A CellDrum™ Based Aortic Co-Culture for Quantifying Vasoactive Agent Efficacy

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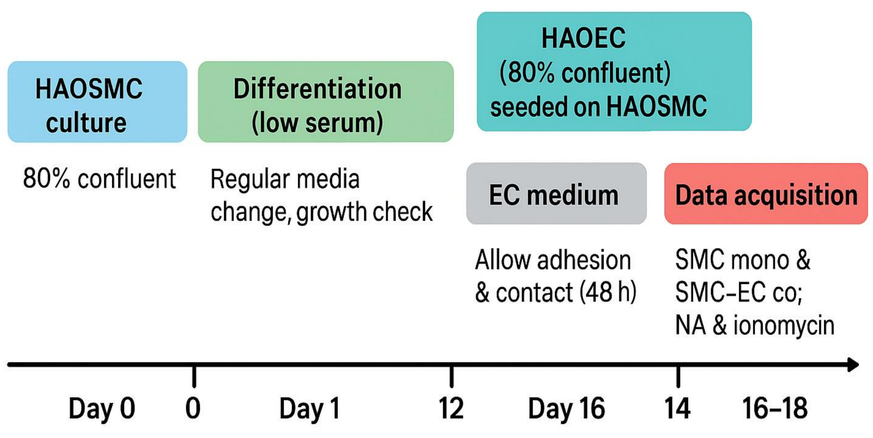
Abstract: The assessment of tensile forces in cell layers and tissues is essential for drug development. Traditionally, such analyses were performed on animal vascular ring explants. A quantitative in vitro co-culture model of primary human aortic smooth muscle cells (hAOSMC) and endothelial cells (hAOEC) was established using CellDrum™ technology in combination with the Cell Force Analyzer (CFA_{refer}) to quantify substance-induced or relaxed cellular tensile forces. hAOSMC were cultured on flexible CellDrum™ membranes, differentiated for eight days, and subsequently co-cultured with hAOEC for two days. Confocal imaging confirmed the layered, confluent structure. The effects of **norepinephrine** (NA) and the calcium ionophore ionomycin were analyzed in hAOSMC monolayers and co-cultures. In hAOSMC monolayers, NA increased tensile tension by 16.9% (EC50: 100.7 nM), whereas in co-cultures it induced relaxation (−12.6%, EC50 not applicable). Ionomycin increased monolayer tension by 10.9% (EC50: 11.44 nM) but showed an amplified effect in co-cultures, reaching up to 60% above control (EC50 <1 nM). The NA-induced relaxation is attributed to stimulation of endothelial α_2-adrenoceptors and nitric oxide release. These findings demonstrate that cellular interactions strongly influence drug responses, underlining the value of CellDrum™ based co-culture models for pharmacological testing.

MATERIALS

- Primary Aortic Smooth Muscle Cells- ATCC
- Primary Aortic Endothelial Cells- ATCC
- Ionomycin Calcium Salt- Sigma Aldrich
- -(-) Norepinephrine- Sigma Aldrich

METHODS



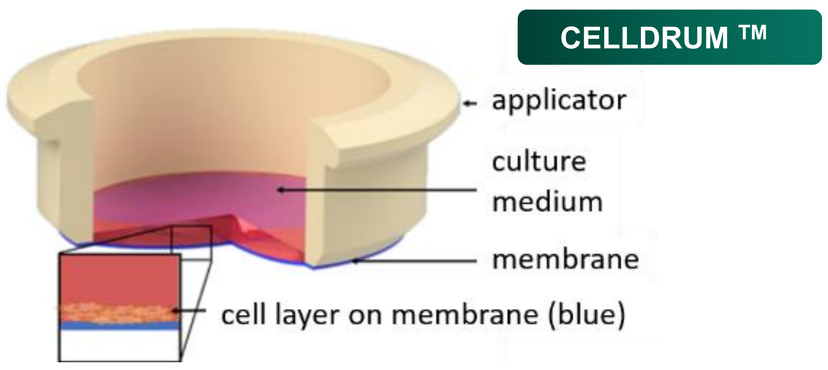
Baseline (negative control) for both conditions
Standard medium, 3-6 technical replicates/sample

