Blood viscosity in tube flow: dependence on diameter and hematocrit

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Pries, A. R., D. Neuhaus, and P. Gaehgens. Blood viscosity in tube flow: dependence on diameter and hematocrit. Am. J. Physiol. 263 (Heart Circ. Physiol. 32): H1770-H1778, 1992. — Since the original publications by Martini et al. (Dtsch. Arch. Klin. Med. 169: 212–222, 1930) and Fahraeus and Lindqvist (Am. J. Physiol. 96: 662–668, 1921), it has been known that the relative apparent viscosity of blood in tube flow depends on tube diameter. Quantitative descriptions of this effect and of the dependence of blood viscosity on hematocrit in the different diameter tubes are required for the development of hydrodynamic models of blood flow through the microcirculation. The present study provides a comprehensive data base for the description of relative apparent blood viscosity as a function of tube diameter and hematocrit. Data available from the literature are compiled, and new experimental data obtained in a capillary viscometer are presented. The combined data base comprise measurements at high shear rates (\(\dot{\theta} \geq 50 \text{ s}^{-1}\)) in tubes with diameters ranging from 3.3 to 1.978 \(\mu\) at hematocrits of up to 0.9. If corrected for differences in suspending medium viscosity and temperature, the data show remarkable agreement. Empirical fitting equations predicting relative apparent blood viscosity from tube diameter and hematocrit are presented. A pronounced change in the hematocrit dependence of viscosity is observed in a range of tube diameters in which viscosity is minimal. While a linear hematocrit-viscosity relationship is found in tubes of \(\leq 6 \mu\), an overproportional increase of viscosity with hematocrit prevails in tubes of \(\geq 9 \mu\). This is interpreted to reflect the hematocrit-dependent transition from single- to multi-filte arrangement of cells in flow.

It has been known for a long time that apparent blood viscosity depends not only on hematocrit, plasma protein concentration, and temperature but also on the shear forces applied and the geometry of the instrument in which it is measured. Martini et al. (33) as well as Fahraeus and Lindqvist (16) were the first to observe a significant decrease of apparent blood viscosity in tubes with diameters ranging between \(\sim 500 \text{ and } 50 \mu\). This reduction in apparent blood viscosity, which has been named Fahraeus-Lindqvist effect, is especially relevant if measurements of apparent viscosity are to be applied to blood flow through the vascular system. Blood vessels exhibit diameter variations over four orders of magnitude ranging from \(\sim 3 \text{ cm}\) in the large systemic vessels down to \(3 \mu\) in skeletal muscle capillaries.

The Fahraeus-Lindqvist effect was confirmed in vitro by a large number of investigators (2, 4–8, 10, 19, 21–23, 25, 34, 41–43, 51, 54) who demonstrated that the decrease of apparent blood viscosity continues down to diameters of \(\sim 10 \mu\). For even smaller diameters approaching the minimum cylindrical diameter of normal human erythrocytes (\(\sim 2.7 \mu\)), Gerbstãdt et al. (21) and Gaehgens (19) reported a steep increase of viscosity. Empirical descriptions of blood viscosity as a function of tube diameter were derived based on compilations of literature data (19, 30, 37, 40, 55). Such compilations are a prerequisite for the development and use of hydrodynamic models of the cardiovascular system and especially of the terminal vascular bed, since the contribution of different size microvessels to total peripheral resistance is strongly affected by diameter-dependent variation of blood viscosity. Hydrodynamic models of vascular perfusion have proved to be important tools, allowing a correlation of data obtained from whole organ studies with those derived from single microvessels (17, 18, 26, 31, 36, 37, 40, 44, 48, 55).

However, earlier data compilations were derived from too limited data material and provide fitting algorithms that do not adequately represent all features of the experimental data. Furthermore, the analysis of the hematocrit dependence of apparent viscosity in different size tubes was hitherto limited by the paucity of available data for wide hematocrit ranges. In the present report, an attempt is therefore made to provide a comprehensive quantitative description of viscosity measurements available in the literature. In addition, new experimental data are presented to obtain a more complete data set relating apparent blood viscosity to vessel diameter in a wider range of hematocrits. In this context, only data obtained at high shear rates (\(\dot{\theta} \geq 50 \text{ s}^{-1}\)) are considered. This may be justified for a first approximation to blood flow in the microcirculation for at least two reasons. 1) The influence of shear rate on viscosity appears to be small in the shear rate range existing in the microcirculation under normal conditions. Pseudo-shear rates (\(\dot{\theta}\), i.e., mean blood velocity divided by vessel diameter) generally range above 50 s\(^{-1}\) (32), whereas significant effects of shear rate on viscosity, at least in tube flow, are to be expected at substantially lower \(\dot{\theta}\) (43). 2) The shear rate dependence of blood is influenced by several additional factors, the importance of which for microcirculatory perfusion is not easily assessed. It has been shown that the increase of viscosity in low-shear-rate tube flow is strongly affected by cell sedimentation (9, 13, 42) and is further complicated by the effect of erythrocyte aggregation tendency. In addition, transit times of blood through the vessel segments of microcirculatory networks under normal flow conditions are probably shorter than required for the development of cell aggregation and sedimentation and thus of steady state viscosity at low shear rates.

