Ca^{2+}-induced arrhythmias: from cellular level to the whole heart

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(1) key issues presented in the conference and the current understanding:

In this Session, several important findings from human heart experiments and computational models were discussed. Analysis of human heart samples revealed sex differences in gene expression during heart failure. In particular, female atria appear to have greater down-regulation of several ion channel and calcium handling genes compared to males.[1] We do not yet know the physiological reasons or consequences of these differences. However, this finding underscores the need for further investigation into the sex- and gender-based mechanisms of atrial and ventricular arrhythmias. Substrate modeling studies using state-of-the-art human heart models fashioned from optical mapping studies[2] have revealed that 1) microvolt T-wave alternans (TWA) can occur at low heart rates only when a significant downregulation of SERCA expression/activity (to ~75% of normal levels) is incorporated into the model, 2) TWA occurring at low heart rates are associated with alternans of action potential shape (i.e., amplitude during plateau phase), not duration, and 3) a direct link between TWA and induced ventricular fibrillation was demonstrated in the model.[3,4] Notably, neither spontaneous ventricular arrhythmias nor triggered events were seen in the model.

(2) consensus and controversies that emerged from discussion

Throughout the discussion, several key points emerged that required further dialogue. Of note, cellular and whole-heart electrophysiologists typically view action potentials (APs) that have been recorded using entirely different methodologies. Therefore, these APs can have surprisingly different morphologies. For example, APs recorded from single isolated cells typically have faster upstroke profiles and a more pronounced spike-and-dome morphology compared to those recorded with optical techniques from intact tissue. This is likely attributable to tissue heterogeneity, effects of propagating wavefronts, light scattering and averaging of optical techniques, among other differences. [5,6] This is a very important point for all investigators to recognize when applying a systems approach to arrhythmia mechanisms: cell-level and tissue-level responses, although mediated by the same mechanisms, may not be identical. Along these same lines, it will be a challenge to establish if focal activity in the intact heart is truly 'Ca^{2+}-mediated'. For example, in single cells, diastolic Ca^{2+} release preceding a triggered AP may be easily distinguishable.[7] However, in multi-cellular preparations, these distinct events may be difficult to recognize due to tissue heterogeneity, electrotonic coupling, and the method of data acquisition.

(3) important questions that warrant further investigation

Despite the consensus reached on many of the topics discussed, several important questions emerged that require further study. With regard to TWA, it still remains unknown whether microvolt TWA at slow heart rates are a *cause* of arrhythmia in heart failure patients, or are they simply an *indicator* of an arrhythmogenic substrate? How could causality (or a lack thereof) be determined experimentally? Although computational models suggest that SERCA downregulation is sufficient to produce TWA, [3,4] is SERCA the main contributor to TWA in human heart failure, or are there other contributing factors? What are those factors and are they important? We can perhaps speculate that changes in I_{K1} along with concomitant changes in I_{Na} (or additional changes in intrinsic I_{Na}) are also important and should be considered when modeling human heart failure.

Additionally, several questions remain regarding focal arrhythmia triggers. It is clear that we need a better understanding of the mechanisms and characteristics of arrhythmia triggers

(e.g., rate dependence) that arise during heart failure or other cardiovascular disease. However, along with the recognition that we need to know more, it is generally very difficult to both model focal arrhythmia triggers as well as map their origin and mechanisms in intact hearts. Future work in developing computational models that fully recapitulate focal activity as well as the development of optical or other mapping techniques to more precisely determine the origin and mechanisms of focal triggers are needed.

References

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