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Viscosity Reduction of Red Blood Cells from Preterm and Full-Term Neonates and Adults in Narrow Tubes (Fahraeus-Lindqvist Effect)

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ABSTRACT. In artificial tubes as well as in blood vessels with diameters less than 500 μm, blood viscosity decreases with decreasing diameter (Fahraeus-Lindqvist effect). Our study measured viscosity of red blood cells (RBC) from 10 preterm infants, 10 term neonates, and 10 adults by means of a capillary viscometer. RBC were suspended in buffer at hematocrits of 0.20, 0.40, and 0.60 1/1 (1.00 l/l = 100%). Tubes with diameters of 50, 100, and 500 μm were perfused with these suspensions. Viscosity in the 500-μm tubes was not significantly different, at any hematocrit, among the three groups. Viscosity decreased at each of the adjusted hematocrits in the three groups when going from a 500-μm tube to a 50-μm tube. At a hematocrit of 0.60 1/1, viscosity reduction averaged 48 ± 7% in the preterm infants, 42 ± 8% in the full-term neonates, and 35 ± 5% in the adults, whereas the reductions at a hematocrit of 0.20 1/1 were only 32 ± 6, 27 ± 4, and 24 ± 6%, respectively. For the combined data from the neonates and adults, there was a significant inverse relationship of the viscosity in 50-μm tubes at a hematocrit of 0.60 1/1 to the mean corpuscular volume ($r = 0.69$). To evaluate whether increased membrane elasticity of neonatal RBC contributes to the stronger viscosity reduction of neonatal RBC in narrow tubes, heated neonatal and adult RBC were also studied. The resulting loss of membrane elasticity caused a marked decrease in the viscosity reduction in 50-μm tubes, particularly in the neonates. These data indicate that both the large cell volume and the increased membrane elasticity of neonatal RBC contribute to the enhanced viscosity reduction in narrow tubes. The stronger viscosity reduction of neonatal RBC in narrow vessels may be an important prerequisite for the low vascular resistance and high flow conditions in neonates. Moreover, the present data suggest that a high hematocrit does not impede blood flow in neonates as much as in adults, unless the neonatal RBC are exchanged for adult RBC. (*Pediatr Res* 25:595–597, 1989)

Abbreviations

MCH, mean corpuscular Hb
MCV, mean corpuscular volume
RBC, red blood cells

Blood viscosity is an important determinant of the resistance to blood flow (1). Hyperviscosity may, therefore, impede blood flow to various organs, compromise their oxygen supply, and result in organ failure or damage (2–6). In particular, hyperviscosity increases the risk of pulmonary hypertension (6), renal failure (2), necrotizing enterocolitis (7), cerebral ischemia (4), intracranial hemorrhage (8), and developmental retardation (9). Blood viscosity is mainly determined by the hematocrit (2–7, 9–13). Moreover, increased plasma viscosity (11, 13, 14), strong RBC aggregation (15), and decreased RBC deformability (16) can also contribute to an increase in blood viscosity. Blood viscosity in capillary viscometers depends on the tube diameter (17–22) in addition to the other determinants of blood viscosity.

In artificial tubes as well as in blood vessels with diameters of less than 500 μm, both the hematocrit (Fahraeus effect) and the blood viscosity (Fahraeus-Lindqvist effect) decrease with decreasing diameter (18–22). This has been attributed to the migration of RBC to the tube center, thereby creating a cell-poor plasma layer on the wall and a cell-rich central core (17–22). The ratio of the cell-poor wall layer diameter to the tube diameter increases as the tube diameter decreases (20). Inasmuch as the flow velocity increases from the tube wall to the axis, the central cell core leaves the tube more rapidly than the slowly flowing plasma layer at the wall. This results in decreased hematocrit which in turn contributes to decreased blood viscosity (20).

Studies using artificial tubes have shown that the viscosity of adult blood with a hematocrit of 0.40 1/1 (= 40%) decreases by about 40% as the tube diameter is decreased from 500 to 50 μm (18–22). At higher hematocrit, the viscosity reduction may be 60% or more (18, 19). Moreover, viscosity reduction in narrow tubes may be enhanced by a large diameter (20), a wide volume distribution (23) and by RBC deformability (20). Inasmuch as neonatal RBCs are larger, have a wider volume distribution and increased membrane deformability compared to adult RBC (24), viscosity of neonatal blood in narrow tubes and small blood vessels may be considerably lower than that measured by means of rotational viscometers.

