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The effect of blood transfusion and haemodilution on cerebral oxygenation and haemodynamics in newborn infants investigated by near infrared spectrophotometry

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Abstract The objective of this study was to investigate the influence of blood transfusion and haemodilution on cerebral oxygenation and haemodynamics in relation to changes in cerebral blood flow velocity (CBFV) and other relevant physiological variables in newborn infants. Thirteen preterm infants with anaemia (haematocrit < 0.33) and ten infants with polycythaemia (haematocrit > 0.65) were studied during blood transfusion and haemodilution respectively using adult red blood cells and partial plasma exchange transfusion. Changes in cerebral concentrations of oxyhaemoglobin ($cO_2Hb$), deoxyhaemoglobin ($cHHb$), total haemoglobin ($cHb$), (oxidized - reduced) cytochrome aa$_3$ ($Cyt.aa_3$) were continuously measured using near infrared spectrophotometry throughout the whole procedure. Simultaneously, changes of mean CBFV in the internal carotid artery were continuously measured using pulsed Doppler ultrasound. Heart rate, transcutaneous partial pressure of oxygen and carbon dioxide, and arterial $O_2$ saturation were continuously and simultaneously measured. Blood transfusion resulted in increase of $cO_2Hb$, $cHHb$, $cHb$ and red cell transport (product of CBFV and haematocrit), whereas CBFV decreased. The increase of $cO_2Hb$ exceeded that of $cHHb$, reflecting improvement of cerebral $O_2$ supply. Haemodilution resulted in a decrease of $cO_2Hb$, $cHHb$ and $cHb$, whereas CBFV increased. Red cell transport was unchanged. The decrease of $cO_2Hb$ exceeded that of $cHHb$, reflecting decreased cerebral $O_2$ supply. $Cyt.aa_3$ decreased after blood transfusion and remained unchanged after haemodilution, but the reliability of these results is uncertain. With the exception of a small, but significant increase in transcutaneous partial pressure of oxygen after blood transfusion, the other variables showed no changes. Each blood withdrawal during exchange transfusion resulted in only a significant increase in heart rate without changes in the other variables measured, suggesting unchanged cerebral perfusion.

Conclusion In newborn infants blood transfusion in anaemia results in improvement of cerebral oxygenation, but haemodilution in polycythaemia does not improve cerebral oxygenation despite possible improvement of cerebral perfusion.

Key words Doppler • Cerebral blood flow • Anaemia • Polycythaemia • Haemoglobin

Abbreviations CBF cerebral blood flow • CBFV cerebral blood flow velocity • $Cyt.aa_3$ (oxidized - reduced) cytochrome aa$_3$ concentration • $cHb$ haemoglobin concentration in blood • $cHb$ deoxyhaemoglobin concentration • $cO_2Hb$ oxyhaemoglobin concentration • $cHb$ total haemoglobin concentration • NIRS near infrared spectrophotometry • RCT red cell transport capacity • $saO_2$ arterial $O_2$ saturation • tcp$CO_2$ transcutaneous partial pressure of carbon dioxide • tcp$O_2$ transcutaneous partial pressure of oxygen

Introduction

Adequate energy supply to cerebral tissue is necessary for normal function and survival of neurons. Under normal circumstances the energy required is supplied by oxidative metabolism for which the presence of oxygen...
is essential [32]. Oxygen supply to the brain depends on a sufficient concentration of haemoglobin in the blood (cHb) and an adequate cerebral blood flow (CBF) [17]. Pathological changes in cHb in the neonate, anaemia as well as polycythaemia, result in a significant alteration in cerebral blood flow (CBF) [1, 22, 25, 28, 30]. Treatment consists of restoration of cHb by blood transfusion and haemodilution (partial exchange transfusion) respectively, which is presumed to improve cerebral circulation and oxygenation [1, 22, 25, 28, 30].

Near infrared spectrophotometry (NIRS) offers the possibility of noninvasive and continuous bedside investigation of cerebral oxygenation in newborn infants [34, 42]. Using this technique we investigated the relationship between changes in cerebral oxygenation and haemodynamics, and changes in some physiological variables during blood transfusion in anaemic, and haemodilution in polycythaemic newborn infants.

