Effect of haemoglobin concentration on brain oxygenation in focal stroke: a mathematical modelling study

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Summary
Acute perioperative anaemia may affect neurological injury from permanent focal ischaemic insults. We modelled the opposing effects of haemodilution (increasing cerebral blood flow, decreasing arterial oxygen content) on oxygen availability and uptake in the ischaemic penumbra. First, we validated a mathematical model of regional cerebral oxygen uptake by using published arterial oxygen content and cerebral blood flow values from normal rabbits with progressive anaemia. Then we applied the model to the problem of interest (i.e. the ischaemic penumbra of a focal embolic stroke). We re-analysed published experimental data giving the cerebral blood flow response to anaemia in the ischaemic penumbra. Penumbral extraction reserves were nearly exhausted at a haemoglobin concentration of approximately 10 g 100 ml\(^{-1}\). Oxygen uptake in the ischaemic penumbra decreased progressively when haemoglobin concentrations decreased to less than 10 g 100 ml\(^{-1}\). We conclude that, given the available clinical and experimental literature, and until a suitable randomized clinical study has been performed, such a predicted haemoglobin concentration would be a rational "transfusion trigger" for the anaemic, normothermic stroke patient. (Br. J. Anaesth. 1997; 79: 346–351).

Key words

More than half a million adults undergo cardiac surgery in Europe and North America each year. Modern cardiac surgery includes operative blood loss, deliberate haemodilution and the desire to limit homologous transfusion. Thus cardiac surgery patients often have haemoglobin concentrations of 7–9 g 100 ml\(^{-1}\) for several days after operation. Currently, 3–5% of cardiac surgery patients also sustain a perioperative cerebral infarction (stroke). It is not known if the marked postoperative anaemia of cardiac surgery patients affects their neurological outcome. Laboratory\(^{4–7}\) and clinical studies\(^{8–11}\) have provided conflicting results. In some studies haemodilution improved neurological outcome\(^{4,5,8,9}\), by increasing cerebral blood flow (CBF), haemodilution may have improved oxygenation of marginally viable brain (the "ischaemic penumbra"). Other studies have found an adverse effect with haemodilution.\(^{8,10,11}\) Under these circumstances, reduced arterial oxygen content may have more than offset increased CBF and resulted in a net reduction in oxygen delivery to the penumbra. In this study, we have modelled the opposing effects of haemodilution (increasing CBF, decreasing arterial oxygen content) on oxygen availability and uptake in the ischaemic penumbra.

Our goal in this study was to see if there was a haemoglobin concentration below which penumbral oxygenation would be impaired rather than improved. Until a suitable randomized clinical study has been performed, such a predicted haemoglobin concentration would be a rational "transfusion trigger" for the anaemic, normothermic stroke patient.

Materials and methods
We adapted our previously described mathematical model of cerebral oxygen transport.\(^{12}\) We used this model to predict regional cerebral oxygenation in normal and penumbral brain as a function of arterial haemoglobin concentration. There are no human CBF data covering a wide range of haemoglobin concentrations in acute stroke. Thus we used CBF and cerebral metabolic rate for oxygen (CMRO\(_2\)) data obtained from rabbits. CBF responses to haemodilution are known for this species, both in the presence\(^{13}\) and absence\(^{13,14}\) of acute cerebral infarction.

We assumed a constant blood and brain temperature of 37 °C. At 37 °C, the human oxyhaemoglobin dissociation curve is described by the following relationship:\(^{15}\)

\[
S_{O_2} = \left[ \frac{23400 (P_{O_2} - 150)}{P_{O_2}^3} \right]^{\frac{1}{1}} + 1
\]

where \(S_{O_2}\) (unitless) = fractional oxyhaemoglobin saturation and \(P_{O_2}\) (mm Hg) = oxygen partial pressure. Diffusion primarily limits oxygen transfer from
haemoglobin to brain.16 Hence we did not include chemical reaction kinetics in the model. The haemoglobin P50 of the rabbit (4.0 kPa) and Hill coefficient (2.8) are almost identical to those of humans (3.5 kPa and 2.9, respectively).17,18 Therefore, human and rabbit oxyhaemoglobin saturation curves can be considered to be equivalent.

