Experimental study of blood flow characteristics in microchannels with stenosis and bifurcations using developed microfluidic devices

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The paper investigates blood flow in microfluidic devices manufactured using soft photolithography, simulating vascular stenosis with different constriction parameters. It was found that with a constriction of 50 μm width, erythrocytes are significantly accelerated, and at 200 μm the flow is more uniform. Tandem stenoses demonstrate a „streamlined“ zone between constrictions, increasing with increasing distance between them. The results can be used to model blood flow and develop methods for diagnosing vascular pathologies.

Keywords: microfluidic device, stenosis, blood, erythrocyte.

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In the human vascular system, branching and constriction of vessels are accompanied by an increase in the total cross section and a reduction in blood flow velocity [1]. Stenosis (pathological constriction) leads to a sharp increase in shear strain rate in the region of constriction, which induces an increase in hydraulic resistance and a reduction in blood flow velocity [2] and poses a risk of intravascular coagulation [3]. Therefore, one needs to understand the specifics of blood flow in vessels with stenosis in order to identify the ways to suppress thrombosis. The geometry of stenosis, its length and depth, and the rheological properties of blood (non-Newtonian behavior, which is characterized fairly well by the Ostwald–de Waele model within the range of shear strain rates of $0.1-500\,\mathrm{s}^{-1}$) exert a critical influence on hemodynamics [4]. The aim of the present study is to examine experimentally the flow of whole blood in microfluidic devices (MFDs) that were designed to simulate single, tandem, and bifurcation stenoses with different occlusions of the main channel. The study of hemodynamic features with MFDs may contribute significantly to the fundamental understanding of the behavior of erythrocytes under stenosis, and the results obtained may have important scientific implications, potentially establishing a theoretical basis for the development of innovative methods for diagnostics and therapy of vascular pathologies.

Parallelepiped-shaped MFDs were designed for this research into blood flow in stenosis. The devices with single stenosis have depth $2h = 50\,\mu$m, an approximate length of 10 mm (two channels with length $l_1 = 5$ mm and a constriction between them), and width $b = 1$ mm with a constriction with length $l_0 = 100\,\mu$m and width $a = 50$, 100, and 200 μm (Fig. 1). The cross-sectional area of the wide channel is approximately equal to the area of a cylindrical vessel 250 μm in diameter, which corresponds to arterioles. Formulae for calculating the volumetric rate of flow through a flat and cylindrical channel and the ratio of pressure differences in the wide and narrow parts of the channel are given in [1]. In the case of a Newtonian fluid, the ratio of pressure differences in the wide and narrow parts for an MFD with a constriction 50 μm in width is 2.5, which corresponds to ratio $r/R = 0.47$ of radii of the constriction (r) and the wide part (R) for a cylindrical vessel. The pressure difference ratio for blood with a non-Newtonian behavior index $n = 0.8$ is 4.55, $r/R = 0.494 \approx 0.5$. This means that the cross-sectional area of the narrow part is 25 % of the area of the wide part (i. e., the degree of occlusion is 75 %). The pressure difference ratio for constrictions 100 and 200 μm in width and blood with $n = 0.8$ is 7.92 and 13.8, respectively, which implies that the ratio of radii of similar cylindrical vessels is 0.582 and 0.685 and the cross-sectional area of the narrow part is 34 % of the area of the wide part (the degree of occlusion is 66 %) and 47 % (53 %). Thus, the designed constrictions cover a substantial proportion of diseases with channel occlusion.