Materials and methods

Study population

The study was approved by the University Hospital ethical committee. Two groups of newborn infants were studied, after obtaining informed parental consent:

Group 1: 13 preterm infants (8 male, 5 female), mean gestational age 30.2 (28.0-34.0) weeks, mean birth weight 1411 (1060-2200) g, mean postnatal age 25 (9-45) days, mean actual body weight 1660 (940-2710) g, requiring blood transfusion because of anaemia (cHb < 6.5 mmol/l, capillary haematocrit < 0.33).

Group 2: ten newborn infants (two male, eight female), mean gestational age 38.4 (32.7-41.9) weeks, mean birth weight 2712 (1060-3505) g, postnatal age 2 (1-5) days, requiring haemodilution because of polycythaemia (venous haematocrit > 0.65).

Infants with congenital malformations, asphyxia, seizures or cerebral haemorrhage were excluded from the study.

The anaemic infants were in a stable clinical condition. One infant was ventilated with a low rate (4 breaths/min) and a low fraction of inspired oxygen (0.25). The other infants were not ventilated; two of them received additional oxygen of 22% and 40% respectively. None of the infants was treated with sedatives or vasoactive drugs. Blood transfusion was performed using 15 ml/kg body weight, and desired haematocrit was chosen as 0.55. Mean total exchange volume was 18.8 (12.9-24.1) ml/kg body weight. The exchange procedure was carried out in three to five steps. In each step a mean volume was 18.8 (12.9-24.1) ml/kg body weight. The exchange volume was calculated as follows:

\[
\text{exchange volume} = \frac{\text{blood volume} \times (\text{observed haematocrit} - \text{desired haematocrit})}{\text{observed haematocrit}}
\]

where blood volume was presumed to be 85 ml/kg body weight and desired haematocrit was chosen as 0.55. Mean total exchange volume was 18.8 (12.9-24.1) ml/kg body weight. The exchange procedure was carried out in three to five steps. In each step a mean of 5.7 (4.5-8.0) ml/kg body weight was exchanged using isovolaemic pasteurized plasma protein solution (Central Laboratory for Blood Transfusion of the Dutch Red Cross, Amsterdam, The Netherlands). The dead space of the system used for exchange transfusion was 1.0 ml. The whole procedure lasted approximately 30 min.

Near infrared spectrophotometry

The NIRS equipment used was developed by the Department of Biomedical Engineering and Medical Physics, University of Keele (UK) and produced by Radiometer (Copenhagen, Denmark) [34]. The method is based on continuous spectrophotometric measurement of oxygenation dependent changes in the absorption properties of haemoglobin and cytochrome a\textsubscript{3} in the near infrared region [15]. Our NIRS measurement procedure has been published earlier [18]. Briefly, near infrared light at three wavelengths (904, 845 and 775 nm) was transmitted through the skull using fibre optic bundles. The transmitting and receiving optodes were fixed to the skull as previously described [19]. Each optode was applied in opposite positions at the parietotemporal region in group 1 (mean distance 6.7, range 5.5-7.8 cm) and at the bifrontal region in group 2 (mean distance 4.8, range 4.0-5.8 cm). Since the interoptode distance was always over 2.5 cm, a constant path length multiplying factor can be used [38]. The use of a constant path length multiplying factor is justified, since it has been shown that this factor is not influenced by changes in light absorption due to changes in haemoglobin oxygenation [9] or due to changes in haemoglobin concentration [D.T. Delpy, personal communication]. A constant path length multiplying factor of 4.27 is used, because this has been shown as the mean value over the wavelength range of 710-840 nm in the brains of live newborn infants using second derivative NIRS [9], which is comparable to values measured using phase resolved spectroscopy [10]. Since the extent of light attenuation caused by scattering and oxygenation independent absorption by tissue is unknown, but considered constant, only concentration changes of oxyhaemoglobin (ΔO\textsubscript{2}Hb), deoxyhaemoglobin (ΔHbHb) and (oxidized - reduced) cytochrome a\textsubscript{3} (ΔCyta\textsubscript{3}) can be calculated from changes in absorption of near infrared light at these three wavelengths. For these calculation we used NIR coefficients which have been developed by the Department of Biomedical Engineering and Medical Physics, University of Keele (UK) [34]. In cooperation with the Department of Medical Physics and Bioengineering, University College of London (UK), these NIR coefficients are further modified in order to take into account the wavelength dependency of the path length when a constant path length multiplying factor is used in the calculation [40]. The modified NIR coefficients are shown in Table 1. Using a value of 1.05 g/ml for brain specific mass these concentration changes are expressed in μmol/100 g. Therefore, during NIRS measurement only changes of these variables are obtained as a trend. ΔO\textsubscript{2}Hb and ΔHbHb reflect changes in cerebral O\textsubscript{2} supply. ΔCyta\textsubscript{3} reflects changes in cerebral O\textsubscript{2} sufficiency [16], but the results of this measurement should be interpreted with caution because its reliability is still a matter of debate. Changes in concentration of total haemoglobin (ΔcHb) were calculated as the sum of ΔO\textsubscript{2}Hb and ΔHbHb. When cHb is unchanged, ΔcHb will reflect changes in cerebral blood volume.

