Cerebral Blood Flow Velocity and Oxygenation in Neonatal Aortic Arch Repair at Two Perfusion Temperatures

Lucy E. M. Finnigan[1], Robyn Lotto[2], *Helen Jones[3] and *Attilio Lotto[4].

*Attilio Lotto and Helen Jones contributed equally to this work.

[1] Radcliffe Department of Medicine, University of Oxford, Oxford, UK.

[2] Allied Health and Nursing, Liverpool John Moores University, Liverpool, UK

[3] Research Institute for Sport and Exercise Science, Liverpool John Moores University, Liverpool, UK

[4] Heart Centre, Alder Hey Children's NHS Foundation, Liverpool, UK.

Corresponding author:

Prof Helen Jones, Liverpool John Moores University, Tom Reilly Building, 3 Byrom Street, Liverpool, L3 3AF, H.Jones1@ljmu.ac.uk

Manuscript was presented at the ECHSA annual meeting (remote) in 2021.

IRAS: 220447

Keywords: Transcranial doppler ultrasound – near infrared spectroscopy – temperature changes – aortic arch repair – neurological deficit.

Visual Abstract:

Key Question: Monitoring cerebral perfusion throughout neonatal aortic arch repair surgery in two temperature groups (20°C and 25°C).

Key Findings: Cerebral perfusion increased during cooling and there was no difference between the two temperature groups.

Take-Home Message: Transcranial doppler ultrasound can provide information about cerebral perfusion and give an insight into how to optimise neuroprotection.

Abstract

Objectives: (i) To monitor cerebral blood flow velocity (CBFv) throughout aortic arch repair surgery and during recovery period in paediatric intensive care. (ii) To examine the relationship between near infrared spectroscopy (NIRS) and transcranial doppler ultrasound (TCD) during cardiac surgery. (iii) Examine CBFv in patients cooled to 20°C and 25°C.

Methods: During aortic arch repair and after surgery, TCD was monitored in 24 neonates, alongside NIRS, blood pH, pO_2, pCO_2, HCO_3, lactate, Hb, Htc (%) and temperature (core and rectal). General linear models were used to examine differences over time and cooling temperature. Repeated measured correlation (rmcor) were used to determine relationship between NIRS and TCD.

Results: CBFv changed during arch repair procedure (main effect of time: p= 0.001). During cooling phase, CBFv increased by 10.0 cm/s (5.97 cm/s, 17.7 cm/s) compared to normothermic (p=0.019). Once recovering in PICU, CBFv had increased from the preoperative measurement by 6.2 cm/s (0.21, 13.4; p=0.045). CBFv changes were similar between patients cooled to 20°C and 25°C (main effect of temperature: p=0.22). Repeated measures correlation identified a statistically significant but weak positive correlation between CBFv and NIRS (r= 0.25, p=<0.001).

Conclusions: Our data suggested that CBFv changed throughout aortic arch repair and was higher during cooling period. A weak relationship was found between NIRS and TCD. Overall, these findings could provide clinicians with information on how to optimise long-term cerebrovascular health.

Abstract keywords: Transcranial doppler ultrasound – near infrared spectroscopy – temperature changes – aortic arch repair – neurological deficit.

Abbreviations:

Antegrade cerebral perfusion (ACP)

Bicarbonate (HCO_{3-})

Cardiopulmonary bypass (CPB)

Cerebral blood flow (CBF)

Cerebral blood flow Velocity (CBFv)

Congenital heart disease (CHD)

Deep hypothermic circulatory arrest (DHCA)

Haematocrit (Htc)

Middle cerebral artery (MCA)

Near infrared spectroscopy (NIRS)

Paediatric intensive care unit (PICU)

Partial pressure of carbon dioxide (pCO_2)

Partial pressure of oxygen (pO_2)

Repeated measures correlations (rmcorr)

Transcranial Doppler (TCD)

Introduction

Survival rates in patients born with congenital heart disease (CHD) have increased due to improvements in clincial care and treatment (1). However, a significant percentage of survivors exhibit neurological deficit (2). The highest rates of deficit are found in those with severe left sided lesions such as hypoplastic or interrupted aortic arch (3). This deficit is likely multifactorial and could be due to disruptions to cerebral blood flow (CBF) (4). There are many factors during aortic arch repair which can lead to instances of cerebral tissue hypoxia and regional hypoperfusion. This includes the establishment of anaesthesia, the cessation of cardiac function, the use of cardiopulmonary bypass (CPB) and the induction of deep hypothermic circulatory arrest (DHCA) (5). Making the monitoring of cerebral perfusion during aortic arch repair imperative in identifying time periods of disrupted flow and to understand how to optimise neurological monitoring during this time.

Currently, neurological monitoring practises vary considerably across centres with no universal guidelines (6). Several strategies are implemented for neurological protection which aim to reduce neural activity in the brain, this includes whole body cooling via CPB perfusion. However, there is a lack of empirical evidence for the optimum minimum temperatures for whole body cooling used during aortic arch repair. The target temperature is often based on surgical complexity and surgeon preference with temperatures ranging from 16-28°C. Another strategy to ensure adequate perfusion is the constant monitoring of near infrared spectroscopy (NIRS). NIRS is a simple, cost-effective measurement of cerebral oxygenation. However, the shortcomings of NIRS have been previously documented. Including high levels of inter-device variability, issues related to absolute vs relative saturations and variability of oxygen saturation targets/thresholds in clinical settings (7).