Let us find the flow rates for the MFD with a constriction 50 μm in width at a pressure difference of $\Delta p = 500$ Pa. The calculated flow rate for a Newtonian fluid ($n = 1$, dynamic viscosity $\mu = 5\,\mathrm{mPa}\cdot\mathrm{s}$ is used instead of consistency k, and a length of 10 mm is set) is 0.104 μl/s without stenosis and 0.087 μl/s with stenosis. The flow rate for blood with rheological parameters $n = 0.8$ and $k = 0.013$ without stenosis is 0.116 μl/s; with stenosis factored in, the ratio of pressure differences is 4.55, and the flow rate is 0.102 μl/s. The flow velocity ($v = Q/S$) and the shear strain rate (v/h) were calculated based on the flow rate (Q) and the cross-sectional area (S). The calculation of flow rates for blood with parameters $n = 0.8$ and $k = 0.013$ at $\Delta p = 500$ Pa for 50×100, 100×100, and $200 \times 100\,\mu$m constrictions (width $Oy\times$ length Ox) yields the values of 0.102, 0.107, and 0.111 μl/s, respectively; i. e., the flow rate increases slightly with an increase in constriction size. The velocities in the wide part of the channel are 2.03, 2.15, and 2.22 mm/s, and the shear strain rates are 81, 86, and $89\,\mathrm{s}^{-1}$.

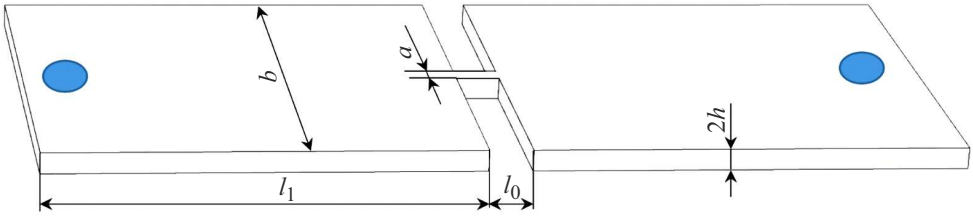

Figure 1. Schematic diagram of the MFD with a constriction. The holes for supply pipes are highlighted with circles.

The shear strain rate is comparable to the one typical of flow in arterioles ($100\,s^{-1}$). Within the constrictions, the velocity and shear strain rate for MFDs with 50×100, 100×100, and $200 \times 100\,\mu$m constrictions are 20, 10, and 5 times greater, respectively.

MFDs with tandem stenosis (two identical constrictions following one another) were designed. The geometry and dimensions of the MFD are the same as those for single stenosis; the distances between constrictions are 200, 300, 400, 500, 1000, and $1500\,\mu$m. Calculations demonstrate that the flow rate for a constriction $50\,\mu$m in width is $0.0885\,\mu$l/s if constrictions are positioned close to each other ($200\,\mu$m); when constrictions are spaced more apart, the flow rate is similar (provided that the total length remains the same). Bifurcation MFDs were designed: a channel with a width of 1 mm was divided at an angle of 20° into two channels 0.6 mm in width, one of which had a single or double constriction. The ratio of sizes of the main and branching channels was chosen so that the velocity decreased similar to how it decreases in the case of branching of vessels in the human body.

A vector pattern for fabrication of photo template masks for the constrictions listed above was designed in CorelDRAW. Masks made of photo emulsion film were printed in accordance with this pattern on a high-resolution printer. The MFDs were fabricated using soft photolithography; the glass and polydimethylsiloxane channels are transparent, which allows for microscopic imaging.

Experiments with whole blood of healthy individuals (with the EDTA K3 anticoagulant) were conducted in these MFDs at a constant pressure difference of 500 Pa in order to identify the characteristics of flow. Microphotographic imaging was performed using a Chronos 1.4 camera at a framing rate of 1500 fps through an inverted biological BDS500 microscope (observation from below) at room temperature. A single measurement was imaged in a fraction of a second (approximately 200 frames), ensuring measurement accuracy (the pressure could not change within this time interval). Prior to the experiment, the prepared MFD was washed with saline solution to remove air bubbles, and a conical test tube was then placed on the water contact and filled with blood. Flow stability was ensured by the constancy of pressure difference set by a hydrostatic pump (liquid column calculated through hydrostatic pressure $P = \rho g h$). Since the experiment was qualitative rather than quantitative, the error in determining the magnitude of this pressure difference as a function of temperature fluctuations was neglected. The MFD cell was significantly smaller in volume than the conical test tube. Therefore, the liquid column could be maintained for a considerable time; If necessary, the blood sample was mixed. Video recording and flow measurements of distilled water were used to calibrate the depth and size of the fabricated microchannels.

