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Dynamic Mechanical Stimulation Platform for Microphysiological Vascular Tissue Models

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Abstract:
Next-generation organ-on-chip systems require precise biomechanical control to replicate native tissue microenvironments under pathophysiological conditions. This paper presents a pneumatically actuated microfluidic platform that applies programmable compressive stresses to three-dimensional vascularized tissue constructs. Engineered microvascular networks cultured within the device exhibit pressure-dependent histological responses, including stress-induced cell death zones, exponential reactive oxygen species generation, and compromised barrier integrity. Finite element modeling validates the mechanical stress distribution patterns, correlating with experimental observations of vascular permeability and junctional protein disruption. This microphysiological system enables quantitative investigation of compression-induced vascular pathogenesis, o*ff*ering a predictive tool for studying tumor microenvironment mechanics, hypertension-related vascular damage, and therapeutic safety evaluation of wearable medical devices. The platform establishes a foundation for integrating dynamic mechanical cues into vascularized organ-on-chip models for disease modeling and drug screening applications.

1. INTRODUCTION

In vivo, vascular endothelial cells are continuously exposed to mechanical stimuli such as shear stress, cyclic stretch, and external compression. These mechanical cues regulate vascular homeostasis, but abnormal mechanical loading can lead to pathological conditions including hypertension, atherosclerosis, and tumor-induced vascular collapse (11; 13). Blood vessels embedded within tissues experience compressive solid stresses from surrounding structures, which can restrict blood flow, induce hypoxia, and promote inflammation (10). De- spite its clinical relevance, the role of compressive stress in vascular dysfunction remains underexplored due to the lack of physiologically relevant in vitro models that replicate the three- dimensional (3D) architecture and mechanical microenvironment of vascular tissues.

Recent advances in microfluidic organ-on-chip technologies have enabled the development of perfusable 3D microvascular networks that mimic key aspects of human vasculature (16; 15). These platforms typically co-culture endothelial cells with stromal fibroblasts within extracellular matrix hydrogels to form lumenized, branched microvessels with barrier function and physiological permeability (8). However, most existing models lack integrated actuation mechanisms to apply con- trolled mechanical stresses, limiting their utility for studying compression-related vascular pathologies.

Pneumatically actuated microvalves, first introduced by Unger et al. (19), o*ff*er a versatile means of applying localized mechanical deformation within microfluidic devices. Known as Quake valves, these elastomeric polydimethylsiloxane (PDMS)-based valves have been used for flow control, cell isolation, and application of tensile strain (20). Their compatibility with soft lithography and optical transparency makes them suitable for integration into multilayer microfluidic tissue culture platforms.

This work introduces a novel multilayer microfluidic de- vice that incorporates pneumatically actuated chambers to apply compressive solid stress to 3D perfusable microvascular networks. The platform

enables real-time visualization of vascular deformation, quantification of cell viability, reactive oxy- gen species (ROS) production, and barrier integrity under con- trolled compressive loading. Finite element analysis (FEA) is employed to model stress distribution and validate experimental observations. By correlating mechanical input with biological output, this system provides a powerful tool for investigating compression-induced vascular injury, with potential applications in cancer biology, vascular disease modeling, and safety testing of wearable devices.

2. RELATED WORK

Recent advances in computational intelligence and adaptive systems o*ff*er valuable methodological parallels for enhancing the design and analysis of microphysiological platforms. Agarwal's work on *Visual Provenance: Adaptive Networks for Synthetic Content Detection* (7) demonstrates the use of lightweight deep learning architectures with attention mechanisms for feature extraction, an approach that could be adapted for automated analysis of vascular imaging data under com- pression. Similarly, the principles of *Adaptive Security Orchestration: Intelligent Policy Enforcement* (1) highlight the role of feedback-driven automation, which aligns with the need for real-time, adaptive mechanical stimulation in organ-on-chip systems.

In the domain of predictive modeling, Agarwal's *Reducing Variability through Adaptive Weighting for Reliable Predictions* (6) introduces methods for managing uncertainty—a challenge also relevant to biomechanical simulations where material properties and biological responses exhibit variability. The comparative study of text-embedding models (2) under- scores the importance of empirical validation in selecting optimal computational tools, a consideration equally critical when choosing constitutive models for finite element analysis of vascular tissues.

