Biomimetic pulsatile flows through flexible microfluidic conduits

Cite as: Biomicrofluidics 13, 014103 (2019); doi: 10.1063/1.5065901

Submitted: 11 October 2018 · Accepted: 17 December 2018 ·

Published Online: 8 January 2019

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ABSTRACT

We bring out unique aspects of the pulsatile flow of a blood analog fluid (Xanthan gum solution) in a biomimetic microfluidic channel. Pressure waveforms that mimic biologically consistent pulsations are applied on physiologically relevant cylindrical microchannels fabricated using polydimethylsiloxane. The *in vivo* features of the relevant waveforms like peak amplitude and diastolic notch are reproduced *in vitro*. The deformation profiles exhibit viscoelastic behavior toward the end of each cycle. Further, the time-varying velocity profiles are critically analyzed. The local hydrodynamics within the microchannel is found to be more significantly affected by pressure waveform rather than the actual wall deformation and the velocity profile. These results are likely to bear far-reaching implications for assessing micro-circulatory dynamics in lab on a chip based microfluidic platforms that to a large extent replicate physiologically relevant conditions.

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I. INTRODUCTION

Starting from the pioneering attempts by William Harvey¹ on the study of microcirculation, dynamics of blood flow in the circulatory network has been an intriguing topic for both scientists and engineers. After the seminal contribution by Poiseuille in the Hagen-Poiseuille flow,² Womersley proposed the mathematical foundation for the pulsatile flow under a time-varying pressure field and evaluated the resulting velocity in a rigid tube.³ Concurrently, Otto Frank formulated the Windkessel theory that considers the wall compliance, accounting for the elastic nature of the arterial vessel.⁴

Even though an *in vivo* investigation is ideal in experimental biofluid mechanics and for probing patient-specific diseased conditions, *in vitro* models are extensively used because of the ease of experimentation, control over parameters, accessibility to minute details, and ethical considerations limiting animal and human trials.⁵ With the emergence of advanced fabrication technologies like soft lithography, miniaturized *in vitro* systems are now common, and channels up to a nanometer scale can be fabricated.⁶ Promisingly, researchers have fabricated microchannels with confluent endothelial

cells cultured on the channel wall to investigate the impact of wall shear stress on the cell morphology and the resulting mechanotransduction.^{7–10} Despite such advantages, major challenges still lie in mimicking realistic blood circulation in an *in vitro* system in terms of addressing the deformability of the vessel wall, the pulsating nature of the flow, and the complex nature of the fluid itself.

In the literature, a large number of investigations on the fluid-structure interaction (FSI) in physiological flows have been reported.^{5,11} Of particular emphasis has been the role of the deformable walls.^{12–16} In addition to the attempt of mimicking an *in vivo* behavior, wall deformation in an *in vitro* system may be exploited in several practical applications like mixing,¹⁷ flow stabilization^{18,19} pumping,²⁰ fluidic diodes,²¹ valves,²² droplet generation,²³ optoelectronic sensors,²⁴ and artificial cilia.²⁵ Recent experimental attempts have also investigated pulsatile flows in microchannels, drawing analogies with electronic circuits.^{26–29} The highly pragmatic analogy of the electronic components like resistor and capacitor to hydraulic resistance and compliance in a fluidic system simplifies the design and analysis of miniaturized

on-chip logic systems³⁰ and smartphone operated microfluidic platforms.³¹

Despite the existence of benchmark models in fluid-structure interaction mediated by Newtonian fluids,^{32,33} reported experimental research on time varying flow of complex biofluids through flexible microfluidic conduits is rather scarce. Birkhofer *et al.* have studied the flow of a power law fluid in a flexible tube of 16 mm inner diameter using ultrasound Doppler velocimetry.³⁴ Nahar *et al.* have studied the time-varying flow of a shear thinning fluid in a collapsible vessel of inner diameter 20 mm, similar to a Starling resistor in a pressure chamber.³⁵ However, pulsatile fluid dynamics of blood in flexible microfluidic conduits is yet to be reported.

