

**ASSESSMENT OF THE TRANSITIONAL CIRCULATION IN LATE PRETERM
AND TERM NEONATES USING NON-INVASIVE BIOMARKERS: A
LONGITUDINAL ANALYSIS AND EVALUATION OF REPEATABILITY**

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1 Abstract

Neonatal circulatory adaptation at birth is unique. If the transition from an in- to ex-utero circulatory system is unsuccessful, circulatory failure ensues resulting in anaerobic respiration and eventual tissue death. This thesis explores the use of novel non-invasive techniques to assess neonatal circulatory adaptation.

Data are reported from three observational cohort studies including infants aged less than 72 hours of age and greater than 33 weeks' gestational age (GA) who received special care (n=50), intensive care (n=25) or total body cooling (n=14). For the first three days of life infants had routine daily clinical assessments (e.g. blood pressure), echocardiographic (superior vena cava flow and right ventricular outflow) and plethysmographic measurements (modified pleth variability index and pulse transit time). Daily longitudinal, comparative and correlational analysis of these measures within and between cohorts of neonates were performed. In addition, their relationships to assessments of short term neurological outcomes and cardiovascular treatment were explored. Bland Altman plots were used to explore the repeatability of plethysmographic and echocardiographic measures.

The results indicate that the cardiovascular systems of between the three cohorts of neonates studied adapt differently over the first three days of life. Specifically, neonates who receive total body cooling exhibited significantly lower blood pressures, heart rates and measures systemic blood flow compared to neonates who are healthy or receiving intensive care. Healthy neonates aged between 33 to <37 weeks GA exhibited daily significant shortening of modified pulse transit time and increased measures of systemic blood flow indicating these neonate's systemic vascular resistances increase more gradually compared to term neonates with end organ perfusion maintained through increased cardiac output. The intra- and inter-observer repeatability of echocardiographic and plethysmographic assessments was poor and excellent respectively (repeatability index range 26-64% vs. 3-13%). Future studies should focus on the use of these biomarkers in the identification of neonates at risk of circulatory failure.

Keywords: Neonate, newborn, echocardiography, plethysmography, circulation

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5 Preface

Neonatal circulation is a unique part of human anatomy and physiology. The processes that underpin the change from an in-utero to ex-utero circulation have been well described. However, these fundamental processes can be affected by a variety of pathologies.¹ When this occurs during the transition phase it can lead to a clinical condition of poor end organ perfusion. This is known as circulatory failure. Due to the unique anatomy of the neonatal circulation identification, accurate measurement and predicting the clinical effect can be challenging. It is known that circulatory failure can lead to a number of adverse short and long-term sequelae in neonates.² Existing evidence suggests that routine bedside measurements poorly correlate to clinical outcomes in neonates, whilst, the effect of treatments remains controversial.

The aim of this thesis is to test the hypothesis that new non-invasive measurements accurately reflect normal cardiovascular adaptation and can therefore be utilised to identify circulatory failure in sick late preterm and term infants. This thesis will also focus on the intra- and inter-observer repeatability of these novel techniques. This thesis contains:

- A review of the literature of the patho-physiology of circulatory adaptation and failure in neonates.
- An appraisal of the evidence that surrounds the methods of measuring cardiovascular adaptation and circulatory failure in neonates with particular focus on non-invasive methods such as superior vena cava flow (SVCF), right ventricular outflow (RVO), modified plethysmographic variability index (mPVI) and modified pulse transit time (mPTT).
- A description of the study designs used and techniques of the measurements utilised.
- An account of the results gained from these studies and the validation of the techniques used in the outlined studies.
- A discussion of the findings from these studies and how this may relate to existing evidence.
- An assessment of the studies limitations and suggestions for future research.

- A conclusion of the thesis with listings of the references used, appendices and publications that have resulted from this work.

6 Author Declaration

I declare that the research contained in the thesis, unless otherwise indicated within the text, is the original work of the author. The thesis has not been submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed 

Dated 21/11//2016

7 Abbreviations/Definitions

aEEG	Amplitude-integrated electroencephalography
BA	Bland-Altman
BSUH	Brighton and Sussex University Hospitals
CO ₂	Carbon dioxide
CRT	Capillary refill time
ECG	Electrocardiogram
GA	Gestational age
HIE	Hypoxic ischemic encephalopathy
IVH	Intraventricular haemorrhage
kPa	Kilopascal
LVO	Left ventricular output
MBP	MAP
MRI	Magnetic resonance imaging
NIRS	Near infra-red spectroscopy
PA _{max}	Maximum pulse amplitude
PA _{min}	Minimal pulse amplitude
PDA	Patent ductus arteriosus
PFO	Patent foramen ovale
PP	Pulse pressure
MAP	Mean arterial blood pressure
mPTT	Modified pulse transit time
mPVI	Modified pleth variability index
NmPTT	Normalised modified pulse transit time
PI	Perfusion index
PP	Pulse Pressure
PVL	Periventricular leucomalacia
RC	Repeatability co-efficient
RI	Repeatability index
RVO	Right ventricular output
SpO ₂	Oxygen saturation (measured by pulse oximetry)
SVCF	Superior vena cava flow
SVR	Systemic vascular resistance

8 Literature Review

8.1 Introduction

The past two decades have seen revolutions in the management of sick premature infants.³ Whilst advances in certain aspects of neonatal care have been dramatic others have lagged behind. For example, with the advent of surfactant the respiratory morbidity of babies born extremely prematurely has significantly improved. However, for more mature neonates with circulatory failure, the morbidity and mortality is similar to neonates born of a lower GA.^{4,5} This is particularly pertinent as experts in the field have approximated that between 20-50% of infants who are admitted to neonatal intensive care may develop circulatory failure.^{6,7}

The cardiovascular adaptation of these infants has not been well researched, and there is no agreed consensus amongst clinicians either on a definition for circulatory failure or on evidence based treatment protocols.⁸ However, with the development of new non-invasive techniques to monitor cardiovascular adaptation further innovations in the care of and treatment sick infants may be emerging.⁹

8.2 The fetal circulation and adaptation at birth

8.2.1 Embryology of the fetal circulation

The heart arises from the splanchnic mesoderm of the developing embryo that initially forms two endocardial tubes that fuse to form one, 21 days after fertilisation. The fusion of the tube begins cranially extending caudally by apoptosis. The resulting single endocardial tube then begins to constrict and dilate at particular points to form the truncus arteriosus, bulbus cordis, primitive ventricles, primitive atria and sinus venosus (Figure 8.1).¹⁰ This structure then undergoes a process known as cardiac looping where it folds into the basic structure of the adult heart with the atria lying cranially behind the ventricles. This process is complete by the fourth week of embryonic development at which point the mesoderm has differentiated into basic myocardial cells that allow the heart to beat at around 65 beats per minute to aid oxygenation and nutrient dispersion.¹¹ Muscular septa begin to form within the heart, which become the atrial and ventricular septa from week 5 onwards, and this coincides with the development of the 4 cardiac valves which are completed by day 49.¹² It is important to note that the atrial septum does not close during fetal life and exhibits intra-cardiac shunting of blood through the foramen ovale. The heart at this point resembles its final basic adult structure.¹²

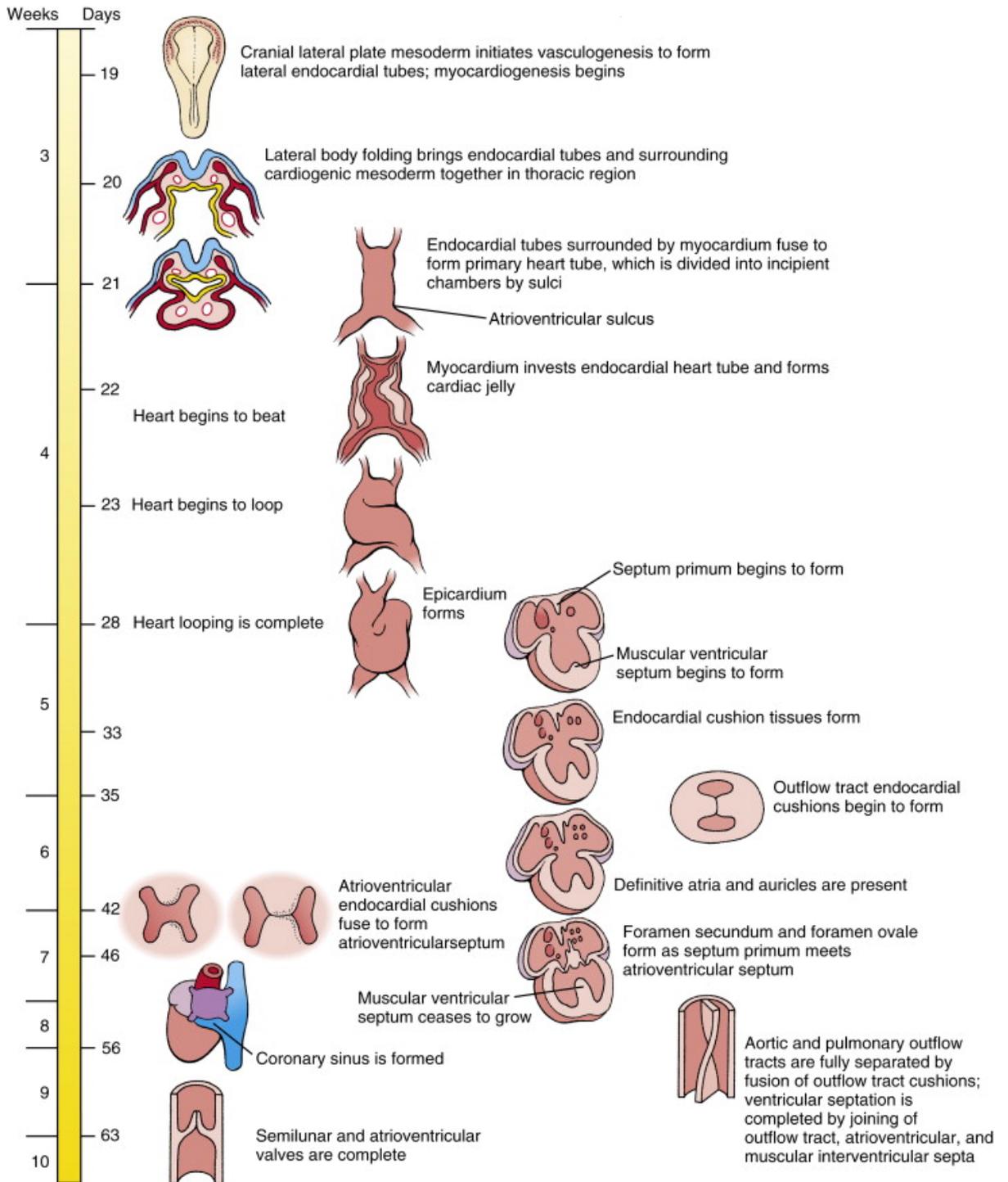


Figure 8.1: Development of the heart over the first 10 weeks of life¹³

At week three of embryonic development the primitive circulatory system develops from the mesoderm (Figure 8.2). The venous system develops from three paired veins that drain into the sinus venosus of the primordial heart tube. The vitelline and cardinal veins return poorly oxygenated blood back from the yolk sac and the body of the embryo respectively. The umbilical veins transport well oxygenated blood back from the placental circulation.^{14,15} The arteriolar system develops from

paired arteries connected to the cardinal end of the endocardial tube. During embryonic folding these vessels are brought forwards to form the aortic arches. The dorsal aortae then fuse to form the aorta from which the vitelline, lateral and dorsolateral branch arteries forming the peripheral arterial vasculature. The ductus arteriosus develops from the sixth pair of these aortic arches and connects the developing left pulmonary artery to the left dorsal aorta and allows for the shunting of blood between these two vessels.¹⁶

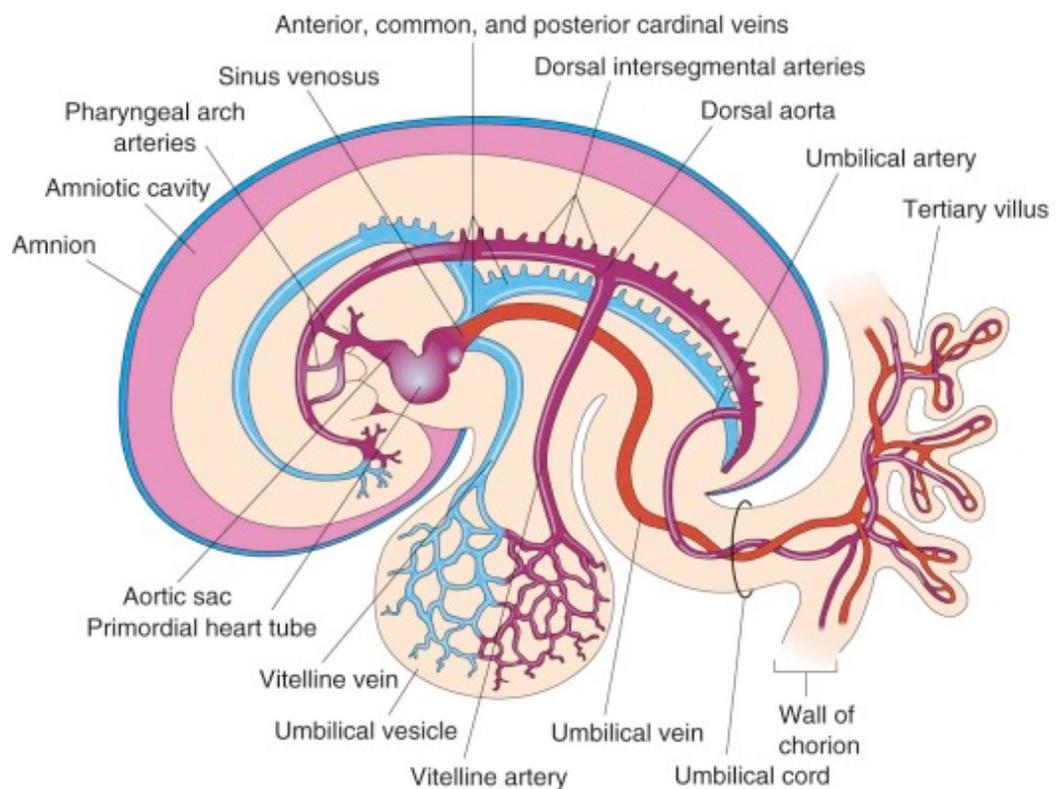


Figure 8.2: Arterial and venous embryonic circulation at 21 days of development¹⁷

