The Effects of an Extracorporeal Circulation on Cerebral Perfusion during Paediatric Critical Care and Cardiothoracic Procedures

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Abstract

The developing brain is highly vulnerable to physiological and pharmacological insults, which can impact cerebral blood flow (CBF), resulting in neurological deficit. Within the clinical environment, a group of patients at particular risk of neurological insult are those who require an extracorporeal circulation. This has a profound effect on CBF due to the use of non-pulsatile blood flow, pharmacological agents and periods of hypo/hyperperfusion. As a result, effective cerebral monitoring is essential to prevent periods of ischaemia and subsequently, enhance quality of life in survivors. Patients requiring an extracorporeal circulation include those treated for acute respiratory and/or cardiac failure using extracorporeal membrane oxygenation (ECMO), and the use of cardiopulmonary bypass (CPB) during cardiac surgery for congenital heart defects. The overarching aim of this thesis was to examine how an extracorporeal circulation impacts cerebral perfusion throughout the entire treatment process and following recovery in paediatric intensive care.

Measurements of cerebral perfusion used throughout the thesis are described in the experimental methods chapter. These include transcranial doppler ultrasound (TCD) and near infrared spectroscopy (NIRS). Another aim of the experimental chapter was to collect TCD data and compare the values to previously published research. Measurements were taken in a 'healthy' neonatal population and then compared to previously published age-matched comparisons. Measurements were also taken in clinically ill patients and then compared to values from previously published ventilated population. Values were comparable to previously published data which suggested the TCD operator was proficient in isonating the middle cerebral artery (MCA).

An observational study was conducted using TCD to measure CBFv at multiple time points during ECMO with a focus on the weaning period in a paediatric population. Fourteen patients that underwent veno-arterial (V-A) ECMO were enrolled. Eight (mean

age 69 days) had central cannulation for post-cardiac surgery support, while six (mean age 84 days) had neck cannulation for respiratory support. CBFv was measured from the MCA during weaning at several time points: full flow ECMO, ¾ flow, ½ flow, ¼ flow, minimum flow, when off ECMO and post decannulation. NIRS, blood pressure, heart rate and arterial oxygen saturation were recorded at the same time points. During the first 5 days of full flow ECMO, CBFv remained relatively stable ($p=0.54$). During weaning, those that successfully decannulated had on average a higher CBFv of 9.1 cm/s compared to those that failed weaning. From the patients decannulated, those receiving conventional treatment had an average higher CBFv of 9.9 cm/s compared to patients on high frequency oscillatory ventilation. Overall, the relationship between NIRS and TCD was positive but weak.

Another study was undertaken to examine CBFv and an extracorporeal circulation during aortic arch repair. Neonates requiring aortic arch repair are unable to maintain adequate oxygenation levels and require surgical intervention. A high percentage of survivor's exhibit signs of neurological deficit possibly due to inadequate CBF during surgery. The aim was to continuously monitor MCA velocity (MCAv) during surgery. A secondary aim was to examine the impact of temperature on CBF, with cooling ranging from 18 to 25°C based on surgeon preference. MCAv was monitored in 24 neonates (age 19±6 days, body mass 3.6±0.6 kg) undergoing surgery on the aortic arch, alongside NIRS, blood pH, pO_2, pCO_2, HCO_3, lactate, Hb, Htc (%) and temperature (core and rectal). Using general linear models, MCAv was compared at several time points. These included: initial sedation; cardiopulmonary bypass (CBP); cooling at 30°c, 25°c, the lowest temperature; during selective cerebral perfusion; whole body perfusion; rewarming at 25°c, 30°c, 36°c; off cardiopulmonary bypass; and after surgery. During and following surgery, MCAv was lower compared to previously published healthy age-matched controls, except during cooling period. CBFv increased during cooling at 30°c, 25°c and the lowest temperature

respectively when compared to CBP (p=0.03). Once off CBP, MCAv returned to pre-surgery values. No significant difference was noted between patients cooled to 20 or 25°c.

Overall, this thesis provides evidence of disruptions in cerebral perfusion during different stages of treatments involving an extracorporeal circulation. The current clinical tool for monitoring cerebral perfusion is NIRS, which may not provide sufficiently sensitive data on cerebral perfusion during treatments using an extracorporeal circulation. Taken together, the findings provide important data for clinicians treating paediatric patients requiring an extracorporeal circulation. It provides data identifying specific time periods of reduced cerebral perfusion, while highlighting limitations of current methods of monitoring.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institution of learning.

Poster Communications directly based on the work described in this thesis:

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Finnigan, L.E.M., Lotto, A., Lotto, R. and Jones, H. Cerebral Blood Flow Velocity during Aortic Arch Repair. Future Physiology, Liverpool, UK (2019).

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List of Abbreviations

Abbreviation	Title
ASD	Atrial Septal Defect
CBF	Cerebral Blood Flow
CBFv	Cerebral Blood Flow Velocity
CHD	Congenital Heart Disease
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
CO_2	Carbon Dioxide
CPB	Cardiopulmonary Bypass
CT	Computerized Tomography
DHCA	Deep Hypothermic Circulatory Arrest
ECHO	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
E-CPR	Extracorporeal Cardiopulmonary Resuscitation
ELSO	Extracorporeal Life Support Organization
HCO_{3-}	Bicarbonate
HFOV	High Frequency Oscillatory Ventilation
HLHS	Hypoplastic Left Heart Syndrome
IJV	Internal Jugular Vein
MAC	Minimum Alveolar Concentration
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MCAv	Middle Cerebral Artery Velocity
MHz	MetaHertz
MRI	Magnetic Resonance Imaging
MUF	Modified Ultrafiltration
$NaHCO_{3-}$	Sodium Bicarbonate
NIRS	Near Infrared Spectroscopy
PA	Pulmonary Artery
PCO_2	Partial Pressure of Arterial Carbon Dioxide
PDA	Patent Ductus Arteriosus
PEEP	Positive End-Expiratory Pressure

PICU	Paediatric Intensive Care
PO_2	Partial Pressure of Oxygen
rSO_2	Brain Regional Oxygen Saturation
$SctO_2$	Cerebral Tissue Oxygenation Saturation
TCD	Transcranial Doppler Ultrasonography
TGA	Transposition of the Great Arteries
VA-ECMO	Veno-Arterial Extracorporeal Membrane Oxygenation
VSD	Ventricular Septal Defect
VV-ECMO	Veno-Venous Extracorporeal Membrane Oxygenation

Chapter One: Introduction

1.1 Introduction

Mortality following admission to a paediatric intensive care unit (PICU) in the United Kingdom has decreased over the past 30 years (Plunkett and Parslow, 2016, Mandalenakis et al., 2020). However, there has been an observed rise in morbidity with survivors exhibiting life-limiting conditions (Fraser et al., 2012). This morbidity concern has led to a shift in the focus of research from mortality rates to improving quality of life in survivors (Cunha et al., 2013). Neurodevelopmental outcomes have become increasingly pertinent (Verstraete et al., 2018). With neurological deficit prevalent in 3-20% of children following admission into PICU (Caprarola et al., 2017). Neurological deficit is a collective term relating to a decline in brain function or problems with the nerve or spinal cord. It can be used to describe a range of problems including mild cognitive delay, speech, and hearing problems. The level of deficit is dependent on a range of confounding factors such as the primary diagnosis, severity of the illness and the interventions required during treatment. One potential cause of neurological deficit is a disruption in cerebral blood flow (CBF). Alterations in CBF, especially in the developing neonatal brain, can cause ischaemia during periods of hypotension and haemorrhaging (Vutskits, 2014). Both of which can contribute to neurological deficit. Several paediatric clinical populations are at high risk of developing neurological deficit including patients with acute respiratory failure, cardiac failure and congenital heart disease (CHD). There are number of potential reasons for the high risk of neurological deficit in these conditions This includes the use of an extracorporeal circulation during treatment or surgery. The adverse effects of an extracorporeal circulation on major organs have been well documented, particularly in the cerebellum (Bauer et al., 2010). This will be further explored in the literature review.

A group of patients that require an extracorporeal circulation are those with severe respiratory and/or cardiac failure. Patients that remain unresponsive to conventional

treatments may become a candidate for a cardiopulmonary bypass technique called extracorporeal membrane oxygenation (ECMO). In the UK, approximately 200-250 neonates and infants receive ECMO each year for both respiratory and cardiac conditions (Robinson and Peek, 2015). ECMO is used to take over the function of the heart and/or lungs to allow them to recover. ECMO is routinely used to help stabilise patients who have arrested following cardiac surgery, a bridge for heart transplantation or to stabilise a patient for further investigations. However, ECMO has been associated with a number of adverse neurological side effects (Nasr and Rabinstein, 2015). The extracorporeal circulation itself can lead to neurological deficit, there are also periods of disrupted non-pulsatile flow, a reduction in blood flow rates during the weaning process and the heavy use of pharmacological substances. These are factors which can impact cerebral perfusion. Due to the high levels of neurological deficit in survivors, one of the aims of the thesis was to understand the impact of extracorporeal membrane oxygenation on cerebral perfusion throughout treatment, while identifying specific time points of disturbed cerebral blood flow velocity (CBFv).

Another group of patients at risk of long-term neurological deficit are patients with CHD (Barkhuizen et al., 2021). CHD is one of the most common congenital anomalies with an estimation of 8 per 1000 births (Norrish and Kaski, 2018). Some forms of CHD can lead to insufficient delivery of oxygenated blood throughout the body such as conditions which affect the aortic arch. These conditions often require surgical repair. During corrective aortic arch surgery, patients are placed onto cardiopulmonary bypass (CPB) with periods of deep hypothermic circulatory arrest (DHCA). CPB alone is a challenge for the regulation of CBF. During aortic arch reconstructive surgery there are sudden changes to pulsatile flow, temperature fluctuations (cooling and rewarming), changes to blood viscosity, low CBP flow rates and periods of total circulatory arrest, which all present a challenge for cerebral autoregulation. Previous research has suggested

that those with left sided lesions exhibit the highest and most severe levels of deficit (Kaltman et al., 2005). This includes hypoplastic aortic arch, interrupted aortic arch and hypoplastic left heart syndrome. Therefore, an aim of the thesis was to identify periods of disrupted cerebral perfusion before, during and after aortic arch repair in neonates.

Due to the prevalence of neurological deficit in these groups, there are neuroprotective techniques used in clinical practise to monitor cerebral perfusion. Near infrared spectroscopy (NIRS) continuously measures cerebral oxygenation in the frontal lobes, however it can only give a regional indication of oxygenation levels. The shortcomings of NIRS have been previously described and are further explored throughout the thesis. A technique used frequently in research, but rarely in clinical practice is transcranial doppler ultrasonography (TCD). The measurements of both NIRS and TCD were implemented throughout the thesis to give a detailed insight into cerebral perfusion during the use of an extracorporeal circulation. TCD can measure flow velocity in the major cerebral vessels and can counteract some of the limitations of NIRS. Specifically, TCD can measure CBFv of the middle cerebral artery (MCA) which provides around 70% of blood flow to the brain. The MCA can usually be visualised via the temporal window in adults and children. In neonates with an open fontanelle, the MCA can also be isonated though this window. The fontanelle window is useful during treatment in a paediatric intensive care unit (PICU) and surgery due to the limited space around the head (temporal window) from clinical equipment. These measurements will be further explored in the experimental methods.

There has been a small body of literature that has previously examined CBFv and NIRS during ECMO and cardiac surgery. A study concluded there are instances during ECMO treatment when cerebral oxygenation levels are low, such as during decannulation (Fenik and Rais-Bahrami, 2009). Other research has focused on specific time points such as the first five days of full flow ECMO, where there have been reports of variation in

daily measurements of TCD (O'Brien and Hall, 2013). However, no research study to date has examined CBF and cerebral oxygenation throughout the entire ECMO treatment and during recovery. Cerebral perfusion has also been examined during paediatric aortic arch repair. CBFv was lower than normal levels with periods of zero cerebral perfusion in one case study (Busch et al., 2016). In a study of adults undergoing aortic arch repair, it was found that TCD was able to identify periods of disrupted cerebral perfusion which NIRS was unable to detect (Estrera et al., 2005). Nevertheless, no research to date has described CBF and NIRS during aortic arch repair and post-surgery in paediatrics. Overall, there are gaps in the knowledge surrounding cerebral perfusion during treatments requiring an extracorporeal circulation. This thesis aims to investigate cerebral perfusion during this time in patients that are suspectable to neurological deficit.

1.2 Aims and Objectives

The overarching aim of this thesis was to examine how an extracorporeal circulation impacts cerebral perfusion during procedures associated with high risk of neurological deficits.

Aims of Chapter 3:

- To give a detailed overview of the current measurements of cerebral perfusion in clinical populations which will be used throughout the thesis.
- To establish if the middle cerebral artery was accurate when isonated using transcranial doppler ultrasound by a sole sonographer in a healthy paediatric population.
- Compare values of cerebral blood flow velocity in a clinically ill, paediatric population to previously published ventilated values.

Aims of chapter 3 were completed through the fulfilment of several objectives:

- Produce an overview of measurements of cerebral perfusion (NIRS and TCD) through reviewing previously publish data and establishing strengths/weaknesses of both.
- Collect CBFv from a 'healthy' neonatal population (<10 days) andcompare values to previously published normative data.
- Collect CBFv in number of critically ill paediatric populations including those ventilated with acute respiratory failure. Then to compare values to previously published research.

Aims of Chapter 4:

- To understand the impact of extracorporeal membrane oxygenation on cerebral perfusion throughout treatment while identifying specific time points of disturbed cerebral blood flow velocity.

- Gain an understanding of overall cerebral perfusion by taking both global and regional measurements of cerebral perfusion.
- Identify if the method of ventilation following decannulation from extracorporeal membrane oxygenation affects cerebral blood flow velocity.

Aims of chapter 4 were completed through the fulfilment of several objectives:

- Taking measurements of both TCD and NIRS daily throughout paediatric ECMO treatment, including during weaning and recovery following decannulation.
- Both NIRS and TCD were measurement throughout ECMO treatment to give an indication of global cerebral perfusion.
- Collect CBFv measurements in patients decannulated onto conventional ventilation and high frequency oscillation with the foresight of comparing the values.

Aims of Chapter 5:

- To identify periods of disrupted cerebral perfusion before, during and after aortic arch repair in neonates.
- To understand the impact of temperature changes to cerebral blood flow velocity during aortic arch repair.
- Potentially establish the relationship between NIRS and TCD at each time point during aortic arch repair surgery.

Aim of chapter 5 will be completed through the fulfilment of several objectives:

- Collect measurements of CBFv immediately before, during the aortic arch repair procedure and after surgery.
- Collect measurements of cerebral perfusion in two groups of patients which were cooled to either 20 or 25°C.

- Compare changes in NIRS with CBFv throughout the aortic arch repair procedure, with a focus on antegrade selective cerebral perfusion where the CPB flow rate are determined by NIRS.

Chapter Two: Literature Review

2.1 Overview

First**,** this literature review provides an overview of cerebrovascular structure and function to outline the control of CBF. It also discusses the measurements of cerebral perfusion in clinical populations. Second, the review focuses on outlining two paediatric critically ill conditions that require the use of extracorporeal circulation during (i) acute respiratory and/or cardiac failure and (ii) cardiothoracic surgery for congenital heart conditions related to the aortic arch. Third, the literature review highlights modes of clinical monitoring of cerebral perfusion and then finally summarises the risk of long-term neurological deficit in these groups.

2.2 The Integrated Control of Cerebral Blood Flow in Healthy and Clinical Populations

As an organ, the human brain is highly suspectable to damage due to its high metabolic demand, despite limited storage capacity (Willie et al., 2014). The adult brain accounts for approximately 2% of body weight, consumes around 20% of resting total body oxygen and 15% of cardiac output (Jain et al., 2011). The complexity of the homeostatic control mechanisms of CBF are described by several key structural components and multiple overlapping regulatory paradigms (Peterson et al., 2011). These components will be described in the current chapter. The term cerebral autoregulation is used to describe the homeostatic controlled mechanism which keeps CBF within narrow limits. Excessive (cerebral hyperaemia) or inadequate (cerebral ischemia) CBF can lead to long term damage to the brain. Arguably, paediatrics may be at a higher risk of neurological deficit as the demand for CBF is crucial for brain development. With the brain volume increasing from 36% of an adult at 2-4 weeks old, to 72% by 1 year and to 83% at 2 years old (Steiner, 2019). Making CBF essential for establishing neuronal networks along with the capacity for the development of cognitive, social, emotional and motors skills. The dramatic changes to brain function and structure make the energetic demands of the paediatric brain pertinent, with an estimation of 60% of basal metabolic rate required for the developing brain. Due to this, there are paediatric critical care populations which are at risk of long-term neurological deficit due to potential disruptions in CBF. The focus of this section is to first describe CBFv in healthy populations and then to explore populations at risk of neurological deficit.

2.2.1 Anatomy of the Cerebral Vasculature

The cerebral circulation is related to the movement of blood throughout the brain. This consists of a network of cerebral arteries which supply the brain with oxygen,

glucose and other nutrients. In the brain around 60% of the energy is utilised to generate neuron electrical activity including the reversal of ion influxes, underlying synaptic and action potentials (Attwell and Laughlin, 2001). With a lack of oxygen and glucose the neurons and glia die or become injured. The remaining 40% of the total energy consumption is for homeostatic cellular functioning to support the cells in the brain (Fyfe et al., 2014). The brain has low storage of energy thus relies on adequate CBF to ensure a sufficient energy supply to maintain normal brain functioning, along with the clearing of metabolism by-products (Durduran and Yodh, 2014). CBF is safeguarded by a dual circulation: anterior and posterior (figure 2.1). The posterior cerebral arteries are supplied via the vertebral arteries from the subclavian arteries. Whereas the anterior circulation is supplied from the internal carotid circulation, which is responsible for ~80% of total CBF to the brain. These circulations ultimately connect through bilateral posterior communicating arteries; this describes the circle of Willis (figure 2.1). These circulations branch exuberantly, supplying all deep and superficial regions of the brain. The circle of Willis provides constant flow despite any occlusions to either anterior or posterior circulation.

2.2.2 An Overview of Cerebral Autoregulation

Cerebral autoregulation is recognised as a marker of brain function and health (Buckley et al., 2014). The brain is protected by a physiological homeostatic mechanism called cerebral autoregulation that attempts to maintain adequate blood flow despite changes in mean arterial pressures (Vesoulis and Mathur, 2017). To meet the metabolic demand of the adult brain, CBF must remain at 50-60 ml/100g/min, with this figure on average higher in women (Slupe and Kirsch, 2018). To a point, reserve blood flow exists but when flow drops below 22 ml/100g/min ischaemic injury may occur. Clinically, this threshold can change in some pathologies such as traumatic brain injury. The mechanisms that control CBF have been under speculation for decades.

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Figure 2.1 Inferior view of the circle of Willis with intra- and extracranial blood vessels which supply CBF throughout the brain. Adapted from (Shahan et al., 2017).

Historically it was believed that cerebral vasculature did not control vascular tone but rather that it passively followed changes in blood pressure. In 1959, cerebral autoregulation was first introduced by Lassen who suggested the metabolic demands of cerebral tissue is governed through autoregulation and that it is independent of a wide range of mean arterial pressures (Lassen, 1959). This has been challenged and the contemporary understanding is that the plateau phase is much smaller than first thought (Brassard et al., 2021). In healthy individuals it is believed that CBF can be maintained across a range of blood pressures (60-150mmHg) in healthy individuals with intact cerebral autoregulation (Willie et al., 2014). In clinical situations with the use of pharmacological interventions, this cerebral autoregulatory plateau becomes significantly

smaller due to the changes in vascular tone (Brassard et al., 2021). When cerebral perfusion is outside normal ranges, the brain becomes susceptible to excessive or inadequate blood flow (Vavilala et al., 2005), with a reduction in CBF potentially leading to ischemic injury (Endoh et al., 2002). Both regional and global ischaemia causes cerebrovascular dysregulation, furthering the ischemic insult, and subsequently amplifying tissue damage (Kunz and Iadecola, 2008). Conversely, an overabundance of CBF relative to metabolic demand can lead to the transudation of fluid into the interstitum and pericapillary astrocytes. This can breakdown the blood-brain barrier (Tzeng and Ainslie, 2014).

During challenges to cerebral autoregulation the arteries respond to mechanical and chemical stimuli. Vasodilator/constrictor substances and sympathetic nerve activity regulate the vascular smooth muscle which is affected by changes in pulsatile flow patterns. This occurs via the response mechanisms within the extracranial and cerebral vessels to ensure there is adequate blood flow to the brain (Chiu and Chien, 2011). CBF is kept consistent over a range of systemic blood pressure changes through a combination of neurogenic, myogenic and metabolic mechanisms. Overall, the regulation of CBF is complex and speculative, and it is not yet fully understood despite progress. It is thought there are two key structural components and three overlapping regulatory paradigms which regulate CBF. The three main paradigms involved are cerebral pressure autoregulation, neurovascular coupling and neurogenic regulation; along with the two structural components which are endothelial cells and astrocytes (Peterson et al., 2011). Previous research has highlighted that cerebrovascular resistance can be impacted by four categories; chemical (PCO_2 and PO_2), blood pressure, neurogenic and metabolic (Greisen, 2005).

2.2.3 Cerebral Pressure Autoregulation

The first paradigm described is cerebral pressure autoregulation which attempts to maintain constant CBF in the cerebral vascular tone between a mean arterial pressure (MAP). The relationship between BP and cerebral autoregulation was initially established in 1895 by Bayliss, Hill and Gulland who suggested with an increase in arterial pressure, there was accelerated blood flow through the brain (Bayliss et al., 1895). The conceptualisation of the cerebral autoregulation triphasic curve was first established by Lassen who had plotted average blood pressure (BP) and CBF from multiple studies. The study suggested an upper limit, plateau and lower limit where cerebral autoregulation is maintained stable. In healthy adults, the limits are MAP pressures (60-150 mmHg) or cerebral perfusion pressures (CPP) (60 and 160 mmHg) (Lassen, 1959). Since then, it has been established that the cerebral autoregulation curve is more passive than originally suggested. There has also been speculation as to whether the plateau exists. If it does exist, it is currently thought to be considerably smaller than Lassen suggested (Tan, 2012).

The mechanism behind the relationship between BP and cerebral autoregulation involves changes in cerebral perfusion pressure (CPP) and cerebrovascular resistance (Tzeng and Ainslie, 2014). CPP is defined as the difference between intracranial pressure and systemic blood pressure, whereas cerebrovascular resistance is the resistance of flow in the cerebral vessels. Cerebral arteries alter vascular tone in response to changes in transmural pressure. When transmural pressure decreases, the vessels vasodilate. Whereas when it increases, the vessels vasoconstrict. This ensures that autoregulation is maintained within the upper and lower limits. There are two types of assessment to manipulate BP to assess cerebral autoregulation, static (steady state) and dynamic (transient). Static autoregulation relies on cerebrovascular resistance and absolute linear changes to flow/velocity versus changes in pressure. Typically, static autoregulation measures several minutes to hours while correlating the steady state relationship between

CBF and BP. Dynamic autoregulation refers to the relationship between acute beat-to-beat changes to both CBF and BP during transient changes. This could be manipulated through a change in posture, a cuff inflation or changes in CO_2/hypercapnia (Tiecks et al., 1995). Despite the concept of cerebral autoregulation determined by BP being well established, there is still speculation into the mechanisms driving this relationship. A combination of metabolic, myogenic, neurogenic and endothelial factors is thought to be interacting to create this paradigm. There is currently also no 'gold standard' for measuring dynamic cerebral autoregulation (Claassen et al., 2016) and a variety of techniques have been used in previous studies. Studies manipulate BP with the idea that CBF will react to the change and will return to the original value. The faster to return, the more adequate the cerebral autoregulation. BP can be manipulated using bilateral thigh cuffs, the periods of inflation produce supra-systolic levels. But the reliability of this method is questionable, along with induced periods of discomfort for individuals. To minimise this discomfort repeated squat-stand manoeuvres can be used to assess cerebral autoregulation. However, in clinical populations, especially the critically ill, the manipulation of BP using these techniques is not possible.

2.2.4 Neurovascular Coupling

Neurovascular coupling or functional hyperemia is another main aspect of autoregulation. It is a mechanism which is preserved during sleep or under general anaesthesia. Regulatory mechanisms are used to control the brain's high metabolic demand. CBF is coupled with neuronal activation and cerebral metabolism (globally and regionally) to ensure an adequate delivery of oxygen over a wide range of perfusion pressures (Junejo et al., 2019). The mechanisms ensure adequate neuronal function. There are increases of blood flow to regions in which neurons are active, this response is called hyperaemia. It was initially thought that a fall in oxygen or glucose concentration (a metabolic signal) triggered an increase in blood flow. However, this has become obsolete.

The discovery of the glutamate neurotransmitter-mediated signalling plays a major role of the regulation of CBF. This leads to a release of nitric oxide from neurons and of arachidonic acid which is controlled by astrocytes. During rest, CBF is paired with cerebral metabolic oxygen rate. Furthermore, during sympathetic nervous system activation, CBF is increased at a greater rate compared with cerebral metabolic rate for oxygen (Udomphorn et al., 2008), leading to a decrease in cerebral oxygen extraction. During neuronal activity, CBF is independent of local tissue levels of oxygen (Mintun et al., 2001).

The exact mechanisms responsible for neurovascular coupling are not well established. The cerebral blood vessels have a close relationship between the smooth muscle wall, neurons and glia, making them unique from other arteries (Willie et al., 2014). When the supply of oxygen, glucose and nutrients is adequate, the state of the pericytes and smooth muscle is basal tone. Outside this range neurotransmitter-mediated signalling controls are regulated by a reduction or increase in oxygen modulates (Attwell et al., 2010). The astrocytes release vasoactive substances causing hyperpolarisation in the pericytes and vascular smooth muscle. The cells either vasodilate (release of nitric oxide, arachidonic acids or adenosine) or vasoconstrict (release of endothelin or thromboxane) (Muoio et al., 2014). In a number of pathologies impaired neurovascular coupling can be seen such as hypertension, stroke and Alzheimer's disease (Girouard and Iadecola, 2006). Impaired neurovascular coupling can lead reduced cerebral vasodilatory reserve through vasodilation of the cerebral arterioles. Visual stimulation can be used to assess neurovascular coupling. Using TCD to isonate the posterior cerebral artery, the magnitude of the response to a visual stimulation is used to assess neurovascular coupling.

2.2.5 Cerebrovascular Responsiveness to CO_2

Cerebrovascular reactivity is described as the ability of the cerebral vessels to constrict or dilate in relation to vasoactive stimuli such as the partial pressure of arterial

carbon dioxide (PCO_2) (Favre et al., 2020). This is an imperative homeostatic mechanism thought to maintain central pH, regulate breathing and cellular function (Ainslie and Duffin, 2009). Previous research has suggested that the cerebral vasculature is highly sensitive to changes in PCO_2 (Willie et al., 2014). During hypercapnia cerebral arteriolar vasodilation occurs, this increases CBF to inhibit the rise in PCO_2. Conversely hypocapnia leads to vasocontraction (Ainslie and Duffin, 2009). This sensitivity is unique to the cerebrovascular system commencing in the large arteries in the neck through to the large intracranial arteries, pial arterioles and parenchymal vessels (Willie et al., 2012). Previous research studies have employed TCD to monitor MCAv and to examine the effects of PCO_2 to the middle cerebral artery, posterior cerebral artery and basilar artery. These studies have suggested a 3-6% increase and/or a 1-3% decrease in flow per millimetre of mercury change above and below eupnoeic PCO_2 (Skow et al., 2013, Battisti-Charbonney et al., 2011). Suggesting the magnitude of the response to hypercapnia is greater than hypocapnia. This also applies to the internal carotid artery and the vertebral artery in studies using Duplex ultrasound (Sato et al., 2012). The mechanism behind cerebrovascular responsiveness to CO_2 remain theoretical. The vascular endothelium appears to be responsive to changes in pH or PCO_2. Prostaglandins and nitric oxide induce vasodilation due to an increase in shear stress (Ainslie and Duffin, 2009). There is also sensitivity to changes to PO_2 bellow ~50 mmHg (Willie et al., 2012). In states of hypoxia, CBF appears to increase to counteract the reduction in oxygen. Ultimately, the exact mechanisms associated with cerebrovascular responsiveness to CO_2 are currently speculative.