With the motivation of addressing the issues in the existing experimental paradigm of interaction between pulsatile blood flow dynamics and the deformation of a biomimetic microfluidic conduit, we have conducted controlled experiments in physiologically relevant cylindrical microchannels with varying softness under pulsatile flow conditions. A frugal pull out soft lithography technique is employed to fabricate cylindrical microchannels of size comparable to arteries. For mimicking the non-Newtonian nature of the blood flow, popular blood analog fluid Xanthan gum (XG) solution is used. A pulsatile waveform is used to mimic biophysically relevant systems, and a high-speed data acquisition system was utilized to identify the finer aspects of the time-varying pressure field combined with a peak finding algorithm. Further, micro-PIV (particle image velocimetry) and phase contrast microscopy are employed to evaluate the flow field and wall deformation. The detailed information obtained from our engineered model holds promises of providing cues toward a fundamental understanding of diseased conditions originating out of a malfunctioning micro-circulatory system.

II. EXPERIMENTAL METHODS

We have fabricated the microchannels by employing a pull out soft lithography process using lumbar puncture (LP) needles (Comet India, nominal diameter = 510 μm) as the mold. To fabricate channels of different softnesses, polydimethylsiloxane (PDMS; Sylgard 184, Dow Corning, Midland, MI, USA) was used with varying base to cross-linker ratios. For the present experiment, microchannels of two different elastic moduli (E) values were fabricated using base to cross-linker ratios: 10:1 (CH10 channel) and 30:1 (CH30 channel). The values of E were estimated to be 2.801 MPa for CH10 and 0.157 MPa for CH30 using standard tensile testing equipment (Hounsfield). After thoroughly mixing the base polymer and the cross-linker, the PDMS mixture was poured over the needle mold housed in a rectangular brass cavity with the bottom kept open for optical access. After curing it in a hot air oven at 95 $^{\circ}\text{C}$ for 12 h, the needle mold is gently pulled off from the PDMS leaving the microchannel in the PDMS block. The inlet, outlet, and pressure sensor ports were connected to the brass cavity using hollow metallic needles.

Deionized (DI) water (Milli-Q, Millipore India) was used as the Newtonian fluid. Xanthan gum (XG) based solutions are

the best choice for non-Newtonian blood analog fluids.^{36–38} It can cover a wide variety of hematocrit and the viscosity values that match with the real blood. An aqueous solution of XG (Sigma-Aldrich) (0.04% w/w) was used as the non-Newtonian fluid in the present experiment. A rheometer (Anton Paar Physica D) with a cone and plate geometry was used to characterize the properties of the non-Newtonian fluid. The test was conducted for increasing shear which provided the variation of viscosity versus shear rate. A power law model: $\mu = m(\dot{\gamma})^{n-1}$ was fit into the experimental data, where $\dot{\gamma}$ is the shear rate and μ is the apparent viscosity. Using regression analysis, the power law coefficients were estimated to be $m = 40 \times 10^{-3} \text{ Pa s}$ and $n = 0.595$.

To achieve a time-varying flow in our experiments, we have used a syringe pump (Harvard PHD 2000) and a solenoid pinch off valve (Cole-Parmer). The syringe pump pumps at a constant flow rate by mechanically pushing the plunger of a fluid-filled 20 ml syringe at a steady rate. The tube that connects the microchannel inlet and the syringe pump has a small section of flexible Tygon[®] tubing which is inserted into the solenoid pinch off valve. Due to the plunging action, the tubing is pinched momentarily, producing a pulsed flow in the circuit. The plunger in the valve is actuated using a 6V_{pp} (peak-to-peak voltage) square waveform of 50% duty cycle with the desired frequency sourced from a function generator (Agilent 33220A). The differential pressure drop (ΔP) across the microchannel length is measured using a differential pressure sensor (Honeywell FDW). A data acquisition system [DAQ (NI 6009, National Instruments)], which is interfaced with the Lab PC running Labview (National Instruments) program, acquires the raw voltage from the pressure sensor at a sampling rate of 1 kHz and converted to physical units based on the instrument calibration chart within the program. The waveforms generated in each experiment are post-processed in MATLAB (Mathworks, USA) to derive the parameters like amplitude and frequency and other features like the peaks and notches. For commonly used rectangular glass-PDMS microchannels, indirect methods are generally used for estimating the deformation of the top wall.¹⁴ Since the present configuration is axisymmetric, the wall deformation can be observed directly under a microscope in the phase contrast mode. The region of interest (ROI) for observing the wall deformation and flow visualizations fixed at half of the axial length of the microchannel (at $z = L/2 = 13.5 \text{ mm}$, where $z = 0$ is the inlet). A high-speed camera (Phantom v741, AMETEK, USA) is attached to the microscope to capture the wall deformation in real-time. The pressure sensor, high-speed camera, and the solenoid valve actuation are triggered in a synchronized manner with a transistor-transistor logic (TTL) signal output from the Labview interface for simultaneous measurement. An in-house MATLAB code is developed to analyze the time-varying deformation using an edge-detection algorithm. Figure 1 shows the schematic of the experimental setup and representative waveforms. A summary of the experimental parameters is summarized in Table I.

