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PHYSIOLOGICALLY RELEVANT PLATFORM FOR CARDIAC AND SKELETAL MUSCLE TISSUE INVESTIGATIONS AND DRUG SCREENING

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Introduction

New approach methodologies (NAMs) based on three-dimensional (3D) *in vitro* tissue models aim to overcome the limited physiological relevance of two-dimensional (2D) cell cultures and animal models in drug testing [1]. Although *in vivo* cardiac and skeletal muscle tissues are subjected to intense mechanical stimulation, primarily due to intrinsic contractile forces and external stretching, mechanical loading is still poorly mimicked in NAMs, which typically rely on simplified loading conditions [2]. In this context, we developed an automated bioreactor for delivering tunable, controlled, and physiologically relevant mechanical stimulation to multiple 3D cardiac and skeletal muscle tissue models, intended as a research and drug-testing platform.

Methods

The bioreactor (Fig. 1A) was designed to be compatible with standard 12-well plates, enabling the simultaneous culture of up to 12 hydrogel-based 3D constructs. Each construct embeds two posts (Fig. 1B), one rigid and one flexible, which are part of a patented support frame designed to facilitate construct handling and deliver passive and active mechanical stimulation [3]. The flexible post provides defined passive mechanical stimulation in response to construct contraction. The rigid post, whose displacement is controlled by an actuator connected to the support frame, delivers active stimulation, which can be isotonic, cyclic, or intermittent. Stretching waveforms can be tuned in terms of pre-strain (5-40%), strain (5-40%), and frequency (0.5-2.0 Hz). Components were prototyped by stereolithography using biocompatible and autoclavable resins (Formlabs 4B). Moreover, the deformation and flexural stiffness of the flexible post were characterized by finite element analysis (FEA, COMSOL Multiphysics) and experimental testing (n = 4, Mach-1 Biomomentum). For real-time monitoring of the mechanical response of the constructs, *ad hoc* strain gauges were designed and printed on the flexible post surface using Aerosol Jet Printing, followed by photonic curing. For preliminary biological experiments, aimed at assessing adhesion to the posts and tissue maintenance during culture (7 days), hydrogel-based constructs laden with stromal cells (HS-27A) were used.

Results

FEA results supported the preliminary selection of flexible post geometries, yielding strain distributions (Fig. 1C) and confirming flexural stiffness values within a physiological range for cardiac tissue (1.2-9.2 N/m [4]). Experimental tests resulted in a flexural stiffness of 2.8±0.3 N/m. Regarding the strain gauges, testing confirmed their printability on flexible posts and functionality, demonstrating the feasibility of real-time monitoring. Preliminary biological outcomes confirmed stable adhesion of the constructs to the posts and their proper remodelling over 7 days of culture. (Fig. 1D).

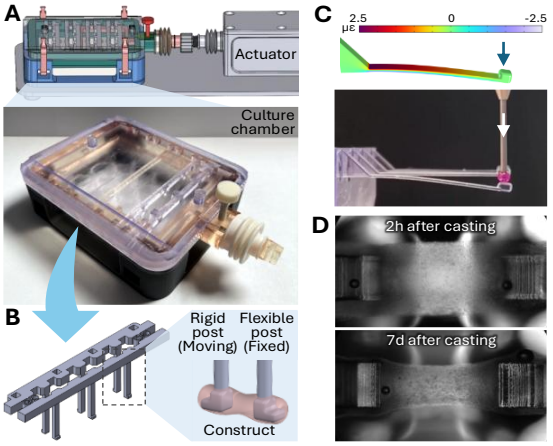


Figure 1: A. Bioreactor setup and picture of the culture chamber; B. Support frame and detail of construct and posts; C. FEA and experimental test of the flexible post; D. Construct remodeling after 2 h and 7 days of culture.

Discussion

These results attest the feasibility of a versatile research platform capable of delivering controlled and physiologically relevant mechanical stimulation to multiple 3D cardiac and muscle tissue models. This platform represents a valuable tool for cardiac and skeletal muscle research and drug screening. Notably, the ability to apply both passive and active mechanical stimulation extends beyond the capabilities of currently available commercial systems. Building on our recent evidence [5,6], future evolutions will focus on combined electro-mechanical stimulation to better replicate the *in vivo* microenvironment. Overall, the proposed platform will support the development of advanced NAMS by enabling in-depth investigation on cardiac and muscle tissue maturation, function, and response to drugs.

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