More in-depth measurements of cerebral perfusion are available such as Transcranial Doppler (TCD) ultrasound which provides CBF velocity (CBFv) of the major cerebral vessels. Previously, both NIRS and TCD were employed during neonatal aortic arch repair during full flow CPB. Periods of hyperpefusion were reported which NIRS was unable to detect (8), however measurements were not acquired throughout the whole procedure. Whereas a case study measured TCD and NIRS in one male infant (10 days old) throughout the entire procedure. An important observation was values in TCD and cerebral oxygenation dropped to near zero at two different time points during DHCA (9), suggesting the patient was subjected to possible periods of cerebral ischemia. This suggests that further research is warranted in a larger population to identify periods of hypo- and hyperperfusion. Therefore, the aim of the study was to continuously monitor CBFv throughout aortic arch repair surgery and during recovery in paediatric intensive care. The secondary aim was to examine the relationship between NIRS and TCD at each time point during cardiac surgery. The final aim was to examine difference in CBFv between patients cooled to 20°C and 25°C as part of the neuroprotection regime.

Patients and Methods

Ethics Statement

Formal written informed consent was obtained from the parent/guardian by a member of the surgical team prior to the procedure. Ethical approval was obtained from the North West Liverpool East Research Ethics Committee (IRAS number: 220447, Approval number 17/NW/0249). The study was registered with ClinicalTrials.gov (Identifier: NCT03047876). Neonates or infants (< 1 years old) who required aortic arch repair surgery, interrupted aortic arch repair or the Norwood

procedure were included. Exclusion criteria consisted of patients in critical clinical conditions, on inotropic support and in metabolic acidosis. Moreover, parents unable to give consent were not considered for the study, which could be for several reasons. Other exclusion criteria were patients with previous documented neurological damage and those suffering from conditions which have been known to affect CBFv such as significant elevated bilirubin levels which would require phototherapy treatment, sickle cell anaemia and moyamoya disease.

Patients

Neonates were recruited in a clinical setting from 22nd November 2018 until 26th February 2020 at Alder Hey Children's NHS Foundation Trust. Study size was limited to a single centre where all patients that met the inclusion criteria during the recruitment period were approached to reduce bias. Patients required surgery for hypoplastic aortic arch repair (n=16), interrupted aortic arch (n=6) or for hypoplastic left heart syndrome (HLHS) (n=2). Five patients in total underwent total circulatory arrest but were included as CBFv was comparable to those that did not require circulatory arrest. Patients were split into 2 groups dependant on lowest temperature achieved during cooling 20°C (n=8) or 25°C (n=16; Table 1). Target cooling temperature was predetermined by operating surgeon's preference, complexity of the procedure and predicted CPB times.

Research Design

A team of three consultant cardiac surgeons, performed the aortic arch repairs with a standardised surgical technique which has previously been described (10). Measurements were taken using a TCD ultrasound system (DWL, Compumedics, Germany) with a 2MHz or 4MHz doppler probe alongside NIRS (ForeSight, Casmed,

United Kingdom). Serial arterial blood gas analysis (pH, pO_2, PCO_2, HCO_3, lactate, Hb, Htc) were recorded during measurements as well as mean arterial blood pressure, heart rate and CPB flow rates. CBFv were obtained firstly through the temporal window where the ultrasound probe was directed horizontally. The depth and sample volume were adjusted until the middle cerebral artery (MCA) was found using previously published normative values for the age range (11). However, during paediatric cardiac surgery access to the temporal window was not always possible due to the draping and positioning of the patient head without disturbing the surgical field. As the patients were neonates with an open fontanelle, this was accessible throughout the procedure. Therefore, during baseline measurements before surgery had begun, the temporal window (which was accessible at this time point) was first used as a reference point, the MCA velocity, depth and power was similar from both windows. For the remaining measurements the probe was placed on the same single vessel (right middle cerebral artery) through the fontanelle. The same position and the same depth were maintained throughout. Previous research has suggested there is no significant difference between blood flow velocities in left and right middle cerebral vessels or hemispheres during paediatric cardiac surgery if the Circle of Willis is intact (12). All patients had a normal cerebral vasculature.

Anaesthetic technique was standard for all patients consisting of intravenous administration of midazolam, fentanyl and inhaled servoflurane. Two blood pressure monitors were used (femoral and right radial or brachial artery) to assess preductal and postductal arterial pressures. Two NIRS probes were positioned on bilateral frontal area and monitoring started. Once the patient was anaesthetised and prepared for theatre a ‘baseline’ measurement was recorded. Surgery was performed via median sternotomy, preparation for the procedure included dissection of the head and

neck vessels, ascending aorta, aortic arch and descending aorta past the aortic isthmus. Patent ductus arteriosus was dissected and encircled with a silk ligature, ready to be ligated upon CPB commencement. Cardiopulmonary bypass (CPB) was achieved with either a single right atrial cannula or bicaval cannulation in those patients requiring intracardiac repairs. Aortic return was procured in the ascending aorta with a straight perfusion cannula. In patients with a systemic duct dependent circulation such as HLHS or interrupted aortic arch, a second cannula was positioned across the patent ductus arteriosus (PDA) via a purse string on the pulmonary trunk. This provided adequate systemic perfusion when on CPB. In such cases flow rates were adjusted to provide 2/3 of the total flow to the lower body, and 1/3 to the upper body. After heparin administration and with an activated clotting time of more than 300 sec, CPB was then commenced and cooling towards the target temperature was accomplished. In all cases core temperature was monitored via rectal and nasopharyngeal temperature probes. CPB full flow rates were calculated at 2.6 L/min/m^2 of body surface area. Body surface area was calculated as the square root of (height (cm) x weight (kg)/3600). PDA was ligated, and in case of a second cannula, a ligature was snagged around the MPA to avoid pulmonary over circulation and relative systemic hypoperfusion.

CBF measurements were recorded at different time points during the operation: on initiation of full flow bypass and named ‘CBP’ (still at normothermia). During the cooling phase, further dissection of the aorta and its branches was performed to ensure a full mobilisation of the structures. Cooling target was either 20°C or 25°C and cooling times were at least 20 minutes and no longer than 23 minutes. CBF measurements were recorded when body temperature reached 30°C, 25°C and the lowest temperature. Once the patient was cooled to 28°C, the perfusion strategy to

manage blood gases (pO_2 and pCO_2) was switched from alpha-stat to pH-stat, which is temperature corrected method. pH-stat management was only used when the patient was cooled at 28°C or lower. At this time pCO_2 was also temperature corrected.