1. NA stimulation

- 100–200–300–400–500 nM
- 3 min incubation → measurement
- 4-6 technical replicates per concentration
- Cumulative dosing (stepwise ↑ conc.)
- Fresh medium between steps

2. Ionomycin stimulation

- 1–10–100–1000–10000 nM
- Immediate measurement post-addition
- 4-6 technical replicates per concentration
- Fresh medium between steps



RESULTS

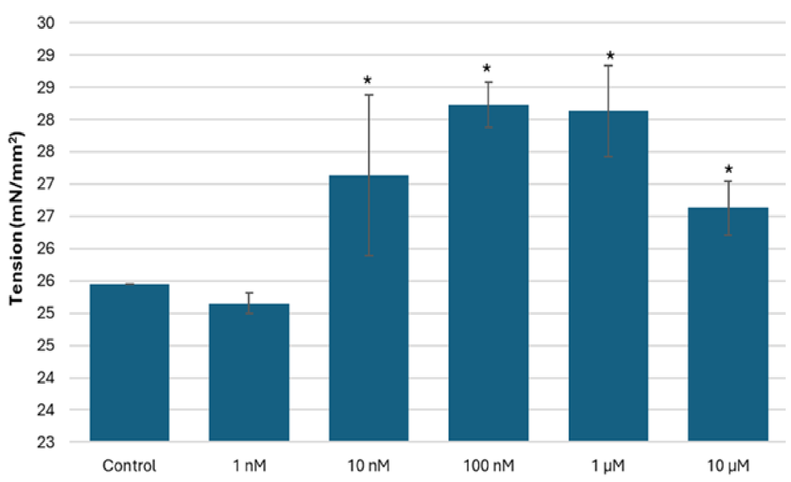


FIGURE 1: Ionomycin concentration vs tensile tension measurements (mean ± SEM) with HAOSMC on CellDrums.

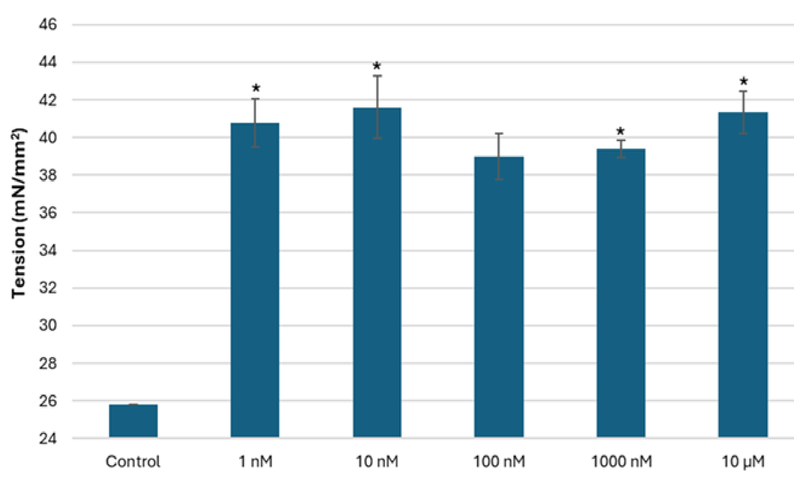


FIGURE 2: Ionomycin concentration vs tension measurements (mean ± SEM) with HAOSMC-HAOEC co-culture on CellDrums.

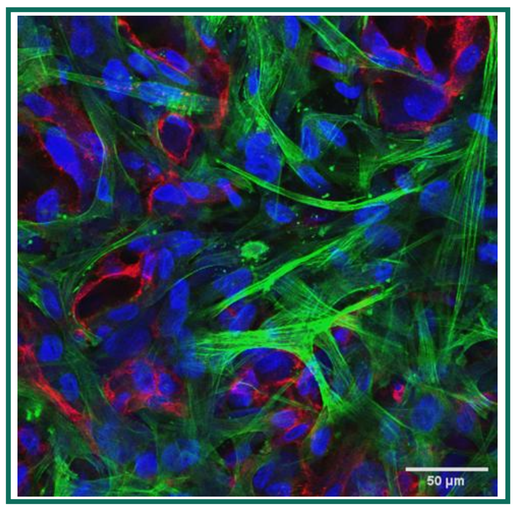


FIGURE 3: Co-culture of HAOSMC- HAOEC on CellDrums stained with CD31 antibody, a-Smooth Muscle Actin Monoclonal Antibody - , and Höchst nuclear staining.