The placenta is the main site of gaseous, nutritional and waste product exchange for the developing fetus and consists of two parts. The fetal half develops from the villous chorion that invades the maternal placenta with finger like structures called chorionic villi that project into the intervillous space. The umbilical arteries extend into these villi transporting de-oxygenated and nutrient depleted blood to the chorionic villi with the umbilical veins returning oxygen rich blood to the fetus.¹⁸ This “invasion” process is mediated by oxygen levels, placental growth factors, interleukins and chemokines.¹⁹ The maternal half of the placental circulation is formed by the decidua basalis. When fully developed it allows the endometrial

spiral arteries and veins to also enter the intervillous space allowing for the diffusion of oxygen, nutrients, carbon dioxide (CO₂) and waste products between the fetal and maternal circulation.²⁰ The maternal blood flow to the placenta is about 600ml/min at term and is aided by a large blood pressure gradient, 60 millimetres of mercury (mmHg), between the spiral arteries and the intervillous space.²¹ Regulation of blood flow to the placenta is determined by maternal blood pressure with local release of nitric oxide and endothelin influencing vascular tone.^{22,23}

8.2.2 Fetal circulation

Energy for adequate fetal development is provided by the trans-placental transfer of glucose and oxygen for oxidative phosphorylation. In-utero, the fetal circulation is very different from that of an adult as the placenta, not the lungs, acts as the main site of gaseous exchange. The umbilical artery delivers deoxygenated blood to the placenta where it is oxygenated to around 4.7 kilopascals (kPa) with the fetal haemoglobin being around 80% saturated.^{24,25} The umbilical vein then supplies well-oxygenated blood to the ductus venosus that subsequently connects to the inferior vena cava and delivers blood to the heart via the right atrium.

There are a number of mechanisms that preferentially “shunt” blood to different areas of the body. At the junction of the right atrium and the inferior vena cava there is the eustachian valve that directs highly oxygenated blood in the dorsal aspect of the inferior vena cava across the foramen ovale and into the left atrium (Figure 8.3). This movement of blood is aided by the difference in pressure gradient across the foramen ovale between the right and left atria (3.5 and 3mmHg respectively).^{26,27} This portion of fetal blood is around 65% saturated with oxygen and is pumped from the left atrium to the left ventricle and subsequently to the coronary sinus and the brain via the ascending aorta.²⁸ These mechanisms ensure that well oxygenated blood is supplied to vital organs such as the developing brain.

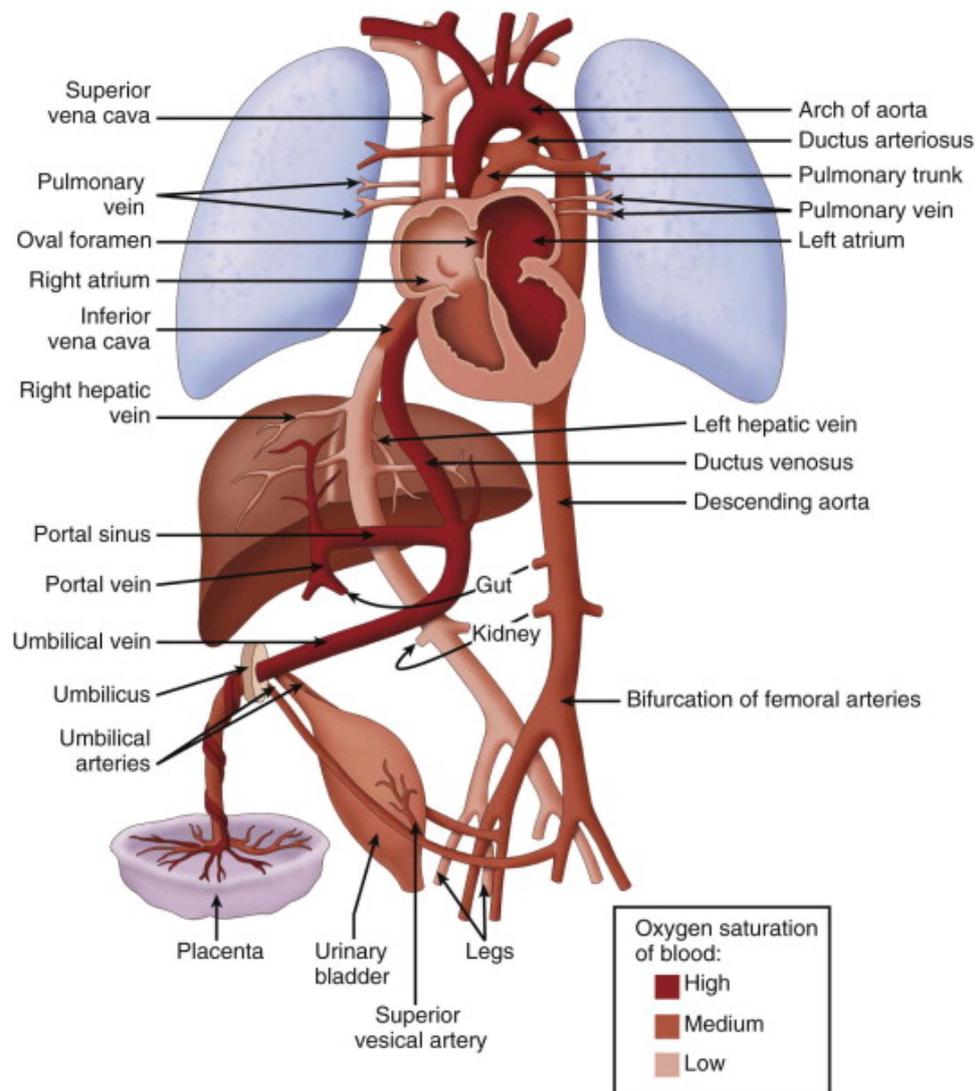


Figure 8.3: Fetal circulatory system²⁹

Desaturated blood (25-40% oxygen) is delivered to the right atrium via the superior vena cava and the coronary sinus. These streams of blood are also present in the anterior portion of the inferior vena cava and are preferentially pumped across the tricuspid valve to the right ventricle where they are driven into the pulmonary artery. Due to the relatively high pulmonary vascular resistance (0.4 mmHg/ml/min/kg in the fetus compared to 0.08 mmHg/ml/min/kg in the newborn) only around 8% of this blood enters the pulmonary circulation whilst the remaining 92% is directed across the ductus arteriosus into the descending portion of the aorta.^{24,30} This means that the lower half of a fetus, whilst in-utero, is supplied with desaturated blood with a partial pressure of oxygen equalling 2.7 kPa.^{12,31-33}

The adult heart pumps blood from both ventricles in series. Due to the intra- and extra-cardiac “shunts” outlined above the total stroke volume of the neonatal heart is therefore dependent on the output of both ventricles (parallel circulation).³⁴ This is because each of the ventricles receive differing amounts of blood from the venous circulation; the left receiving 35% of venous return in comparison to 65% in the right ventricle. As a result of the dynamic and changing circulation it is thought that only 8% of the fetal cardiac output goes to the pulmonary circulation.³⁵ The combined cardiac output increases with GA and in a term fetus is 450ml/kg/min with the right ventricle contributing two thirds of this compared to one third from the left ventricle: this is in part responsible for the relative right ventricular hypertrophy found in fetal life.³⁶ Table 8.1 outlines the distribution of cardiac output to fetal organs.

Organ	Percentage of Cardiac Output
Placenta	40%
Body	25%
Brain	13%
Lung	8%
Intestines	5%
Heart	4%
Kidney and Adrenal glands	3%
Liver	2%
Spleen	1%

Table 8.1: Organ distribution of fetal cardiac output³⁷

8.2.2.1 Fetal heart

The function of the fetal heart is vastly different to the adult heart and there are many factors that potentially disadvantage it in maintaining cardiac output.³⁶ Firstly the low filling pressures tend to reduce ventricular filling.²⁴ However this is partially offset by the compliance of the myocardium is increased in utero owing to difference in the sarcomere protein titin.^{36,38} Secondly a higher resting heart rate reduces ventricular filling, and thus cardiac output.³⁹ Thirdly contractility is reduced due to the immaturity of sarcoplasmic reticulum, t-tubules and reduced troponin C levels. Finally the myocardium has fewer adrenergic receptors meaning sensitivity to catecholamine stimulation is decreased.^{36,38}

8.2.2.2 Fetal haemoglobin

The total blood volume of a term neonate is around 80mls/kg with a haemoglobin concentration of 16g/dl.⁴⁰ Despite the relatively low oxygen tension in the fetal circulation adequate oxygenation to the developing embryonic tissues is aided by the increased oxygen affinity of fetal haemoglobin compared to adult haemoglobin (Figure 8.4). This is due to reduced levels of 2,3-diphosphoglycerate in fetal haemoglobin and enables the passive diffusion from the maternal to fetal circulation even if the partial pressures of oxygen are similar in both.^{41,42} Whilst this is an advantage at a placental level it impedes oxygen release to fetal tissue. This is compensated for by the relative acidity of the fetal environment (pH 7.25-7.35) that leads to a right shift in the oxygen dissociation curve (Bohr effect) promoting the release of oxygen from fetal haemoglobin.²⁴

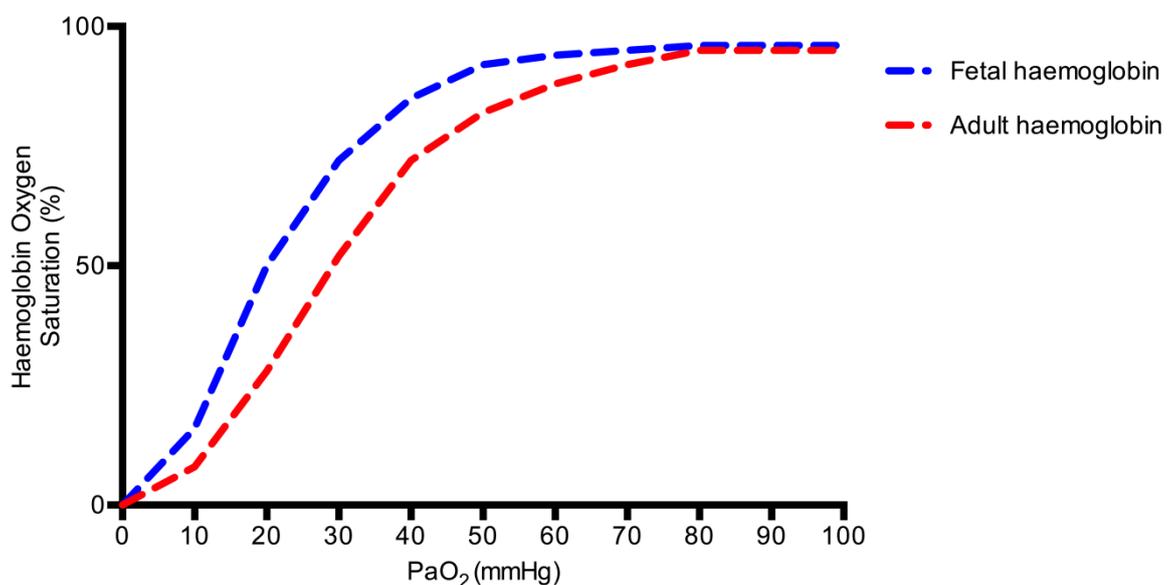


Figure 8.4: Oxygen haemoglobin dissociation curves for fetal and adult haemoglobin

8.2.3 Fetal circulation homeostasis and regulation

The regulation of the fetal circulation is poorly understood but is probably achieved through a combination of both neuronal and hormonal regulation.⁴³ The systemic fetal circulation has a high vascular resistance through vasoconstriction of the blood vessels due to local vasoactive substances as well as catecholamines such as noradrenaline.⁴⁴ The fetal pulmonary circulation also has a high vascular resistance owing to the high muscle mass in the arterioles and increased vascular

tone. The ductus arteriosus remains open due to a relatively low resting oxygen tension and high circulating levels of prostaglandin E₂.^{45,46}

8.2.3.1 Autonomic nervous system regulation

The primitive autonomic nervous system develops in the fetus from 5 weeks GA with the parasympathetic emerging prior to sympathetic innervation.⁴⁷ This is demonstrated by alterations in heart rate and blood pressure by the injection of cholinergic and adrenergic antagonists into lamb fetal animal models as early as 60 days of gestation.^{48,49}

8.2.3.2 Baroreflex regulation

Arising from afferent feedback from baroreceptors within the aortic arch and carotid bodies the purpose of the baroreflex is to minimise the fluctuations in blood pressure by altering vascular tone and heart rate.⁵⁰ For example, the reflex responds to an increase in blood pressure by decreasing heart rate and systemic vascular resistance (SVR).⁵¹ This has been demonstrated in an ovine fetal model at about 80 days gestation by sinoatrial denervation which resulted in increasing blood pressure and heart rate variability.⁵²⁻⁵⁴

8.2.3.3 Chemoreflex regulation

Mediated by receptors in the aortic arch and carotid bodies it is present from around 80 days GA.⁵² Chemoreflex regulation responds to changes in the partial pressure of oxygen and carbon dioxide in the circulation, with hypoxia, for example, producing bradycardia and hypertension, a response abolished by carotid de-innervation in fetal lamb models.⁵⁵

8.2.3.4 Hormonal regulation

The renin-angiotensin system and the adrenal medulla are important in the hormonal regulation of the fetal circulation. The latter is formed from the coelomic epithelium of the embryonic ectoderm during the fourth week of development with the renin-angiotensin system being present from 90 days GA.⁵⁶ The complex

interplay of hormonal regulation on fetal circulation is demonstrated during episodes of fetal hypoxia. The adrenal medulla secretes catecholamines (adrenaline and noradrenaline) increasing heart rate through β adrenergic stimulation. This combined with an increase in the release of vasopressin, adrenocorticotrophic hormone, atrial natriuretic peptide and adrenomedullin leads to the redistribution of blood flow in the fetus to the adrenal glands, brain, heart and placental circulation through selective vasoconstriction of vascular beds.⁵⁶⁻⁵⁸

8.3 Neonatal adaptation at birth

At birth the neonatal circulation has to undergo a number of major physiological and anatomical changes in order to switch from an in-utero to ex-utero circulation. The majority of our knowledge with regards to circulatory adaptation comes from animal studies.⁵⁹ Successful transition to an adult type circulation is dependent on a number of inter-related processes between the respiratory, endocrine and cardiovascular systems.