Net regional oxygen transport from blood to brain tissue (i.e. regional brain oxygen uptake) is described using Fick’s law of diffusion for a parallel plane layer geometrical configuration19,20:

\[
\text{rCMRO}_3 = \frac{11358 \times 10^{-3} \times 13 \times (8.22 \times 10^{-4}) \times P_{OCO} - P_{NO}}{27 \times 10^{-4}}
\]

where \(\text{rCMRO}_3\) = regional (CMR\(_{O_2}\)) (ml O\(_2\) 100 g\(^{-1}\) min\(^{-1}\), \(P_{OCO}\) (mm Hg) = regional end-capillary oxygen partial pressure and \(P_{NO}\) (mm Hg) = regional interstitial oxygen partial pressure. The term 11 358 cm\(^2\) 100 g\(^{-1}\) = the sum of arteriole, capillary and venule surface areas available for oxygen exchange\(^{21}\); the term 27 \(\times 10^{-4}\) cm = the sum of capillary and tissue thickness\(^{20}\); the term 2.9 \(\times 10^{-3}\) ml O\(_2\) ml\(^{-1}\) mm Hg\(^{-1}\) = oxygen solubility in brain at 37 °C\(^{22}\); the term 8.22 \(\times 10^{-4}\) cm\(^2\) min\(^{-1}\) specifies the net oxygen diffusion coefficient in blood and brain\(^{23}\); 13 (unitless) is a correction factor shown by Schachterle, Ribando and Adams to be necessary for Fick’s law to attain the level of oxygen transport measured experimentally.\(^{24}\) The correction is needed because oxygen diffuses intracellularly through areas of high solubility (i.e. lipid).\(^{25}\) Thus this correction factor has been shown to come from the oxygen diffusion properties of lipids. As such, it is unlikely to be affected by changes in regional CBF, intracellular pH, etc, as may occur in the ischaemic penumbra. Also, the factor is unlikely to vary greatly among species.

\(\text{rCMRO}_3\) can be determined by mass balance\(^{19}\):

\[
\text{rCMRO}_3 = \text{rCBF} (1.34 \text{ Hb} \text{ Sa}_O + \alpha_{O_2} \text{ Pa}_O - 1.34 \text{ Hb} \text{ Sec}_O - \alpha_{bl} P_{OCO})
\]

where \(\text{rCBF}\) = regional CBF (ml g\(^{-1}\) min\(^{-1}\), \(\text{Hb}\) = haemoglobin concentration (g 100 ml\(^{-1}\)); \(\alpha_{O_2}\) = oxygen solubility in blood (0.0029 ml O\(_2\) 100 ml\(^{-1}\) mm Hg\(^{-1}\)); \(\text{Sa}_O\) = arterial oxyhaemoglobin saturation, \(\text{Pa}_O\) (mm Hg) = arterial oxygen partial pressure and \(\text{Sec}_O\) (unitless) = cerebral end-capillary oxyhaemoglobin saturation. Our model is for cardiac surgery patients undergoing mechanical ventilation and therefore we used \(\text{Pa}_O = 100\) mm Hg and \(\text{Sa}_O = 1.0\) in all simulations.

Todd, Weeks and Warner recently reported that, in rats, brain haemoglobin concentration is less than systemic arterial haemoglobin concentration.\(^{26}\) Other groups have not confirmed this finding.\(^{27}\) Nevertheless, whole brain haemoglobin concentration can be less than systemic arterial and jugular haemoglobin concentrations, if erythrocytes travel through the capillary beds faster than plasma.\(^{26}\) Thus the experimental findings of Todd, Weeks and Warner do not change the validity of mass balance for the amount of oxygen being delivered to and leaving the brain.\(^{26}\) Equation (3) only uses haemoglobin concentration in this manner (i.e. to specify mass balance for oxygen for a region of brain).

Regional cerebral oxygen consumption varies with intermittent oxygen partial pressure\(^{24,28}\):

\[
r\text{CMRO}_3 = \frac{3.5 \times P_{NO}}{P_{NO} + 2.0}
\]

Normal human \(\text{rCMRO}_3 = 3.5\) ml O\(_2\) 100 g\(^{-1}\) min\(^{-1}\).\(^{29}\) The term 2.0 mm Hg specifies the intermittent oxygen partial pressure at which \(\text{rCMRO}_3\) is 50% of normal.\(^{29}\) Thus, as interstitial oxygen partial pressure increases, \(\text{rCMRO}_3\) asymptotically approaches a maximal (normal) value. Back, Kohno and Hossmann found that brain interstitial oxygen partial pressures were 28 mm Hg in normothermic rats.\(^{30}\) Substituting this value into equation (4) gives a \(\text{rCMRO}_3\) value of 93% of normal. We consider 93% to be a value clinically indistinguishable from normal. Conveniently, 3.5 ml O\(_2\) 100 g\(^{-1}\) min\(^{-1}\) is not only a normal \(\text{rCMRO}_3\) value for awake humans, but also in anaesthetized rabbits.\(^{31}\) This equivalence allows the use of \(\text{rCBF}\) and \(\text{rCMRO}_3\) data from anaesthetized rabbits with acute embolic stroke to estimate the effect of anaemia on the human ischaemic penumbra.