The purpose of our study was to measure viscosity of RBC from preterm infants, term neonates, and adults by means of a capillary viscometer.

MATERIALS AND METHODS

Placental blood samples from 20 newborn infants were studied with the approval of the Department of Pediatrics Human Subjects Research Committee. Ten were healthy full-term infants with gestational age of 38 to 41 wk and birth wt of 3350 to 3620 g; 10 were preterm infants with gestational age of 28 to 33 wk and birth wt of 1560 to 2130 g. The gestational age of each infant was derived from the maternal history and confirmed by clinical assessment of maturity. All infants had birth wt appropriate for

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gestational age (10th to 90th percentile according to unpublished Munich Growth Charts). Infants with malformations, erythroblastosis, diabetic mothers, hemorrhage, intrauterine asphyxia, and those delivered by cesarean section were excluded, as were twins and infants with proven infection or high risk of infection.

Blood (10–20 ml) was collected from the placenta into EDTA (1 mg/ml) immediately after cord clamping before delivery of the placenta. Adult blood samples were collected from 10 healthy hospital personnel via venipuncture into EDTA. All measurements were made within 4 h after collection. Previous studies have shown that keeping neonatal or adult blood for this duration does not alter its rheologic properties (11).

RBC were isolated by centrifugation at 2000 × g for 10 min and, by gentle aspiration, the plasma was removed and the buffy coat discarded. The cells were washed once in an isotonic PBS solution (0.122 mol/liter NaCl, 0.030 mol/liter KH_2PO_4 + Na_2HPO_4, 290 mosmol/kg, pH 7.42 at 25°C) containing 1 g/liter of human serum albumin. RBC from each donor were then resuspended in the PBS albumin solution. The hematocrits of the suspensions were adjusted to 0.20, 0.40, and 0.60 1/1 (1.00 1/1 = 100%). In order to evaluate the effect of RBC membrane elasticity on the viscosity in narrow tubes, RBC were heated to 50°C for 1 min and then allowed to cool to 37°C (22, 25). This treatment results in decreased membrane elasticity (increased shear elastic modulus) (25).

Viscosity was measured using a modification (11) of the technique described by Gupta and Seshadri (20). Glass tubes of 50, 100, and 500 μm internal diameter and length of 10 mm were connected to compressed air and a water manometer and maintained at 37°C. Glass tubes were hand-drawn and microscopically inspected for taper and bore uniformity. Tube diameters were checked against those calculated using the Hagen-Poiseuille Law by measuring pressure drop-flow rate relations using water of known viscosity. The pressure drop-flow rate data were found to be linear for all tubes and calculated diameters agreed with those measured optically within ±2%. Experiments were performed using pressure drops of 5 cm H_2O (500-μm tubes), 25 cm H_2O (100-μm tubes), and 50 cm H_2O (50-μm tubes) resulting in a nominal wall shear stress of 62.5 dynes/cm^2. In each experiment, the passage times of the suspending medium and the RBC suspension through the tube were measured. Relative viscosities were calculated as ratio of the passage times of the sample to that of the suspending medium.

Hematocrit was measured in duplicate by the microhematocrit method. The values were not corrected for trapped plasma, which is about 2% for normal RBC from full-term neonates and adults (11) and 11% for heated adult RBC (22). RBC count, MCV (and sample SD) and Hb concentration were determined with a Coulter Counter (Coulter Electronics Inc., Harpenden, Herts, England). Hb F was quantified by the alkali denaturation test (26).

Statistical analyses were performed to test for differences in measurements among the preterm infants, the full-term neonates, and the adults (analysis of variance) (27). Regression analyses (27) were used to determine overall correlations between red cell suspension viscosities, MCV, variation coefficient of MCV, and Hb F.

RESULTS

General data. MCV, MCH, and Hb F of RBC decreased with increasing gestational age and reached the lowest values in the adults (Table 1). The variation coefficient of MCV (computed as ratio of SD and MCV) averaged 24% in the preterm infants, 21% in the term neonates, and 16% in the adults.

