Filterability of Erythrocytes and Whole Blood in Preterm and Full-Term Neonates and Adults

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ABSTRACT. Filtration techniques are widely used to assess red blood cell (RBC) deformability and flow behavior of RBC in microcirculation. In this study filtration rates of RBC from 10 very low birth weight infants (24–30 wk gestation), 10 more mature preterm infants (31–36 wk gestation), 10 full-term neonates, and 10 adults were measured by using Nucleopore filters with pore diameters of 5 μm and filtration pressures of 1, 2, 5, and 10 cm H_2O. The major results follow: 1) At each of four filtration pressures, filtration rates of washed RBC were significantly ($p <$ 0.05) lower in the preterm infants than in the term neonates who in turn showed lower values than adults. The differences among the four groups became less as the pressure was increased from 1 to 10 cm H_2O. 2) The filtration rates increased with decreasing MCV ($r = -0.86$). 3) The filter flow resistance (computed as ratio of filtration pressure and filter flow rate) decreased as the filtration pressure was raised from 1 to 10 cm H_2O. The largest drop, 31% ($p < 0.05$), was observed in the most immature infants, the smallest, 10% ($p > 0.05$), was seen in adults. 4) At a pressure of 1 cm H_2O the calculated mean transit time for RBC through the 5-μm pores was on an average 3.7 times longer in the smallest preterm infants than in the adults (19.7 ± 7.8 and 5.3 ± 1.4 ms, respectively), whereas the factor was only 2.7 at a pressure of 10 cm H_2O (13 ± 0.4 and 0.5 ± 0.1 ms, respectively). 5) Filtration rates of whole blood were determined at a pressure of 10 cm H_2O. These filtration rates were significantly ($p < 0.05$) less compared with filtration rates of washed RBC. The largest difference was observed in the smallest preterm infants (−77%), the smallest difference in adults (−41%). In conclusion, the filtration rate of RBC from preterm and term neonates may be lower than that of adults because of the larger size of neonatal RBC. At high pressure, filterability of neonatal RBC improves, possibly because of decreased resistance of neonatal RBC to elastic deformation. Filtration of whole blood from neonates may, in addition, be impaired because of the higher number of poorly deformable leukocytes and erythroblasts. (*Pediatr Res* 20:1269–1273, 1986)

Abbreviations

RBC, red blood cells
PBS, phosphate buffered saline
MCV, mean corpuscular volume

Hyperviscosity in neonates is a frequent and potentially serious condition, which may cause circulatory failure and impaired microcirculation in various vital organs (1). Blood viscosity is mainly determined by hematocrit. However, decreased RBC deformability can also contribute to an increase in blood viscosity. At high hematocrit, the deformability of RBC is particularly crucial because blood viscosity exhibits a larger increase with increasing hematocrit when RBC deformability is impaired (2). Moreover, decreased RBC deformability may hinder the entry of 8-μm diameter RBC into capillaries with diameters of 3–4 μm (3), slow down oxygen uptake and release in capillaries (4), and block the passage through narrow splenic slits, thereby aiding in destruction of RBC by immunological mechanisms (5). Decreased RBC deformability has been observed in neonates with severe septicemia, necrotizing enterocolitis (6), and vitamin E deficiency (7). The markedly shortened life-span of neonatal RBC (8) has also been referred to impaired RBC deformability (9, 10). This explains the great interest in the measurement of RBC deformability in neonates.

Filtration techniques are widely used to assess RBC deformability because they can be performed without a special apparatus. Moreover, RBC filterability is regarded as a model of *in vivo* microcirculation (11). However, RBC filterability depends on several factors (2, 11–13): 1) RBC deformability (*i.e.* shape change in response to a given force), 2) RBC size (*i.e.* necessary deformation for entry into a filter pore), 3) presence of large rigid particle (*i.e.* leukocytes and RBC aggregates, and 4) filtration pressure. These factors must be considered if filtration studies are performed.