Doppler-ultrasound

Cerebral blood flow velocity (CBFV) in the internal carotid artery was measured continuously by a 3.5-MHz pulsed Doppler flowmeter (ATL 400 B, Advanced Technology Laboratories, Bellevue, Table 1 NIR coefficient used in this study

<table>
<thead>
<tr>
<th>Waveband</th>
<th>O\textsubscript{2}Hb</th>
<th>HbHb</th>
<th>Cyta\textsubscript{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>775 nm</td>
<td>1.157</td>
<td>0.081</td>
<td>-0.014</td>
</tr>
<tr>
<td>845 nm</td>
<td>-1.642</td>
<td>-1.020</td>
<td>0.635</td>
</tr>
<tr>
<td>904 nm</td>
<td>1.176</td>
<td>-0.221</td>
<td>-0.661</td>
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WA, USA) using the anterior fontanelle as an acoustic window. The depth of the suprachindal internal carotid artery was determined from a two-dimensional real time scan (Ultramark 4, Advanced Technology Laboratories, Bothell, WA, USA) during cranial ultrasound screening for cerebral haemorrhage. The insolation angle was assumed to be negligible (< 10°). The Doppler transducer was kept in a holder as described previously [18]. Instantaneous frequency in the Doppler flowmeter was estimated using a zero crossing technique (time interval histogram). The time interval histogram output was filtered by a 0.3-Hz low pass filter and the obtained mean (time-averaged) velocity stored simultaneously with the NIRS data. Changes in the mean CBFV (ΔCBFV) after blood transfusion or haemodilution were expressed as a percentage of their values before the procedure. Assuming that the internal carotid artery diameter did not change, these CBFV changes will indicate similar CBF changes. A good correlation has been found between mean CBFV as measured by Doppler-ultrasound and CBF as measured by the 133Xenon clearance method [13]. As an index of red cell transport capacity (RCT) the product of CBFV and haematocrit was calculated [22, 25] and the changes in RCT were expressed as a percentage of their value before the procedure.

Other physiological measurements

Heart rate was recorded continuously using a neonatal monitor (HP 78801 B, Hewlett Packard, Boeblingen, Germany). The abdominal transcutaneous partial pressure of oxygen and carbon dioxide (tcpO2 and tcpCO2) (Transend, Sensorsmedics Corp., Anaheim, CA, USA) and arterial O2 saturation (saO2) at the foot by pulse oximetry (N 200, Nellcor Inc., Hayward, CA, USA) were also measured continuously. These additional data were stored together with the NIRS and Doppler data. Since most of the infants studied were not critically ill, it was considered unethical to insert an arterial catheter for blood pressure measurement only for this investigation. Therefore data on arterial blood pressure were not available. During blood transfusion a sampling frequency of 0.125 Hz was used, since only slow changes in the measured variables were expected to occur. During haemodilution, however, a sampling frequency of 1 Hz was used, because rapid changes in these variables were expected to occur. Measurements were started 10 min before the start of blood transfusion or haemodilution and continued until 10 min after this procedure was ended. Blood samples for the determination of CHb and haematocrit were drawn from the umbilical venous catheter before and after haemodilution and from a capillary heel puncture before and after blood transfusion.

