Patient-derived lamin A/C mutant cardiomyocytes demonstrate altered electrophysiological characteristics and responses to hypoxia induced stress

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Abstract
Dilated cardiomyopathy (DCM) is a severe cardiac disease associated with increased mortality rates. Prevalence of DCM is 1:2500 and approximately 20–48% of cases are of familial origin. [1] Several mutations in lamin A/C gene (*LMNA*) have been shown to cause DCM, often leading to sudden cardiac death. [2] Human induced pluripotent stem cell (hiPSC) -derived cardiomyocytes (CMs) provide valuable resources in further research of the condition and in the development of effective treatments.

In the present study, hiPSC-CMs were exposed to acute hypoxic and reoxygenation conditions to investigate the effects of acute hypoxia on *LMNA* mutant and healthy CMs. Our aim was to observe and measure CMs' response to acute hypoxic stress via electrophysiological variables such as beat rate, conduction velocity, depolarization time, and field potential duration.

In this study hiPSC-CMs carrying the p.S143P mutation in *LMNA* gene were compared to healthy CMs. Our aim was to define electrophysiological responses of CMs to acute hypoxic stress. Cells were exposed to three hours of hypoxic gas environment, while recording their electrophysiological functions via microelectrode arrays.

Upon acute hypoxia exposure, the *LMNA* mutant CMs altered their beat rate less than the control CMs. The conduction velocity was different between the cell lines, being significantly lower in the *LMNA* mutant CMs. For the control samples, 0.227 m/s and for the *LMNA* samples 0.055 m/s under baseline conditions (19% O2).

This study demonstrates that cardiomyocytes carrying the p.S143P mutation in lamin A/C gene respond differently to acute hypoxic stress compared to healthy control CMs. These features suggest regulatory dysfunctions in *LMNA* mutant cells and may sensitize to cellular injury under acute hypoxia.