# Blood flow in non-circular microchannel under pulsating condition

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#### Abstract

With the advent of point-of-care diagnostics systems, investigation into properties of blood at micron scales is gaining fundamental importance. Past research has shown that blood displays significantly different properties at small scales than at conventional scales. This study investigates properties of blood flow in small non-circular passages (hydraulic diameter:  $95-960 \mu$ m) under pulsatile condition. The observations are compared with flow of water under otherwise similar conditions. Prominent observation includes a more stable response to abrupt mass flow rate fluctuations as compared to water, which is attributed to the presence of deformable cells in blood. The study also reveals that, the pressure drop for blood flow with pulsations is less than for steady condition with the difference increasing with a reduction in microchannel size and flow rate. Such a comparative study facilitates development of models for blood flow at micro-scales, and will eventually aid in the design of future micro-Total Analysis Systems.

Keywords: microfluidics, blood circulation, non-Newtonian fluid, pulsatile flow, micro-Total Analysis System

## **1. INTRODUCTION**

Understanding the characteristics of blood flow in micro-environment is essential for the design and development of lab-on-a-chip micro-Total Analysis Systems ( $\mu$ TAS).  $\mu$ TAS are heavily dependent upon flow physics and rheology of blood. Such systems will be instrumental in early diagnosis of diseases and monitoring the health of patients [1]. In view of the importance of  $\mu$ TAS devices, a number of recent studies have examined blood flow in microchannels. Ji and Lee [2] performed velocity measurements using micro-PIV (particle image velocimetry) in a 100 micrometer capillary with up to 40% hematocrit blood. Similarly, Sugii et al. [3] and Kikuchi and Mochizuki [4] have reported micro-PIV based measurements with blood where the former study has measured the velocity of both plasma and blood cells. The high temporal resolution (6000 Hz) measurements of Sugii et al. [3] are for steady blood flow through a 100  $\mu$ m diameter capillary. Lima et al. [5,6] and Patrick et al. [7] utilized non-circular microchannels (square and rectangular) for velocity profiling using confocal micro-PIV. The measurements reveal fluctuations in the velocity profile in high hematocrit blood. Whereas these earlier studies have mostly focused on measurement of velocity, other important fluidic parameters such as variation of pressure and relative viscosity versus strain rate were not considered; the present study focuses on these latter aspects. The present study therefore complements the earlier works and in conjunction with the earlier studies helps provide a more complete picture on blood flow in non-circular microchannels.

In addition, ever since the initiation of microfabrication process, microfluidic research on cardiovascular systems has been subjugated by studies conducted in microfabricated microfluidic devices [8-12]. Among those, the devices made from PDMS soft lithography are cost-efficient, oxygen-permeable and non-cytotoxic. Moreover, the capability to duplicate intricate geometries of the micro-cardiovascular system and to accurately adjust the proportions of microchannels has made the microfabrication technique exceptionally favorable for cell studies [11]. Definitely, the data on blood flow in microchannel is relevant for improving our understanding of microcirculation in the human body. Microcirculation refers

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to the flow of blood in arterioles, venules and capillaries with diameter of the order of tens to hundreds of microns. Studies by Fenton and Zweifach [13], Popel and Johnson [14], among others, have been directed at understanding flow of blood through such vessels. Lipowsky and Zweifach [15] measured rheological parameters like relative viscosity and wall shear stress in small vessels. Jain [16] reviewed these studies and observed that the apparent viscosity of blood is dictated by hematocrit and shear rate in large vessels. In smaller vessels, tube diameter also affects the blood viscosity. Despite these and numerous other studies, modeling of blood flow in small passages is still considered to be challenging suggesting that additional experimental data is required [17-27]. Additionally, the devices fabricated by the soft-lithography technique typically have rectangular/trapezoidal cross-section microchannels, and the experimental data of blood flow in such small passages are not readily available. The present study fills this gap by providing measurements and insights into flow behavior with microchannel size.

Most importantly, the flow of blood in human body is inherently pulsatile in nature; pulsating flows are also widespread in microfluidic systems [28-35]. Recent analysis and experimental study on pulsatile flow are available in Massoudi and Phuoc [36], Tikekar et al. [37] and Haddad et al. [38]. If the microfluidics based biosensing device is intended to be implanted inside the human circulatory system, the pulsatile nature of blood flow needs to be considered. The present study therefore considers pulsating flow in microchannels as well; a topic not well researched.