Viscosity data. Table 1 shows the viscosities of RBC suspensions with three different hematocrits for tube diameters of 50 and 500 μm. Viscosity in the 500-μm tubes was not significantly different, at any hematocrit, among the three groups. In the 50-μm tubes, viscosity of RBC from the preterm and full-term infants was significantly lower at each adjusted hematocrit compared to the adults. The preterm infants showed lower viscosities, at hematocrits of 0.40 and 0.60 1/1, than the term neonates. The differences among the three groups increased with increasing hematocrit. In the 100-μm tubes, significant differences among the three groups were observed at hematocrits of 0.40 and 0.60 1/1 (Fig. 1).

Viscosity decreased significantly, at any hematocrit, in the three groups when going from a 500-μm tube to a 50-μm tube (Table 1; Fig. 1). The viscosity reductions increased with increasing hematocrit and were higher in the neonates than in the adults.

Figure 2 shows the hematocrit-viscosity relationships for the three groups and three tube diameters. The hematocrit viscosity curves obtained by perfusing 500-μm tubes were similar in the three groups. The steepness of the curves decreased with decreasing tube diameter. The flattest curves were observed for RBC from preterm infants in the smallest tubes.

For the combined data from the 20 neonates and 10 adults, there were significant ($p < 0.01$) inverse relations of the viscosity in 50-μm tubes at a hematocrit of 0.60 to the MCV ($r = -0.69$; Fig. 3), to the variation coefficient of MCV ($r = -0.54$) and to the Hb F ($r = -0.48$). The combined influence of MCV, variation coefficient of MCV, and Hb F on the viscosity has been analyzed by calculation of a multiple regression equation. The regression coefficients of the variation coefficient of MCV and of the Hb F

Table 1. *Hematologic and viscosity data for red cells from preterm and full-term infants, and adults**

	Hematocrit (l/l)	Tube diameter (μm)	Preterm infants (n = 10)	Full-term infants (n = 10)	Adults (n = 10)	Significant differences among the three groups ($p < 0.05$)
General hematologic data						
MCV (fl)			118.6 ± 10.7 (± 28.3)†	105.6 ± 8.2 (± 22.6)	91.0 ± 5.3 (± 14.2)	a > b > c
MCH (pg)			38.1 ± 3.6	33.9 ± 3.0	29.8 ± 2.2	a > b > c
MCHC (g/dl)			32.8 ± 1.5	32.4 ± 1.2	33.3 ± 1.1	a = b = c
Hemoglobin F (%)			87.5 ± 8.4	67.2 ± 7.3	0.5 ± 0.2	a > b > c
Relative viscosity	0.20	50	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	a = b < c
	0.20	500	1.6 ± 0.2	1.6 ± 0.3	1.6 ± 0.3	a = b = c
	0.40	50	1.6 ± 0.2	1.8 ± 0.3	2.1 ± 0.4	a < b < c
	0.40	500	2.8 ± 0.5	2.8 ± 0.6	2.9 ± 0.5	a = b = c
	0.60	50	2.3 ± 0.5	2.7 ± 0.4	3.2 ± 0.5	a < b < c
	0.60	500	4.6 ± 0.6	4.7 ± 0.5	4.9 ± 0.7	a = b = c

* Values represent mean ± 1 SD.

† Figures in parentheses are the average SD values for the cell volume distributions.