8.3.1.1 Respiratory adaptation

When an infant is born it is believed that breathing is initiated by the stimulation of chemoreceptors through increasing partial pressures of CO₂, hypoxia and physical stimulation such as light and handling.⁶⁰⁻⁶² Throughout fetal life the lungs are filled with fluid that contributes to their normal development.⁵⁶ At birth increases in adrenaline release from the adrenal medulla activates luminal sodium and aquaporin channels, prompting the reabsorption of lung liquid.⁶³ The initiation of inspiration also contributes to the reabsorption of fluid through increasing the transpulmonary pressures.^{56,64,65} This lung fluid is transported to the surrounding interstitial tissue where it is re-absorbed by the blood and lymph vessels.⁵⁶ For sufficient gaseous exchange the lung needs to establish a functional residual capacity (FRC). After the first inspiration, breathing strategies involving panting (i.e. short expiratory time) and grunting (i.e. partial vocal cord closure during expiration) may be utilised to create and maintain a FRC between 23-32mls/kg.⁶⁵⁻⁷⁰ The increase in FRC with the reduced surface tension created by surfactant promotes lung fluid reabsorption and helps establish uniform aeration of the lungs.¹ This change in gaseous exchange leads to arterial oxygen saturation in a neonate increasing from 50% in utero with half of infants then having oxygen saturations of 66% and 89% at 1 and 5 minutes of age respectively after delivery.^{71,72}

8.3.1.2 Endocrine adaptation

In the week prior to birth there is a gradual increase in the fetal production of cortisol that peaks at delivery.⁷³ It is thought that this primes an infant for delivery

by maturing liver gluconeogenesis pathways, β receptor density in cardiovascular tissue and conversion of triiodothyronine to thyroxine.⁵⁶ These cortisol driven changes coupled with increased catecholamine and angiotensin 2 release (both observed at delivery) all lead to increases in blood pressure and the availability of fatty acids and glucose for energy production.^{24,74}

8.3.1.3 Cardiovascular adaptation

Whilst normal respiratory and endocrine adaptation take hours to complete, cardiovascular adaptation is distinctive as it can take a number of days to conclude.^{30,75}

At birth there is a large increase in the alveolar partial pressure of oxygen as the first breaths lead to rapid expansion of the lungs. The increase in the alveolar partial pressure of oxygen promotes the release of nitric oxide, bradykinin and prostaglandin I₂ from the pulmonary vascular epithelium leading to stimulation of the pulmonary stretch receptors.^{24,76} This leads to a dramatic fall in pulmonary vascular resistance and a 10 fold increase in blood flow to the pulmonary vessels.^{28,31,77}

Anatomically the rise in pulmonary blood flow increases the venous return to the left atrium. This leads to an equalisation of the pressures within the left and right atrium causing the patent foramen ovale (PFO) to functionally close.⁷⁸ Because of the increase in pulmonary blood flow and vascular resistance the flow of blood across the patent ductus arteriosus (PDA) becomes bi-directional. The ductus eventually closes in response to the increased arterial partial pressure of oxygen leading to contraction of the smooth muscle in its wall.⁷⁹ Furthermore after placental delivery the levels of prostaglandin E₂ decrease rapidly which is believed to also promote ductal constriction.^{60,80} The functional closure of the ductus arteriosus should occur by 96 hours of age in healthy term babies.^{1,81} At the placental site the increase in partial pressures of oxygen lead to the vasoconstriction of the umbilical vessels. This leads to a reduction in the flow in the inferior vena cava and in the ductus venosus which subsequently closes at 10 days after birth. Traditional obstetric care has promoted immediate cord clamping

once an infant is born.⁸² When this occurs the low resistance placental circulation is removed completely, prompting a sudden increase in the SVR. The surge in adrenaline, noradrenaline and cortisol also contributes to increased SVR through promoting vasoconstriction.^{60,80}

Owing to these anatomical changes the cardiac ventricles change from a “parallel” to a “series” circuit. The output of each ventricle, in response to surges in adrenaline and cortisol, doubles to 400ml/kg/min increasing blood flow to the lungs, kidneys and gastrointestinal tract.³¹ It is important to note that in fetal life cardiac function is dependent upon venous return from the placenta.⁸³ When changing to a “series” circulatory system left ventricular output becomes dependent on pulmonary blood flow and venous return.^{56,84} It is therefore preferable to ensure an infant is breathing before clamping the cord to promote pulmonary blood flow and therefore preloading of the left ventricle. This may be facilitated by the process of delayed cord clamping; where the umbilical cord is left un-clamped for approximately 1 to 3 minutes after birth. This is reflected in recent animal studies which observed that carotid blood flow, heart rate and right ventricular output (RVO) were more stable when breathing was established before the cord was clamped at 3 to minutes of age.⁸⁵

8.4 Circulatory failure and abnormal neonatal adaptation

Circulatory failure during neonatal adaptation is a unique condition. Biologically it is defined as tissue hypo-perfusion leading to abnormal tissue oxygenation due to a mismatch in oxygen delivery and consumption. This complex physiological relationship can be expressed mathematically into the equations below.^{86,87}

$$DO_2 = Q \times O_{2 \text{ arterial}}$$

$$VO_2 = Q \times O_{2 \text{ arterial}} - O_{2 \text{ venous}}$$

$$OER = VO_2 / DO_2$$

Where DO_2 = oxygen delivery VO_2 = oxygen consumption, Q = blood flow, $O_{2 \text{ arterial}}$ = arterial oxygen content, $O_{2 \text{ venous}}$ = venous oxygen content and OER = oxygen extraction ratio

When mismatches in DO_2 and VO_2 occur this leads to reduced oxidative phosphorylation, anaerobic respiration, ensuing lactic acidosis and organ failure. Clinically this is most commonly defined as tissue hypoxia secondary to a state of abnormally low arterial blood pressure affecting perfusion.⁸⁸ It is reported that up to 50% of infants who enter intensive care experience circulatory failure.⁸⁹

8.4.1 Pathophysiological mechanisms of circulatory failure

Figure 8.5 outlines the multiple factors that are either extraneous or innate to a neonate's circulation that can lead to circulatory failure.⁹⁰

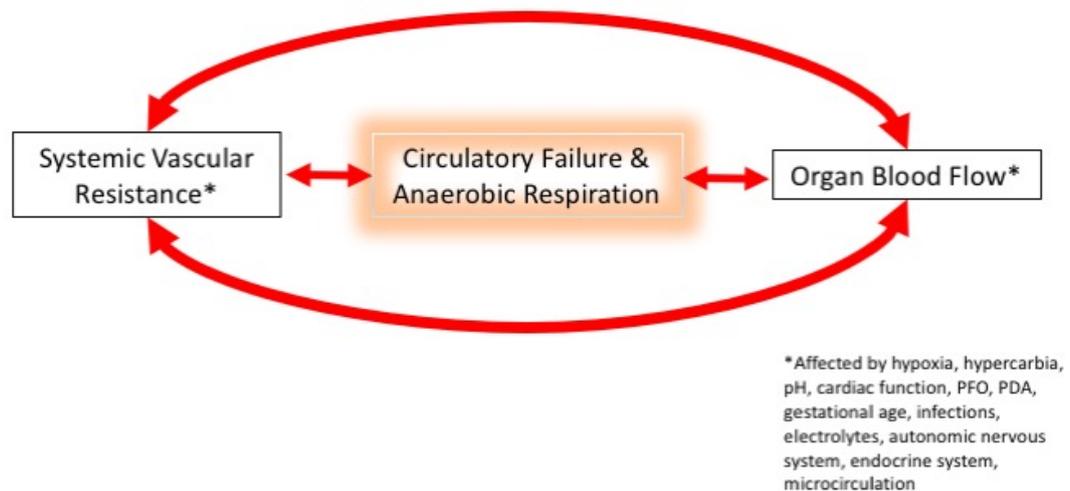


Figure 8.5: Pathophysiological mechanisms interplaying in circulatory failure

Sufficient oxygen delivery to an organ is dependent on adequate blood flow. In general terms, the flow of blood in a blood vessel follows Poiseuille's equation-

$$Q = (\Delta P \times \pi r^4) / 8\mu l$$

Where Q = flow, ΔP = pressure difference across a vessel, r = radius of a vessel, μ = viscosity of the fluid and l = length of the vessel.

However, the above equation describes laminar flow through a tube, which cannot be applied to the neonatal vasculature as the flow is not laminar. In addition, blood viscosity cannot be repeatedly measured. However, given that flow is proportional to the pressure gradient, we can simplify the relationships that influence the development of circulatory failure as an analogue of Ohms law.⁹¹

$$I = \frac{V}{R} \approx CO = \frac{MAP}{SVR}$$

Where I = current, V = voltage, R = resistance, CO = cardiac output, MAP = mean arterial blood pressure and SVR = systemic vascular resistance

As previously mentioned, mean arterial blood pressure is the most commonly used measure to define circulatory failure, so the equation is often adjusted as:

$$MAP = CO \times SVR$$

This has its limitations as there may be no apparent changes in systemic blood pressure despite significant alterations in systemic vascular resistance that, for

example, could be compensated for by changes in cardiac output. Thus a single measure is inappropriate for assessing a neonate's haemodynamic status. Furthermore, it can be argued that both cardiac output and systemic vascular resistance have multiple influences indicating that circulatory failure requires multi-modal assessment (Figure 8.6).

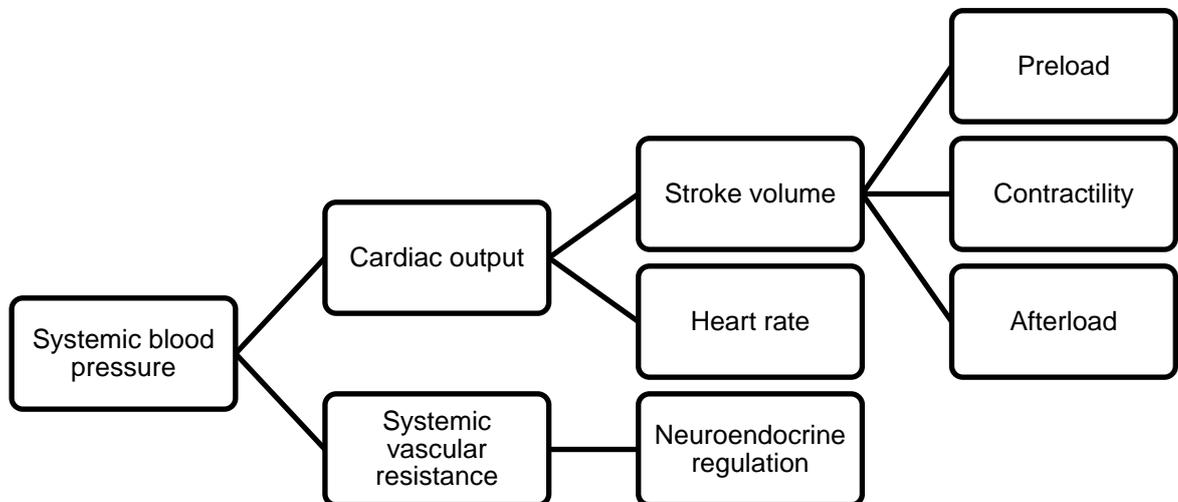


Figure 8.6: Factors influencing the haemodynamic status of a neonate⁹²

8.4.1.1 Cardiac output

Cardiac output is determined by preload, myocardial contractility, afterload and heart rate.