Data base

Literature data. The data base used in this report comprises measurements of viscosity of blood or red cell suspensions from 13 studies in the literature. These measurements were carried out in a wide range of tube diameters (\(\sim 3–2,000 \mu\)) and hematocrits up to 0.9 with different experimental methods (Tables 1 and 2). In addition, results of earlier viscosity measurements by two of the authors (Gaehgens and Pries) and by Barbee and Cokelet (personal communication) that were not previously...
Table 1. Methodological characteristics of viscosity measurements and relationship between apparent viscosity and hematocrit

<table>
<thead>
<tr>
<th>Authors</th>
<th>Species</th>
<th>Sample (anticoagulant)</th>
<th>Temp. °C</th>
<th>Tube Diameter, μm</th>
<th>Tube Length, mm</th>
<th>Pseudo-Shear Rate, diam/s</th>
<th>Method of Flow Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martini et al. (1930)</td>
<td>Human</td>
<td>Whole blood (Hirudin)</td>
<td>36</td>
<td>70000</td>
<td>24-194</td>
<td>1,300-800</td>
<td>Fluid-air meniscus in series-coupled pipette</td>
</tr>
<tr>
<td>Fahraeus &amp; Lindqvist</td>
<td>Human</td>
<td>Whole blood (EDTA)</td>
<td>38</td>
<td>40-505</td>
<td>13-127</td>
<td>&gt;200</td>
<td>Fluid-air meniscus in series-coupled pipette</td>
</tr>
<tr>
<td>Bayliss (1952)</td>
<td>Dog</td>
<td>Defibrinated blood</td>
<td>Room</td>
<td>14-139 (scaled)</td>
<td>~1.5-3</td>
<td>?</td>
<td>Fluid-air meniscus in series-coupled pipette</td>
</tr>
<tr>
<td>Haynes &amp; Burton (1959)</td>
<td>Human</td>
<td>RBC (ACD)</td>
<td>25.5</td>
<td>114-944</td>
<td>&gt;175</td>
<td>&gt;200</td>
<td>Fluid-air meniscus in series-coupled pipette</td>
</tr>
<tr>
<td>Prothaler &amp; Burton (1962)</td>
<td>Human</td>
<td>Whole blood (ACD)</td>
<td>23.5</td>
<td>9.4</td>
<td>~1</td>
<td>&gt;3,000</td>
<td>Size of droplet produced at capillary tip</td>
</tr>
<tr>
<td>Cerbotadi et al. (1966)</td>
<td>Human</td>
<td>Whole blood (heparin)</td>
<td>20</td>
<td>4.2-70</td>
<td>~2,500-diam</td>
<td>120-300</td>
<td>Fluid fluid meniscus in series coupled pipette</td>
</tr>
<tr>
<td>Brasch &amp; Jenett (1980)</td>
<td>Pig</td>
<td>Defibrinated blood</td>
<td>Room</td>
<td>5.6-47 (scaled)</td>
<td>~1-2</td>
<td>100-400</td>
<td>Pressure created by outflow in sealed chamber, oscillating flow</td>
</tr>
<tr>
<td>Gupta &amp; Seshadri (1977)</td>
<td>Human</td>
<td>RBC in saline</td>
<td>31</td>
<td>86-444</td>
<td>75-82</td>
<td>&gt;50</td>
<td>Fluid-air meniscus in series-coupled pipette</td>
</tr>
<tr>
<td>Voss (1983)</td>
<td>Human</td>
<td>RBC in saline (EDTA)</td>
<td>37</td>
<td>34-95</td>
<td>~1,000-diam</td>
<td>180-140</td>
<td>Pressure created by outflow in sealed chamber</td>
</tr>
<tr>
<td>Reimke et al. (1986)</td>
<td>Human</td>
<td>Whole blood (EDTA)</td>
<td>Room</td>
<td>31-94</td>
<td>55-65</td>
<td>~50</td>
<td>Fluid-fluid meniscus in series-coupled pipette</td>
</tr>
<tr>
<td>Reimke et al. (1987)</td>
<td>Human</td>
<td>Whole blood (FIDTA)</td>
<td>Room</td>
<td>31-132</td>
<td>38-73</td>
<td>100</td>
<td>Fluid-fluid meniscus in series-coupled pipette</td>
</tr>
<tr>
<td>McKay &amp; Meiselman (1988)</td>
<td>Human</td>
<td>RBC in saline</td>
<td>21</td>
<td>33-146</td>
<td>~65</td>
<td>630-420</td>
<td>Flow imposed by syringe, pressure difference measured</td>
</tr>
<tr>
<td>Stadler et al. (1990)</td>
<td>Human</td>
<td>RBC in plasma (EDTA)</td>
<td>37</td>
<td>50-500</td>
<td>10-100</td>
<td>&gt;100</td>
<td>Fluid-air meniscus in series-coupled pipette</td>
</tr>
<tr>
<td>Barbee &amp; Cokelet, personal commun</td>
<td>Human</td>
<td>Whole blood (ACD)</td>
<td>23</td>
<td>29-99</td>
<td>200-380</td>
<td>~90</td>
<td>Flow imposed by syringe, pressure difference measured (Barbee and Cokelet, 1971)</td>
</tr>
<tr>
<td>Gahtgens &amp; Pries, personal commun</td>
<td>Human</td>
<td>RBC in saline (EDTA)</td>
<td>Room</td>
<td>3.3-6</td>
<td>~4</td>
<td>&gt;50</td>
<td>Optical measurement of RBC and plasma velocity (Albrecht et al., 1979)</td>
</tr>
<tr>
<td>Present data</td>
<td>Human</td>
<td>RBC in plasma (EDTA)</td>
<td>Room</td>
<td>9-40</td>
<td>6-11</td>
<td>&gt;200</td>
<td>Fluid-air meniscus in series-coupled tube</td>
</tr>
</tbody>
</table>