For flow visualization, a commercial micro-PIV apparatus (TSI) is utilized. Polystyrene beads of 1 μm diameter

FIG. 1. (a) Experimental setup indicating the solenoid valve actuation using a function generator, the pressure measurement system, and the DAQ. A cross-sectional schematic in the transverse plane is also shown. (b) Typical waveforms of the applied voltage to the function generator, pressure gradient, and the deformation of the channel at the center.

(Sigma-Aldrich) with an excitation/emission wavelength of 542/612 nm are used as the seeding particle. The dual pulsed green laser with a wavelength of 532 nm and a pulse rate of 15 Hz is employed to capture the frames at 2048×2048 pixel resolution. During imaging, frame straddling technique is employed to achieve time interval (Δt) as small as $10 \mu s$. An iterative multi-pass cross-correlation algorithm with a final sub-window size of 32×32 pixel with an overlap of 50% is chosen to evaluate the final velocity field. Phase averaging over ten cycles is analyzed for each run of the experiment.

III. RESULTS AND DISCUSSIONS

In the present experiment, CH10 is considered as a non-deformable microchannel, whereas CH30 is considered deformable.¹⁴ The time-varying pressure drop is plotted in Fig. 2 for all the four cases for a constant base flow rate of $Q_{base} = 500 \mu l/min$ and an excitation frequency of 1 Hz and 2 Hz. The frequency of the pressure wave is computed using a power spectrum analysis and found to be exactly the same as the frequency of the applied pulse (electrical waveform from a function generator). The fluid response is effected without any delay in the system, which was verified by a direct comparison of the two waveforms in the Labview interface.

TABLE I. Experimental parameters.

Quantity	Value/range	Expression/unit
Diameter (D)	510 ± 5	μm
Length (L)	27	mm
Flow rate (Q)	500	$\mu l/min$
Reynolds number (Re)	40	$\frac{\rho U D}{\mu}$ (Dimensionless)
Pulsation frequency (ω)	0–2	Hz
Womersley number (Wo)	0–2.17	$\frac{D}{2} \sqrt{\frac{\rho \omega}{\mu}}$ (Dimensionless)

The rise in the pressure is very fast, and the peak is attained within the $1/10$ th time of the cycle. Though the initial response is very similar, there is a clear difference in the waveforms attributed to the variation in both solid and fluid parameters. Both the peak pressure and mean pressure is higher for XG than DI for both CH10 and CH30. For CH10, an interesting physiologically relevant feature, namely, the dicrotic notch associated with the closing of the aortic valve in *in vivo* systems, is clearly visible after the waveform peak which can be identified by a peak finding algorithm.³⁹ Previous studies could not identify such features due to a lower sampling frequency of the pressure waveform.²⁷ This is the first time the dicrotic notch in an *in vitro* system reported in an experimental microfluidic system. Here, the notch is the direct consequence of the wave reflection from the outlet of the microchannel which is a pressure traveling in the opposite direction of the fluid flow. Even though CH30 does have a slight deviation from the decay after the peak, it does not qualify as a notch in the peak finding algorithm and hence not detected. The absence of the notch is because of the damping effect imparted by the deformable wall that acts as a flow stabilizer.^{18,19}

Figure 3 shows the mean and peak values of the pressure waveforms. Error bars denote the standard deviations of measurements from three separate microchannels. Comparing the peak magnitudes for both frequencies, for the case of DI, the softness of the channel walls does not affect the peak magnitudes, and the values are closer for CH10-DI and CH30-DI. However, the same comparison done for XG shows that the peak magnitudes are higher for CH30 than CH10. This is an indication that the blood-mimicking fluid enhances the peak fluid pressure for a pulsatile flow inside the softer channel despite the shear thinning effect. This is likely due to the added reflection from the stored fluid in each cycle. Since the deformation is lesser in DI, the stored fluid is also less and