Thus, this study provides experimental data for steady/pulsatile blood flow in trapezoidal and circular passages formed in three different materials, with the aim of bringing out the effects of microchannel shape, size and material on the flow characteristics. It is noted that studies on blood flow in the literature are mostly with circular passage; that is, non-circular passages have received little attention, whereas  $\mu/TAS$  devices mostly have a non-circular cross-section. Earlier studies have been conducted on microchannel made from flexible PDMS material, whereas hard fabrication materials are usually preferred for optical detection based microfluidics devices [39-40]. For experimentally studying blood flow through vessels, the elastic property of blood vessel wall should ideally be modeled.

Because material that has an equivalent elastic behavior as arteries is not available, the consequence of wall elasticity on the flow characteristic is difficult to study experimentally. Consequently, an assumption of negligible alteration in diameter of blood vessels is generally made and rigid walls are mostly studied. Considering these issues, we focused our study on microchannels made from rigid materials (i.e. silicon and glass) only.

Blood is composed of red blood cells ( $\sim$ 45% v/v) and white blood cells ( $\sim$ 1% v/v) suspended in blood plasma (~54% v/v). Plasma is 92% water by volume, and contains proteins (mainly albumin), glucose, mineral ions, hormones, carbon dioxide and blood cells, in suspended or dissolved form. Blood cells are typically 65% water by volume. The viscosity of blood depends on the viscosity of the plasma, and its hematocrit content. The viscosity of plasma depends upon its water-content, protein type and concentration. However, the effect of plasma composition on viscosity is insignificant as compared to the effect of hematocrit [41]. An increase in the plasma viscosity correlates with the development of peripheral and coronary vascular diseases [41-42]. Anemia (i.e. decrease in hematocrit content) can lead to decreased blood viscosity, which may lead to heart failure. In polycythemia (i.e. increase in hematocrit up to 60 or 70%), the blood viscosity may increase up to 10 times that of water [42], and its flow through blood vessels may be seriously retarded owing to amplified resistance to flow [43]. This may cause decreased oxygen transport [44]. The temperature of body also affects the blood viscosity and in hypothermic state of the body, an increase in the blood viscosity causes problems with blood circulation (hypothermic circulatory arrest). These facts indicate that although blood is about 80% water, its flow behavior is rather different as compared to that of water. The properties of blood (particularly viscosity) vary with several parameters including strain rate and passage size; understandably, modeling it has not been entirely successful.

Here we propose a relatively novel approach whereby measurements are performed with both water and blood under identical conditions. Since most design rules are available for steady flow of Newtonian fluids, it was thought that such data can aid in model development of blood flow. Our approach yields insights about the behavior of whole blood at micro-scale under pulsating flow conditions, which is not readily available in the literature. In a recent work, Anatasiou et al. [45] utilized micro-PIV for velocity profiling of pulsatile blood flow (19% hematocrit) in microchannel. They showed that the shear thinning behavior of blood considerably affects the velocity profiles, and consequently the ensuing wall shear stress and hemodynamic forces. Their experiments were however not carried out with whole blood. In view of the above, the objectives of this work are to study non-circular microchannel and to bring out differences between (i) water and blood flow under pulsatile condition, (ii) steady and pulsatile flow of blood, and (iii) to explore whether any optimal value exists for either microchannel size or blood flow rate under pulsatile condition. The differences in flow behavior for the various cases are documented in terms of relative viscosity, instantaneous pressure signals, or time-averaged pressure drop values. The investigation reveals important differences between flow of water and blood, particularly at micro-scales under pulsating condition.

#### 2. EXPERIMENTAL METHOD

Whole human blood and de-ionised (DI) water are used as the working fluids. Fresh whole blood obtained from healthy adults by venipuncture was anti-coagulated by heparin or citrate-phosphate dextrose adenine and tested for communicable diseases before use [52].

A summary of all the microchannels used and their denotation is given in Table 1. The hydraulic diameter is calculated as four times the cross-sectional area divided by the perimeter. Microchannels in glass, silicon and quartz with trapezoidal and circular cross sections are used in this study. The fabrication details of in-house silicon microchannels employed in this study is provided elsewhere [46-47].

