Cardiac Biowires mimicking Native Cardiac Bundles generated by Microfabricated Bioreactors

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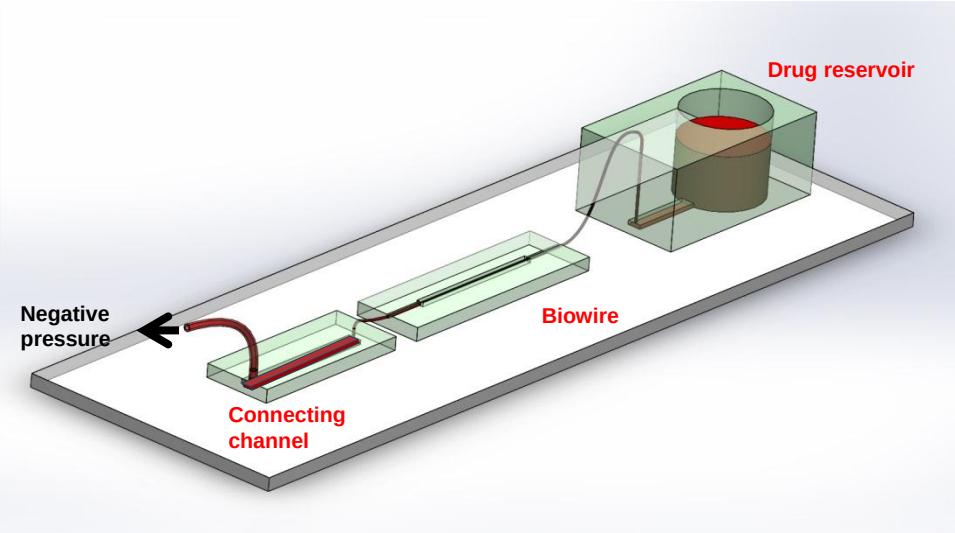
Introduction:

In the native myocardium, cardiomyocytes are grouped into cardiac bundles and this highly oriented cytoarchitecture is extremely critical for the impulse propagation and electromechanical coupling of cardiomyocytes. In current study, we designed a bioreactor to generate cardiac biowires that mimic both the structure and function of native cardiac bundles. The main hypothesis is that cardiac biowires would form around a suspended template by gel compaction and this platform would improve the alignment and maturation of cardiomyocytes within biowires. The ultimate goal is to provide perfusion through the cardiac biowires and develop a novel platform that better mimic native myocardium for drug testings.

Materials and Methods:

A two-layer polydimethylsiloxane (PDMS) device with a cell culture channel and template channels at both ends was fabricated by standard soft lithography. Either a 6-0 suture or a 44 AWG polytetrafluoroethylene (PTFE) tubing material was assembled into the template channel. Neonatal rat cardiomyocytes (CMs) were isolated and suspended in collagen-based hydrogel and then seeded into the cell culture channel. The CMs-gel composite was cultured in the bioreactor over 1-2 weeks with or without field electrical stimulation. The PTFE tubing was be connected to drug reservoir and negative pressure by add-on microchannels as shown in following figure. Perfusion through the PTFE tubing was driven by a miniature pump.



Results:

The CMs-gel composite compacted around the template around day 1-3 depending on the seeding density and dimension of the cell culture channel. The CMs started spontaneous beating around day 3-7. CMs nuclei were elongated and aligned along with the suture template and the CMs were further matured by parallel field stimulation with stronger mechanical properties characterized by AFM. The PTFE tubing template can be perfused by connecting to add-on drug reservoir and connecting channel. Nitric oxide released from sodium nitroprusside (SNP) can diffuse through the tubing wall and be detected within the cell culture channel.

Discussion:

Our microfabricated bioreactor can serve as a novel platform to study drug effects on CMs by perfusion through the central lumen, which better recapitulate the *in vivo* scenario. However, the tubing material could be further optimized as current PTFE tubing is non-porous, which renders limitation on the potential drug candidates for this platform. It would be most ideal if the tubing material is elastic so that the platform can provide electrical and mechanical stimulation at the same time.