Termination of reentrant tachyarrhythmias by light: from electroshock towards shockless cardioversion by cardiac optogenetics

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Purpose: Atrial Fibrillation (AF) is the most common cardiac rhythm disorder of clinical significance. Electric cardioversions remain the mainstay of treatment in symptomatic AF-patients. However, the used electroshocks result in severe discomfort and tissue damage, which necessitate anaesthesia and preclude the use of implantable devices in AF. Hypothetically, forced expression of light-gated cation-channels in cardiomyocytes and subsequent activation (optogenetics), might deliver the depolarizing force sufficient for cardioversion, circumventing aforementioned drawbacks of electroshocks. Therefore, we investigated the feasibility of optogenetics in the termination of spiral wave reentry-a mechanism underlying fast activation during AF-and compared it to conventional electrotherapy.

Methods: Neonatal rat atrial cardiomyocyte monolayers were transduced with lentiviral vectors encoding the calcium-translocating channelrhodopsin (CatCh†) or eYFP as control (eYFP†), and burst-paced to induce fibrillation based on spiral wave reentry. Effects of optogenetic light-therapy on reentry were investigated using optical and micro-electrode array mapping (MEA) techniques. Westernblot and immunocytochemistry were used to confirm CatCh and eYFP expression.

Results: Pulsed blue light (10 ms/470 nm) elicited action potentials in cultures transduced with CatCh† but not eYFP†, confirming functional CatCh-mediated photocurrent. Reentry was terminated by a 500-ms light pulse in 100% CatCh† (n=35) vs 0% (n=11) in eYFP†-transduced atrial cultures. Mechanistically, uniform depolarization by CatCh-activation resulted in decreased excitability of the fibrillating monolayer (MEA peak-to-peak amplitude decreased 304.5±254 vs 12.6±11.5 μV in eYFP†). This caused an increase in the coresize of functional reentry and phase-singularity (PS) drift, which increased the chance of PS-PS or PS-boundary collisions, leading to reentry termination. In comparison, electrical reentry termination could be achieved only with 10 ms shocks of 60.5±15 V.

Conclusions: For the first time it is shown that reentry can be terminated effectively by using tissue-endogenous depolarizing currents triggered by light, using energy levels well below pain threshold, in contrast to electroshock therapy in our model. This approach can potentially circumvent the necessity of electroshocks for cardioversion. Hence this study provides a new rationale for the design of shockless/painfree anti-fibrillatory treatment strategies.