Only after the target core temperature was reached, in patients with two arterial cannulas, the systemic cannula was removed. The aortic cross clamp was applied, and myocardial arrest/protection was achieved with infusion of cold blood cardioplegia (ratio 1:4 blood to St. Thomas II solution) in the aortic root. Cardioplegia infusion was repeated at 30 minutes intervals. The head and neck vessels (innominate artery, left common carotid and left subclavian arteries) already fully dissected ready to be snared when the ascending aorta cannula was advanced into the innominate artery to initiate selective ACP. At this point a measurement was taken labelled ‘antegrade cerebral perfusion or ACP’. The aortic cross clamp in the descending aorta was then positioned and CPB flow rates were manipulated manually to keep cerebral oxygenation measurements (measured using NIRS) within the antegrade cerebral perfusion (ACP) target to maintain NIRS within ~10% of when the patient is placed onto full flow bypass. Five patients underwent complete hypothermic circulatory arrest (mean time 22 ± 37 minutes). The aorta was transected at the isthmus above and below the duct insertion and ductal tissue completely removed; the arch was opened in the inner curvature till the mid ascending aorta. End-to-end posterior anastomosis was performed between the descending aorta and distal arch. A pulmonary homograft was used for the reconstruction of the aortic arch in all patients. In two patients that underwent the Norwood operation; the pulmonary trunk, previously detached from the pulmonary bifurcation, was anastomosed to the previously positioned pulmonary homograft in the inner curvature of the reconstructed aortic arch. Once accomplished, the arch was deaired by releasing the distal clamp. The clamps from the head and neck vessels

were removed. The tip of the aortic cannula was moved back into the aortic arch to perfuse the whole body and the heart was re-perfused with blood and rewarming started. Once the suture lines were checked gradual rewarming was induced. If further procedures were needed such as a VSD closure or ASD closure, further doses of cardioplegia were used, and intracardiac repair was accomplished accordingly. In such cases longer CPB and cross clamp time was also needed. A measurement was recorded following whole-body reperfusion labelled as 'whole-body'. Patients were then rewarmed to normothermia. Measurements were recorded at temperatures 25°C, 30°C and 36°C. Once a temperature of 28°C was achieved, the stat management was switched from pH to alpha-stats. When normothermia was reached, the patient was weaned off CPB. A further measurement was recorded and labelled 'off CBF' when haemodynamics were stable. All patients recovered in the paediatric intensive care unit (PICU), and the following post-operative day a measurement was recorded labelled as 'PICU'.

Statistical Analysis

The data were explored for normality using quantile-quantile plots, the data was normally distributed. SPSS (SPSS Version 26, IMB Statistics, USA) was used to perform linear mixed models to account for missing data points. Analysis were exploratory in nature with all variables were compared during the entire procedure which included the time points baseline, CBP, during cooling at 30ºC, 25ºC, the lowest temperature, during cerebral perfusion, whole body perfusion, during rewarming at 25ºC, 30ºC, 36ºC, once off CPB and after surgery on PICU (12 time points) and between *a priori* target temperatures of 20ºC and 25ºC (2 temperatures). Follow up post hoc comparisons to explore main effect of time, were defined *a priori*. Each time point was compared to both baseline and the initiation of CBP (time points used to

define cerebral perfusion during the procedure). To examine the correlation between CBFv and NIRS repeated measures correlations (rmcorr) were employed using R statistical package (RStudio: Integrated Development Environment for R, USA). The repeated measures variable was time which included 12 levels. Main effects, time*temperature interactions and correlations demonstrating a P value < 0.05 were considered statistically significant.

Results

24 patients with a mean age (and standard deviation) 19 (± 7) days, weighed 3.63 (± 0.66) kg and height 51.8 (± 3.4) cm (table 1) were recruited. All patients eligible were recruited with no patients withdrawing from the study. Patients had missing TCD data at a time point (n=6) and missing NIRS (n=7). All patients had a follow up measurement taken on PICU the following day and there were no dropouts. There were no reports of neurological events during cardiac surgery or recovery on PICU. CBFv changed during the entire arch repair procedure (main effect of time: p=0.001). During cooling CBFv increased by 6.6 cm/s (2.7, 12.8), 10.0 cm/s (5.97, 17.7) and 9.5 cm/s (5.85, 16.6), at 30°, 25°C and lowest temperature, respectively when compared to during CPB (p=0.019). Once recovering in PICU, CBFv increased from the baseline by 6.2 cm/s (0.21, 13.4; p=0.045) and by 7.1 cm/s (1.2, 12.1; p=0.005) from CPB. CBFv changes were similar between patients cooled to the *a priori* 20°C and 25°C (main effect of temperature: p=0.22; time*temperature interaction; p=0.86). NIRS values changed during aortic arch repair procedure (main effect of time: p=0.028). NIRS increased during cooling from CPB by 10% (3, 11), 7% (7, 15) at 25°C and the lowest temperature. There was also an increase from CPB at selective cerebral perfusion by 8% (4,12) and whole-body reperfusion by 8% (4, 12). NIRS values were similar between patients cooled to the a priori 20°C and 25°C (main effect of

temperature p=0.19; time*temperature interaction p=0.59). Repeated measures correlation identified statistically significant but weak positive correlations between CBFv and NIRS (r=0.25, p=0.001; Figure 2). The CPB flow rates were maintained within the start of CPB except for during selective cerebral perfusion where they were reduced by 0.26 l/min^{-1} (0.29, 0.41). The main effect of time (p=0.001), temperature (p=0.47), and time*temperature (p=0.49).

