MICROFLUIDIC PLATFORM FOR INVESTIGATING SMALL BLOOD VESSELS

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ABSTRACT

Small resistance arteries are important mediators of peripheral vascular resistance, and by extension hypertension. Current methods for small blood vessel investigation however are tedious and not scalable. We have designed, fabricated and tested a versatile microfluidic device to study resistance artery structure and function and potentially long-term culture. The presented scalable platform may ultimately accelerate the development of antihypertensive drugs.

KEYWORDS: Small resistance arteries, hypertension, cardiovascular, microfluidic platform for blood vessels

1. INTRODUCTION

Small resistance arteries (SRAs), with diameters between 60 - 250μm, are crucial components of the cardiovascular system, and through dynamically changing artery diameter (tone), play a key role in regulating peripheral vascular resistance, an important factor in the development of hypertension [1]. The current understanding of small artery structure and function is limited by a lack of experimental tools for probing them. Traditional methods employed to study 1-2mm segments of resistance arteries excised from mice are expensive, time-consuming, and are conducted manually, requiring highly specialized training. Despite the clinical and economical importance of cardiovascular diseases, the development pipelines of major pharmaceutical companies currently lack innovative antihypertensive drugs.

We present a microfluidic device that allows functional and structural assays to be conducted on small blood vessels, while overcoming the aforementioned limitations.

2. EXPERIMENTAL

The microfluidic device was fabricated using standard multilayer soft-lithography techniques. Figure 1 illustrates key device features of the device. An approximately 1mm long resistance artery segment is introduced through a 5mm diameter loading well. Pressure-driven flow is used to guide it through the loading channel (labelled A) to the inspection area. The artery is then spatially fixed by applying suction pressures at locations "E" close to its end points. Subsequently, the center of the artery segment is subjected to a microenvironment mimicking physiological conditions by simultaneously superfusing the outer vessel wall (B→C), perfusing the inside vessel lumen (A→D) and applying a defined pressure difference across the vessel wall

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(transmural pressure). Unwanted crosstalk between the two streams is completely prevented by the fixation channels (E), which was simulated using a multiphysics analysis package (Comsol, Fig. 2) and experimentally verified using fluorescence microscopy. The artery temperature, transmural pressure as well as the flow rates and compositions of the superfusing/perfusing streams can be adjusted.

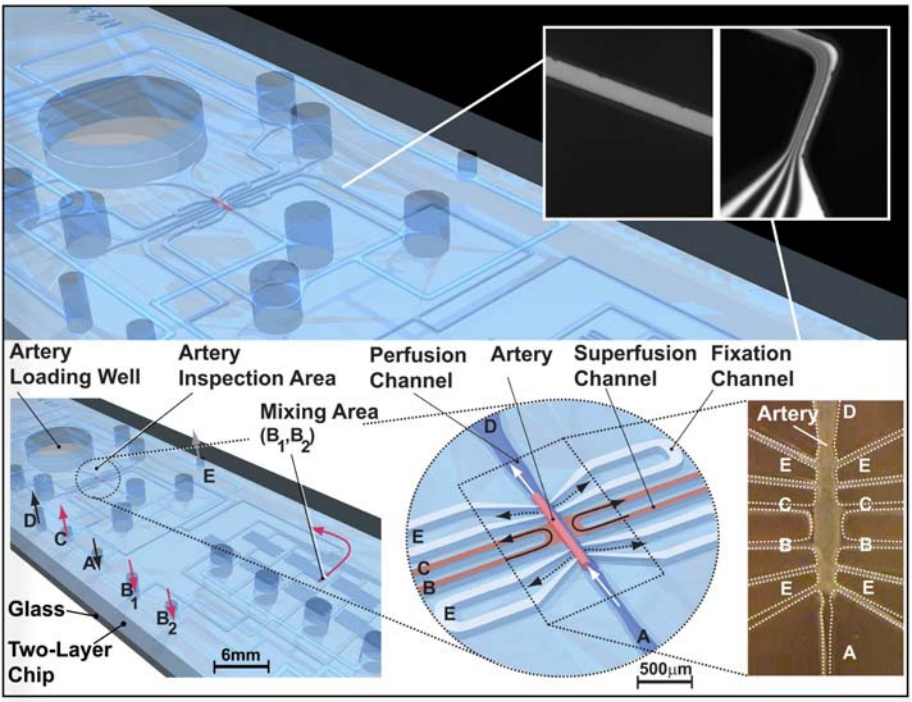

Figure 1: *Rendered device image with perfusion inlet (A) and outlet (D). The superfusion inlet consists of a drug-containing stream (B_1) that interdiffuses with stream (B_2), passes the outer wall of a loaded mesenteric artery and leaves through port (C). Ports (E) allow fixation of the artery segment and prevent unwanted cross-talk*