FIG. 2. Time-varying pressure drop for a base flow rate of $Q_{base} = 500 \mu\text{l/min}$ for (a) 1 Hz and (b) 2 Hz for CH10 and CH30 for de-ionized water. CH10 is the non-deformable, and CH30 is the deformable microchannel. (DI) and Xanthan Gum (XG). The waveform is plotted after the system attained a steady state. The inset shows the region near the micrototic notch.

does not significantly affect the peak pressure. Furthermore, it refers to a fluidic capacitor in the hydraulic analogy. The peak pressure is lower for all the cases in 2 Hz than 1 Hz indicating larger stored fluid for the lower frequency of the pump operation. It is noteworthy that in the current experimental system, the maximum flow velocity in the channel is far lower than the pulse velocity. This follows from the Moens-Korteweg (MK) wave equation which gives the wave speed (c) in a flexible tube as $c = \sqrt{\frac{Eh}{2\rho R}}$, where h is the thickness of the tube, ρ is the density of the fluid, and R is the radius of the tube.⁴⁰ Clearly, c is lower for soft tubes with a lesser E , and this principle is further used to measure the wall stiffness in *in vivo* systems non-invasively.

The deformation profile of the channel wall $[\delta(t)]$ at the ROI for deformable channel CH30 is plotted in Fig. 4. Since there is no visible deformation in CH10, it is not plotted.

It shows a similar pattern of the pressure waveform, a peak and a subsequent decay. The highest deformation is for XG for 1 Hz, and the lowest is for DI for 2 Hz. The position of the peak is delayed from that of the pressure waveform peak. This is due to the inertia of the solid wall in response to the rise in the fluid pressure in the channel. Further, there is an expected delay due to the location for probing deformation being at the center. Interestingly, the peak is at 1/30th of the total cycle time for both 1 Hz and 2 Hz and indicates that the relative time for the wall response is not affected by the frequency of pulsation. The initial rise is linear, and then after a linear fall, it is followed by an exponential decay to the undeformed diameter. The delay compared to the fluid wave peak is due to the inertia of the solid wall. The maximum deformation is higher for XG compared to DI for the CH30 channel. This implies that the blood-analog fluid has enhanced the fluid loading on the walls. The maximum deformation in

FIG. 3. Mean and peak pressure drop for a base flow rate of $Q_{base} = 500 \mu\text{l/min}$ for (a) $\omega = 1$ Hz and (b) $\omega = 2$ Hz for CH10 and CH30 for DI and XG. Error bars denote the standard deviations of measurements from three separate microchannels.

FIG. 4. (a) Time-varying deformation profile of the wall for CH30 at the ROI ($z = 13.5$ cm). (b) Mean and peak values of deformation for various cases.

the pulsatile flow is $17\mu\text{m}$ which is 3% of the undeformed channel diameter. The same microchannel under a steady flow [without any pulsation ($\omega = 0$)] with the same base flow rate exhibited a deformation of $4\mu\text{m}$.³⁸ However, it will significantly affect the hydraulic resistance of the channel. It is important to note here that inertial effects are likely to be consequential for hollow cavity channels, which may not be important in a thin-walled tube with considerably lesser solid material resisting the pulsations. Further, there is a signature of the viscoelasticity of PDMS, resulting in the nonlinear deformation toward the end of the cycle. The viscoelastic nature of PDMS has been previously studied in microchannels.^{41,42} We hypothesize that for highly accurate prediction of the deformation in a pulsatile flow, the viscoelastic behavior of the material needs to be accounted for. Another interesting point is that the effect of the dicrotic notch is not reflected in the deformation profile. Since it is primarily the result of the pressure pulse and its reflection in the fluid, it is dissipated in the bulk of the fluid, and no effect has reached the wall.