Cerebrovascular responsiveness to CO_2 reactivity is typically assessed in a seated or supine position. There are several ways to assess cerebrovascular reactivity. The Valsalva manoeuvre involves a moderately forced attempt to exhale against a closed airway. This method can be dependent on participant characteristics such as lung size,

age and gender which can impact the CBFv response (Fierstra et al., 2013). PCO_2 can also be manipulated through rebreathing exhaled gases using an exhaled gas reservoir and gas sensors. The favourable method is to use an externally supplied gas with a higher concentration of CO_2 (2-7%). However, these methods can be difficult to perform in clinical settings on critically ill, sedated patients but changes in PCO_2 are clinically important to monitor during extracorporeal circulation.

2.2.6 Acid-Base Balance and Cerebral Blood Flow

As discussed previously, CBF is reliant on an integrative relationship between arterial pH, PCO_2, and cerebrovascular tone. With a great importance placed on the impact of PCO_2 on CBF (Drapeau et al., 2021). Now, pre-clinical studies have suggested that bicarbonate (HCO_{3-}) may also directly influence intracellular pH and smooth muscle cell contractility (Caldwell et al., 2021a). Suggesting changes occurring in the bicarbonate buffering system may impact CBF. An essential part of homeostasis is the regulation of pH in the blood, which needs to be maintained within 7.35-7.45. This is largely dependent on how many hydrogen ions are present in the blood. The bicarbonate buffering system ensures that pH is maintained within these limits and can be explained through the equation below:

$$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_{3-}$$

During an increase in carbon dioxide (CO_2) the molecules bind to water (H_2O) in the blood which then produces carbonic acid (H_2CO_3). Carbonic acid is a weak acid which means it is partially dissociated to give hydrogen ions. Once this happens, HCO_{3-} is also produced, this is a reversible chemical reaction. Levels of $CO_2 + H_2O$ are regulated through changes to lungs (i.e increased exhalation when CO_2 accumulated). Whereas $H^+ + HCO_{3-}$ are regulated through the kidneys (adding/reducing the levels of bicarbonate in the blood). Overall, this demonstrates a very close relationship between CO_2, bicarbonate

(HCO_3) and pH, all of which regulate cerebral autoregulation. This explains why changes in CBF have been found in clinical population with disrupted acid-base balance such as chronic obstructive pulmonary disease. During acute acidosis or alkalosis there are alterations in arterial PCO_2, HCO_3 and pH which are now recognised as the proximal compartment of cerebral autoregulation which changes vascular smooth muscle cells, thus regulating CBF (Caldwell et al., 2021a).

The notable study from Caldwell et al., (2021), which was the first study to find evidence in humans of a direct vasodilatory changes in the cerebral vessels mediated through HCO_{3-}. It concluded that during acute metabolic alkalosis, CBF was regulated by PCO_2 rather than arterial pH. This was due to CBF being continuously matched with PCO_2, with no changes in CBF following an infusion of a hypertonic solution of sodium bicarbonate ($NaHCO_{3-}$). However, during a $NaHCO_{3-}$ with PCO_2 remaining constant, there was an observed rise in CBF (~7%). It is key to highlight this study only included young adult men. There have been studies which have investigated CBF and HCO_{3-} in clinical paediatrics populations. A bolus of $NaHCO_{3-}$ led to a linear increase in CBF in patients with hypoplastic left heart syndrome (HLHS). The effects of HCO_{3-} on cerebral vasculature are through to be more predominant in a sedated population. An increase in HCO_{3-} led to an increase in pCO_2. It is well established that an increase in pCO_2 leads to an increase in CBF. Specifically, an increase in pCO_2 elicits shear stress induced vasodilation of the vascular smooth muscle walls via endothelial nitric oxide synthase activation, resulting in increased CBF (Caldwell et al., 2021b). In awake populations this increase in pCO_2 can be cleared through increased breathing. However, in sedated populations this is unable to occur as breathing is usually mechanically regulated. Therefore this may make the response to HCO_{3-} more predominant in these populations (Buckley et al., 2013).

2.2.7 Cerebral Blood Flow Velocity and Neurological Deficit in Paediatrics Patients

In the early postnatal period, the human neonatal brain far exceeds the adult brain in terms of CBF demands (Vutskits, 2014). Brain development and maturation is a complex process which relies on cellular and molecular events at specific time points. This begins at the third week of gestation and continues into adulthood (Stiles and Jernigan, 2010). In the first year of life brain volume increases over 100% and an additional 15% after the second year (Knickmeyer et al., 2008). The brain's rapid development and high metabolic demand during childhood, make the paediatric brain susceptible to damage (Georgieff et al., 2018). This early period has been identified as a hallmark of brain development (Stiles and Jernigan, 2010), making damage at this time detrimental in the long term. Autoregulation in the paediatric brain has also been described as fragile and immature (Greisen, 2005), making the developing brain susceptible to ischaemia, during periods of severe hypotension and haemorrhaging during periods of hypertension. Normative CBFv and autoregulation is poorly defined in healthy neonates and paediatrics, with sparse data available around CBFv in paediatric critically ill populations. This is surprising due to the documentation of neurological deficit paediatric critically ill populations throughout lifespan, which can start as early as childhood (IJsselstijn and van Heijst, 2014). By school age a high percentage of children who had experienced an episode of critical illness as a neonate or infant perform at a lower level than their healthy counterparts (Knoester et al., 2007). This deficit includes lower academic achievement, behavioural problems, speech impediments, poor fine and gross motor skills and higher incidences of learning disabilities (Marelli et al., 2016).

2.2.8 Summary

There are several specific populations at risk of neurological deficit which will be explored in the following sections of the literature review. These include paediatrics with

cardiac and/or respiratory problems stabilised using extracorporeal membrane oxygenation, and patients with congenital heart disease undergoing surgery to repair the aortic arch which also includes extracorporeal circulation.

2.3 Critical Care Procedures and Cerebral Perfusion

2.3.1 Acute Respiratory Failure

Respiratory distress affects approximately 7% of neonates born at term and is a leading cause of admission onto a paediatric intensive care unit (PICU) (Reuter et al., 2014). Respiratory distress is characterised by abnormally low levels of oxygen, difficulties breathing and cyanosis (a bluish cast to the skin and mucous membrane). Respiratory distress can progress into acute respiratory failure which is a prominent cause of morbidity and mortality amongst neonates and infants (Engle, 2008), with a survival rate of ~35-50% (Dalton et al., 2015). Acute respiratory failure is defined as a common complication following cardiorespiratory disease and exacerbations of chronic respiratory disease (Creagh-Brown, 2016). There are several treatment options available for acute respiratory failure. These are dependent on the patient, symptoms and responses to previous treatments. The use of pharmaceutical intervention such as inhaled nitric oxide and surfactant can be a first line of defence (Rimensberger, 2009). Conventional ventilation is another treatment option in which oxygen is delivered through nasal cannulas, facial masks and intubation (Ware and Matthay, 2000). An alternative to conventional treatment is a high frequency oscillatory ventilation (HFOV) which delivers small tidal volumes via an oscillatory diaphragm or piston at high speeds to deliver high levels of positive end-expiratory pressure (PEEP). These treatments usually involve sedation and tracheal intubation, surfactant instillation and extubation. All treatment options may impact CBF. One study investigated the effects of PEEP in patients suffering from acute respiratory failure and suggested PEEP could potentially increase intracranial blood volume, reduce cerebral venous return and that cerebral autoregulation was impaired in 11 out of 20 patients (Schramm et al., 2013). There has been limited investigation into the effects of ventilation types on CBFv in paediatric populations

suffering from acute respiratory failure. This is surprising due to the reduction in oxygen saturations and risk of ischemic injury in this population.

2.3.2 Veno-Arterial Extracorporeal Membrane Oxygenation and Cannulation Types

In cases where patients are unresponsive to conventional treatments for respiratory support, they may be a candidate ECMO (Kane et al., 2010). ECMO is used for cardiopulmonary resuscitation, as a bridge for transplantation/surgery and for the treatment of acute but reversible conditions (Schmidt et al., 2012). This includes acute respiratory and cardiac failure. Survival rates vary between conditions. According to the Extracorporeal Life Support Organisation (ELSO) registry in 2013 the lowest rate of survival was diaphragmatic hernia (51%) compared with the highest being meconium aspiration syndrome (MAS) (94%). Each year in the United Kingdom (Total population 65 million, 15 million children), roughly 200-250 neonates and children receive ECMO support per year (Robinson and Peek, 2015). Of whom, 100 neonates and 45 children receive respiratory support whilst approximately 80 neonates and children receive cardiac support (Robinson and Peek, 2015). During ECMO treatment, venous blood is drained by a central or peripheral cannulation and passed through a membrane to be oxygenated, and carbon dioxide is removed. The oxygenated blood is then returned to the body via a central or peripheral artery (Butt and MacLaren, 2016).

There are two common types of cannulation methods used during paediatric VA-ECMO which are central and peripheral. Patients that are cannulated centrally have venous and arterial cannulas placed through an open chest into the right atrium and aorta. If a patient requires central cannulation, they have significantly impaired cardiac function from both a cardiac output and ejection fraction perspective. This means the brain is solely reliant on the pump for CBFv (Fukuda et al., 1999). Patients cannulated peripherally have venous and arterial cannulas placed into the right internal carotid artery and the right

internal jugular artery. There are noticeable differences in the cannulation methods. Higher flow rates can be achieved using central cannulation as larger cannulas can be used. However, there is a higher rate of infections in centrally cannulated patients due to the requirements of an open chest. This means that patients cannot stay centrally cannulated for long periods of time. Whereas patients cannulated peripherally, can stay on ECMO for longer periods. However, the occlusion of major neck vessels may cause disruption to CBF and cerebral venous hypertension (Weber and Kountzman, 1996). In some cases, the vessels cannot be reconstructed and there is a permanent ligation of the neck vessels. Both types of cannulations methods can directly impact cerebral perfusion during treatment, with a high percentage of paediatric ECMO survivors exhibiting neurological deficit later in life.

There are several factors that can contribute to this deficit, these include pre-ECMO severity of the illness, complications during treatment, ECMO management and patient characteristics (Polito et al., 2013). An analysis from the Extracorporeal Life Support Organisation (ELSO) suggested there are several factors which led to higher levels of neurological risk such as neonates weighing <3 kg, prematurity, those re-cannulated after prior ECMO, those suffering from severe acidosis, those supported with VA-ECMO and neonates that needed CPR prior to ECMO (Polito et al., 2013). Additionally, brain immaturity in general leads to higher susceptibility of neurological complications. Another confounding factor which can impact neurological deficit is the time spent on ECMO. Every 24 hours on ECMO there was a 12% increase in morbidity along with higher hospital stay, higher time duration in ICU, longer length of mechanical ventilation (Gupta et al., 2015). Due to this, clinicians attempt to separate patients from ECMO as early as possible. However, in some cases the patient not ready, meaning they need to be placed back onto ECMO either during weaning or following decannulation. Again, these are factors which can impact CBFv.

2.3.3 The Prevalence of Neurological Deficit in ECMO Survivors

The first successful use of ECMO was documented in 1972 (Hill et al., 1972). This resulted in major blood losses and decades past before ECMO was no longer used as a 'final resort'. Despite the improvements in treatment, ECMO has been associated with a number of adverse neurological side effects (Nasr and Rabinstein, 2015). A follow up study of patients that had undergone ECMO and survived were reassessed at five years old, a key age in the development into school. Motor performance was assessed, and out of 174 children, 22% had died before their fifth birthday, of the survivors 13% were diagnosed with severe disabilities and another 9% had impaired motor development which was either combined with behavioural or cognitive problems (Nijhuis-van der Sanden et al., 2009). In a separate study of 98 previously treated ECMO children at five years old, it was found that 17% had neurological defects with 6% being identified as having a major disability and thus did not undergo the neuro-motor assessment. In the remaining children 15% had motor problems, a further 11% were at risk of developing motor problems later on in life and 14% of the children had cognitive delay (Hanekamp et al., 2006). An issue with previous research into neurological deficit in ECMO patients is that the studies generally use comparison with groups with children that do not have equally severe respiratory stress or critical illness. Nevertheless, the potential reasons for neurological deficit during ECMO should be examined alongside exploration of the processes during clinical treatment that might be able to be monitored to help identify neurological deficit.

2.3.4 Reasons for Neurological Deficit in ECMO-Factors affecting Cerebral Blood Flow

There may be times during ECMO when CBF is disrupted, which could contribute to neurological deficit. During cannulation, cerebral perfusion is temporarily impaired

due to the carotid artery and internal jugular vein becoming ligated (Fenik and Rais-Bahrami, 2009). During the 'weaning' process the ECMO flow rates are reduced over a period of several hours to determine if the infant can survive without ECMO. Nevertheless, no study to date has measured CBFv during these processes. Moreover, during ECMO decannulation, in some cases the arteries and veins cannot be reconstructed, especially if the patient has been on ECMO for prolonged periods. This results in permanent ligation and single sided cerebral perfusion. Potentially the effect of one sided cerebral perfusion may have an impact on these deleterious outcomes such as haemorrhagic and ischemic cerebral lesions (Van Heijst et al., 2004).

The lack of definitive research into the effects of ECMO on cerebral perfusion make it difficult to determine if the underlying cardiac/respiratory issues or the ECMO treatment itself are contributing factors to the neurological issues identified. Presumably both contribute, with many speculative reasons for high levels of deficit in survivors. For example, the ECMO cannulation of arteries may affect the blood flow to the brain and how the brain is perfused by altering pulsatile flow patterns, thus impacting cerebral autoregulation. Additionally, the rate of ECMO flow rates have also impacted on CBF and autoregulation in infants (Papademetriou et al., 2012). Levels of cerebral oxygenation and mean arterial blood pressure fluctuated in 53% of infants undergoing ECMO treatment which subsequently reduced cerebral autoregulation (Tsuji et al., 2000). Moreover, ECMO management itself may also impact CBFv. Anticoagulation parameters are essential for ECMO patients. The blood needs to be thin enough to prevent clots in tubing (Khaja et al., 2010), but viscous enough to prevent excessive bleeding. Anticoagulation is maintained through administering heparin (between 0.3 and 0.7 U/mL), preserving anti-thrombin III levels (>80%) (Agati et al., 2006). The effects of anticoagulation parameters could impact CBFv (Raman, 2017), as blood viscosity has been recognised as an important regulator of CBFv (Akcaboy et al., 2018). The viscosity

is also immediately affected when the blood enters the extracorporeal circulation combined with the effects of anticoagulants. This can potentially lead to hypercoagulations due an inflammatory response (Esper et al., 2014).

2.3.5 Interventions affecting Cerebral Blood Flow Velocity during Extracorporeal Membrane Oxygenation

A percentage of paediatric ECMO patients are exposed to cardiac catheterisation as part of treatment, and this could expose the patients to periods of disturbed cerebral perfusion. Cardiac catheterisation is an invasive diagnostic and interventional technique which can provide information or improve cardiac function and structure. Cerebral infarction levels have been shown to be low during cardiac catheterisation (Hamon et al., 2008, Segal et al., 2001). However the rate in unperceived asymptomatic cerebral injury and cerebral embolisms is an unexpectedly high (Büsing et al., 2005, Lund et al., 2005). Moreover, cardiac catheterisation can also lead to reperfusion injuries after an ischemic period. It has been previously suggested that cardiac catheterisation poses a greater risk to cerebral perfusion than previously thought (Kreeger et al., 2012).

2.36 Measurements of Neurological Deficit in Extracorporeal Membrane Oxygenation

2.3.7 Cranial Ultrasounds

Currently, cranial ultrasound scans can be used to monitor any changes to the white matter, the periventricular leukomalacia and to investigate signs of haemorrhaging. This is used in clinical practise in younger patients with an open fontanelle during ECMO treatment (Bembea, 2013). The major limitation to cranial ultrasounds is that they can only be performed on young paediatric patients with an open fontanelle. It is also noted that measurements of CBFv are not commonly assessed or interpreted during cranial ultrasound scans.

2.38 Magnetic Resonance Imaging

Arterial spin-labelled perfusion magnetic resonance imaging (ASL-pMRI) has been used to measure CBF clinically. The technique magnetically labels arterial blood by two different techniques, either inversion or saturation proximal to the cerebral tissue (Goff et al., 2010). MRI is also able to look at structures of the brain and potential brain injury. However, this cannot be used as a tool to continuously monitor and can only indicate when brain injury has occurred. MRI is also costly and moving critically ill patients is not always practical. It is also not possible to perform an MRI while the patient is on ECMO due to the ferromagnetism of the circuit. But MRI could be a useful tool in assessing neurological injury following ECMO treatment. There has been some studies which have used MRI scans to investigate neurological deficit in ECMO patients. One study investigated the number of abnormal cranial ultrasounds of 50 neonates during ECMO treatment and compared them to post-ECMO MRI findings. It was concluded that during ECMO the head ultrasounds were abnormal in 24% of the neonates. Whereas the number of abnormal MRI scans post-ECMO was 62% (Rollins et al., 2012).

2.3.9 Computerised Tomography Scans

For older children, cranial computed tomography (CT) scans are the gold standard of detecting cerebral infraction or haemorrhaging during ECMO with one study suggesting that at least 25% of ECMO patients have abnormal CT scans (LaRovere et al., 2017). However, usually CT scans require patients to be mobile, which is rarely possible during ECMO. The portable head CT scans are not widely available in clinical settings and transporting ECMO patients is difficult with the potential of decannulation. The findings of previous neurological monitoring research suggest a clear requirement for optimised neurological monitoring during ECMO treatment to prevent/minimise this deficit (Rhee et al., 2018). Taken together, these findings suggest clinical monitoring of

cerebral injuries may be insufficient through NIRS and cranial ultrasounds, which are the current measurement tools employed in clinical practice.

2.3.10 Near Infrared Spectroscopy

NIRS is used clinically during ECMO treatment to monitor cerebral oxygenation levels. A study investigated NIRS values during ECMO cannulation and for at least 48 hours post-cannulation in 17 neonates (Fenik and Rais-Bahrami, 2009). It was found that 12 of the neonates experienced low cerebral tissue oxygenation saturation ($SctO_2$) following ECMO cannulation, one neonate experienced $SctO_2$ levels of <40%. After the onset of ECMO all neonates remained stable and $SctO_2$ levels remained elevated (~60%). In another study it was reported that during carotid cannulation only the right cerebral hemisphere had a reduction in $SctO_2$ levels in three individuals (Ejike et al., 2006). Moreover 10 individuals experienced a bilateral reduction in cerebral oxygenation following carotid cannulation (Van Heijst et al., 2004). Another study found that all of the patients in the study (n=20), had a significant drop in bilateral cerebral oximetry during ECMO treatment, leading to increased oxygenation (Wong et al., 2012). Pre-ECMO factors such as hypoxia, hypertension, hypercapnia can affect cerebral perfusion making the brain vulnerable to blood pressure changes and potential damage. One of the major limitations is that NIRS is only able to measure at a microvascular level of capillaries, arterioles and venules (Benni et al., 2005). Meaning NIRS is unable to measure blood flow in the major arteries in the brain and how the blood is perfused. NIRS is ultimately used as a trend monitor, which can give a clinical suggestion that intervention is needed but interpatient variability is high (Van Bel et al., 2008).

2.3.11 Transcranial Doppler Ultrasound

Transcranial Doppler Ultrasound (TCD) can measure the flow velocity in the major vessels of the cerebral arteries. TCD is currently not used in routine clinical practice

during ECMO treatment. It has been suggested that during ECMO age-specific normal values of cerebral perfusion were outside of normal ranges during full flow ECMO and de-cannulation (Rilinger et al., 2017). Specifically, the values of cerebral perfusion were lower in all major cerebral vessels (middle cerebral artery, anterior cerebral artery and posterior cerebral artery). Another study found that CBFv in the middle cerebral arteries (MCA) was significantly lower in ECMO patients when compared to published normative values for critically ill, sedated, ventilated age matched values in paediatrics (0-18 years). The study investigated 44 paediatrics without neurological injury. Reduced MCAv was found on the first five days of full flow ECMO (O'Brien et al., 2019). Another study measured MCAv using TCD on the first 7 days of VA-ECMO and one additional day following decannulation in 27 paediatrics. MCAv was significantly lower during full flow ECMO compared to normative age matched values. CBFv then increased following decannulation (Rilinger et al., 2017). However, no research to date has previously investigated continuous changes to CBFv and NIRS throughout ECMO treatment, with a focus on the weaning period and recovery following decannulation.

The weaning period may be an important time in which there are fluctuations in CBFv. During the weaning period, the flow rates of the ECMO machine are reduced as the patient's heart and lungs begin to take over full function. This process takes several hours. Weaning from ECMO is not always successful as the patient may need further time on full flow ECMO. In which case the patient may be exposed to time periods of reduced CBFv. There are no set criteria for understanding when a patient may fail a wean. The decision is based on the clinical team rather than empirical evidence. Understanding the differences in CBFv between patients that fail and are successful could lead to rationale for cerebral perfusion to become a factor that could indicate potential success from weaning. Therefore, the focus of chapter 4 is to describe NIRS and TCD throughout ECMO treatment with a focus on the weaning period.

2.3.12 Summary

In summary, patients requiring ECMO are at risk of ischemic brain injury due to disruption in CBFv and cerebral oxygenation. Neurological deficit is prevalent in patients suffering from cardiac and/or acute respiratory failure. The use of TCD could provide more information on daily changes to cerebral perfusion in this cohort and during important times points such as weaning.

2.4 Impact to Cerebral Perfusion during Cardiothoracic Procedures in Congenital Heart Disease

High incidence of neurological deficit is also found in survivors of congenital heart disease (CHD). CHD is usually treated by corrective surgery. There are various reasons that could contribute to neurological deficit including the underlying medical condition itself, pre-treatment conditions, anticoagulation parameters, the treatment and patient characteristics. To perform corrective surgery, patients are placed onto cardiopulmonary bypass (CPB) which may also include periods of deep hypothermic circulatory arrest (DHCA). It has been well documented that CPB is a challenge for the regulation of CBFv (Rajaram et al., 2020). The sudden changes to pulsatile flow, temperature fluctuations (cooling and rewarming), changes to blood viscosity, low flow rates and periods of total circulatory arrest all present a challenge for cerebral autoregulation. Previous research has suggested that those with left sided lesions exhibit the highest and most severe levels of deficit (Kaltman et al., 2005). This includes hypoplastic aortic arch, interrupted aortic arch and hypoplastic left heart syndrome. It is key to note that survival rates of these patients have dramatically increased over the years due to advances in surgical palliation and knowledge of the conditions/treatment available. Due to the high levels of neurological injury found in this population, the focus has moved towards improving quality of life for these patients. A better understanding is needed regarding how aspects of surgery may compromise CBFv and potentially how it can be prevented/monitored effectively and is the focus of chapter 5 of the thesis.

2.4.1 Congenital Heart Disease

Congenital heart disease is associated with multiple risk factors and the aetiology may not be specific to one deformity. It has been estimated that of 1000 live births approximately 8-12 will have a cardiovascular malformation (Hoffman et al., 2013).

Infants born with CHD often weigh less, have small head circumferences, exhibit respiratory distress and are born cyanotic (Lee, 2010, Matthiesen et al., 2016). In most cases following birth, neonates with CHD need surgical treatment which usually occurs within the first few months of life. Research studies suggest that later in life survivors of CHD can have impaired neurological development (Morton et al., 2017). This is because neonates with CHD are at risk of brain injury in the white matter (tissue that connects different regions of the brain). White matter injury is associated with an impairment in cognitive and motor systems, which are imperative to learning and development. Out of 41 term newborns with CHD, 32% had white-matter injury measured using MRI, compared with none in a control group of healthy neonates (Miller et al., 2007). Cardiac arrests are also common in patients with CHD (Lynge et al., 2018). The severity of the cardiac arrest can also cause injury to the structures of the brain due to a deprivation in nutrients and oxygen.

2.4.2 Neurological Development and Congenital Heart Disease

The advances in surgical palliation have increased the survival rates dramatically in CHD. Despite these advances it has been identified that these patients are at high risk of neuro-motor, cognitive and psychosocial problems. Due to this improvement in mortality rates, there has been a shift in research focus from improving survival to improving quality in life (Morton et al., 2017), through reducing post-natal neurological sequelae. Research predominately uses psychological evaluations and neuroimaging to assess neurological outcomes. The neurological issues impact most profoundly during school when language, mathematics, organisation, memory and visuospatial skills are needed (Bellinger et al., 2011). A child behaviour checklist was completed by parents of 155 children between the ages of four and eight that had undergone neonatal corrective surgery for CHD. The surgical repair involved deep hypothermia with predominantly total circulatory arrest or predominately low-flow continuous cardiopulmonary bypass.

20% of the children had scores of clinical concern on the child behaviour checklist along with academic challenges at the age of 8 (McQuillen and Miller, 2010). This altered brain development has been suggested to begin as early as the foetal period which may then get progressively get worse due to a number of associations, such as cardiac surgery (McQuillen and Miller, 2010). There is a small number of research studies which have reported reduced CBF and oxygen delivery in the CHD foetus (Kaltman et al., 2005), which may indicate that neonates with CHD have inherently lower CBF prior to surgical repair.

2.4.3 Aortic Arch Repair

Aortic arch repair is a term used to describe several procedures which involve increasing the diameter of the aortic arch. These conditions are characterised by aortic coarctation with or without posterior arch hypoplasia (Gargiulo et al., 2008). This includes patients suffering from hypoplastic aortic arch, interrupted aortic arch and hypoplastic left heart syndrome. Patients undergoing aortic arch repair are particularly at risk of cardiovascular complications and neurological deficit (Donofrio and Massaro, 2010). Historically, all the sections of the aorta had been successfully repaired by the 1950's except the aortic arch, this was due to the issues surrounding stopping the flow of blood to essential organs (Coselli and Green, 2009a). During that time attempts to repair the aortic arch were unsuccessful until the development of cardiopulmonary bypass (CPB) with an early form of antegrade cerebral perfusion. This led to a successful repair of the aortic arch, although mortality rates and incidences of neurological complications in those that survived were high. There are subtle differences in how an aortic arch repair is performed. Usually, the approach is based on surgeon/centre preference rather than scientific rigour.

2.4.4 Hypoplastic Left Heart Syndrome

Neonates born with a congenital heart condition named hypoplastic left heart syndrome (HLHS) require surgery which carries high morbidity and mortality risk. Before the 1980's HLHS was uniformly fatal (Goldberg et al., 2000). Typically, those suffering from HLHS are born with a severely underdeveloped, non-functioning left ventricle and aorta. Typically, during the foetal stage the right ventricle is functioning as the left ventricle. After birth the patent ductus arteriosus closes, causing blood flow to diminish, which without intervention can lead a lack of blood flow to vital organs. HLHS is usually diagnosed early using obstetrical screening ultrasounds. This early diagnosis leads to an initial stabilisation period and precautions are put in place ready for birth. Some centres use cardiac transplantation as a treatment, but the most common treatment is staged therapy. This involves staged surgery to provide the patient with a single ventricle circulation. The Norwood procedure is the first of this staged surgery performed shortly after birth. The operation attempts to increase the aortic arch and make the right ventricle the main pumping chamber. A fenestration is placed between the ventricles, allowing free flow. A shunt is also attached to allow blood to flow to the lungs (Ohye et al., 2010). Brain MRI was used before and at a median of 9.5 days after surgery in patients undergoing the Norwood procedure. It was found that commonly before surgery some patients had cerebral ischemic lesions primary due to pre-treatment conditions associated with CHD. However, following surgery this increased with most patients exhibiting cerebral ischemic lesions (Dent et al., 2006). This high incidence of cerebral injury makes the monitoring of cerebral perfusion essential in preventing cerebral deficit.

