Medium-high throughput optical measurements of multiparametric endpoints for cardiac safety assessment. Analysis of inotropic drug action on human iPSC-derived cardiomyocytes

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The inotropic state (IS) of the heart is a fundamental property of the cardiovascular system due to its role in determining cardiac output. Normal hearts can compensate for small decrements in IS and maintain cardiac output, but in disease states, such as heart failure or diabetic cardiomyopathy, the capacity to compensate for IS depression is limited and may adversely affect these patient groups. For this reason it is advisable to evaluate drugs in pre-clinical stages for inotropic actions. CellOPTIQ® (Clyde Biosciences Ltd), a multiparametric medium-high throughput assay platform was used in conjunction with hiPSC derived cardiomyocytes, to develop a suitable biological assay for screening inotropic actions on the heart. Both electrical activity and contractility were assessed using iCell² hiPSC cardiomyocytes (Cellular Dynamics Inc.) using a Voltage Sensitive Dyes (VSD) and a cell motion-based contractility assay. The cells were paced at constant rate (1Hz) rate throughout. After recording the baseline activity, the cells were treated with a set of drugs with known inotropic effect. For example, the L-type calcium channel blocker Nifedipine (negative inotropic) decreased the amplitude of contraction to 51.9 ± 5.3% of baseline at 0.1μM (n=8); this was accompanied by shortening of APD (APD90= 47.1 ± 6.9% of baseline). Blebbistatin decreased contractility (to 59.7 ± 6.9% of baseline) at 3μM, with minimal changes in electrical activity (APD90=86.5 ± 2% of baseline). In conclusion, the implementation of an IS assay to the CellOPTIQ® was tested using CDI iCell² hiPSC-CMs. The utility of this assay for cardiac safety assessment was established using several drugs with established inotropic actions.