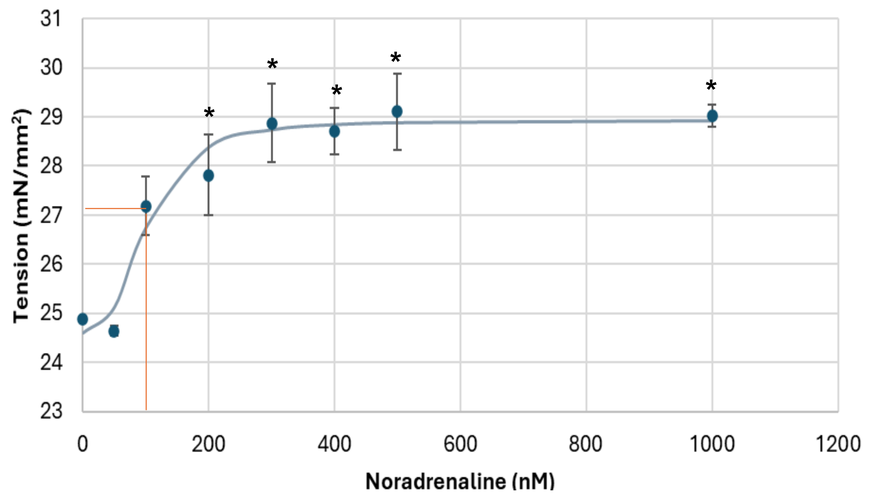


FIGURE 4: Noradrenaline concentration vs tension measurements (mean ± SEM) with HAOSMC monolayers on CellDrums. The *EC50* calculated from the fit is 100.70 nM (red line).

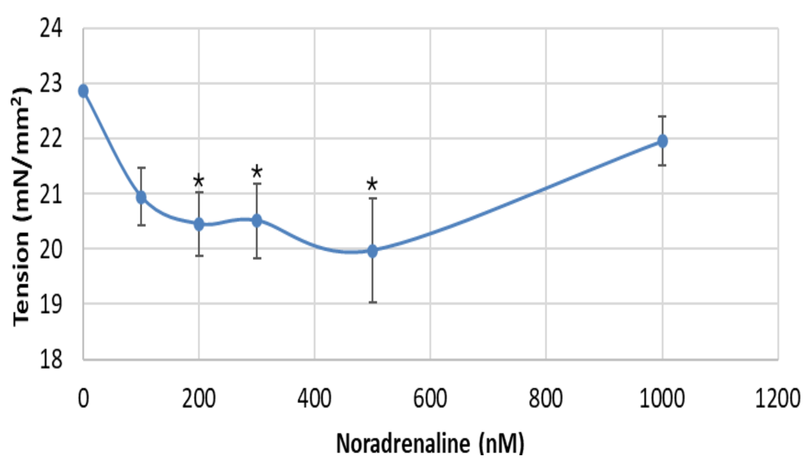


FIGURE 5: Noradrenaline concentration vs tension measurements (mean ± SEM) with HAOSMC- HAOEC co-cultures on CellDrums.

CONCLUSION

Our study shows that endothelial-smooth muscle interactions can fundamentally alter drug responses, converting noradrenaline-induced contraction in hAOSMC monolayers into relaxation in co-cultures, and greatly enhancing the contractile effect of ionomycin. These findings highlight the critical role of cellular context in vascular drug responses. By capturing these interactions, the Cell Force Analyzer (CFA_{refer}) with CellDrum co-cultures offers a human-relevant platform for studying vascular mechanobiology. This approach enables more accurate prediction of drug effects, reduces reliance on animal tissue models, and supports the development of safer and more effective cardiovascular therapeutics.

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