Most studies on the filtration rate of RBC from term neonates have shown that neonatal RBC are less filterable than adult RBC (9–11, 14, 15). However, Bergqvist *et al.* (16) found no difference in filterability between RBC from term neonates and adults possibly because they used a very high filtration pressure of 34 cm H_2O. Two papers reported inverse relationships between filtration rate and MCV of RBC from term neonates and adults (9, 15). Buchan (14) measured lower filtration rates in preterm infants with gestational age of 34–37 wk. In a preliminary report, Holland *et al.* (17) described decreased filterability of RBC from preterm infants with gestational age of 27–35 wk. However, in both studies RBC were examined without eliminating leukocytes. Since the resistance of leukocytes to filtration through 5-μm pores is 1000 times more than that of RBC (13), these previous studies cannot distinguish between RBC and leukocyte filterability (2).

The present study was designed to measure filtration rates of RBC from newborn infants with gestational ages of 24–41 wk and from adults by using filtration pressures of 1, 2, 5, and 10 cm H_2O. Furthermore, we determined the influence of plasma and leukocytes on filtration rates.

MATERIALS AND METHODS

Study population and blood samples. Placental blood samples from 30 newborn infants were studied with approval of the

Department of Pediatrics Human Subjects Research Committee. Ten were healthy full-term infants with gestational ages of 38–41 wk and birth weights of 3250–3640 g; 10 were preterm infants with gestational ages of 24–30 wk and birth weights of 780–1410 g; and 10 had gestational ages of 31–36 wk and birth weights of 1400–2590 g. Infants with malformations, erythroblastosis, diabetic mothers, hemorrhage, perinatal asphyxia, and caesarean section were excluded, as were twins and infants with proven infection or high risk of infection. All infants had birth weights appropriate for gestational age (10th–90th percentile according to unpublished Munich charts).

For the 30 neonates, 10–20 ml blood were 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 (18). Part of each whole blood sample was diluted with cell-free autologous plasma at a hematocrit of 10% to assess the influence of nucleated cells (i.e., leukocytes and erythroblasts) on the filtration rates. Note that the nucleated cells were diluted in proportion to the hematocrit, which varied moderately among the four groups (Table 1). Another part of each blood sample was centrifuged at 2,000 × g for 10 min, and, via gentle aspiration, the plasma was removed and the buffy coat discarded. The RBC were washed three times in an isotonic PBS solution (0.122 mol/l NaCl, 0.030 mol/l KH$_2$PO$_4$ + Na$_2$HPO$_4$; 290 mosmol/kg, pH 7.42 at 25° C) containing 2 g/l of human serum albumin. Albumin was added to prevent echinocytic transformation of red blood cells. After the last wash, RBC was resuspended in the PBS albumin at a hematocrit of 10%. These suspensions contained fewer than 100 leukocytes and erythroblasts per microliter (i.e., <1 nucleated cell/10,000 RBC).

Filtration method. The filtration technique described by Schmid-Schönbein et al. (11) was used (equipment available through Effenberger, Munich, FRG). The filter holder consists of three parts. The upper part, which has the form of a funnel, is filled with 2 ml of sample and is connected to compressed air. The middle part is shaped like a flat dome and contains the filter with a filtration area of 0.385 cm^2. The lower part is aerated and collects the filtrate. The whole filter chamber is watertight and is inserted into a thermocontrolled water bath (37° C). Six of these chambers can be used simultaneously. HemafilNucelopore filters with 5-μm diameter pores (Nucleopore Corp., Pleasanton, CA) were used. Positive pressures of 1, 2, 5, and 10 cm H$_2$O were applied using compressed air and a water manometer. Filtration rates of RBC in plasma suspensions were measured by using only one pressure of 10 cm H$_2$O since initial studies in our laboratory indicated that filters may become clogged at lower pressure if leukocytes have not been removed. The filtration time of 2 ml of the cell suspension with a hematocrit of 10% was measured by using a stopwatch. The filtration rate of RBC (in μl/s/cm^2 filter area) was calculated as the ratio of filtered RBC (i.e. 0.2 ml of RBC) and the product of the filtration time and the filter area (0.385 cm^2). In each measurement, the testing of RBC suspension was preceded by passing the suspending medium (PBS or plasma, respectively) through the same filter (11–13). Each filter was used for only one RBC suspension at one pressure. Thus 10 filters were used for each blood sample.