Serum Lactate changed during aortic arch repair procedure (main effect of time: p=0.001). When compared to baseline lactate increased by 2.1 mmol/l (0.93, 2.85) and remained significantly higher throughout the procedure. Compared to CPB lactate increased by 1.4 mmol/l (0.08, 2.01; p=0.010) at 30ºC. The 25ºC temperature group elicited the highest lactate levels, but there was no interaction between time and temperature (p=0.60). HCO_{3-} changed during aortic arch repair procedure (main effect of time; p=0.001). When compared to baseline, HCO_{3-} increased during cooling at 25°C and the lowest temperature by 3.2 mmol/l (0.03, 4.72) and 3.1 mmol/l (0.50, 4.70; p=0.002) respectively. Then decreased at whole body reperfusion, re-warming at 25°C, 30°C and when off CPB, by 2.0 mmol/l (0.60, 5.29), 3.5 mmol/l (0.78, 7.45), 4.3 (1.27, 8.11) and 2.2 mmol/l (0.92, 5.21) respectively. When compared to CPB, HCO_{3-} decreased during whole body, 25°C, 30°C and off CPB by 2.1 mmol/l (0.07, 5.78), 3.6 mmol/l (0.29, 7.76), 4.4 mmol/l (0.79, 8.42) and 3.2 mmol/l (0.20, 5.75), respectively. HCO_{3-} changes were similar between patients cooled to 20°C and 25°C (main effect of temp; p=0.094, time*temperature p=0.92).

pO_2 changed throughout aortic arch repair (main effect of time: p=0.001). Compared to baseline pO_2 increased by 11.6 kPa (3.10, 15.9) on CPB (p=0.005) and by 8.7 kPa (1.47, 14.6) at 30ºC. pO_2 remained lower from 25ºC of cooling until off CPB. pO_2 changes were similar between patients cooled to the *a priori* 20°C and 25°C (main

effect of temperature p=0.37; time*temperature interaction: p=0.16). pCO_2 changed throughout aortic arch repair (main effect of time; p=0.009). Compared to baseline pCO_2 decreased (p=0.001) by 2.3 kPa (0.93, 3.43) at CPB, by kPa (0.12, 2.64) at 30°C, by 1.9 kPa (0.12, 2.64) at 25°C, by 1.7 kPa (0.33, 2.75) at the lowest temperature of cooling, 1.8 kPa (0.40, 2.85) at selective cerebral perfusion,1.6 kPa (0.61, 2.55) at 30ºC and by 1.8 kPa (0.43, 2.89) at 36°C. Compared to baseline pCO_2 increased by 0.5 kPa (0.21, 1.36) at 30°C, by 0.4 kPa (0.10, 0.97) at lowest temperature, by 0.5 kPa (0.17, 1.11) at selective cerebral perfusion, by 1.2 kPa (0.43, 1.07) at whole body reperfusion, by 0.9 kPa (0.63, 1.97) at 25°C, by 0.7 kPa (0.19, 1.55) at 30°C and by 1.0 kPa (0.21, 1.89) off CPB. pCO_2 changes were similar between patients cooled to the *apriori* 20°C and 25°C (main effect of temperature p=0.47; time*temperature interaction p=0.22).

Htc changed during aortic arch repair procedure (main effect of time: p=0.001). Htc decreased by 5.5% (0.72, 8.92) when on CPB compared to baseline and remained significantly lower until off CPB. When compared to CPB there was an increase during whole body perfusion 3.7% (0.72, 6.59), 30°C by 3.6% (0.60, 5.92) and when placed off CPB by 5.0% (0.18, 10.2). There was no main effect of temperature (p=0.17) or time*temperature interaction (p=0.96). Hb changed during aortic arch repair procedure (main effect of time: p=0.003). Hb decreased by 1.4 g/dl (0.06,2.40) when on CPB and remained lower until off CPB. When compared to CPB, Hb decreased by 1.5 g/dl (0.02, 2.20) at selective cerebral perfusion, 1.7 g/dl at whole body reperfusion (0.48, 2.54) and 1.6 g/dl at 25°C rewarming. With a main effect of temperature being higher in the group cooled to 20°C (p=0.011) and main effect of time*temperature (p=0.74).

Discussion

The aims of the study were threefold (i) to continuously monitor CBFv throughout aortic arch repair surgery, (ii) investigate the relationship between NIRS and TCD and (iii) compare CBFv in patients cooled to 20°C and 25°C as part of the neuroprotection regime. The current data indicate (i) during the cooling process there was an increase in CBFv and NIRS, although NIRS appears to have a delayed response following increase in CBFv and (ii) that cooling to either 20°C or 25°C did not alter the CBFv response during aortic arch repair surgery. Taken together, the results imply cerebral perfusion is maintained despite deeper cooling in the more complex and longer surgical time periods. Nevertheless, during the cooling process there are physiologically important changes in CBFv and NIRS. Which highlighted that NIRS alone may not be reflective of cerebral perfusion during the whole aortic arch procedure.

A novel observation from the current data shows that NIRS values increased during the cooling period. A previous study has also reported an increase in cerebral oxygenation from 63 ± 11% to 88 ± 7% after 15 minutes of cooling during cardiac surgery (13). In the current study there was also a significant increase in TCD values during cooling which corresponds with other previous research into paediatric aortic arch repair (9). It appears that the changes during cooling are not mediated through CPB flow rates as these remained the same throughout the cooling period. There are other possible physiological explanations for this change in perfusion during cooling. Firstly, the type of stat management used may account for these changes. In the present study, once the patients were cooled to 28ºC, pH stat management was used rather than alpha stats. pH stat management is a standardised practised used at the centre, the purpose of switching stat management at lower temperatures is to increase tissue oxygenation during deep hypothermic circulatory arrest. pH stat management