Apparent viscosity and hematocrit

| Whitaker & Winton (1933) | Dog     | Whole blood defibrinated (ACD) | 37 | 930 | 303 | ~150 | Sampling of tube outflow |
| Barbee (1973)            | Human   | Whole blood (ACD)              | 23, 37 | 811 | 280 | 100  | Flow imposed by syringe, pressure difference measured |
| Brooks et al. (1969)     | Human   | RBC in saline                  | 25 (170.8 s⁻¹) | (52 s⁻¹) | Rotational viscometer, Coaxial cylinder type |
| Chien et al. (1971)      | Human   | RBC in saline                  | 37 (170.8 s⁻¹) | (52 s⁻¹) | Rotational viscometer, coaxial cylinder type |

RBC, erythrocytes; ACD, acid-citrate-dextrose.

Published in the present form are included.

The viscosity of blood during tube flow is strongly correlated with the volume concentration of erythrocytes within the tube. The tube hematocrit (Hctₜ) is the hematocrit of the blood entering the capillary tube (discharge hematocrit, Hctₜ₋), which is taken to be identical to Hct in those data sets in which discharge hematocrit was not explicitly stated.

Three of the literature studies analyzed have been performed with blood from species (pig, dog) other than humans. Because the mean red cell volume (MCV) of these species differs from that found in humans, the tube diameters given in these reports were scaled using the cube root of the ratio of the respective MCVs. This recognizes the fact that apparent blood viscosity is closely related to the cell-to-tube diameter ratio (λ).

Some references that have been included in previous compilations (19, 30) are not included in the present data base. Jay et al. (28) used a conical measuring capillary, which may have caused uneven hematocrit distribution along the tube. In the studies of Barres (5-7), the viscosity reported from measurements in tubes with diameters of 1 mm is significantly lower than that measured in rotational viscometers, whereas in tubes of ~0.5 mm diameter the viscosity is much higher. Although specific reasons for these discrepancies are not clear, these data have not been included.
Table 2. Statistical results for dependence of apparent blood viscosity on hematocrit

