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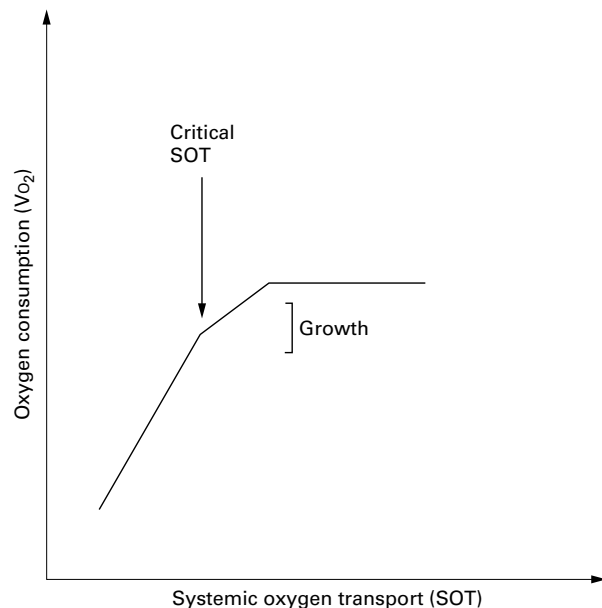
Critical haemoglobin thresholds in premature infants

Blood transfusion is an integral part of neonatal intensive care. Unfortunately, transfusion practice is often based on expert opinion^{1,2} and anecdote rather than scientific evidence. Historically, blood transfusions have been used as therapy for apnoea and bradycardia, poor feeding, poor weight gain, and pallor. Although many studies have examined these outcomes,³ few are methodologically sound, many lack sufficient power, and most contribute little to the discussion.

Theoretically, red blood cell transfusion is used to avoid the pathological state in which oxygen demand is greater than supply.^{4,5} As such, the principal outcome of any study of transfusion practice would need to incorporate measures of end organ hypoxia, specifically ischaemic brain injury, chronic lung disease, retinopathy of prematurity, and death. At the present time there are no methodologically sound prospective trials of transfusion practice that include long term neurodevelopmental outcome, the end result of brain hypoxia. This is in part because of the complexities of a randomised, non-blinded study but also because of the dynamic balance between systemic oxygen transport (SOT) and oxygen consumption (VO_2) (see fig 1).

In order to understand the concept of a critical haemoglobin threshold, if one exists, it is necessary to examine the balance between SOT and demand or VO_2 .

Oxygen is used by the electron transport chain within the mitochondria for oxidative phosphorylation. Its supply depends on many factors, in particular the distance between the capillary and the cell, the diffusion characteristics, and the oxygen pressure gradient between the capillary and the cell.⁶ This pressure gradient depends on regional blood flow, oxygen transport, and the characteristics of the haemoglobin-oxygen dissociation curve (HODC).⁶



Systemic oxygen transport

SOT is cardiac output multiplied by arterial oxygen content. The arterial oxygen content is determined by the haemoglobin concentration, oxygen carrying capacity, oxygen saturation, and PaO_2 :

$$[\text{Hb}] \times \text{SaO}_2 \times 1.36 + \text{PaO}_2 \times 0.0031$$

with 1.36 ml of oxygen dissolved in 100 ml of blood and 0.0031 being the solubility coefficient of blood.

Cardiac output

Cardiac output (CO) is one of the principal contributors to systemic oxygen delivery. The critical mixed venous oxygen saturation (MvO_2) at which oxygen demand is supply limited is higher for stagnant than for anaemic or hypoxic hypoxia.⁷⁻¹⁰ This is in part because other compensatory mechanisms such as increases in fractional oxygen extraction (FOE) and redistribution of flow away from low consumption organs are dependent on the maintenance of CO. Compared with adults, CO as a proportion of weight is high in newborns. Single ventricular output is 400 ml/kg/min compared with 100 ml/kg/min in adults.^{11,12} Newborn infants operate with relatively fast heart rates and have limited capabilities to respond to increases in both preload and afterload.¹³ In a small non-blind, non-randomised study of “acceptably resuscitated” postcardiac surgery children, adrenaline infusion (0.05 to 0.3 $\mu\text{g}/\text{kg}/\text{min}$) increased both SOT (from 19.9 (5.0) to 25.9 (6.1) ml/min/kg post treatment) and VO_2 (from 4.3 (0.8) to 5.5 (1.2) ml/min/kg post treatment); however, an increase in preload with packed red blood cell transfusion (10–15 ml/kg) increased SOT (from 20.5 (6.4) to 26.2 (7.1) ml/min/kg post treatment) but not VO_2 (from 4.5 (0.8) to 4.4 (0.8) ml/min/kg post treatment).¹⁴ As there was no increase in FOE, it is most likely that the increase in consumption represents increased cellular metabolism that mirrors normal exercise (endogenous catecholamines) rather than supply dependence.