Channel Name	Cross section shape	Material	Aspect Ratio α	Hydraulic Diameter $\mathbf{D}_{h}(\mu \mathbf{n})$
Capillary 1	Circular	Glass	-	960
Needle 1	Circular	Stainless Steel	-	241
Channel 1	Trapezoidal	Silicon	0.348	163
Channel 2	Trapezoidal	Silicon	0.495	143
Channel 3	Trapezoidal	Silicon	0.634	136
Channel 4		Quartz	0.799	108
Channel 5	Trapezoidal	Silicon	0.701	95
Needle 6	Circular	Stainless Steel	-	584
Needle 7	Circular	Stainless Steel	-	686

Table 1: Details of microchannels used for the experiments

The schematic diagram of the experimental setup is shown in Fig. 1. The pressure gauge has the following specifications: make - Keller, Leo 1; range of-1 to 3 bar, least count -1 mbar, and sampling time of 1 s. The pressure gauge is connected to a PC through a data logger. The working fluid is pumped from a reservoir using a micro-pump (Masterflex Easyflow II with range of 0.1-6 ml/min, resolution of 0.01 ml/min, and maximum pressure head of 1.7 bar) and the pressure versus time data is recorded for each flow rate. The flow rate is varied and pressure time series is recorded for each flow rate and microchannel. The experiments are done for both DI water and whole blood. The methods to generate pulsatile flow have been discussed elsewhere [37, 48, 49]. The mean pressures obtained from the time series are used to evaluate the non-dimensional parameters (Reynolds number and friction factor). The experimental setup has been validated before proceeding further. The experimentally obtained value of f.Re was found to compare well against theoretical calculations. The validity of the experimental setup has been demon-





strated elsewhere [46-47]. The maximum uncertainty in volume flow rate is 0.01 ml/min, in pressure drop is 2 mbar, in Reynolds number is 4.0%, and in friction factor is 8.4%.

#### 3. MEASUREMENTS UNDER STEADY FLOW CONDITION

The fluid density and viscosity as a function of strain rate were first measured. The density of blood was found to be 1061 kg/m<sup>3</sup>. The blood viscosity was measured using a viscometer (Contraves Low Shear 30). The instrument has the following range of operation: Viscosity:  $1.5 \times 10^{-3} - 6 \times 10^6$  mPa-s, Strain Rate:  $3.5 \times 10^{-3} - 250$  s<sup>-1</sup>, Shear Stress:  $20 \times 10^{-6} - 0.1$  Pa. In order to validate the experimental setup, the viscosity of DI water was also measured. The values of the viscosity of DI water obtained were within 4% of the accepted value. Since DI water is a Newtonian fluid, its viscosity is constant with respect to strain rate. This aspect was also corroborated by our measurements [48]. In contrast, blood behaves as a non-Newtonian fluid. Our measurements showed that for low shear rates (< 50 s<sup>-1</sup>) the viscosity of blood varies non-linearly. At higher shear rates, it asymptotically reaches a constant value. Also, the viscosity of blood at lower shear rates is much higher (around 100 cP) than that at higher shear rates (< 10 cP). There is no well-defined threshold to mark the transition of blood behavior from Newtonian to non-

Newtonian; this observation is in-line with that reported earlier by Yilmaz and Gundogdu [50], among others. These measurements suggest that the ratio of viscosity of blood at high strain rate to viscosity of water is about six, which agrees with the reported range of five to ten in the literature.

Pressure drop with steady blood flow through various microchannels was measured for a range of flow rates from 0.1-6 ml/min, for both blood and water. The results are quantified in terms of relative viscosity. Here, relative viscosity ( $\mu_r$ ) has been defined as the ratio of the pressure drops obtained for whole blood and DI water for a given flow rate, under otherwise identical conditions. The relative viscosity is therefore the ratio of fluid viscosities under flow condition, with water acting as the baseline fluid. Figure 2 presents the plot of relative viscosity as a function of strain rate, for different microchannels. The value of relative viscosity for the entire set of microchannels is in the range of 1.6 - 2.8. The maximum uncertainty in strain rate and relative viscosity is 10.6% and 11%, respectively, although for most measurements it is much less than this. Notice that these values are smaller than that obtained from the viscometer measurement (= 6). It is probably due to the higher shear thinning effect (due to higher shear rate) near the microchannel wall region; which makes the near-wall region virtually cell free as opposed to the central region of the microchannel (which is full of cell aggregates). Hence the blood erythrocytes and its aggregates voyage easily over the center of the vessel, leaving plasma near the walls of the microchannel; with a consequent decrease in blood viscosity. This effect is also known as Fåhraeus-Lindqvist effect and the effect increases with a decrease in the microchannel diameter.