<table>
<thead>
<tr>
<th>Authors</th>
<th>$D$, μm</th>
<th>$n$</th>
<th>$Hct_D$ min</th>
<th>$Hct_D$ max</th>
<th>$B$</th>
<th>$C$</th>
<th>$r^2$</th>
<th>$r^{'2}$ (linear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gahtgens &amp; Pries</td>
<td>3.3</td>
<td>72</td>
<td>0</td>
<td>0.33</td>
<td>12.99</td>
<td>-0.431</td>
<td>0.852</td>
<td>0.844</td>
</tr>
<tr>
<td>Gahtgens &amp; Pries</td>
<td>4.4</td>
<td>96</td>
<td>0</td>
<td>0.65</td>
<td>-0.80</td>
<td>1.539</td>
<td>0.776</td>
<td>0.769</td>
</tr>
<tr>
<td>Gahtgens &amp; Pries</td>
<td>5.6</td>
<td>44</td>
<td>0</td>
<td>0.36</td>
<td>-0.42</td>
<td>3.850</td>
<td>0.773</td>
<td>0.737</td>
</tr>
<tr>
<td>Gahtgens &amp; Pries</td>
<td>6</td>
<td>170</td>
<td>0</td>
<td>0.63</td>
<td>-0.49</td>
<td>2.66</td>
<td>0.533</td>
<td>0.505</td>
</tr>
<tr>
<td>Present data</td>
<td>9</td>
<td>45</td>
<td>0</td>
<td>0.87</td>
<td>0.82</td>
<td>-0.879</td>
<td>0.937</td>
<td>0.899</td>
</tr>
<tr>
<td>Present data</td>
<td>12</td>
<td>54</td>
<td>0.03</td>
<td>0.89</td>
<td>0.36</td>
<td>-1.299</td>
<td>0.948</td>
<td>0.512</td>
</tr>
<tr>
<td>Present data (medium viscosity 1.85 cP)</td>
<td>20</td>
<td>59</td>
<td>0.05</td>
<td>0.8</td>
<td>0.86</td>
<td>-0.908</td>
<td>0.935</td>
<td>0.731</td>
</tr>
<tr>
<td>Present data (medium viscosity 5.5 cP)</td>
<td>20</td>
<td>67</td>
<td>0.03</td>
<td>0.84</td>
<td>0.91</td>
<td>-0.814</td>
<td>0.968</td>
<td>0.723</td>
</tr>
<tr>
<td>Present data (medium viscosity 9 cP)</td>
<td>20</td>
<td>37</td>
<td>0.05</td>
<td>0.8</td>
<td>1.41</td>
<td>-0.599</td>
<td>0.926</td>
<td>0.788</td>
</tr>
<tr>
<td>Bayliss (1952)</td>
<td>26</td>
<td>10</td>
<td>0.05</td>
<td>0.9</td>
<td>1.15</td>
<td>-0.988</td>
<td>1.000</td>
<td>0.570</td>
</tr>
<tr>
<td>Reinke et al. (1986)</td>
<td>31</td>
<td>8</td>
<td>0.12</td>
<td>0.64</td>
<td>1.07</td>
<td>-0.907</td>
<td>0.986</td>
<td>0.799</td>
</tr>
<tr>
<td>Present data</td>
<td>40</td>
<td>64</td>
<td>0.03</td>
<td>0.8</td>
<td>1.16</td>
<td>-0.930</td>
<td>0.975</td>
<td>0.726</td>
</tr>
<tr>
<td>Reinke et al. (1986)</td>
<td>41</td>
<td>13</td>
<td>0.15</td>
<td>0.65</td>
<td>1.31</td>
<td>-0.930</td>
<td>0.962</td>
<td>0.679</td>
</tr>
<tr>
<td>Bayliss (1952)</td>
<td>55</td>
<td>10</td>
<td>0.05</td>
<td>0.9</td>
<td>3.54</td>
<td>-0.743</td>
<td>1.000</td>
<td>0.645</td>
</tr>
<tr>
<td>Barbee &amp; Cokelet</td>
<td>75</td>
<td>7</td>
<td>0.18</td>
<td>0.59</td>
<td>2.10</td>
<td>-0.801</td>
<td>0.999</td>
<td>0.964</td>
</tr>
<tr>
<td>Reinke et al. 1986</td>
<td>94</td>
<td>5</td>
<td>0.2</td>
<td>0.59</td>
<td>2.53</td>
<td>-0.749</td>
<td>0.975</td>
<td>0.850</td>
</tr>
<tr>
<td>Barbee &amp; Cokelet</td>
<td>99</td>
<td>7</td>
<td>0.15</td>
<td>0.55</td>
<td>2.15</td>
<td>-0.875</td>
<td>0.997</td>
<td>0.894</td>
</tr>
<tr>
<td>Barbee &amp; Cokelet</td>
<td>128</td>
<td>5</td>
<td>0.23</td>
<td>0.345</td>
<td>2.04</td>
<td>-0.851</td>
<td>0.996</td>
<td>0.870</td>
</tr>
<tr>
<td>Barbee &amp; Cokelet</td>
<td>153.5</td>
<td>7</td>
<td>0.2</td>
<td>0.54</td>
<td>2.86</td>
<td>-0.769</td>
<td>0.998</td>
<td>0.892</td>
</tr>
<tr>
<td>Barbee &amp; Cokelet</td>
<td>221</td>
<td>4</td>
<td>0.2</td>
<td>0.65</td>
<td>3.18</td>
<td>-0.721</td>
<td>0.996</td>
<td>0.843</td>
</tr>
<tr>
<td>Barbee &amp; Cokelet</td>
<td>811</td>
<td>9</td>
<td>0.12</td>
<td>0.59</td>
<td>2.92</td>
<td>-0.808</td>
<td>0.997</td>
<td>0.876</td>
</tr>
<tr>
<td>Barbee (1973)</td>
<td>811</td>
<td>15</td>
<td>0.12</td>
<td>0.59</td>
<td>2.93</td>
<td>-0.813</td>
<td>0.996</td>
<td>0.886</td>
</tr>
<tr>
<td>Whittaker &amp; Winton</td>
<td>930</td>
<td>90</td>
<td>0.05</td>
<td>0.8</td>
<td>1.49</td>
<td>-0.885</td>
<td>0.996</td>
<td>0.881</td>
</tr>
<tr>
<td>Whittaker &amp; Winton</td>
<td>930</td>
<td>11</td>
<td>0</td>
<td>0.84</td>
<td>3.46</td>
<td>-0.778</td>
<td>0.996</td>
<td>0.787</td>
</tr>
<tr>
<td>Brooke et al. (1970)</td>
<td>11</td>
<td>11</td>
<td>0.08</td>
<td>0.70</td>
<td>4.15</td>
<td>-0.900</td>
<td>0.991</td>
<td>0.826</td>
</tr>
<tr>
<td>Chien et al. (1971)</td>
<td>6</td>
<td>54</td>
<td>0.25</td>
<td>0.93</td>
<td>9.12</td>
<td>-0.733</td>
<td>0.975</td>
<td>0.488</td>
</tr>
</tbody>
</table>