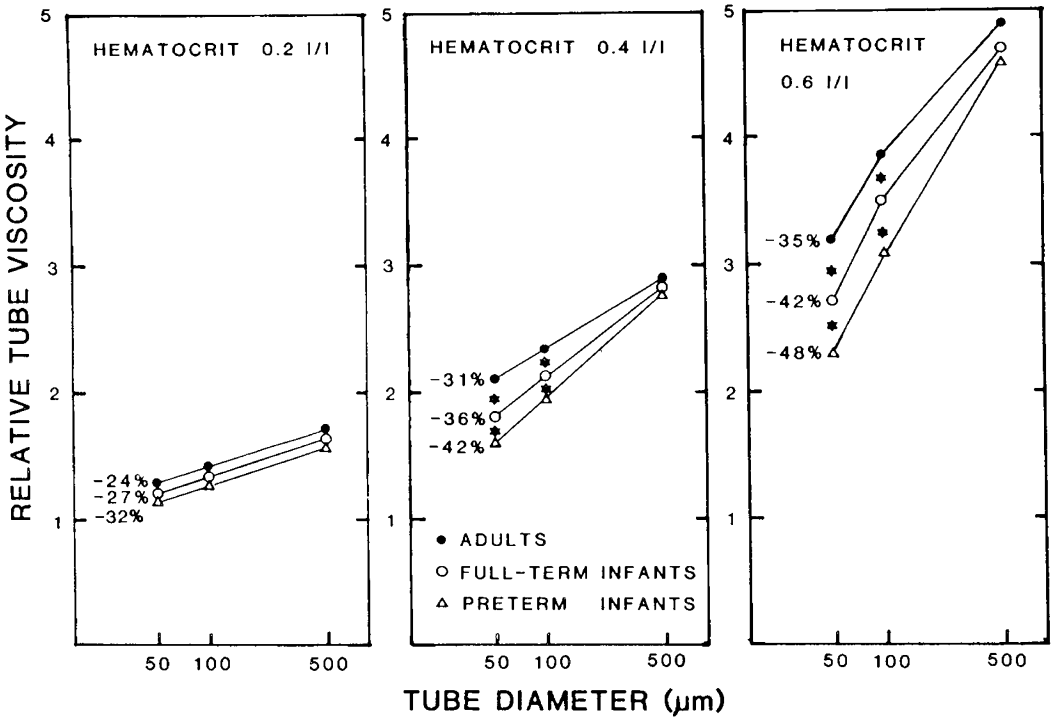

Fig. 1. Effect of tube diameter on relative viscosity of RBC suspensions for three groups (preterm infants, term neonates, and adults). RBC were suspended in buffer solution at hematocrits of 0.20, 0.40, and 0.60 1/1.00 = 100%). Note that the viscosity reduction (Fahraeus-Lindqvist effect) increased with increasing hematocrit and that the viscosity reduction was more pronounced in the neonates than in the adults. Asterisks indicate significant differences ($p < 0.05$) among adults and full-term and preterm infants.

