41.3.4 - Arrhythmias

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The COVID-19 viral 3a protein forms a potassium channel that can be inhibited by antiarrhythmic drugs

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Background/Introduction: Supraventricular and ventricular arrhythmias can often be observed in patients with COVID-19 infection. Both, the clinically observed increase in cardiac biomarkers as well as histological studies indicate virus replication within cardiomyocytes. The 3a open reading frame of the viral genome encodes for a transmembrane protein that is transported to the cell membrane where it can serve as a potassium channel.

Purpose: The aim of this study was to investigate whether COVID-19 infected induced pluripotent stem cell (iPSC)-derived cardiomyocytes also express the 3a protein and whether the potassium currents that are conducted through the 3a protein can be inhibited by clinically used antiarrhythmic drugs.

Methods and Results: iPSC-derived cardiomyocytes were infected with COVID-19 and subsequently subjected to immunoblotting, where expression of the 3a protein could be observed. Plasmid DNA, encoding the COVID-19 3a protein, was generated by gene synthesis and used for in vitro transcription of cRNA. 3–5 days after intracytoplasmic injection of the 3a protein cRNA into Xenopus laevis oocytes, potassium currents could be measured by two-electrode voltage clamp recordings. While class I and class IV antiarrhythmic drugs showed only minor effects on the potassium currents of the 3a protein, a robust inhibition by several beta-blockers and by class III antiarrhythmic drugs could be observed. The strongest effects were found with dofetilide (58.1 % inhibition at 100 µM) and amiodarone (50.1 % inhibition at 100 µM, IC50 level 4.7 µM). An in silico docking analysis, based on the recently revealed crystal structure of the 3a protein, identified the amino acid residues K61 and D142 as part of the binding site of amiodarone. After deactivation of these amino acid residues by site-directed mutagenesis, the inhibition by amiodarone was significantly attenuated.

Conclusion: The COVID-19 viral 3a protein is expressed in COVID-19-infected iPS-derived cardiomyocytes and forms a potassium channel that can be inhibited by antiarrhythmic drugs.