The mean transit time (T$_c$) for a single RBC to pass through a pore was calculated from a formula derived from that given by Kikuchi et al. (19)

$$T_c = AdV_c \left[1/F_c + (1/F_b)(1 - 1/h + V_p/V_c)\right]$$

Where A is effective filtration area (0.385 cm^2), d is pore density (4 × 10^5 cm^{-2}), h is hematocrit (0.1 l/l), V$_p$ is mean pore volume (255.3 fl), V$_c$ is mean corpuscular volume (MCV in fl), F$_b$ is buffer flow rate (in μl/s) determined for each filter, F$_c$ is RBC flow rate (in μl/s), and T$_c$ is mean transit time (in ms) for a single RBC. When the constant values are inserted into the equation it can be transformed into

$$T_c = 0.4 V_c \left[1/F_c + (1/F_b)(255/V_c - 9)\right]$$

General hematological methods. Hematocrit was measured by the microhematocrit method. The values were not corrected for trapped plasma, which is about 2% in full-term neonates and adults (17). RBC count, hemoglobin concentration, and white blood cell count were determined using a Coulter Counter (Coulter Electronics Inc., Harpenden, Herts, UK). Differential blood count was performed after Giemsa's stain for staining blood

Table 1. *Hematological data and filtration rates of red cells and of whole blood**

| | Filtration pressure (cm H$_2$O) | Neonates (wk of gestation) | | | Adults D | Significant differences (p < 0.05) |
		A 24–30	B 31–36	C 38–41		
Hematocrit (%)		43.5 ± 2.2	48.0 ± 2.8	49.4 ± 4.7	44.3 ± 3.1	A < C > D; A = B = D
MCV (fl)		123.2 ± 10.1	117.2 ± 7.8	107.8 ± 5.7	90.1 ± 4.9	A = B > C > D
MCH (pg)		40.5 ± 2.6	38.5 ± 2.2	35.7 ± 1.9	29.9 ± 1.9	A = B > C > D
MCHC (g/dl)		32.6 ± 1.7	32.9 ± 1.5	33.0 ± 1.5	33.2 ± 1.3	A = B = C = D
Hemoglobin F (%)		92.4 ± 6.7	85.7 ± 6.1	70.3 ± 8.2	0.8 ± 0.4	A = B > C > D
Reticulocytes (% RBC)		11.1 ± 4.4	6.8 ± 2.9	3.2 ± 1.4	1.1 ± 0.3	A > B > C > D†
Nucleated cells						
Erythroblasts (% WBC)		70.3 ± 56.7	18.7 ± 13.8	6.3 ± 2.8	0.0 ± 0.0	A > B > C > D†
WBC (× 10^9/l)		12.8 ± 5.0	11.5 ± 4.3	15.6 ± 4.1	6.2 ± 1.7	A = B = C > D†
Segmented neutrophils (%)		45.7 ± 15.6	48.5 ± 16.2	51.7 ± 15.0	53.5 ± 11.6	A = C = C = D
Band and juvenile neutrophils (%)		12.8 ± 5.9	7.5 ± 3.6	4.1 ± 3.4	0.5 ± 0.3	A > B = C > D†
Eosinophils (%)		0.5 ± 0.4	1.1 ± 1.0	1.7 ± 1.5	3.4 ± 1.4	A = B = C < D†
Basophils (%)		0.0 ± 0.0	0.1 ± 0.2	0.4 ± 0.3	0.7 ± 0.4	A = B < C < D†
Lymphocytes (%)		34.6 ± 15.3	37.0 ± 17.6	35.9 ± 14.2	36.4 ± 7.2	A = B = C = D
Monocytes (%)		6.4 ± 4.5	5.8 ± 3.9	6.2 ± 3.7	5.5 ± 3.6	A = B = C = D†
Filtration rates of RBC (μl/s/cm^2)						
RBC in buffer	1	2.3 ± 0.6	2.9 ± 0.6	3.8 ± 0.7	5.0 ± 0.8	A = B < C < D
	2	4.8 ± 1.3	5.9 ± 1.3	7.6 ± 1.5	10.3 ± 1.5	A = B < C < D
	5	13.5 ± 2.7	15.9 ± 3.0	19.8 ± 3.5	26.3 ± 3.8	A = B < C < D
	10	32.3 ± 5.3	36.8 ± 5.9	44.7 ± 6.8	55.3 ± 7.9	A = B < C < D
Whole blood	10	7.2 ± 2.9	13.0 ± 3.6	20.9 ± 5.2	32.4 ± 6.3	A < B < C < D

