Abstract: **P130**

**Antiarrhythmic effects of carvedilol and flecainide in cardiomyocytes derived from catecholaminergic polymorphic ventricular tachycardia patients**

**Authors:**
R-P Polonen¹, K Penttinen¹, H Swan², K Aalto-Setala³, ¹University of Tampere, BioMediTech - Tampere - Finland, ²Helsinki University Central Hospital - Helsinki - Finland, ³Tampere University Hospital, Heart Center - Tampere - Finland,

**On behalf:** Heart group

**Topic(s):**
Basic Science - Cardiac Diseases: Arrhythmias

**Citation:**
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Academy of Finland, the Finnish Cultural Foundation, the Finnish Foundation for Cardiovascular Research, the Finnish Funding Agency for Technology

Background: Mutations in the cardiac ryanodine receptor (RYR2) are the leading cause for catecholaminergic polymorphic ventricular tachycardia (CPVT). In this study, we evaluated the antiarrhythmic efficacy of carvedilol and flecainide in CPVT patient-specific induced pluripotent stem cell (iPSC) -derived cardiomyocytes carrying different mutations in RYR2.

Purpose: The purpose of this study was to assess which one of the tested antiarrhythmic agents would be the most efficient for abolishing calcium abnormalities in CPVT patient specific cardiomyocytes in vitro. The study would be one step towards personalized medicine in the treatment of CPVT patients.

Methods: iPSC-derived cardiomyocytes were generated from skin biopsies of three CPVT patients carrying exon 3 deletion, L4115 or V4653F mutation in RYR2 and from a healthy individual. Calcium kinetics and drug effects were studied with Fluo-4 AM calcium indicator.

Results: Carvedilol and flecainide abolished almost similar amounts of calcium abnormalities in CPVT cardiomyocytes (table 1). In healthy control cells, flecainide caused more abnormal calcium transients compared to carvedilol. Moreover, both drugs lowered the intracellular calcium level and beating rate of all cardiomyocytes significantly. Furthermore, calcium abnormalities were categorized into different groups and distinct abnormality profiles were discovered between the CPVT cardiomyocytes.

Conclusions: Carvedilol and flecainide were equally effective in treating arrhythmias in CPVT specific iPSC-derived cardiomyocytes. However, the proarrhythmic risk of flecainide should be recognized as it induced arrhythmias in control cells. Even though the CPVT cardiomyocytes carrying the exon 3 deletion had the most severe calcium abnormalities, they had the best response to drug therapies. Both carvedilol and flecainide are used in the clinics for the treatment of CPVT. However, according to this study, the arrhythmia abolishing effect of neither of them is optimal. iPSC-derived cardiomyocytes provide a unique platform for testing new potential drugs for CPVT.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control (wild type)</th>
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<th>CPVTb (V4653F)</th>
<th>CPVTc (Exon 3 del.)</th>
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<tr>
<td>Carvedilol</td>
<td>26%</td>
<td>31%</td>
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</tr>
<tr>
<td>Flecainide</td>
<td>61%</td>
<td>33%</td>
<td>30%</td>
<td>52%</td>
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Antiarrhythmic efficacy of carvedilol and flecainide in CPVT cardiomyocytes and proarrhythmicity in controls. Values indicate percentages of cells in which arrhythmias were abolished (CPVT) or triggered (control) by the drugs.