Using a classic paper by Robin Fåhraeus and Torsten Lindqvist to teach basic hemorheology

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Toksvang LN, Berg RM. Using a classic paper by Robin Fåhraeus and Torsten Lindqvist to teach basic hemorheology. Adv Physiol Educ 37: 129–133, 2013; doi:10.1152/advan.00009.2013.—“The viscosity of the blood in narrow capillary tubes” by Robin Fåhraeus and Torsten Lindqvist (Am J Physiol 96: 562–568, 1931) can be a valuable opportunity for teaching basic hemorheological principles in undergraduate cardiovascular physiology. This classic paper demonstrates that a progressive decline in apparent viscosity occurs when blood flows through glass capillary tubes of diminishing radius, which was later designated the “Fåhraeus-Lindqvist effect.” Subsequent studies have shown that apparent viscosity continues to decline at diameters that correspond to the arteriolar segments of the systemic vascular tree, where the majority of the total peripheral resistance resides and is actively regulated in vivo. The Fåhraeus-Lindqvist effect thus reduces microvascular resistance, thereby maintaining local tissue perfusion at a relatively lower blood pressure. The paper by Fåhraeus and Lindqvist can be used as a platform for a plenary discussion of these concepts as well as of the relationships among hematocrit, vessel diameter, red blood cell deformability, and resistance to blood flow, and how these factors may affect the work of the heart.

blood flow; hematocrit; microcirculation; red blood cell; viscosity

When teaching cardiovascular physiology to undergraduate students, the basic principles of hemorheology, the study of the flow properties of blood and its elements, are essential to conveying the factors that ultimately determine tissue perfusion. In this context, Poiseuille’s law, which describes the steady, laminar volume flow of a Newtonian fluid through a uniform and rigid cylindrical tube (18), provides a useful starting point:

\[ Q = \frac{\pi \times \Delta P \times r^4}{8 \times L \times \eta} \]

where \( Q \) is the volume flow through the tube, \( \Delta P \) is the pressure drop along the tube, \( L \) is the length of the tube, \( r \) is the tube radius, and \( \eta \) is the viscosity of the fluid. This relationship was derived as a special case of the Navier-Stokes equation, based on observations on the passage of simple fluids through long, narrow-bore tubes, made by the French physician J. L. M. Poiseuille in the first half of the 19th century (13, 18).

According to Poiseuille’s law, the resistance to flow is determined by the fourth power of the tube radius, the length of the tube, and the fluid viscosity. The latter comprises a material property of the fluid, describing its inertial resistance to the shearing motions that occur during laminar flow, in which different parts of the fluid form concentric layers that move with increasing flow velocities from the tube wall toward the center (18). Viscosity is measured in Pascal-seconds (Pa·s), which is sometimes referred to as Poiseuilles, or in poise (dyn·s·cm\(^{-2}\)); 1 poise is equivalent to 0.1 Pa·s. For a Newtonian fluid, the viscosity is constant. Since blood is not a fluid per se, but rather a suspension of formed elements (principally red blood cells) in a relatively homogenous fluid (plasma), its behavior is not Newtonian. Hence, the viscosity of blood depends on a number of factors, including hematocrit, temperature, flow rate, and, of particular importance, tube diameter. In larger tubes, the viscosity of flowing blood is thus relatively constant, whereas it diminishes progressively as tube diameter decreases below 0.3 mm, corresponding to the onset of the microcirculation in the intact organism, where most of the total peripheral resistance to blood flow resides. In accordance with the fourth power dependence of volume flow on tube radius in Poiseuille’s law, this mainly depends on the vascular radius, which is actively regulated through changes in vascular tone by the myogenic response, sympathetic tone, paracrine factors (e.g., local metabolites), and humoral factors (e.g., ANG II). However, due to the tube diameter-dependent changes in viscosity, the vascular resistance is lower than expected at a given level of the microvasculature.