The effects of strain rate and hydraulic diameter on relative viscosity are apparent from the results, although the results are not strictly monotonic with respect to these parameters. Figure 2b demonstrates that the relative viscosity decreases upon increasing the strain rate. Sharp corners in trapezoidal microchannels might be the cause of this, as well as difference in the trend between Figs. 2a and 2b. In rectangular cross section microchannels, cells may not be conformally encircled by sharp corners of microchannel. Thus, the flow of the incessant liquid phase (i.e. plasma) may take place more effectively through the four corners of the microchannel, which may alter the shear stress acting on the cell and may finally affect the pressure drop across the microchannel.





Figure 2. Graphs of relative viscosity of blood to water versus strain rates for (a) circular and (b) trapezoidal microchannels. See Table 1 for dimensions of the microchannels

#### 4. MEASUREMENTS UNDER PULSATILE FLOW CONDITION

A direct comparison of blood flow under steady and pulsating conditions, as well with water under pulsating conditions, is provided in this section. The flow rate follows a square waveform (of period 20 s), as depicted in Fig. lb.

#### 4.1 Comparison of instantaneous and mean pressure drops

The pressure time-series corresponding to water and blood flow, at two different mean flow rate values are shown in Figs. 3a and 3b respectively. Some important differences are noticed between the two waveforms: the pressure rise is more linear with blood as compared to water. Also, the sudden fall in pressure, due a sudden reduction in flow rate, is not observed with blood. The peak-to-peak variation is slightly smaller with blood for both the flow rates. Because the average pressure is larger with blood, the normalized pressure fluctuation  $((\delta p) \operatorname{rm.s}/(\delta p) \operatorname{avg})$  due to pulsating nature of the flow is smaller with blood. The smaller value of  $(\delta p)r.m.s/(\delta p)avg$  with blood is attributed to its viscoelastic nature; the cells in the blood store and release energy differently over the flow cycle. This leads to a relatively gradual rise and fall in pressure, and consequently to a smaller value of normalized pressure fluctuation with blood, as compared to water. The response times for pressure to rise and fall were explicitly measured, assuming that a first-order model describes the system [37]. The results are documented in Table 2 for two flow rates, with both water and blood. Notice that the response time with water is independent of both flow rate and rise/fall in pressure, whereas this is not true with blood. Further, the response time of blood is substantially more than water; the response time of blood is also more during pressure rise as compared to that when the pressure falls. Blood is a fluidized suspension of elastic cells, which gives it a viscoelastic property. Energy given to the blood by the mi-



Figure 3. Pressure drop time series for pulsatile flow in a 241  $\mu m$  needle with (a) DI water and (b) whole blood

Flow rate	Action	Blood	Water
2 ml/min	Pressure rise	14.3	2.46
	Pressure fall	6.2	2.49
3 ml/min	Pressure rise	15.9	2.42
	Pressure fall	8.2	2.45

Table 2. Flow response times (in seconds) of blood and water in a 241  $\mu$ m needle

cropump is to some extent stored in the elastic structure (i.e. blood cells), partly dissipated by viscosity, and the balance is transferred as its kinetic energy. During the pressure rise section of the pulsatile flow cycle, the blood cells are prone to a relatively high degree of deformation [51], because of the increase in the shear rate caused by the increased fluid velocity. The deformation of the flowing cells takes some definite time to reach its final shape. The deformation process hinders energy transfer to the flow. This leads to a higher response time to reach equilibrium as compared to when the pressure falls, in-line with the result in Table 2. During fall in pressure, the blood cells return back to the state of lesser degree of deformation because of decrease in shear rate caused by decreased fluid velocity.