We first tested the validity of the model; to do this we checked that the model predicted the effect of haemodilution on cerebral oxygenation (CMR\(_{O_2}\), oxygen extraction) in normal brain. We used data from Todd and colleagues.\(^{14}\) They decreased the haemoglobin concentration of anaesthetized rabbits from 13 to 4.5 g 100 ml\(^{-1}\) and measured changes in CBF, oxygen extraction and CMR\(_{O_2}\). We inserted their values for mean haemoglobin concentration, arterial oxygen contents and CBF into our model. Algebraic equations (1)–(4) were numerically solved simultaneously.\(^{32}\) Solutions for CMR\(_{O_2}\) were constrained to be less than or equal to the maximal (normal) CMR\(_{O_2}\).\(^{32}\) Iterations were continued until CMR\(_{O_2}\) was calculated to within 0.01%. We compared predicted CMR\(_{O_2}\) and oxygen extraction ratios with those measured by Todd and colleagues.\(^{14}\)

Next we modelled the effect of anaemia on penumbral oxygenation; to do this we used the CBF data of Korosue and Heros.\(^{13}\) They measured \(\text{rCBF}\) in the ischaemic penumbra of rabbits after embolic stroke and acute isovolaemic haemodilution, and simultaneously measured \(\text{rCBF}\) in the non-embolized contralateral hemisphere:

\[
\text{rCBF} = \begin{cases} 0.384 (-7.4 (1.34 \text{ Hb} \text{ Sa}_O + \alpha_{O_2} \text{ Pa}_O) + 212.7), & \text{normal brain} \\ 0.201 (-3.0 (1.34 \text{ Hb} \text{ Sa}_O + \alpha_{O_2} \text{ Pa}_O) + 150.4), & \text{ischaemic penumbra} \end{cases}
\]

As before, algebraic equations (1)–(4) were solved simultaneously to determine \(\text{rCMRO}_3\), and oxygen extraction as a function of haemoglobin concentration.

Results

We first used data from Todd and colleagues\(^{14}\) to test the model. Table 1 gives measured and...
which were substituted into the mathematical model. The maximum normal cerebral metabolic rate for oxygen (CMR\textsubscript{O2}) was set equal to the maximum observed mean CMR\textsubscript{O2} (4.0 ml O\textsubscript{2} 100 g\textsuperscript{-1} min\textsuperscript{-1}), rather than 3.5 ml O\textsubscript{2} 100 g\textsuperscript{-1} min\textsuperscript{-1}, as used in equation (4). Measured oxygen extraction ratio and CMR\textsubscript{O2} are reported as mean (SD) (n=6). CBF = Cerebral blood flow.

<table>
<thead>
<tr>
<th>Model parameters</th>
<th>Measured</th>
<th>Predicted</th>
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<tr>
<td>Haemoglobin concn (g 100 ml\textsuperscript{-1})</td>
<td>Arterial oxygen content (ml O\textsubscript{2} 100 ml\textsuperscript{-1})</td>
<td>CBF (ml 100 g\textsuperscript{-1} min\textsuperscript{-1})</td>
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<tr>
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Table 1 Comparison of model predictions with data from Todd and colleagues.\textsuperscript{14} Model parameters are the mean experimental values predicted by us, and the measured values from Todd and colleagues.\textsuperscript{13} The comparison of model predictions with data from Todd and colleagues\textsuperscript{13} was made to validate our model.

However, the magnitude of the increase was much less in the ischaemic penumbra than that in normal brain (fig. 1, top). In the non-ischaemic brain, reduction in haemoglobin concentration from 12 to 6 g100 ml\textsuperscript{-1} caused a 65% increase in CBF (or 23 ml 100 g\textsuperscript{-1} min\textsuperscript{-1}). However, in the ischaemic penumbra, the same reduction in haemoglobin concentration caused CBF to increase by only 24% or 5 ml 100 g\textsuperscript{-1} min\textsuperscript{-1}.