consists of maintaining pH at ~7.4 at lower temperatures. To achieve this CO_2 was added to the CPB oxygen admixture in the oxygenator (pCO_2 is kept at ~40 mmHg) (14). CO_2 has been identified as a key regulator of cerebral perfusion, increases in CO_2 lead to increases in CBF (15). One previous study measured TCD differences between pH and alpha stat management during CPB (16). During pH stat management there was a global CBF and MCA velocity increased at 28°C by 45.9% and 51.8% respectively. Whereas in patients that underwent alpha-stat management throughout cooling, CBF and MCA velocity had a decrease by 26.4 and 22.4% respectively at 28°C. In the current study, CBFv had already increased at 30ºC, therefore stat management was not the only contributing factor. Another possible factor for the increase in CBFv during cooling could be changes in HCO_{3-}. It can be seen from figure 1 and 3 that changes in HCO_{3-} and CBFv follow a similar pattern of change throughout aortic arch repair. The impact of HCO_{3-} on CBFv has recently been highlighted as an important factor in cerebral autoregulation (17). Changes occur through the bicarbonate buffering system. With an increase in HCO_{3-}, there is an increase in pCO_2 and hydrogen ions. This activates the gated calcium channels, hyperpolarising the endothelial cells leading to vascular vasodilation in the arterioles and precapillary sphincter (18). This has been suggested to be more predominant in sedated populations (19). As in non-sedated individuals, with an increase in pCO_2, usually there is a response to increase breathing to reduce the amount of pCO_2 in the blood. However, this is unable to happen in sedated individuals with muscle relaxants, such as during paediatric cardiac surgery. This may provide insight into the pattern of change seen in CBFv during paediatric aortic arch repair.

Cerebral perfusion measurements obtained during selective cerebral perfusion demonstrated a decrease in CBFv. Interestingly, NIRS values at remained elevated.

The current data suggests that NIRS and CBFv does not follow the same pattern during ACP. One potential physiological explanation for the elevated oxygenation despite reductions in CBFv could be the reduced brain metabolism as a result of cooling (20). This may suggest that despite a reduction in CBFv, cerebral oxygenation remains elevated. Another novel aspect of this study was CBFv measurements taken during rewarming and subsequently in PICU. CBFv values obtained in PICU were higher when compared to baseline and CBP. The values evident post-surgery was comparable to normative CBFv in healthy neonates [11].

We also aimed to examine the overall relationship between NIRS and TCD at each time point during surgery. Previous studies have suggested a moderate and statistically significant correlation ($r=0.55$, $p<0.0001$) between NIRS and TCD during CPB in adult cardiac surgery (21). However, a number of concerns have been raised about solely using NIRS as a clinical tool during sedation such as the inability to measure hyperperfusion (7). In the current study, repeated measures correlations (rmcorr) were employed to examine the relationship at each time point during surgery. Rmcorr was employed as it averages repeated measures for each individual, therefore the assumption of independence is not violated using this method (22). The current data suggested a statistically significant but weak correlation. Physiologically, even small changes in CBFv could have an impact on cerebral perfusion which could potentially be underestimated by NIRS. This discrepancy was highlighted at the time point named ‘ACP’, where CBFv values decreased and NIRS remained elevated.

During this time the discrepancy may not necessarily be detrimental. Similar findings were documented during neonatal cardiac surgery, where despite a reduction in CBFv at ACP, high levels of oxygenation remained elevated (23). With the conclusion that the requirement of oxygenated blood decreases during deep

hypothermic circulatory arrest. However, this finding has highlighted a discrepancy between NIRS and CBFv which may have clinical importance at time periods outside of DHCA. Taken together, the additional measurement of TCD alongside NIRS might be beneficial to indicate global brain perfusion in this patient group. As opposed to NIRS alone which can only give regional measurements of the frontal lobes. TCD can also indicate hyperperfusion which NIRS cannot. This would give further information about perfusion in the main cerebral arteries and reduce the likelihood of perfusion injuries during CPB.

The final novel aspect of the current study was examining the differences between two temperature groups. Currently in clinical care, cooling patients to specific target temperature is based on surgeon or centre preference. The rationale for cooling temperatures of 18°C or 20°C during aortic arch repair is to maximise neurological protection during complex and longer operations. Data from the current study suggest there was no significant difference in CBFv or NIRS between patients cooled to 20°C or 25°C. Using a higher temperature such as 25°C might prevent the systemic drawback of perfusing the body at lower temperatures. Moreover, it could be beneficial in reducing the cooling and rewarming times, hence allowing for a shorter CPB time. However, this would need to be explored further in subsequent studies to impact clinical practise.

Methodological Considerations and Limitations

A limitation to the study was the relatively small sample size as this was a single centred study. Future research should consider a larger study. A limitation of TCD is the inability to measure vessel diameter, therefore absolute flow cannot be quantified. However, during a rested state vessel diameter is expected to be maintained, meaning

TCD can give an accurate indication of flow. The anaesthetic technique was formulated to have minimal effect on vessel diameter and CBF. Previous research has suggested that the use of fentanyl and inhaled sevoflurane does not affect CBF (24). and midazolam has minimal effect on CO_2 reactivity, CBF and blood oxygenation (25). Future studies should consider measuring vessel diameter to ensure diameter remains constant during cardiac surgery. Another limitation of TCD is that it is operator dependent. To minimise, all CBFv measurements were taken by one trained individual. The final limitation is the inclusion of two patients with HLHS. It was acknowledged that patients with HLHS have differing cardiac physiology. However, the inclusion criteria stated any patient that was undergoing arch repair using a hyperthermic circulation. HLHS patients met this criterion. It was also important to the main aim of the study to capture these patients as those cooled to lower temperatures are often undergoing more complex procedures such as the Norwood (which includes DKS anastomosis needing longer CPB and ASCP times). It is important to highlight, these patients had similar clinical interventions with prostaglandin being used to keep the PDA open and ages were comparable to other patients enrolled. Once they were on CPB flow rates were maintained as per general protocol. During the Norwood operation with Sano modification, it was anticipated that CBFv levels would be comparable across all patients, irrespective of physiology. As this is a feasibility study, it was believed it was important to capture these patients so the comparison between the two temperatures could be included in the analysis, which is a novel aspect of the study.

