Integrative computational modeling of calcium handling and cardiac arrhythmias

Propositions

1. Cardiomyocyte calcium handling is the key determinant of excitation-contraction coupling in the heart and its dysregulation is strongly associated with cardiac arrhythmias (Chapters 1 and 2).

2. The subcellular distribution of cardiac ryanodine receptors modulates proarrhythmic cardiomyocyte calcium handling abnormalities independent of total protein expression or single-channel function (Chapter 3).

3. Calcium-dependent regulation of cardiac potassium channels can modulate arrhythmogenesis through the inhibition of triggered activity and stabilization of reentrant arrhythmias (Chapter 5).

4. The proarrhythmic effects of excessive alcohol or drug-induced ion-channel and calcium-handling abnormalities depend on both the underlying structural remodeling and acute electrophysiological conditions modulated by the autonomic nervous systems and electrolyte disturbances, explaining the dynamic occurrence of cardiac arrhythmias (Chapters 6 and 8).

5. Due to its complex interplay with major regulating proteins, cardiomyocyte calcium handling serves as a potential therapeutic target for cardiac arrhythmias.

6. Integrative clinical, experimental and computational studies provide a better understanding on the determinants, precipitating factors and pathophysiology of complex cardiac arrhythmias.

7. Multiscale computational modeling has undergone significant development in the past 80 years and is now able to provide novel mechanistic insights and assist both bench and bedside cardiac electrophysiology.

8. MANTA is a freely available educational tool to improve understanding of the complex cellular effects of antiarrhythmic drugs by employing the perfect control and observability of computational modeling.

9. All models are imperfect, but they are nonetheless useful. (adapted from a quote by George P. Box)

10. With four parameters I can fit an elephant, and with five I can make him wiggle his trunk, but even with thousands of parameters, I cannot make him alive. (adapted from a quote by John von Neumann)

11. "*Science cannot solve the mystery of nature. And that is because, in the last analysis, we ourselves are a part of the mystery that we are trying to solve*." – Max Planck