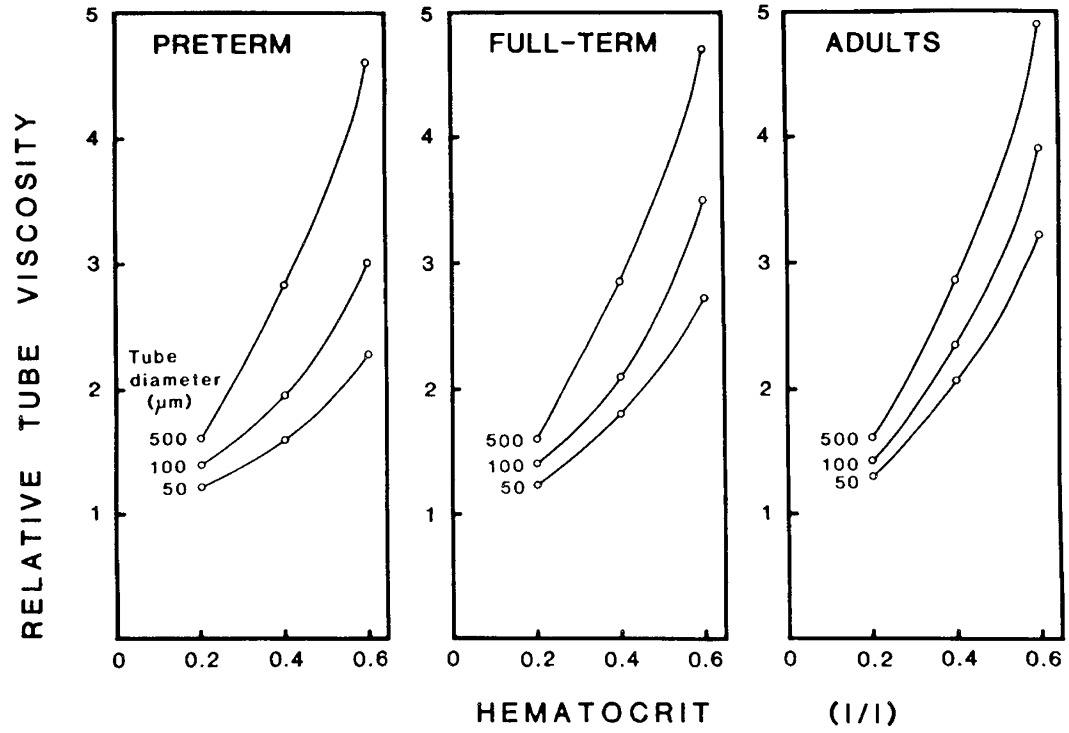

Fig. 2. Relative viscosity of RBC suspensions in tubes with diameters of 50, 100, and 500 μm plotted against the hematocrit. Note that the viscosity of adult RBC in 50- and 100-μm tubes increased more with increasing hematocrit than that of neonatal RBC (hematocrit 1.00 = 100%).

were not significantly different from zero and the consideration of these two variables in addition to the MCV increased the correlation coefficient only from −0.69 to −0.70. This suggests that the MCV was a major determinant of viscosity in narrow tubes.

Figure 4 shows the effect of heating on the viscosity of RBC suspended at a hematocrit of 0.60 1/1. Viscosity reductions in the three groups were less after RBC heating. A significant difference ($p < 0.05$) in the viscosity reduction of heated RBC was observed only between adults and preterm infants.

DISCUSSION

From the present data we come to four major conclusions. *1*) The viscosity of RBC buffer suspensions as measured in 500-μm

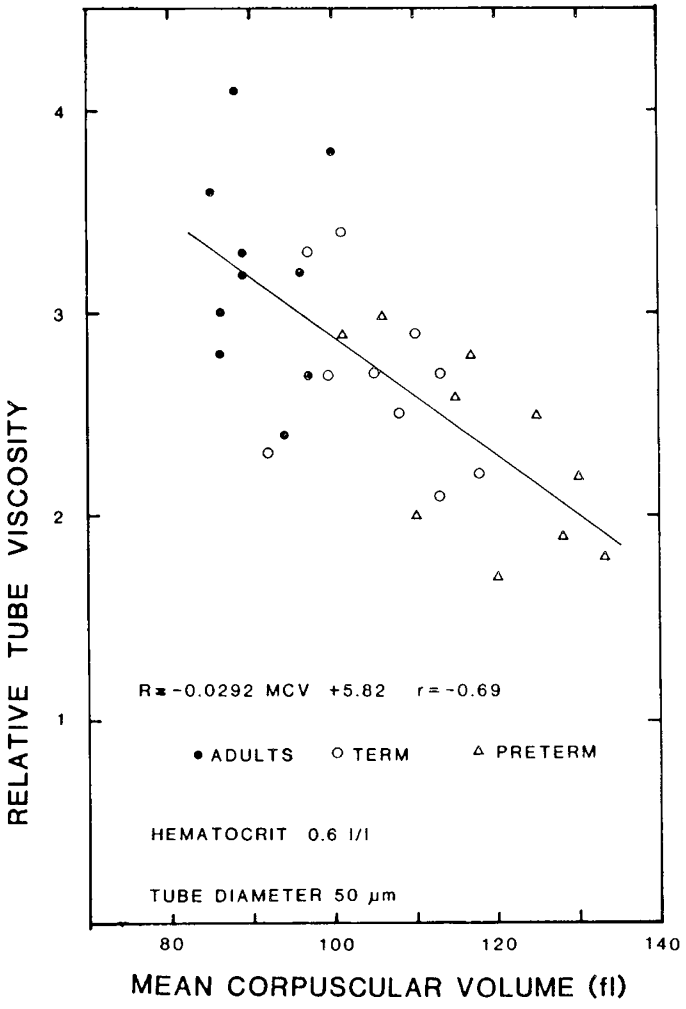

Fig. 3. Relative tube viscosity of RBC suspensions with a hematocrit of 0.60 l/l (= 60%)plotted against MCV. There was a highly significant inverse relationship ($p < 0.001$).