Next, we look into time constant (τ) of the decays from both the pressure waveform ($\tau_{\Delta P}$) and the deformation profile (τ_{δ}) as given in Fig. 5. τ is evaluated by curve fitting an exponential curve on the experimental waveform profile. Theoretically, it gives the time required to reach 36.8% of the initial magnitude, in this case, from the peak amplitude. This can further aid in the electronic analogy models by serving as the RC time constant.²⁷ For all the cases, τ_{δ} is more than $\tau_{\Delta P}$, indicating a larger response time from the solid wall than the flowing fluid. Further, XG has a lower time constant for both frequencies. It is also interesting to note that though there is a remarkable difference among peak amplitude (almost double), the time constants stayed nearly the same with a change in frequency. Furthermore, the ratio $\tau_{\Delta P}/\tau_{\delta}$ is 0.61 for DI and 0.38 for XG, indicating that the higher viscosity is offering a comparably larger resistance to the pulse propagation. It can also be seen that τ_{δ} of XG is of the same order of $\tau_{\Delta P}$ of DI for both frequencies. Incidentally, it points out to the fact that the time constants can be tuned by

changing the frequency to match the pulsatile characteristics of solid and fluid in the same channel. This will have significant consequences while designing microfluidic systems with deformable elements based on timing operation and network systems, especially in wearable electronics with flexible sensors.⁴³ The response time can directly affect the sensor response and thereby affect the actuation under consideration.

In a rigid tube of radius R , the pulsating velocity profile $u(r, t)$ for a Newtonian fluid in the axial (z) direction is given by the Womersley solution, which is given by⁴⁴

$$u = u(r, t) = \frac{A}{i\omega\rho} \left[1 - \frac{J_0\left(i\sqrt{\frac{\omega\rho}{4\mu}} \frac{r}{R}\right)}{J_0\left(i\sqrt{\frac{\omega\rho}{4\mu}}\right)} \right] e^{i\omega t}.$$

FIG. 5. Time constants (τ) associated with both pressure and deformation profiles.

Here, $Wo = R\sqrt{\frac{\rho\omega}{\mu}}$ is the Womersley number and J_0 is the zeroth-order Bessel function. Wo indicates the ratio of oscillatory inertia force to the shear force. For low-frequency pulsations, the velocity profile has the time to develop within the period of the cycle, and the phase difference between the flow rate $Q(t)$ and the time-varying pressure gradient $-\frac{dp}{dz}(t)$ is negligible. At this state, the Poiseuille profile can be approximated with the instantaneous pressure gradient. For a large $Wo(>10)$, the velocity profiles become blunter like a slug flow, characterized by steep near wall velocity gradients with a phase lag of 90° between $Q(t)$ and $-\frac{dp}{dz}(t)$. The pressure gradient profile from the waveform in Fig. 2 is utilized to calculate the velocity profiles for the entire cycle, by considering this velocity profile, with the sole objective of serving as a control case representing the behavior of an idealized rigid tube. The pulsating pressure gradient is decomposed into the respective Fourier components, and the Womersley solution is applied to find the velocity profile. The same measured with micro-PIV from instantaneous velocity fields is also plotted along with in Fig. 6. In our case, with Wo being small (~ 2), we assume that the Womersley analysis still holds even with small deformation. We attempt to compare the ideal

Womersley solution (i.e., CH10-DI case) with the other three cases to delineate the effects of the deformability and the non-Newtonian fluid flow on the averaged velocity profile at the same ROI in the channel for different phase angles in the cycle. Velocity profiles are plotted for the phase angle 90° comprising the rise to the peak and 180° encompassing the decay part in the deformation profile for all the four cases and two frequencies. In our experiments, near wall velocity is not probed due to inaccurate results mostly because of the optical distortion and the curvature effects. In the case of flow in a stenotic vessel, there is a possibility of the formation of secondary structures at the section where the cross-sectional area changes as reported before.⁴⁵ Furthermore, in a deformable channel, the deformation itself can induce a cross-stream velocity component and thus form secondary structures. These vortices can be extremely useful for mixing applications. It should be noted here that it is fundamentally different from the “soft wall turbulence” reported elsewhere⁴⁶ which occurs in a steady flow.