For classification tasks involving sparse or imbalanced data, such as rare vascular phenotypes, Agarwal's *Optimizing Classification of Infrequent Labels* (5) o*ff*ers strategies to improve performance through architecture design and knowledge trans fer. Furthermore, the evaluation of autonomous computational agents (4) provides insights into goal-oriented, multi-step reasoning that could inform the development of intelligent control systems for dynamic mechanical stimulation.

The generation of faithful explanations for model behavior, as explored in *Energy-Guided Counterfactual Generation* (3), is relevant to interpreting complex biomechanical outputs and ensuring the trustworthiness of simulation results. Lastly, Ku- mar's work on *Enhancing Web Accessibility for Mathematics Through Semantic Enrichment of MathML* (17) addresses the challenge of making technical content interpretable—a con- sideration for disseminating complex biomechanical data and models in an accessible manner.

Together, these studies illustrate a broader trend toward adaptive, explainable, and empirically grounded computational systems. Integrating such approaches into vascular mechanobiology could enhance the predictive power, usability, and translational relevance of microphysiological platforms like the one presented in this work.

3. DEVICE DESIGN AND FABRICATION

The microfluidic platform consists of two vertically stacked PDMS layers fabricated using multilayer soft lithography (19). The bottom layer contains the microvascular tissue culture region, while the top layer houses pneumatically actuated air channels. The two layers are separated by a thin PDMS mem- brane (70 µm thick) that deflects downward upon pressurization of the air channels, applying compressive force to the underlying vascular network.

The tissue culture layer comprises five parallel microchannels, each 800 µm wide and 70 µm high: a central channel for endothelial cell seeding, two adjacent stromal cell channels, and two outer media channels. The central and stromal channels are separated by arrays of microposts (100 µm gaps) that allow soluble factor exchange and endothelial cell sprouting while maintaining initial compartmentalization. This design enables the formation of a 3D perfusable microvascular network through vasculogenic self-assembly over 5–6 days of culture.

The pneumatic actuation layer contains air channels aligned above the central tissue channel. A CellASIC pneumatic pump system (Merck KGaA) regulates air pressure (0–2.5 psi) with

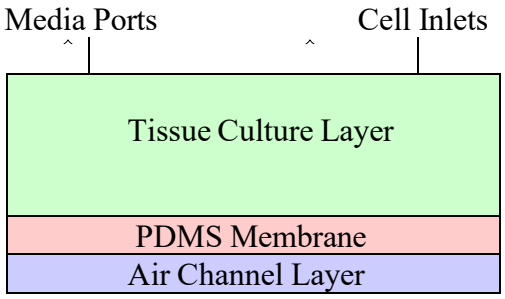

Figure 1: Schematic of the multilayer microfluidic device with integrated pneumatic actuation for applying compressive stress to 3D vascular networks.

Table 1: Material properties used in finite element simulations.

Material	Young's Modulus	Poisson's Ratio
PDMS	2.05 MPa (14)	0.49
Blood Vessel	90 kPa (18)	0.45

1-minute hold times for experimental consistency. The PDMS membrane deflection was calibrated using fluorescent dextran solution, showing pressure-dependent displacement correlated with FEA simulations (Fig. 1).

4. FINITE ELEMENT MODELING OF VASCULAR COMPRESSION

To predict the mechanical behavior of the PDMS membrane and vascular tissue under compression, nonlinear finite element analysis was performed using ABAQUS (Dassault Systèmes). The model comprised a rigid glass substrate, a cylindrical blood vessel (inner diameter 50 µm, wall thickness 2 µm), and a PDMS membrane (70 µm thick). The hydrogel-filled interstitial space was omitted due to its negligible mechanical contribution. Material properties are summarized in Table 1.

Simulations revealed that membrane–vessel contact initiates at 0.1 psi, with progressive vessel deformation leading to self- contact at 1.6 psi. Von Mises stress increased exponentially above 1.5 psi, reaching a maximum of 5.54 MPa at full com- pression (2.5 psi). The stress distribution patterns matched experimental observations of cell death and ROS induction, con- firming the role of high stress concentration in vascular injury (Fig. 2).

5. EFFECTS OF COMPRESSION ON MICROVASCULAR FUNCTION

The functional consequences of compressive stress were assessed through perfusion assays, viability staining, ROS quantification, and permeability measurements. Perfusion with 7 µm microbeads revealed

complete flow obstruction at 1.5 psi, with bead accumulation in compressed regions (Movie S3). Upon pressure release, perfusion resumed, indicating reversible vessel collapse without permanent blockage.