2.4.5 Potential Disruptions to Cerebral Blood Flow Velocity during Aortic Arch Repair

2.4.6 The Adverse Effects of Cardiopulmonary Bypass

Cardiac surgery requires a bloodless field. To achieve this the patient is placed on CPB machine sometimes known as a heart and lung machine (Sarkar and Prabhu, 2017). The heart is isolated from the rest of the body through a cross-clamp placed on the ascending aorta. The CPB machine takes over control of blood circulation and gaseous exchange in the lungs. The CPB machine drains blood from the venous cannulas in the right side of the heart where it enters a reservoir. Drugs can be mixed with the blood and sent to an oxygenator for gaseous exchange. The blood is then heated, filtered and returned generally to the aorta (Machin and Allsager, 2006). Cerebral injury is prolific factor during bypass, with time spent on CPB a confounding factor (Brown et al., 2000). In paediatrics metabolic indicators of neurological injury are increased following CPB which include glutamine, myoinositol and decreased N-acteylaspartate (Lee et al., 2008). CPB causes an inflammatory response and subsequently leads to damaging effects (Bronicki and Hall, 2016). These can include mechanical shear stress, tissue ischemia/reperfusion, hypotension, non-pulsatile perfusion, and haemodilution with relative anaemia (Kozik and Tweddell, 2006). Due to their higher metabolic demands, immature organ system and reactive pulmonary vasculature, infants are more susceptible to an inflammatory response (Kozik and Tweddell, 2006). Additionally, for neonates the circuit is often between 200-300% greater than the patient's circulating blood volume which also adds to an inflammatory response (Caneo et al., 2018). It is possible that this inflammatory response may contribute to a disruption in CBFv.

The temperature changes used during CPB also impacts cerebral perfusion. Previous research into core body temperature changes and CBFv in healthy adults has suggested that with a one degree increase in core body temperature there is a 10-15%

change in MCAv (Bain et al., 2013). Therefore, the use of hypothermia during CPB directly effects CBFv, metabolic activity and the cerebral metabolic rate of oxygen. During cardiopulmonary bypass it was found that 24% of patients had impaired autoregulation and during re-warming patients experienced hypothermia (Joshi et al., 2010b). Finally, separation from CPB has also been found to lead to high incidences of hyperperfusion, cerebral ischaemia and embolisms (Ohmae et al., 2007). Overall, there are many factors associated with CPB which can disrupt CBF. This may be more predominant in paediatric populations which is why it is imperative research is conducted in these patients.

2.4.7 Blood Viscosity Changes during Cardiac Surgery

According to Poiseuille's equation, haemodynamic equilibrium is determined through viscosity, pressure, flow artery and vessel diameter (Çinar et al., 2001), all of which are affected during cardiac surgery. Viscosity is defined as the resistance of a fluid against flow. Flow rates are directly manipulated by the CPB machine. Oedema formation is also common complication that impacts the viscosity of the blood during CPB. Patients undergo a process called modified ultrafiltration (MUF) to remove excess water in the blood, reduce the need for a blood transfusion, filter inflammatory markers and improve post-CPB organ function (Ames, 2019). MUF is a procedure which is performed at the end of CPB until the desired haematocrit level is achieved. It works through the retrograded draining of the blood from the aorta down the arterial line and the MUF circuit where haemoconcentration occurs. During which water and low-molecular weight substances are removed from the blood under a hydrostatic pressure gradient (Luciani et al., 2001). Blood is then reinfused into the right atrium. This has been thought to improve postoperative cardiopulmonary function, improve cerebral circulation and oxygenation, increase haemoglobin content and alleviate oedema through reducing inflammatory markers. Conversely, paediatric cardiologists have suggested that MUF may create a left

to right shunt due to the diversion of aortic blood into a high flow, short duration circuit. This in turn may decrease affect CBFv and perfusion along with the drastic changes to blood viscosity that are occurring. To reduce the duration of MUF high flow rates are often used. This could be potentially problematic, especially in infants weighing <10kg. Draining from the aorta can lead to a reduction in the carotid circulation and thus reduced CBFv, this has been labelled as 'cerebral stealing' (Medlin and Sistino, 2006). Moreover, the rapid intravascular and hemodynamical changes can lead to an imbalance which could also be affecting the cerebral circulation.

2.4.8 Anaesthesia and Cerebral Blood Flow

It has been suggested that at high doses volatile anaesthetics abolish cerebral autoregulation (Oshima et al., 2003). It is accepted that most intravenous anaesthetics lead to a reduction in cerebral metabolic rate of oxygen ($CMRO_2$) and CBFv. Whereas volatile inhalational anaesthetics lead to an increase in CBFv and a decrease in $CMRO_2$. Typical neonatal sedation during cardiac surgery consists of midazolam and fentanyl along with inhaled sevoflorane. Sevoflorane is inhaled as it is cardio-depressive which is why it is used in small doses and combined with intravenous agents. It was suggested that sevoflorane is associated with intact cerebral autoregulation even at high doses (as high as 1.5 minimum alveolar concentrations). A study investigating sevofloride found that it increased CBF (25%) and decreased $CMRO_2$ (37%) in adults anaesthetised with fentanyl and midazolam (Oshima et al., 2003). In healthy children, 0.5, 1.0 and 1.5 minimum alveolar concentration (MAC) sevofloride did not lead to significant changes to CFBv over a 90 minute period (Fairgrieve et al., 2003). Conversely, after an inspired concentration of sevofloride resulted in a 17% decrease in CBF in older adults undergoing elective open valve surgery (Reinsfelt et al., 2011). This appeared to be due to a vasodilatory response that led to a partial loss of flow metabolism coupling. It is important

to highlight other anaesthetic agents were used during the surgery along with mild hypothermia which could also be contributing to the reduction in CBFv.

It has been suggested that midazolam decreases CBF through a decrease in cerebral metabolic rate in oxygen. A study compared midazolam and propofol in relation to cerebral autoregulation. It suggested that cerebral dynamic autoregulation was maintained following only midazolam administration through a decrease in transfer function gain in low-frequency range (Ogawa et al., 2010). In preterm neonates a bolus dose of midazolam (0.1mg/kg) led to a mean decrease in CBFv from baseline by 12% five minutes after administration, this decrease was not significant from baseline. After five minutes CBFv returned to baseline values (Harte et al., 1997). Conversely, it has been suggested that midazolam has minimal effect on CO_2 reactivity, CBF and blood oxygenation (Kiviniemi et al., 2005). When comparing fentanyl and propofol in adults undergoing normothermic CPB, it was found that fentanyl lead to significant lower jugular venous oxygen haemoglobin saturation but neither lead to postoperative cognitive dysfunction (Kadoi et al., 2003).

2.4.9 Neuroprotection during Aortic Arch Repair

The above literature suggests that there are many confounding factors that can impact cerebral perfusion during arch repair. Several neuroprotective techniques have been developed, such as keeping complete circulatory arrest to a minimum (<45 minutes) (Andropoulos et al., 2003). Circulatory arrest was the first technique to be widely used for aortic arch repair (Griepp et al., 1975). However, this led to a high number of neurological issues following surgery. Therefore, cooling the patients was implemented to further protect the brain. Theoretically, hypothermia reduces metabolic activity. It has been suggested that cooling should cease when the temperature in the oesophagus has reached 10°C to 13°C and oxygen saturation above 95% in the jugular venous bulb, this

indicates maximal metabolic suppression (McCullough et al., 1999). Cooling should be more than 20 minutes with the ideal being 30 minutes or above to prevent gradual up-drift. Additionally, the head should be packed with ice to prevent an increase in cranial temperature during surgery (Griepp, 2001).

The rewarming stage is also important to protect the brain. Rewarming should be gradual and should avoid sudden high perfusate temperatures. Haemodynamics should also be closely monitored during theatre and in the postoperative period (approximately 8 hours) to ensure appropriate oxygen delivery. Specifically, during lower temperatures the stat management should be switched from Alpha stats to pH stats. It was concluded that pH stats led to higher levels of CBFv during paediatric cardiac surgery at lower temperatures (figure 2.2). This corresponds with findings of a study which investigated the stat management of 52 patients. Those that underwent pH stat management had increased jugular venous oxygen concentrations, which implied an increased in CBFv (Kiziltan et al., 2003). Other research investigating NIRS and pH stat management found that pH stat management led to greater levels of cerebral oxygenation (Sakamoto et al, 2004). Antegrade selective cerebral perfusion with moderate hypothermia is another neuroprotective technique used during cardiac surgery, which has reduced mortality compared to hypothermic circulatory arrest (Taşdemir et al., 2002). This technique has been shown to be advantageous as it allows a longer interval of safe circulatory arrest. The low flow supplying of oxygen and nutrients maintains appropriate levels of oxygen metabolism while the body is hypothermic. This is the most time consuming technique, however has been shown to lead to the higher levels of adequate cerebral protection (Hagl et al., 2001). Especially when compared to previous techniques such as retrograde cerebral perfusion (Okita et al., 2001).

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Figure 2.2 Cerebral blood flow and cerebral blood flow velocity with Alpha vs pH stat management during cardiopulmonary bypass (Polito et al., 2006).

2.4.10 Measurements of Cerebral Perfusion during Aortic Arch Repair

2.4.11 Near Infrared Spectroscopy

Due to the volume of confounding factors which may affect CBFv during cardiac surgery, the need for continuous monitoring of cerebral perfusion is essential. Currently NIRS is used operatively to monitor cerebral perfusion, to guide the flow rates of CPB and post-operatively to identify adverse outcomes (Andropoulos et al., 2003, Phelps et al., 2009). A study investigated cerebral perfusion using NIRS in neonates undergoing the Norwood procedure. Ischemic lesions were identified using pre and post MRI scans. It was suggested that before surgery ischaemic lesions occur in approximately 23% of

infants, and that after surgery 73% of infants had new or worsened ischaemic lesions (Dent et al., 2006). It was also concluded in the same study that there is an association between ischaemic lesions and low postoperative brain regional oxygen saturation (rSO_2)(<45%). These lesions are associated with behavioural issues later in life. A study measured neurological development at the age of four to five of children that had previously undergone treatment for HLHS (Hoffman et al., 2013). It was concluded that those with low NIRS levels 48 hours postoperatively were at risk of neurological deficit in childhood. A major limitation to the current clinical practice is the sole reliance on NIRS as a method for measuring cerebral perfusion during cardiac surgery. Specifically, NIRS cannot detect hyperperfusion and cerebral embolisms exacerbated by ischemia/reperfusion injuries which are a primary cause of perioperative brain injury (Hogue Jr et al., 2006).

2.4.12 Transcranial Doppler

TCD can overcome some of NIRS shortcomings such as its ability to detect hyperperfusion. In a study which implemented TCD during cardiac surgery for 29 patients, they concluded TCD was able to identify perfusion abnormalities early to prevent neurological consequences in four patients, it also identified three patients that had periods of hyperperfusion. It was also able to guide perfusion rates (Catena et al., 2013). Additionally, a case study measuring CBFv during aortic arch repair of a 10-day old neonate found that during DHCA both TCD and cerebral oxygenation levels decreased to near zero at two time points (Busch et al., 2016). This suggests that during aortic arch repair patients are exposed to times of extreme reductions to CBFv and consequently oxygenation. There is a clear disruption to CBFv during aortic arch repair. However, no research to date has described both NIRS and TCD throughout aortic arch repair with a focus on temperature changes between two groups (20 and 25°C), which is the focus of Chapter 5 in present thesis.

2.4.13 Summary

In conclusion previous research has suggested that many components of aortic arch repair pose a threat to maintaining CBFv and cerebral autoregulation. In depth cerebral perfusion monitoring during the entire procedure is warranted.

2.5 Chapter Summary

The literature suggests that extracorporeal circulatory support has an impact on CBF that likely contributes to neurological deficit. Given that a larger number of patients are surviving following neonatal extracorporeal circulatory support, an enhanced understanding of the changes in cerebral perfusion required and is thus the focus of the present thesis.

Chapter Three: Experimental Methods

3.1 Introduction

This chapter will give a detailed overview of measurements used to assess cerebral perfusion in clinical populations and the limitations to each method. Specifically, the focus was to measure cerebral oxygenation through near infrared spectroscopy (NIRS) and cerebral blood flow velocity (CBFv) using transcranial doppler ultrasound (TCD). The chapter will explore normative values of these measurements in healthy and clinical populations. The chapter also included data to demonstrate that the operator of TCD from the thesis collected accurate measurements which are comparable to previous published data, in both healthy and clinical paediatrics. This chapter had several aims which included, firstly to give a detailed overview of the current measurements of cerebral perfusion in clinical populations which were used throughout the thesis, this was achieved through reviewing previous literature. Secondly, to establish if the middle cerebral artery (MCA) was accurate isonated using TCD by a sole sonographer in a healthy paediatric population. Finally, to compare values of cerebral blood flow velocity in a clinically ill, paediatric population to previously published ventilated values.

3.2 Literature Review of Cerebral Perfusion Measurements

3.2.1 Measurements of Cerebral Perfusion in Clinical Populations

Measures of cerebral perfusion can provide information of the functional status of the blood vessels, which can indicate cerebrovascular health. Clinically it can be used to ensure patients at risk of ischaemic injury have adequate perfusion to reduce the risk of long-term neurological deficit. In adult patients assessments of cerebral perfusion using transcranial doppler (TCD) can detect and diagnose intracranial arterial steno-occulsive disease and vasospasm (Aaslid et al., 1984, Felberg et al., 2002). While paediatric populations have previously been used to identify risk of stroke in children with sickle cell anaemia (Adams et al., 1990, Adams et al., 1998). More recently, assessing cerebral perfusion has identified patients with traumatic brain injury, hydrocephalus, intracranial hypertension, cerebrovascular disorders, central nervous system infection and stroke (LaRovere and O'Brien, 2015). There are several factors in clinical paediatric settings which can globally affect CBFv such as anaemia, increased cardiac output, changes in body temperature, elevated pCO_2 and the use of drugs which can have cerebral vasodilator responses (Bor-Seng-Shu et al., 2012). There are several ways cerebral perfusion can be recorded in clinical paediatric settings.

3.2.2 Near Infrared Spectroscopy

The current method used in clinical practise to measure cerebral perfusion is near infrared spectroscopy (NIRS). Glenn Millikan developed optical methods which were originally developed to measure muscle oximeter in the 1940's (Ferrari and Quaresima, 2012). Following this it was highlighted that brain activity is associated with physiological events such as changes in the optical properties of brain tissue which could be assessed using these techniques. In 1977 the near infrared (NIR) range enabled a real time measurement using a non-invasive technique to detect haemoglobin oxygenation

using trans-illumination spectroscopy (Jobsis, 1977). Consequently in 1985, NIRS was used in some of the first human cerebral oximetry studies (Ferrari et al., 1985). NIRS works on the principle that the biological tissue is relatively transparent to light at wavelengths of 700-1000 nm which is the near infrared spectrum (Pellicer and del Carmen Bravo, 2011). The NIRS monitor can produce near-infrared light using laser diodes at the spectrophotometer which is then carried across the tissue via fiberoptic bundles to the distal end known as the optode (Murkin and Arango, 2009). Reflection, absorption and scattering are principles that NIRS relies on to determine oxygenation levels. There are two different approaches to measuring cerebral oxygenation using NIRS. Firstly, NIRS can be used to measure oxygenation from one side of the forehead to the other, which can be positioned as a straight trajectory. The second approach is through an angular arrangement on the same side of the forehead which is a diffused trajectory. The straight trajectory is usually suitable for neonates and infants as it can be used to assess global brain perfusion and oxygenation whereas the angular simply provides regional information of the brain. The first application of NIRS in clinical research was to transilluminate a neonatal head (Brazy et al., 1985). This is now used in routine clinical practice such as in PICU, cardiac theatres, ECMO, acute respiratory failure and traumatic brain injury. NIRS is also used to estimate cardiopulmonary bypass flow rates during cardiac surgery. The advantages of NIRS in a paediatric clinical setting is that it is non-invasive, robust, does not require frequent calibration and once placed on the forehead does not need to be moved (Steiner et al., 2009). It can safely provide continuous measurements of cerebral oxygenation.

The figure originally presented here cannot be made freely available via LJMU E-Theses Collection because of copyright. The image was sourced from (Davie and Grocott, 2012).

Figure 3.1 Image of the Fore-sight NIRS monitor. Adapted from (Davie and Grocott, 2012).

3.2.3 Limitations of Near Infrared Spectroscopy

Currently near infrared spectroscopy is used clinically to monitor cerebral oxygenation. NIRS is a non-invasive estimation of regional tissue haemoglobin oxygenation saturation in the frontal lobes (Hyttel-Sorensen et al., 2015). However, NIRS is only able to measure oxygenation at a regional level (frontal lobes) and cannot fully convey information on blood flow within the main vessels of the brain. Accordingly, an injured brain could potentially show normal levels of oxygenation during periods of ischaemia. Additionally, it has been noted that there is great inter-device variability, issues related to what is absolute versus relative saturations, variability of oxygen saturation targets and thresholds, equating to a lack of confidence in clinical settings (Grocott and Davie, 2013). Another inherent issue with NIRS is its reliance on the algorithm that cerebral blood is 15% venous and 25% arterial, as this has not been verified within paediatric populations. It was also reported that following the induction of a hypocapnia-ischaemia through the inflation of a pneumatic head cuff on the forehead, there was a significant reduction in three different types of NIRS monitors. Suggesting that NIRS values do not solely reflect cerebral oxygenation alone as extracranial tissue desaturation led to a reduction in NIRS values (Davie and Grocott, 2012). Despite these

shortcomings, NIRS has been suggested to assist in the detection of low-flow states in paediatric patients at risk of ischaemia (Mittnacht, 2010). Research has found NIRS to be useful in adult cardiac surgery, paediatric cardiac surgery and now intensive care settings (Chan et al., 2017, Mittnacht, 2010, Desmond and Namachivayam, 2016). NIRS has been suggested to be an indication of low CBF rates and has been linked to long term cognitive development. Research into long term implications of low NIRS values has suggested in paediatric populations lower values are associated with lower developmental scores at 2 years old in preterm infants (Alderliesten et al., 2014).

3.2.4 Transcranial Doppler Ultrasonography

Another method of measuring cerebral perfusion is transcranial doppler ultrasound (TCD). The principle of Doppler ultrasound was first suggested by Christian Johann Doppler in 1842, however it was initially limited due to the inability to penetrate the skull. It wasn't until 1982 when a lower-frequency (1-2 MHz) ultrasound was used to measure CBF velocities (CBFv) in the vessels of the circle of Willis (Aaslid et al., 1982). This became known as TCD which is now widely used as a non-invasive ultrasound technique which is able to measure real time CBFv in the middle, anterior and posterior cerebral arteries (Verlhac, 2011). Acoustic windows in the skull are used to measure the speed and direction of blood flow in the intracranial arteries. An ultrasound probe is used to send a pulsed Doppler ultrasonic beam to an artery of the circle of Willis, where moving red blood cells scatter sound energy which is reflected back to the probe. This Doppler-shift is then proportional to the velocity of the blood (Willie et al., 2011). TCD can be used to isonate the middle cerebral artery (MCA), anterior cerebral artery and posterior cerebral artery. These blood vessels are distinguishable through differences in depth, mean and peak velocities. These can be found in table 3.1.

Table 3.1 Transcranial doppler velocities of the middle cerebral artery in healthy, awake children through the temporal window (Truemper and Fischer, 1993).

Age	Depth	Mean Velocity (cm/s)	Peak Systolic Velocity (cm/s)	End-diastolic Velocity (cm/s)
0-10 days	25	24 (±7)		
11-90 days	25	42 (±10)	46-75 (±15)	12-24 (±8)
3-12 Months	30	74 (±14)	114 (±20)	46 (±9)
1-3 Years	35-40	85 (±10)	124 (±10)	64 (±11)
3-6 Years	40-45	94 (±10)	147 (±17)	65 (±9)
6-10 Years	45-50	97 (±9)	143 (±13)	72 (±9)
10-18 Years	45-50	81 (±11)	129 (±17)	60 (±8)

3.2.5 Limitations of Transcranial Doppler

TCD has its own inherent limitations. A major limitation to TCD is that it is unable to obtain two-dimensional B-mode ultrasound of the vessel. Without vessel diameter, you cannot measure CBF (absolute metric flow) but rather the velocity of the red blood cells, with only the larger cranial vessels able to provide adequate images. Due to this TCD can only give a global indication of cerebral perfusion as these larger blood vessels are provide the oxygenated blood to the large regional areas of the brain. However, the Hagen-Poiseuille law can be applied to CBF, which states flow in a rigid tube is:

$$F = P * \pi * r^4/8 * \eta * l$$

P is the difference between the pressure at the beginning and at the end of the tube. r is the radius of the tube. η is the viscosity of the fluid and l is the length of the tube, the relation between the flow and the velocity (v) is:

$$F = v * \pi * r^2$$

From the previous formula and from the Hagen-Poiseuille law we can obtain:

$$v = P * r^2/8 * \eta * l$$

These formulas suggest that flow in a vessel is dependent on both the flow velocity and the radius of the vessel. Velocity itself is dependent on the viscosity of the blood (hematocrit), perfusion pressure and the radius of the vessel. If we assume that MCA diameter remains unchanged, the assumption is that changes in velocity equate to changes to flow velocity (Polito et al., 2006). There is evidence that has suggested that vessel diameter does change. But in clinical populations such as those undergoing cardiopulmonary bypass for cardiac surgery, it has been reported that the MCA does not significant change in diameter (Van der Linden et al., 1991).

Another major limitation of TCD is the measurement is operator dependant, which requires knowledge of the cerebrovascular anatomy. This makes the widespread clinical of transcranial doppler potentially difficult, especially for long term, continuous use and in emergency situations. Additionally, in 10-15% of the population, adequate signals are unable to be obtained relating to the porosity and thickness of the temporal bone (Tsivgoulis et al., 2009), however this is not usually an issue in neonates.

Currently there are few studies which have investigated normative data in 'healthy' paediatric populations. From the few studies normative data can be found in table 3.1. CBFv varies throughout childhood, starting at birth. This is also a time in which the paediatric brain is developing rapidly and is vulnerable to ischemic injury for several reasons. Following delivery autonomous nervous system is in a hyper-sympathetic, and drastic changes to the cardiovascular system occur as the neonate is become independent from their mother's circulation. This happens in stages. Firstly, heart rate and respiration decrease while diffuse motor activity reaches its peak then diminishes. The second stage respiration becomes irregular with potential incidences of apnoea and a large variation of heart rates (Theorell, 2002). The foramen ovale closes due to difference in pressure between both sides of the heart. This can take several weeks and in approximately 15-

20% of the population this does not happen at all. This transition to an independent respiratory and circulatory system leads to potential haemodynamic instability, carrying a greater risk of cerebral hypoxia and hyperoxia (Hyttel-Sorensen et al., 2015). There is also an increase in PO_2 and subsequently, a decrease in PCO_2 due to the onset of respiration, leading to a reduced pulmonary vascular resistance. The difference in the decrease in pulmonary vascular resistance and increased systematic vascular resistance results in left to right shunting through the patient ductus arteriosus (PDA) and generally stops after the third postnatal day. CBFv continuously rises after birth until the age of between 6-8 years, then a decline until 18 years old consistent with normal adult values (table 3.1).

3.2.6 Methodological Considerations for measuring Cerebral Blood Flow in 'Healthy' Paediatric Populations

There has been limited studies investigating cerebral autoregulation in 'healthy' paediatric populations (Greisen, 2005). In neonates and infants, the direct manipulation of blood pressure is unattainable which could be accountable for the lack of research into the immature brain. Early studies suggested that in full term, stable neonates without an evidence of brain injury, there is a pressure-flow reactivity, suggesting that static autoregulation is intact (GREISEN, 1986, Pryds et al., 1990). Following this, a study measured cerebral autoregulation using NIRS in neonates born between 24 to 34 weeks. It was concluded that the lower threshold for autoregulation in these neonates was less than 30 mmHg (Tyszczuk et al., 1998). Furthermore, in preterm (median 24 weeks or 60% gestation) there was no association between CBF (measured using NIRS) and blood pressure change (Noone et al., 2003). From the few studies investigating autoregulation in neonates, it was suggested that static autoregulation was intact even in those without evidence of cerebral autoregulation. But the number of studies is sparse and lacking consistency.

3.2.7 Methodological Considerations for Measuring Cerebral Blood Flow in Critically Ill Patients

This heightened demand for CBFv throughout childhood makes the paediatric brain more susceptible to damage during critical periods of brain development. There are a small number of studies that have measured CBF velocity in critically ill populations. CBFv is affected in paediatric critically ill populations when compared to 'normal' counterparts. CBFv was measured in children that had undergone a global hypoxic-ischemic event (cardiopulmonary arrest, asphyxial injury and submersion injury). CBFv was measured every day until either post-injury day 8, discharge or death. It was found that by day three, CBFv was above normal where it then declined. Those that had an 'unfavourable outcome', CBFv was significantly higher following a global hypoxic-ischemic event compared to those with favourable outcomes (O'Brien, 2015). This study included a variety of ages (birth to 17 years old) with a relatively small number of patients (n = 26) which makes comparisons and conclusions difficult to draw. Nevertheless, TCD has not been used as a clinical tool to monitor the changes in velocity during surgical procedures or treatment. Another study investigated CBFv in mechanically ventilated paediatrics (table 3.2). CBFv was lower than previously published normal values (O'Brien, 2019). However, this study had limited numbers and the reasons for mechanical ventilation varied. Critically ill populations are incredibly heterogenous populations, taking measurements of around 30 patients cannot represent the entire critically ill population.

Cerebral autoregulation has also been investigated in paediatric critically ill populations. A widely used assessment of autoregulation is to increase inhaled CO_2 while monitoring blood pressure response. In neonates this technique has been shown to be reliable while also monitoring oxygenation levels (Durduran et al., 2010). A common reason for admission into a paediatric critical care unit is cardiac arrest. Previous research

has suggested following a cardiac arrest various organs recover from global ischemia, including the brain and the heart, this takes weeks (Sundgreen et al., 2001). This has been associated with a high metabolic demand for glucose and oxygen. The neurovascular unit is disturbed and as a result CBF, autoregulation and metabolism are impaired. Current guidelines suggest that a mean arterial pressure of above 65 mm Hg should be achieved due to a rightward shift of autoregulation following arrest. Dynamic autoregulation was also monitored in clinically ill neonates. The researchers combined the measurement of gradient CBFv response to transient blood pressure. Autoregulation was said to be absent in pre-term and high-risk infants but those that were neurologically classed as healthy but admitted to intensive care were said to have intact cerebral autoregulation (Boylan et al., 2000). A study also examining cerebral perfusion after severe traumatic brain injury found that 12 out of 28 children had impaired autoregulation six months after the brain injury (Vavilala et al., 2006). These cohorts are at high risk of neurological deficit and the rationale for this deficit remains speculative.

There has been a limited amount of research comparing NIRS and TCD in adult populations. It was found in a comparison between NIRS and TCD in healthy adults that NIRS was less sensitive to changes in cerebral perfusion during hypercapnia but not hypocapnia (Lipnick et al., 2018). In clinical populations involving older adults undergoing carotid endarterectomy, NIRS or TCD was used to monitor cerebral perfusion during the procedure (Cho and Jang, 2017). They concluded that NIRS was a safe and reliable measurement of cerebral perfusion during cardiac surgery. However, the patients in this study were split into two groups and no patients had both NIRS and TCD, therefore the study was unable to directly compare the two measurements. There is limited paediatric studies that have compared NIRS and TCD. Comparing TCD and NIRS in a paediatric population would give an insight into how NIRS could be utilised regarding

changes to flow. Despite previous research using both methods to measure cerebral perfusion, there are limited studies which have directly compared NIRS and TCD.

Table 3.2 Transcranial doppler velocities of the middle cerebral artery in sedated, mechanically ventilated (O'Brien et al., 2019).

Age	Number of Participants	Mean Velocity (cm/s)	Peak Systolic Velocity (cm/s)	End-diastolic Velocity (cm/s)
0-90 days	31	28 (±14)	73 (±21)	19 (±7)
3-12 Months	25	58 (±15)	103 (±24)	30 (±10)
1-3 Years	19	66 (±21)	113 (±32)	39 (±14)
3-4 Years	13	75 (±18)	125 (±28)	45 (±21)
5-10 Years (female)	12	52 (±18)	87 (±28)	33 (±14)
5-10 (male) Years	13	62 (±13)	106 (±26)	38 (±9)
11-17 Years (female)	12	61 (±21)	115 (±45)	35 (±13)
11-17 (male) Years	15	58 (±14)	96 (±25)	38 (±11)

3.3 Methods

3.3.1 Participants

Neonates (n=12) were assessed at Liverpool Women's Hospital. Neonates were born at term and classed as being 'healthy' with no birth or antenatal complications for neonate or mother (see table 3). Patients had a mean age of 2 ± 1 days, body mass 3 .45 ± 0.65 kg and a ratio of 3:9 (males: females). Clinically ill patients were recruited from Alder Hey Children's Hospital which included paediatrics conventionally ventilated (n=6) with a mean age of 57 ± days, and ratio of 4:2 (males:females). Patients supported using high frequency oscillator (HFOV) (n=2) both males with a mean age of 696 ± 968 days and stable cardiac patients >6 months old without ventilatory support (n=3). Sedated patients were clinically stable and free from any conditions which are known to affect CBFv such as increased bilirubin levels.

