Blood viscosity in the newborn

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Mackintosh, T. F., and Walker, C. H. M. (1973). *Archives of Disease in Childhood*, 48, 547. **Blood viscosity in the newborn.** The blood of the newborn has been shown to possess viscoelastic properties similar to adult blood, with a straight line relation between blood viscosity and PCV (packed cell volume) at normal PCV levels, and progressively disproportionate increases in viscosity at PCV levels above 65. The viscosity/shear rate curve indicates an increase in viscosity as shear rate declines. The mean values for viscosity of the blood from 110 normal term infants increased from 5.5 cps (centipoise) at 232 sec^{-1} to 33.7 cps at 1.16 sec^{-1} , whereas the corresponding values for adults are considerably lower, 4.3 to 14.5 cps. This tends to make the blood flow in infants more susceptible to changes in haematocrit. Corresponding values for 21 normal preterm infants (5.0 to 30.6 cps) did not differ significantly from those of normal infants. Those for 13 small-for-dates infants were higher (6.6 to 44.6 cps). There was no clear relation between viscosity and the respiratory distress syndrome, the values in 20 distressed infants being 4.8 to 28.1 cps. However, 13 of 24 babies with 'cerebral' signs had values above the normal 2 SD limit, the range for these babies being 6.9 to 47.0 cps. Among the 188 infants studied, 19 were regarded as hyperviscous with values above 2 SD from the mean. Of these, 4 were symptom free, 4 showed plethora and cyanosis only, and 11 had 'cerebral' signs, 2 having additional RDS and 1 prolonged physiological jaundice. 7 of the symptomatic infants were pre-term and 4 were small-for-dates. 6 infants received haemodilution therapy by partial plasma exchange, with clinical improvement in 5. It is concluded that haemodilution should be considered in any infant with cardiopulmonary or cerebral symptoms and in whom the haematocrit is above 65 to 70%.

In recent years the viscosity of blood, the occurrence of hyperviscous states, and the effects of hyperviscosity on blood flow have been studied fairly extensively (Wells and Merrill, 1961a, b; Wells, Denton, and Merrill, 1961; Wells, 1964; Dintenfass, 1966; Replogle, Meiselman, and Merrill, 1967). It is now recognized that certain pathological states are accompanied by hyperviscosity and that treatment directed towards reducing it may improve the patient's condition (Kellog and Goodman, 1960; Bergentz *et al.*, 1963; Pringle, Walder, and Weaver, 1965; Dintenfass, Julian, and Miller, 1966). However, the study of blood viscosity in children has not attracted much attention, and little is yet known about the effects of hyperviscosity in the newborn. Stimulated by the finding of a very high haematocrit (PCV) in an infant with respiratory distress, an investigation was begun first to confirm the report that a relation

exists between PCV and blood viscosity in the newborn (Baum, 1966), second to determine whether hyperviscous states could occur and cause symptoms, and third to see whether haemodilution could influence the clinical state of the infant.

Material and method

Many studies of blood viscosity have, in the past, been undertaken using capillary viscometers (Fahraeus and Lindqvist, 1931; Mayer, 1966). These have several disadvantages, the most important being that the early measurements of viscosity were made at shear rates well above those found under normal physiological conditions. Thus, a variety of instruments have been developed (Wells and Merrill, 1961b; Dintenfass, 1962; Baum, 1966; Mayer, 1966) with which it is possible to measure blood viscosity over the range of rates of shear which normally occur within blood vessels.