Experiments on blood flow were conducted in the designed MFDs with 50×100, 100×100, and $200 \times 100\,\mu$m constrictions: single, tandem, and bifurcation ones. The PIVlab_App module built into Matlab was used to compare visually the orientation and study the features of motion of erythrocytes. A total of 30 video frames were selected for analysis; the program identifies the shift of particles (erythrocytes) between two frames and substitutes the particles with arrows indicating the direction of this shift. To determine the size and velocity, the frame width in pixels was equated to the actual channel width of 1 mm, and time was counted based on the framing rate of 1519 fps. Figure 2 shows a section of the MFD with single stenosis at pressure difference $\Delta p = 500$ Pa with arrows indicating the velocities of erythrocytes; the constriction dimensions correspond to the indicated scale bar, and the length of arrows corresponds to the scale arrow (i. e., if the arrow length is reduced by a certain factor, the velocity indicated by it should decrease accordingly). Since observations were conducted from below, erythrocytes located primarily in the lower plane are visible; in the acceleration zone upstream of the constriction, certain erythrocytes move from the lower plane to the higher one. The comparison of flow velocities for single stenosis (Fig. 2) reveals significant acceleration in the channel upstream of a $50\,\mu$m constriction. The flow within a $200\,\mu$m constriction is more uniform than in a $100\,\mu$m constriction: the velocities are lower, and the acceleration is not as strong.

Figure 3 illustrates the flow in tandem stenosis for a $100 \times 100\,\mu$m constriction at a pressure difference of 500 Pa; the distance between the constrictions is 200 (a) and $300\,\mu$m (b). The following 100-μm-long zones are formed within an interconstriction interval of $200\,\mu$m (Fig. 3, a): (1) deceleration zone of residual fast motion after the first constriction; (2) zone of acceleration upstream of the second constriction. Thus, erythrocytes „darting out“ of the first constriction are accelerated again to enter the second constriction. As the constriction width increases to $200\,\mu$m, the region of „spread“ of erythrocytes grows

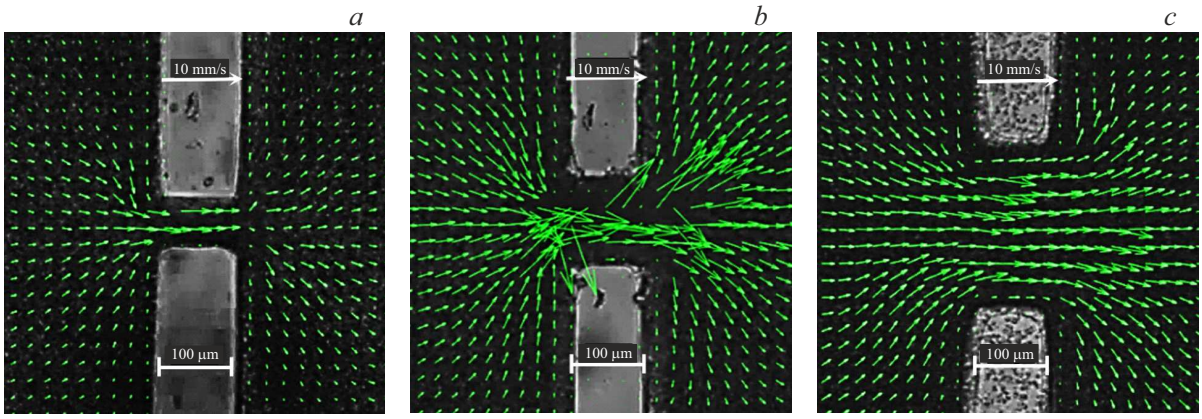

Figure 2. Erythrocyte velocities in the MFD with single stenosis at $\Delta p = 500$ Pa represented by arrows. The length of arrows corresponds to the indicated speed scale. The constriction sizes ($Oy \times Ox$), μm, are as follows: 50×100 (a), 100×100 (b) and 200×100 (c).

