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Combining Physiological Relevance and Throughput for In Vitro Cardiac Contractility Measurement

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[Introduction] Despite increasing acceptance of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) in safety pharmacology, controversy remains about the physiological relevance of existing *in vitro* models for their mechanical testing. We hypothesize that existing signs of immaturity of the cell models result from an improper mechanical environment.

[Methods] We cultured hiPSC-CMs in a 96-well format on hyperelastic silicone membranes imitating their native mechanical environment, resulting in physiological responses to compound stimuli.
Using freely-swinging, ultra-thin and hyperelastic silicone membranes, the weight of the cell culture medium deflects the membranes downwards. Rhythmic contraction of the hiPSC-CMs resulted in dynamic deflection changes which were quantified by capacitive distance sensing. The cells were cultured for 7 days prior to compound addition. Acute measurements were conducted 10-30 minutes after compound addition in standard culture medium. For chronic treatment, compound-containing medium was replaced daily for up to 7 days. Electrophysiological properties of the employed cell types were recorded by automated patch-clamp (Patchliner) and the results were integrated into the electromechanical model of the system.

[Results] We validated cell responses on the FLEXcyte 96, with a set of reference compounds covering a broad range of cellular targets, including ion channel modulators, adrenergic receptor modulators and kinase inhibitors. Acute (10 – 30 min) and chronic (up to 7 days) effects were investigated. The measurements were complemented with electromechanical models based on patch clamp recordings.
Calcium channel agonist S-Bay K8644 and beta-adrenergic stimulator isoproterenol induced significant positive inotropic responses without additional external stimulation. Kinase inhibitors displayed cardiotoxic effects on a functional level at low concentrations. The system-integrated analysis detected alterations in beating shape as well as frequency and arrhythmic events and we provide a quantitative measure of these.

[Conclusion] In summary, the system presented is a reliable high throughput tool for *in vitro* cardiac contractility research, providing the user with data obtained under physiological conditions which resemble the native environment of the human heart.