$D$, tube diameter; $Hct_D$, discharge hematocrit; $B$, steepness; $C$, curvature; $r^2$, correlation coefficient.

The absolute apparent viscosities given in the literature reports show a high degree of variability even at a given tube diameter and hematocrit. This can in part be attributed to the variation of suspending medium viscosity used, which covers a 2.5 fold range between different studies. Therefore data were corrected for medium viscosity by calculating a relative apparent blood viscosity ($\eta_{rel}$). If medium viscosity was not given in a study, the respective value was deduced from the type of medium used (e.g., saline) and the temperature. Corrections for temperature were not made, since $\eta_{rel}$ is supposed to be independent of temperature (3).

Experimental data. The present study also includes new experimental data obtained by tube flow viscometry in glass capillaries with diameters between 9 and 40 μm at hematocrits between 0.05 and 0.89. The capillary viscometer was described in detail elsewhere (35). In brief, the viscometer (Fig. 1) consisted of a small (2 ml) reservoir connected to the vertical glass capillary (length between 6 and 11 mm). The exit orifice of the capillary was connected to one end of a horizontal measuring tube with an inner diameter 10–20 times larger than that of the capillary. The other end of the measuring tube was connected to negative-pressure source and a mercury manometer. The system was initially filled with isotonic degassed saline, which was then replaced in the reservoir by the sample to be analyzed.

For measurement of viscosity, a negative pressure (between -100 and -300 mmHg) was applied and the advancement of the saline-air meniscus in the measuring tube per time recorded with a stereomicroscope. With each sample, at least six determinations of meniscus velocity were made at each driving pressure, and at least three different driving pressures were employed. Results were averaged for calculation of viscosity. Plasma perfusion always preceded a perfusion with a red cell suspension.

Human venous blood was obtained by venipuncture from healthy donors and anticoagulated with EDTA (2.5 mg/ml).

Erythrocytes were washed with buffered saline and resuspended in autologous plasma at hematocrits up to 0.89. From each blood sample, at least six suspensions with different hematocrits were prepared. Additional cell suspensions were prepared in which the suspending medium viscosity was elevated from 1.85 cP to 5.5 and 9.0 cP (values measured at room temperature), respectively. By addition of dextran (40,000 mol wt) to the plasma. The red cell suspension in the reservoir was gently stirred to prevent erythrocyte sedimentation. The relative apparent viscosity of the red cell suspensions was obtained by dividing the meniscus velocity obtained with plasma by that determined with the red cell suspension at the same pressure head.

![Fig. 1. Capillary viscometer setup. Vertical capillary is perfused from a feeding reservoir by applying a negative pressure to downstream end of horizontal measuring tube. Advancement of fluid-air meniscus in measuring tube is recorded per unit time. Comparison of meniscus velocity measured at identical driving pressures for plasma, and red cell suspension to be tested yields values of relative apparent viscosity.]
The perfusion pressures chosen provided shear rates exceeding 200 s\(^{-1}\) even for the high hematocrit samples. Systematic variations of relative viscosity with \(\dot{\gamma}\) were not observed. All measurements were carried out at room temperature (20-23°C).

