Nonphysiological anaemia of prematurity

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SUMMARY Clinical and haematological findings at the nadir of the refractory, early anaemia of prematurity were compared in a study of 95 preterm infants. 53% of 30 babies <32 weeks' gestational age at birth had abnormal clinical features resulting from anaemia at its nadir, with a combination of tachycardia, tachypnoea, dyspnoea and feeding difficulties, diminished activity, and pallor. The expression 'available oxygen', derived from the Hb concentration and Hb-O₂ affinity, correlated more closely with clinical features of anaemia than did the Hb concentration alone. A formula is presented that predicts the 'available oxygen', provided the Hb concentration and post-conceptual age are known; this avoids the need for direct measurement of Hb-O₂ affinity. Clinical anaemia is common in preterm infants with Hb concentrations of up to 10.5 g/dl, consequent on the high O₂ affinity of fetal Hb. This is the first description of any common clinical consequence of high Hb-O₂ affinity.

Refractory anaemia in the early weeks of life is common after preterm delivery, but its significance is controversial. Although the anaemia is usually regarded as 'physiological' and benign because it is self-limiting, blood transfusion becomes essential in some infants, prompted by such symptoms and signs as dyspnoea and feeding difficulties, diminished activity, poor weight gain, and even apnoeic attacks. Transfusion has also been recommended when the Hb concentration falls below 6–7 g/dl (Gairdner *et al.*, 1955; Seip and Halvorsen, 1956; O'Brien and Pearson, 1971; Davies *et al.*, 1972; Stockman, 1975). However, in addition to the low Hb concentration, the high Hb-O₂ affinity of the preterm infant's blood (Delivoria-Papadopoulos *et al.*, 1971; O'Brien and Pearson, 1971; Stockman *et al.*, 1977) may impair O₂ release to the tissues. Consideration of this phenomenon is important to gain a meaningful assessment of this anaemia (Lancet, 1977a), but no information is available on the significance of altered Hb-O₂ affinity to the preterm infant.

We report the interaction of the low Hb concentration and high Hb-O₂ affinity in preterm infants. These findings are correlated with the clinical features of the early anaemia of prematurity.

Patients and methods

Babies admitted during a period of 2 years to two

special care baby units in Cardiff were studied. Gestational ages were <37 weeks by Dubowitz scoring. Ethical permission was obtained from hospital ethical committees. Clinical assessment was continuous in hospital and was repeated weekly or fortnightly after discharge. Investigative blood losses were <2 ml/baby each week. Supplements were given to prevent deficiencies of iron, folate, and vitamin E (Dallman, 1974).

Clinical features were assessed by medical and nursing staff in charge of the infants. These staff were not connected with the study and knew only the Hb concentrations. The signs sought were: feeding difficulties, dyspnoea, tachycardia, tachypnoea, diminished activity, and pallor. These were recorded in the case notes at the time of observation. Babies showing a combination of these signs with no other clinical explanation were judged clinically anaemic. Capillary blood was examined in a Coulter S counter.

Hb-O₂ affinity (P50 standard)* was derived from the simultaneously measured Hb-O₂ saturation and PO₂ in fresh whole blood at saturations of 40–50% and 50–60% using the IL 217 blood gas laboratory (Instrumentation Laboratories, UK). P50 *in vivo* was calculated from the P50 standard, correcting for pH and base excess (Lichtman *et al.*, 1974) measured on arterialised capillary blood.

*P50 standard is the O₂ tension required to give 50% Hb-O₂ saturation at 37°C, pH 7.4, Pco₂ 5.32 kPa (40 mmHg).[†]

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'Available oxygen' derived from the Hb concentration and P50 *in vivo*, is the amount of O₂ calculated to be capable of release per dl blood, using the measured arterialed capillary PO₂ and a mixed venous PO₂ of 2.66 kPa (20 mmHg) (Jones *et al.*, 1978).

Results

Results are reported from 95 preterm infants according to gestational age (group 1) 28–32 weeks, (group 2) 33–34 weeks, and (group 3) >35 weeks' gestation.

Haematological findings (Table 1a). In all babies the

Hb concentration showed the expected fall until the nadir at 3–11 weeks after birth and then a rise. The nadir was taken as the time of lowest Hb concentration. At the nadir, the haematological values on which oxygen transport depends—the Hb concentration, P50, and therefore the 'available oxygen'—were all lower than normal adult values. These differences were most pronounced in the infants of the shortest gestation (group 1), in whom the nadir also developed earlier than that of the infants in groups 2 and 3.