The mean pressure drops for steady and pulsatile flows have been compared in Fig. 4. It is observed that the mean pressure drop curve for blood flow with pulsations lies below that for steady flow, even when the average flow rate is same between the two cases (Fig. 4b). Water can also display smaller pressure drop with pulsations as compared to steady flow condition [37]. However, for the set of parameters considered here, the difference in pressure drop for water between pulsating and steady conditions is negligible (Fig. 4a). Also the mean pressure drop with pulsations varies linearly with respect to flow rate for both the cases (DI water and whole blood). The result therefore suggests that great benefit can be derived by pulsing the flow, with the benefit being more with blood as compared to water for a given set of parameters.

These experiments further reveal that the relative viscosity of whole blood decreases for pulsatile flow, keeping other factors constant (Fig. 5). (The strain rate ( $\dot{\gamma}$ ) in the figure is estimated as twice the average velocity divided by smaller channel dimension for trapezoidal channels and diameter for circular channels.) The percentage decrease in relative viscosity with pulsations is about 27% as compared to the steady flow value. The friction factor (f) and Reynolds number were also calculated for all the cases (Fig. 6). The friction factor is calculated as  $\delta p/(1/2\rho u^2)$  where  $\rho$  is density of the fluid, u is the cross-section and time averaged velocity. From f.Re versus Re plot in Fig. 6 it is observed that f.Re value suffers a maximum reduction of 20% in pulsatile flow as compared to steady flow with blood as the working fluid. During the steady flow condition, cells remain deformed to the same extent; whereas in pulsatile flow so for a higher degree of freedom in the orientation and Brownian motion of the cells which results in the reduction in viscosity and pressure drop as compared to steady flow.

Based on this observation, it can be argued that blood flow in human body is pulsatile (instead of steady) because of the smaller value of relative viscosity (or pressure drop) with pulsations. The square waveform (with sharp gradients at both the rise and fall parts of a cycle; Fig. lb) employed in the present experiments is an extreme case of pulsations encountered in nature. Remarkably, the properties of blood are such so as to better mitigate these discontinuities than other fluids such as water. Although these measurements are for parameter values different from those encountered in human body, nonetheless they bring out an important aspect of the circulatory system.



Figure 4. Comparison of mean pressure drops for 241  $\mu m$  needle with (a) DI water and (b) whole blood



Figure 5. Comparison of relative viscosity of blood under steady and pulsatile flows.



Figure 6. Comparison of f.Re versus Re for whole blood under steady and pulsatile flows

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#### 4.2 Effect of hydraulic diameter and flow rate on mean pressure drop

The mean pressure drops obtained during pulsatile flow condition of blood in various needles are also compared. The pulsatile flow was created by the superposition of a steady flow at 2 ml/min and an intermittent flow at 2 ml/min, giving a resultant average flow of 3 ml/min. The pressure drop obtained in these needles in the case of steady blood flow at 3 ml/min was also noted and plotted on the same graph (Fig. 7). As seen from the figure, the nature of the graph is highly non-linear with an upward concavity. It is also worthwhile to note that the difference in the pressure drops between the pulsatile and the steady cases, observed for the smaller needles is much more than that observed in the larger needles (Fig. 7b). This result reinforces the one presented in Fig. 4; it further shows that the benefit of pulsing the flow is also size-dependent. The results suggest that in larger size microchannels, due to a lesser channel resistance, relatively small fraction of the cells (while moving upon application of a pressure gradient) are liable to deform at any cross-section. Hence, for larger dimension channels, the pressure drop across its length for steady flow condition may not be significantly different from pulsed flow.

Further experiments were performed in order to check if the benefit of pulsing the flow is flow rate dependent. For these experiments, the intermittently varying component was set at 2 ml/min flow rate peak-to-peak, while switching on/ off interval is fixed at 10 s. The continuously flowing pump was set at different flow rates in order to change the mean flow rate. The mean pressure versus mean flow rate is plotted for both pulsating and steady cases. It was observed that there was no significant difference in the values of mean pressure drops obtained in the steady and pulsatile case for DI water (Fig. 8a). However with whole blood a maximum difference of 13.7% was noted in pressure drops at a certain flow rate value (Fig. 8b, 8c). Figure 8c further suggests that there is an optimal flow rate, which needs to be confirmed through further experiments. At higher flow rates under pulsatile condition, blood cells gain higher momentum (compared to lower flow rate state) and remain more often in deformed state than a relaxed state. This may shift the flow resistance (and consequently the pressure drop) more towards steady flow condition at similar average flow rate condition. This may be the reason for similar pressure drops at pulsatile and steady flow condition at higher flow rates.