Preload is the end diastolic volume that stretches ventricles of the heart. It is therefore affected by the amount of blood that fills each cavity. Extraneous factors influencing preload include hypovolaemia secondary to maternal placental abruption or during neonatal resuscitation through the use of high inspiratory pressures to support respiratory effort, but also decrease venous return to the heart.⁹² Intrinsically factors in the newborn include reduced rotational flow patterns and relatively high heart rate, which decreases ventricular filling time and therefore preload.^{36,37}

Neonatal myocardium is underdeveloped with a greater water content than that of an adult's, altered calcium release, reduced number of adrenoceptors and immature sarcoplasmic reticulum.³⁶ Therefore, the innate contractility of the a neonate's heart is limited and is more reliant on heart rate to increase cardiac

output.^{93,94} Pathologies such as perinatal asphyxia also decrease cardiac output through negatively affecting myocardial contractility.^{95,96}

Afterload is the force that the ventricles have to overcome in order to eject blood out of the heart. Studies have shown that the neonate's heart responds poorly to afterload.^{97,98} Thus the increase in SVR seen after birth with the removal of the placental circulation can be detrimental to myocardial contractions and reduce cardiac output. Increases in afterload can also be seen in states of hypovolaemia or hypothermia.⁹⁹

8.4.1.2 Systemic vascular resistance

Systemic vascular resistance is affected by the arteriolar and microcirculatory systems. Blood flow to the arteriolar and microcirculatory systems is determined by vessel diameter and thus vascular resistance. The balance of vascular tone is dependent on various mediators exerting their effects through promoting or inhibiting the influx of calcium through cell membranes via voltage gated channels and its release in smooth muscle sarcoplasmic reticulum required for muscle contraction. Other cell membrane receptors identified as important in the maintenance of vascular tone are adenosine triphosphate dependent potassium channels.¹⁰⁰ These channels are known to promote vasodilation, presumably to increase perfusion when there is increasing tissue concentration of hydrogen and lactate. These channels are under the influence of the autonomic nervous system that is mediated by baroreceptors and chemoreceptors in the aortic arch and carotid sinus. Furthermore, local paracrine factors such as the endothelial release of nitric oxide promote the activation of cyclic guanosine monophosphate increasing calcium entry to smooth muscle cells. Other vasodilator substances include prostacyclin, prostaglandin and endothelin. Local vasoconstriction substances include thromboxane A_2 , vasopressin and natural catecholamine's such as adrenaline.^{92,101}

During pathological states such as hypoxia, these adaptive mechanisms ensure that blood vessels in vital organs, such as the brain, vasodilate to provide an adequate blood supply, with vessels in the non-essential organs constricting e.g.

the skin. These mechanisms are underdeveloped in neonates and therefore these infants may be unable to mount an appropriate response, leading to the development of circulatory failure.^{102,103}

The peripheral vascular system is also the main site of oxygen, nutrient and waste product exchange. Blood flow to these vessels is mediated by local tissue oxygen requirements and the tissues' ability to extract oxygen. When the local tissues reach the limit of their ability to extract oxygen, oxygen delivery will then become blood flow dependent.⁸⁶ Thus alterations in vessel tone facilitated by the mechanisms outlined, occur to ensure that blood flow is adequate to maintain oxygen delivery.⁹¹ However, when pathological disturbances in these mechanisms occur, such as inappropriate vasodilation due to increased levels of tumour necrosis factor alpha during episodes of sepsis or asphyxia, disruption to end organ blood flow ensues. This leads to a mismatch in oxygen delivery and consumption and ultimately to circulatory failure.⁹²

8.4.1.3 Systemic blood pressure

Interpreting the role of systemic blood pressure in the development of circulatory failure is challenging as it has multiple influences that are difficult to monitor constantly (Figure 8.6). It may also be due to the difficulty in defining the normal blood pressure range in neonates and how this may relate to pathological states.¹⁰⁴ This is discussed later in this thesis.

8.4.2 Circulatory failure in the context of fetal hypoxia

Hypoxic ischemic encephalopathy (HIE) occurs in approximately 1-6 out of every 1000 live births and may account for up to 28% of cases of cerebral palsy.¹⁰⁵⁻¹⁰⁷ Worldwide hypoxia at birth accounts for 23% of all neonatal deaths and is the fifth largest cause of death in children under 5.¹⁰⁸ Two trials looking at the effects of selective head or total body cooling on morbidity and mortality in babies found that between 23-27% of those with moderate to severe HIE died before discharge.^{109,110} Before the advent of cooling treatment for HIE, approximately 26% those who survived with moderate to severe HIE developed long term neurodevelopmental problems with up to 13% developing cerebral palsy.¹¹¹⁻¹¹³

HIE is associated with multi-organ pathology and frequently this includes circulatory failure. In addition to the initial hypoxic injury to the brain, there is also hypoxic injury to the heart, as evidenced by increased blood markers of myocardial injury such as troponin and creatinine kinase-MB.¹¹⁴⁻¹¹⁶ Echocardiographic studies have demonstrated that these infants can suffer from impaired left ventricular contractility, valvular dysfunction and reduced cardiac output.^{115,117,118}

Since the publication of the “TOBY trial,” infants older than 36 weeks’ gestation with HIE may be treated with total body cooling therapy.¹¹⁹ This involves actively cooling an infant to a body temperature of 33-34°C for 72 hours before re-warming them to a normal temperature of 37°C over a 12-hour period. The cooling process has an effect on circulatory homeostasis – it decreases a neonate’s heart rate through slowing depolarisation in the sinoatrial node.¹²⁰ Cardiac output in cooled infants has been found to be 60% that of normothermic babies.¹²¹ In addition, cooling also increases systemic vascular resistance through promoting peripheral vasoconstriction.¹²¹ By interfering with normal cardiovascular physiology, therapeutic cooling can affect postnatal circulatory adaptation or contribute to the development of circulatory failure.¹²² There is however a paucity of research looking into this topic.

8.4.3 Cerebral consequences of circulatory failure

Inadequate perfusion and oxygenation of the brain is a concern in the context of circulatory failure. During early phases of circulatory failure blood is preferentially re-directed to vital organs such as the forebrain.¹²³ This means that despite dynamic or compensatory changes in the circulatory system at birth, perfusion to the brain is maintained and this is known as cerebral autoregulation.¹²⁴ However, during periods of circulatory failure or HIE the dynamic processes involved in cerebral autoregulation, such as vasoconstriction during periods of hypocarbia, become absent.¹²⁴⁻¹²⁶ Thus cerebral blood flow becomes static, pressure passive and dependent on systemic blood flow.¹²⁴

One type of brain injury that may occur in neonates with circulatory failure is intraventricular haemorrhage (IVH), which is thought to occur via the “hypoperfusion-reperfusion” theory.¹²⁷ This can be associated with a short period of circulatory failure, e.g. one hour, where cerebral autoregulation fails and a state of low blood flow leads to ischemia and eventual loss of the structural integrity of the blood vessels within the germinal matrix.¹²⁸ Thus, when blood flow to these areas of the brain is increased, for example with inotropic treatment, bleeding into the lateral ventricles can occur with reperfusion, due to the friable nature of these vessels. If the bleeding is severe blood can fill the ventricles and exert an increased pressure on the surrounding tissues. This can lead to venous stasis and eventual haemorrhagic infarction of the brain parenchyma. Studies have estimated that its incidence may lie between 1-5% in term infants.¹²⁹⁻¹³² A prospective study that performed cranial ultrasonography in 505 healthy term infants within 72 hours of birth found that 3.8% had evidence of an IVH.¹³³ However the true incidence of IVH in term infants may be difficult to decipher as only a fraction may present with symptoms and thus be investigated further.¹³⁴ Moreover, unlike preterm infants, routine surveillance neuroimaging such as cranial ultrasounds are not always performed in term neonates.¹³⁴⁻¹³⁶ IVH appears to be more common in those with HIE treated with total body cooling who are haemodynamically unstable during the re-warming period (8%).¹³⁷ This is likely to be due to the peripheral vasodilation and mismatch in oxygen delivery and consumption that occurs during rewarming.¹³⁷ Whilst the true incidence of this injury is unknown, in unwell term and late preterm infants it can lead to poor long-term neurodevelopmental outcomes in affected neonates.¹³⁷⁻¹⁴⁰ The significance of these injuries and the association with poor long term outcomes in term infants is contentious.¹⁴¹

Another recognised pattern of injury is periventricular leucomalacia (PVL). This describes a pattern of injury that occurs in the white brain matter that is adjacent to the lateral ventricles and consists of focal necrosis and cyst formation. The incidence of this injury in term and late preterm infants is not known, although has been quoted to be as high as 61% in infants undergoing cardiopulmonary bypass surgery for congenital heart disease.^{142,143} However, this is unrepresentative of the infants in neonatal intensive care units. Similarly to IVH, PVL is believed to be due to abnormal cerebral vascular autoregulation and ischemia relating to end arteries

in the periventricular regions. It is also well recognised that infants who are born with risk factors for infection are at high risk of this cerebral injury. This is due to cytokine activation directly injuring pre-oligodendrocytes in the developing brain.¹⁴³

Infants suffering from HIE are also at risk of further brain injury through the initial hypoxic injury experienced at birth. Perinatal hypoxia leads to immediate necrotic neuronal cell death as a result of acidosis from anaerobic respiration, excitotoxicity from the influx of sodium and calcium ions into brain cells and activation of *N*-methyl-D-aspartate receptors via increased extracellular glutamate concentrations. After this initial damage the injured part of the brain then becomes re-perfused and delayed neuronal apoptosis or secondary energy failure occurs. This arises from the uncontrolled activation of enzymes such as caspase, increased inflammatory interleukins, tumour necrosis factor alpha and secondary messenger systems within brain cells. Re-perfusion also leads to the formation of excess reactive oxygen free radicals from ischaemic tissue, normally stopped by scavenger mechanisms, causing damage to the blood brain barrier allowing cytokines to enter brain cells.¹⁴⁴⁻¹⁴⁶ Further injury has been hypothesised in infants with HIE who have haemodynamic instability because there may be increased release of nitric oxide from the cerebral blood vessel epithelium in order to maintain blood flow to the brain.¹⁴⁷ Nitric oxide is implicated in oxidative stress in HIE that may contribute further to the hypoxic injury.

8.4.4 Clinical detection of the consequences of circulatory failure

With improvements in imaging technology, particularly cranial ultrasound, the bedside detection of these injuries is relatively easy with little disturbance to the neonate. Many neonatal units employ standardised protocols to monitor cerebral injury in neonates.¹⁴⁸

8.4.4.1 Cranial ultrasound

The most commonly used acoustic window to image the neonatal brain is the anterior fontanelle. Initial ultrasound examinations are used to confirm normal anatomy and then to identify pathology if present. Cranial ultrasound has good

accuracy for detecting PVL and IVH, and there are well-structured published grading systems that provide prognostic information for both types of injury.¹⁴⁹⁻¹⁵¹ However subtle white matter injuries may be missed using cranial ultrasound.¹⁴⁸ Not only does the identification of pathology provide prognostic information, Doppler imaging and calculation of the resistance index in the middle cerebral artery can be of use in infants with HIE, with values of less than 0.55 on day 2 of life predicting adverse neurological outcome.^{148,152}

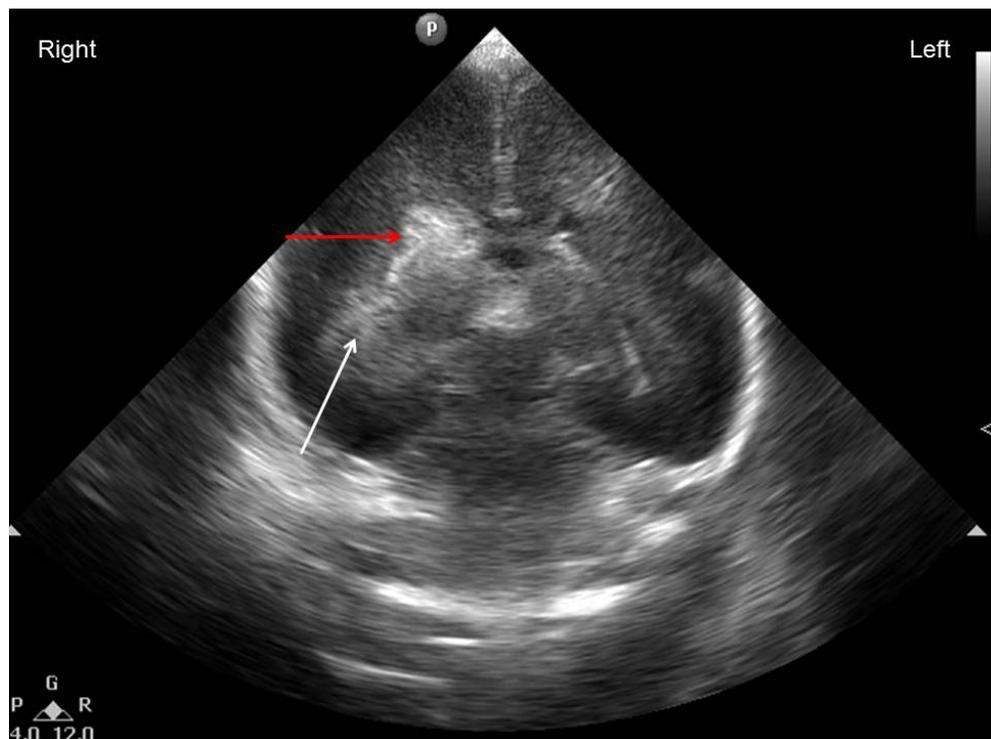


Figure 8.7: Large intraventricular haemorrhage within the lateral ventricle of the brain (red arrow) with associated parenchymal venous infarction (white arrow)

8.4.4.2 Magnetic resonance imaging studies

It is recognised that there are limitations to cranial ultrasound studies in detecting the cerebral consequences of circulatory failure, especially with regards to lesions in areas supplied by end arteries such as PVL.¹⁵³ Whilst not as practical as cranial ultrasound, magnetic resonance imaging (MRI) is possible in very sick infants.¹⁵⁴ It is also well established that MRI may confer additional benefits over ultrasound, especially when assessing myelination and neurological outcomes. For example,

the assessment of injury to the posterior limb of the internal capsule predicting motor outcomes in HIE is very robust in MRI and difficult to achieve by ultrasound.^{153,155}