For the purpose of these studies, a cone-plate Wells-Brookfield Viscometer, adapted for use with small samples of blood, was used (Wells and Merrill, 1961b). 2 ml venous blood was placed into a tube containing

TABLE
Viscosity in the newborn (centipoise, cps)

Shear rate (sec ⁻¹)	Adult	Normal newborn (110)		Normal preterm (mean) (21)	Small-for-dates (mean) (13)	Respiratory distress syndrome (mean) (20)	Cerebral (mean) (24)
		(mean)	(1 SD)				
1.16	14.5	33.7	9.5	30.6	44.6	28.1	47.0
2.32	13.7	23.8	5.6	21.3	29.9	19.6	31.6
5.70	10.1	15.0	3.2	13.5	18.9	13.1	20.1
11.50	8.2	11.2	2.1	10.2	14.0	9.8	14.7
23.00	6.8	9.0	1.6	8.3	11.2	7.9	11.6
46.00	4.7	7.3	1.3	6.7	9.2	6.5	9.5
116.00	4.7	6.0	1.0	5.5	7.5	5.3	7.7
232.00	4.3	5.5	1.1	5.0	6.6	4.8	6.9
PCV		55.0	5.8	54.0	62.0	54.5	63.0

Note: Numbers in parentheses are total in the group.

25 IU heparin, and of this, 1.5 ml was placed in the viscometer and the shear stress determined at shear rates of 1.16, 2.32, 5.7, 11.5, 23, 46, 116, and 232 sec⁻¹. Each specimen was studied twice and the mean of the two observations recorded.

The viscometer was calibrated using a standard oil of known viscosity and all estimations were carried out at a constant temperature of 37 °C. Serial estimations showed that the instrument was accurate to within 3% and consistent results were obtained if the blood was analysed within 4 hours of sampling. Preliminary studies indicated that newborn infant blood did not alter significantly within this 4-hour period but after this time some haemolysis usually occurred and, as this increases viscosity, all haemolysed specimens were discarded.

The remaining 0.5 ml blood was used to determine the haematocrit by calculating the mean values after 7 minutes centrifugation of duplicate samples in a Hawkesley microhaematocrit centrifuge.

A total of 188 newborn infants was studied. The 110 normal babies were singletons born after 38 weeks' gestation, weighing over 2500 g, who showed normal clinical behaviour. Blood was only taken from these babies after obtaining informed consent from the mothers. The 21 normal preterm babies were those under 2500 g at birth who were above the 10th centile by weight for their gestational age. The 13 small-for-dates babies were all below the 10th centile for their gestational age and showed clinical evidence of placental insufficiency (wasting, wrinkled skin, and in some cases small liver) and relatively mature behaviour. Of the 20 infants with respiratory distress syndrome (RDS) studied, 17 weighed less than 2500 g and 5 eventually died. The 24 babies categorized as 'cerebral' all showed typical cerebral signs including excessive irritability, stiffness, jitteriness, and fits or, conversely, severe lethargy, inability to suck, and marked hypotonia, associated at times with apnoea and cyanosis.

Results

The blood of the normal newborn infant showed the same viscoelastic properties as that of adults,

but the mean values for viscosity were considerably higher at all shear rates, ranging from 5.5 cm/sec (centipoise, cps) at a shear rate of 232 sec⁻¹ to 33.7 cps at a rate of 1.16 sec⁻¹ (Table). There was virtually a straight line relation between viscosity and PCV over the normal range, but at PCV values greater than 65% there was a progressively larger increase in viscosity for each unit change in PCV (Fig. 1).

FIG. 1.—Relation between viscosity and PCV in the newborn infant. Open circles indicate infants regarded as hyperviscous.

The results for normal preterm infants over the same shear rates ranged from 5.0 to 30.6 cps and were not significantly different from the results of the normal term babies. However, both viscosity and PCV differed in the small-for-dates infants in whom the mean viscosity values ranged from 6.6 to 44.6 cps. These were within 2 SD of the normal mean values (Fig. 2) but the results for several of these babies fell outside this normal range. The comparison is clearly seen when the range of viscosity values are plotted for any particular shear rate, e.g. 23 sec⁻¹ (Fig. 3).