Data analysis

From each variable the mean value of a selected period of ten successive recorded datapoints were taken just before the start and directly after completion of each procedure were taken. The differences were used for further statistical analysis using the Wilcoxon signed-rank test. Level of significance was chosen as 0.05. The results are presented as median and range of the individual changes. Withdrawal of blood during each step of partial exchange transfusion can be considered as a haemorrhagic event, therefore the influence of this event on the homeostasis of cerebral oxygenation and circulation was assessed in the same way. Only the first three blood withdrawals were analysed, since partial exchange transfusion was performed in three steps in most of the infants.

Results

Blood transfusion

After blood transfusion CHb and haematocrit levels increased from the initial median value of 6.2 (5.1-6.5) mmol/l and 0.29 (0.24-0.30) to 8.1 (7.1-9.5) mmol/l and 0.39 (0.34-0.44) respectively (P < 0.05). A statistically significant increase in cO2Hb, cHb and cHb also occurred (Table 2, Fig. 1). The increase in cO2Hb was higher than that of cHb. CBFV decreased, but there was a statistically significant increase in RCT. There was a small, but statistically significant decrease in cCyt.aa3. The other variables showed no statistically significant changes except for an increase in tcpO2.

Haemodilution

After haemodilution CHb and haematocrit levels decreased significantly from an initial median value of 13.5 (11.7-14.8) mmol/l and 0.67 (0.61-0.74) to 10.8 (9.5-12.7) mmol/l and 0.53 (0.44-0.63) respectively (P < 0.05). A statistically significant decrease in cO2Hb, cHb and cHb was also observed (Table 2, Fig. 1). The decrease of cO2Hb was higher than that of cHb. CBFV increased, but RCT was unchanged as well as cCyt.aa3. The other variables showed no statistically significant changes except for an increase in saO2.

Blood withdrawal

After each blood withdrawal a small but statistically significant increase of heart rate was observed with a

<table>
<thead>
<tr>
<th>Table 2 Changes in measured variables after blood transfusion in anaemic preterm infants and after haemodilution in polycythaemic infants</th>
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<tbody>
<tr>
<td>After blood transfusion (n = 13)</td>
</tr>
<tr>
<td>ΔcO2Hb</td>
</tr>
<tr>
<td>μmol/100 g</td>
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<tr>
<td>ΔcHb</td>
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<td>μmol/100 g</td>
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<td>ΔcHb</td>
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<td>μmol/100 g</td>
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<tr>
<td>ΔcCyt.aa3</td>
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<tr>
<td>μmol/100 g</td>
</tr>
<tr>
<td>ΔCBFV</td>
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<tr>
<td>%</td>
</tr>
<tr>
<td>ΔRCT</td>
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<tr>
<td>%</td>
</tr>
<tr>
<td>ΔsaO2</td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td>ΔtcpO2</td>
</tr>
<tr>
<td>mm Hg</td>
</tr>
<tr>
<td>ΔtcpCO2</td>
</tr>
<tr>
<td>mm Hg</td>
</tr>
<tr>
<td>Δheart rate</td>
</tr>
<tr>
<td>beats/min</td>
</tr>
<tr>
<td>ΔCHb</td>
</tr>
<tr>
<td>mmol/l</td>
</tr>
<tr>
<td>Δhaematocrit</td>
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<td>%</td>
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Values are median (range)

