AF on Demand : A Human iPSC-Derived Screening Assay Targeting Atrial Fibrillation

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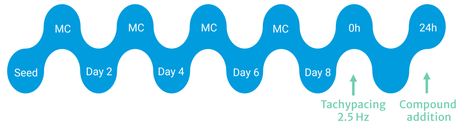
Abstract

- Atrial fibrillation (AF) is the most common form of cardiac arrhythmia, significantly impacting morbidity and mortality worldwide.
- Using commercially available human induced pluripotent stem cell (hiPSC)-derived atrial cardiomyocytes (axoCells™, Axol Bioscience Ltd.), we developed an AF-like human phenotype *in vitro* disease model.
- The drug screening assay is designed to assess AF-related functional changes in a human-relevant context, with extracellular field potential duration (EFP, CardioExcyte 96) as readout parameter.

Methods

- Preculture of atrial hiPSC-CMs on CardioExcyte plates for 9 days including medium change (MC) every other day
- Begin of tachypacing on day 9 for 24 h -> induction of AF phenotype with reduced EFP duration
- Compound addition 24 after begin of tachypacing and chronic EFP duration assessment

1.



Discussion

- Antiarrhythmic drugs ibutilidie, dofetilide and sotalol are known therapeutics for restoring normal heart rhythm in AF.
- All three compounds show respective EFP duration prolonging effects in the here presented *in vitro* disease model using hiPSC-atrial CMs.
- This human-based disease model presents a significant advancement for atrial fibrillation research, providing a human-relevant platform for identifying novel therapies with greater translational potential and accelerating the development of effective AF treatments.

Results

2.

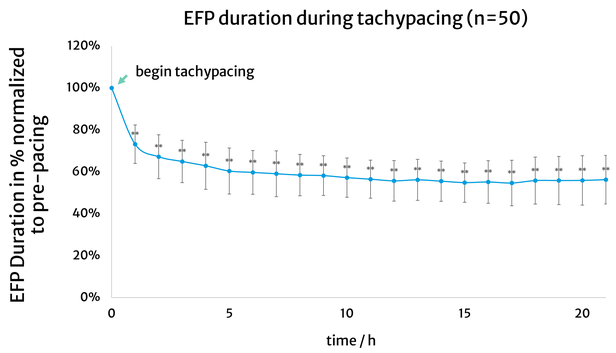


Figure 2. Effect of 2.5 Hz tachypacing on human iPSC-derived atrial CMs. Cells were electrically paced for 24h showing a 40% decrease in EFP duration after approx. 5 h (n=50). Statistical analysis performed with Wilcoxon-Mann-Whitney (WMW) test.

3.

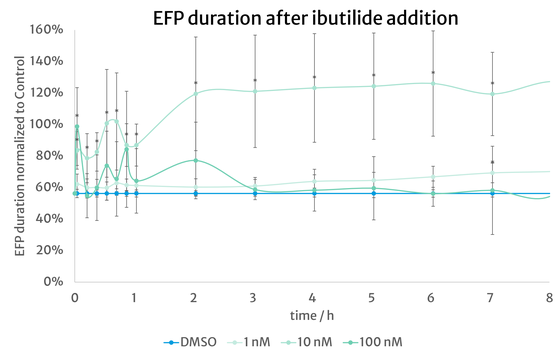


Figure 3. Effect of ibutilide on human iPSC-derived atrial CMs under 2.5Hz tachypacing condition. 10 nM of ibutilide exhibit a significant increase in EFP duration from 60% - due to tachypacing - up to 120%. Statistical analysis performed with WMW test.

4.

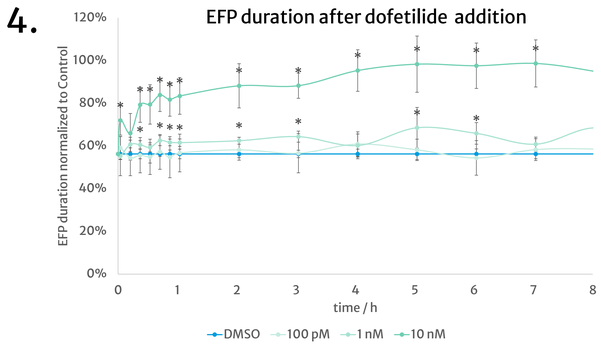


Figure 4. Effect of dofetilide on human iPSC-derived atrial CMs under 2.5 Hz tachypacing condition. Cells show a concentration-dependent increase in EFP duration from 60 % - due to tachypacing - to almost 100 % after 10 nM dofetilide addition. Statistical analysis performed with WMW test.

5.

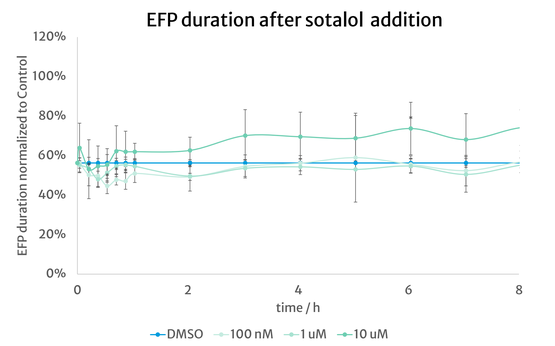


Figure 5. Effect of sotalol on human iPSC-derived atrial CMs under 2.5 Hz tachypacing condition. Cells show an increase in EFP duration from 60 % - due to tachypacing - up to 75% after 10 µM sotalol addition. Statistical analysis performed with WMW test.

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