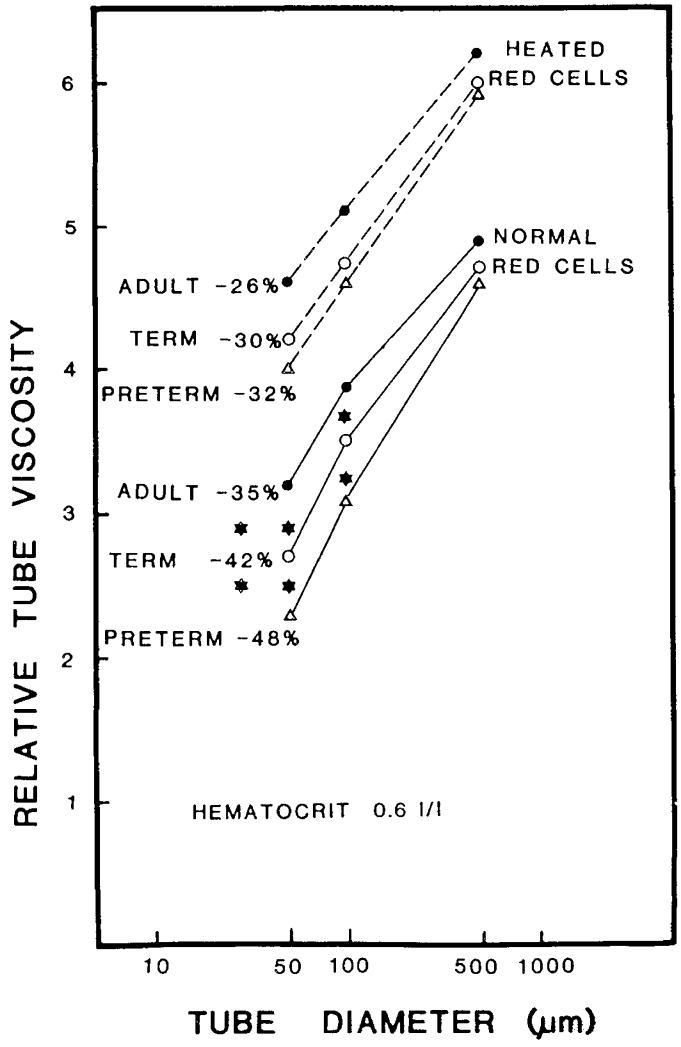

Fig. 4. The effect of tube diameter on relative viscosity of normal and heated RBC suspensions. Note that the viscosity reduction (Fahraeus-Lindqvist effect) was less pronounced after RBC heating, particularly in the neonates (hematocrit 0.6 l/l = 100%).

tubes is not different among preterm infants, term neonates, and adults. *2*) Viscosity of RBC from preterm and term neonates decreases more than that of adult RBC as the tube diameter is decreased from 500 to 50 μm. *3*) The viscosity reduction in narrow tubes is more pronounced at high hematocrit, particularly in neonates. *4*) The greater viscosity reduction of neonatal RBC appears to be related to the larger MCV and to specific RBC properties lost during heating.

Viscosity of whole blood as studied by means of a cone-plate viscometer depends on the hematocrit, RBC deformability, plasma viscosity, RBC aggregation and leukocyte properties. If RBC are washed and resuspended in a non-aggregating buffer solution, viscosity depends only on the hematocrit and on RBC deformability (14). A recent study has shown that RBC from preterm and term neonates and adults show similar viscosity when the cells are suspended in a buffer solution at a constant hematocrit and when viscosity is measured by means of a cone-plate viscometer (14). This corresponds to our viscosity results determined in relatively wide 500-μm tubes (Table 1). In smaller tubes, viscosity of RBC suspensions depends on the tube diamter in addition to the hematocrit and RBC deformability (20–22). Blood viscosity drops with decreasing tube diameter until the tube diameter approaches the RBC diameter (21). This Fahraeus-Lindqvist effect results from RBC accumulation in the rapidly flowing central tube core (20).