* Values are means ± SD; n = 10 in each group. MCHC, mean corpuscular hemoglobin concentration; WBC, white blood cells.
† Friedman rank test.

smear. Reticulocytes were counted after the staining of a blood smear by brilliant cresyl blue. Hemoglobin F was quantified by the alkali denaturation test (20).

Statistics. A two-tailed paired t test was used to test for differences between paired observations (*e.g.* filtration rates at different pressures). Differences among the four groups were tested using analysis of variance (21). A Friedman rank test was used when no normal distribution existed. Regression analyses were utilized to determine overall correlations between filtration rates, MCV, hemoglobin F, and reticulocyte count.

RESULTS

General data. MCV, mean corpuscular hemoglobin, hemoglobin F, and reticulocyte count decreased throughout gestation and reached the lowest values in the adults (Table 1). Mean corpuscular hemoglobin concentration was similar in preterm infants, term neonates, and adults. Leukocyte and differential blood counts are shown in Table 1. Total neutrophils were about 55% in the four groups. However, the percentage of band neutrophils was higher in the smallest preterm infants and decreased as the gestational age increased.

Filtration studies. At each of the four filtration pressures, filtration rates of RBC in buffer suspensions were significantly lower in the preterm infants than in the term neonates who in turn showed lower values than the adults (Table 1). The differences depended on the filtration pressure: at a filtration pressure of 1 cm H_2O, the RBC filtration rate in the adults was on an average 117% higher than in the smaller preterm infants, whereas the difference was only 71% at a pressure of 10 cm H_2O.

Figure 1 shows the RBC filtration rates measured at a pressure of 1 cm H_2O plotted against the MCV. The inverse relationship was highly significant ($r = -0.86$; $p < 0.001$). Smaller correlation coefficients were found for the relationship between hemoglobin F and filtration rate ($r = -0.48$) and between reticulocyte count and filtration rate ($r = -0.61$). In all four groups, the filtration rates increased with increasing filtration pressure (Table 1). However, the rise in filtration rates was different among the four groups: As the pressure was increased from 1 to 10 cm H_2O, the filtration rate increased by a factor of 15 in the smallest preterm infants, 13 in the larger preterm infants, 12 in the term neonates, and 11 in the adults.

