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MEETING ABSTRACT

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Electrophysiological characterization of cardiac organoids

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Background: The number one cause of human fetal death are defects in heart development. Because the embryonic heart is inaccessible and no chamber-specific *in vitro* models exist, determining the causes of disease is difficult. Therefore, a human cardiac organoid (cardioid) platform was recently established recapitulating the development of all major embryonic heart compartments, including right and left ventricles, atria, outflow tract, and atrioventricular canal [1, 2]. Here, we characterize the electrophysiological properties of these cardioids.

Methods: The following methods were used in this study: (i) multi-electrode arrays for the estimation of action-potential duration of 3D cardioids determined by extracellular field potential recordings; (ii) single-cell patch-clamp experiments to perform spontaneous action-potential recordings and subsequent parameter analysis; and (iii) optical calcium signaling experiments employing genetically encoded GCaMP6f reporter lines to optically visualize calcium transients.

Results: We revealed embryonic electrophysiological properties of cardioids. Single-cell patch-clamp experiments demonstrated high homogeneity of the cardiomyocyte cell populations, and action-potential durations matched those of humans. Multi-electrode-array measurements of 3D cardioids showed RT intervals, an indicator for action-potential duration, that were similar to the patch-clamp data. Finally, calcium signaling experiments further validated the cardioid platform by showing calcium-transient durations closely matching patch-clamp and multi-electrode-array experiments.

Discussion: In this study we characterized the electrophysiological traits of cardioids and confirmed their embryonic-like identity. Low upstroke velocities and a lack of chamber-specific action-potential characteristics in atrial cardiomyocytes further support the embryonic-like character. The high overlap of experimental data between the three different techniques used in this study underlines the robustness of the cardioid system, especially because multiple different biological replicates were used. Preliminary pharmacological experiments (data not shown) revealed responsiveness to multiple known ion-channel blockers, however complete pharmacological profiling is still outstanding. Future attempts at metabolic maturation of cardioids should yield cardioids more closely resembling the adult-like state, thereby generating a platform suitable for disease modeling (*e.g.* Brugada syndrome, Long-QT syndrome) and precision pharmacology. Moreover, the possibility to fuse cardioids and work with a multi-chambered system to evaluate chamber-specific pharmacological effects has the potential to revolutionize preclinical cardiac safety pharmacology.

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Keywords: cardiac electrophysiology – organoids – patch clamp

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