The tube diameter-dependent reduction in the viscosity of blood is called the Fåhraeus-Lindqvist effect, and it was first reported almost simultaneously by two independent research groups in the interwar period (4, 8). Hence, a German research group consisting of Martini and co-workers first documented this phenomenon in Deutsches Archiv für Klinische Medizin in 1930, whereas the Swedish physicians Fåhraeus and Lindqvist, after whom it was subsequently named, published their findings in the American Journal of Physiology in 1931 (8). For clarity, the term “apparent” (or “effective”) viscosity is widely used for the derived value of blood viscosity and reflects the viscosity of a Newtonian fluid that would yield the same flow under otherwise identical conditions.

The now classic paper by Fåhraeus and Lindqvist is a valuable opportunity for teaching basic hemorheological principles and may be used as a platform for a plenary discussion of the limitations of Poiseuille’s law in vivo as well as the relationships among hematocrit, vessel diameter, viscosity, red blood cell deformability, resistance to blood flow, and blood pressure, and how these factors may affect the work of the heart. This discussion may benefit from including a figure and a table from the original article (Figure 1 and Table 1) as well as from a later extensive review by Pries and co-workers that
was also published in the American Journal of Physiology (Fig. 2).

Discovery of the Fåhraeus-Lindqvist Effect

In the late 1920s, Robin Fåhraeus, who was a professor of pathology in Uppsala, Sweden, had become widely known for a number of ground-breaking studies on the suspension stability of blood (5, 12). One day, a frustrated Torsten Lindqvist, a young physician working in his laboratory, complained that he kept getting flawed measurements in one particular experiment, since he never got the results he expected. Fåhraeus replied: “When you get unexpected results you should be darn happy! If you always get the results you anticipate you can never hope to discover anything new!” (12) Presumably, the “unexpected” results were seemingly aberrant viscosity estimates, findings that serendipitously turned out to form the basis of the Fåhraeus-Lindqvist effect.

Fåhraeus and Lindqvist constructed a viscometer for determining the resistance to blood flow through glass capillary tubes with different diameters. The glass capillaries were placed between glass tubes of larger diameters, which were reduced to capillary dimensions in a nonabrupt manner. The glass capillaries were placed in a horizontal position, kept at a constant temperature (38°C), and rotated at a constant rate to prevent red blood cell sedimentation. With the use of blood samples from each other, Fåhraeus and Lindqvist measured the blood flow rate through glass capillaries with diameters ranging from 0.04 to 0.505 mm at a constant driving pressure of 100 mmHg (8); since the blood flow, driving pressure, and dimensions of the glass capillaries were known, they could calculate the contribution of viscosity to the resistance to blood flow at a given tube diameter.

Their findings demonstrate that the apparent viscosity of blood is constant for glass capillaries with a diameter above 0.3 mm, whereas it progressively declines at lower diameters (Fig. 1). Fåhraeus and Lindqvist thus concluded that Poiseuille’s law does not apply to the flow of blood in capillary tubes of a diameter below about 0.3 mm and proposed that this non-Newtonian behavior of blood functions to maintain microvascular perfusion at relatively lower driving pressures in vivo than would be possible if blood was a Newtonian fluid (8).

The authors considered their findings to be related to the axial accumulation of the flowing red blood cells (8). Since the pioneering studies of Poiseuille on the mesenteric microcirculation of the frog a century earlier, it had been known that flowing red blood cells tend to accumulate axially, thus leaving a cell-free plasma layer near the vessel wall (18). In 1929, Fåhraeus had published a comprehensive review on hemorheology in Physiological Reviews (3), in which he elaborated on
Mechanisms of the Fåhraeus-Lindqvist Effect

Since the 1931 paper in American Journal of Physiology, the Fåhraeus-Lindqvist effect has been confirmed in a number of in vitro and in vivo studies (14). Hence, the apparent viscosity progressively decreases as tube diameter decreases below 0.3 mm, which corresponds to the smallest arteries in vivo, and continues to decline until a tube diameter of ~7 μm is reached, which approximately coincides with the diameter of the smallest precapillary arterioles; when the tube diameter decreases further to values below ~3 μm, a sharp increase in apparent viscosity is observed (Fig. 2).