Figure 2 shows the mean transit time for single RBC through filter pores. These mean transit times decreased with both increasing gestational age and increasing filtration pressure. The

Fig. 2. Mean pore transit time of single RBC plotted against filtration pressure. Values are means ± SD.
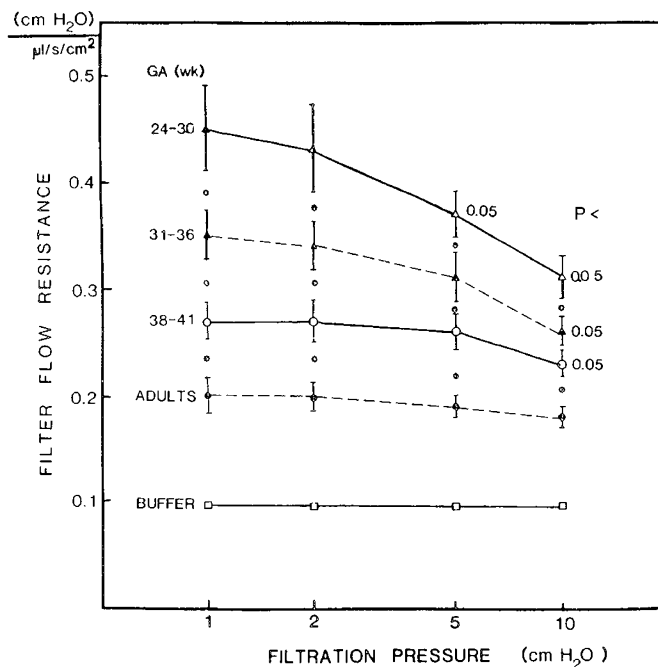
Fig. 3. Filter flow resistance (computed as ratio of filtration pressure and flow rate) of RBC plotted against filtration pressure. Values are means ± SD. Note that resistance of RBC from preterm infants decreased markedly as pressure was raised.

differences among the four groups were larger at lower filtration pressures than at high filtration pressures. At a filtration pressure of 1 cm H_2O, RBC transit time was on an average 3.7 times longer in the smallest preterm infants than in the adults, whereas the facter was only 2.7 at a pressure of 10 cm H_2O.

Figure 3 shows the filter flow resistance (computed as ratio of filtration pressure and filter flow rate). Flow resistance was significantly higher in the preterm infants compared with term
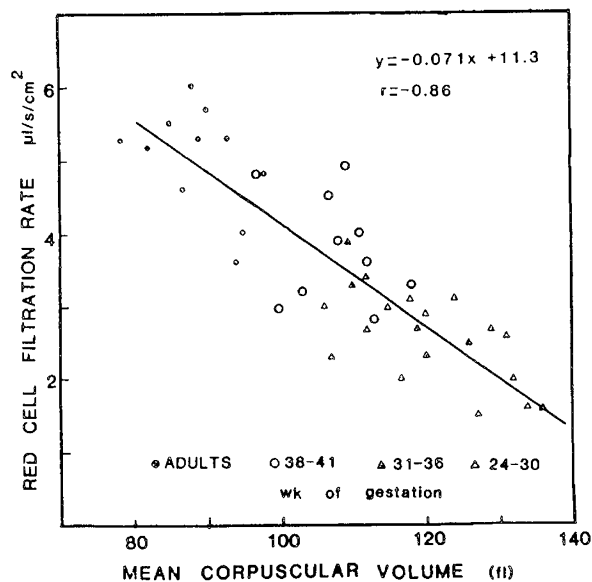
Fig. 1. Filtration rate of RBC (suspended in buffer at a hematocrit of 10%) plotted against MCV. There was a highly significant inverse relationship.
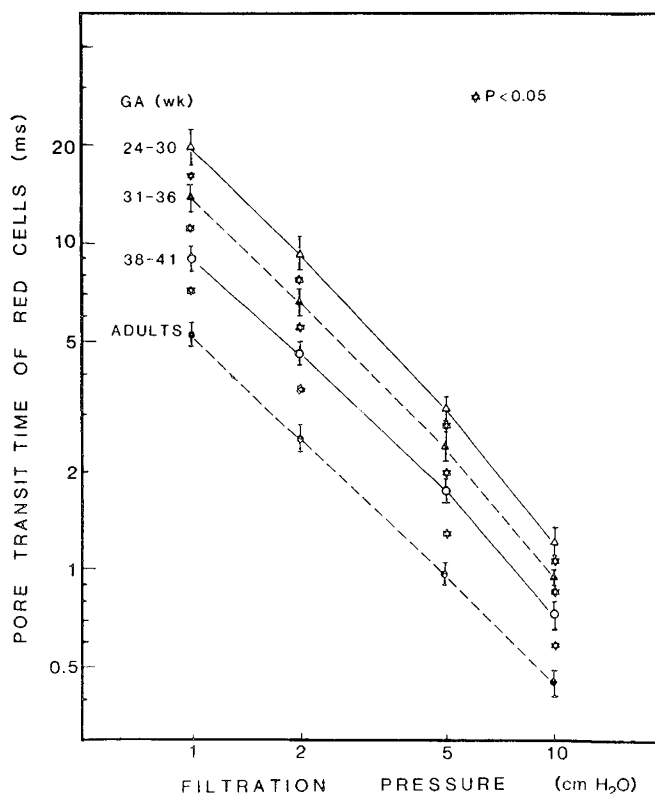
neonates who in turn showed higher flow resistance than the adults. In the three neonatal groups, flow resistance decreased significantly ($p < 0.05$) as the filtration pressure was increased from 1 to 10 cm H_2O. The largest drop, 31%, was observed in the most immature infants, the smallest, 10%, in adults. In the other groups the decrease was 26% (31–36 wk of gestation) and 15% (term neonates).