There is a linear correlation between the 'available oxygen' per g Hb and gestational age at birth+postnatal age (total age) of preterm infants (Fig. 1). It is, therefore, possible to predict the

Table 1a *Haematological findings (mean±SD) at nadir of anaemia*

	Group			Adult*	P values†		
	1 (n=30)	2 (n=35)	3 (n=30)		1 cf 2	1 cf 3	2 cf 3
Gestational age at birth (weeks)	28–32	33–34	35+	—	—	—	—
Age at nadir (weeks)	5.9±2	7.4±2	7.8±2	—	<0.01	<0.001	>0.20
Hb concentration (g/dl)	9.5±1.2	10.0±0.9	10.6±0.9	—	<0.01	<0.001	>0.20
Reticulocyte count (%)	4±3	2.5±3.5	2.5±2	<2	<0.05	<0.04	>0.20
P50 standard kPa	2.7±0.3	2.8±0.3	2.9±0.3	3.2±0.2	>0.20	<0.02	>0.10
in vivo kPa	3.0±0.3	3.1±0.3	3.2±0.3	3.6±0.3	>0.20	<0.06	>0.15
Available oxygen per dl blood	6.6±1.3	7.6±0.9	8.0±1.1	12.2±1.3	<0.01	<0.001	>0.10
Fe (μmol/l)	18±6	16±6	20±7	10–35	—	—	—
TIBC (μmol/l)	42±17	44±12	49±17	35–70	—	—	—

*Values for O₂ transport parameters are based on findings in healthy adults (8 men, 13 women).

†Student's *t* test.

TIBC=total iron binding capacity.

Conversion: SI to traditional units—P50: 1 kPa ≈ 7.5 mmHg. TIBC and Fe: 1 μmol ≈ 5.6 μg.

Fig. 1 *Correlation between 'available oxygen' per g Hb and gestational+postnatal age (total age) in weeks.*

Fig. 2 Hb concentrations and 'available oxygen' values in infants with and without symptoms of clinical anaemia at the nadir. Bars represent means $\pm$ SD.

'available oxygen' from the measured Hb concentration and the total age of an infant between 30 and 50 weeks after conception from the formula (Table 1b)

'Available oxygen' (ml/dl blood) = (0.54 + 0.005 total age (weeks)) $\times$ Hb concentration (g/dl)

Clinical features at the nadir (Table 2, Fig. 2). 53% of group 1 infants showed clinical signs of anaemia; this clinical anaemia correlated well with the depression of 'available oxygen' but less well with either the low Hb concentrations or the low P50 values alone (Fig. 3). In group 2 infants, of whom

Table 1b Comparison of observed and predicted* 'available oxygen' values (mean $\pm$ SD)

	Group		
	1	2	3
Gestational + postnatal age (weeks)	36	41	43
'Available oxygen' at nadir of anaemia			
Observed (ml/dl)	6.6 $\pm$ 1.3	7.6 $\pm$ 0.9	8.0 $\pm$ 1.1
*Predicted (ml/dl)	6.8	7.5	7.9

*Derived from formula.

Fig. 3 'Available oxygen' v. P50 and Hb (means $\pm$ SD) in group 1 infants with and without symptoms of clinical anaemia.

Table 2 Clinical and haematological data in all infants judged by ward medical staff to be anaemic and to need blood transfusion on standard clinical grounds

Case	Gestational age at birth (weeks)	Age at Tx (days)	Hb (g/dl)	Available O ₂ (ml/dl)	Indication for transfusion	Heart rate		Respiration rate	
						Before Tx	After Tx	Before Tx	After Tx
1	28	29	10.3	6.5	↑ HR ↑ RR; poor weight gain; systolic murmur. ECG, chest x-ray normal	180	160	70	40
2	32	40	10.3	6.8	↑ HR ↑ RR, ECG, chest x-ray normal	170	140	58	40
3	30	44	9.6	6.5	↑ HR ↑ RR; lethargic, ECG, chest x-ray normal	162	140	56	40
4	31	31	9.7	5.1	↑ HR ↑ RR	172	150	50	48
5	32	39	8.0	5.6	Slow with feeds	158	150	50	48
6	31	46	8.0	6.5	Slow with feeds due to dyspnoea	160	160	40	40
7	32	37	8.6	5.8	Systolic murmur; ECG, chest x-ray normal	172	156	40	40
8	30	27	9.5	7.2	Persistent apnoea requiring O ₂	160	150	70	54
9	31	30	8.5	6.1	Poor weight gain; lethargic	158	155	48	40
10	28	41	9.4	6.2	Dyspnoea with feeds; lethargic	158	155	48	40
11	30	37	9.3	6.1	Dyspnoea with feeds	150	140	50	40
12	32	46	8.6	6.8	Dyspnoea with feeds	160	150	50	40
13	32	39	7.7	3.9	Dyspnoea with feeds	160	150	52	40
14	33	24	8.1	5.8	Slow with feeds	170	160	50	48
15	34	21	8.1	5.9	Persistent severe apnoea	160	158	48	40
16	34	34	9.1	7.5	↑ RR; systolic murmur, hepatosplenomegaly	164	158	60	40
17	34	27	9.3	6.8	↑ RR; pale; lethargic	160	160	60	40
18	36	35	9.8	6.9	↑ RR ↑ HR systolic murmur	170	140	60	40

HR = heart rate; RR = respiratory rate; Tx = transfusion.