The measured CBF \textit{vs} haemoglobin relationships from figure 1 were used to validate our model. Regional brain oxygen uptake (i.e. CMR\textsubscript{O2}) was predicted from the haemoglobin concentration (fig. 1). The model predicted that, at a haemoglobin concentration of 12 g 100 ml\textsuperscript{-1}, rCMR\textsubscript{O2} in the ischaemic penumbra is only slightly (10%) less than that in normal tissue (2.9 \textit{vs} 3.2 ml 100 g\textsuperscript{-1} min\textsuperscript{-1} (fig. 1, bottom), because of greater oxygen extraction (fig. 1, middle). This model prediction is consistent with experimental studies of regional oxygen metabolism in focal cerebral ischaemia. Acute, penumbral CMR\textsubscript{O2} has been found to be only 7–20% less than that of non-ischaemic brain.\textsuperscript{33–36}

For the non-ischaemic brain, the model predicted that increases in CBF from anaemia do not fully compensate for decrease in arterial oxygen content. A moderate increase in oxygen extraction is needed to maintain normal brain oxygen uptake (fig. 1, middle). However, with this increase, normal brain maintains oxygen uptake, even with marked anaemia. As stated before, this model prediction is consistent with the study of Todd and colleagues\textsuperscript{14} of isovolaemic anaemia in rabbits (table 1).

In contrast, the model predicted that, in the ischaemic penumbra, increased CBF (fig. 1, top) and oxygen extraction (fig. 1, middle) are not sufficient (fig. 1, bottom) to compensate for decreases in arterial oxygen content. Oxygen uptake (rCMR\textsubscript{O2}) in the ischaemic penumbra decreased progressively with greater anaemia. For example, at a haemoglobin concentration of 6 g 100 ml\textsuperscript{-1}, predicted oxygen uptake in the ischaemic penumbra was 36% less than that in non-ischaemic brain. Our model predicted that anaemia of less than 10 g 100 ml\textsuperscript{-1} decreased oxygen availability to penumbral tissue.

**Discussion**

**PREVIOUS CLINICAL AND LABORATORY STUDIES**

Cardiac surgery patients sustain perioperative
cerebral infarction at a rate exceeding 3%. They are also routinely haemodiluted to haemoglobin concentrations of 7–9 g 100 ml−1. It is not clear if, after operation, red blood cell transfusion may improve neurological outcome. There is evidence to suggest that it may. Neuropsychological impairment 9 days after cardiac surgery is associated with haemoglobin concentrations of less than 10 g 100 ml−1 in the first 12 h after surgery.36 Also, acute neurological and neuropsychological outcome is significantly worse in cardiac surgery patients with the greatest perioperative reductions in haemoglobin concentration.37 Lee and colleagues used a middle cerebral artery occlusion model in dogs.7 They found that infarction volumes were less in animals with a haemoglobin concentration of 10 g 100 ml−1 than in those with a concentration of 8 g 100 ml−1. Similarly, we recently used an embolic stroke model in rabbits.6 Animals allocated randomly to a haemoglobin concentration of 6 g 100 ml−1 had larger infarction volumes than those allocated to a haemoglobin concentration of 11 g 100 ml−1. Collectively, these studies suggest that acute anaemia can exert a detrimental effect on neurological outcome, especially when postoperative haemoglobin concentrations are less than 10 g 100 ml−1. Our model predictions strongly support this suggestion.

PENUMBRAL OXYGEN UPTAKE

Our model predicted that at haemoglobin concentrations of 10–12 g 100 ml−1, increased CBF and oxygen extraction were sufficient to permit penumbral oxygen uptake to remain nearly normal. As stated previously, this result is consistent with the experimental literature. However, the model predicted that there is an abrupt decrease in penumbral oxygen uptake when haemoglobin concentrations decrease to less than 10 g 100 ml−1. This is because, in the ischaemic penumbra, increases in CBF and oxygen extraction are insufficient to compensate for decreases in arterial oxygen content when haemoglobin concentrations are less than 10 g 100 ml−1. Penumbral oxygen extraction reserves are nearly exhausted even after only moderate anaemia (haemoglobin concentration of 12 g 100 ml−1). Progressively greater degrees of anaemia limit oxygen uptake in the ischaemic tissue.

Optimal management of patients with acute perioperative stroke should include efforts to support penumbral oxygenation. Penumbral tissue sustains a series of membrane depolarizations in the hours after onset of focal ischaemia. These depolarizations, lasting 5–10 min, do not change penumbral CBF, but appear to transiently increase cerebral metabolism. The increase in cerebral metabolism is probably a result of the increased ion pump activity needed to re-establish transmembrane ionic homeostasis.40 42 Therefore, ischaemic membrane depolarizations increase penumbral energy requirements, exacerbating the mismatch between metabolic demand and substrate supply. This mismatch may explain why the number and duration of depolarizations correlate(s) with final infarction volume.43

Haemoglobin concentrations less than 10 g 100 ml−1 progressively limit oxygen availability to the penumbra. Thus marked anaemia seems likely to slow restoration of ionic homeostasis. Doing so may promote a more rapid deterioration of the penumbra. Rapid deterioration of the penumbra converts what was potentially salvageable tissue into infarct.41