Filtration rates of whole blood were measured at a pressure of 10 cm H_2O (Table 1). The filtration rates were significantly ($p < 0.001$) less compared with the filtration rates of RBC in buffer in all four groups. The largest difference was observed in the smallest preterm infants (−77%), the smallest difference in adults (−41%).

DISCUSSION

From the present data we reach four major conclusions: 1) at given pressure, RBC filtration rates through 5-μm pores are lower, and mean RBC transit times are longer in preterm infants than in term neonates and adults; 2) slow RBC filtration rates in neonates are related to large cellular volume; 3) the filter flow resistance of RBC from preterm infants decreases more with increasing pressure than that of RBC from term neonates and adults; and 4) filterability of whole blood is markedly less than that of washed RBC, particularly in preterm infants.

Previous RBC deformability studies using the rheoscope and viscometry techniques showed no meaningful differences among preterm infants with 24–36 wk of gestational age, term neonates, and adults (22, 23). These data are not necessarily contradictory to the present results because RBC filtration rates are affected by factors that exert minor or no influence on rheoscope and viscometry results. These factors include: 1) RBC diameter and surface area (*i.e.* necessary RBC deformation), 2) presence of a small subpopulation of poorly deformable RBC, 3) pressure acting on the cells, and 4) presence of poorly deformable cells (*e.g.* leukocytes) and particles (*e.g.* RBC aggregates) (2, 11–13).

The ratio of RBC to pore diameter and the membrane surface area determine how much a cell has to deform to enter a pore. A small RBC with a diameter of 5 μm does not need to deform to enter and pass a 5-μm pore, whereas a large cell has to deform markedly. Since cellular deformation requires time (24), the transit time of individual RBC through filter pores increases with increasing cellular volume (19), thereby decreasing the overall filtration rate. This explains the prolonged mean transit times and decreased filtration rates of the large RBC from preterm infants when compared with the smaller RBC from term neonates and adults (Figs. 1 and 2). The smallest cylindrical pore a RBC can enter without loss of volume is determined by the minimum cylindrical diameter of the cell. The average RBC from a term neonate has a minimum cylindrical diameter of 3.04 ± 0.25 μm, whereas that of an adult RBC is 2.81 ± 0.23 μm (25). It can be calculated that even RBC with a volume of 200 fl have a minimum cylindrical diameter of <4 μm so that all RBC from preterm and term neonates should be able to enter and pass 5-μm pores without obstructing them.