As pointed out by Fåhraeus and Lindqvist, the tube diameter-dependent changes in viscosity are related to the axial accumulation of red blood cells in the flowing blood (8). During laminar flow through a tube or blood vessel, the concentric layers of plasma shearing against each other impart a spin on the red blood cell when it is caught between two layers. This pushes the red blood cell toward the center of the bloodstream, where the flow velocity is highest and the shearing forces are lowest, and consequently yields a cell-rich core that moves with a high flow velocity and a marginal cell-free layer consisting only of plasma. In the marginal plasma layer, flow velocity is lower and decreases in the radial direction, reaching a flow velocity of zero in the plasma layer right at the vessel wall. The axial accumulation of red blood cells notably depends on the deformability of the red blood cell (6). Accordingly, a sharp reversal of the Fåhraeus-Lindqvist effect occurs when red blood cells are rendered rigid by exposing them to heating or glutaraldehyde, so that the apparent viscosity exhibits a sharp increase rather than a decrease when tube diameter is reduced (9, 16).

Red blood cell deformability supposedly contributes to the Fåhraeus-Lindqvist effect through axial accumulation by means of at least two distinct mechanisms (5, 14). One is, as suggested by Fåhraeus and Lindqvist, the tube diameter-dependent change in hematocrit (8); since red blood cells tend to accumulate in the faster axial portions of the bloodstream, they will traverse the tube faster than plasma, and at a given time point the amount of red blood cells relative to plasma will therefore be lower. The diameter-dependent reduction in hematocrit is, however, maximal at 10–15 μm and thus in slightly larger tubes than where the Fåhraeus-Lindqvist effect is maximal; therefore, it cannot fully explain the changes in viscosity (14).

An additional mechanism involves the relative contribution of the axial stream of red blood cells and the marginal cell-free layer to the viscous resistance as tube diameter decreases (5, 14). Plasma in the marginal cell-free layer decreases the local viscosity near the wall where the shearing forces are greatest. This cell-free layer occupies a larger fraction of the tube diameter in smaller than in larger tubes. Hence, the impact of the lubricating sleeve of plasma in the marginal cell-free layer on viscous resistance is enhanced as tube diameter decreases toward ~7 μm, where the cell-free layer engages the largest fraction; meanwhile, energy dissipation due to internal friction between the red blood cells is also reduced, because red blood cells travel on different streamlines with different velocities in larger tubes and then align as tube diameter decreases (Fig. 3) (14). Hence, the lubricating sleeve of plasma contributes relatively more to the viscous resistance than cell-to-cell interactions as tube radius decreases, thus causing a reduction in apparent viscosity. The sharp increase in apparent viscosity that is observed when tube diameter approaches the minimum cylindrical red blood cell diameter of ~3 μm (Fig. 2) is thought to occur because the lubricating sleeve of plasma is displaced by the red blood cells (Fig. 3), thus increasing the viscous resistance to flow (14).

Clinical Implications of the Fåhraeus-Lindqvist Effect

The Fåhraeus-Lindqvist effect is mainly effective in the arteriolar segments of the systemic vascular tree, where the majority of the total peripheral resistance resides and is actively regulated. Thus, the Fåhraeus-Lindqvist effect has been suggested to be an evolutionary trait that alleviates the impact of arteriolar vasoconstriction upon total peripheral resistance and thereby maintain local tissue perfusion at a relatively lower blood pressure than would be possible if blood was a Newtonian fluid (17). Accordingly, it has been reported that approximately a doubling of blood pressure is required to maintain adequate O2 delivery to tissues if the Fåhraeus-Lindqvist effect is eliminated by replacing blood with a Newtonian hemoglobin solution with a similar O2-binding capacity (17).

Discrepancies between predictions of vascular resistance based on vascular dimensions and apparent viscosity estimates made in vitro and actual measurements of resistance in vivo have been observed in a number of studies (see, e.g., Ref. 15). Although irregularities of the vessel wall and the presence of white blood cells may contribute to this, the critical factor to this disparity is that the measurements of vascular dimensions must take the so-called endothelial surface layer into account.