**DATA PRESENTATION AND ANALYSIS**

**Diameter dependence.** A total of 163 original values of relative apparent viscosity of red cell suspensions obtained from the 18 studies (Table 1) are shown in Fig. 2. These measurements were made at Hct\(_F\) between 0.4 and 0.45. If Hct\(_F\) was <0.45, the viscosity was extrapolated to a hematocrit of 0.45

\[
\eta_{rel,0.45} = 1 + (\eta_{rel} - 1) \cdot (0.45/\text{Hct}_F) \quad (I)
\]

The data demonstrate a consistent trend according to the Fahraeus-Lindqvist effect. \(\eta_{rel, 0.45}\) reaches a value of \(\sim 3.2\) at tube diameters of \(>1,000 \mu m\), which is in agreement with the values obtained in rotational viscometers (11, 12). In tubes with diameters of \(<1,000 \mu m\), \(\eta_{rel, 0.45}\) decreases with decreasing diameter. The lowest values of \(\eta_{rel, 0.45}\) (\(\sim 1.25\)) are found at tube diameters of \(\sim 7 \mu m\). This statement is, however, based on the results of only four studies, and only one of these (21) allows a direct determination of the viscosity minimum because of the diameter range covered. The paucity of data in this range reflects the experimental difficulties encountered in perfusion studies with tube diameters of capillary dimensions.

A number of analytical approaches have been developed to describe the variation of \(\eta_{rel}\) with tube diameter. In some of these approaches blood flow is modeled by assuming a cell-rich core surrounded by a marginal cell-poor layer (14, 24, 45, 53, 56), whereas others assume a number of concentric, unsheared laminae of finite size (24, 29). Secomb and co-workers (46, 47, 49) used the lubrication theory to model apparent blood viscosity under single-file conditions, whereas Barbee and Cokelet (4) deduced the changes in apparent viscosity from changes in Hct\(_F\) relative to the hematocrit in the feed reservoir. Each of these models provides predictions for a limited diameter range only (30), and a comprehensive theory for a larger diameter and hematocrit range still seems to be lacking.

Therefore a purely empirical fit appears to represent the best way to describe the experimental data and to allow application of the results to model simulations of
blood flow through vascular beds. In such a fit, the residual variance of experimental data from an arbitrary function is minimized and the parameters of the function generally have no specific physical meaning. In the present study, a combination of two exponential equations was used, in which the first term dominates the increase of viscosity with decreasing tube diameter ($D, \mu m$) in the range below $\sim 7 \mu m$, and the following two terms govern the fit to the viscosity data at higher tube diameters

$$\eta_{rel,0.45} = 220 \cdot e^{-1.3D} + 3.2 - 2.44 \cdot e^{-0.06D^{0.445}}$$

This equation was designed to asymptotically approach, with increasing diameter, a preset viscosity value at infinite tube diameter, to show a minimum in an intermediate diameter range and a steep increase in the smallest tubes. An asymptotic increase of viscosity to infinity for vessel diameters approaching the theoretical minimum cylindrical cell diameter (2.7 $\mu m$) was not attempted, since such a behavior of the equation did not allow an optimal fit of the available data at the low end of the diameter scale. This might be due to the fact that a fixed-diameter threshold estimated from averaged quantities of red cell volume and surface area underestimates the influence of the large variability of these parameters within the cell population of a given blood sample. Even a small fraction of large erythrocytes might lead to a substantial increase of viscosity in tubes that are much larger than the idealized theoretical minimum cylindrical cell diameter.

The numerical parameters of the final fit were adjusted interactively on the basis of the correlation coefficient of the fit and its residuals (Fig. 2). An automatic nonlinear regression procedure was not used, since the number of available data points is not uniformly distributed in the diameter range. In addition, in the low tube diameter range the number of data points given in the individual studies differs strongly. The $r^2$ value reached for the final fit of the data was 0.919 ($n = 163$).

**Hematocrit dependence.** In rotational viscometers, apparent blood viscosity increases in an nonlinear fashion with hematocrit (11, 12). A qualitatively similar behavior is found in glass tubes down to a diameter of $\sim 9 \mu m$ (Fig. 3). In even smaller tubes, however, the relationship between viscosity and hematocrit seems to be linear, at least in the experimentally investigated range. To account for these differences in a parametric mathematical description, it is necessary to include a term reflecting the count for these differences in a parametric mathematical description. Although a number of authors provide viscosity values for more than one hematocrit, the range of hematocrits covered and/or the number of samples with different hematocrits is too low in many cases. Results of some studies were not utilized in the present analysis, since the cell suspensions were obtained from patients exhibiting largely differing systemic hematocrits (e.g., Ref. 38). In addition, data obtained in Ostwald viscometers (e.g., Ref. 92) were not included, since the shear rates in this instrument are rather low and in turn depend on viscosity, which could have resulted in an overestimation of the viscosity increase with increasing hematocrit.

