Mechanisms of ventricular heart rate adaptation as an indicator of arrhythmic risk

Esther Pueyo, PhD, Pablo Laguna, PhD and Blanca Rodriguez, PhD.

University of Oxford, Oxford, United Kingdom,
University of Zaragoza, Zaragoza, Spain

Abstract:
Introduction: Clinical studies show that impaired QT interval adaptation to abrupt heart rate (HR) changes is an arrhythmic risk marker in cardiac patients. The goal of this study is to investigate the ionic mechanisms of QT rate adaptation and its relationship to arrhythmogenesis.

Methods: A human ventricular tissue computer model is developed using the ten Tusscher action potential (AP) model. The simulated ECG is computed, and QT adaptation studied using a protocol identical to that used in clinical studies. Tissue is stimulated at the endocardium, first at 1Hz for 8 min, then at 1.67Hz for 8 min, and finally, at 1Hz for 8 min. A similar protocol is also applied to individual endo, mid and epicardial cells to study AP duration (APD) adaptation, and its relationship to QT adaptation. Simulation results are validated using clinical ECG and monophasic AP (MAP) recordings in patients. The ionic mechanisms underlying QT and APD adaptation to HR changes are investigated under normal and pathological conditions.

Results: Simulation results show that time for QT complete adaptation following an abrupt HR change is 3.5 min, consistent with clinical data. QT adaptation dynamics are directly related to APD adaptation times, which are faster in midmyocardial cells (2.2 min) than in endo or epicardial cells (3.6 min), as previously shown in MAP recordings in patients. Simulations show two main phases of QT and APD adaptation: a fast initial phase of 10 sec duration, related to L-type calcium, slow-delayed rectifier potassium currents and Na-Ca exchanger dynamics; and a second slow phase due to [Na]i dynamics. Simulations show that block of NaK pump and overexpression of NaCa exchanger, as in heart failure, results in protracted rate adaptation, AP triangulation and APD instability, all of them indicators of arrhythmic risk in patients. This is related to Na overload and increased risk of afterdepolarizations.

Conclusions: This study shows that sodium dynamics play a key role in heart rate QT interval adaptation. Increased risk of cardiac arrhythmias in patients with protracted rate adaptation might be due to altered Na dynamics resulting in Na overload, afterdepolarizations and APD instability.