Heart and respiration rates are means of 3-hourly observations during 24-hour periods before and 2 days after transfusion.

15% showed the clinical signs of anaemia, the Hb concentration correlated as closely with these clinical abnormalities as did the 'available oxygen'. Only one baby in group 3 showed clinical anaemia.

Table 2 shows clinical and haematological data on infants judged by ward medical staff to need transfusion on standard clinical grounds.

Discussion

The haematological findings give detailed information on the ability of the blood to supply oxygen to the tissues at the nadir of the anaemia of prematurity. The lowest values are found in infants of the shortest gestation. The low level of 'available oxygen' in group 1 is a result of the interaction of the low Hb concentration and high Hb-O₂ affinity. The high Hb-O₂ affinity is a result of the infant's dependence on fetal Hb, which is relatively insensitive to the effect of 2,3 diphosphoglycerate in facilitating O₂ release. In group 1, the higher reticulocyte counts, which also correlate inversely with 'available oxygen', suggest increased erythropoietin-related drive to the bone marrow—i.e. the infants are experiencing and partially responding to hypoxia. This runs counter to the suggestion that the anaemia reflects physiological autoregulation of erythropoiesis by the preterm infant in whom oxygen requirements are diminished because of a low basal metabolic rate (Stockman, 1975). However, this question is vexed (E. N. Hey, 1977, personal communication) and the basal metabolic rate and O₂ consumption of preterm babies have been found to be increased compared with those of term infants (Hill and Robinson, 1968; Alvear and Brooke, 1977).

Blood transfusion for anaemia was given, on standard clinical indications, on the decision of ward medical staff not connected with the study. Transfusion corrected the raised heart and respiratory rates as well as the other clinical abnormalities associated with anaemia (Table 2). This information further supports the concept of this anaemia as a pathological state.

The cause of the refractory anaemia is probably a combination of the shortened survival of the fetal red cell (Pearson, 1967) and inadequate erythropoietic response by the immature bone marrow of the preterm infant. Iron deficiency is not a contributory feature (Table 1a).

The indications for blood transfusion should be based on clinical and haematological assessment (Davies *et al.*, 1972; *Lancet*, 1977a; Stockman *et al.*, 1977). The clinical recognition of this anaemia is often difficult and Hb estimation alone may not be adequate for the diagnosis of anaemia, particularly in infants with other complications. Our findings show that the

assessment should include P50 measurement as well as Hb estimation, at least in the more immature infants. In these, Hb concentrations as high as 10.5 g/dl may be associated with clinical anaemia due to reduced availability of O₂ because of the high Hb-O₂ affinity.

Most babies <33 weeks' gestation with a Hb concentration <10.5 g/dl have clinical anaemia. The clinical features of anaemia correlated better with the depression of 'available oxygen' than with the low Hb concentration alone in group 1 infants (Fig. 3). Equally good identification of clinically anaemic infants was obtained using 'available oxygen' values derived from the formula (Table 1b). As only the Hb concentrations were known to the ward staff making these observations, the better correlation with 'available oxygen' could not be attributed to observer bias. If facilities are not available for measuring P50 the 'available oxygen' can be predicted using the above formula. Figs 2 and 3 show that anaemia may be the cause of symptoms and signs in any preterm infant in whom the Hb concentration at the nadir is <10.5 g/dl. Calculation of 'available oxygen' appears to offer no advantage over Hb estimation alone in the laboratory diagnosis of anaemia in most infants >35 weeks' gestation.

Early anaemia of the preterm infant, which would not occur during normal intrauterine development or during postnatal progress in the term infant, should be presumed unphysiological until proved harmless.

We have demonstrated a highly unphysiological phenomenon—a defect in O₂ supply during the early weeks of life which correlates with a clinical syndrome of anaemia, most commonly seen in infants of shortest gestation. Clinical features—such as diminished activity, feeding difficulties, and dyspnoea at rest—while not usually life-threatening, signify an impairment of O₂ supply because of reduced availability from the blood. This occurs during the period of maximum brain growth (Dobbing, 1974) and could prejudice the child's chances of achieving full potential in later life. It could also contribute to the chronic hypoxaemia which may underlie cot deaths (*Lancet*, 1977b). In the short term, the syndrome is readily corrected by blood transfusion; more information is needed about the effects of this anaemia on development and to determine the indications for and benefits of blood transfusion. The situation may parallel that in severe haemoglobinopathies where transfusion improves growth and development.

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