3.3.2 Experimental Protocol

Using a 2MHz or 4MHz doppler probe and a pulsed transcranial Doppler (TCD) ultrasound system (DWL, Compumedics, Germany), the middle cerebral artery velocity was isonated while patients were at rest. The probe was placed on the temporal window and was adjusted until the MCA was visualised and was then optimised in line with the best practise guidelines (Willie et al., 2011). A continuous measurement was obtained for a minimum of one minute of undisturbed velocity (Healthy n=12, Sedated n =6, cardiac not ventilated n=3). This was repeated for multiple days on the 2 patients in HFOV (9 and 2 days).

3.3.3 Measurements

The temporal window is approximately 1-2 cm above the zygomatic arch and 1cm in front of the external auditory meatus. From here the ultrasonic beam was directed

horizontally, then the depth and sample volume were adjusted until the MCA was visualised using previously published guidelines to assess vessel characteristics. The probes were adjusted until optimal MCAv signal was attained. Real time measurements were observed to ensure probe remained measuring the MCA uninterrupted. The data was also visualised on LabChart Pro version 7 (ADInstruments, Austrailia). Measurements were taken for at least one minute depending on the time and space availability during clinical care. If measurements were able to be performed for longer, than up to three minutes were be taken. The depth and probe placement were maintained in the same position for any repeated measurements. All measurements were recorded on Labchart and then converted into excel where the data was analysed second-by-second.

3.4 Results

Table 3.3 Patient information of 'healthy' patient group.

Age (Days)	Sex	Type of Birth
1	F	Spontaneous normal vaginal
1	M	Induced, normal vaginal
1	M	Non-rotational forceps
1	F	Elective c-section
3	F	Emergency c-section
1	F	Elective c-section
2	F	Spontaneous normal vaginal
1	F	Elective c-section
1	M	Spontaneous normal vaginal
2	F	Spontaneous normal vaginal
2	F	Elective c-section
2	F	Elective c-section

Table 3.4 Information of ventilated patients.

Age (Days)	Sex	Type of Ventilation
1381	M	HFOV
11	M	HFOV
53	F	Conventional
26	M	Conventional
47	F	Conventional
25	M	Conventional
175	M	Conventional
14	M	Conventional

3.4.1 Cerebral Blood Flow Velocity in 'Healthy' and Sedated Neonates

Mean MCAv of the healthy neonatal group was 24 ± 4 cm/s, this falls within previously published normative values for healthy neonates which is defined as 24 ± 7 cm/s (Truemper and Fischer, 1993)(Figure 3.2). The mean CBFv for patients conventional ventilated was 24 ± 2. cm/s, which is low compared to 42 ± 10 cm/s in healthy previously published values (O'Brien et al., 2019) (Figure 3.3). However, this is within the same range of previously published age-matched, sedated, mechanically ventilated paediatrics (28 ± 14 cm/s) (O'Brien, 2019). The HFOV patient aged 1381 days had a mean CBFv of 43 ± 16 cm/s over 9 days, this was low compared to healthy published normal values of 94 ± 10 cm/s, and previous published conventional ventilated paediatrics 75 ± 18 cm/s (Figure 3.4). Mean CBFv for the 11-day old was 23.9 ± 3.3 cm/s (Figure 3.5) which is lower than 'healthy' age matched normative values (42 ± 10 cm/s) but comparable to published previously ventilated patients (28 ± 14 cm/s). The cardiac patients mean CBFv was 30.1 ± 2.6 cm/s which was within normal range (Figure 3.6).

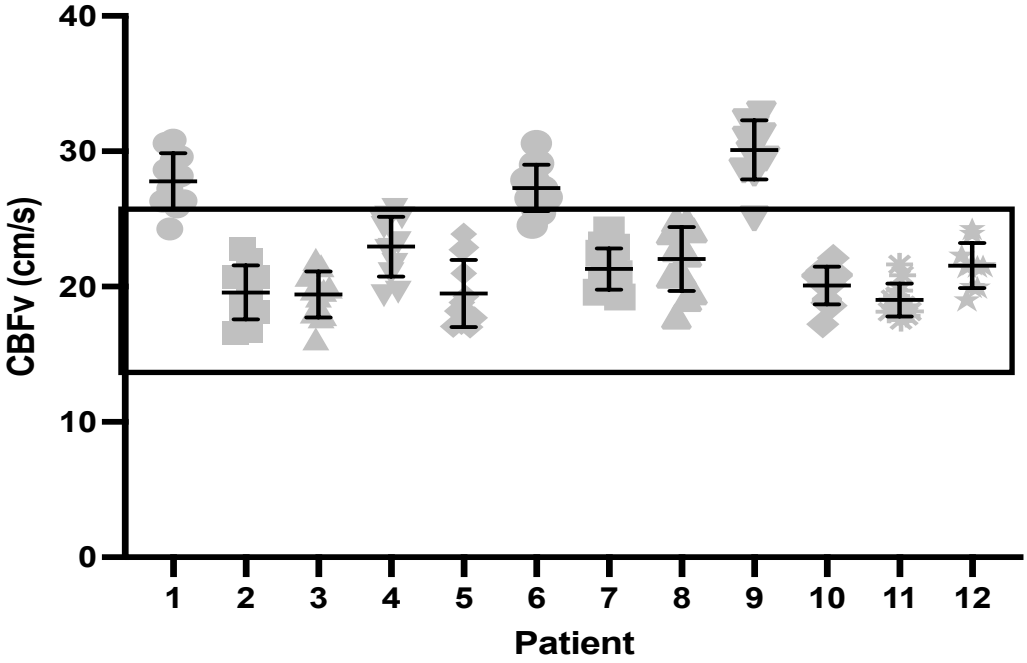

Figure 3.2 CBFv obtained from the temporal window every 5 seconds over one minute for each healthy neonate from the temporal window. Error bars are SD. The box represents the normative previously published range for the same age group (Truemper and Fischer, 1993).

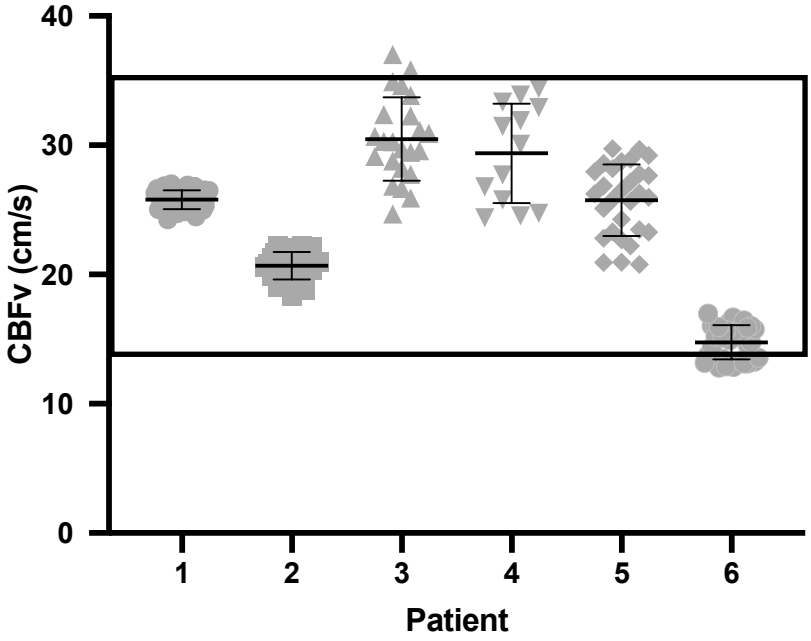

Figure 3.3 CBFv obtained in conventionally ventilated paediatrics from the temporal window every 5 seconds over one minute from the temporal window. Error bars are SD. The box represents the normative previously published range for the same age group.

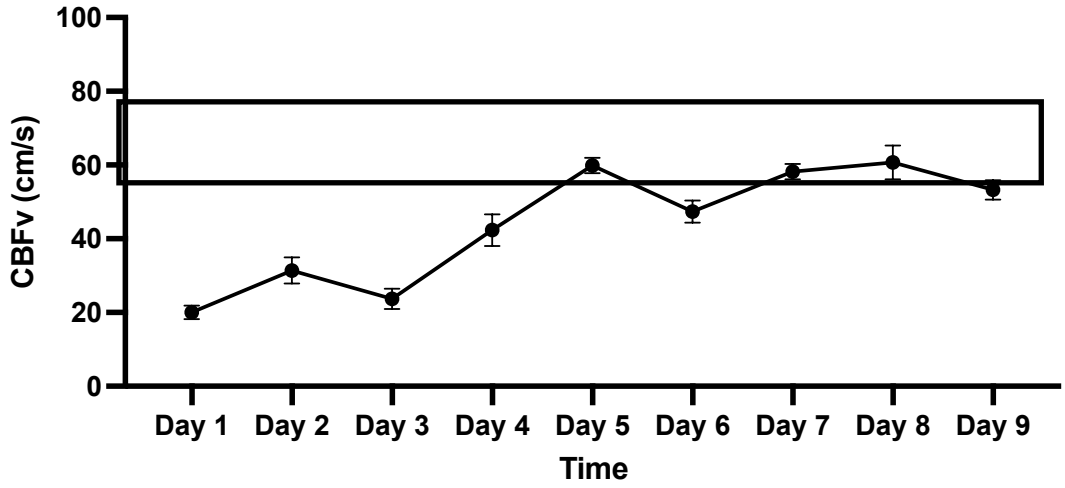

Figure 3.4 One HFOV patient aged 1381 days with CBFv measurements through the temporal window over nine days. Mean and standard deviation is represented using error bars.

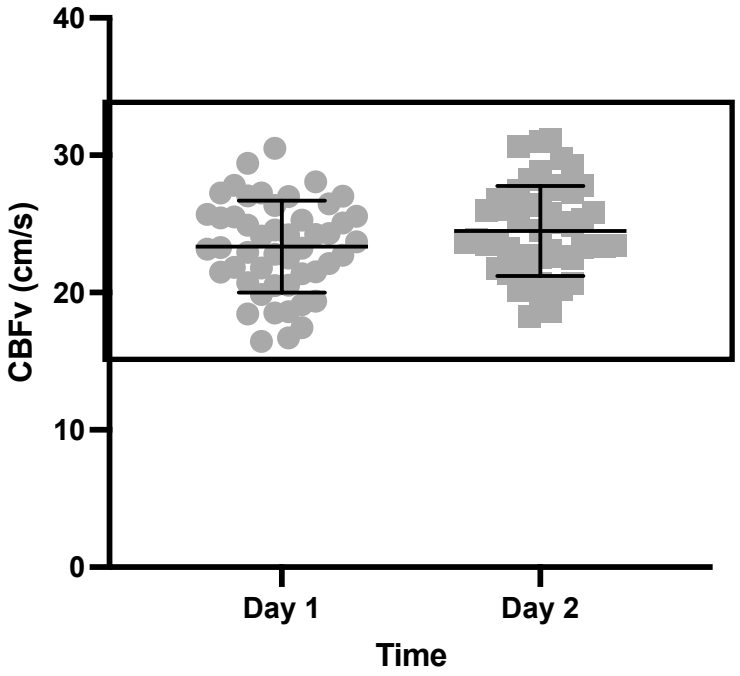

Figure 3.5 11-day old patient supported using HFOV over two days with CBFv measured from the temporal window. Mean and standard deviation is represented using error bars.

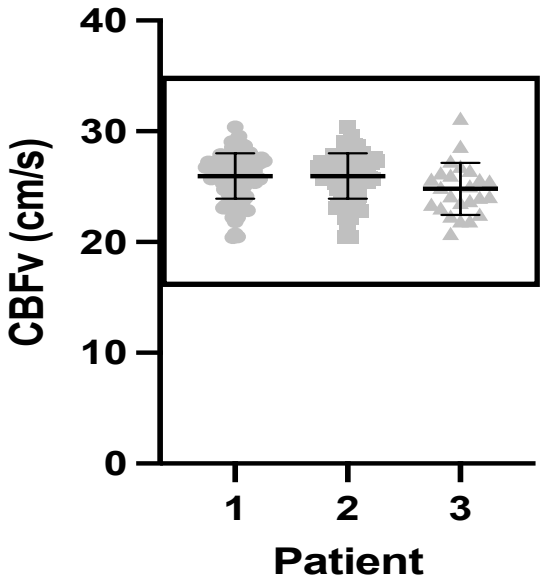

Figure 3.6 CBFv from three cardiac patients for ~one minute from the temporal window in 3 patients <6 months old. Mean and standard deviation is represented using error bars.

3.5 Discussion

This chapter had several aims which included to give a detailed overview of the current measurements of cerebral perfusion used in the clinical practise and research of paediatric clinical populations. The secondary aim was to establish if the MCA was accurately isonated using TCD by a sole sonographer in a healthy paediatric population. This chapter also aimed to compare values of cerebral blood flow velocity in a clinically ill, paediatric population to previously published ventilated values.

Overall, the positives and negatives of TCD and NIRS have been well documented in previous research (Grocott and Davie, 2013). NIRS is only able to give a regional indication of cerebral perfusion in the frontal lobes. This previously has been shown to be a useful tool in clinical populations such during cardiac surgery. Resulting in NIRS being used in routine clinical practise. However, the accuracy of NIRS has been questioned and the confidence in NIRS has been questioned by healthcare professionals. Whereas TCD is able to give a global indication of cerebral perfusion by measuring the blood flow velocity in the major cerebral vessel. When taking these measurements together, it has the capacity to give a more detailed understanding of cerebral perfusion in clinical populations. Through researching both measurements, it may be possible to establish a relationship between the two measurements can give an insight into

Firstly, the MCAv was isonated in a group of healthy neonates (n=12). This data was then compared to previously published normative values in a paediatric population. was within normal ranges when compared to age-matched previously published data (Truemper and Fisher, 1993). Neonates were measured at up to 3 days old. This was chosen as CBFv within the first 10 days is relatively stable (~24 cm/s), but after 10 days this increases rapidly to ~42 cm/s and then continues to do so throughout childhood past normal adult values. Eventually at ~18 years old it reduces to normal adult values where it then remains stable. The comparison to previously published values indicated that

operator was able to correctly identify and obtain data from the MCAv through the temporal window.

Data from a population of critically ill, paediatric patients was also collected. There has been previously published normative data in sedated, mechanically ventilated patients from the temporal window (O'Brien et al., 2019). Values from figure 3.3 are comparable to these previously published values. Again, this suggests that the operator was able to accurately isonate the MCA in a ventilated population. There was one patient ventilated using HFOV that had a lower CBFv than both normative and ventilated normative values. The HFOV patients are harder to directly compare to conventional ventilated patients. Patients are escalated onto HFOV when conventional ventilation is unable to oxygenate the patient sufficiently. Arguably HFOV patient's conditions are worse, with them being less stable and harder to treat. It is key to note that although there appears to be improvements in CBFv in figure 3.4, the patient was withdrawn from treatment. Unfortunately, there is no published data on normative values for HFOV. This may be difficult to establish normative values. These patients as critically ill populations that are heterogeneous. They have unique, individualised treatment pathways, and pre-treatment condition. Making comparisons/normative data difficult to define.

3.6 Conclusion

Measurements of cerebral perfusion through NIRS and TCD were defined in this chapter. NIRS can give an indication of cerebral perfusion through measuring oxygenation at a regional level. Whereas TCD can offer measurements of velocity from a global perspective. Taken together, they can offer an in-depth view of cerebral perfusion in clinical populations. This chapter also aimed to obtain the CBFv within normal ranges to indicate the proficiency of the TCD operator of the thesis. From the data obtained from a healthy neonatal and clinical populations, the mean velocity was within ranges of previously published age-matched research. Overall this suggested that the measurements were taken from the MCA in both populations.

Chapter Four: Cerebral Blood Flow Velocity during Paediatric Extracorporeal Membrane Oxygenation with a Focus on the Weaning Process

4.1 Introduction

Extracorporeal membrane oxygenation (ECMO) is an advanced form of cardiopulmonary bypass (CPB). ECMO provides life support via gas exchange and systemic perfusion. It can allow the heart and/or lungs to rest/recover, as a bridge to transplantation or can stabilise patients following cardiac arrest which is described as cardiopulmonary resuscitation (E-CPR) (Thiagarajan et al., 2007). ECMO was initially used as a 'last resort' treatment in critically ill patients but is now a safe, plausible, clinical tool. Despite improvements in ECMO management, survival rates have remained unchanged for 20 years. It is likely this is due to ECMO being used more frequently and for more increasingly complex medical conditions (Zabrocki et al., 2011).

A high rate of neurological deficit is evident in individuals who have undergone ECMO treatment (Xie et al., 2017). Neuroimaging shows ~10-62% of survivors exhibit neurological deficit (Rollins et al., 2012, Wien et al., 2017, van Heijst et al., 2014). Behavioural studies also show long-term deficit in ~10-60% of survivors (Waitzer et al., 2009, Boyle et al., 2018). For example, in one study of 29 respiratory ECMO survivors, 34% were diagnosed with developmental delay; of which 80% had received ECMO as a neonate, 67% had moderate to severe abnormal MRI, and 33% were classed as having severe ischemic changes. Importantly, even in patients diagnosed without any developmental delay, 18% had abnormal MRI scans (Dhar et al., 2020). This high incidence of neurological deficit in survivors may suggest that the neurological monitoring techniques are inadequate at determining cerebral injury during ECMO treatment (O'Brien and Hall, 2013).

There are a number of potential reasons for the high rates of neurological deficit during ECMO, including the extracorporeal circulation itself (Nomura et al., 2018), the onset of surgery (Wang et al., 2020) and the high number of varying pharmacological

substances the patients are used for prolonged periods of time (Vutskits, 2014). The monitoring of cerebral perfusion and injury can be challenging during ECMO treatment. CT scans cannot be used as ECMO patients cannot be moved and MRI is not possible during ECMO treatment due to the ferromagnetic perfusion circuitry (Xie et al., 2017). Cranial ultrasound can be used to monitor changes in white matter, the periventricular leukomalacia and for signs of haemorrhaging but only in younger patients with an open fontanelle.

In current clinical practise, the index of cerebral perfusion is near infrared spectroscopy (NIRS). NIRS is a bedside tool which can monitor oxygenation in the frontal lobes. A retrospective study investigating NIRS values in 135 ECMO patients found 44% had abnormal findings neurological imaging. Despite the abnormal findings 64% survived to discharge and 83% were considered to have 'favourable' outcomes. In those with 'unfavourable' outcomes, it was found during ECMO treatment NIRS values were >40% and/or they had >20% decline in NIRS values from a baseline (Tsou et al., 2020). In addition, ECMO has also been associated with complications such as cranial haemorrhaging (Le Guennec et al., 2018). This may lead to instances of hyperperfusion which NIRS alone is unable to detect. It is likely that NIRS monitoring alone cannot provide adequate insight into small changes to cerebral perfusion during ECMO treatment. Previous research studies have employed transcranial doppler ultrasonography (TCD) to investigate CBFv during paediatric ECMO. CBFv was lower when compared to healthy age-matched normative values during ECMO even in patients that suffered no clinical apparent neurological deficit while on ECMO, CBFv then increased following decannulation (O'Brien and Hall, 2013). Whereas those that had suffered haemorrhaging demonstrated higher than normal CBFv days prior to clinical recognition of bleeding (O'Brien and Hall, 2013). In a subsequent study by the same research group, CBFv was measured in 18 paediatric ECMO patients (mean age 3.8 ± 7.2 years), although data was

only reported as an average during ECMO and following ECMO. The CBFv values were significantly lower in ECMO patients when compared to published normative values in critically ill paediatric populations not treated with ECMO (O'Brien et al., 2019). It is important to highlight that both aforementioned studies recruited a heterogenous population with ages from 2 days up to 18 years old. They did not report daily measurements during full flow ECMO, weaning or following ECMO decannulation. There was also no record of NIRS measurements (i.e. current clinical practice) to use as a comparison.

The weaning period is an important time point as it is a major challenge to cerebral perfusion. During weaning, ECMO flow rates are gradually reduced over a period of several hours and if patients can maintain sufficient oxygenation without any cardiovascular stress, then a 'bridge' is placed into the circuit. Followed by decannulation onto conventional respiratory support or high frequency oscillation ventilation. This is a process that can take several hours and could potentially be leading to instances where patients are exposed to disturbances in cerebral perfusion. The weaning period is a pinnacle timepoint in treatment where there is a clear need for cerebral monitoring. Despite this, to the authors knowledge there has been no research that has focused on CBFv during the weaning period. Therefore, the aim of this study was to measure CBFv using TCD and NIRS daily throughout paediatric ECMO treatment, including weaning and recovery following decannulation. The secondary aim was to examine the relationship between NIRS and TCD throughout ECMO treatment.

4.2 Methods

4.2.1 Participants

A total of 14 infants were recruited from Alder Hey NHS Foundation Trust. Patients were treated using VA-ECMO for cardiac (n = 6, aged = 85 ± 161 days) or respiratory (n = 8; aged = 70 ± 92 days, weight =) lesions (Table 4.1). Parental informed consent was obtained in two stages. First, consent was obtained to take measurements. After at least 24 hours a second consent form was obtained to use the CBFv data for research purposes. Ethical approval was sought from the NHS Liverpool East Research Ethics Committee (IRAS: 240082). Inclusion criteria were neonates or infants requiring VA-ECMO (<5 years old). Exclusion criteria included those deemed inappropriate by the clinical team and patients suffering from conditions which have been known to affect CBFv including elevated bilirubin levels, sickle cell anaemia and moyamoya disease.

4.2.2 Research Design

Measurements during treatment included cerebral perfusion through a 2MHz or 4MHz doppler probe along with a pulsed TCD ultrasound system (DWL, Compumedics, Germany) and NIRS (ForeSight, Casmed, United Kingdom). Heart rate, mean arterial pressure and ECMO flow rates were all monitored from clinical equipment at Alder Hey Children's Hospital. These measurements were taken at specific time points which included every day on full flow ECMO, where possible during the weaning period (quarter flow, minimum flow and bridge) and once decannulated onto either conventional ventilation or high frequency oscillatory ventilation (HFOV) (Figure 4.1). Due to the nature of the research, taking measurements was not always appropriate due to the potential disruption to medical care. If measurements were taken, then TCD data would be collected for at least one minute, uninterrupted. Timings of measurements can be found for each individual patient on Figure 4.2.

4.2.3 Respiratory Extracorporeal Membrane Oxygenation

Some patients were referred to Alder Hey Children's Hospital from other regional and national centres for respiratory failure after being unresponsive to conventional treatments. Other patients were already receiving treatment at Alder Hey Children's Hospital but did not respond to maximal conventional ventilation methods, including HFOV, so were assessed as potential candidates for VA-ECMO. All patients were already intubated receiving intensive care treatment prior to ECMO initiation. The clinical team for each ECMO cannulation consisted of consultant intensivist, cardiac surgeon, ECMO coordinator, cardiologist and perfusionist who assessed suitability for ECMO in a Multi-Disciplinary Team (MDT). Cannulation was performed in the intensive care unit. All patients were sedated and paralysed before the procedure with an anaesthetic technique involving intravenous administration of fentanyl, midazolam, inhaled servoflurane and rocuronium. Heparin was administered to achieve an Activated Clotting Time (ACT) of more than 300 seconds. Following surgical exposure of the right neck vessels, patients were placed onto full flow VA-ECMO after cannulation of the right internal carotid artery and the right internal jugular vein by arterial and venous cannulas respectively. Once on ECMO, flows were calculated according to body mass of the patient to maintain 150 - 200 ml/kg/min flow.

4.2.4 Cardiac Extracorporeal Membrane Oxygenation

Cardiac ECMO was used in patients with post-cardiotomy syndrome who could not be separated from cardiopulmonary bypass (CPB) circulation following open heart surgery. Some patients suffered a cardiac arrest in the postoperative period and were rescued with VA-ECMO as part of E-CPR. In both groups of patients, ECMO was established centrally via an open chest with cannulation of the right atrium and the aorta with venous and arterial cannulas respectively. The cannulation was either performed in

theatre, following surgery, or in the intensive care unit as part of E-CPR protocol for post-surgery cardiopulmonary arrest.

4.2.5 Weaning from Extracorporeal Membrane Oxygenation

The decision to wean was reviewed daily using several clinical investigations including chest X-Ray, CT scans, lung compliance assessment, hemodynamic changes and echocardiograms. Once the patient indicated signs of improvement, a 'stress' echocardiogram was performed. This involved reducing the ECMO flow rates gradually over the course of 10-15 min, the circuit was then clamped, which allowed the patient's heart and lungs to fully function while an echocardiogram was performed for a few minutes. If the 'stress' echocardiogram showed positive features, a plan for a full weaning trial was made. During the weaning process (see figure 4.1), ECMO flow rates were progressively reduced over a period of several hours (approximately 30-minute intervals) to allow a gradual increase of workload while assessing respiratory and cardiac function. If patients remained stable throughout the weaning phase, once at minimal flow, the circuit was clamped with the ECMO tubing maintaining recirculation flow via a bridge. Therefore, if at any point during the weaning process the patient became unstable, ECMO could be re-established using the same circuit and cannulas. If, on the other hand, the patient remained stable and after a variable time of one-two hours their clinical parameters remained favourable, the cannulas were removed from the neck vessels or the intracardiac chambers, and ECMO support was ceased. Some patients needed additional inotropic support or increase of respiratory support. A small number of patients, once decannulated from ECMO, suffered severe clinical deteriorations needing to be placed back onto ECMO. In some cases, the patient never successfully weaned from ECMO, and the decision was made to withdraw treatment (individual treatment pathways are seen on figure 4.2).

4.2.6 General Principles of Veno-Arterial Extracorporeal Membrane Oxygenation

VA-ECMO drains venous blood through a central or peripheral cannula connected to a centrifugal pump which pumps deoxygenated blood to a membrane oxygenator. The blood is then reinfused at the given temperature into the body via an arterial cannula positioned in a peripheral artery or centrally in the aorta. Target ECMO flow rates are between 150 and 200 ml/kg/min for neonates and infants. Intravenous heparin is administered for anticoagulation purposes to maintain an active clotting time between 180 and 220 seconds. Renal replacement therapy could also be used to aid the fluid balance in presence of oliguria (urine output <0.5ml/kg)

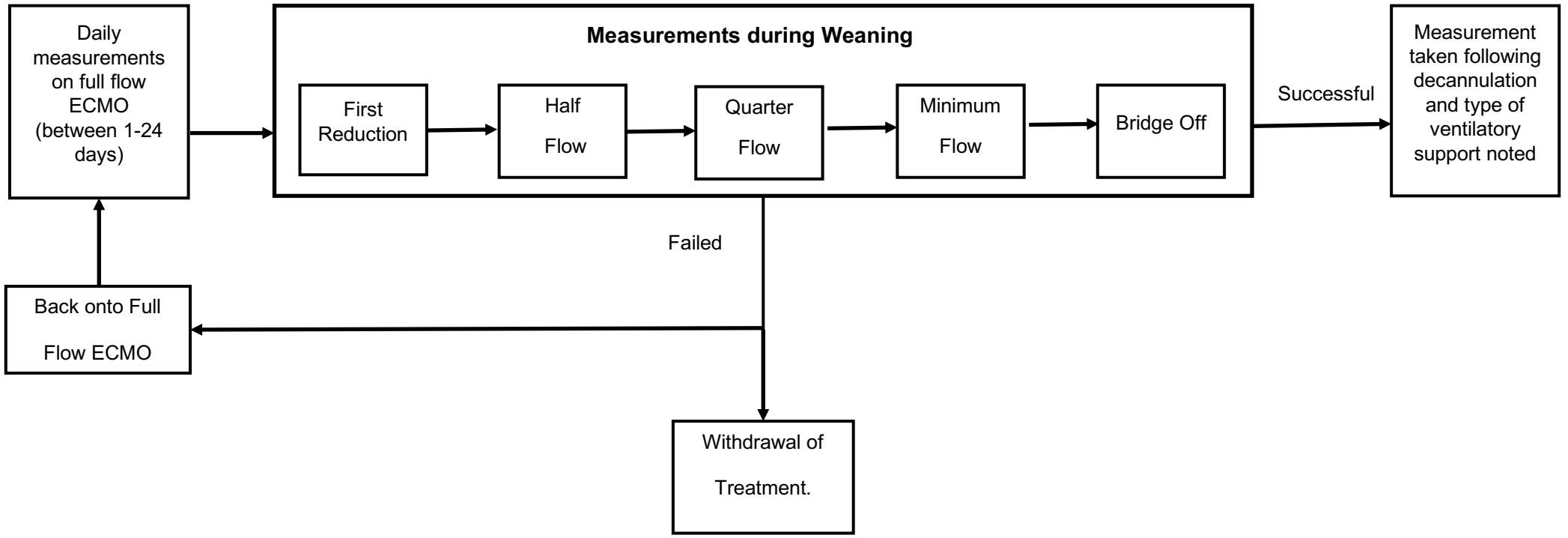

Figure 4.1 Schematic showing the timings of opportunities for measurements of cerebral perfusion following cannulation onto full flow ECMO. If a measurement could be taken, then data would be collected for at least one minute. Measurements began at daily measurements on full flow ECMO. If patients were withdrawn from treatment, then measurements would stop.