The viscosity and PCV values for the 20 infants with respiratory distress fell within the normal 2 SD limits (range 4.8 to 28.1 cps) but, while 2 babies were strikingly hyperviscous, there was no relation between the viscosity value and the severity of distress. The mean values for the cerebral babies (range 6.9 to 47.0 cps), however, was only just within the upper limit of normal and in fact 13 of

FIG. 2.—Viscosity curves at shear rates varying from 1.16 to 232 sec⁻¹ displayed on log scale. 1, hyperviscous infants; 2, small-for-dates; 3, preterm; 4, respiratory distress; dotted lines represent normal range (2 SD).

FIG. 3.—Distribution above and below the mean of viscosity values at a shear rate of 23 sec⁻¹ of various groups of newborn infants. RDS, respiratory distress syndrome.

the 24 in this group had values greater than 2 SD above the mean (Fig. 3).

Among the 188 infants studied, there were 19 who had values greater than 2 SD from the normal mean, and these babies were regarded as 'hyperviscous'. Their viscosity values rose from 8.4 cps at 232 sec⁻¹ to 59.4 cps at 1.16 sec⁻¹, and of these only 4 were symptom free. Of the remaining 15, 4 showed plethora and cyanosis but were otherwise normal; 11 had cerebral signs (as defined above), of which 2 preterm infants also had respiratory distress and 1 also had prolonged 'physiological' jaundice. 7 of these symptomatic infants were preterm (below 2500 g) and 4 were small-for-dates.

Treatment

The 19 infants who were found to be hyperviscous were managed in three ways. 11 required no treatment as their clinical condition gave no cause for concern, and their symptoms, if any, disappeared over several days. Additional oral fluids were given to 3 infants with no effect on their symptoms or viscosity values. 6 infants (including 1 who had not responded to additional fluids) received partial plasma exchange transfusions. The technique was the same as that used for exchange blood transfusion except that the infant's blood was replaced by 20 ml and, latterly, by 30 ml/kg body weight of plasma. The effect of this haemodilution on viscosity was striking, especially when the larger volume of plasma was used (Fig. 3). The fall of viscosity to within normal limits was, in several cases, associated with regression of symptoms within 8 hours as opposed to the slower resolution over 2 or 3 days in the milder cases not receiving active treatment. The 1 baby who did not clinically improve after the exchange, even though the viscosity was successfully lowered, was later found at follow-up to be microcephalic and severely retarded.

Discussion

The only previous study of blood viscosity in the newborn period was reported by Baum in 1966. He found that there was a consistent relation between viscosity and haematocrit, but at the relatively high haematocrit values found in the newborn infant a small rise in PCV produced a considerable rise in blood viscosity to the extent that viscous forces trebled between a haematocrit of 50 and 80%. Though it has been subsequently recognized that polycythaemia may produce symptoms in the newborn infant (Gatti *et al.*, 1966; Fouron, 1967; Oh *et al.*, 1967), this work apparently has attracted little attention.

In this investigation the findings of Baum (1966) have been confirmed. In addition, preterm infants were found to have a slightly lower mean viscosity than term babies, and though there is no general correlation between viscosity and birthweight, the present findings suggest that babies under 1500 g tend to have low levels of haematocrit and blood viscosity. The inclusion of such babies displaces the mean viscosity curve for all preterm infants slightly downwards from that for term infants, but this difference is not statistically significant.

The configuration of the viscosity/shear rate curve is the same for the newborn as for the adult, the viscosity increasing as shear rate declines, but whereas the viscosity values of the infant's blood increase from about 5.5 cps at 232 sec⁻¹ to 33.7 cps at 1.16 sec⁻¹, those of the adult are considerably lower, rising from 4.3 cps to 14.5 cps (Skovborg *et al.*, 1966). This upward displacement of the viscosity curve probably makes the infant more susceptible to changes in haematocrit than the adult. The possibility that hyperviscosity might produce clinical abnormalities is apparent from the shape of the viscosity curve (Fig. 2). This shows that at the low shear rates which exist under certain physiological conditions, hyperviscosity could result in reduced blood flow in the microcirculation even to the extent of complete blood stasis.