Haemoglobin

AFFINITY

Haemoglobin affinity is described by the P50—that is, the PaO_2 at which 50% of Hb is saturated. The P50 of fetal Hb (HbF) is low (high affinity) and to the left of HbA on the HODC. This favours oxygen scavenging from maternal Hb at the placenta. As the Hb changes from fetal to adult, the HODC shifts to the right, affinity falls, and P50 rises from approximately 19.4 (1.8) to 30.3 mm Hg.¹⁵ This change in affinity favours tissue unloading. In low birth weight infants (1001–500 g) Delivoria-Papadopoulos has shown that despite a significant fall in haemoglobin concentration from 151 (13) to 82 g/l over 10 weeks, oxygen unloading capacity increased from 1.0 to 2.1 ml/100 ml of blood.¹⁵ This was caused by the concomitant increase in 2,3-diphosphoglycerate with a resultant increase in P50 from 18 (1.8) to 24.0 mm Hg.¹⁵

The HODC shifts to the right with increases in H^+ ions (fall in pH), temperature, and pCO_2 (Bohr effect). This, in combination with morphological changes in haemoglobin (from HbF to HbA), favours tissue oxygen delivery by increasing the oxygen gradient between the perfusing capillary and the utilising cell.⁶

A similar change in $P50$ would occur with transfusion of adult red cells of low affinity.¹⁶ However, functional integrity of these cells depends on their storage and age.

AMOUNT

In a lamb model of anaemic hypoxia, van Ameringen and colleagues¹⁷ showed that the critical point at which oxygen supply limits demand is higher for lambs with low Hb affinity anaemia ($P50$ 19.4 mm Hg) compared with lambs with high Hb affinity anaemia ($P50$ 32 mm Hg) who were exchanged with maternal blood ($P50$ 30 mm Hg). The critical MvO_2 at which demand is supply limited was higher for anaemic versus hypoxic hypoxia across species.^{9 18} In mature dogs with isovolaemic anaemia (pretreatment haematocrit 42–43%), compensatory adjustments to cardiac output, blood flow redistribution, and increased oxygen extraction maintain oxygen delivery until the haematocrit is lowered to 10%.⁷ In a large randomised study of haemoglobin thresholds in euvoalaemic adults ($n = 838$) admitted to intensive care and stratified for illness severity (APACHE), those maintained on a low (Hb 7–9 g/l) versus high (10–12 g/l) Hb threshold had similar 30 day mortality though reduced in-hospital mortality.¹⁹

In low birth weight infants, transfusion algorithms^{20 21} have been shown to reduce packed red cell transfusions, although this is most likely caused by the standardisation of transfusion criteria and the reduction in individual physician variation. More recently, Maier and colleagues²² have shown, using historical controls, that a restrictive transfusion practice resulted in a reduction in blood volume and donor exposure, but had no effect on survival or acute complications in extremely low birth weight infants. However, there was no information on long term neurodevelopmental follow up.

Arterial oxygen tension (P_{aO_2})

In low birth weight infants with predominance of fetal Hb, the $P50$ and $P90$ are 18.3 (1.9) mm Hg and 40.8 (3.6) mm Hg respectively.²³ P_{aO_2} increases as Hb changes from HbF to HbA. In 3 day old mature piglets with stable Hb and acid–base balance, a P_{aO_2} of 40 mm Hg or greater was sufficient to maintain adequate oxygen delivery.²⁴ However, with a P_{aO_2} less than 40 mm Hg compensatory mechanisms start to fail and lactate accumulation begins from both production and reduced metabolism. At less than 30 mm Hg, rapid progressive lactic acidosis occurs.