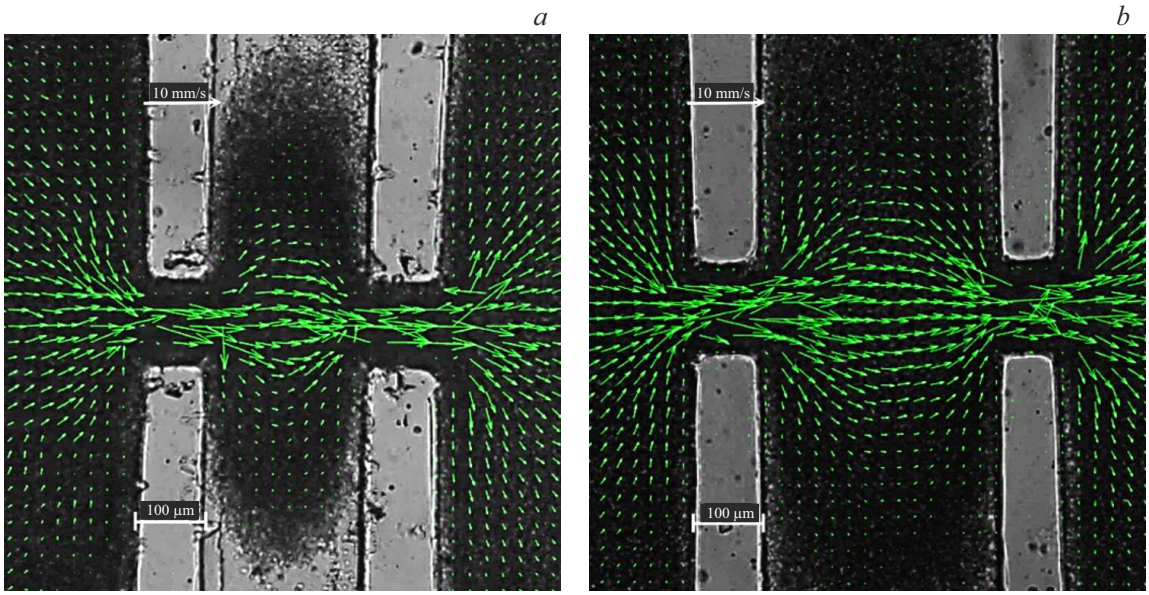

Figure 3. Erythrocyte velocities in the MFD with tandem stenosis represented by arrows. The size of constrictions is $100 \times 100\,\mu$m, and $\Delta p = 500$ Pa. The length of arrows corresponds to the indicated speed scale. The distances between the constrictions are 200 (a) and $300\,\mu$m (b).

larger, since the constriction area expands and erythrocytes „dart out“ at high velocities in different directions. With an increase in distance between the constrictions to $300\,\mu$m (Fig. 3, b), a more uniform filling of the gap between the constrictions is observed. The „streamlined“ zone grows with an increase in constriction width; notably, the zone for a $200\,\mu$m constriction turned out to be smoother than in the previous case. A further increase in distance between the constrictions leads to expansion of the „streamlined“ zone. The nature of motion at an interval of 1000 and $1500\,\mu$m between stenoses is virtually the same as the one observed with a single constriction: high velocity before and after constrictions (acceleration and deceleration zones) and subsequent coverage of the entire visible front of the device.

Channels with bifurcations reveal a similar pattern: with single stenosis, complete coverage with acceleration and deceleration zones is observed; with tandem stenosis, a streamlined zone is seen (Fig. 4, a) at a small distance between the constrictions ($300\,\mu$m). This zone expands and vanishes as the distance between the constrictions increases to 1 mm (Fig. 4, b). In all cases with bifurcations, the velocity in the channel without any constriction is approximately 30–40 % higher than the one measured in the channel with a constriction.