The filtration technique is extremely sensitive to the presence of a small percentage of poorly deformable RBC that may gradually plug more pores, thereby hindering the passage of subsequent RBC and decreasing the overall filtration rate (2). A recent study has shown that blood from term and preterm neonates contains slightly larger numbers of poorly deformable RBC compared with adult blood (22). Moreover, reticulocytes are more resistant to passage of narrow micropipettes than mature RBC (26). Thus, both a small subpopulation of rigid RBC and a higher reticulocyte count (Table 1) may contribute to the decreased filtration rates of neonatal RBC.

RBC enter narrow channels (*e.g.* capillaries, pores) by membrane extension and folding. At low pressure, membrane extension prevails, whereas at higher pressure the whole cell folds (24). The pressure at which folding begins is important for the entrance

behavior of RBC, since the resistance to membrane folding is markedly less than the resistance to membrane extension. A recent study has shown that the membrane of neonatal RBC extends slightly more in response to a given force and begins to fold at a lower pressure than the adult RBC (24). This may explain why the flow resistance of neonatal RBC dropped more than that of adult RBC with increasing filtration pressure (Fig. 3).

Leukocytes exert 700–1000 times more resistance to the passage of 5-μm filter pores than RBC (12). Thus, if whole blood with a 1:1000 ratio of leukocytes to RBC is filtered through 5-μm pores, about 50% of the flow resistance is provided by the leukocytes. In other words, the leukocytes in whole blood slow down filtration rates by about 50%. This agrees with our finding from adult blood (Table 1). In the neonates, the presence of nucleated cells reduced the filtration rates more than in adults (Table 1). Possible explanations of this finding include the higher leukocyte and erythroblast count (Table 1), decreased deformability of neonatal granulocytes (27), and the presence of extremely rigid immature granulocytes (28).

Plasma could reduce filtration of RBC because of the higher viscosity of plasma compared with a buffer solution (23) and because plasma macroproteins (*e.g.* fibrinogen) cause RBC aggregation under low shear conditions (29). Both plasma viscosity and RBC aggregation are less in neonates than in adults as a result of low fibrinogen concentration in neonatal blood (23, 29). Thus, the presence of plasma proteins should decrease the differences in filtration rates between neonates and adults rather than increasing the differences as observed in the present study (Table 1). This points to a minor role of plasma proteins and to a major role of leukocytes in the filterability of RBC in plasma.

In conclusion, the filtration rate of RBC from preterm infants and term neonates may be decreased compared with adults because of the larger size of neonatal RBC and the presence of a small subpopulation of rigid cells (22). These disadvantages may be partially compensated by the decreased resistance of neonatal RBC to elastic deformation (24). Filtration of whole blood from preterm infants and term neonates may, in addition, be impaired because of the higher leukocyte and erythroblast count and decreased deformability of leukocytes.

Delayed entry time of neonatal RBC into filter pores suggests that the passage time through the small splenic slits is also prolonged (30). This could aid in the destruction of RBC by macrophages (5) and explain the shortened RBC survival time in neonates (8). In preterm infants, RBC life-span is even shorter than in term neonates (8), which agrees with our finding of decreased filterability of RBC from preterm infants when compared with term neonates (Table 1).

Decreased filterability of the large neonatal RBC could also imply impaired microcirculatory dynamics in narrow vessels. However, there is no evidence that neonatal RBC are indeed disadvantageous for adequate circulation since the circulation in the neonate is characterized by low vascular resistance and high flow conditions (31). Moreover, a recent study on newborn lambs suggests that polycythemia induced by adult RBC impedes pulmonary blood flow more than a similar polycythemia induced by neonatal RBC (32). However, it cannot be ruled out that large RBC with diminished deformability (*e.g.* in septicemia) (6) may impair circulation more than smaller RBC with poor deformability.

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