4.2.7 Measurements of Cerebral Perfusion

4.2.8 Transcranial Doppler Ultrasound

First, the MCAv was located through the temporal window, which is approximately 1cm above the zygomatic arch and 1cm in front of the external auditory meatus. From here the ultrasonic beam was directed horizontally, then the depth and sample volume were adjusted until the MCA was located. The MCA was identified, using velocity and depth, using the normative values for age and sex. While patients were on ECMO only one side of the head is available to image due to cannula positioning, these measurements were only obtained from one side of the head or from the open fontanelle depending on the age of the patient. If it was taken from the fontanelle, first measurements from the temporal window would be used to confirm the mean velocity of the MCA. The ultrasonic beam was placed in the open fontanelle and directed vertically, and the depth and sample volume were adjusted until the MCA was located.

4.2.9 Near Infrared Spectroscopy

NIRS monitor (Casmed, Foresight, United Kingdom) was used to measure cerebral oxygenation levels through the Beer-Lambert law. NIRS is a non-invasive optical technique where two sensors are applied to the forehead to the left and right of the midline to assess frontal oxygenation levels. Laser-emitting diodes generate light at four different wave lengths (690, 778, 800 and 850mm). Within each sensor there is spacing between the two light detectors which gives both shallow and deep detection of oxygenation with a maximum penetration of ~2.5cm from the emitter. The NIRS monitor relies on an algorithm that cerebral arterial: venous ratio is 30:70. NIRS was continuously monitored by the clinical team to ensure no catastrophic events and to ensure adequate cerebral perfusion. This involved ensuring that a threshold values of >70% with no fluctuation >15%.

4.2.10 Statistical Analysis

The data was explored for normality using quantile-quantile plots. To explore cerebral perfusion changes daily, patients who received the full flow ECMO for the first 5 consecutive days were included in the one factor linear mixed model analysis (n=7). A two-factor linear mixed model was employed to compare cerebral perfusion during the weaning period when the patient was still on full flow ECMO, when the flow rates had been reduced to a quarter of full flow, at minimum flow (one third of full flow) and bridge time points and whether the patient had successfully weaned or failed to decannulated. Follow up post-hoc comparisons were employed to explore significant interactions using the least significant difference approach. Linear mixed models and post-hoc comparisons were analysed using SPSS (SPSS Version 26, IMB Statistics, USA). To examine the repeated measures correlation (rmcorr) between CBFv and NIRS, data collected during any full flow ECMO day was included in the analysis (this was not limited to the patients with five full flow ECMO days). Repeated measures correlation analysis was also performed using the weaning period data (the first reduction, half flow, quarter flow, minimum flow and bridged off). Rmcorr was employed using RStudio statistical package (RStudio: Integrated Development Environment for R, USA). All effects, interactions and correlations demonstrating a p value < 0.05 were considered statistically significant.

4.3 Results

4.3.1 Overall Patient Characteristics

Mean age of the cohort was 81 ± 124 days, with a mean 4.6 ± 2.6 kg and a ratio of females: males 8:6. Overall, patients were cannulated for cardiac support through an open chest (n=8) and or respiratory support (n=6) through the carotid artery and internal jugular vein (Table 4.1). All patients were on ECMO for a minimum of one day and a maximum 24 days (Figure 4.2). 8 patients were successfully weaned off ECMO at the first attempt, 5 patients at the second attempt and one patient were weaned off after a further surgical procedure in theatre. Three patients had two ECMO runs where they were decannulated and then needed re-cannulation for profound haemodynamic instability (n=3). Following successful decannulation patients were supported with either HFOV (n=4) or conventional ventilation (n=7). Two patients were unable to be separated from ECMO. The 30-day mortality was 35%.

4.3.2 Patient Characteristics (Peripheral Cannulation)

Six patients underwent peripheral cannulation with mean age 60 ± 92 days, body mass 3.9. ± 1.3 kg and a ratio of female: males 2:6 (Table 4.1). Patients received ECMO support for the following diagnosis: congenital diaphragmatic hernia, persistent pulmonary hypertension in the neonate and respiratory failure (Table 1). 3 patients (17%) died within 30-day following successful decannulation and 2 (12%) were never successfully separated from ECMO. Extracorporeal cardiopulmonary resuscitation (E-CPR) was used in 4 patients and 4 patients underwent cardiac interventions (figure 4.1).

4.3.3 Patient Characteristics (Central Cannulation)

Eight patients underwent cardiac cannulation. Mean age of the patients was 85 ± 161 days, body mass 5.3 ± 3.6 kg and a ratio of female: males of 4:2 (Table 4.1). Patients

received ECMO support for a variety of reasons including cardiac arrest following cardiac surgery, cardiomyopathy, and E-CPR following cardiac surgery (Table 4.1).

Table 4.1 Individual patient characteristics of each ECMO patient.

Sex	Age (Days)	Weight (kg)	Cannulation Type	Cardiac/ Respiratory	Cath Lab	Surgery	E-CPR	No of Weans	Mortality	Diagnosis
M	8	3.1	Neck	Respiratory	No	Pre	No	2	Yes	Left congenital diaphragmatic hernia, severe PPHN, hypospadiasis
M	406	12.0	Neck	Respiratory	No	No	No	2	No	Adenovirus pneumonia, rhinovirus positive
F	2	2.8	Neck	Respiratory /Cardiac	Yes	Yes	No	1	No	Disconnected pulmonary artery, severe PPHN
M	138	3.4	Chest	Cardiac	No	Post	Yes		No	Myhre syndrome, periarrest with desaturation. AP window, VSD, RVIT, PHTN, sepsis
F	88	7.8	Neck	Cardiac	No	Post	Yes	1	No	Cardiac arrest
M	56	4.0	Chest	Cardiac	No	Post	Yes	1	No	Cardiac arrest
F	274	7.0	Chest	Cardiac	No	Post	No	1	Yes	Pericardial effusion, dilated cardiomyopathy
F	11	3.5	Chest	Cardiac	Yes	No	Yes	0	Yes	Cardiac arrest
M	17	3.3	Chest	Cardiac	No	Post	Yes	2	No	Cardiac arrest
M	29	2.9	Chest	Cardiac	Yes	Post	No		Yes	Cardiac arrest
M	25	3.8	Chest	Cardiac	Yes	Post	No	1	Yes	Cardiac arrest.
F	1	3.4	Neck	Respiratory	No	Pre	Yes	1	No	Congenital right sided diaphragmatic hernia
M		3.3	Chest	Cardiac	Yes	Yes	No	1	No	Cardiac arrest
F	3	3.4	Neck	Respiratory	No	Post	No	1	No	Acute respiratory failure
8 =M 6= F	81 ± 124	4.6 ± 2.6								

PPHN= persistent pulmonary hypotension of the newborn, AP= Aortopulmonary window, VSD= ventricular septal defect, RVIT= right ventricular inflow tract, PHTN= pulmonary hypotension.

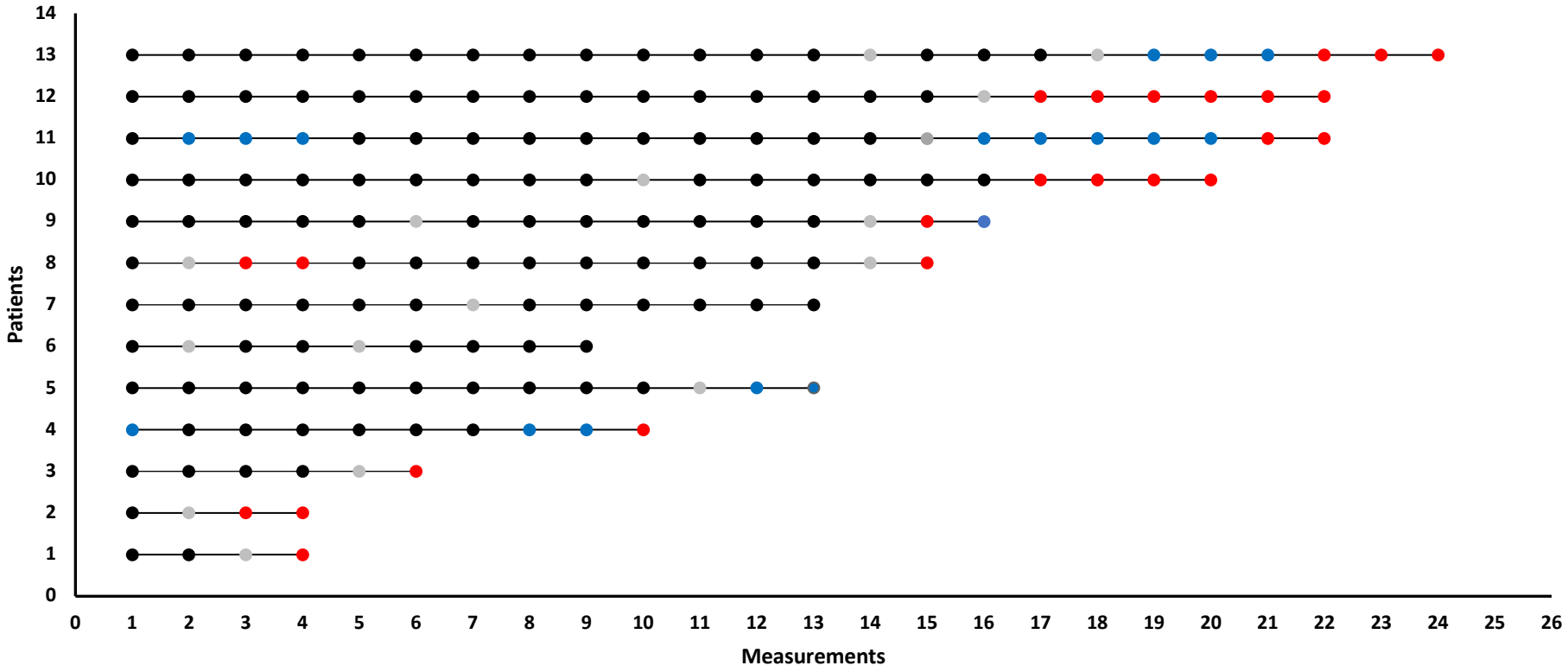

Figure 4.2 Representation of each individual patients ECMO journey. All patients were on ECMO for a minimum of one day and a maximum 24 days. Black circle indicates a day on full flow ECMO, grey circle indicates an attempted wean, red indicates patient decannulated onto conventional ventilation and blue indicates patient decannulated onto HFOV.

4.3.4 Daily Changes in Cerebral Perfusion on Full Flow Extracorporeal Membrane Oxygenation

During the first five days of full flow ECMO (n=8) CBFv and NIRS were similar (main effect of time; $p > 0.54$; Figure 4.3).

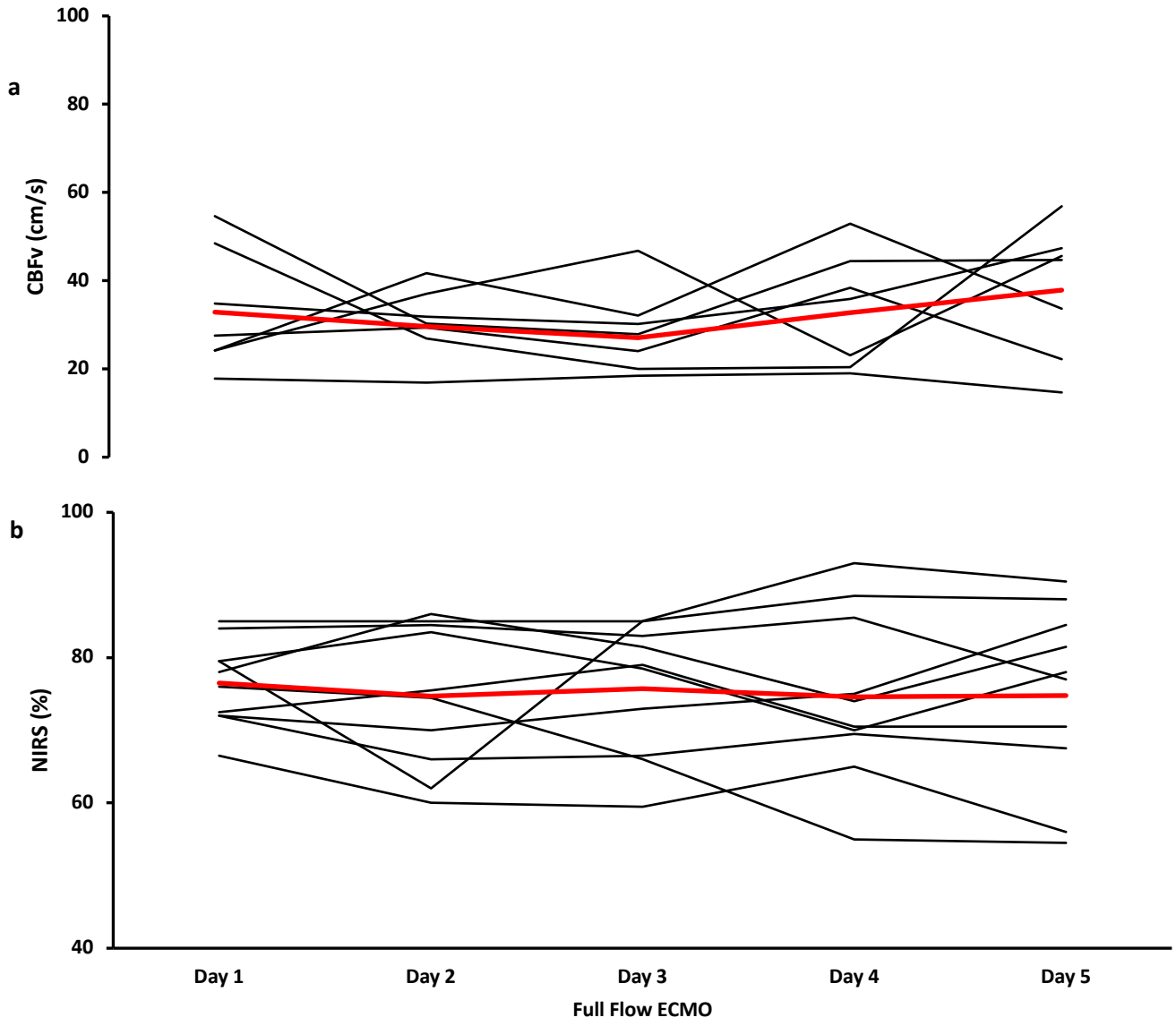

Figure 4.3 Individual CBFv (a) and NIRS (b) values for the first 5 days of full flow ECMO for 8 individual patients. Red lines represent the mean.

4.3.5 Cerebral Perfusion during the Weaning Period

Prior to the weaning period the difference in the two groups at full flow was 1.5 cm/s (15.9, 19.0; p=0.85). During the weaning period (quarter flow, minimum flow and bridge) CBFv was similar (main effect of time: p = 0.67; figure 4.4a). CBFv was on average 9.1 cm/s (0.04, 18.1) higher in those patients who successfully weaned compared to those that failed (main effect of success: p=0.05). There was no interaction between time and success (time*success interaction; P = 0.47). There was no change over time in NIRS (main effect of time; p = 0.92; figure 4.4b), no difference between those successful or failed (main effect of success; p = 0.95) and no interaction between time and success (time*success interaction; p = 0.94). By design, flow rates were reduced over time during the weaning period quarter flow, minimum flow, bridge) (main effect of time: p = 0.001; figure 4.4c) with an interaction (time*success interaction; p = 0.001).

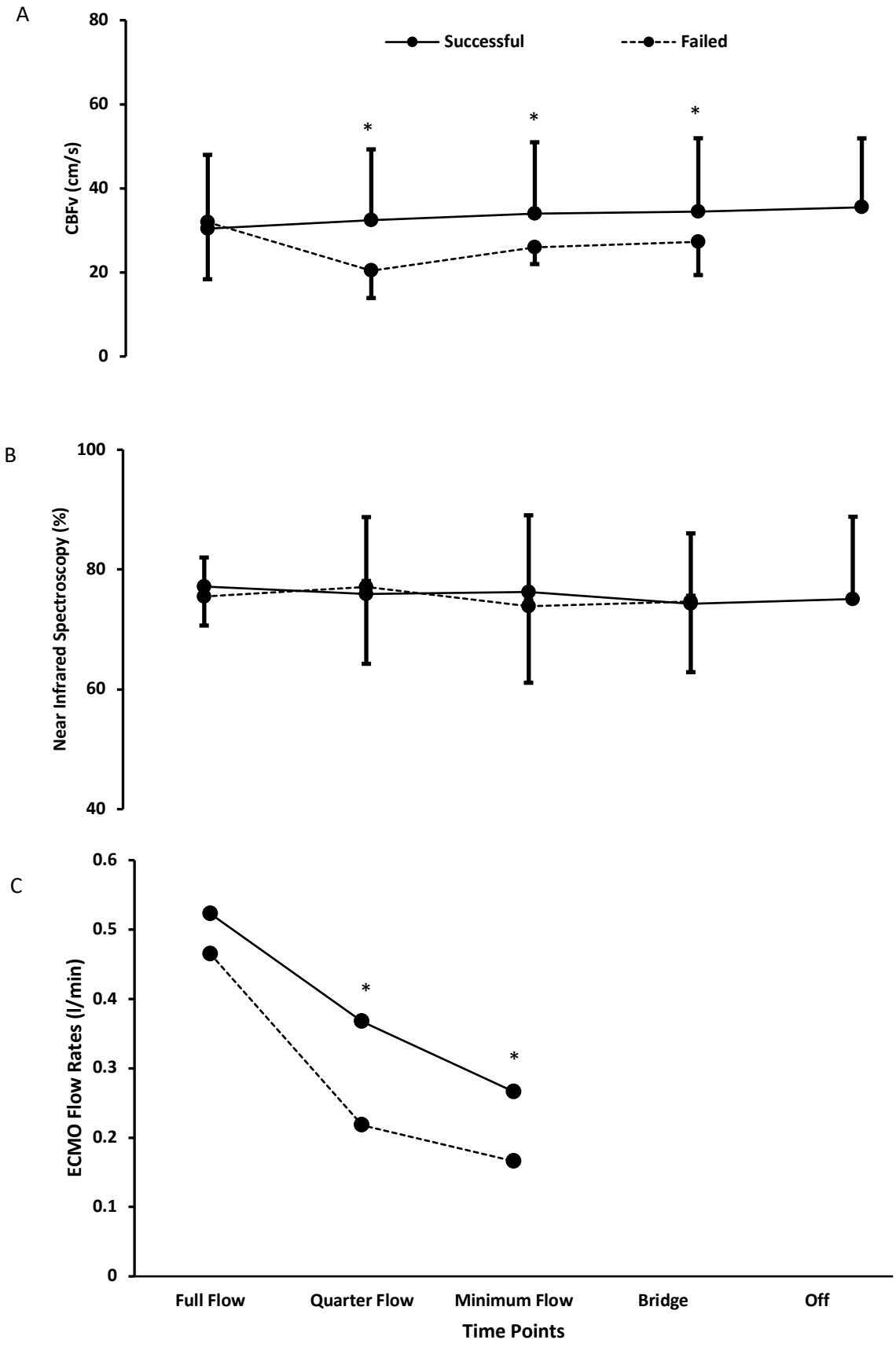

Figure 4.4 CBFv (a), NIRS (b) and flow rates (c) values during the weaning period, separated by those that successful weaned (n= 8) and failed (n=6) (data are mean ± SD).

Heart rate did not change over time with a mean of 141 bpm (132, 151) with those successful having no difference than the patients that failed (p = 0.63; figure 4.5a) and no interaction between time*success (p = 0.51). MAP was not significant during full flow prior to the wean with the mean being 61 mm Hg (53, 69). In the failed group the mean was 65 mmHg (51, 79) and success 57 mm Hg (50, 65). MAP did change overall throughout the weaning period with a mean MAP of 56 mm Hg (52, 61; p = 0.01; figure 4.5b). The mean for those that were successful was 56 mmHg (48, 63) and successful 58 mm Hg (53, 63) with the difference between groups not being significant (p = 0.30). There was no interaction between time*success (p = 0.10).

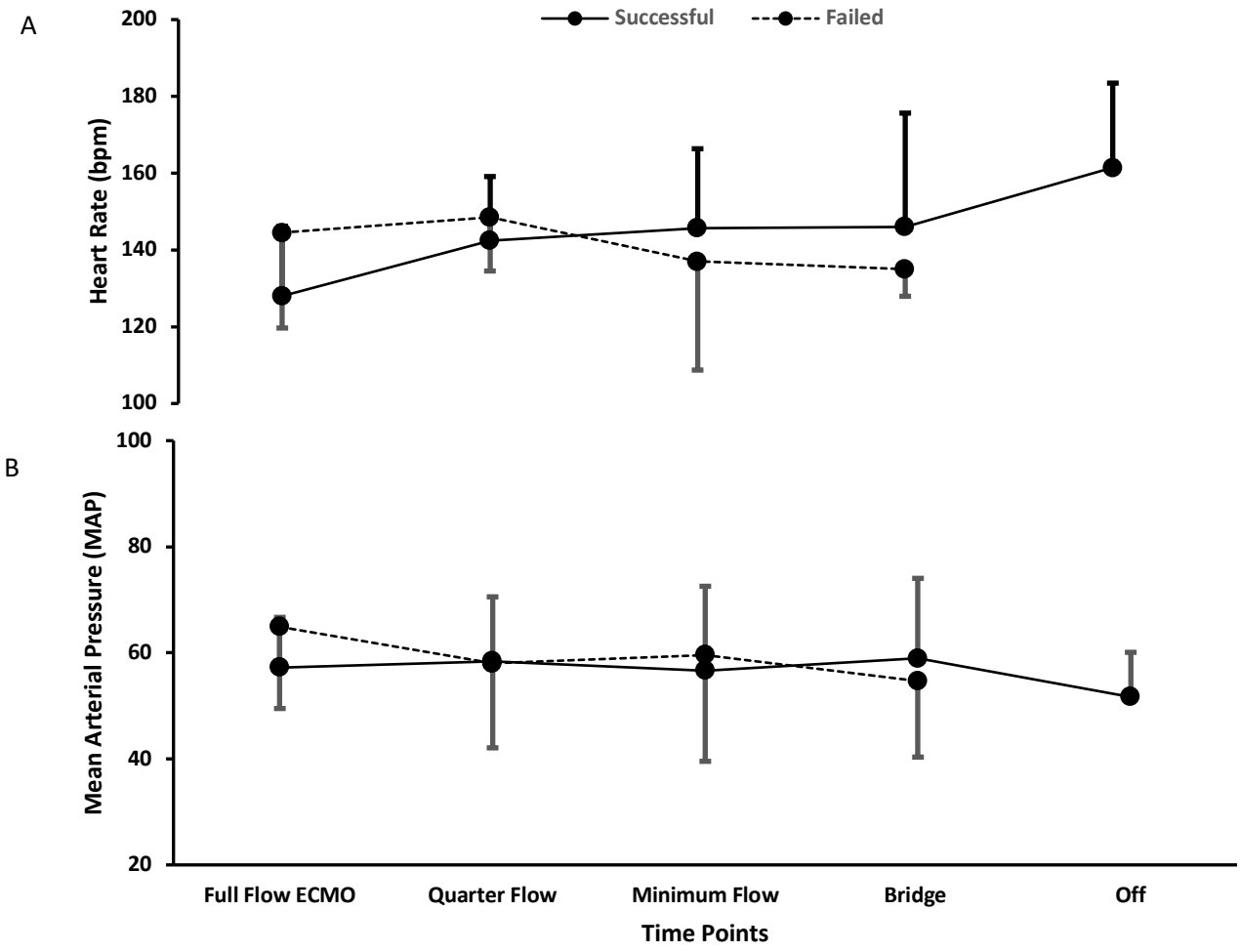

Figure 4.5 Heart rate (a) and MAP (b) values during the weaning period, separated by those that successful weaned and failed (data are mean ± SD).

4.3.6 Cerebral perfusion following Decannulation

CBFv was 14.1 ± 9.9 cm/s higher in those receiving conventional ventilation compared to HFOV following decannulation (p = 0.09; figure 4.6).

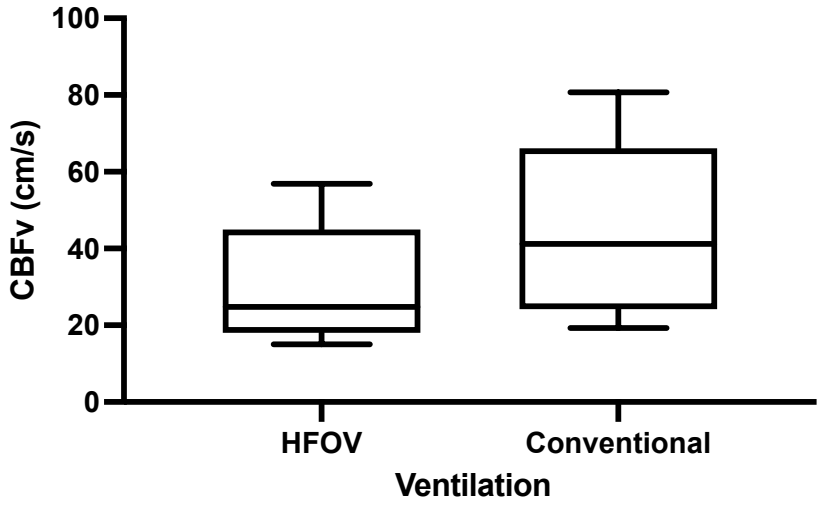

Figure 4.6 CBFv of patients that were successfully decannulated onto either conventional ventilation (n = 7) or HFOV (n = 5).

4.3.7 Near Infrared Spectroscopy and Transcranial Doppler Ultrasound Correlations

A weak relationship was evident between NIRS and CBFv during daily measurements while the patients were on full flow ECMO, this was not statistically significant (r =0.10; p = 0.32; CI= 0.11-0.30; figure 4.7a). There was no relationship between NIRS and TCD during weaning time points (r = 0.02, p = 0.90; CI = 0.28, 0.32; figure 4.7b).