Earlier studies have also attempted evaluating the velocity profiles from experiments based on the Womersley analysis with non-ideal conditions and heavily simplifying

FIG. 6. Theoretical Womersley profiles and experimental values at different time intervals in a single cycle (with time period T) for various cases at $\omega = 1$ Hz and $\omega = 2$ Hz. Normalized phase is given in brackets. Error bars represent average over 10 cycles (a) $T/4$ for $\omega = 1$ Hz ($\pi/2$), (b) $T/4$ for $\omega = 2$ Hz (π), (c) $T/2$ for $\omega = 1$ Hz (π), and (d) $T/2$ for $\omega = 2$ Hz (2π).

assumptions. Pielhop *et al.* have studied the FSI on macro-sized tubes and used a correction factor to account for the wall deformability³³ in the original Womersley flow equation. Qian *et al.* have shown that the median pressure severely affected the velocity profiles in a microfluidic phantom.⁴⁷ Further, there are several theoretical works built around the Womersley model for simple and complex cases of hydrodynamics and wall deformation with an aim to predict the velocity profiles in pulsatile blood flow. Some of them relied on viscoelastic effects⁴⁸ and lubrication analysis,⁴⁹ while others considered slip effects⁵⁰ to estimate the velocity distribution within the channel.

In our case, since the deformation is small (maximum deformation within 5% of the diameter) and there is no chance of any collapse of the vessel since it resides within a solid cavity rather than in a thin tube configuration which has ample scope for bending and twisting. Hence, we consider only the pulsating pressure gradient and the diameter taken as the original undeformed diameter and plot the analytical velocity profiles using the Womersley solution. The viscosity of the blood flow is assumed to be attaining an asymptotic value of 3.5 mPa s at higher shear rates⁵¹ which is similar to the rheological behavior of the present working fluid. In pulsatile flow, due to the acceleration of the fluid within the cycle, the high shear assumption is reasonable due to the high Q incurred while the plunging action of the solenoid valve takes place. Effectively, the Wo is not a constant now and rather dynamic due to the changing diameter and the apparent viscosity. Further, the Womersley analysis considers only the longitudinal velocity component. There is a significant contribution from radial velocity components and secondary structures. The possibility of flow separation near the wall could only be ascertained if we can probe the near wall velocity, which is a limitation of the current experimental system. This also limits the accurate determination of the wall shear stress from the velocity profile.

For DI, the experimental values are closely matching with the theoretical values for both CH10 and CH30. The closeness of the velocity profiles for DI indicates that the deformability plays a minor role. The situation is dramatically different for the blood analog fluid. For XG, the velocity profiles exhibit a blunt nature similar to that appearing in a steady flow. This effectively culminates in the overprediction of the maximum velocity varying between 9% for 90° phase angle for 2 Hz and 16% for 180° phase angle for 1 Hz. Since CH30 with XG have the highest deformation, the influence of the deformability of the wall is the most prominent toward altering the velocity profiles for this case. Furthermore, no other profiles show a variation of the velocity magnitudes toward the wall. The typical characteristics of velocity profiles with DI are attributed to the decayed pressure gradient toward the end of the cycle. Interestingly, for 180° phase angle, the experimental data on XG for CH30 are the closest with the theoretical prediction considering rigid walls for both the frequencies. This indicates that the local hydrodynamics within the microchannel marked by the average velocity profile is affected by pressure waveform rather than the actual deformation profile of the wall. Moreover, the

reduction of the maximum velocity with increasing frequency is also in accordance with the reduction in magnitudes of the pressure waveform. It should be noted here that the maximum Reynolds number addressed in the present experiment is around 400 and is well within the assumptions of the laminar velocity field in a cylindrical channel.

IV. CONCLUSIONS

We have experimentally investigated the complex fluid-structure interaction in a physiologically relevant flexible microchannel transporting a blood analogue fluid under time-varying pressure pulsations. Possible new studies could also be directed along these lines towards probing frictional characteristics of flexible channels,⁵² studying peristaltic transport,^{53–55} developing mass flow controllers,^{56,57} energy conversion devices,⁵⁸ and flexible devices for blood diagnostics.^{59,60} Our results have brought out striking implications of the complex interaction between fluid rheology, channel deformability, and flow pulsation toward dictating the prominent hydrodynamic characteristics. A temporal analysis has been carried out by considering the microchannel as a first order system with implications in frequency specific lab-on-a-chip systems biomedical applications. Conceptual understanding developed from this study may turn out to be critical toward understanding the dynamics of blood flow through human vasculature *in vitro*. This, in turn, may open up possibilities of developing engineered microfluidic systems for studying relevant details of blood flow through microcirculatory passages under physiologically relevant conditions, opening up avenues toward a deeper understanding of the fundamental premises of several diseased conditions without executing *in vivo* probing.

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