Conclusion

The main findings suggested that during the cooling process there was an increase in both CBFv and NIRS, although there appears to be a delayed response in NIRS. Although this delay did not appear to be detrimental during cooling due to the reductions in brain metabolism. It has highlighted that NIRS alone may not be truly reflective of cerebral perfusion, despite its current heavy reliance during cardiac surgery. This corresponds with the finding of an overall weak relationship between NIRS and TCD. Another key finding was that cooling to 20°C or 25°C did not alter the CBFv response during neonatal aortic arch repair surgery. Overall, these findings could provide clinicians with information on how to optimise long-term cerebrovascular health in this population.

Data availability statement: The data underlying this article will be shared on reasonable request to the corresponding author.

Funding statement: This work was supported by LJMU internal funding.

Acknowledgement: Dr Andrew Thompson aided in the coding of R statistical package which was used to perform the repeated measures correlation.

Conflict of interest statement: none declared.

Author contribution statement:

Conceptualisation: HJ, RL,LF, AL

Data curation: LF, HJ, AL

Formal Analysis: LF, AL, AT, HJ.

Funding acquisition: HJ, RL, AL.

Investigation: LF.

Methodology: LF, RJ, HJ, AL.

Project administration: LF, RL, HJ, AL.

Resources: HJ, AL.

Software: LF, HJ, AT.

Supervision: HJ, RL, AL.

Validation: LF, RL, HJ, AL.

Visualisation: LF, RL, HJ, AL.

Original draft: LF, RL, HJ, AL.

Writing-review and editing: LF, RL, HJ, AL.

Figure Legends:

Figure 1. Mean and standard deviation of cerebral blood flow velocity throughout aortic arch repair. * indicates significant change from ‘baseline’ time point.

Figure 2. Near infrared spectroscopy throughout aortic arch repair, represented as mean and standard deviation. * shows significant difference from ‘baseline’. # indicates significant difference from ‘on CPB’ time point.

Figure 3. Bicarbonate throughout aortic arch repair represented as means and standard deviation. * shows significant difference from ‘baseline’. # indicates significant difference from ‘on CPB’ time point.

Table 1. Patient characteristics of two temperature groups.

References

1. Feinstein JA, Benson DW, Dubin AM, Cohen MS, Maxey DM, Mahle WT, et al. Hypoplastic left heart syndrome: current considerations and expectations. Journal of the American College of Cardiology. 2012;59(1 Supplement):S1-S42.
2. Mussatto KA, Hollenbeck-Pringle D, Trachtenberg F, Sood E, Sananes R, Pike NA, et al. Utilisation of early intervention services in young children with hypoplastic left heart syndrome. Cardiology in the young. 2018;28(1):126-33.
3. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012;126(9):1143-72.
4. Serraino GF, Murphy GJ. Effects of cerebral near-infrared spectroscopy on the outcome of patients undergoing cardiac surgery: a systematic review of randomised trials. BMJ open. 2017;7(9):e016613.
5. Kinney HC, Panigrahy A, Newburger JW, Jonas RA, Sleeper LA. Hypoxic-ischemic brain injury in infants with congenital heart disease dying after cardiac surgery. Acta neuropathologica. 2005;110(6):563-78.
6. Meyer DB, Jacobs JP, Hill K, Wallace AS, Bateson B, Jacobs ML. Variation in perfusion strategies for neonatal and infant aortic arch repair: contemporary practice in the STS congenital heart surgery database. World Journal for Pediatric and Congenital Heart Surgery. 2016;7(5):638-44.
7. Grocott HP, Davie SN. Future uncertainties in the development of clinical cerebral oximetry. Frontiers in physiology. 2013;4:360.
8. Andropoulos DB, Stayer SA, McKenzie ED, Fraser Jr CD. Novel cerebral physiologic monitoring to guide low-flow cerebral perfusion during neonatal aortic arch reconstruction. The Journal of thoracic and cardiovascular surgery. 2003;125(3):491-9.
9. Busch DR, Rusin CG, Miller-Hance W, Kibler K, Baker WB, Heinle JS, et al. Continuous cerebral hemodynamic measurement during deep hypothermic circulatory arrest. Biomedical optics express. 2016;7(9):3461-70.
10. Ashry A, Harky A, Tarmahomed A, Ugwu C, Mohammed HM, Kutty R, et al. Contemporary outcomes of aortic arch hypoplasia and coarctation repair in a tertiary paediatric cardiac surgery centre. Cardiology in the Young. 2022;32(7):1098-103.
11. Truemper E, Fischer A. Cerebrovascular developmental anatomy and physiology in the infant and child. Transcranial Doppler ultrasonography St Louis: Mosby. 1993:355-75.
12. Rüffer A, Tischer P, Münch F, Purbojo A, Toka O, Rascher W, et al. Comparable cerebral blood flow in both hemispheres during regional cerebral perfusion in infant aortic arch surgery. The Annals of Thoracic Surgery. 2017;103(1):178-85.
13. Tobias JD, Russo P, Russo J. Changes in near infrared spectroscopy during deep hypothermic circulatory arrest. Ann Card Anaesth. 2009;12(1):17-21. Epub 2009/01/13. doi: 10.4103/0971-9784.43057. PubMed PMID: 19136750.
14. Hirata Y. Cardiopulmonary bypass for pediatric cardiac surgery. Gen Thorac Cardiovasc Surg. 2018;66(2):65-70. Epub 2017/12/01. doi: 10.1007/s11748-017-0870-1. PubMed PMID: 29185163.