Many factors have been found to influence blood viscosity (Begg and Hearn, 1966). These include fibrinogen (Weaver, Evans, and Walder, 1969), pH (Rand *et al.*, 1968), temperature (Virgilio *et al.*, 1964), and haematocrit (Strumia and Phillips, 1963; Virgilio *et al.*, 1964), and of these the most important is the haematocrit. The difference between viscosity curves of the newborn and the adult relate, in part at least, to the higher haematocrit in the former. A plot of haematocrit against viscosity for our 110 normal infants is virtually a straight line (Fig. 1) within the normal haematocrit range, but above a PCV of around 70% small changes in haematocrit produce big increases in viscosity. Consequently, a venous PCV level of 65 to 70%, at which a more vertical rise in viscosity occurs with haematocrit change, should probably be regarded as the limit above which clinical symptoms could be anticipated.

The haematocrit of the newborn is greatly influenced by the time allowed to elapse before the umbilical cord is clamped, late clamping resulting in a large placental transfusion and a smaller residual placental blood volume. It is estimated that the proportion of the total infant/placenta blood volume in the infant at birth is 67%, and that this increases to 80% in one minute and to 87% at the termination

of placental transfusion (Yao, Moinian, and Lind, 1969). The advisability of permitting such a transfusion is still debated (Cort and Pribylova, 1964; Moss and Monset-Couchard, 1967). Infants whose cords are clamped late have larger blood volumes (Lind, 1965; Moss and Monset-Couchard, 1967), higher haematocrits (Oh and Lind, 1966), and altered haemodynamics (Oh *et al.*, 1967) when compared to infants whose cords are clamped early. Such studies suggest that very late cord clamping may result in pathologically high levels of haematocrit and viscosity, causing, at times, impaired pulmonary function from excessive venous filling (Oh *et al.*, 1967). As there is little doubt that the PCV and blood viscosity are directly related in the newborn (Dunn, 1970), it is to be expected that both peripheral and pulmonary blood flow may be impaired by an overloaded circulation. Electron microscopical studies have revealed larger numbers of fenestrated small blood vessels in infants with late clamped cords. These permit an increased transudation into the extravascular space (Pietra *et al.*, 1968) of up to one-half of plasma volume (Buckels and Usher, 1965).

The mean viscosity of the 13 small-for-dates infants was higher than that of the term infants and was only just within the normal range (Fig. 3). Several of these babies had very high levels of blood viscosity and this appeared to be related to the production of symptoms. The cause for the high level in these small-for-dates babies was not readily apparent. There was no clinical or biochemical evidence of dehydration in any of them, yet it has been shown that many such infants are polycythaemic and symptomatic (Humbert *et al.*, 1969). Studies of body water spaces have, to date, produced conflicting results (Cassady, 1970; J. C. Maclaurin, personal communication, 1970.) Important in this context, however, is the observation of Cassady (1970) that the estimated plasma volume in small-for-dates infants falls dramatically over the first 4 hours of life. The exact timing of sampling and observation of symptoms was unfortunately not recorded in this series, but attention to these factors may prove rewarding.

Full details of the time of cord clamping of the hyperviscous infants in this study are not known, but the circumstances in 12 of the deliveries were such that the obstetrician would not have delayed clamping the cord and one would not expect these infants to be polycythaemic. This paradox may be explained by the work of Philip *et al.* (1969) which showed that hypoxia at delivery could result in the placenta having a very low residual blood volume due to a transfer of blood from placenta to fetus *in*

utero (Flod and Ackerman, 1971). It is known that maternal hypoxia and fetal asphyxia at birth increase the blood catecholamines in their respective circulations. The experimental evidence, which has yet to be fully substantiated, suggests that these cause more vasoconstriction of the umbilical artery than of the vein, thus encouraging transfer of blood from placenta to fetus. Philip *et al.* (1969) also suggested that the hypoxic induction of uterine contractions could potentiate this effect.