*Significant changes (P < 0.05, Wilcoxon signed-rank test)
Blood transfusion as therapy for anaemia will improve the arterial O2 content which is presumed to enhance the O2 supply to many organs including the brain. In the present study the increase in cO2Hb was larger than in cHHb, which may reflect an increased cerebral O2 supply. However, a reduction of CBFV was found, but interpolation of this finding to decreased CBF might be critical because information about changes in blood vessel diameter, blood pressure and intravascular velocity profile due to haemodynamic changes caused by blood transfusion was not available. CBF estimation using NIRS with O2Hb as an intravascular tracer was impossible, because an adequate sO2 swing could not be performed, since most of the infants had already sO2 values of nearly 100% while breathing room air. Nevertheless, a similar reduction of CBFV in the internal carotid artery after blood transfusion in preterm infants has been reported [25]. Another factor which has to be taken into account is the use of adult red cells for blood transfusion, which will reduce the concentration of fetal haemoglobin, resulting in a decrease of oxygen affinity of haemoglobin. Decreased oxygen affinity of haemoglobin has been shown to result in decreased CBFV [28], CBF [20] and increased cerebral O2 extraction [29]. It is possible that the expected decrease in oxygen affinity of haemoglobin in our patients might partly explain the decrease in CBFV, but as discussed earlier, it is uncertain whether CBF is also reduced. Increased cerebral O2 extraction will normally result in decreased cO2Hb and increased cHHb, provided that CBF and CBV are unchanged. However, the NIRS data showed a larger increase of cO2Hb than cHHb. It is very likely that the increased arterial O2 content has a greater influence on cerebral oxygenation than the changes in oxygen affinity of haemoglobin.

Surprisingly, despite increased cerebral O2 supply after blood transfusion, most infants showed a decrease in cCyt.aa3 which might reflect a decreased cerebral O2 sufficiency. However, these results should be interpreted with caution [27, 33]. Since the absorption signal of cytochrome aa3 is much weaker than that of haemoglobin, the use of accurate NIR coefficients is necessary for the calculation of ΔcCyt.aa3. However, the NIR coefficients for calculating ΔcCyt.aa3 are derived from experiments on rat brains after exchange transfusion with fluorocarbon. Therefore, these data might be inaccurate due to noise caused by residual haemoglobin after fluorocarbon exchange or different scattering properties of fluorocarbon [27]. Due to the interference of other redox centres like cytochrome c with the cytochrome aa3 related light absorption, it is assumed that ΔcCyt.aa3 less than 0.1 μmol/100 g may be physiologically irrelevant [8]. Accordingly, our findings of ΔcCyt.aa3 after blood transfusion can be considered irrelevant. Inconsistent and insignificant ΔcCyt.aa3 were also found during light to moderate hypoxaemia in newborn infants [11, 41]. On the other hand, in animal models severe reduction in cCyt.aa3 seemed to be correlated with intracellular energy deficit [36] and neuronal loss [24], indicating that reduction of cCyt.aa3 might be a late signal of cerebral hypoxia [8]. However, the exact role of cerebral O2 supply in the regulation of the redox state of cytochrome aa3 is still unclear [3].

In newborn infants the observed clinical signs during polycythaemia are generally attributed to decreased microcirculation in many organs [4, 26]. The adverse neurodevelopmental outcome was thought to be related to decreased CBF. The need for treatment of polycythaemia in newborn infants is still a matter of debate, but haemodilution by partial plasma exchange transfusion is generally recommended [4, 26]. Haemodilution will reduce the red cell mass resulting in improvement of microcirculation in many organs including the brain [1, 22, 30]. The increased CBF after haemodilution seems to be the result of the compensation for decreased arterial O2 content and not to be related to decreased blood viscosity [7, 31, 39]. Therefore, determination of the blood viscosity in our patients was considered unnecessary. In the present study, after haemodilution, CBFV increased possibly as a result of increased CBF. However, it did not result in improvement of cerebral RCT. Data from the literature are conflicting, showing increased [22] as well as unchanged cerebral RCT [23]. However, as mentioned above, due to its limitations the value of the Doppler ultrasound investigation is uncertain. After haemodilution the decrease in cO2Hb was

**Fig. 1** Box plots of changes in cerebral NIRS and Doppler variables after blood transfusion and haemodilution. Horizontal line within the box represents the median value; the box covers the interquartile range; the bar covers the whole range. *indicates statistically significant changes.

The median value of 7 (-1 to +16), 6 (-2 to +12) and 3 (-1 to +9) beats/min respectively.