Fractional oxygen extraction

FOE is a measure of the venous oxygen reservoir. Blood returning from the heart and brain is less well saturated (30–60%) than blood from the liver, kidneys, and skin (80–90%). In stable, euvoalaemic, low birthweight infants, FOE increases to meet demand following a reduction in P_{aO_2} .²⁵

MvO_2 is a measure of total body oxygen extraction. It quantifies the available residual oxygen in the blood following return to the heart. In a piglet model of graded hypoxia,²⁴ a central venous oxygen saturation (SvO_2) of greater than 40% excluded oxygen restricted metabolism (raised lactate:pyruvate ratio) and an SvO_2 of less than 15% was associated with oxygen restricted metabolism.

Oxygen consumption (Vo_2)

Vo_2 is equivalent to minute ventilation multiplied by the difference between inspired and expired oxygen tension. In utero, the fetus uses 30–50% for growth alone.¹³ With

chronic in utero hypoxia, consumption is reduced at the expense of growth.¹³ Compared with levels in resting adults (4 ml/kg/min), neonates have high resting consumption (8.3 (1.8) ml/kg/min²⁶ to 8.3 (0.9) ml/kg/min at 24 hours²⁷). Mature newborn infants increase consumption in the first 24 hours after birth in order to meet the needs of heat generation and respiratory work.¹³ For the growing preterm infant, coexisting morbidities, such as bronchopulmonary dysplasia,²⁸ may result in further demands.

Critical value

MvO_2 provides an estimate of the oxygen supply–demand equilibrium. In the absence of a left to right shunt, the saturation in the right atrium is marginally higher than the pulmonary artery.^{29 30} It can be measured in premature infants^{31 32} using a central venous catheter, though the correct placement of the catheter is critical.³¹ In addition, with the use of a central arterial catheter, FOE ($(S_{aO_2} - S_{vO_2})/S_{aO_2}$) can be calculated. However, neither MvO_2 nor FOE incorporate cardiac output directly and both measures require invasive catheters in preterm infants. Clearly, the measurement of MvO_2 in combination with a non-invasive measure of cardiac output (echocardiogram) may be useful in neonatal intensive care. It may also offer clues as to the most appropriate therapy for hypoxia and hypotension. Unfortunately, its use is limited to preterm infants with invasive central catheters and therefore cannot be used in the day to day management of growing preterm infants. Measurement of peripheral oxygen metabolism with near infrared spectroscopy and partial venous occlusion is non-invasive. It has yet to be shown that these measurements reflect the global oxygen dynamic, though preliminary work is promising.^{33–35}

Extrapolation of the aforementioned work from mature adults and animals to newborn infants is difficult. This is because the premature infant has immature skin, high relative surface area, a high requirement for heat production, and large consumption for growth. It is clear, however, that isovolaemic anaemia is better tolerated than hypovolaemic anaemia, and that anaemic hypoxia is less well tolerated than hypoxic hypoxia, though better tolerated than stagnant hypoxia.³⁶ Also, with changes in haemoglobin affinity, either endogenously or with transfusion of adult cells, the infant's ability to maintain adequate supply at critical levels improves by increasing tissue unloading.

Conclusion

Hypovolaemic anaemia, as would occur in haemorrhagic shock, is poorly tolerated and requires a high critical threshold, though exactly how high is not clear. Isovolaemic anaemia, including euvoalaemic anaemia of prematurity, is better tolerated and allows a substantially lower critical threshold.

The overwhelming majority of infants less than 1000 g receive at least one transfusion,³⁷ though most receive many more. Unfortunately, despite the widespread clinical use of transfusion thresholds, they are not based on evidence. It is clear that the dynamic balance between supply and demand is complicated, and a reliance on Hb threshold as a marker for oxygen restricted metabolism is naïve at best. More research is necessary in order to unlock the fine balance between supply and demand, and it is imperative that this work be methodologically sound and include long term neurodevelopmental outcomes.

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