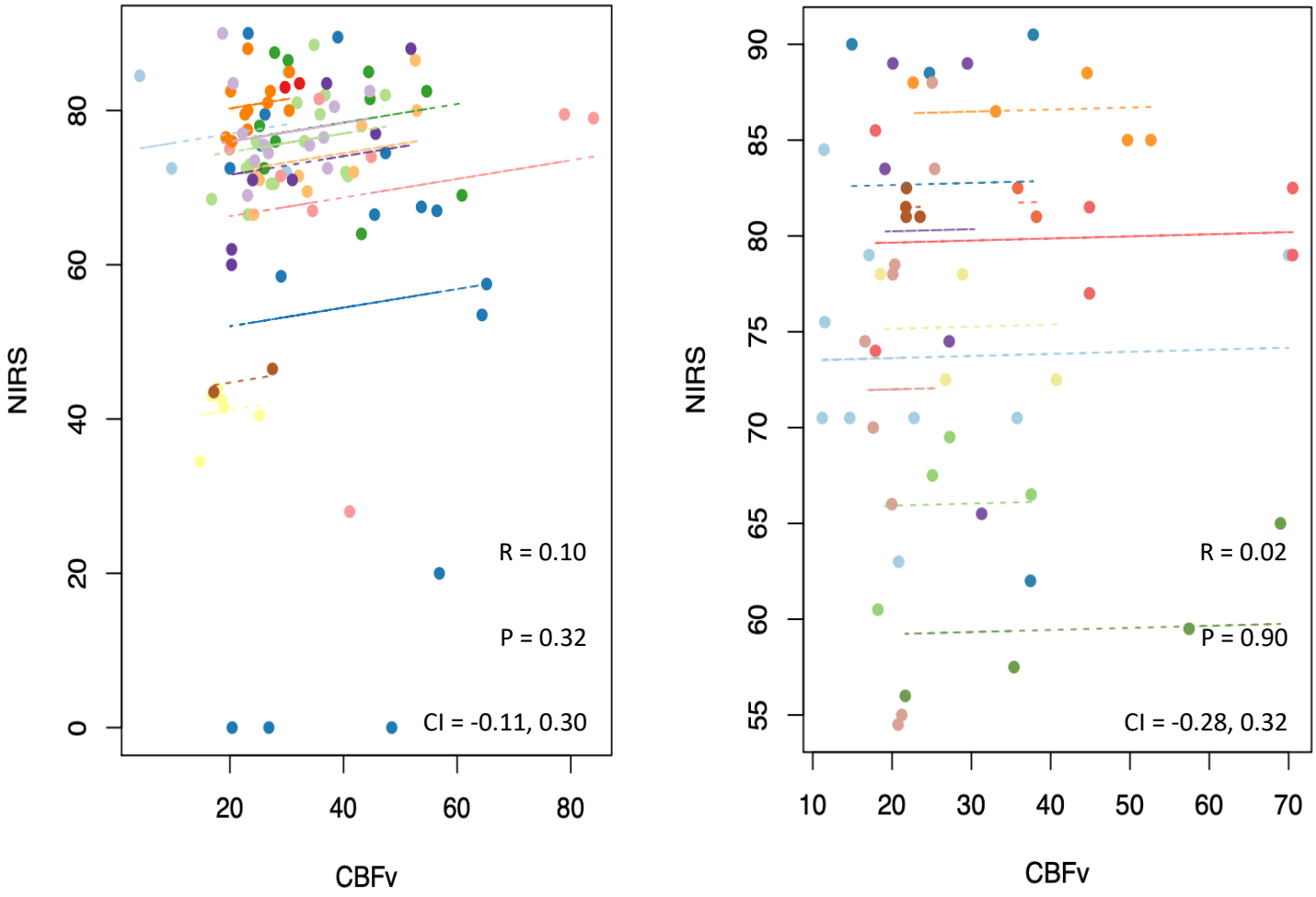

Figure 4.7 NIRS and CBFv correlation during daily measurements during full flow ECMO (a) and during the weaning process (where possible; first reduction, half flow, quarter flow, minimum flow and bridge) (b). Each colour represents an individual patient.

4.4 Discussion

The aim of the current study was to measure CBFv using TCD and NIRS daily throughout paediatric ECMO treatment which included weaning and recovery following decannulation. The current data indicates that cerebral perfusion measured using CBFv and NIRS are similar across the first 5 days on full flow ECMO in neonates. During the weaning period, patients were divided into those who were successfully decannulated and those who failed decannulation. The data provides some evidence that those who were successfully decannulated had ~9.1 cm/s higher CBFv than the ones who failed but this was not reflected in the NIRS measurements. Moreover, once decannulated, there was some evidence suggesting that those patients supported using conventional ventilation had a higher CBFv than those who required HFOV. Taken together, the data suggest that CBFv measurements during ECMO could provide more detailed insight into cerebral perfusion, especially during the weaning and recovery phases.

4.4.1 Measuring Cerebral Perfusion during Full Flow Extracorporeal Membrane Oxygenation:

In the group of 14 neonatal patients recruited in the current study, the number of days spent on ECMO ranged between 1 and 15 days without an attempted wean. Which eight neonates were on full flow ECMO for five days (days 1-5 of treatment). During this first five days of ECMO, both daily CBFv and NIRS were not statistically different. This finding supports previous research data that also examined CBFv during the first five days of full flow ECMO in paediatrics (0-18 years old) and found no statistical change (O'Brien and Hall, 2013). In the study by O'Brien and Hall, (2013) they also reported that CBFv was significantly lower on the first five ECMO days and then increased on following this period. In the current study the mean over the first 5 days over ECMO remained relatively unchanged. NIRS was also

included within the current study and likewise to CBFv, did to not change daily. Nevertheless, one patient had a difference of 28% over three days between the lowest and highest point during full flow ECMO. Clinically this variation may have some importance. Previous research into neurological outcomes and NIRS during ECMO found that those with a >20% change in NIRS across the entire ECMO period, were more likely to have neurological deficit (Tsou et al., 2020). Whilst overall the means of CBFv and NIRS found little change in perfusion during daily during ECMO, it is still important to monitor daily cerebral perfusion/magnitude of change on an individual basis. As there was some evidence to suggest that individuals may experience daily fluctuations whilst on full flow ECMO.

4.4.2 Cerebral Blood Flow Velocity during Weaning and Following Decannulation

A novel finding of the study was that CBFv was measured during the weaning period. During weaning, flow rates were reduced progressively which may impact CBFv, especially in the patients who may fail to separate. In the current study CBFv was compared in those that had successfully weaned (n=4) and those who had failed (n=4). There was no statistical difference in perfusion between the two groups, but there was a trend for a higher CBFv at each weaning time point in those who were successfully weaned off ECMO. There are no universal guidelines or specific criteria which enables clinicians to know which patients will fail to separate. The decisions occurring during the weaning process, including the timing of the trial itself are mainly based on the experience of the clinical team. Despite our sample size being small, the current data supports the need for a larger study to elucidate the role of CBFv measurements during ECMO weaning, and its potential ability to predicting successful weaning from ECMO.

Another novel aspect of this study is the measurements of CBFv following decannulation with the patients supported on HFOV or conventional mechanical ventilation.

Those placed onto conventional ventilation had a higher CBFv than those on HFOV, even if it did not reach statistical significance. This finding might be somewhat expected, because patients who are haemodynamically unstable are more frequently, post decannulation, in need of HFOV. But compared to previously published normative data for the same age range, CBFv is lower compared to healthy paediatrics. The small sample size needs to be taken into consideration when considering the lack of statistical significance. But the data does provide a base for further investigation.

4.4.3 The Correlation between Near Infrared Spectroscopy and Transcranial Doppler Ultrasound

Given that NIRS is the current clinical tool to measure cerebral perfusion, it is important to understand the relationship between changes in NIRS and changes in CBFv measured using TCD during ECMO. In the current study, the relationship was examined daily throughout the ECMO treatment (beyond the fifth day of support). A positive but weak relationship was found between NIRS and TCD measurements. The overall relationship between cerebral perfusion and ECMO is difficult to describe due to the multiple factors involved including flow rates and mean arterial pressure (Papademetriou et al., 2012). From the ECMO circuit perspective, cerebral perfusion is affected by the ECMO fluid dynamics which is not pulsatile due to the centrifugal pumps used. This in turn, can affect cerebral vascular autoregulation (Tian et al., 2017). Centrifugal pumps, on the other hand, have several advantages like reduced haemolysis, increased ECMO circuit durability, prolonged oxygenator lifespan and are less traumatic on the blood cells, reducing the need for blood transfusions (Thiara et al., 2007). However, non-pulsatile flow has been suggested to increase muscle sympathetic nerve activity which may lead in turn to cerebral hyperaemia and hypertension (Markham et al., 2013). It has also been suggested that non-pulsatile flow may also lead to reduced production of nitric oxide by the endothelium and promote endothelial dysfunction (Lanzarone et al., 2009).

Measuring both NIRS and TCD is advantageous. The drugs administered during ECMO reduce the cerebral metabolic demand. NIRS was unable to provide information on both cerebral oxygen supply and oxidative metabolic demand (Kazmi et al., 2018), which TCD is unable to achieve. Whereas TCD measures both hyper- and hypoperfusion which NIRS cannot. This could partially explain the weak relationship between in NIRS and CBFv in this cohort. The reductions in metabolic demand can imply that despite a reduction in CBFv, cerebral oxygenation may still be adequate (i.e NIRS remains elevated). In addition, the relationship was examined throughout all weaning time points where the relationship between NIRS and TCD became weaker. This is possibly due to CBFv being relatively reliant on the CPB flow rates during full flow ECMO. Once the weaning begins the ECMO flow rates are reduced and the heart and/or lungs begin to take over function. In those that fail weaning, the heart and lungs are not able to function adequately enough to be independent from ECMO. This is a sensitive time point when patients would be potentially undergoing cardiovascular stress, this gives less control in understanding why there are differences between NIRS and TCD at this time. Overall, there appears to be a weak relationship between NIRS and CBFv throughout the entire ECMO treatment in neonates. This supports previous research that has reported that NIRS is not an accurate/direct measurement of cerebral perfusion during critical care treatments (Goff et al., 2010). Thus, there is accumulating evidence that NIRS alone, may not be the optimal measurement for neurological monitoring during ECMO.

4.4.4 Methodological Considerations and Limitations

It is likely that some of the methodological limitations may have impacted the results. First, CBFv using TCD were obtained from one side of the head and/or the open fontanelle. During ECMO there was limited space, especially when the clinical team were cannulating or decannulating. In addition, during ECMO patients were positioned so that only one side of the head was available, especially in those cannulated peripherally. Given that, previous research

has suggested that there is no difference in CBFv between the left and right middle cerebral arteries during ECMO (O'Brien and Hall, 2013), meaning unilateral measurements should provide detailed insight. CO_2 measurements were not taken simultaneously during the scans, as pCO_2 is usually measured through blood samples, which could not be collected by the researcher. It is also important to acknowledge the limitation in the sample size. Due to the coronavirus pandemic, recruitment was terminated early. It is also key to note that this was a single centred observational study. Therefore, the specialist ECMO centre was limited to the number of ECMO patients they can cannulate due to the availability of specialist equipment and staff. Prior to the pandemic, all patients that met the inclusion criteria was approached. Despite the study recruitment being stopped early, the sample size of 14 is comparable to other ECMO studies such as the study by O'Brien and Hall (2013).

4.4.5 Research Implications

Overall, the research suggested that there was no significant difference between both NIRS and TCD over the course of ECMO treatment. However, there is potential for the observed changes to be clinically important. Future research should consider investigating what is clinically significant rather than statistically significant. These subtle differences may be impacting neurological development of paediatrics. Further research should also consider focusing on the weaning period. This was the first study to the authors knowledge to focus on cerebral perfusion during weaning. This could be due to the logistical difficulties with taking CBFv measurements at that time. During weaning there is a high volume of individuals bedside, vast amounts of equipment and limited space available. It was also not plausible to take measurements during cannulation and decannulation due to the limited space bedside and the limited space for the surgeons to perform the procedure. This is also a potentially important period of disrupted cerebral perfusion. Future research could also investigate whether TCD would add further clinical information about the potential success of weaning. TCD may be

used as a tool to highlight any variations or reductions in CBFv during weaning, which could be an early indication that weaning may be unsuccessful. This would allow clinicians to recognise earlier that the patient will need to go back onto full flow ECMO. Currently, there is no universal guidelines as to whether a patient will fail weaning. It is based on the decision/experience of the clinical team and the process can take hours to decide. NIRS is unable to give this information which was evident through the weak correlation between NIRS and TCD. NIRS is used clinically, however this may be not reflective as to the flow rates in the cerebral vessels. This may lead to periods of unknown disrupted perfusion and subsequently, neurological deficit in the long-term.

4.5 Conclusion

Cerebral perfusion measured using CBFv and NIRS are similar across the first five days on full flow ECMO. During weaning there was some evidence that those that were successfully separated had a higher CBFv than the failed group. Moreover, there was some evidence to suggest that following decannulation, patients supported using conventional ventilation had a higher CBFv than those that required HFOV. Further research is needed to investigate the relationship of NIRS and TCD and to establish if TCD could be an additional clinical tool during weaning.

Chapter Five: Cerebral Blood Flow Velocity during Neonatal Aortic Arch Repair

5.1 Introduction

Infants born with hypoplastic or interrupted aortic arch are often born cyanotic requiring immediate medical and surgical intervention. Historically these conditions were fatal (Barron et al., 2009). Now, a high percentage of patients survive to adulthood (Feinstein et al., 2012). Improvements to foetal diagnosis, surgical technique and the management of congenital heart disease (CHD) all contribute to the increases in survival rates (Tabbutt et al., 2008). Yet a high percentage of survivors exhibit neurological deficit (Mussatto et al., 2018). Common neurological complications associated with CHD include cognitive impairment, speech/language disorders, lower academic achievement and fine/gross motor deficits (Wernovsky, 2006). The highest rates of deficit are seen in those with severe left sided lesions such as hypoplastic or interrupted aortic arch (Marino et al., 2012). Potential causes for neurological complications associated with CHD, may be related to the procedures that are required during surgical repair of the aorta. It has been suggested this neurological deficit is multifactorial but involves tissue hypoxia and regional hypoperfusion often within the vascular beds, which may already be abnormal due to the underlying conditions (Serraino and Murphy, 2017). Other direct causes of disruption to cerebral perfusion could be due to the cessation of cardiac function, the use of cardiopulmonary bypass (CPB) and the induction of deep hypothermic circulatory arrest (DHCA) (Kinney et al., 2005). Whilst catastrophic brain injury is a well-documented complication (McCrindle et al., 2005). Ensuring adequate cerebral perfusion during surgery is paramount to neurological protection, as subsequently this may enhance the quality of life in survivors.

Surgery itself has been identified as a controlled trauma which occurs alongside the establishment of anaesthesia, directly impacting cerebral blood flow velocity (CBFv) (Slupe and Kirsch, 2018). Currently there are several strategies implemented for neurological protection including minimising the time spent in DHCA; cooling of skull and brain by topical

application of ice packs to further reduce neural activity; and the continuous monitoring of blood gases to optimise oxygen delivery to the brain. Moreover, antegrade cerebral perfusion throughout CPB is used to perfuse the brain with oxygenated blood to reduce prolonged periods of cerebral ischaemia. Nevertheless, there are still instances of neurological deficit in this population and perfusion strategies vary considerably across centres (Meyer *et al,* 2016). There are a lack of universal guidelines regarding the target temperature of cooling, cerebral protection strategies and surgical repair techniques (Ortuno et al., 2019). For example, target temperature for DHCA is usually based on surgeon preference, previous experience, type of procedure performed and its complexity. Taken together, the optimum neuroprotection strategy is currently unknown.

Near infrared spectroscopy (NIRS) is used in routine practise during cardiac surgery as an index of cerebral perfusion. Adequate CPB flow rates are largely reliant on NIRS to monitor cerebral perfusion during surgery. NIRS is a simple, cost-effective measurement of cerebral oxygenation. However, the shortcomings of NIRS have been previously well documented (Erdoes et al., 2018). For example, NIRS is only able to measure oxygenation at a regional level (frontal lobes) as an in-direct marker of global cerebral perfusion. An injured brain could potentially show normal levels of oxygenation during periods of ischaemia. Moreover, there has been documentation of high levels of inter-device variability, issues related to absolute vs relative saturations and variability of oxygen saturation targets/thresholds in clinical settings (Grocott and Davie, 2013). More in-depth measurements of cerebral perfusion are available including Transcranial Doppler (TCD) ultrasound which provides cerebral blood flow velocity (CBFv) of the middle cerebral artery (MCA). One previous study has employed NIRS and TCD during aortic arch repair during full flow CPB. Periods of hyperpefusion were reported which NIRS was unable to detect (Andropoulos et al., 2003). In the aforementioned study CBFv and NIRS were also only measured during pre and post repair while on full flow CPB

and not during periods of selective cerebral perfusion. A more recent case study employed TCD and NIRS in one male infant (10 days old) throughout aortic arch repair. An important observation from this case study were that values in TCD and cerebral oxygenation dropped to near zero at two different time points during DHCA (Busch et al., 2016), suggesting the patient was subjected to possible periods of brain ischemia. Therefore, examination of the changes in cerebral perfusion alongside NIRS during each stage of surgery to repair the aortic is warranted. The aim of the current study was to continuously monitor CBFv throughout aortic arch repair surgery. The secondary aim was to examine difference in CBFv between patients cooled to 20°C and 25°C as part of the neuroprotection regime. The final aim was to examine the relationship between NIRS and TCD at each time point during surgery.

5.2 Methods

5.2.1 Participants

Neonates recruited from Alder Hey NHS Foundation Trust were aged 19 ± 7 days, weighed 3.63 ± 0.66 kg and had a mean height of 51.8 ± 3.4 cm. Patients required surgery for hypoplastic aortic arch repair (n =16), interrupted aortic arch (n = 6) or for HLHS (n = 2). Informed consent to participate in the study was obtained by a member of the surgical team prior to the procedure. Ethical approval was obtained from the NHS Liverpool East Research Ethics Committee (IRAS number: 240082). Neonates or infants (< 1 years old) who required aortic arch repair surgery were included. Exclusion criteria consisted of those deemed inappropriate by the clinical team, patients with previous documented neurological damage and those suffering from conditions which have been known to affect CBFv such as elevated bilirubin levels, sickle cell anaemia and moyamoya disease.

5.2.2 Research Design

Cerebral perfusion measurements included a pulsed TCD ultrasound system (DWL, Compumedics, Germany) using 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) was performed by the clinical team, the researcher took note of numbers from the report generated. The researcher recorded mean arterial blood pressure, heart rate and CPB flow rates throughout the procedure from the clinical equipment. The measurement time points were at baseline, which was defined as following induction of anaesthesia before surgery, at CPB initiation, during cooling (30ºC, 25ºC, lowest temp), cerebral perfusion, body re-perfusion, rewarming (25ºC, 30ºC, 36ºC), off CPB and on paediatric intensive care unit (PICU) the following day.

5.2.3 Surgical Technique for Hypoplastic Aortic Arch and Interrupted Aortic Arch

A team of three consultant cardiac surgeons, six anaesthetists and six perfusionists were involved in the aortic arch repairs. On arrival to theatre all patients were sedated and prepared for the procedure. Two blood pressure monitors were used (femoral and right radial or brachial artery) to assess distal and cerebral aortic pressures. Anaesthetic technique consisted of intravenous administration of midazolam, fentanyl and inhaled servoflurane. Once the patient was anaesthetised and prepared for theatre 'baseline' measurements was recorded. Preparation for the procedure included dissection of the head and neck vessels, ascending aorta and aortic arch and descending aorta past the aortic isthmus. Cardiopulmonary bypass was achieved with either a single right atrial cannula or bicaval cannulation in those patients requiring intracardiac repairs. 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. If a patent ductus arteriosus was present, this was ligated to prevent pulmonary over-circulation. Measurements were recorded on initiation of full flow bypass and named 'CBP', this was still during normothermia. 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). 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 25°C or 20°C and cooling times were 20 minutes or longer. Measurements were recorded at 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. pH-stat management was only used when the patient was at cooled at 28°C or lower.

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 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) were fully dissected ready to be snared when the ascending aorta cannula was advanced into the innominate artery to perfuse the brain with blood. At this point a measurement was taken labelled 'selected cerebral perfusion' An aortic cross clamp in the descending aorta was then positioned and CPB flow rates were manipulated manually to achieve to keep cerebral oxygenation measurements (measured using NIRS) within the antegrade cerebral perfusion target. This target was to maintain NIRS within ~10% of when the patient is placed onto full flow bypass. Five patients underwent complete circulatory arrest (mean time 22 ± 37 minutes). The aorta was transected at the isthmus and ductal tissue completely removed; the arch was opened in the inner curvature till the mid ascending aorta. The back wall of the aorta was anastomosed to the distal descending aorta and a patch of heterologous pulmonary artery homograft was attached to augment the whole arch from the descending to transcending aorta to enlarge the hypoplastic aortic arch. Once accomplished, air was evacuated from the arch by relapsing one of the head and neck vessels and the clamps removed. The neck vessels snares were released, and the tip of the aortic cannula was moved to perfuse the whole body and the heart was re-perfused with blood. A measurement was recoded 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. Again, once at 28°C the stat management was switched from pH to alpha-stats. Once at normothermia, the patient was weaned off CPB. Once the patient maintained stable haemodynamics, a further measurement was recorded labelled 'off CBF'. All patients recovered in the paediatric intensive care unit (PICU), and the following post-operative day a measurement was recorded labelled as 'PICU'.

5.2.4 Additional Surgical Technique for the Norwood Procedure

Specific types of arch repair procedures are listed in Table 5.1. Those with hypoplastic left heart syndrome (HLHS) had a different surgical approach to those with hypoplastic aortic

arch or interrupted aortic arch. HLHS often requires staged surgery resulting in the patient acquiring a permanent, single ventricular circulation known as the Fontan circulation (Goldberg et al., 2000). HLHS is characterised as an underdeveloped/non-functioning left ventricle, patent ductus arteriosus, atrial septal defect and an hypoplastic aortic arch (Barron et al., 2009). Mostly, the arch reconstruction needed during the Norwood procedure is more extensive due to the severe arch hypoplasia extending to the ascending aorta. Moreover, the procedure also requires the reconstruction of the arch using the stump of the main pulmonary artery, adding to the complexity of the procedure. Therefore, arch reconstruction and augmentation with homograft patch in the Norwood procedure takes longer thus more time is spent on CPB and DHCA. A surgical atrial septectomy is also performed to increase mixing of blood, and a connection from the RV or systemic circulation (Sano shunt or BT shunt respectively) are constructed to maintain pulmonary blood flow.

5.2.5 Measurements of Cerebral Perfusion

5.2.6 Transcranial Doppler Ultrasound

CBFv measurements were obtained through the temporal window, which is approximately 1 cm above the zygomatic arch and 1 cm in front of the external auditory meatus. From here the ultrasonic beam was directed horizontally, then the depth and sample volume were adjusted until the MCA was found using previously published normative values for the age range (see chapter 3, table 3.1). 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, in which the MCAv, depth and power was

similar from both windows. For the remaining measurements the probe was placed in the same position and the same depth was maintained at both windows.

5.2.7 Near Infrared Spectroscopy

NIRS was used to measure cerebral oxygenation levels through the Beer-Lambert law. NIRS is a non-invasive optical technique where two sensors are applied to the forehead just to the right and left of the midline to assess frontal oxygenation levels. Laser-emitting diodes generate light at four different wave lengths (690, 778, 800 and 850mm). Within each sensor there were spacing between the two light detectors which gave both shallow and deep detection of oxygenation with a maximum penetration of ~2.5cm from the emitter. NIRS monitors rely on an algorithm that cerebral arterial: venous ratio is 30:70. NIRS was continuously monitored by the clinical team to ensure no catastrophic events and to ensure adequate cerebral perfusion throughout aortic arch repair. This involved ensuring that a threshold values of >70% with no fluctuation >15% throughout the procedure from when they are placed on full flow bypass.

5.2.8 Antegrade Cerebral Perfusion Target

Antegrade cerebral perfusion is a CPB technique in which a cannula is placed in the innominate artery to exclusively perfuse the brain in neonatal and paediatric aortic arch repair (Fraser and Andropoulos, 2008). This is used as a neuroprotective technique during deep hypothermic circulatory arrest (DHCA) to reduce the likelihood of hypoxic ischaemic injury. Generally, CPB flow rates during selective cerebral perfusion are targeted at ~15% of full flow (CBP measurement). This is because cardiac output to the brain is normally around 15% of total cardiac output. In addition, a NIRS value recorded at CPB time point was also used as a marker of flow. The aim was to maintain NIRS within 10% of the CPB value.

5.2.9 Statistical Analysis

The data was explored for normality using quantile-quantile plots. SPSS (SPSS Version 26, IMB Statistics, USA) was used to perform linear mixed models, 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 baseline and the initiation of CBP (time points used to define cerebral perfusion during the procedure). Pearsons correlation co-efficient were also employed to examine relationships between measurements of cerebral perfusion with an *a priori* target temperature and actual minimum temperature reached at the rectal and oesophageal sites. 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.

5.3 Results

5.3.1 Overall Patient Characteristics

Mean age of the patients was 20 ± 21 days, height 49.8 ± 10.5 cm, weight 3.6 ± 0.75 kg and a ratio of female: males 9:15 (Table 5.1). Procedures included type B interrupted aortic arch (n=5), hypoplastic aortic arch (n=17) and hypoplastic left heart syndrome (n=2). Patients were split into 2 groups dependant on lowest temperature achieved during cooling 20 (n=8) or 25 (n=16; Table 1). Mean coronary bypass time during aortic arch repair was 156 ± 49 minutes, with a cross clamp time of 80 ± 38 minutes. Four patients underwent total circulatory arrest (mean time 22 ± 37 minutes). Mean antegrade cerebral perfusion time was 55 ± 23 minutes. Mean lowest oesophageal temperature was 22.5 ± 2.2°C. Three patients were placed onto veno-arterial extracorporeal life support following surgery. Other intraoperative problems included cases of bleeding, the need for intubation and cardiac catheterisation post-surgery. The 30-day mortality of the patients undergoing aortic arch repair was 4.2%.

5.3.2 Participants Cooled to 20°C

Mean age of participants (n = 8) cooled to 20°C was 20 ± 16 days with a ratio of 1:1 female:males. Mean height was 48.7± 4.76 cm and body mass 3.32 ± 0.74 kg. Operation consisted of repair of the hypoplastic aortic arch (n = 4), interrupted aortic arch (n = 3) and hypoplastic left heart syndrome (n = 1). The average bypass time was 197.2 ± 44.7 minutes, cross clamp time 118.8 ± 33.8 minutes and antegrade cerebral perfusion time 78.1 ± 17.8 minutes. Two patients underwent total circulatory arrest, one for interrupted aortic arch repair (90 minutes) and the other for hypoplastic left heart syndrome (7 minutes).

5.3.3 Participants Cooled to 25°C

The ratio of males: females of patients was 11:5. Mean age of the patients cooled to 25°C was 18 ± 19 days, height 52.3 ± 3.9 cm, and body mass 3.6 ±0.7 kg. The average bypass time was 136.2 ± 38.4 minutes, with a cross clamp time 87.8 ± 105 minutes and an antegrade cerebral perfusion time 60.9 ± 22.8 minutes. Operations performed were hypoplastic aortic arch (n = 13), interrupted aortic arch (n = 2) and hypoplastic left heart syndrome (n = 1). Three patients underwent complete circulatory arrest. One patient underwent repair of hypoplastic aortic arch (2 minutes), another during interrupted aortic arch (4 minutes) and another during hypoplastic left heart syndrome repair (8 minutes).

Table 5.1 Individual patient characteristics and operation information.