**Discussion**

Blood transfusion as therapy for anaemia will improve the arterial O2 content which is presumed to enhance the O2 supply to many organs including the brain. In the present study the increase in cO2Hb was larger than in cHHb, which may reflect an increased cerebral O2 supply. However, a reduction of CBFV was found, but interpolation of this finding to decreased CBF might be critical because information about changes in blood vessel diameter, blood pressure and intravascular velocity profile due to haemodynamic changes caused by blood transfusion was not available. CBF estimation using NIRS with O2Hb as an intravascular tracer was impossible, because an adequate sO2 swing could not be performed, since most of the infants had already sO2 values of nearly 100% while breathing room air. Nevertheless, a similar reduction of CBFV in the internal carotid artery after blood transfusion in preterm infants has been reported [25]. Another factor which has to be taken into account is the use of adult red cells for blood transfusion, which will reduce the concentration of fetal haemoglobin, resulting in a decrease of oxygen affinity of haemoglobin. Decreased oxygen affinity of haemoglobin has been shown to result in decreased CBFV [28], CBF [20] and increased cerebral O2 extraction [29]. It is possible that the expected decrease in oxygen affinity of haemoglobin in our patients might partly explain the decrease in CBFV, but as discussed earlier, it is uncertain whether CBF is also reduced. Increased cerebral O2 extraction will normally result in decreased cO2Hb and increased cHHb, provided that CBF and CBV are unchanged. However, the NIRS data showed a larger increase of cO2Hb than cHHb. It is very likely that the increased arterial O2 content has a greater influence on cerebral oxygenation than the changes in oxygen affinity of haemoglobin.

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greater than in cHHb, reflecting a decreased cerebral O$_2$ supply. Since we could not determine the absolute level of cerebral O$_2$ supply due to the limitation of the NIRS method, it is unknown whether the reduction of cerebral O$_2$ supply will be hazardous for cerebral tissue. The level of cCytochrome aa$_3$ was unchanged, which might suggest unchanged cerebral O$_2$ sufficiency. Using NIRS in rabbits it has been shown that cCytochrome aa$_3$ began to decrease after isovolaemic haemodilution of 30 ml/kg [21], while in our patients the total exchange volume did not exceed 30 ml/kg. However, as discussed earlier, the reliability of the cCytochrome aa$_3$ signal is uncertain. From animal studies there is some evidence that the decreased O$_2$ content after haemodilution has been compensated for by increased CBFV in order to maintain cerebral O$_2$ supply [14, 35]. However, the results of our study might raise the question whether polycythaemic infants might benefit from haemodilution. Data from the literature are conflicting, showing both improved [5, 6] as well as adverse [2, 12, 37] neurodevelopmental outcome after treatment with haemodilution.

During partial exchange transfusion the mean volume of each blood withdrawal was estimated to be about 7% of total blood volume, which is assumed to be 85 ml/kg body weight. Since CBFV and cHHb did not change, it appears that such a small reduction in the circulatory volume will not influence cerebral perfusion. Although blood transfusion and haemodilution result in changes in cHHb of the same magnitude but in the opposite direction, the effects on cerebral oxygenation and haemodynamics are not simply a reversal of each other. This confirms that arterial O$_2$ content is not the single regulator of cerebral oxygenation and haemodynamics [17]. The influence of arterial pCO$_2$ on changes in cerebral oxygenation and haemodynamics seemed to be negligible since tcpCO$_2$ was unchanged after both procedures. However, there were differences between both procedures, which might influence the regulation of cerebral oxygenation and haemodynamics. During non-isovolaemic blood transfusion the circulatory volume was increased by about 18%, which might improve tissue perfusion, including the brain, and might explain why the decrease in CBFV after blood transfusion was proportionally less than the increase in CBFV after haemodilution, despite the same magnitude of cHHb changes. Increased circulatory volume may also explain the observed improvement in skin circulation and oxygenation as reflected by a small, but significant increase in tcpO$_2$ after blood transfusion. Finally, haemodilution was performed over a relatively short time compared with blood transfusion. It is possible that the new steady state in cerebral microcirculation after haemodilution was not as complete as after blood transfusion.

In summary, in newborn infants using NIRS and Doppler ultrasound we have demonstrated an improvement in cerebral oxygenation after blood transfusion in anaemia. Haemodilution in polycythaemia, however, did not improve cerebral oxygenation despite a possible improvement in cerebral perfusion. Blood withdrawal during exchange transfusion not exceeding 7% of the circulatory volume does not seem to influence cerebral perfusion.

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