Experiments with whole blood were visualized via high-speed photography (1500 fps) and processed in Matlab. The results illustrate the influence of stenosis geometry on hemodynamics. A $50\,\mu$m constriction induces the maximum acceleration of erythrocytes, while a $200\,\mu$m constriction shapes a smoother flow; more pronounced constrictions (with smaller luminal areas) generate significantly higher velocities and shear strain rates within them. The study

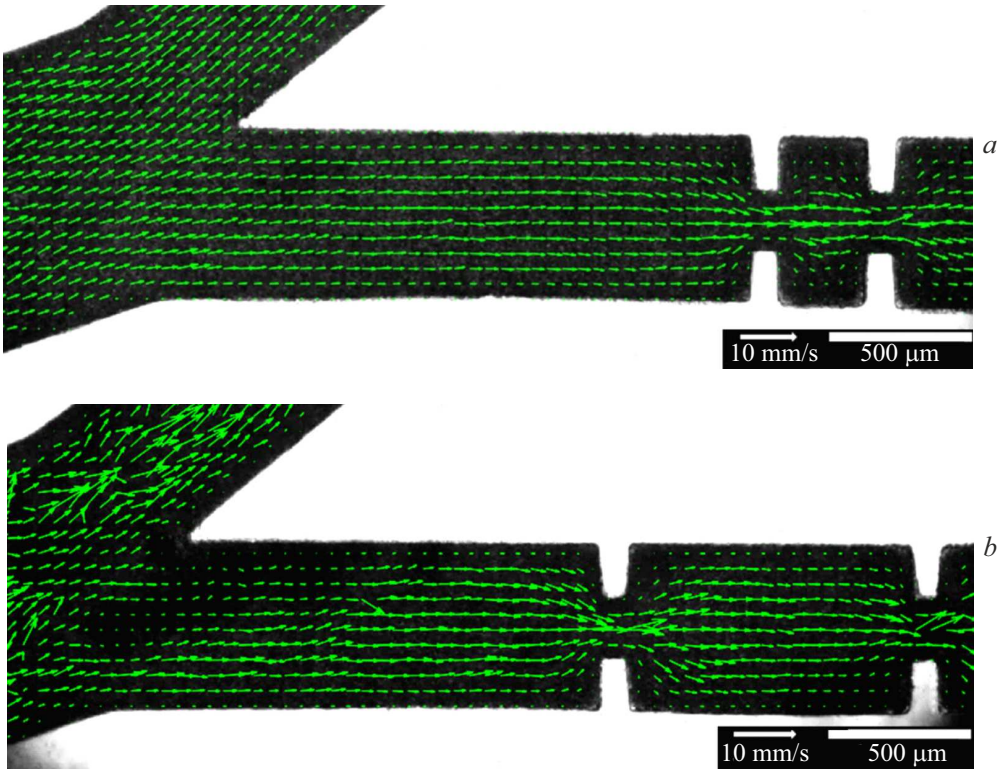

Figure 4. Erythrocyte velocities in the MFD with a bifurcation channel with tandem stenosis ($200 \times 100\,\mu$m, $\Delta p = 500$ Pa) represented by arrows. The length of arrows corresponds to the indicated speed scale. The distances between the constrictions are 300 (a) and $1000\,\mu$m (b).

revealed the critical importance of the distance between successive constrictions: at distances comparable to the constriction length ($200-500\,\mu$m), a zone of dynamic interaction of flows forms. Erythrocytes „ejected" from the first constriction with high velocities immediately enter the acceleration zone upstream of the second constriction, having no time to restore laminar flow with „streamlined" zones between the constrictions. Such motion leads to the formation of a turbulent zone between stenoses, potentially increasing the risk of cellular damage and activation of thrombosis. As the distance between the constrictions increases, the „streamlined" zones expand, and the flow at a distance over 1000 μm becomes similar to the flow observed in the case of single stenosis. The obtained data may be used in modeling of blood flow under pathological conditions and help develop methods for early diagnosis of vascular diseases.

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Compliance with ethical standards

This study does not contradict international ethical standards and was approved by the Bioethics Committee of the Institute of Biochemistry and Genetics of the Ufa Federal Research Center of the Russian Academy of Sciences (protocol No 1 dated April 17, 2025). Blood samples were taken from healthy individuals who gave their informed voluntary consent to participate in this research. The results are provided without personal data; the study complies with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest

The authors declare that they have no conflict of interest.

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