	Age (Days)	Sex	Height (cm)	Weight (kg)	Bypass Time (Mins)	Cross Clamp Time (Mins)	Antegrade Cerebral Perfusion Time (Mins)	Diagnosis	Operation
Group 20ºC	24	F	51	3.1	156	98	62	HAA, VSD, PDA	HAA repair, VSD closure and PDA ligation and division
	14	M	47	2.8	189	134	90	IAA (Type B), Muscular VSD	IAA repair, VSD closure PDA ligation and division
	11	M	52	4.7	207	147	87	IAA (type B), VSD, ASD, PDA and narrow LVOT.	IAA repair, LVOTO relief, VSD closure, ASD closure and PDA ligation.
	21	F	50	2.8	227	170	80	Truncus arteriosus (Type 2) and interrupted aortic arch (Type B)	IAA and truncus repair, RV-PA conduit
	12	M	44	3.3	201	98	71	IAA (Type B), perimembranous VSD, additional inlet VSD ,PDA,.	IAA repair with PA band, PDA ligation and division
	5	F	50	3.2	285	141	111	HLHS (MA/AA) severe	Norwood stage 1 with Sano modification RV-PA conduit
	59	F	51	2.5	146	73	68	HAA	Arch repair and PDA ligation and division
	14	M	55	4.1	167	89	56	HAA, small VSD, PDA	HAA repair, PDA ligation and division
Mean ± SD	20 ± 15	F =4 M= 4	50 ± 3	3.3 ± 0.7	197 ± 44	119 ± 34	78 ± 17		
Group 25ºC	13	M	54	4.1	94	34	28	HAA with CoAo, large apical VSD	HAA repair, PA band
	18	F	51	3.8	146	106	36	HAA, muscular VSD,	Arch repair and VSD closure
	27	M	56	4.35	142	64	54	IAA (Type B), Muscular VSD	IAA repair, PA band,
	9	F	50	2.7	126	55	39	HAA, borderline LV, MS, Large VSD.	HAA repair, PA banding, PDA closure and ASD enlargement
ligation	6	M	49	3.2	125	72	64	HLHS (Shones' complex) with HAA, borderline LV with bicuspid aortic valve.	HAA repair and aortic valvotomy

	8	M	50	3.3	122	58	44	HAA. CoAo with PDA	HAA repair
	8	M	52	3.3	247	112	103	Tricuspid atresia, restrictive VSD, IAA, small PFO.	Classic Norwood (BT shunt) with IAA repair with atrial septectomy.
	18	F	50	3.47	153	57	50	HAA	HAA repair
	8	M	46	3.1	108	36	33	HAA	HAA repair
	9	F	48	3.2	122	70	30	HAA, CoAo, inlet muscular VSD and PDA.	HAA VSD closure, PDA ligation and division.
	20	M	51	3.27	114	69	34	HAA, CoAo, VSD and PFO	HAA repair, VSD closure, PFO closure.
	87	M	62	5.9	125	52	42	HAA, CoAo	HAA repair
	7	F	57	3.4	201	63	38	HAA, ASD, CoAo.	HAA repair and ASD closure
	16	M	54	3.6	113	44	40	HHA, PDA	HAA , PDA ligation and division
	14	M	55	4.01	107	36	56	HAA small muscular VSD	HAA repair, PDA ligation and division
	14	M	51	3.45	134	46	42	HAA, large PDA	HAA repair, PDA ligation and division
Mean SD	17 ± 19	F = 5 M = 11	52 ± 4	3.6 ± 0.7	136 ± 38	60 ± 22	46 ± 18		

HHA-Hypoplastic aortic arch, VSD- ventricular septal defect, PDA- patient ductus arteriosus, IAA- interrupted aortic arch, LVOTO- left ventricular outflow tract obstruction, RV- right ventricle, PA- pulmonary artery, MA- mitral atresia, AA- aortic atresia, CoAo- coarctation of the aorta, LV- left ventricle, MS- mitral stenosis, TGA- transposition of the great arteries, PFO- patent foramen ovale, ASD- atrial septal defect.

5.3.4 Cerebral Blood Flow Velocity using Transcranial Doppler Ultrasound

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 = 0.03; Figure 5.1a). Once recovering in PICU, CBFv had increased from the baseline by 6.2 cm/s (0.21, 13.4; P = 0.05) and by 7.1 cm/s (1.2, 12.1; p = 0.02) 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). There were no correlations between CBFv and *a priori* target temperature or temperature reached during cooling (P>0.05, Figure 5.2).

5.3.5 Cerebral Oxygenation using Near Infrared Spectroscopy

NIRS values changed during aortic arch repair procedure (main effect of time: p=0.05). 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%) (Figure 5.1b). NIRS values were similar between patients cooled to the a priori 20 and 25°C (main effect of temperature P=0.19; time*temperature interaction p = 0.59). There were no correlations between NIRS and *a priori* target temperature or temperature reached during cooling (P>0.05, Figure 5.2).

5.3.6 Cardiopulmonary Bypass Flow Rates

The CPB flow rates (Figure 5.1c) 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).

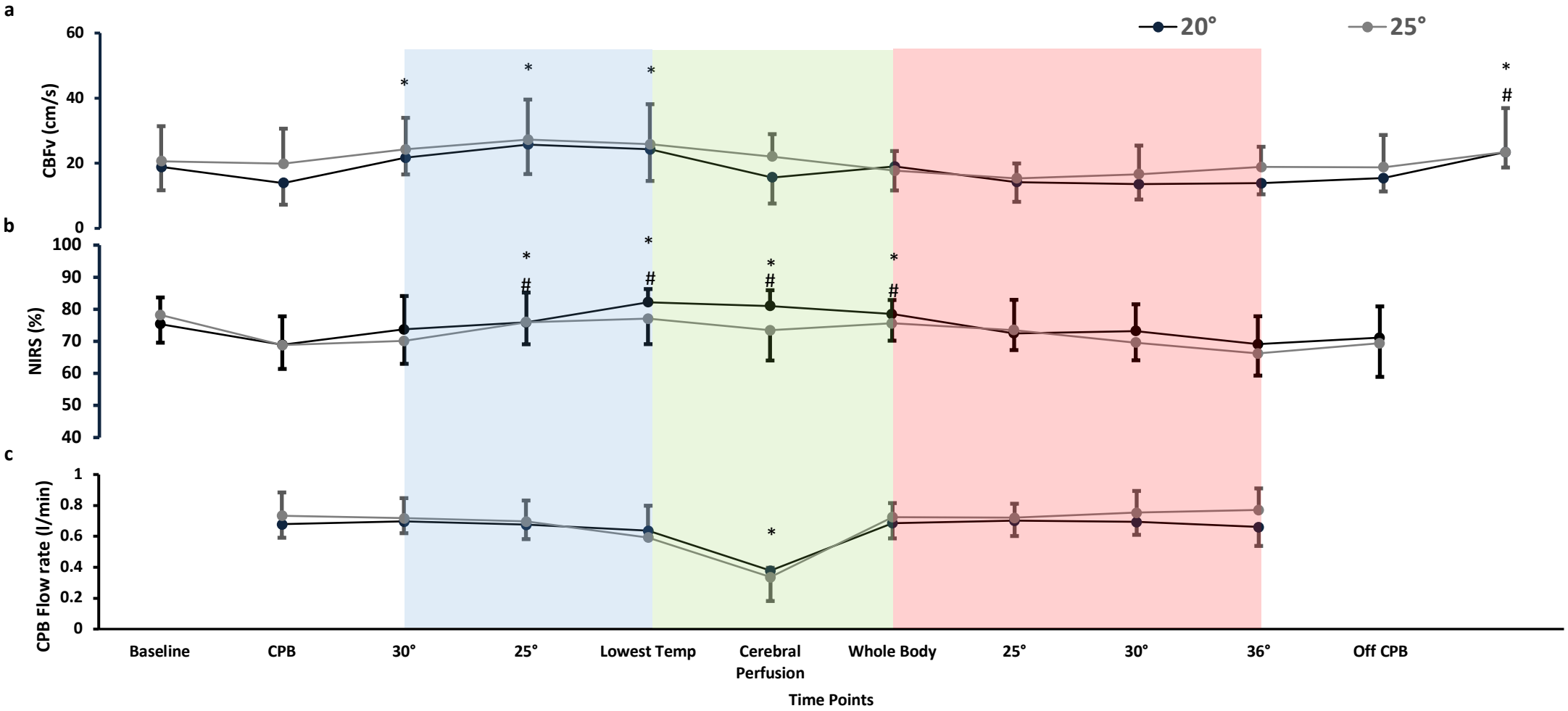

Figure 5.1 Cerebral blood flow velocity (a), NIRS (b) and CBP flow rates (c) throughout aortic arch repair (mean ± SD). Black line represents cooled to 20ºC and the grey lines 25ºC. Blue shading is cooling, green shading is selective cerebral perfusion and whole-body reperfusion and red shading re-warming. # represents significant difference from baseline. * denotes significant difference from CPB.

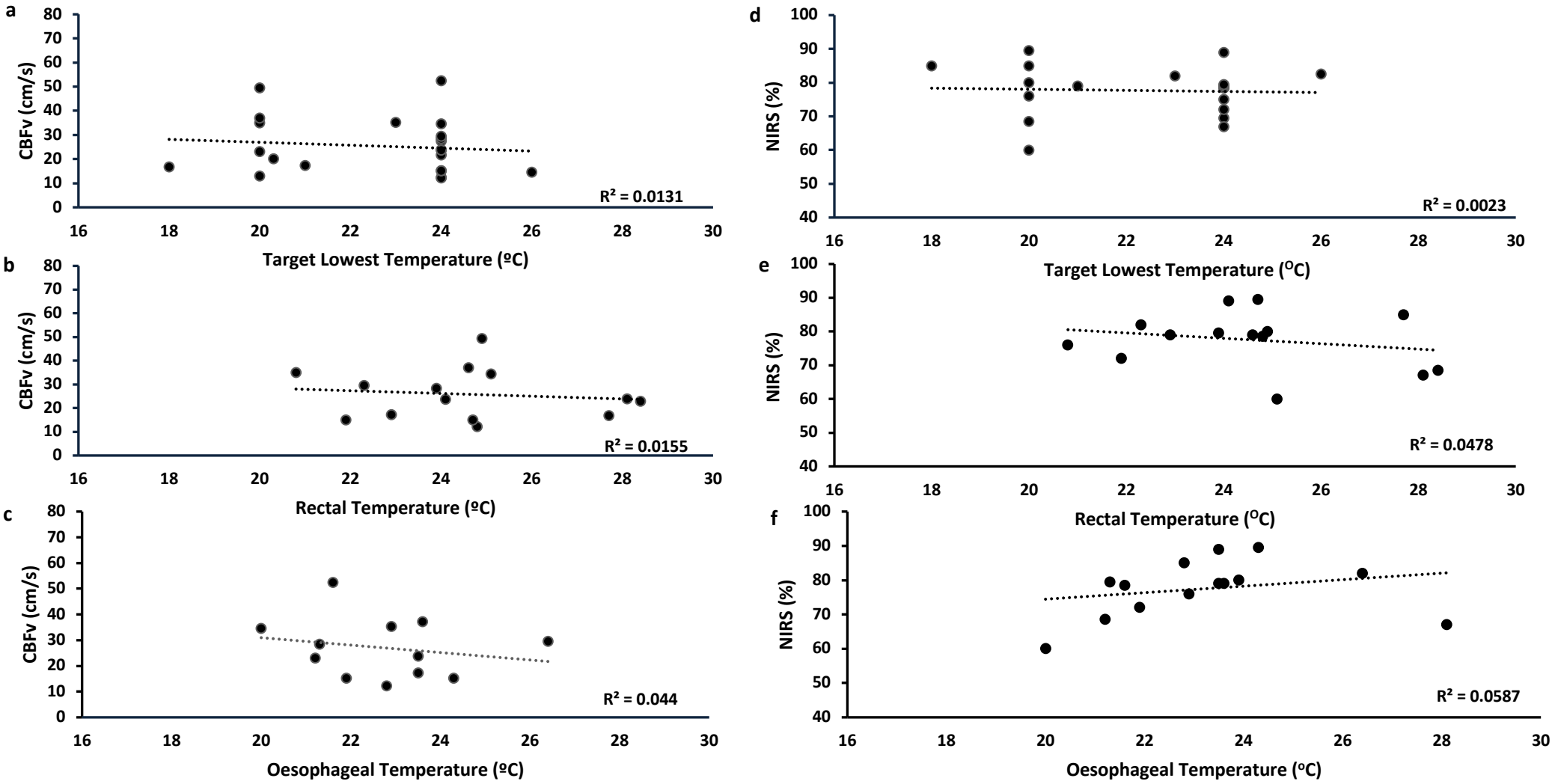

Figure 5.2 Correlations between CBFv and target lowest temperature (a), actual lowest rectal temperature (b) and actual oesophageal temperature (c). Correlations between NIRS and target lowest temperature (c), actual lowest rectal temperature (d) and actual oesophageal temperature (e).

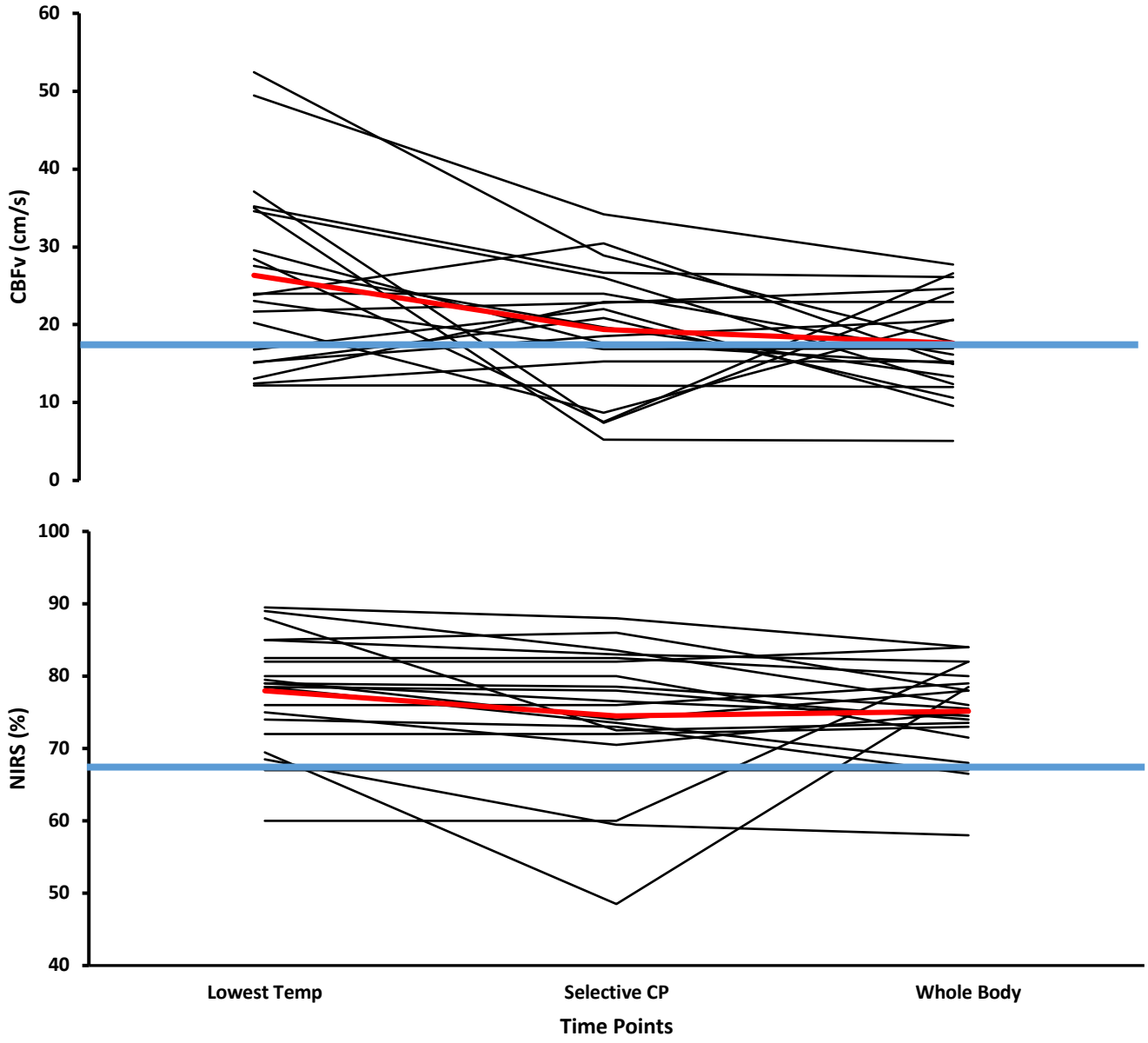

Figure 5.3 Individual patient CBFv (a) and NIRS (b) values from the lowest temp, selective cerebral perfusion and whole-body reperfusion with the red line representing the mean. The blue line represents the mean CBFv and NIRS at CPB time point which was used as a reference point for CPB flow rates.

5.3.7 Arterial Blood Gas Analysis

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 = 0.03) at 30ºC. There was a significant main effect of temperature (p=0.03, Figure 5.4) with 25ºC temperature group eliciting 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= >0.03) 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=0.09, time*temperature p=0.92).

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 patients were separated from CPB. When compared to CPB there was an increase during whole body perfusion 3.7% (0.72, 6.59), 30° 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). pH changed during aortic arch repair procedure (main effect of time: p= 0.001). pH increased by 0.14 (0.07, 0.20) when on CPB compared to baseline (P=0.05) and at 36°C by 0.07 (0.03, 0.15). When compared to CPB pH reduced at lowest temperature time point by 0.11 (0.01, 0.19), selective cerebral perfusion by 0.10 (0.04, 0.15), whole body perfusion by 0.22 (0.01, 0.14), 25°C by 0.17 (0.12, 0.25) and 30°C by 0.10 (0.22, 0.67), respectively. pH changes were similar between patients cooled to 20°C and 25°C (main effect of temperature: P=0.82; time*temperature: P=0.19). 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 ($p= 0.05$) and main effect of time*temperature ($p= 0.74$).

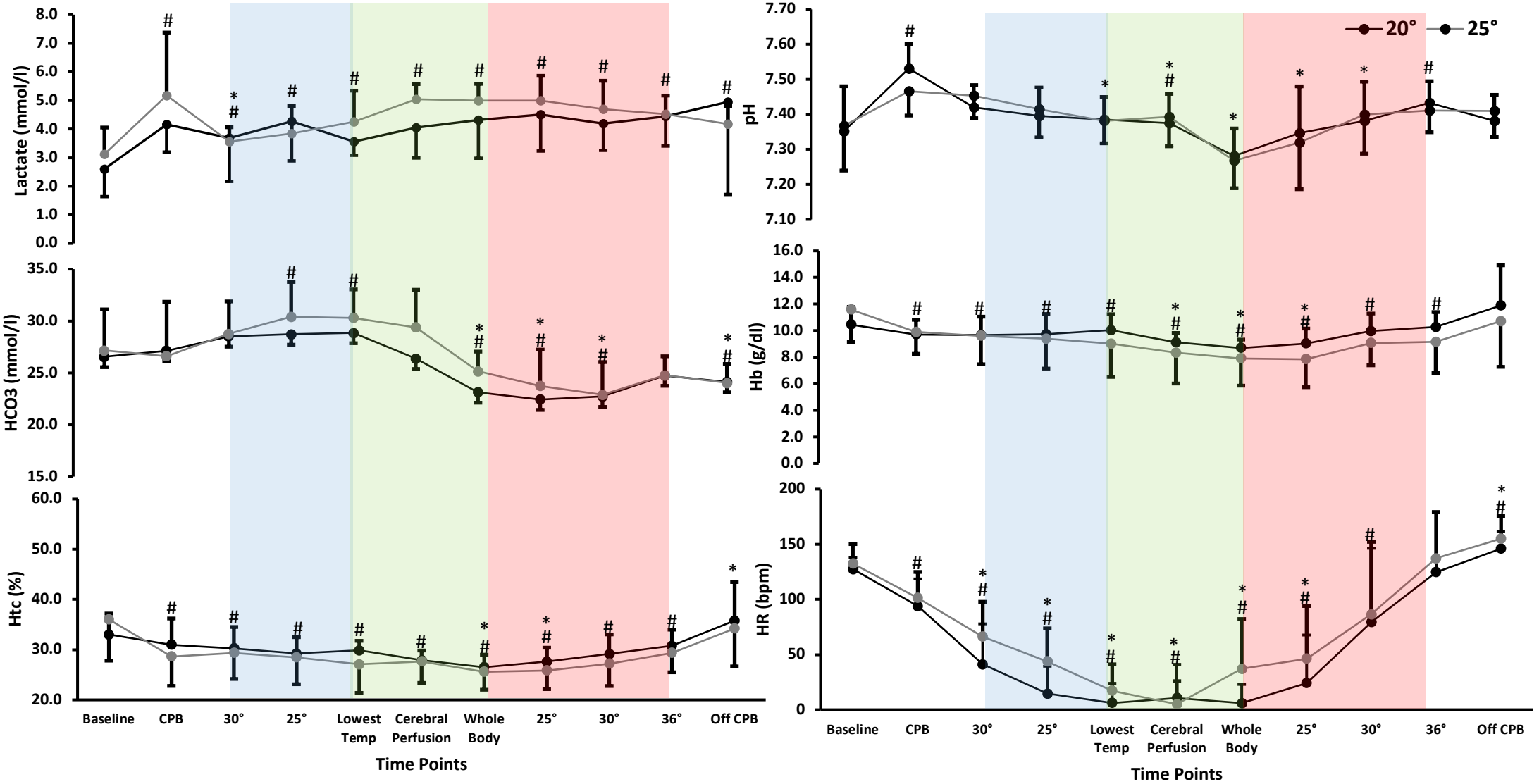

Figure 5.4 Mean and standard deviation hemodynamical data (mean ± SD). Black line represents cooled to 20ºC and the grey lines 25ºC. Blue shading is cooling, green shading is selective cerebral perfusion and whole-body reperfusion and red shading re-warming. # represents significant difference from baseline. * denotes significant difference from CPB.

pO_2 changed throughout aortic arch repair (main effect of time: P= 0.001, Figure 5.5a). 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. pO2 changes were similar between patients cooled to the *apriori* 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 pCO2 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 and 25°C (main effect of temperature p=0.47; time*temperature interaction p=0.22; figure 5.5b).

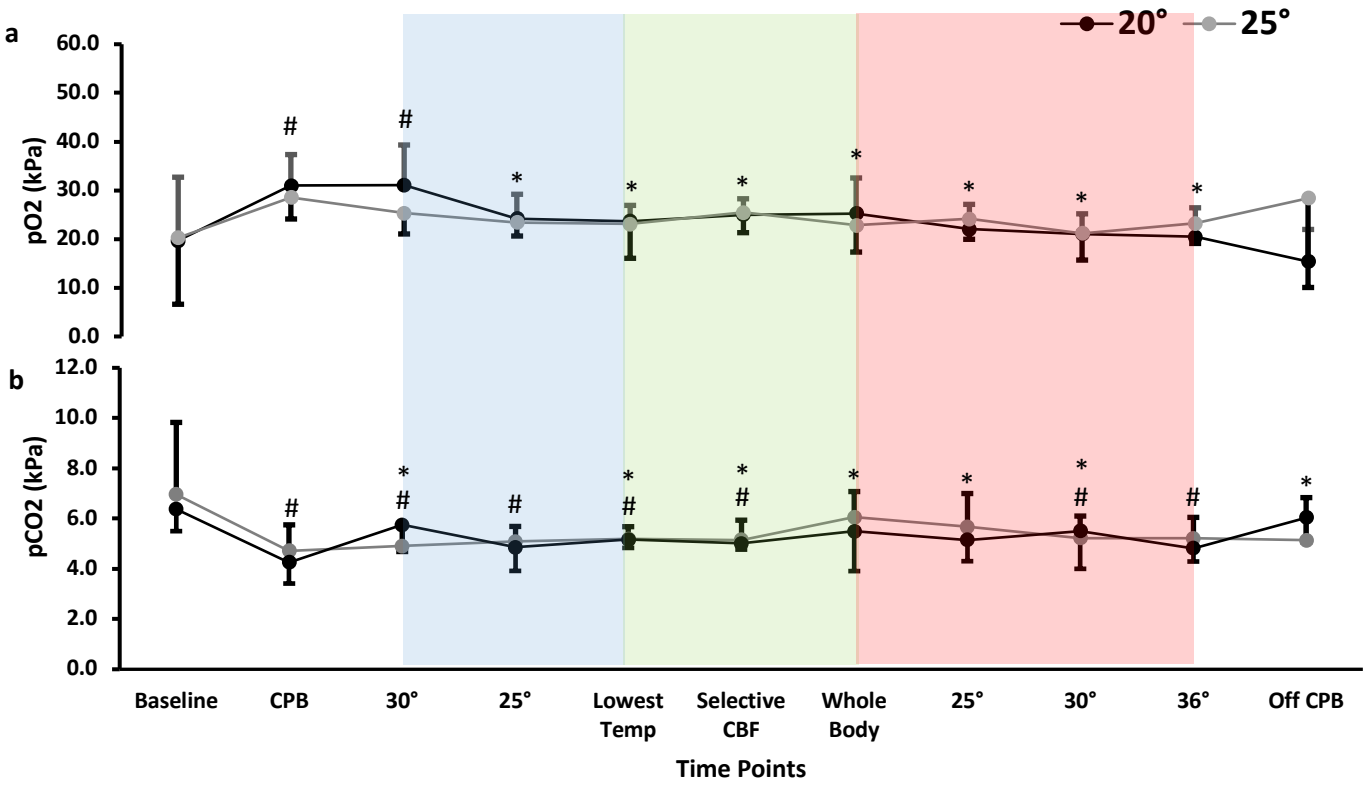

Figure 5.5. pO2 and pCO2 throughout aortic arch repair (mean ± SD). Black line represents cooled to 20ºC and the grey lines 25ºC. Blue shading is cooling, green shading is selective cerebral perfusion and whole-body reperfusion and red shading re-warming. # represents significant difference from baseline. * denotes significant difference from CPB.

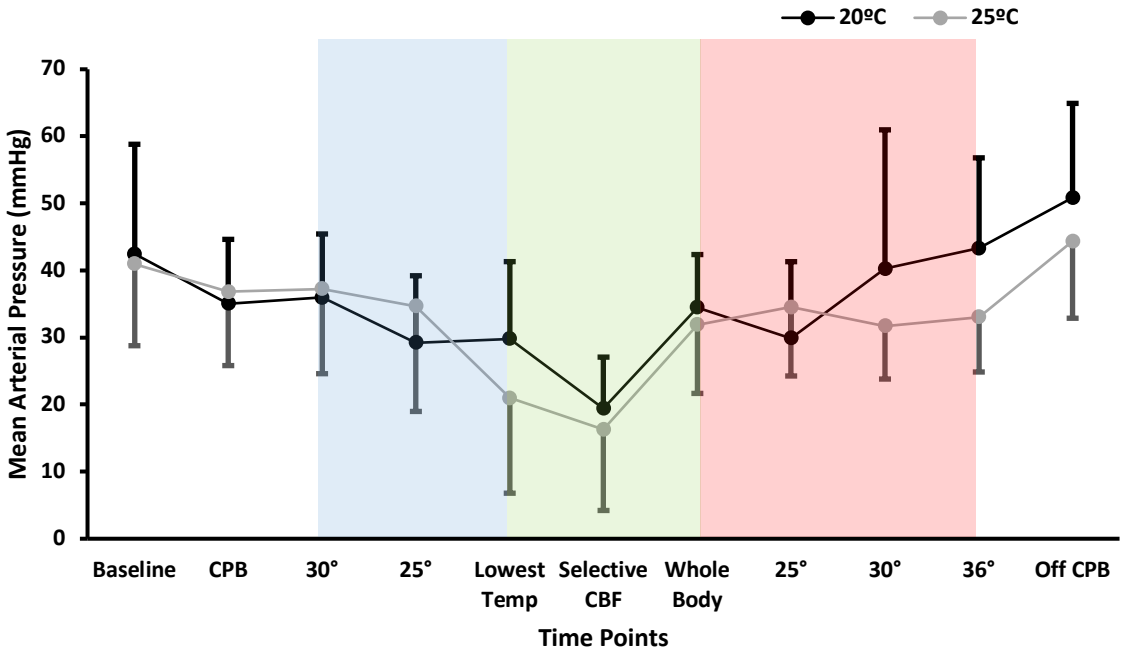

Figure 5.6 Mean arterial pressure (MAP) throughout aortic arch repair (mean ± SD). Black line represents cooled to 20ºC and the grey lines 25ºC. Blue shading is cooling, green shading is selective cerebral perfusion and whole-body reperfusion and red shading re-warming.

5.3.8 Repeated Measure Correlations between Near Infrared Spectroscopy and Transcranial Doppler Ultrasound

Statistically significant but weak positive correlations were evident between CBFv and NIRS (r=0.25, P=0.001; Figure 6).