![Fig. 3. Human red blood cells flowing through glass capillary tubes with different inner diameters. The flow direction is from left to right. [Modified from Ref. 13 with permission.]](http://advan.physiology.org/)
The endothelial surface layer is a relatively thick (0.5–1 μm) layer of macromolecules that consists of absorbed plasma components attached to the luminal face of the microvascular endothelium. If the endothelial surface layer is taken into account when the vascular dimensions are assessed, in vitro-derived estimates of apparent viscosity have been found to accurately predict vascular resistance in vivo (15), thus supporting that the Fåhraeus-Lindqvist effect is present in the intact organism and not merely an in vitro phenomenon.

The red blood cell deformability that forms the mechanistic basis of the Fåhraeus-Lindqvist effect depends on a number of factors (1). Hence, changes in temperature, osmolality, and intracellular ATP levels as well as membrane and cytoskeletal structure may all affect vascular resistance and microvascular perfusion, and this may have implications for a number of clinical conditions (1, 11). In preterm and term neonates, red blood cell deformability is increased, and the subsequently enhanced Fåhraeus-Lindqvist effect may function to maintain tissue perfusion at lower blood pressures, thus reducing cardiac work (10, 19). In contrast, red blood cells become less deformable in a large number of hematological and nonhematological conditions (1, 11). Sickle cell disease is a classic hematological disease in which a point mutation in the β-globin chain of hemoglobin causes red blood cells to assume an abnormal, rigid, sickle shape, which is associated with impaired microvascular perfusion (11). This involves so-called vasoocclusive crises, in which the sickle-shaped red blood cells cause vascular obstruction, tissue ischemia, and potentially irreversible organ injury, all of which may be facilitated by an impairment of the Fåhraeus-Lindqvist effect. Essential hypertension, on the other hand, is a common nonhematological condition that may be associated with reduced red blood cell deformability (2). This may further increase total peripheral resistance and, consequently, cardiac afterload, thus worsening the condition.

**Teaching Points**

**Teaching point 1.** Define Poiseuille’s law and specify what presuppositions need to be fulfilled for it to be applicable to determine flow of a fluid though a tube.

**Answer.** Poiseuille’s law is written as follows:

\[ Q = \frac{\pi \times \Delta P \times r^4}{8 \times \eta \times L} \]

where \( Q \) is the volume flow through the tube, \( \Delta P \) is the pressure drop along the tube, \( L \) is the length of the tube, \( r \) is the tube radius, and \( \eta \) is the viscosity of the fluid. The premises of Poiseuille’s law are that the flow has to be laminar and steady, and that the fluid has to be Newtonian (which means that the viscosity needs to be constant). Furthermore, the tube must be uniform, rigid, and cylindrical.

**Teaching point 2.** Based on Fig. 2 in the paper by Fåhraeus and Lindqvist (4), explain whether Poiseuille’s law applies to the flow of blood through glass capillary tubes.

**Answer.** Since blood exhibits non-Newtonian behavior, in that its viscosity is not constant but is progressively reduced when the tube diameter decreases below 0.3 mm, Poiseuille’s law does not apply to the flow of blood through glass capillary tubes with a diameter of <0.3 mm. This roughly corresponds to the onset of the microcirculation in vivo.

**Teaching point 3.** Specify at which level in the arterial system the majority of total peripheral resistance resides in vivo and how it is mainly regulated.

**Answer.** The majority of the total peripheral resistance is situated in the microcirculation, more specifically, in the arterioles, which are arterial vessels with diameters from 150 to ~10 μm. In the resting condition, total peripheral resistance is primarily regulated at this level by the myogenic response, sympathetic tone, paracrine factors (e.g., local metabolites), and humoral factors (e.g., ANG II).

**Teaching point 4.** Based on Fig. 2 in the paper by Fåhraeus and Lindqvist (4), discuss what impact the tube diameter-dependent changes in viscosity (Fåhraeus-Lindqvist effect) have on tissue perfusion.

**Answer.** Due to the Fåhraeus-Lindqvist effect, vascular resistance is lower than expected in the microvasculature; hence, blood can flow through the tissue microcirculation at a relatively lower driving pressure.

**Teaching point 5.** Explain how axial accumulation of red blood cells may contribute to the findings in the table on p. 568 in the paper by Fåhraeus and Lindqvist (4) as well as to the Fåhraeus-Lindqvist effect per se.