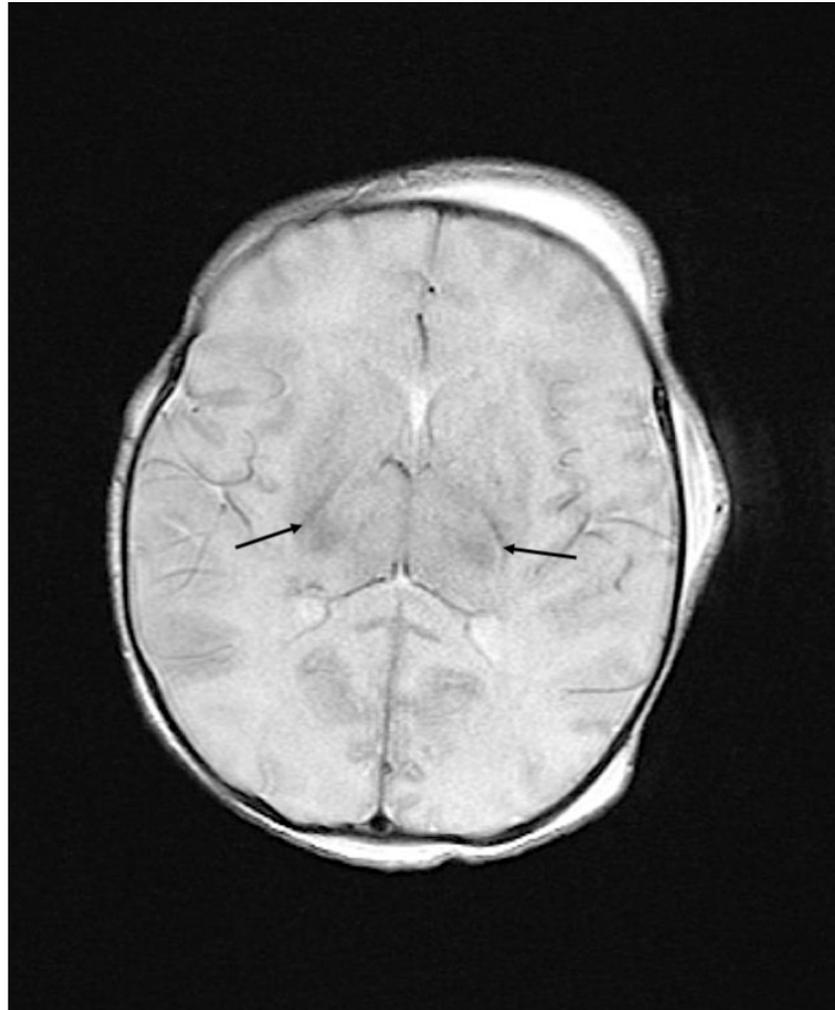


Figure 8.8: MRI study (T2 relaxation weighted image) of an infant showing abnormal signal within the posterior limb of the internal capsule (black arrows)

8.4.5 Bio-psychosocial implications of circulatory failure

The neurodevelopmental consequences of circulatory failure, such as cerebral palsy, can lead to significant burden on the children, their families and society.¹⁵⁶⁻

¹⁵⁸ The annual costs to the public sector of looking after all premature babies in Europe until they are 18 years old is approximately €9 billion, according to data scaled up from England and Wales registries.¹⁵⁹ Whilst in less premature infants, the risk of death or major neurodevelopmental disability is lower than in extremely

premature neonates, the health outcomes for those who have cardiovascular problems requiring drug treatment are as poor as for more immature infants.^{5,160}

8.4.6 Late preterm neonates

The World Health Organisation define infants born between 32 to <37 weeks GA.¹⁶¹ There is emerging evidence that infants who are considered to be of late prematurity are twice as likely to suffer neurodevelopmental delay when compared to term neonates.¹⁶² This is due to increased recognition that these infants are not fully developed, have increased risk of acute respiratory and neurological morbidity, as well as a threefold increase in mortality compared to full term neonates.¹⁶³ Whilst it is believed that this cohort of infants have reduced cardiovascular reserve, one knowledge gap is cardiovascular adaptive physiology and how this may relate to the increased risk of morbidity.¹⁶⁴ This is a particularly important as this cohort makes up to 70% of preterm births.¹⁶⁴

8.5 Current techniques of monitoring circulatory failure

An accurate clinical history and examination can give clues as to both the presence and the underlying aetiology of circulatory failure. However, many features of end organ dysfunction, such as oliguria, occur late in neonates and are of limited value during the transitional circulation.¹⁶⁵ Therefore, there is an increased reliance on monitoring various clinical parameters to try and identify circulatory failure early. Furthermore, it is important that a clinical monitoring parameter identifies the correct patho-physiological mechanism, such as vasodilation in septic shock, enabling a clinician to instigate treatment to prevent the progression of circulatory failure before end organ damage ensues.¹⁶⁶

It has been well documented that there is wide variation in the diagnosis of circulatory failure. Current methods of monitoring vary greatly between clinicians and are hampered by a lack of an adequate definition or clinical algorithm.¹⁶⁷ In a recent international survey of 216 neonatologists, 73% utilised the definition of MAP being less than an individual baby's GA as guide to diagnosing circulatory failure.¹⁶⁸

Measurement	Number (%)
Echocardiography	134 (75)
Left cardiac output	87 (65)
Right cardiac output	45 (34)
Fractional shortening of the left ventricle	67 (50)
Superior vena cava flow	51 (38)
Perfusion index	31 (17)
Body temperature measure	85 (47)
Central venous pressure measure	22 (12)
Mixed venous oxygen	18 (10)
EEG/aEEG	6 (3)
Near infrared spectroscopy	27 (15)

Table 8.2: Survey reporting ancillary measurements used by 180 neonatologists for assessing circulatory failure.¹⁶⁸

All clinicians included in the survey commented that they clinically assessed perfusion in affected infants in order to guide treatment. The most common clinical

measurement was capillary refill time with many also using biochemical methods such as base deficit and lactate. In addition, 180 respondents reported the use of novel or ancillary methods of measuring perfusion in neonates to aid in the diagnosis and monitoring of circulatory failure (Table 8.2).¹⁶⁸

8.5.1 Mean arterial blood pressure

The most common definition used for circulatory failure is a mean arterial blood pressure (MAP) is less than the neonate's approximate GA (arterial hypotension).¹⁶⁸⁻¹⁷⁰ Many studies have attempted to define normal MAP for the neonatal population, but are flawed in their methodology, such as the method of blood pressure measurement, small population sizes and the use of retrospective data.^{167,171-176} Research has also used a MAP of ≥ 30 mmHg as defining an acceptable blood pressure.¹⁷⁷ This is based on the assumption that cerebral autoregulation becomes abnormal and pressure dependent below 30mmHg.¹⁷⁸ This assumption disregards the fact that a neonate's MAP increases spontaneously over the first three days of life, therefore the definition of abnormal autoregulation (and blood pressure) will also increase.¹⁶⁷ This has led some to ask if the use of this definition lacks an evidence base.^{88,167} A retrospective cohort study found that in those neonates whose MAP was less than the neonate's approximate GA, but who exhibited no clinical signs of poor perfusion and did not receive treatment for circulatory failure, the overall clinical outcome was similar to those infants whose blood pressure remained within normal limits throughout the course of the study.¹⁷⁹ Furthermore there are wide variations in the reported incidence of hypotension between neonatal units even when the same diagnostic definition is used.¹⁸⁰

The suggestion for hypotension as a good marker of poor perfusion is due to frequent associations with adverse neurological outcomes such as IVH.^{138,181,182} MAP is determined by the cardiac output multiplied by the vascular resistance exhibited by the receiving arterial blood vessels. Quantifying cardiac output relies on the measurement of blood flow in a major vessel, such methods are limited in their availability.⁸⁸ Vascular resistance can only be calculated if both blood pressure and cardiac output are known, and therefore that clinicians tend to utilise

blood pressure measurements as a surrogate of systemic perfusion. However this has limitations as there could be various changes in either the cardiac output or vascular resistance that could result in small alterations in blood pressure but large changes in the overall systemic perfusion and markers of cerebral blood flow.^{183,184} This is further complicated by the presence of the PDA and the PFO altering haemodynamics during the transitional neonatal circulation.^{185,186} There is also evidence to suggest that during the transitional circulation there might be an negative correlation between MAP and systemic blood flow.¹⁸⁷ For example Osborn *et al.* found that a mean arterial blood pressure of less than the GA or less than 30mmHg had a sensitivity and specificity of 30% and 59%, respectively, for identifying infants with a superior vena cava flow (SVCF) of less than 41mls/kg/min.¹⁸⁴ Thus there is not a linear relationship between MAP and markers of systemic blood flow.¹⁷⁸

8.5.1.1 Invasive measurements of mean arterial blood pressure

The gold standard measurement of MAP is performed via an arterial catheter inserted into a baby's umbilical or peripheral artery.⁸⁸ An arterial catheter is placed into an appropriate artery and connected to heparin/saline filled tube that is connected to a transducer and monitoring device. The fluctuation in the vascular pressure causes a pulsation in the saline column connected to the catheter displacing the electromanometer's diaphragm within the transducer. This displacement is sensed electronically and a waveform is produced from which the MAP is derived. The transducer requires frequent calibration and needs to be kept at the level of the heart in order to give an accurate reading.¹⁸⁸ Due to partial occlusion of the catheter, there is often a dampening of the derived waveform leading to inaccurate readings.¹⁸⁹ There are a number of complications that can arise from the insertion of an arterial catheter. These range from pain at insertion, to the development of vascular thrombosis, ischemia in a distal limb and a potential vector for infection.^{190,191} Such complications are prevented through strategies such as short duration of use and accurate placement in large vessels such as the aorta.¹⁹²

8.5.1.2 Non-invasive measurements of mean arterial blood pressure

There are a number of ways to measure blood pressure non-invasively. Perhaps the most accurate is doppler ultrasonography. This method involves detecting the arterial flow of blood distal to an appropriately sized inflatable cuff, placed on an infant's arm. The cuff is then filled with air which compresses the arm. The systolic blood pressure is then recorded when the doppler signal from the ultrasound probe ceases.¹⁹³ A similar method utilises the plethysmographic trace gained from a pulse oximeter. By gradually inflating a blood pressure cuff in small increments on the same arm as a pulse oximeter you are able to determine the systolic blood pressure as the average of two readings; the blood pressure reading on the cuff when the plethysmographic trace disappears during its inflation and when the plethysmographic trace reappears on deflation.¹⁹⁴ Both of these methods show good agreement with intra-arterial methods of measuring blood pressure.¹⁷⁰

The most popular non-invasive method of measuring blood pressure is based on the principle that oscillations from the pulsations of blood through an arterial wall are transmitted to a blood pressure cuff placed around a limb from which blood pressure can be derived. Whilst oscillometric methods of measuring blood pressure show positive correlation with invasive arterial methods.¹⁹⁵ However they are considered to perhaps be the most inaccurate way of taking blood pressure.¹⁷⁰ This is due to its dependency on the selection of an appropriate blood pressure cuff size and its precise application.¹⁹⁶ There are concerns that this method may be unreliable at low blood pressures, a situation in which measurements are required to be at their most accurate.¹⁹⁷

8.5.2 Pulse pressure

Pulse pressure (PP) is the difference between the systolic and diastolic blood pressure. Physiologically this parameter is reduced by decreasing cardiac stroke volume or increasing compliance of the aorta. Most often it is used clinically in the detection of a PDA in a neonate. This is because the PDA allows the shunting of blood between the systemic and pulmonary circulation, this "stealing" of blood can lead to a reduction in the diastolic blood pressure and hence increased pulse pressure.¹⁹⁸ PDA also can lead to increasing pre-load of the left ventricle. If the

pre-load becomes too great, it can lead to cardiac failure and thus lower blood pressure. Typically, pulse pressure is considered to be pathological if it is greater than 15-25 mmHg. The use of this parameter for the diagnosis or management of circulatory failure has not been systematically tested.¹⁹⁹

8.5.3 Other clinical parameters

As mentioned previously many clinicians utilise various clinical parameters to aid their decision-making regarding the diagnosis and management of circulatory failure.

8.5.3.1 Heart rate

The cardiac output of a neonate is dependent on changes in heart rate, as stroke volume is believed to be relatively fixed in neonates.¹⁷⁸ A heart rate above 160 beats per minute in a neonate can be a sign of poor cardiac output and therefore circulatory failure, as the infant's circulatory system attempts to increase cardiac output in the only way available to it, by increasing heart rate.²⁰⁰ However, a number of studies have shown that the heart rate is similar in well infants and in infants who meet the definitions of circulatory failure.^{178,201} There is also evidence that the loss of the natural heart rate variability seen in neonates in the hours before the identification of sepsis can indicate circulatory failure.²⁰² This is mediated through autonomic nervous system activation and vagal stimulation of the heart through anticholinergic anti-inflammatory pathways.¹⁰ There are many reasons for a persistent tachycardia in a neonate that a clinician will need to consider before instigating treatment for circulatory failure.

