

FLEXcyte: A New *In Vitro* Tool to Study Cardiac Contractility under Physiological Mechanical Conditions

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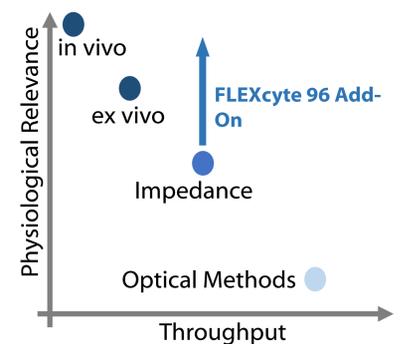
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Abstract

Common systems for the quantification of cellular contraction rely on animal-based models, complex experimental setups or indirect approaches. Integration into standard lab procedures remains a challenge for current *in vitro* systems. The FLEXcyte 96 system has the potential to scale-up mechanical testing towards medium-throughput analyses. We show here that, using stem cell-derived cardiomyocytes, this system enables predictive recordings of contractile behavior in the presence of well-known reference compounds.

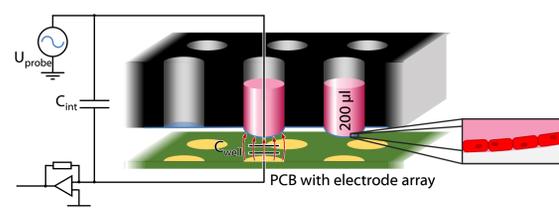
Objectives

Here we present a technology for measuring drug induced alterations in cardiac contractility with stem cell-derived cardiomyocytes. The FLEXcyte 96 system based on the CellDrum technology combines physiological relevance with a scalable throughput while providing an environment that reflects the mechanical properties of real human cardiac tissue. The 96-well format is compatible to standard lab automation systems and minimizes sample volumes compared to *ex vivo* and *in vivo* approaches. Isoprenaline and sotalol were selected as examples for well-characterized tool compounds to investigate inotropic effects. In particular, aspects such as force-frequency relation are subject of current scientific discussions and require an assay technology that can accurately quantify them.



Technology

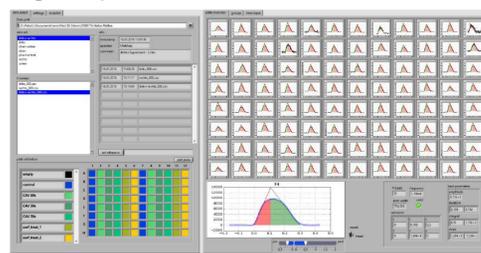
Within the FLEXcyte 96 system, the cells are cultured on a physically defined reference material consisting of an ultra-thin silicone membrane. While being deflected by the weight of the culture medium, rhythmic contraction of the cardiomyocytes lifts the membrane upwards.



Based on Nanion's CardioExcyte96 platform the deflection can be acquired on 96 channels simultaneously with high spatial and temporal resolution.

Our multi-parameter analysis algorithms provide information on time domain parameters (e.g. frequency, contraction duration, relaxation duration) as well as beating amplitude.

Combining this set of measures enables to describe the contraction shape quantitatively. This way, information can be obtained on the underlying mechanisms of how cellular functions are affected.

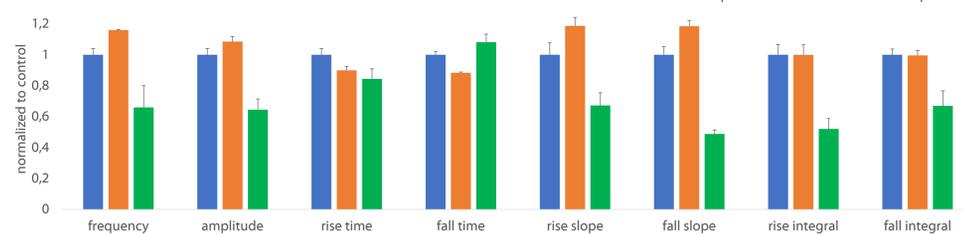
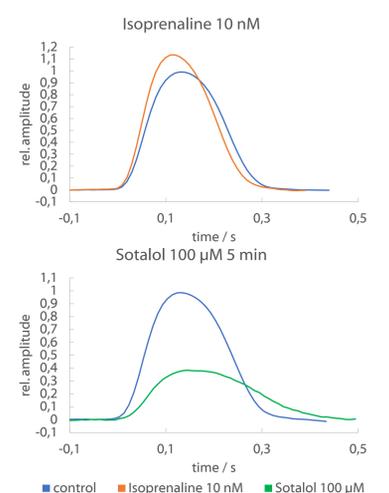


Simulation

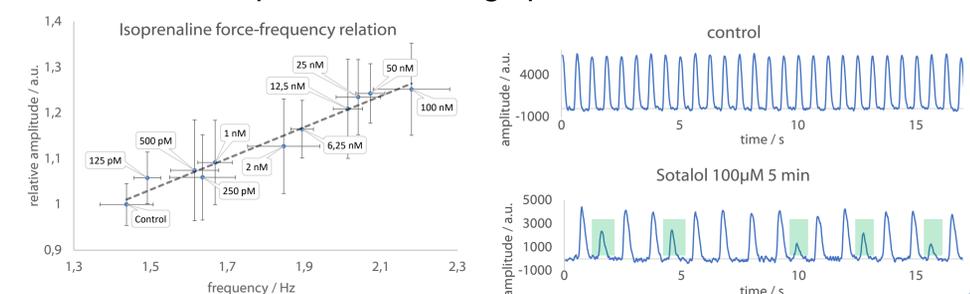
Our multiscale *in silico* model of the FLEXcyte 96 contains the electrophysiological cell model by Paci et al., which is combined with a reaction-diffusion equation to account for the propagation of the action potential in the tissue. The action potential dependent Ca^{2+} concentration is input to the mechanical cell model by Land et al., which computes the active stress during the contraction-relaxation cycle. The active stress is added to the passive stress to compute the deflection. Models of drug actions have been implemented and successfully tested against inotropic and chronotropic effects measured in the FLEXcyte 96 system.

Results

Isoprenaline and sotalol were selected to demonstrate two inotropic effects on stem cell-derived cardiomyocytes (Cor.4U, Ncardia). The recorded beats are shown on the right hand. Isoprenaline increases the contraction amplitude while shortening the total beat duration. On the opposite, the sotalol beat shows a decreased amplitude and a prolonged relaxation phase. An overview of the acquired parameters is given below.



Due to the physiological testing environment the positive force-frequency effect of isoprenaline is reflected as expected by the acquired data. In addition, arrhythmic events induced by sotalol can be detected and quantified with high precision.



Conclusion

The FLEXcyte 96 system provides a versatile tool to measure real contractility on 96 samples simultaneously. This enables to test the impact of drug candidates at early stages on human cardiac tissue. The multi-parameter analysis detects alterations in beating shape as well as frequency and arrhythmic events and provides a quantitative measure for these.

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