ROLE OF MATHEMATICAL MODELLING

Factors other than haemoglobin concentration have important effects on neurological outcome, such as the timing of therapy, species studied, vascular territories involved and arterial pressure. These factors, almost certainly, are responsible for some of the discrepancies between previous studies.4–11 The regional CBF data of Korosue and Heros13 were obtained at normal arterial pressures and temperatures. Thus our model predictions apply to the condition of normotension and normothermia. On the other hand, the mechanism of CBF response to haemodilution (e.g. viscosity vs metabolism) is of no importance to our model predictions. CBF is an independent variable in the mathematical model (eqn (5)). The magnitude of the CBF response to haemodilution is important and may depend on both the viscosity characteristics of the haemodiluant and arterial oxygen content.43 Korosue and Heros used plasma to haemodilute their rabbits,13 while Todd and colleagues used hetastarch.14 Our results apply to acute haemodilution with similar substances. Haemodilution with cross-linked haemoglobin would, for example, be expected to give results different from those predicted by our model.43

The multiple factors that can influence neurological outcome demonstrate the advantage of using mathematical modelling. We focused only on haemoglobin concentration (fig. 1). The mathematical model used in this study was intentionally simplistic with respect to the process of oxygen diffusion from blood to brain. Decisions to apply existing models to this study were based on four limitations. First, terms must have been measured under the conditions of focal embolic stroke. The only values that have been measured reliably are regional CBF (i.e. Korosue and Heros’ rabbit data13). Additional dependent variables, such as intracapillary red blood cell spacing and spatial heterogeneity of red blood cell flow, are not available. Additional experimental data are not likely to be forthcoming soon. Tissue PO2 electrodes could be placed into the ischaemic penumbra. However, as equation (4) shows, tissue PO2 and regional CMRO2 are not equivalent. The model makes predictions for the effect of haemodilution on regional CMRO2 not tissue PO2. Furthermore, to identify the ischaemic penumbra, simultaneous regional CBF measurements would be needed. The only technique that can accomplish both of these requirements is positron emission tomographic scanning. Second, CBF data were available only for gross regions of the brain, not at the microcirculatory level. Thus a model based on space-averaged oxygen tensions was necessary. Third, we used CBF and CMRO2 data obtained from rabbits. Korosue and Heros13 also
studied rabbits. Rabbits and humans share many key physiological characteristics (cerebrovascular anatomy, arterial pressure, haemoglobin concentration, CBF, CMRO₂, haemoglobin P₅₀ and cooperativity). Hence, conclusions regarding cerebrovascular physiology derived from rabbit data are likely to be applicable to humans. Fourth, not all of the biophysical variables we needed were available for rabbits or humans. Biophysical transport variables from species other than rabbits would not be expected to differ significantly. Therefore, we doubt that this limitation had much effect on the simulation results, at least qualitatively. Additional model complexity would not have compensated for this latter weakness. Thus increased model complexity would not have substantively increased model accuracy. However, despite our model's limitations, it successfully predicted the data of Todd and colleagues¹⁴ (table 1). The basic processes of regional brain oxygen uptake alone can accurately predict the effect of anaemia on oxygen extraction. We used the mathematical model to make clinically significant predictions only after we had verified the validity of the model.

**CLINICAL SIGNIFICANCE**

An American Society of Anesthesiologist’s task force recently published practice guidelines for blood component therapy.¹¹ The task force concluded that red blood cell transfusion is rarely indicated when the haemoglobin concentration exceeds 10 g 100 ml⁻¹ but is almost always appropriate when it is less than 6 g 100 ml⁻¹. In addition, the task force concluded that “the determination of whether intermediate haemoglobin concentrations (6–10 g 100 ml⁻¹) justify or require red blood cell transfusion should be based on the patient’s risk for complications of inadequate oxygenation.” Our results showed that, in the presence of an acute focal stroke, penumbral oxygenation is likely to be inadequate at haemoglobin concentrations less than 10 g 100 ml⁻¹. Our model predictions do not stand in isolation; they are consistent with other clinical³⁶ ³⁷ and laboratory⁶ ³⁸ studies. All of these studies suggest that haemoglobin concentrations less than 10 g 100 ml⁻¹ worsen neurological outcome after embolic stroke. We conclude that, given the available clinical and experimental literature, and until a suitable randomized clinical study has been performed, a haemoglobin concentration of 10 g 100 ml⁻¹ is the rational transfusion “trigger” for the acutely anaemic stroke patient.

**References**