8.5.3.2 Capillary refill time

This is defined as *“the time required for the return of colour after the application of blanching pressure to a distal capillary bed”*.¹⁶⁵ As a clinical marker of blood flow to the peripheral circulation, prolonged values greater than 3 seconds are indicative of poor peripheral perfusion or increased SVR.¹⁶⁵ There is conflicting evidence as to whether capillary refill time is reliable in assessing end organ perfusion.²⁰³ Normative values exist in term neonates, and a negative correlation ($r = -0.42$) has

been found between capillary refill time and SVCF a biomarker associated with intracranial haemorrhage.¹⁸⁴ The sensitivity and specificity of a capillary refill time greater than three seconds to predict low SVCF is 55% and 81%.¹⁸⁴ This increases to 78% and 63% respectively when combined with a blood pressure measurement less than 30mmHg.¹⁸⁴ In addition, a negative correlation has been found between capillary refill time and cardiac index (cardiac output from the left ventricle per minute divided by body surface area) measured via Doppler ultrasound in neonates.²⁰⁴ However capillary refill time is dependent on the ambient temperature, and this may render this particular measurement unreliable in situation such as total body cooling in HIE.²⁰⁵ The vasomotor tone of the surface capillaries is not yet established in very premature or low birth-weight neonates making it a very subjective and unreliable measure.^{188,206} This is illustrated by two studies showing poor inter-observer variability with the chest wall being the most reliable site of measurement.^{207,208}

8.5.3.3 Core to peripheral temperature gap

This is a measurement of peripheral perfusion as temperature affects vasoconstriction through stimulation of the autonomic nervous system and the release of local vasoactive substances such as nitric oxide.²⁰⁹ Therefore in an environment where the temperature is highly regulated such as a neonatal incubator, a discrepancy between the temperature at a peripheral site and central skin site could be due to selective vasoconstriction and a marker of circulatory failure. For clinical purposes a gap of $>1^{\circ}\text{C}$ in core to peripheral temperature gap has traditionally been considered abnormal.¹⁷⁸ However, Osborn *et al.* and Tibby *et al.* found no correlation between an abnormal core to peripheral temperature gap and systemic blood flow, measures of SVR or stroke volume index.^{184,210} Moreover, this biomarker would not be of any use in therapeutic cooling for HIE, when there is a deliberate attempt to reduce the core temperature.

8.5.3.4 Urine Output

A significant association between low SVCF and urine output in preterm infants has been found ($r= 0.25$).²¹¹ A number of studies have also found that urine output

increases with treatment for circulatory failure presumably due to improving renal perfusion.²¹²⁻²¹⁴ However this interpretation in the first 24 hours is questionable as urine output is normally very low.¹⁷⁹ Furthermore if a reduction in urine output is observed it usually occurs late and after other markers of systemic perfusion become abnormal.^{188,211}

8.5.4 Biochemical parameters

Markers of abnormal physiology such as lactate represent a consequence of poor end organ perfusion, and are also often used by clinicians to assess circulatory failure in neonates.¹⁶⁸

8.5.4.1 Lactate

Lactate is a marker of anaerobic respiration. It accumulates when there is inadequate oxygenation of end organs. Levels above 3 mmol/L indicate significant tissue hypoxia in infants at birth,²¹⁵ but such measurements taken in isolation are poor at detecting decreased systemic perfusion.¹⁷⁸ Serial abnormal lactate levels have been found to be predictive of adverse outcomes in neonates. For example, a retrospective study found that in infants less than 32 weeks' GA with serial lactate levels greater than 5.6 mmol/L 50% either died or had severe IVHs.²¹⁶ A similar study found a mortality of 57% in neonates aged between 23 to 40 weeks' GA if two serial lactate levels were above 5.6mmol/L.²¹⁷

Previous literature has demonstrated that when lactate has been combined with other clinical measures, such as a capillary refill time, it can be predictive of poor perfusion.²¹⁶ For example Moran *et al.* found that when capillary refill time was greater than 4 seconds and lactate was greater than 4 mmol/L there was a 97% probability of finding low SVCF.²¹⁸ In infants receiving cardiovascular support, raised lactate levels have been found to be an early predictor of adverse outcome. However, these elevated levels fall in response to drug treatment.^{212,213,219}

Studies differ in their findings of lactate levels in Neonates with HIE. In a prospective cohort study of 7 asphyxiated neonates the lactate was found to be

normal throughout treatment with total body cooling.¹²² With other studies finding increased levels of lactate levels in neonates treated with hypothermia.^{220,221}

8.5.4.2 Base deficit

Physiologically this is the calculated estimate of the metabolic component of the acid-base balance that contributes to the pH of blood. Base deficit can be used to predict adverse outcomes in preterm neonates: a value of -7.3 mmol/L or more negative on day one of life has been reported to have a sensitivity and specificity of 100% and 72% respectively for death and/or cerebral injury.²¹⁶ Correlations with lactate levels in preterm infants have been found.^{216,222} However, the causes of abnormalities in acid-base balance are multiple thus making it a non-specific marker of circulatory failure. Furthermore, a Cochrane review concluded that treatment of metabolic acidosis with sodium bicarbonate infusions or albumin shows no improvement in morbidity or mortality in preterm neonates with metabolic acidosis.²²³

8.5.4.3 Blood pH

pH is a direct measure of the concentration of hydrogen ions in the circulation, a by-product of tissue acidosis from anaerobic respiration. Studies have repeatedly shown that it is a poor, and often late, marker of circulatory failure.¹⁷⁸

8.5.4.4 Haematocrit

Haematocrit, the volume percentage of erythrocytes in whole blood, is a measure of blood viscosity that according to Poiseuille's equation will influence the speed of blood flow. Therefore haematocrit will have a direct effect on oxygen delivery and the development of circulatory failure.¹⁶⁵ For example increasing haematocrit whilst increasing oxygen carrying capacity, also increases viscosity and so can lower blood flow. A study conducted in 36 preterm infants found that whilst haematocrit was negatively associated with measurements of cardiac output and cerebral blood flow ($p < 0.05$), it was poorly predictive of these measures when assessed by linear regression ($r^2 = -0.148$ to -0.238).^{224,225} Considering the low blood volume of neonates, repeated measurements of haemoglobin and

haematocrit would be inappropriate. Commercial non-invasive devices that measure haemoglobin and haematocrit levels do exist; the use of such devices in monitoring neonatal haemodynamics has yet to be examined.^{226,227}

8.5.4.5 Natriuretic peptides

These are a family of peptides that are released from the neonatal myocytes, brain and coronary epithelium in response to increasing preload and ventricular stress. They cause increased diuresis, peripheral vasodilation and inactivation of the renin-angiotensin system, leading to a reduction in preload and afterload on the heart.²²⁸ In clinical studies natriuretic peptides have not been found to correlate with blood pressure, SVCF or shortening fraction.^{229,230}

8.5.4.6 Troponin

This complex consists of three subunits located on the myofibrillar thin filament that helps regulate the contraction of cardiac muscle. They are markers of cardiac muscle damage with blood concentrations increasing in response to myocardial ischemia.²³¹ Numerous studies have found increasing concentrations of troponin subunits in unwell preterm and asphyxiated term infants, reflecting myocardial ischemia. Many of these studies have also found these increases to be associated with abnormal echocardiographic markers of poor heart function such as decreased shortening fraction, ejection fraction, stroke volume and left ventricular output.²³¹ Whilst these echocardiographic markers directly influence cardiac output and thus the development of circulatory failure, repeated measurements to assess cardiac function would not be appropriate owing to the reduced blood volume in neonates. Furthermore, studies quote a wide range of normal values for neonates, which are further dependent on a neonate's GA.²³¹ It has been suggested that measurements of troponin, and that of natriuretic peptides, could serve a function where echocardiographic services are not available to differentiate between a respiratory or cardiac cause of clinical deterioration.²²⁸

8.5.5 Emerging and experimental techniques

There are a number of novel techniques beginning to be utilised in clinical practice to measure cerebral perfusion and its relationship with systemic blood flow.¹⁶⁸

8.5.5.1 Amplitude-integrated electroencephalography (aEEG)

This utilises a number of probes that are attached to a neonate's head (Figure 8.9). The electrical activity between these probes is recorded and gives a representation of electrocortical activity in an infant's brain.



Figure 8.9: Example of an amplitude-integrated electroencephalography (aEEG) device²³²

aEEG is already used in the management of term infants with HIE with recognisable patterns, such as depressed aEEG activity, associated with poor long term neurological outcomes.²³³ It has also been utilised in preterm infants where depressed activity has been associated with adverse short-term outcomes.²³⁴ Research has attempted to find an association with aEEG readings and measures of systemic perfusion. Studies in very preterm infants have found that reduced electrical activity on an aEEG recording is associated with reduced right ventricular output (RVO) and SVCF.^{235,236} Interestingly, one study found that infants who required inotropic treatment for circulatory failure had a significantly depressed aEEG amplitude compared with those who did not, even when

haemodynamic parameters such as SVCF, blood pressure and RVO had returned to normal.²³⁵ This may indicate that aEEG is more indicative of a hypoxic or ischemic insult to the brain rather than being an adequate real-time method of monitoring haemodynamics of a neonate. aEEG has been shown to have a good inter-observer variability ($\kappa=0.85$) but is reliant on electrode placement, background impedance and on the actual equipment used.^{237,238} It is predictive of the development of post-haemorrhagic hydrocephalus and long term neurodevelopmental outcomes in preterm infants.^{239,240} In neonates with HIE undergoing therapeutic hypothermia aEEG is established as a monitoring tool where particular voltage patterns can be highly predictive of neurodevelopmental outcomes.²⁴¹ It's use for monitoring peripheral haemodynamics or in the monitoring of the treatment of circulatory failure in this cohort has not been investigated.

8.5.5.2 Near infra-red spectroscopy (NIRS)

NIRS is based on the Beer-Lambert Law, which states that light transmitted through a solution decreases exponentially as the solute of a solution increases. The technology uses light in the near infrared regions (700-1000nm) that is transmitted through a region of interest. Primarily in neonatal care this technology has been utilised to measure oxygenation in the brain (Figure 8.10). It takes advantage of the high degree of transparency in the neonatal skin and skull. It can determine regional oxygenation because the absorption spectra of oxygenated and deoxygenated blood differ, thus the type of haemoglobin within a specific tissue can be determined in real time.²⁴² From this, a number of different algorithms can be applied to allow for the calculation of oxygen extraction in different organs.²⁴³ Common examples of such indices include tissue oxygenation index as an indicator of cerebral oxygenation.²⁴⁴ As oxygen extraction is directly related to blood flow, NIRS has the potential to continuously monitor organ blood flow. However, this assumption is subject to a number factors including haemoglobin concentration and the ratio of arterial to venous blood flow in a target organ during an assessment period.²⁴³



Figure 8.10: Example of a near infra-red spectroscopy (NIRS) device on a model of a baby²⁴⁵

Given that cerebral perfusion can be independent of mean arterial blood pressure,¹⁸³ considerable interest surrounds this technology and its ability to measure cerebral perfusion non-invasively. Interestingly, there have been many links identified between profound fluctuations in NIRS measurements and brain injury such as intraventricular haemorrhages, peri-ventricular leucomalacia and poor long-term neurodevelopmental outcomes.²⁴⁶⁻²⁵⁰

Cerebral tissue oxygenation index, a calculation of the balance between oxygen delivery and utilisation in an area of the brain, readings have demonstrated a positive correlation ($r=0.32$, $p=0.01$) with SVCF measurements in low birth weight infants, perhaps indicating that NIRS potentially could be a marker of systemic perfusion.²⁵¹ However this positive association was no longer significant after 12 hours and no association has been found between NIRS measurements and blood pressure.²⁵¹⁻²⁵³ The association with SVCF may reflect that the latter has been found to represent up to 80% of the cerebral blood flow in a neonate, thus NIRS may better reflect intracranial and not systemic haemodynamics.²⁵⁴ Therefore NIRS might be useful in the determination of when end-organs are affected by circulatory failure rather than in the earlier compensated phase of this condition. NIRS has also been used in infants suffering from HIE where abnormally high regional oxygen saturation was found to be associated with poor neurodevelopmental outcomes. The authors hypothesised that this was due to

poor oxygen extraction despite increased blood flow associated with the loss of cerebral autoregulation.²⁵⁵ This technique is still not in widespread clinical use.¹⁸⁸ In addition, there have been questions raised about the reliability of NIRS with significant differences in results gained from NIRS measurements (up to 12.6%) found between different probes and commercially available machines.²⁵⁶⁻²⁵⁸

8.5.5.3 Impedance electric cardiometry

This is based on the principle that the electrical conductivity of blood is higher than that of muscle, fat and air. A low electrical current is placed across a baby's chest wall and changes in thoracic blood volume will change the electrical impedance recorded. Thus, these changes will be proportional to the changes in blood flow and allows for continuous measurement of cardiac output.²⁵⁹ This has been investigated in term infants and has shown similar precision to cardiac output measured by echocardiography and by invasive pulmonary artery Swan-Ganz catheter in animal studies.²⁵⁹⁻²⁶¹ Whilst feasible, it has been found that impedance electric cardiometry underestimates cardiac output and that further validation studies in neonates and animal models are needed.^{260,262}

8.5.5.4 Magnetic resonance imaging (MRI)

Phase contrast MRI has been used in neonates to assess cardiac output and systemic perfusion.²⁶³ It has been shown not only to be feasible in preterm and term neonates, but measurements including SVCF, left ventricular outflow, ejection fraction and ventricular volumes are highly repeatable.²⁶⁴⁻²⁶⁷ Phase contrast MRI shows very good correlation with echocardiographic measurements of left ventricular outflow (LVO) ($r^2=0.83$).²⁶⁶ Its correlation with echocardiographic measurements of SVCF are poor however ($r^2=0.22$).²⁶⁶ Whilst cardiac MRI provides robust measurements of cardiovascular parameters it has yet to be used to aid diagnostic decision making in infants with circulatory failure. Moreover, phase contrast MRI examinations are time consuming and are not appropriate in the care of sick neonates.

