Integrating dynamic clamping with automated patch clamping devices: adding virtual I_{K1} channels to iPSC-CM

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An important aspect of the CiPA (Comprehensive *In Vitro* Proarrhythmia Assay) proposal is the use of human stem cell-derived cardiomyocytes and the confirmation of their predictivity in drug safety assays. The benefits of this cell source are clear, drugs can be tested in vitro on human cardiomyocytes, with patient-specific genotypes if needed, and differentiation efficiencies are generally excellent, resulting in a virtually limitless supply of cardiomyocytes.

There are however several challenges that will have to be surmounted before successful establishment of hSC-CM as an all-round predictive model for drug safety assays. An important factor is the relative electrophysiological immaturity of hSC-CM, which results in limited arrhythmic responses to unsafe drugs that are pro-arrhythmic in humans. Potentially, immaturity may be improved functionally by creation of hybrid models, in which the dynamic clamp technique joins simulations of lacking cardiac ion channels (e.g. I_{K1}) with hSC-CM in real-time during patch clamp experiments. This approach is used successfully in manual patch clamping experiments, but throughput is low.

In this study, we combined dynamic clamping with automated patch clamping of iPSC-CM in current clamp mode. The dynamic clamp system that we designed functions as a stand-alone, remote-controlled device requiring no direct user interaction. All control of the dynamic clamp system is managed through the software used to control the automated patch clamp device (PatchControlHT or HEKA PatchMaster), allowing complete automation of dynamic clamp experiments with iPSC-CM on this platform. In line with earlier work in manual patch clamp experiments, addition of virtual I_{K1} channels resulted in hyperpolarisation of the resting membrane potential, increased upstroke velocity and prolonged action potential duration. We conclude that dynamic clamping can be used successfully to add I_{K1} conductances to iPSC-CM on an APC, resulting in an improved electrophysiological maturity and higher throughput.