3. RESULTS AND DISCUSSION

The mircofluidic device was assessed by loading mesenteric arteries from mice, and performing functional assays to determine vessel viability after loading. Two individual feed streams (B_1 and B_2) were mixed on chip. By changing the relative flow rates of the feed streams via computer-controlled syringe pumps, the concentration of active substances in the resultant superfusion was selected, and the dynamic evolution of artery tone was recorded on an inverted microscope. An aggregate dose-response curve for phenylephrine (PE), a vaso-constrictor which acts on the smooth muscle cells of blood vessels, was derived from multiple sets of time-resolved bright-field measurements demonstrating viability of the vessel after loading (Fig.3a). Aggregate vessel response obtained with the microfluidic platform (Fig. 3b,c) was consistent with measurements obtained in conventional cannulation systems [2,3]. The presented microfluidic chip provides a versatile platform that can be easily adapted to a variety of animal-derived small resistance arteries. This scal-

able chip-based approach may allow standardization in microvascular research by replacing the current manual approaches and potentially accelerates the discovery of antihypertensive drugs.

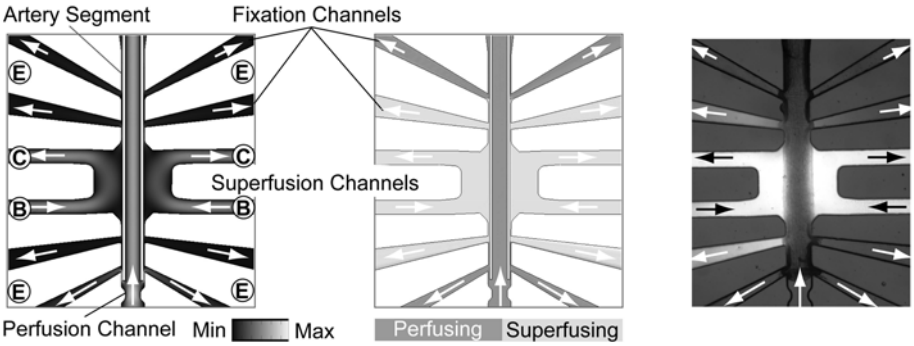

Figure 2. *Numerically obtained velocity (a) and concentration field (b) indicating the complete separation of the perfusing and superfusing streams. (c) Fluorescence micrograph with a fixed and pressurized blood vessel segment (superfusing stream fluorescently labelled) confirmed the complete separation of the two streams*

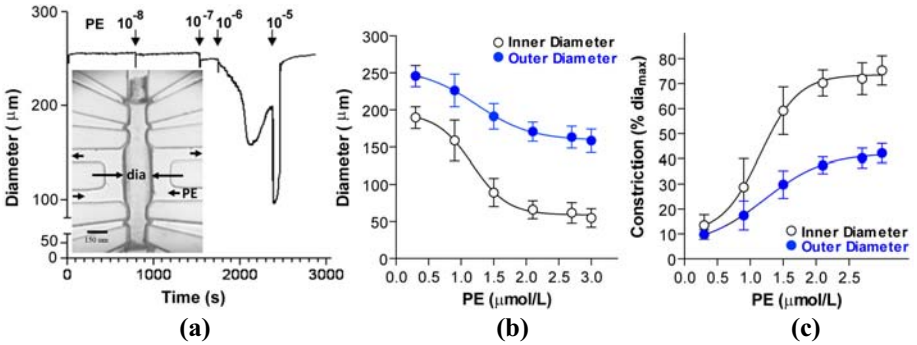

Figure 3. *(a) Single representative measurement of the artery diameter (tone) in response to step changes in the concentration of phenylephrine (PE) in the superfusing stream, and (b,c) aggregate dose response curves*

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