Cell viability remained high (96%) up to 1.5 psi but dropped sharply at higher pressures (66.9% at 2.0 psi, 40.3% at 2.5 psi). Dead cells formed spatial patterns aligned with the sagittal axis of compression, correlating with FEA-predicted high- stress zones. Calcein-AM staining confirmed that cell death resulted from direct mechanical crushing between the PDMS membrane and glass substrate.

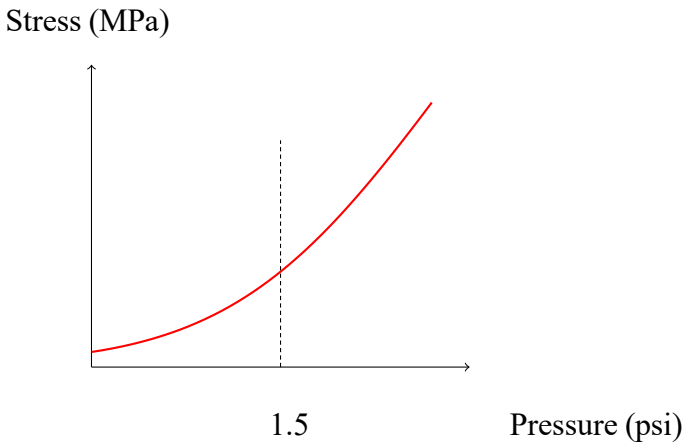

Figure 2: Finite element analysis showing nonlinear increase in von Mises stress with applied pressure. Dashed line indicates onset of severe vascular deformation.

ROS levels increased exponentially with pressure, rising 6.75-fold at 1.5 psi, 12.1-fold at 2.0 psi, and 28.63-fold at 2.5 psi compared to controls. This surge indicates oxidative stress induction, a known mediator of endothelial dysfunction in hypertension and diabetes (12). The abrupt rise beyond 1.5 psi aligns with the FEA-predicted stress threshold for severe vascular deformation.

Vascular permeability, assessed using 20 kDa FITC-dextran, increased significantly at 1.5 psi (4.44×10^{-7} cm/s) com- pared to controls (4.78×10^{-7} cm/s). Immunostaining for VE- cadherin revealed discontinuous junctional staining under com- pression, suggesting adherens junction disruption as a mechanism for barrier compromise (9). These findings highlight the dual impact of compression: direct physical damage and mechanotransduction-mediated barrier dysfunction.

6. DISCUSSION

The developed platform successfully reconstitutes key aspects of compression-induced vascular injury observed in vivo, including vessel collapse, endothelial cell death, oxidative stress, and barrier disruption. The integration of pneumatic actuation with 3D microvascular culture enables precise control over mechanical input and quantitative assessment of biological responses, o*ff*ering advantages over traditional monolayer or ex vivo models.

The observed threshold behavior around 1.5–2.0 psi suggests a critical stress level beyond which vascular integrity is rapidly compromised. This may have clinical relevance in conditions such as tumor growth, where solid stresses can exceed 1.5 kPa (13), or in external compression from tight clothing or medical devices. The platform could be used to establish safety thresh- olds for wearable technologies by correlating applied pressure with cellular damage.

The correlation between FEA predictions and experimental outcomes validates the use of computational modeling to guide device design and interpret biological results. Future iterations could incorporate patient-specific vascular geometries or disease-specific cells to create personalized models of vascular compression.

Limitations include the use of static compression rather than cyclic loading, which may better mimic physiological conditions such as pulsatile tissue pressure. Additionally, the current model does not include immune cells or smooth muscle cells, which modulate vascular responses to mechanical stress. Future work will integrate these elements to create more comprehensive vascular models.

7. CONCLUSION

This study presents a pneumatically actuated microfluidic platform for applying controlled compressive stresses to 3D perfusable microvascular networks. The system mimics key aspects of compression-induced vascular injury, including cell death, ROS generation, and barrier dysfunction, with responses validated by finite element modeling. This platform provides a versatile tool for studying vascular mechanobiology in contexts such as tumor microenvironment, hypertension, and medical device safety. By bridging mechanical engineering and vascular biology, it advances the development of physiologically relevant organ-on-chip models for disease research and therapeutic testing.

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