15. Claassen JA, Thijssen DH, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiological reviews. 2021;101(4):1487-559.
16. Trivedi UH, Patel RL, Turtle MR, Venn GE, Chambers DJ. Relative changes in cerebral blood flow during cardiac operations using xenon-133 clearance versus transcranial Doppler sonography. Ann Thorac Surg. 1997;63(1):167-74. Epub 1997/01/01. doi: 10.1016/s0003-4975(96)01017-x. PubMed PMID: 8993260.
17. Caldwell HG, Howe CA, Chalifoux CJ, Hoiland RL, Carr JM, Brown CV, et al. Arterial carbon dioxide and bicarbonate rather than pH regulate cerebral blood flow in the setting of acute experimental metabolic alkalosis. The Journal of Physiology. 2021;599(5):1439-57.
18. Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. The Journal of physiology. 2011;589(12):3039-48.
19. Buckley EM, Naim MY, Lynch JM, Goff DA, Schwab PJ, Diaz LK, et al. Sodium bicarbonate causes dose-dependent increases in cerebral blood flow in infants and children with single-ventricle physiology. Pediatric research. 2013;73(5):668-73.
20. Manetta F, Mullan CW, Catalano MA. Neuroprotective Strategies in Repair and Replacement of the Aortic Arch. Int J Angiol. 2018;27(2):98-109. Epub 2018/06/14. doi: 10.1055/s-0038-1649512. PubMed PMID: 29896042; PubMed Central PMCID: PMC5995688.
21. Ono M, Zheng Y, Joshi B, Sigl JC, Hogue CW. Validation of a stand-alone near infrared spectroscopy system for monitoring cerebral autoregulation during cardiac surgery. Anesthesia and analgesia. 2013;116(1):198.
22. Bakdash JZ, Marusich LR. Repeated Measures Correlation. Frontiers in Psychology. 2017;8(456). doi: 10.3389/fpsyg.2017.00456.
23. Ferradal SL, Liao SM, Eggebrecht AT, Shimony JS, Inder TE, Culver JP, et al. Functional Imaging of the Developing Brain at the Bedside Using Diffuse Optical Tomography. Cereb Cortex. 2016;26(4):1558-68. Epub 2015/01/18. doi: 10.1093/cercor/bhu320. PubMed PMID: 25595183; PubMed Central PMCID: PMC4785947.
24. Abdallah C, Karsli C, Bissonnette B. Fentanyl is more effective than remifentanil at preventing increases in cerebral blood flow velocity during intubation in children. Can J Anaesth. 2002;49(10):1070-5. Epub 2002/12/13. doi: 10.1007/bf03017905. PubMed PMID: 12477681.
25. Kiviniemi VJ, Haanpää H, Kantola J-H, Jauhiainen J, Vainionpää V, Alahuhta S, et al. Midazolam sedation increases fluctuation and synchrony of the resting brain BOLD signal. Magnetic resonance imaging. 2005;23(4):531-7.

Table 1. Patient characteristics of two temperature groups.

	20°C	**25°C**
Mean age (days)	20 ± 16	18 ± 19
Height (cm)	48.7 ± 4.8	52.3 ± 3.9
Weight (kg)	3.3 ± 0.7	3.6 ± 0.7
Sex (females: males)	1:1	5: 11
Mean cardiopulmonary bypass time (minutes)	197 ± 45	136 ± 38
Mean cross clamp time (minutes)	119 ± 34	88 ± 105
Mean total circulatory arrest time (minutes)	48 ± 59 (n = 2)	5 ± 3 (n = 3)
Mean antegrade cerebral perfusion time (minutes)	78 ±18	61 ± 23

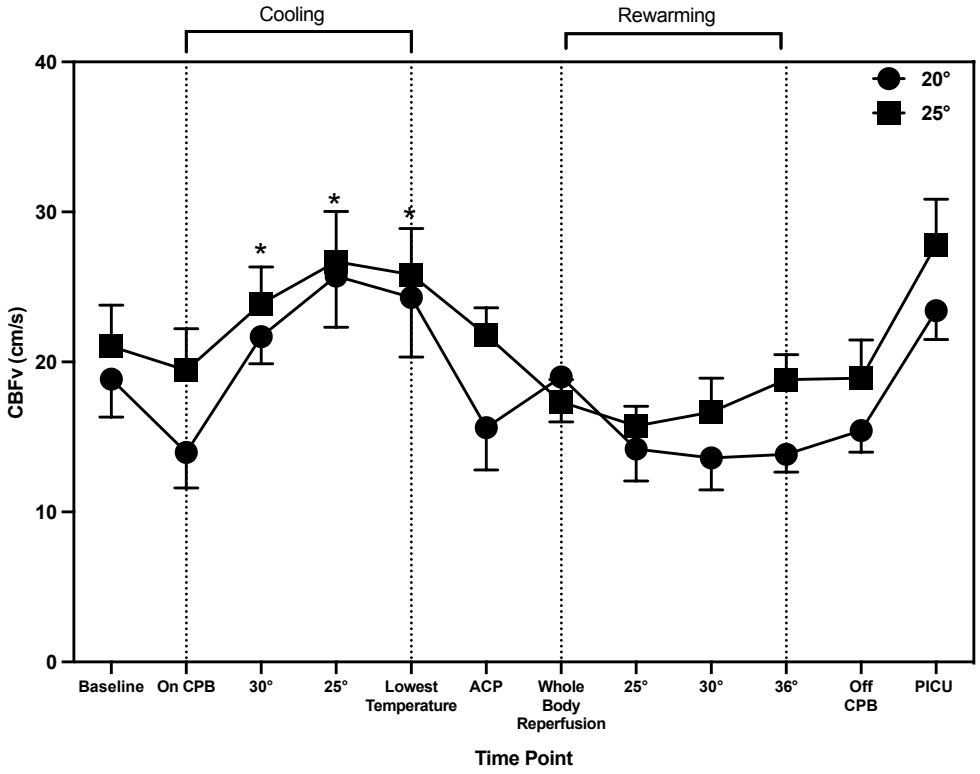

Figure 1. Mean and standard deviation of cerebral blood flow velocity throughout aortic arch repair. * indicates significant change from ‘baseline’ time point.

