Physiological and pharmacological characterization of human engineered heart tissue

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Objective: Human induced pluripotent stem cell (iPS cell)-derived cardiomyocytes represent a valuable tool in cardiovascular research of tremendous potential. However, these cells are still immature and characterized by poor sarcomeric organization and cellular orientation in 2D cell culture. Therefore, the measurement of contractile force, the most important and best understood function of cardiomyocytes in vivo, is not established for these cells. This study describes the generation of three-dimensional, strip-format, force generating engineered heart tissues (EHTs) from human iPS cell-derived cardiomyocytes and presents a characterization of physiological and pharmacological parameters based on force development.

Methods and results: Cardiomyocyte differentiation of human induced pluripotent cells was achieved by a growth factor-based three stage protocol. Strip-format EHTs were generated from dissociated cardiomyocytes in fibrin matrix between flexible silicone posts. Within two weeks after casting coherently beating human EHTs were formed and EHTs displayed a regular beating pattern for several weeks. Histological analysis revealed a high degree of sarcomeric organization and alignment of cardiomyocytes in EHTs. Functional analysis was performed by measuring force response to calcium concentration, pre-load, pacing frequency, beta-adrenergic and muscarinic agonists, modulators of sodium, calcium and potassium channels and revealed concentration-dependent effects. Comparison with native human heart tissue suggests an overall high level of similarity and minor differences.

Conclusions: This study demonstrates feasibility to characterize human iPS cell-derived cardiomyocytes in EHTs by measuring contractile force. The analysis suggests high levels of similarity between EHTs and native human heart tissue. Human EHTs are a promising platform for automated toxicology screens in future drug development and for in vitro experiments on human cardiomyocytes in general.