Leon Glass, who asked "Is the Normal Heart Rate Chaotic?" CHAOS 19, 028501 (2009). Here the issue of spatial versus spatial-temporal effects is again fundamental, simply because wave interaction is involved.