Using the present experimental results as well as those available in the literature (Table 1), we found that a consistently satisfying description of the hematocrit-viscosity relationship was obtained with the following equation

$$\eta_{rel} = 1 + B \cdot [(1 - Hct)^C - 1]$$

In this equation, the parameter $C$ describes the curvature of the relationship between relative apparent blood viscosity and hematocrit. A value of 1 corresponds to a linear dependence, whereas values of $<1$ indicate a convex shape of the relationship toward the abscissa, as generally described for larger tubes or rotational viscometers. By use of an iterative procedure maximizing the correlation coefficient ($r^2$) between measured and predicted values, $C$ was optimized for each data set analyzed (Table 2). For tube diameters between 3.3 and 6 $\mu m$, the values of $r^2$ obtained upon optimization of $C$ showed no statistically significant difference from those for a linear relationship ($r^2$ linear). Therefore capillaries in that diameter range were assigned a $C$ value of 1. The resulting values of $C$ are plotted as a function of tube diameter in Fig. 4 along with values calculated for data obtained in rotational viscometers.

The data shown in Fig. 4 indicate a rapid transition from a linear ($C \sim 1$) to a convex shape of the viscosity-hematocrit relationship in the diameter range between
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Combined dependence of viscosity on diameter and hematocrit. To allow a combined description of apparent blood viscosity as a function of both vessel diameter and hematocrit, Eq. 2 was used to derive diameter-dependent values for the parameter B of Eq. 3. According to Eq. 3, the relative viscosity for a hematocrit of 0.45 ($\eta_{rel,0.45}$) is given as

$$\eta_{rel,0.45} = 1 + B \cdot [(1 - 0.45)^C - 1] \quad (5)$$

This equation can be solved for B to give

$$B = \frac{\eta_{rel,0.45} - 1}{(1 - 0.45)^C - 1} \quad (6)$$

Substitution of Eq. 6 into Eq. 3 results in

$$\eta_{rel} = 1 + (\eta_{rel,0.45} - 1) \cdot \frac{(1 - Hct_D)^C - 1}{(1 - 0.45)^C - 1} \quad (7)$$

Numerical values for $\eta_{rel,0.45}$ and C for a given diameter may be obtained from $\eta_{rel,0.45}$ and C for a given diameter under comparable conditions. Predictions of relative apparent blood viscosity based on this procedure are compared in Fig. 5 with experimental values for the Hct_D levels of 0.2, 0.45, and 0.60.
If the fitting equations presented here are to be used in applications in which Hct_D, but not Hct_T, is known, empirical information on the Fahraeus effect and its dependence on tube diameter and hematocrit must be used. In the present context, a previously compiled (40) parametric description of the Fahraeus effect is used

\[
\frac{\text{Hct}_T}{\text{Hct}_D} = (1 - \text{Hct}_T) \cdot (1 + 1.7 \cdot e^{-0.38D} - 0.6 \cdot e^{-0.01D})
\]

In the following, the numeric term will be replaced by

\[
X = 1 + 1.7 \cdot e^{-0.38D} - 0.6 \cdot e^{-0.01D}
\]

for reasons of simplicity. Equation 8 can be solved for Hct_D using standard procedures

\[
\text{Hct}_D = \frac{X}{2 - 2X} + \left[ \frac{X}{\left(2 - 2X\right)} + \frac{\text{Hct}_T}{1 - X} \right]^{0.5}
\]

to allow the calculation of apparent relative viscosity using the fitting algorithms presented here. The results of such calculations are shown in Fig. 6 in which the dependence of viscosity on diameter is compared for three fixed Hct_T levels with that given in Fig. 5 for Hct_D.

**DISCUSSION**

The experimental data of apparent blood viscosity derived from the literature for a hematocrit of 0.45 show remarkable agreement despite the large variability of suspension media and experimental conditions of measurement (Table 1). The composition of suspensions in the data sets presented here ranges from anticoagulated whole blood to washed erythrocytes in saline, the temperatures between 15 and 30°C, and the viscosity of the suspending medium from 0.49 to 1.93 cP. As obvious from Fig. 2, these differences seem to exert no major effect on relative viscosity for a hematocrit of 0.45. The effects of temperature and medium viscosity were quantified by analyzing the deviation of the individual data points from the fitting line according to Eq. 2 (Fig. 2). The regression of these residuals against temperature and medium viscosity yielded extremely weak correlations, with slopes of -0.005 for the dependence on temperature (in °C) and 0.069 for the dependence of \( \eta_{rel} \) on medium viscosity (in cP). The corresponding correlation coefficients \( r^2 = 0.052 \) and 0.036, respectively) indicate that only \( \sim 5\% \) of the residual variance of viscosity can be explained by these factors. It therefore appears to be justified for a large range of experimental conditions (temperature, blood composition) to calculate apparent blood viscosity from the relative viscosity as given here and the viscosity of the suspending medium used.

A minor but systematic effect of medium viscosity was, however, found in the shape of the relation between \( \eta_{rel} \) and Hct_T in the experiments in which the viscosity of the suspending medium was deliberately elevated from 1.85 cP to 5.5 and 9 cP, respectively (Table 2). Although \( \eta_{rel} \) at a hematocrit of 0.45 showed no systematic changes under these conditions, the C value increased from -0.901 to -0.814 and -0.599, respectively, with increasing suspending medium viscosity indicating more linear relations between viscosity and hematocrit at high medium viscosities.