8.5.5.5 Other experimental techniques

Many of the current techniques used for monitoring haemodynamic status in neonates are subject to operator bias or inaccuracy. Thus a number of experimental objective methods have been proposed. However, many of these methods are technically not feasible in babies or are awaiting validation.²⁶⁸ Table 8.3 outlines some of these techniques, their advantages and disadvantages.

Technique	Principle	Advantages	Limitations of Use
Oxygen Fick Principle	Blood flow is equal to the amount of oxygen entering the blood stream divided by the concentration of oxygen measured downstream to the point of entry.	Considered to be the research gold standard of measuring blood flow accurately.	Affected by cardiac shunts, requires mixed venous blood sampling and enhanced in neonates with chronic lung disease.
Modified Carbon Dioxide (CO₂) Fick Method	The principle is the same as the Oxygen Fick Principle but CO ₂ is measured at the endotracheal tube.	Reliable despite cardiac shunts and relatively non-invasive.	Requires frequent blood sampling and inaccurate due to the measurement of CO ₂ in the blood.
Pulse Dye Densitometry	A dye is injected into a neonate and its flow is detected via a fingertip sensor.	Non-invasive.	Limited repeated measurements, inaccurate in neonates due to poor peripheral perfusion, excess light or limb movement.
Pulmonary Artery Thermodilution	Cold fluid is injected into the right atrium and the indicator dilutions curve can be measured through a catheter placed in the pulmonary artery.	Widely used in adults and can provide additional parameters.	Very invasive, physically not possible in neonates and shunts affect results.

Table 8.3: Experimental techniques of measuring circulatory failure in neonates^{165,166,268}

Technique	Principle	Advantages	Limitations of Use
Lithium Dilution	A lithium ion detector is attached to a peripheral arterial line which then measures lithium that is injected intravenously in a known quantity.	Uses existing catheters and provides continuous monitoring.	Lithium toxicity, affected by cardiac shunts and hyponatraemia.
Transpulmonary Thermodilution	Isotonic saline is injected via a venous catheter and it is detected by a thermistor tip catheter present in a major artery. The modified Stewart-Hamilton equation is then used to assess blood flow.	Considered to be the clinical gold standard of measuring blood flow accurately.	Invasive and repeated measurements can affect fluid balance in a neonate.
Transesophageal Doppler	A Doppler probe is placed in the oesophagus and blood flow velocity is measured in the ascending aorta.	Continuous monitoring.	Not feasible in babies less than 3kg and can be inaccurate due to alterations in the angle of insonation.
Transcutaneous Doppler	Aortic blood flow is measured by a probe placed on a neonate's sternal notch.	Continuous monitoring and non-invasive.	Large inter-observer variability.

Table 8.3: Experimental techniques of measuring cardiac output in neonates^{165,166,268}

Technique	Principle	Advantages	Limitations of Use
Arterial Pulse Contour Analysis	Measures stroke volume from a beat to beat analysis of the arterial pressure waveform.	Continuous monitoring and non-invasive.	No published data in neonates, requires frequent calibration, accuracy influenced by changes in vasomotor tone and heart rate.
Laser Doppler	A wavelength of light between 700-790nm is shone on to the skin and uses the Doppler shift principle to measure the peripheral blood flow.	Real time and non-invasive.	Few published studies in term neonates.
Orthogonal polarisation spectral imaging	Emits a light at 548nm which is in the haemoglobin absorption spectrum. Red blood cells appear dark and can be visualised moving on a computer screen.	Non-invasive monitoring of microvascular perfusion.	Few published studies and not able to detect real time changes in peripheral haemodynamics.
Multimodular monitoring	Data from multiple monitoring systems (e.g. NIRS, aEEG) are integrated into a computer modelling system to create real time predictive models of outcomes and treatment.	Continuous monitoring that offers treatment recommendations.	No published data in neonates. Still in the developmental phases of creation.

Table 8.3: Experimental techniques of measuring cardiac output in neonates^{165,166,268}

8.6 Functional echocardiography and its clinical application

The use of bedside ultrasound provides real time assessment of pathology and is increasingly being utilised in the care of neonates. This has led to improvements in ultrasound technology and increased availability. It has also highlighted the need to develop an accurate way of monitoring systemic blood flow in a developing circulatory system.²⁶⁹⁻²⁷¹ Much of the development in the use of this technology has arisen from the limitations of clinical assessment tools used to gather information regarding systemic blood flow.²⁶⁹ For example, bedside echocardiography assessment can determine the effect of shunting within the heart through the PDA and PFO and the overall effect on systemic blood flow. There is also evidence that suggests when echocardiography is utilised alongside clinical examination, there are improvements in the identification of cardiovascular compromise, its treatment and outcomes.²⁷²

8.6.1 Principles of ultrasound and tissue interaction

First developed in the 1950's, ultrasound technology utilises sound waves that induce rarefaction and compression of tissue that they pass through.²⁷³ The human ear can hear sound waves between 20 to 20,000 Hertz (Hz). Medical ultrasound uses frequencies typically above 2 to 12 MegaHertz (MHz). These are generated when an alternating electrical current is placed across piezoelectric crystals which then oscillate to produce an ultrasonic wave. For clinical practice these waves are then emitted by the crystals in an ultrasound probe and penetrate the tissue beneath. The ultrasound waves are reflected back to the probe by the insonated tissue. The ultrasound waves that return to the crystals in the probe, are converted to an electrical signal by computer processing and an image is produced. Depending upon the characteristics of the returning ultrasound waves, such as their amplitude, the computer processing software will make alterations to the resulting ultrasound image. The properties of an ultrasound probe and waves are outlined in Figure 8.11.²⁷⁴

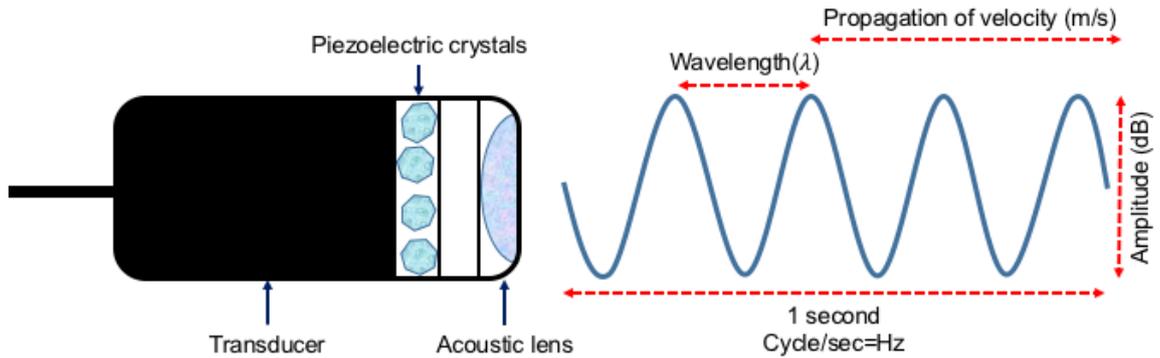


Figure 8.11: Properties of an ultrasound probe and wave

The speed at which an ultrasound wave moves through tissue is known as the velocity of propagation. The frequency is the number of ultrasound waves produced in a second with the wavelength being the distance between the adjacent peaks. The relationships between these factors are outlined below.

$$v = f \times \lambda$$

Where v = velocity of ultrasound wave, f = frequency and λ = wavelength.

This alters depending on the tissue insonated. For example, it is relatively slow through gas (330m/s) as ultrasound waves have to travel long distances before interacting with other molecules. In bone where the distance between molecules is very small, the velocity of ultrasound waves is much greater (3000m/s). Given that the velocity of propagation is dependent on the insonated tissue and the frequency of an ultrasound beam is determined by the emitting transmitter, the wavelength is therefore inversely proportional to frequency (the longer the wavelength the lower the frequency). These relationships are very important in clinical ultrasound as image resolution (the ability to distinguish between two points) is dependent on the wavelength of an ultrasound beam. Resolution can be no greater than the distance of 1-2 ultrasound wavelengths which is no greater than 1mm. Ultrasound waves with short wavelengths and high frequency produce images of high resolution. However, ultrasound wavelengths are only able to image superficial structures.²⁷⁵ This is because they lead to increased molecular oscillation and friction as they enter the tissue of interest. This leads to the conversion of ultrasound waves to potential and then kinetic energy, meaning that some of this energy is lost as heat, a process known as attenuation. Ultrasound waves of lower frequencies are therefore more appropriate for imaging deeper organ structures. These relationships are outlined in Figure 8.12.²⁷⁴ With regards to neonates, typically

frequencies of 7-10 MHz adequately penetrate the chest wall of preterm and term neonates with good resolution of the images produced.

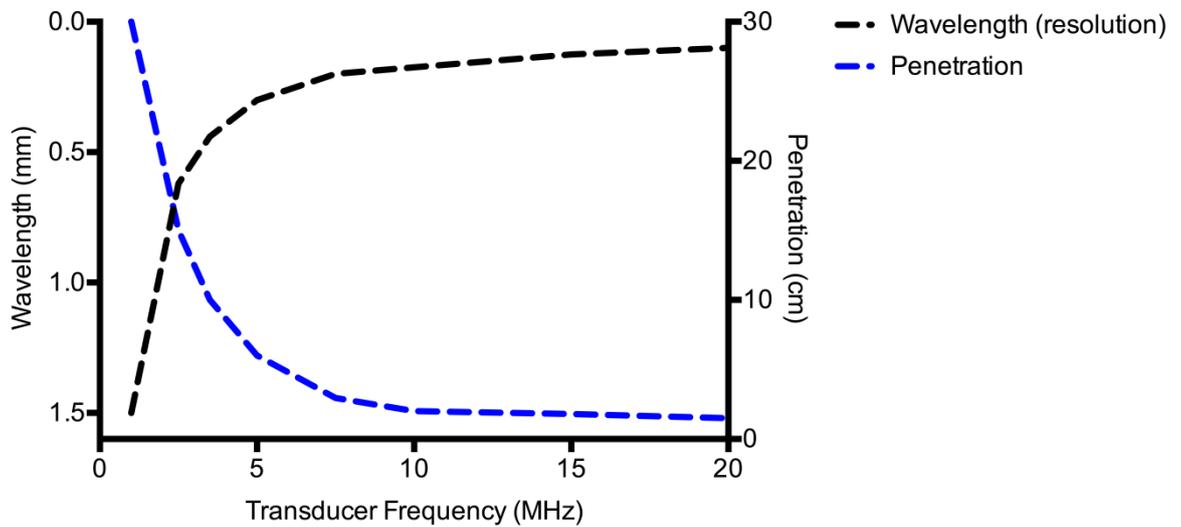


Figure 8.12: The relationship between ultrasound wavelength and frequency to tissue penetration and image resolution.

The amplitude of an ultrasound wave indicates the power of the signal. Power is the measure of energy per unit time; however, as ultrasound waves are focused on a small area this is expressed as the amount of power per unit area or intensity. The relationship is outlined below-

$$I = P^2$$

Where I = intensity and P = power.

For each unit of power the ultrasound beam is increased there is a quadrupling of its intensity. The amplitude of the ultrasound wave is described through a decibel logarithmic scale.

$$dB = 20 \times \text{Log} \times \left(\frac{W_1}{W_{ref}} \right)$$

Where dB = decibels, W_1 = power of the wave to be compared and W_{ref} = power of the reference wave.

As this is a logarithmic scale when there is a 6 dB change in an ultrasound wave it represents a halving or doubling of the ultrasound wave's amplitude.

8.6.2 Ultrasound beam interaction with tissue

Ultrasound images are dependent upon the medium they travel in. As human tissue is inhomogeneous some of the ultrasound waves are reflected, scattered, refracted and attenuated.

In order to observe an organ on ultrasound it must reflect ultrasound waves back to the emitting ultrasound probe. Reflection is influenced by the angle of insonation and the acoustic impedance between tissues. Reflection is greatest when an ultrasound beam is reflected by a smooth surface with dimensions greater than its wavelength and perpendicular to the emitting probe.²⁷⁶ Acoustic impedance is dependent on both tissue's density as well as the propagation of velocity through that tissue. The relationship is outlined below

$$Z = D \times V$$

Where Z = acoustic impedance, D = is tissue density and V = propagation velocity.

The difference in acoustic impedance results in ultrasound waves being reflected at tissue boundaries thus allowing delineation between organs. As ultrasound waves penetrate the body they meet tissues of different acoustic impedances.²⁷⁵ This means that some ultrasound waves are reflected back to the ultrasound probe and some will continue to penetrate deeper into the body. Reflected ultrasound signals that return to the probe are subjected to a computer processing, resulting in a visible image.

Scattering occurs when ultrasound waves interact with particles, such as red blood cells, that are smaller than the wavelength of the ultrasound signal. This leads to random reflection of the ultrasound beam in all directions. Therefore, only a small number of scattered ultrasound waves are received by the ultrasound transducer. The amplitude of these returned scattered waves is also significantly smaller than the waves reflected by specular reflection tissues. Scattering is dependent on particle size, the number of particles, their compressibility and ultrasound frequency. In clinical echocardiography the most common cause of scattering is red blood cells. With the former three factors being relatively fixed in neonates, frequency is therefore the primary determinant of scattering.²⁷⁶

Refraction is the deviation from a straight path in an ultrasound beam as it passes through a tissue of different acoustic impedance. This can occur in a random fashion and results in artefact images.²⁷⁶

Attenuation is the loss of ultrasound energy through its conversion to heat, scattering and reflection as it passes through tissue. As noted previously the energy of an ultrasound wave decreases as it passes through tissue, causing molecular friction and vibration resulting in the conversion of ultrasound energy to kinetic and then thermal energy. Attenuation is contingent on the tissue's attenuation coefficient, its thickness and the frequency of the ultrasound wave.

$$A = CoA \times F \times T$$

Where A = attenuation, CoA = attenuation coefficient, F = frequency of ultrasound and T = tissue thickness.