Although the extent of axial RBC accumulation in narrow tubes is traditionally related to the tube diameter, this phenomenon does in fact depend on the ratio of vessel diameter to RBC diameter (20). Thus, large RBC tend (more than small RBC) to migrate towards the quickly moving central core. A wide volume distribution of RBC may enhance this phenomenon since small particles tend to push larger particles to the tube center (23). Neonatal RBC show both a larger size and a wider volume distribution than adult RBC (Table 1). Moreover, at a given hematocrit, neonates have a lower RBC count per unit volume of blood. This may also contribute to the greater viscosity reduction of neonatal RBC. In this context, it is interesting to note that small iron-deficient RBC show a smaller viscosity reduction in narrow tubes compared to normal adult RBC (28).

At high hematocrit, RBC are closely packed in the high speed central core of a narrow tube whereas the plasma layer remains relatively cell poor (18–20). The resulting "plug flow" of RBC explains why the viscosity reduction in narrow tubes increases with increasing hematocrit. Packing of RBC is facilitated by RBC deformation (20). Partial or complete loss of RBC deformability by RBC heating results in a decreased Fahraeus-Lindqvist effect and a steeper hematocrit-viscosity curve in narrow tubes (22, 23). RBC from preterm and term neonates and adults show similar deformability (16). However, the membrane of neonatal RBC is slightly more elastic than that of adult RBC (24). This may facilitate close packing of neonatal RBC in the central tube core, particularly at high hematocrit.

The contribution of RBC deformability to the viscosity reduction in narrow tubes has been studied by RBC heating (Fig. 4). Heating of RBC to 50°C for 1 min primarily decreases membrane

elasticity (increase in shear elastic modulus) (25). Moreover, RBC heating may also result in damage of enzymes and other cytoplasm proteins, in spherocytosis and fragmentation of RBC. Figure 4 shows that heating decreases the differences in the viscosity reduction between neonatal and adult RBC without completely eliminating these differences. Thus, both different cell geometry and membrane elasticity appear to contribute to the stronger viscosity reduction of neonatal RBC.

The decrease in hematocrit and blood viscosity with decreasing tube diameter occurs both *in vitro* and *in vivo*. Direct microscopic observation of narrow vessels in various animal species revealed that the hematocrit decreases by 75% as the blood flows from wide arteries to capillaries with diameters approaching the resting RBC diameter (29, 30). The hematocrit reduction in small vessels explains why in adults the total body hematocrit is 10% lower than the large vessel hematocrit (29). In neonates, the difference between the total body hematocrit and the large vessel hematocrit tends to be larger than in adults (31). This suggests a greater hematocrit reduction in the small vessels of the neonate.

The extent of viscosity reduction in small vessels cannot be directly measured. However, it appears likely that the viscosity reduction in narrow vessels is similar to that in narrow tubes (21). This should markedly facilitate blood flow, because vascular resistance originates mainly from small arteries and arterioles with diameters of 10 to 500 μm (1). Our results indicate that the viscosity reduction in narrow vessels is more pronounced for neonatal RBC, particularly at a high hematocrit (Fig. 1). The enhanced viscosity reduction of neonatal RBC in narrow vessels may be an important prerequisite for adequate circulation in the neonate, particularly in preterm infants whose circulation is characterized by low vascular resistances, low vascular pressures, and high flow conditions (3, 4). Increased blood flow to vital organs of the fetus and neonate may be necessary to compensate for the increased affinity and decreased release of oxygen from Hb F (4).

Moreover, our results suggest that a high hematocrit impedes blood flow in the neonate less than in adults and that the exchange of neonatal RBC for adult RBC impairs blood flow in the neonate, unless the hematocrit is decreased. A recent study by Fouron *et al.* (6) provides evidence for this hypothesis. They compared the hemodynamic effects of polycythemia in newborn lambs induced by exchange with either fetal lamb or adult sheep RBC. Fouron *et al.* (6) found that the pulmonary resistance increased by a factor of six when the exchange transfusion was performed with adult RBC, whereas the increase was only 2-fold with fetal RBC. These data together with our results imply that neonatal RBC have favorable flow properties in narrow vessels and that an exchange transfusion with adult RBC may be hazardous for the neonate if the hematocrit is markedly raised. This should also be considered when small preterm infants receive several RBC transfusions to counterbalance frequent blood sampling.

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