Adaptation mechanisms of the QT interval during stress test and its dependency with adrenergic stimulation: a simulation study

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Aim: QT interval adaptation to changes in heart rate (HR) has been proposed as an arrhythmic risk marker. Step-like changes in HR have been generally considered to measure this adaptation, but recently ramp-like HR changes have been proposed since they can be easily obtained from regular stress tests. The delay between the QT interval and the expected HR-dependent memoryless QT interval during a HR ramp in a stress test has been reported to progressively reduce when approaching the stress peak. Here, we hypothesized that changes in β-adrenergic stimulation contribute to this phenomenon and we assessed it by in silico simulations.

Materials and methods: We coupled an electrophysiological model of a human ventricular cardiomyocyte with a β-adrenergic signaling cascade model. We simulated cell stimulation according to RR intervals as measured from stress test recordings of patients. We measured the action potential duration (APD) in response to HR changes and searched for the β-adrenergic stimulation pattern that best replicated the QT interval response to the same HR changes.

Results: The simulated APD trends presented similar behavior to the measured QT interval trends for the same RR interval time series. The optimal β-adrenergic stimulation pattern involved a sharp linear increase close to the stress test peak. The APD adaptation time became remarkably reduced in response to β-adrenergic stimulation during heavy stress, as initially hypothesized. During stress test recovery, the delay between QT and RR remains almost constant, which can be explained by a much faster return from high β-adrenergic stimulation to baseline levels than during the stress phase.

Conclusion: β-adrenergic stimulation plays a fundamental role in QT interval adaptation to HR during stress by reducing QT adaptation time close to the stress peak and limiting the time interval suitable to measure QT adaptation for arrhythmic risk purposes.

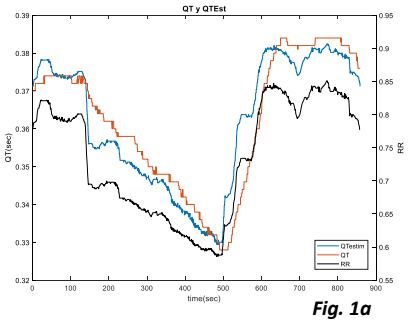

Fig. 1a

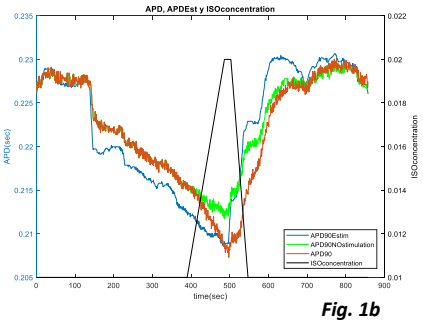

Fig. 1b

Fig. 1 a) QT interval response (orange) obtained from RR value (black) in a patient and compared to estimated QT value (blue). b) APD response (orange) to HR changes after β-adrenergic stimulation is applied (black) and estimated APD (blue) from the RR interval, compared with APD response (green) when there is no stimulation.