**Answer.** The axial accumulation of red blood cells may cause a decrease in hematocrit (the Fåhraeus effect) because the axial stream of red blood cells will traverse the vessel at a higher velocity than the slower flowing marginal plasma stream. The consequent dilution of the blood at a given tube diameter furthermore reduces its viscous resistance, that is, the apparent viscosity of the flowing blood (the Fåhraeus-Lindqvist effect).

**Teaching point 6.** The axial accumulation of flowing red blood cells mainly depends on their deformability, so that more flexible cells migrate toward the center of the blood vessel during laminar flow. Studies have shown that neonates have more deformable red blood cells than adults. Discuss the impact of this on the Fåhraeus-Lindqvist effect and elaborate on how blood transfusion with adult blood may theoretically affect tissue perfusion and the work of the heart in the neonate.

**Answer.** Since the red blood cells of neonates are relatively more deformable, the Fåhraeus-Lindqvist effect will be enhanced, maintaining tissue perfusion at a relatively lower driving pressure, thus reducing the work of the neonatal heart. Blood transfusion with the less deformable adult red blood cells may theoretically impede this enhanced Fåhraeus-Lindqvist effect; this may increase total peripheral resistance and consequently put a larger strain on the neonatal heart.

**Teaching point 7.** In a healthy young man, noninvasive blood pressure and heart rate are measured with conventional automatic oscillometric equipment and cardiac output is measured by an inert gas rebreathing method in the upright sitting position and after 10 min in the supine position. A blood sample for determining hematocrit is obtained in both positions. Data from the subject are reported below (Table 2).

**A.** What is the probable cause of the observed change in hematocrit upon the posture change?

**B.** Calculate how mean arterial blood pressure, stroke volume, and total peripheral resistance are affected by the posture change, assuming that central venous pressure is zero in both positions.
C. Account for the basic baroreflex-mediated factors that cause the change in mean arterial blood pressure and discuss how the change in hematocrit may contribute to this change.

**Answers**

A. Due to the hydrostatic effects of the posture change, blood is moved from the veins in the lower extremities and abdomen toward the heart, consequently reducing intravascular pressure in capillaries located caudally of the heart. This shifts the Starling forces in the capillaries so that the extravasation of fluid into the interstitial space is reduced; plasma volume is consequently increased, whereby hematocrit decreases.

B. Mean arterial blood pressure = 1/3 systolic blood pressure + 2/3 diastolic blood pressure

Mean arterial blood pressure (upright) = 1/3(124 mmHg) + 2/3(82 mmHg) = 96 mmHg

Mean arterial blood pressure (supine) = 1/3(113 mmHg) + 2/3(82 mmHg) = 82 mmHg

Stroke volume = cardiac output/heart rate

Stroke volume (upright) = (4.9 l/min)/82 min⁻¹ = 0.060 liters = 60 ml

Stroke volume (supine) = (6.3 l/min)/64 min⁻¹ = 0.098 liters = 98 ml

Total peripheral resistance = mean arterial blood pressure/cardiac output

Total peripheral resistance (upright) = 96 mmHg/(4.9 l/min) = 19.6 peripheral resistance units

Total peripheral resistance (supine) = 82 mmHg/(6.3 l/min) = 13.0 peripheral resistance units

C. The increased venous return to the heart in the supine position increases cardiac preload, which, in accordance with Starling’s law of the heart, consequently increases stroke volume. The baroreflex responds by increasing parasym pathetic and decreasing sympathetic tone to the heart, thus reducing heart rate, and decreasing sympathetic tone to the systemic arterioles, which causes vasodilation and thus reduces total peripheral resistance.

The decrease in hematocrit will decrease blood viscosity and, according to Poiseuille’s law, thus reduce total peripheral resistance. Theoretically, this may contribute to the posture-dependent decrease in mean arterial blood pressure. The impact of this hematocrit-dependent change in viscosity on total peripheral resistance is, however, minor compared with the effects of systemic arteriolar vasodilation.

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**AUTHOR CONTRIBUTIONS**

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