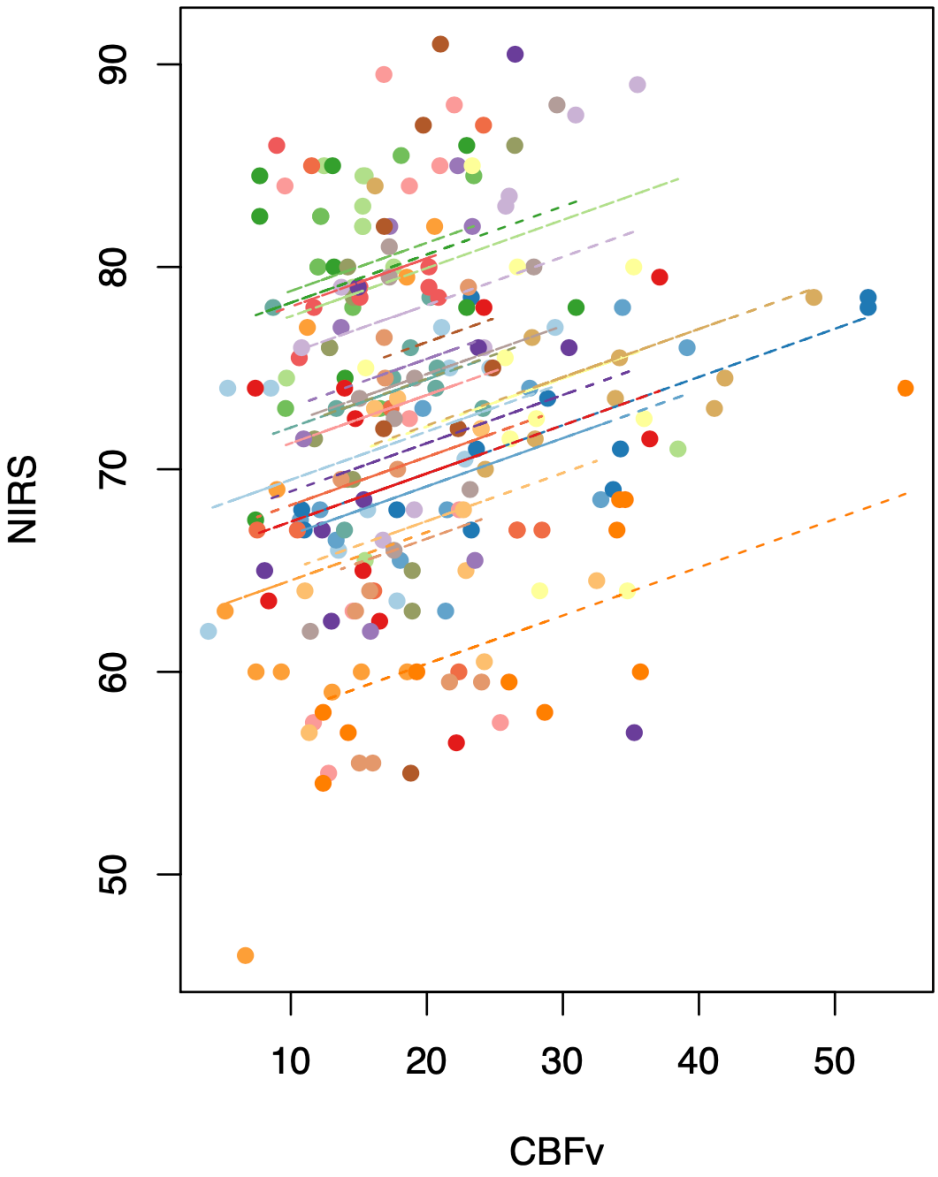

Figure 5.7 Individual CBFv and NIRS at time points throughout aortic arch repair. Each colour represents a patient.

5.4 Discussion

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

5.4.1 Differences between Temperature Groups

Currently in clinical care, the rationale for cooling patients to specific temperature is based on surgeon or centre preference. Consequently, there is a large variation in minimum temperature strategies. Data from the current study suggest there was no difference in CBFv or NIRS between cooling patients to 20 or 25°C. The rationale for cooling to lower temperatures during aortic arch repair is to maximise neurological protection, which is especially important in more complex cases which may require longer cross clamp time where patients are exposed to an extracorporeal circulation for prolonged periods. The target temperature was agreed prior to surgery by the surgeon and the perfusionist. Nevertheless, as shown in the current data the target temperature was not always achieved, this may be due to the time constraints. It is important that cooling takes at least 20 minutes to guarantee an even distribution of cooling throughout the body. The current data suggest that any core temperature below 25°C had little additional impact on changing cerebral perfusion.

5.4.2 Cerebral Blood Flow Velocity changes throughout Aortic Arch Repair

Historically, aortic arch repair was the most challenging cardiac surgery (Coselli and Green, 2009b), due to the direct manipulation of the head and neck vessels (Manetta et al., 2018). Left sided lesions were considered to have the highest risk of neurological deficit (Marino et al., 2012). Survival rates in this population have increased significantly (St. Louis et al, 2015). For example, the mortality rate of the current study was 4%, compared to published results of 30-day mortality rate of 50% in a study from 1977-1997 (Tláskal et al., 1998). Improving quality of life by reducing neurological deficit is now recognised to be one of the most important factors to reduce long term disabilities in this group of patients. Monitoring of cerebral perfusion during such complex and intricate surgery has the advantage of identifying periods of reduced or disturbed perfusion which could be responsible for neurologic damage. A novel observation from the current data shows that cerebral perfusion measured using NIRS, the current clinical practice tool for monitoring perfusion, increased during cooling to minimum temperature. One previous study has also reported an increase in cerebral oxygenation from 63 ± 11% to 88 ± 7% after 15 minutes of cooling during cardiac surgery (Tobias et al., 2009). It is important to note that the increase in NIRS during cooling does not match CBFv measured using TCD, the current data suggests there was a delay in the increase in NIRS, and the increase begins at lower temperatures rather than during the onset of cooling. Taken together, the increase in NIRS during CBP cooling is a noteworthy physiological observation that provides insight for perfusionists and anaesthetists.

In the current study there was an increase in CBFv during cooling, with a significant increase beginning at the onset of cooling. This observed cooling mediated an increase in CBFv did not cause hyperperfusion as the CBFv values during cooling are comparable to normative values for healthy neonates (i.e. 24-42 cm/s, Truemer and Fisher, 1993). Previous

research studies have focused on investigating cooling and CBFv in healthy adults similarly demonstrate CBFv increases in response to cooling (Brown et al., 2003), Whilst some animal studies suggest CBFv decreases during cooling, (Ehrlich et al., 2002), swine and human neonatal neurological response during CPB and DHCA are different (Mavroudis et al., 2018). The neonatal and paediatric physiological responses to cooling are unclear, with limited research focusing on CBFv throughout the entire cooling process. In one case study by Busche et al., (2016), although not highlighted as a main finding, the data suggested that CBFv increased during cooling which was comparable to the current findings. The data from this study similarly suggests that a higher cerebral perfusion was not mediated by CBP flow rates, which can be manually altered during aortic arch repair, as CPB flow rates were similar during cooling. Haemodynamic and blood gas changes were evident throughout the aortic arch procedure. It is important to highlight the monitoring of haemodynamic variables during aortic arch repair changes during cooling. Once the patient is cooled to 28 ºC pH stat management is used rather than alpha stats. The use of pH stats is to prevent and control acidosis. This is a temperature correct method, at lower temperatures pH is kept low at ~7.4. To achieve this CO_2 was added to the CPB oxygen admixture in the oxygenator (pCO_2 is kept at ~40 mmHg) (Hirata, 2018). This is also an advantageous method for maintaining cerebral perfusion as increases in CO_2 will increase CBF at lower temperatures when CPB flows are relatively reduced. One previous study measured TCD differences between pH and alpha stat management during CPB. During pH stat management there was a global CBF and MCAv increase at 28°C by 45.9% and 51.8% respectively. Whereas in patients that underwent alpha-stat management, CBF and MCAv had a decrease by 26.4 and 22.4% respectively at 28°C (Trivedi et al., 1997). Therefore, changing pH stat management might have contributed to the increase in CBFv during cooling but it was not the only contributing factor. CBFv was already significantly elevated before (i.e. at 30 ºC) the change to pH stat

management and the elevated CBFv was not maintained during cerebral and whole body perfusion. Another factor which could explain the increases in CBFv during cooling is the changes in HCO_{3-} during cooling. It can be seen from Figure 5.4 that changes in HCO3- and CBFv follow a similar pattern of change throughout aortic arch repair. The impact of HCO_{3-} on CBFv recently been highlighted as an important factor in cerebral autoregulation (Caldwell et al., 2021b). Changes occur through the bicarbonate buffering system. With an increase in HCO3-, there is an increase in pCO_2 and hydrogen ions. This activates the gated calcium ion channels, hyperpolarising the endothelial cells leading to vascular vasodilation in the arterioles and precapillary sphincter (Battisti-Charbonney et al., 2011). This is thought to be more predominant in sedated populations (Buckley et al., 2013). When there is an increase in pCO_2, 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, which is used in paediatric cardiac surgery. This may give an insight into the pattern of change seen in CBFv during paediatric aortic arch repair.

Another neuroprotective technique used during aortic arch repair is selective antegrade cerebral perfusion. During this period the arterial cannula is moved into the innominate artery to ensure only the brain is perfused. At this point the CPB flow rates are reduced based on normal cardiac output to the brain at rest in an attempt to reduce the number of embolisms (Mitchell and Merry, 2015). The CPB flow rates are manipulated manually to maintain NIRS values at ~15% of when the patient was placed onto full flow CPB. At this time point there was a decrease in CBFv. Previous research has suggested that in clinical populations, the cerebral vessels are unable to buffer large reductions in MAP which in turn leads to hypoperfusion (Selnes et al., 2012). A reduction in MAP was observed at this time point, which could explain the reduction in CBFv. Intriguingly, NIRS values at this point were higher than the CBP timepoint during cerebral and whole-body perfusion,

thus not lower like the pattern seen in CBFv, which had decreased to levels similar to the CPB timepoint. Whilst previous research has suggested that during cardiac surgery there are instances when cerebral oxygenation and CBFv follow the same pattern of change (Andropoulos et al., 2003). The current data suggests that NIRS and CBFv does not follow the same pattern at this important period of cerebral and whole-body perfusion. One potential physiological explanation for the elevated oxygenation despite reductions in CBFv could be the reduced brain metabolism as a result of cooling (Manetta et al., 2018). The current data highlights that CBFv decreased, whilst NIRS was maintained as adequate, highlighting that NIRS may not be reflective of cerebral perfusion during the whole aortic arch procedure.

Another novel aspect of this study was that CBFv measurements were taken during rewarming and recovery on PICU. Following selective and whole-body reperfusion the patients were rewarmed and the manual flow rate was increased again to full flow. During this time both CBFv and NIRS levels were maintained at similar levels to CBP timepoint. Nevertheless, CBFv was higher 24 hours post-surgery in paediatric intensive care compared to baseline and CBP (i.e. when sedated) suggesting the repair was adequate. The values evident post-surgery were comparable to normative CBFv in healthy neonates (Truemper and Fisher, 1993).

5.4.3 The Correlation between Near Infrared Spectroscopy and Transcranial Doppler Ultrasound

Another aim of the study was to examine the relationship between NIRS and TCD at each time point during surgery. NIRS is used as a clinical tool to assess cerebral perfusion and to ensure adequate CPB flow rates. 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 (Joshi et al., 2010a). This corresponds with previous research that has suggested NIRS is a useful tool during aortic arch repair. In previous research NIRS was correlated with trends in cerebral haemoglobin saturation during aortic arch repair (Santo et al., 2008). 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 (Grocott and Davie, 2013). 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 (Bakdash and Marusich, 2017). The current data suggests a statistically significant but weak correlation. Physiologically, small changes in CBFv could have an impact on cerebral perfusion which could potentially be underestimated by NIRS. However, it has been established that in paediatrics undergoing hypothermic CPB, cooling has been exponentially related to a significant reduction in brain metabolism (Ferradal et al., 2016), meaning the requirement of oxygenated blood decreases. In the aforementioned study they measured CBF and cerebral metabolic rate of oxygen to assess the cerebral metabolism in the brain. They had five measurement points and found that after cooling there was a reduction in CBF. However, unlike the current study, they did not take measurements throughout cooling. There was no indication as to the metabolic changes during the cooling phase or when the patients were first placed on to CPB. They did find, despite a reduction in CBF, CBF was still more than cerebral demand which was shown by high levels of oxygenation. Suggesting that during deep hypothermia, despite a reduction in CBFv, the demand for oxygen is adequate during neonatal cardiac surgery. It is noted that 2/9 subjects in the study had neurological sequalae. One patient required ECMO immediately post-operatively for poor cardiac output and another had multiple foci of white matter injury evidential through an MRI 13 day post-surgery.

NIRS is used clinically as a bedside monitor with the foresight of reducing incidences of neurological deficit. NIRS is an easy to administer measurement which has previously been shown to give a good indication of reductions in cerebral oxygenation during cardiac surgery. However, it is unable to measure hyperperfusion and it is only a regional (frontal lobes) indication of cerebral oxygenation. TCD has several methodological advantages over NIRS including measuring velocity within the main cerebral vessels which provides an insight of global perfusion as well as periods of hypo- and hyperperfusion. It is also important to note, although not reported in the results. There was no significant difference between NIRS in the left and right side, so the data was averaged. Then the mean data was used for the analysis. This corresponds with previous research which has found no difference between perfusion in the left and right during neonatal aortic arch repair (Rüffer et al., 2017). In summary, the relationship between NIRS and TCD in the current study suggested that although there was a relationship, it was weak. This corresponds with previous data which has suggested that the relationship between NIRS and TCD is unpredictable, with NIRS overestimating oxygenation especially at lower levels (Ferradal, 2017).

5.4.4 Methodological Considerations and Limitations

As part of the planned post hoc comparisons to examine the main effect of time, two time points were chosen to compare CBFv. The time points were baseline (sedated before CBP) and CBP. Previous research suggests when patients are placed onto CPB that CBFv is reduced (Reves, 2019). Moreover, the CBP time point is used clinically to determine CBP flow rates later in the procedure based upon NIRS values. Therefore, both time points were used for comparison. Significant changes from these time points would indicate important changes in perfusion.

Whilst TCD is unable to measure flow as it does not measure vessel diameter, in a rested state where vessel diameter is expected to be maintained, TCD can give an accurate indication of flow. The anaesthetic technique can affect vessel diameter. To recue this a combination of fentanyl, midazolam and inhaled sevoflurane was used to sedate the patients during cardiac surgery. Previous research has suggested that the use of fentanyl and inhaled sevoflurane does not affect CBF compared to other anaesthetic such as remifentanil (Abdallah et al., 2002). In regards to midazolam, it was suggested that midazolam has minimal effect on CO_2 reactivity, CBF and blood oxygenation (Kiviniemi et al., 2005).

All CBFv measurements were taken by one trained individual. Given the equipment and space restriction in theatre, access to head was limited and measuring MCAv via the temporal window was not always possible. The MCAv was thus isonated via the open fontanelle in all participants. Where possible, dual measurements were obtained from the temporal window. The TCD probe was placed in the same position on the fontanelle and the same depth (~30-40mm) was used for all measurements.

5.4.5 Research Implications

There are no universal guidelines for the minimum temperature achieved during cooling and is often based on centre/surgeon preference. Achieving lower temperatures takes longer and could potentially lead to further complications. However, the current data suggests little difference in CBFv and NIRS between patients cooled to 20 and 25°C. Using a higher temperature could be beneficial as cooling could be quicker, allowing for a shorter time in DHCA. Currently NIRS is used as the clinical tool to monitor perfusion via oxygenation of the frontal lobes and indicated whether the CPB flow rates are adequate. The current data suggest that NIRS might not be reflective of cerebral perfusion at important time periods during the surgery and the correlation between TCD and NIRS is weak.

Therefore, additional measurements of cerebral perfusion might be beneficial to ensure neuroprotection in this patient group.

5.5 Conclusion

Cooling to either 20 or 25°C as part of neuroprotection regime does not alter the CBFv response during aortic arch repair surgery. Nevertheless, the process of cooling caused an increase in cerebral perfusion, and these changes appeared to be delayed in the NIRS measurements. This was reiterated with the reported weak relationship correlation between NIRS and TCD. This could be accountable through the changes in pH stat management that occurs at lower temperatures and the changes in HCO_3. Taken together, cooling to 25°C may be sufficient for neuroprotection but to change clinical practise extensive clinical trials would need to be implemented.

Chapter Six: General Discussion

6.1 Aims of the Thesis

The focus of the thesis was to examine paediatric, clinical populations undergoing treatments that included extracorporeal circulatory support who are at risk of neurological deficit. The overriding aim of the thesis was to assess cerebral perfusion throughout their treatment using TCD which is not usually deployed as part of routine clinical care. The experimental studies within the current thesis included both TCD and NIRS. NIRS is used in clinical practice but has many documented shortcomings which were outlined in chapter 4. TCD was used in adjunction to NIRS within the chapters of the thesis to gain a better understanding of cerebral perfusion during the use of an extracorporeal circulation.

A group of patients which were identified as at risk of neurological deficit were those undergoing ECMO for acute respiratory failure and/or cardiac failure. This group are reliant on extracorporeal support for potentially long periods of time (days/weeks) and are prolific in developing neurological deficit lesions. The aim of chapter 4 was to measure cerebral perfusion during ECMO with a focus on the weaning period. This is a pinnacle point in treatment when individuals may be decannulated or placed back onto full flow ECMO. The weaning period is a specific time period when cerebral perfusion is likely to be disrupted for up to several hours, which may be detrimental to the patients that ultimately fail weaning.

Chapter 5 then focused on neonates undergoing aortic arch repair. Again, an extracorporeal circulation is used during this procedure but for shorter periods of time. However, there are temperature manipulations during CPB with patients being cooled to temperatures as low as 18°C. Temperature changes are known to impact cerebral perfusion, but the differences in cerebral perfusion between patients cooled to 20 or 25°C have not been investigated previously, with no universal guidelines available. The overall aim of

chapter 5 was to measure cerebral perfusion before, throughout aortic arch repair and during recovery on PICU. The difference between the two temperature groups was also explored.

6.2 Summary of Major Findings

The novel findings from the current thesis include:

- There were daily fluctuations in cerebral perfusion during full flow ECMO, which were not statistically significant, but could potentially be clinically important.
- During the weaning period from ECMO, cerebral perfusion was higher in those that successfully weaned and decannulated, compared to those that failed.
- Decannulated patients that were placed onto conventional ventilation had a higher mean CBFv than those supported using HFOV.
- Cerebral perfusion of patients cooled to 20°C were comparable to those cooled to 25°C during aortic arch repair.
- CBFv significantly increased during the cooling period and returned to pre-CPB levels following separation from CPB during aortic arch repair.
- During both ECMO and aortic arch repair, NIRS and TCD broadly followed a similar pattern of change. The relationship between the two measurements was weak, which declined further during the weaning period of ECMO.

6.3 General Discussion of Findings

6.3.1 Changes in Cerebral Blood Flow Velocity during Full Flow Extracorporeal Membrane Oxygenation

In chapter 4, NIRS and TCD were measured daily throughout full flow ECMO. Overall during full flow ECMO, CBFv was lower than previously published normal values for healthy age matched individuals (Truemper and Fisher, 1993; Table 3.1). This finding

corresponds with previous research which suggested ECMO patients have a lower CBFv than previously published normative values for healthy age matched individuals (O'Brien, 2019). The aforementioned study included paediatric patients up to 18 years old with a large variety of aetiologies. In Chapter 4 a more homogeneous population was recruited with inclusion up to 5 years old (actual age range 1-406 days). This age group has previously been identified as a key age in neurological development, and the focus of previous research into neurological deficit of ECMO survivors. The acute and chronic clinical importance of these daily variations in CBFv are currently unknown. It is possible that such daily variation in CBFv, even at the magnitudes observed within the current thesis, could impact the critically ill paediatric brain. Future research is warranted examining daily variation in CBFv of critically ill neonates, which include longitudinal follow up to examine neurological deficit.

6.3.2 Cerebral Blood Flow Velocity during Weaning

In chapter 4, CBFv was also monitored for the first time during the weaning period, a process which most ECMO patients will experience. The weaning period is a crucial part of the treatment process where the patient is attempted to be separated from ECMO. The probability of the patient being successful is currently undetermined. With no clear guidelines as to identify if a patient will successfully wean. Often the view of clinicians is to wean the patient from ECMO as early as possible as the detrimental effects of prolonging ECMO treatment have been established (Gupta et al., 2015). However, if a patient is not ready to wean this can potentially cause CBFv to be disrupted for prolonged periods of up to several hours before being placed back onto full flow ECMO. Being able to add physiological or clinical assessments to further aid this critical clinical decision is imperative. Identifying patients who will fail weaning is important in shortening the exposure to disruptions in CBFv. Chapter 4 has provided preliminary evidence that cerebral

perfusion could be an additional measurement that could be useful in providing information on whether a patient will successfully wean. Patients who were successfully weaned maintained a higher CBFv than those which failed. If CBFv is indeed a marker or can provide additional clinical information, it could be a useful tool to aid clinical decisions. Nevertheless, a full powered randomised control trial is required to provide more definitive data on whether CBFv measurements provide insight into the successful weaning from ECMO.

6.3.3 Cooling and Cerebral Blood Flow Velocity

The concept of cooling to lower core temperature to provide neurological protection is a common clinical treatment in paediatric clinical care. The target lowest temperature achieved during aortic arch repair is dependent on a variety of factors. This includes, centre, surgeon preference, type of procedure, estimated cross clamp time or the use of circulatory arrest. Nevertheless, even within similar procedures there are differences between the lowest temperature achieved during the cooling period, with some surgeons cooling to temperatures as low as 18°C and others at 25°C. Chapter 5 investigated for the first-time cerebral perfusion during cooling and compared the perfusion within the two temperature groups. The novel finding was cerebral perfusion was similar between the two temperature groups. This finding could provide the first evidence to suggest that less time is needed to cool during surgery which could be important for all cardiac surgeries employing cooling, especially during longer procedures.

Another novel finding from the current thesis is that CBFv increased during the cooling procedures for aortic arch repair. Cooling to low temperatures during CBP has been explored previously in animal studies. In swine studies it was found that CBFv decreases during cooling whilst undergoing CPB (Ehrlich et al., 2002). However, animal models

cannot simulate the complexity of the developing neonatal brain. Particularly in patients with a cardiac deformity when disturbances in cerebral perfusion begin antenatally (Kaltman et al, 2005). Moreover, human studies also suggest that CBFv increased during cooling. An example would be a case study of a 10-day old neonate undergoing aortic arch repair also reported an increase in CBFv during cooling (Busch et al., 2016). The impact of CBF during cooling also appears to be influenced through the stat management during CPB. In a study directly measuring alpha versus pH stats during paediatric cardiac surgery, it was found when patients had been cooled to 28°C with alpha stat management, there was a decrease in CBF from baseline measurement. Whereas the patients that had undergone pH stat management, an increase in CBF from baseline was seen at 28°c (Polito et al., 2006). However, in the aforementioned study only one measurement was taken when 28°C was achieved. The relationship between pCO_2, HCO_{3-} and CBFv could also be taken into account when understanding the pattern of change in CBFv during cooling. From chapter 5, HCO_{3-} and CBFv followed a similar pattern of change through aortic arch repair. Changes in HCO_{3-} lead to changes in pCO_2. When there is an increase in HCO_{3-}, there is an increase in pCO_2 and hydrogen ions. This cause vasodilation, thus an increase in CBFv. Taken together, the current finding from the thesis suggests that cooling procedures for aortic arch repair increase CBFv.

6.3.4 The Relationship between Near Infrared Spectroscopy and Transcranial Doppler Ultrasound

In Chapters 4 and 5 a relationship between NIRS and TCD was evident, albeit weak. Moreover, whilst NIRS and TCD broadly followed the same direction of change, the differences in the magnitude of changes were large, especially during ECMO. The presumption used by clinical teams during ECMO is that if NIRS is within a specific range, the flow rates of the ECMO machine are adequate, and thus the brain is being perfused

sufficiently. As outlined previously within the thesis, NIRS has several limitations and only monitors oxygenation in the frontal lobes. The data from the current thesis suggest at important time periods NIRS does not adequately reflect CBF within the main cerebral vessels. Thus, patients may be exposed to periods of inadequate CBFv. The current data suggests additional monitoring of CBF as an adjunct to NIRS could provide further information on cerebral perfusion. Another limitation of NIRS is that it cannot indicate hyperperfusion, which is a common issue in ECMO patients (Lorusso, 2017). Further research is warranted to examine if TCD can detect periods of hyperperfusion during ECMO.

During aortic arch repair, especially when patients are cooled to low temperatures, metabolism in the brain is lower due to a decrease demand for oxygenated blood. Making the reduction in blood flow potentially not detrimental. The NIRS data in chapter 5 could suggest at this time period the oxygenation in the brain is maintained, despite a reduction in CBFv. The demand of oxygen decreases during this period and it has been suggested that there is adequate blood supply and no evidence of ischaemic brain injury using antegrade cerebral perfusion (Pacini et al., 2010). It is key to note that cooling is only performed for a section of the surgical procedure and that overall, the relationship between NIRS and TCD was weak. Once the rewarming period is initiated, NIRS may not be adequate enough at detected reperfusion injuries or changes to CBFv such as hyperperfusion, cerebral ischaemia and embolisms (Ohmae et al., 2007).

6.4 Methodological Considerations

Measuring CBFv using TCD in this population is advantageous as it is a non-invasive measurement which can be taken daily at bedside with minimum disruption. TCD has shaped the understanding of cerebrovascular physiology. It is a relatively low cost, easy

to use, portable, non-invasive measurement (Willie et al., 2011). Clinically, the use of TCD includes sickle cell disease, brain death, stenosis, vasospasm, shunt and emboli detection (Willie et al., 2011). TCD also has limitations which need to be considered (Willie et al., 2011). An inherent issue with TCD is the inability to measure artery diameter. Changes in vessel diameter affect the accuracy of the CBF measurement with only velocity being measured. Measurements of absolute flow of CBFv is adequate when assuming the vessel diameter remains constant over time (Ainslie and Hoiland, 2014). In a rested state, the assumption that vessel diameter remains unchanged is plausible. In patients undergoing aortic arch repair; cooling, the use of pH stat management, cardioplegia and anaesthesia may impact vessel diameter. Similar principles are applied to ECMO patients who are exposed to anaesthesia, non-pulsatile blood flow, pre-ECMO conditions and underlying medical conditions can all impact vessel diameter. However, previous research has suggested that there is no significant change in MCA diameter during cardiac surgery (Polito et al., 2006). Also, recent advances in ultrasound technology and analysis techniques allow calculations of absolute blood flow using velocity and diameter measurements from a duplex ultrasound. Therefore, it is possible to obtain absolute blood flow of the MCAv in neonates with an open fontanelle, although this would require post-process analysis. This technique may overcome the limitations of both NIRS and TCD.

The clinical populations used in this thesis also need to be considered. Research into critically ill populations is sparse. This is due to the limited number of patients and the access to these individuals. Potential methodological issues are associated with this cohort, such as the availability of taking measurements and disrupting clinical treatments. It is important to take into consideration that these patients have 24-hour care, with constant interventions from the medical team. Opportunity to take additional measurements is limited. Conducting

research of a sensitive nature also needs to consider parental needs, measurements at a sensitive time are not always plausible.

Overall, whilst TCD can offer an additional insight into cerebral perfusion during these treatments, it is not logistically currently possible to implement TCD as part of routine clinical practice, and that was not the aim of the thesis. The thesis aimed to use TCD as an adjunct measurement technique to describe CBFv during treatments and to establish the strength of the relationship between NIRS and TCD. TCD has been demonstrated as a useful tool in scientific research and has paved the way for developing an understanding of the cerebrovasculature and cerebral autoregulation. However, it relies on a trained individual with an in-depth knowledge of the cerebrovasculature. Whereas NIRS can be used quickly and does not require specialist training. In the future, TCD could be used to optimise NIRS through understanding the correlation between changes in NIRS to changes in TCD. This may develop a further understanding of both global and regional cerebral perfusion during treatments.

6.5 Recommendations for Future Research which are Based on the Findings of this Thesis

1. Future research in CBFv during cardiothoracic procedures and critical care should consider the use of duplex ultrasound to measure vessel diameter alongside flow velocity. This can provide absolute cerebral perfusion within a given vessel (e.g. MCA) and would be possible in younger patients with an open fontanelle. This would be useful in populations such as neonatal ECMO and CHD patients. This could be plausible as most sites conduct daily cranial ultrasounds which are performed to assess structural changes. Therefore, most sites have trained sonographer available within the care team. However, this would require the

purchase of additional software, a compatible ultrasound machine and time post imaging to calculate the CBF values.

2. Using data from the current thesis, a fully powered multi-centre study examining whether TCD or ultrasound can predict the success of weaning from ECMO would be useful in aiding current clinical practise.
3. Longitudinal study is required that measures TCD during ECMO with a follow up period to assess long-term neurological outcomes of survivors.
4. Further research is warranted to exam cooling during aortic arch repair surgery. With a focus on the impact of cooling to different temperatures on cerebral perfusion and long-term outcomes. This could lead towards a more universal approach to neuroprotective strategies implemented during cardiac surgery.
5. Future research should also consider monitoring cerebral perfusion during cooling procedures in different types of congenital heart surgery in neonates, paediatrics and adults. This can establish differences between conditions, identify patients most at risk of ischaemic injury and to understand the differences between paediatrics and adults.

Chapter 7: References

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