The diameter dependence of blood viscosity is indirectly related to the \( \lambda \) (the cell-to-tube diameter ratio). This is true for both the steepness (\( B \) in Eq. 3) and the curvature (C in Eq. 3) of the relation between \( \eta_{rel} \) and hematocrit. The relative amount of energy dissipation due to cell-cell interactions in the central flow regions decreases with increasing \( \lambda \), whereas the impact of the marginal cell poor flow regions on apparent viscosity increases. This leads to a continuous decline of \( \eta_{rel} \) with decreasing tube diameter starting at diameters of \( \sim 1,000 \) \( \mu m \) down to a diameter range in which the deformation of erythrocytes is limited because of their surface area and volume ratio. At even smaller tube diameters, the thickness of the lubricating plasma layer around the erythrocyte core decreases and the apparent blood viscosity starts to increase (48).

The changes of the curvature index C with decreasing tube diameter probably reflect the transition from multifile flow conditions found in larger tubes to the single-file conditions in small capillaries. Under multifile flow conditions, addition of erythrocytes to the flowing blood leads to an overproportional increase of the energy dissipation due to augmented cell-cell interactions. This leads to a strong curvature of the relation between \( \eta_{rel} \) and Hct_D and a low value of C. In single file flow, which occurs in small tubes with high values of \( \lambda \), however, interactions between individual erythrocytes are minimal at low hematocrits and each additional erythrocyte leads to a finite increase of total pressure drop along the vessel. Therefore the relation between hematocrit and blood viscosity is linear (50). At higher hematocrits, the stacked coin model (50) predicts a less than proportional increase of \( \eta_{rel} \) due to plasma trapping between erythrocytes. The overall shape of the viscosity-hematocrit relationship should therefore be bent away from the abscissa, yielding curvature indexes of \( >1 \). Such a tendency was in fact found in capillaries with diameters between 6 and 4.4 \( \mu m \) (Table 2). However, the limited hematocrit range tested in these capillaries and the large scatter of the data points does not allow a thorough evaluation of the observed curvature. For the smallest capillary tested (\( D = 3.3 \mu m \),
the optimized $C$ value falls to $<1$, indicating an overproportional increase of viscosity with hematocrit, but there was again no statistically significant difference compared with the $C$ value of a linear fit. We therefore chose to represent the data for all capillaries with diameters from 6 to 3.3 $\mu$m with a $C$ value of 1.

The data given in Fig. 4 indicate a sharp transition between single- and multifile flow regimes between tube diameters of 6 and 9 $\mu$m. In addition, there is some indication of a minimum of $C$ in the diameter range just above the transition zone.

A hypothetical explanation of these findings can be deduced from the available knowledge of the hematocrit and diameter dependence of the erythrocyte arrangement in tube flow. In tubes of $<6 \mu$m, erythrocytes will travel in a single-file flow pattern regardless of hematocrit, since only one cell can be accommodated in a given tube cross section. In slightly larger tubes, however, direct observations (20) have shown that single-file flow occurs at low hematocrit, whereas multifile flow conditions prevail at higher hematocrits. In this diameter range, $\eta_{rel}$ should therefore increase approximately linearly with hematocrit in the low hematocrit range, whereas above a certain threshold viscosity should increase overproportionally. Combining a linear initial with a curved segment would result in a relationship between $\eta_{rel}$ and $HctD$, characterized by lower $C$ values than those determined for larger tubes in which multifile flow conditions prevail over most of the hematocrit range. These considerations suggest the use of a two-phase fitting equation to the viscosity-hematocrit relationship that describes the hematocrit threshold at which the transition between the linear and the overproportional domain takes place. However, the available experimental data do not support such a procedure for the investigated diameter range. In most studies, this might be due to the limited hematocrit range covered in the experiments or the low number of data points obtained. But even in the diameter range between 9 and 40 $\mu$m, in which the present experimental data provide a large data base (Fig. 3), no sharp transition in the viscosity-hematocrit relationship can be identified and the experimental data are adequately fitted with the continuous Eq. 3.

The present study was aimed at providing an empirical description of experimental data correlating apparent blood viscosity, tube diameter, and hematocrit. This was intended to allow the developments of models simulating blood flow through microvascular networks. Because this compilation demonstrates consistent trends and remarkable agreement, it might also stimulate the development of theoretical concepts for a rheological analysis of apparent blood viscosity in tube flow. A comparison of theoretical predictions with combined experimental results from various studies would provide a better evaluation criterion than those available for theoretical treatments up to date (14, 24, 27, 29, 53, 56).

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