Possible importance of viscosity in clinical syndromes. There are no studies available with which these results in infants can be compared, but the study of adults has revealed that hyperviscosity occurs in myocardial infarction (Burch and DePasquale, 1962; Mayer, 1964), Waldenstrom's macroglobulinaemia (Fahey, Barth, and Solomon, 1965), Raynaud's disease (Pringle *et al.*, 1965), collagen disorders (Jasin, Lospalluto, and Ziff, 1970), hyperlipaemia (Merrill *et al.*, 1964), and polycythaemia (Wells and Merrill, 1962; Putnam, Kevy, and Replogle, 1965).

Minkowski (1962) attributed cardiac failure to polycythaemia in 7 babies and reported rapid improvement after venesection. The importance of high haematocrit in the management of cyanotic heart disease has also been stressed (Kontras *et al.*, 1970). Gatti *et al.* (1966) considered that an excessive placental transfusion at delivery was the cause of plethora, cyanosis, and cardiovascular strain in 10 infants, and others (Danks and Stevens, 1964; Gatti *et al.*, 1966; O'Connor, Shapiro, and Ingall, 1968) have reported that RDS is occasionally associated with polycythaemia.

The evidence in relation to RDS is, however, conflicting. On the one hand the syndrome has undoubtedly been associated with high haematocrit, and on the other the incidence is said to be reduced by deliberately permitting placental transfusion (Bound, Harvey, and Bagshaw, 1962) and the prognosis may be improved in the presence of higher red cell volumes (Usher *et al.*, 1971). Some even advocate deliberate raising of the placenta to ensure such a transfusion (Secher and Karlberg, 1962; Redmond, Isana, and Ingall, 1965). However, an occasional case of RDS may be due primarily to hyperviscosity, and the haematocrit should be determined in all such infants as haemodilution can result in clinical improvement. It is of note that Harrison *et al.* (1971) recorded improvement in adults given exchange transfusions with dextran 40 for polycythaemia due to hypoxic lung disease.

The question remains as to whether infants of all

gestational ages and birthweights can equally well accommodate the increase of over 50% of their blood volume thus infused (Buckels and Usher, 1965) and overcome the reduced pulmonary compliance so imposed (Oh *et al.*, 1967). It is also unresolved whether the improvement with delayed cord clamping observed by some is due to the increased infant blood volume, or to the delay in clamping till after the first breath, or to both.

In 1958 Chaptal *et al.* described 5 infants with dyspnoea and convulsions attributable to polycythaemia, and Wood (1959) studied 2 polycythaemic infants with symptoms of lethargy, cyanosis, and convulsions who improved after venesection and the infusion of plasma.

The results of our study confirm that hyperviscosity of the blood in neonates can be associated with 'cerebral' behaviour, and changes in viscosity have been shown to influence red cell velocity in the cerebral microcirculation (Rosenblum, 1972). Hypoxia at birth may well induce polycythaemia and the resultant hyperviscosity, in conjunction with the initial anoxic insult, may together be responsible for the abnormal signs in 12 of the 19 hyperviscous infants. In some cases these signs respond rapidly to treatment directed at lowering viscosity, suggesting that hyperviscosity of itself was of importance. Though hyperviscosity is probably not a very common cause of cerebral symptoms, it now seems necessary to consider it in any infant with such signs (Chaptal *et al.*, 1958), and the haematocrit should feature along with blood sugar, calcium, and magnesium estimations in the routine testing of the 'cerebral' infant.

As polycythaemia is so easily diagnosed and treated, a PCV estimation is advised for any infant with cerebral, cardiovascular, or respiratory signs. When the venous PCV is over 65 to 70% (the capillary PCV usually being 5 to 6% higher) and the baby has abnormal clinical signs, a plasma or albumin exchange transfusion using 30 ml/kg body weight may produce gratifying results.

Further studies are needed to improve the understanding of the relations between polycythaemia, blood viscosity, abnormal clinical signs, and birth anoxia, particularly in respect to the time of cord clamping.

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