Figure continued



Figure 7. Comparison between mean pressure drop for blood under steady and pulsatile flow conditions, for a wide range of needles



Figure continued



Figure 8: Mean pressure drop versus flow rate for (a) DI water and (b) whole blood. Plot (c) shows the percentage difference between mean pressure drops for steady and pulsatile flow conditions for blood. The measurements are for a 241  $\mu$ m needle

#### 5. DISCUSSION

Both water and blood can display a reduction in pressure drop under pulsatile case, with respect to the steady flow case, keeping the mean flow rate constant between them (Fig. 4). However, the distinction is much more prominent in the case of blood than for water, especially for smaller dimensional channels (Fig. 7). Also, friction factor values are lower in pulsatile flow of blood, thus reducing pumping power for pulsatile flows (Fig. 6). This observation can also be viewed with respect to human circulatory system. One of the benefits of having pulsatile mechanism for pumping blood to distant organs is that it leads to a reduction in f.Re value, thereby reducing the power required by the heart for this task.

A signification difference between viscosities of blood as measured by viscometer and as seen in microchannel flows is also noted in Section 3, with the flow viscosity being almost 2.1 to 3.8 times smaller (Fig. 2). This is attributed to the dominance of viscoelastic nature of blood while flowing. Blood is also able to dissipate the pressure fluctuations much more effectively than water (Fig. 3). This is confirmed from the values of normalized pressure fluctuations, which are lower for blood. The behavior of water in Fig. 3 can be described using a first-order model; see Tikekar et al. [37], with a characteristic flow resistance and response time. Measurements along this direction revealed that the response time of blood is substantially different during the rising and falling parts of the square wave, which is an important difference with respect to water having equal response times (Table 2). Owing to such differences, a severe discontinuity in the input (in the form of square wave) is either weakened or damped out altogether.

The hydraulic diameter of the microchannel is also found to strongly affect the flow (Fig. 7). A smaller viscosity in microchannels of smaller dimensions is in accord with the Fahraeus-Lindqvist effect. The result on size dependence is significant because it suggests that with a decrease in the hydraulic diameter, the pressure drop does not increase at the same rate with blood as with water (or any other Newtonian fluid). Further, the difference in behavior between blood and water becomes wider, with a decrease in the hydraulic diameter. The result interestingly suggests that the pressure drop penalty ( $\delta p \propto d^{-4}$  expected for Newtonian fluid for a given flow rate under fully developed condition in a circular tube), which would become very severe in small capillaries, is partly offset by this property of blood. The pressure drop penalty is further reduced by pulsing the flow (Figs. 4, 6).

#### 6. CONCLUSIONS

An experimental study of steady flow and pulsatile flow of blood has been conducted for a wide range of microchannel size (hydraulic diameter: 95-960  $\mu$ m). Similar experiments were also performed with water as the working fluid under otherwise similar conditions. Experiments with water serve as the baseline case against which blood flow data are compared. Blood, being a complex, non-Newtonian fluid is expected to exhibit significantly different flow behavior as compared to flow of water. Since most design rules are available for steady flow of Newtonian fluids, such a study can provide the necessary relationship between water and blood, under both steady and pulsatile flow conditions and can aid in the development of models for blood flow.

The following conclusions can be drawn from this work:

- 1. The relative viscosity of blood with flow is 2.1 3.8 times smaller when compared to that obtained in a viscometer. This is clearly an advantage with blood as compared to other fluids.
- Blood is more effective in responding to a sudden change in the input parameter as compared to water.
- 3. The average pressure drop with pulsations is less than that with steady flow for the same flow rate. This difference is more than the corresponding difference obtained with water flow under otherwise similar conditions.
- 4. The difference in steady and pulsating pressure drops with blood seems to increase with a reduction in hydraulic diameter and a decrease in flow rate.

The above results taken together go on to demonstrate ways and means employed by nature to minimize pressure drop penalty during blood flow in numerous small-size passages. These points and other insights can be advantageously utilized in the design of  $\mu$ TAS devices involving blood flow.

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