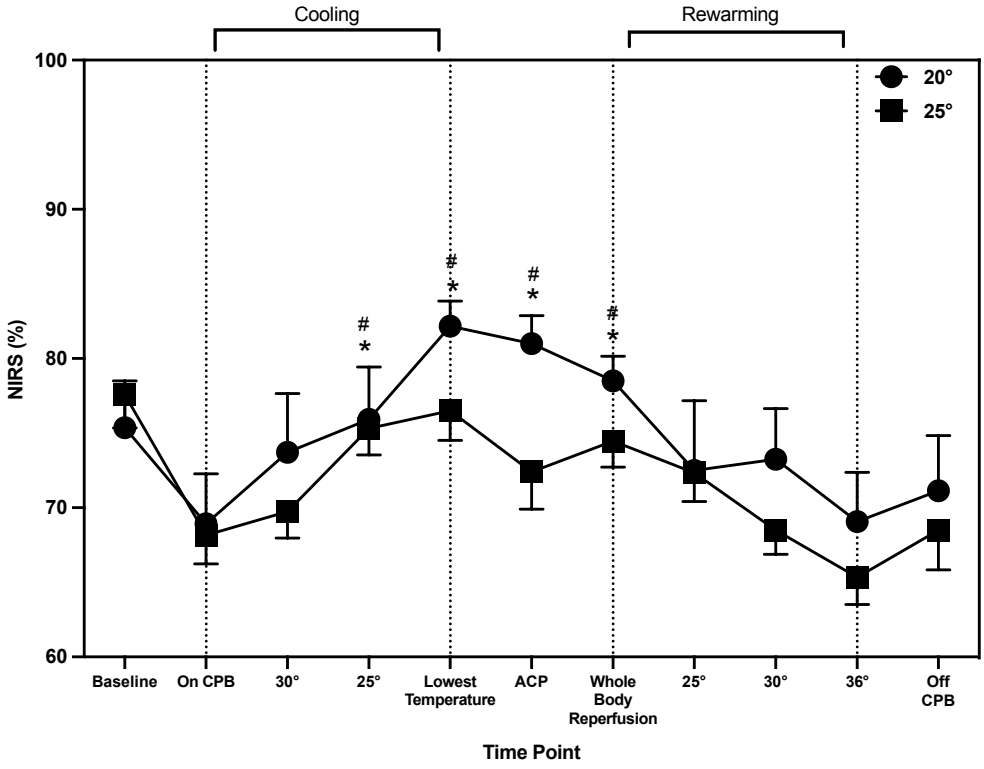

Figure 2. Near infrared spectroscopy throughout aortic arch repair, represented as mean and standard deviation. * shows significant difference from 'baseline'. # indicates significant difference from 'on CPB' time point.

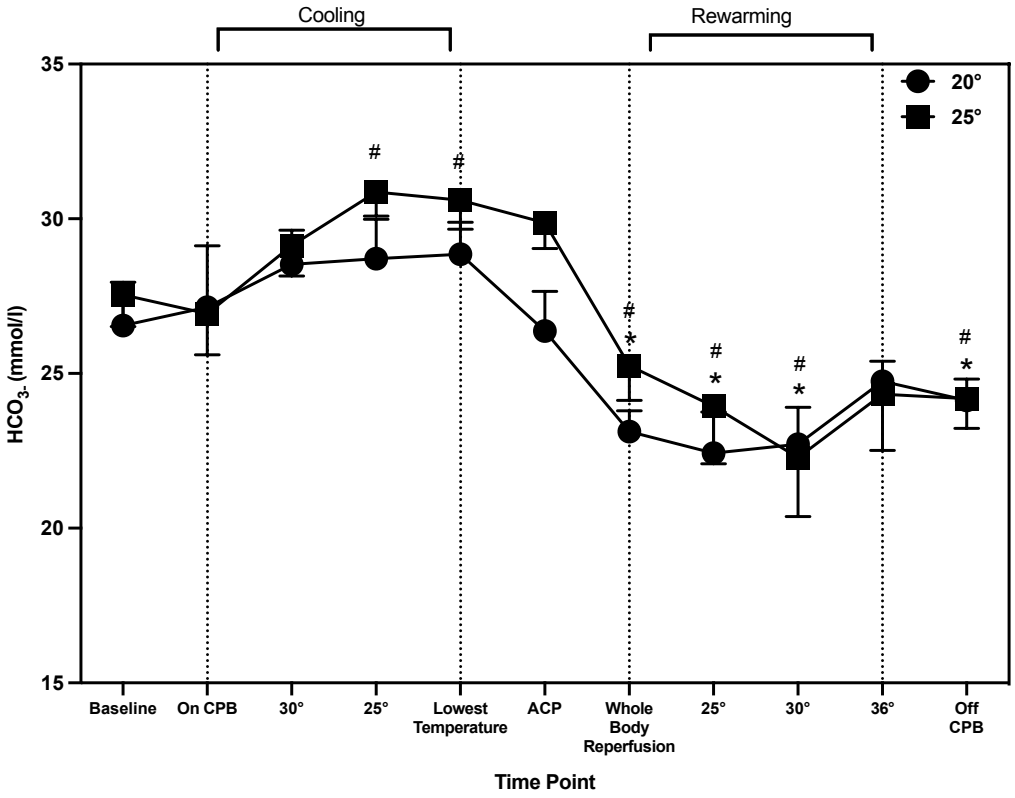

Figure 3. Bicarbonate throughout aortic arch repair represented as means and standard deviation. * shows significant difference from 'baseline'. # indicates significant difference from 'on CPB' time point.