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A Higher Throughput Approach to Investigate Cardiac Contractility In Vitro Under Physiological Mechanical Conditions

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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, e.g. negative inotropy upon adrenergic stimulation, result from an improper mechanical environment. 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. The objective of the present study was to validate cell responses on a new assay system, the FLEXcyte 96, with a set of reference compounds covering a broad range of cellular targets, including ion channel modulators (SBay K8644, nifedipine), adrenergic receptor modulators (isoproterenol, sotalol) and kinase inhibitors. Furthermore, the measurements were complemented with electromechanical models based on electrophysiological recordings of the used cell types. hiPSC-CMs from commercial sources were cultured on freely-swinging, ultra-thin and hyperelastic silicone membranes. Due to the cell culture medium weight, the membranes were deflected downwards. Rhythmic contraction of the hiPSC-CMs resulted in dynamic deflection changes which were quantified by means of capacitive distance sensing. The cells were cultured for 7 days prior to compound addition. Acute measurements were conducted 10-30 minutes after compound addition. For chronic treatment, compound containing medium was replaced daily for up to 7 days. 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. Omecamtiv Mecarbil increased the duration of the contraction- relaxation-cycle via activation of the myosin complex. The system-integrated analysis detected alterations in beating shape, frequency and arrhythmic events and provides a quantitative measure of these. We demonstrate that the results obtained show consistency with the respective physiological responses in humans. 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.