Thinking outside the cardiac box: Calcium physiology in iPSC-CMs in a virtual or mechanically induced pro-maturation environment

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Background: Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) are attractive due to their unlimited availability and human origin, making them a promising tool for cardiac research and safety pharmacology. However, they can show an immature phenotype such as lower inward rectifier potassium current (I_{K1}), atypical expression pattern of ion channels, divergent response to pharmacological agents and contractile behaviour compared to adult CMs. Thus, their detailed characterization and optimized recording environments are essential.

Purpose: We aimed to characterize and modulate electrophysiological and contractile properties of hiPSC-CMs using automated dynamic clamp and contraction measurements on flexible substrate.

Methods: Commercially available hiPSC-CMs were recorded in voltage and current clamp using a combined automated patch clamp and dynamic clamp device (Patchliner Dynamite[8]), and contractility recordings were made using the FLEXcyte 96.

Results: Simulated I_{K1} and seal compensation were applied up to 8 hiPSC-CMs simultaneously. The Ca^{2+}-channel activator S-BayK 8644 (10µM) significantly prolonged the action potential duration at 90% repolarization (APD_{90}), while the selective blocker Nifedipine (10µM) reversed this effect (114.8±12ms vehicle vs. 144.2±17ms S-BayK 8644 vs. 118,2±13ms Nifedipine n=16 mean±SEM, ANOVA, *p<0.05). Addition of increasing concentrations of S-BayK 8644 revealed an EC_{50}=11.9nM (n=4). The short-term variability of APD_{90} revealed a low variability of 3.5±1.5 (n=5, mean±SEM). In addition, recordings at room vs. physiological temperature affected the shape of the action potential (AP).
The effects of Ca^{2+} channel activation and inhibition on contractility were studied in a dose-dependent manner. S-BayK 8644 (30nM) increased the contraction amplitude (150% of control) and caused the relaxation phase prolongation, further prolonging total duration of the contraction-relaxation-cycle (120% of control). Nifedipine (30nM) decreased the contraction amplitude (60% of control) and shortened the relaxation phase (80% of control).

Conclusion: Seal compensation and virtual I_{K1} in hiPSC-CMs resulted in more stable and longer APs with low APD variability. Consequently, the dynamic clamp approach enabled reliable calcium channel pharmacology on these cells. Culturing conditions that support contractility, i.e. flexible membrane substrates, demonstrate Ca^{2+} channel pharmacology equivalent to that expected from adult CMs.