Getting to the heart of ectopic beats

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Heart disease accounts for ~1:4 deaths in our community. Of those deaths, ~50% can be attributed to failure of the heart to be able to pump sufficient blood to maintain life. The other ~50% of deaths occur suddenly and are largely caused by ventricular arrhythmias. Cardiac arrhythmia suppression and reducing the risk of sudden cardiac arrest has been a topic of intense basic and translational research interest for over a century. The clinical impact of this research, however, has been more noted for its failures (*e.g.* the cardiac arrhythmia suppression trial in the 1980s) than its successes (*e.g.* the empirical findings of MADIT and similar trials). Whilst automatic implantable defibrillators can reduce the incidence of sudden cardiac death they are expensive, associated with significant side-effects and largely deployed on an empirical basis. To make further progress in this important area we need a more detailed mechanistic understanding of arrhythmias and in particular: why do arrhythmias occur when they do (and not at other times) and what maintains them once they have been initiated? Central to these questions is the role of ectopic beats. Specifically, how can we explain why almost all arrhythmias are initiated by an ectopic beat, whereas very very few ectopic beats result in the initiation of an arrhythmia.

My interest in cardiac electrophysiology started in the mid 1990s during a post-doc with Trevor Powell and Denis Noble in Oxford. This was an exciting time for cardiac electrophysiology with 1995 aptly described as an “annus mirabilis for the molecular delineation of ventricular arrhythmia substrates” (Grace & Chien, 1995). In particular the discovery of hERG K^+ channels with their unusual gating kinetics piqued my interest in understanding how the interplay between repolarization and refractoriness influenced the heart’s response to premature beats (Lu *et al.*, 2001). After a decade of studying the molecular basis of their unusual gating properties and the kinetics of drug binding to hERG K^+ channels (Vandenberg *et al.*, 2012), the work in my lab shifted to trying to understand how molecular level studies of cardiac ion channels can provide insights into cardiac arrhythmia phenotypes. Central to this shift has been the use of computer modeling to establish causally cohesive relationships between genotypes and phenotypes at first the cellular (Zhao *et al.*, 2009; Mann *et al.*, 2012) and then the whole organ level (Sadrieh *et al.*, 2014).

I expect that the next decade is going to be an even more exciting time for electrophysiology research as we link advances in genomics technology, computer modeling and big data science to gain insights into integrated cardiac electrical function which will impact our ability to stratify arrhythmia risk, initially in patients with inherited arrhythmia phenotypes and hopefully then in patients with acquired arrhythmia syndromes.

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