Tissues such as myocardium and muscle have a relatively low ultrasound attenuation and therefore can be imaged easily in this modality.

8.6.3 Tissue bio-effects of ultrasound

One of the main consequences ultrasound can have on tissue of insonation is thermal effects due its absorption and conversion from ultrasound energy to heat. The degree that ultrasound raises the temperature of a tissue depends upon the absorption co-efficient for a given frequency of the ultrasound, the tissue density, tissue temperature and the intensity of the ultrasound exposure. These relationships are outlined in the equation below.

$$Rti = \frac{2 \times F \times I}{Td \times C_m}$$

Where Rti = rate of temperature increase, f = frequency, I = ultrasound intensity, Td = tissue density, and C_m = tissue temperature.

Predicting the degree of temperature increase is difficult as many of these factors are difficult to measure. In clinical practice the increase in heat is negated by the blood flow through the tissue leading to heat loss through convection and diffusion.

Thermal index describes this relationship and is the ratio of the transmitted acoustic power of the ultrasound waves to increase tissues temperature by 1°C.

Another potential bio-effect of ultrasound is cavitation. This is the creation of small gas filled bodies (micro bubbles) by an ultrasound beam. This can lead to rapid changes in the size of micro bubbles and places mechanical stress on surrounding tissues. This phenomenon is most influenced by the frequency of ultrasound used. The mechanical index describes the non-thermal effects of ultrasound such as cavitation. It is the square root of the peak rarefactional pressure to the square root of the transducer frequency.

When both the thermal and mechanical index are less than one, then an ultrasound examination is considered safe. If either ratio exceeds this the benefits of the study against the potential bio-effects on a patient need to be considered.

8.6.4 M-Mode & B-Mode cardiac imaging

Motion mode or M-mode is considered the most basic type of ultrasound imaging as it assesses insonated tissue along a single line over time. The resulting images are those of the reflected echo along the ultrasound wave with a flat line representing motionless and wavy lines representing moving tissue. This means that it is not appropriate for delineating anatomy. However, M-mode ultrasound is updated up to one thousand times per second providing good temporal resolution. Brightness mode or B-mode is considered conventional ultrasound imaging. A phased array ultrasound probe emits an echo beam that sweeps from side to side. The ultrasound waves are reflected back to the transmitter and generate a two dimensional image of the underlying anatomy. B-mode ultrasound is updated up to 40 times per second and so simultaneously provides information on cardiac structure and motion. Both modalities are often used in the measurement of vessel size or diameter.²⁶⁹ Examples of B- and M-mode ultrasound imaging is given in Figure 8.13.

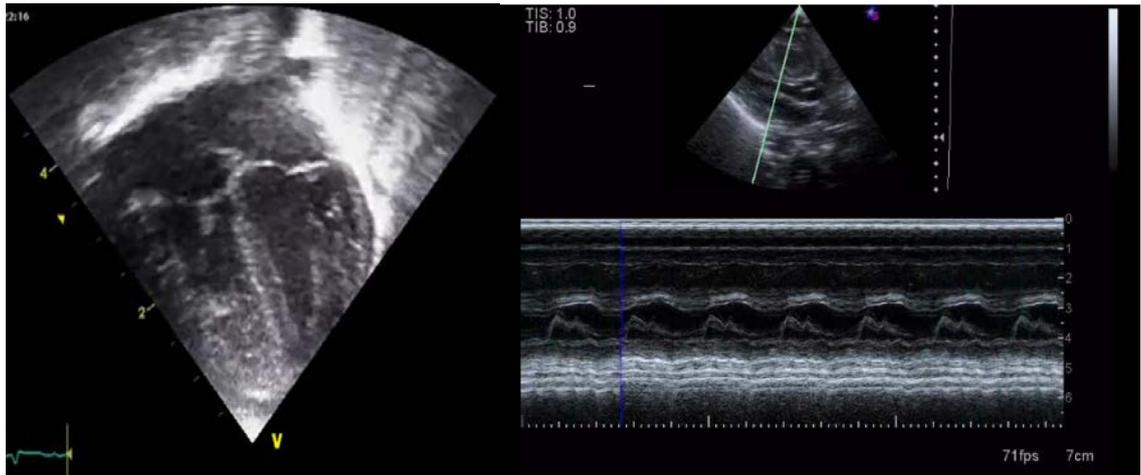


Figure 8.13: B-Mode (left) and M-Mode ultrasound imaging of the neonatal heart (right)

8.6.5 Doppler imaging

The Doppler Effect is based on the principle that the velocity of a moving object is proportional to the change in the frequency of the returning echo sound wave reflected back. For the purpose of measuring blood flow, Doppler imaging allows the detection of the movement of red blood cells within a vessel. For clinical application the velocity of the travelling red blood cells is calculated via the Doppler equation-

$$Velocity = \frac{Ds \times c}{2 \times f \times \cos(q)}$$

Where Ds = Doppler shift, c = speed of sound, f = insonating frequency, $\cos(q)$ = angle of insonation.

In order to get accurate measurements of the velocity of red blood cells within a vessel, it is essential that the angle of insonation or the angle at which an ultrasound beam is placed is minimal as $\cos(0^\circ)=1$. This is because the higher the angle of insonation, the greater the underestimation of flow velocity.²⁷⁷

The two types of Doppler imaging that are commonly used clinically to measure blood flow are continuous wave and pulsed wave Doppler. With continuous wave Doppler, an ultrasound probe constantly emits ultrasound waves whilst simultaneously receiving reflected ultrasound waves along an ultrasound beam (Figure 8.14). This has advantages in that it can accurately measure blood flow

travelling at high velocities (e.g. blood travelling through a constricting PDA). However, this means that the placement of the continuous wave beam has to be accurate, as it will measure the movement of all cells along that beam.

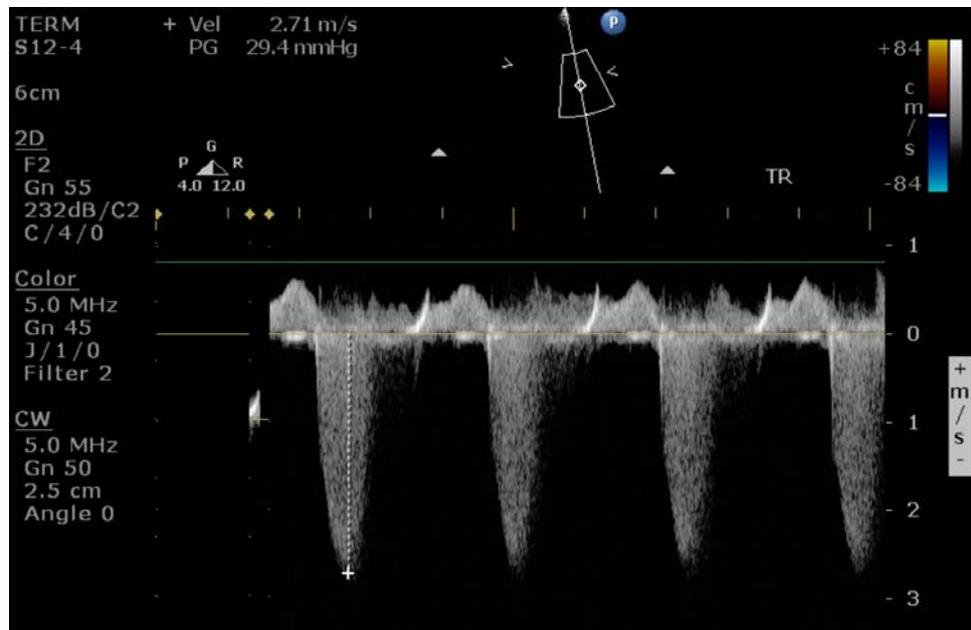


Figure 8.14: Ultrasound imaging depicting the measurement of blood flow through the tricuspid valve measured by continuous wave Doppler.

Pulsed wave Doppler overcomes this as the ultrasound probe alternates between emitting and receiving ultrasound echoes. This enables the operator to define a point along the ultrasound beam where velocity measurements are taken. This is known as the “sample gate” or “sample volume”.²⁶⁹ Thus, velocity measurements derived from that “sample gate” are calculated with other beams reflected back to the probe ignored (Figure 8.15). This is good at measuring low velocities (less than 2 m/s), but it cannot be used for measuring blood flow at higher velocities, due to the aliasing phenomenon. Aliasing phenomenon is when the time difference between the probe emitting and receiving an ultrasound wave is too long relative to the flow of blood in the “sample gate”. This means the ultrasound device is unable to determine blood flow direction and velocity.

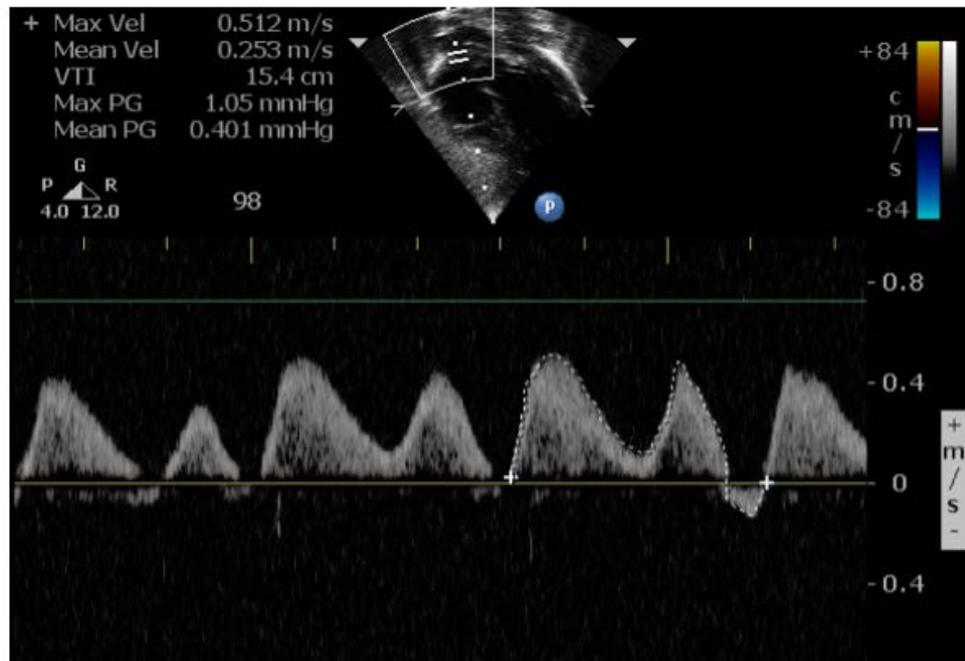


Figure 8.15: Ultrasound imaging depicting the measurement of blood flow through the superior vena cava by pulsed wave Doppler.

8.6.6 Colour flow imaging

Most modern ultrasound devices now have the ability to process Doppler signals and depict the blood flow as colour. This enables clinicians to visualise the flow of blood through a vessel, thus allowing the identification of particular areas of interest (e.g. assessment of flow across a heart valve).

8.6.7 Calculation of blood flow

In order to determine true blood flow there are two components that need to be calculated by ultrasound; the flow velocity and the cross sectional area of the vessel. There is an assumption that the Doppler measurement is the average velocity for blood travelling through the cross section of the vessel. Plotting the average Doppler velocity against time allows the calculation of the volume time integral (VTi). Conventional ultrasound provides 2D images of a vessel and thus can only measure the diameter. To calculate the cross sectional area of a vessel the diameter must be squared, multiplied by pi and divided by four. The resulting value is then multiplied by the heart rate and then divided by body weight in order to calculate blood flow in mls/kg/min-

$$Q = \frac{VTi \times HR \times (\pi \times d^2/4)}{BW}$$

Where Q = blood flow, VTi = volume time integral, HR = heart rate, d = vessel diameter and BW = body weight

This measurement has been used in clinical practice to assess systemic blood flow as a proxy of cardiac output. There are three researched assessments where systemic blood flow is measured from the heart in neonates.²⁶⁹ This includes LVO, RVO and SVCF. Table 8.4 outlines the normative values for each measurement over a variety of time points during the neonatal transitional circulation.

Measurement	Population	Time Since Birth (Hours)		
		4-6	24-48	72-96
SVCF (mls/kg/min)	Preterm (<29 weeks)	81± 26	93± 46	106± 30
	Term	68 (32–166)	89 (54–167)	
RVO (mls/kg/min)	Preterm (<29 weeks)	264± 90	312± 83	360± 112
	Term	216 (122–338)	207± 47	
LVO (mls/kg/min)	Preterm (<29 weeks)	243± 69	294± 77	311± 93
	Term	193 (148-278)	294± 25	

Table 8.4: Normative values for measures of systemic blood flow during the transitional circulation; data displayed as mean (standard deviation) or median (IQR)²⁷⁸

8.6.8 Left ventricular outflow (LVO)

This is calculated from measuring the diameter of the aorta valve at the annulus or the internal diameter in the ascending aorta. VTi is obtained from the high suprasternal, apical or subcostal views.^{95,186,201,279-288} Studies have shown good repeatability with this technique within and between observers.^{286,289} The main problem with LVO is the effect of a PDA. A large shunt across the PDA will lead to increased preload on the left side of the heart and thus stroke volume. Increased LVO will overestimate the systemic blood flow.²⁶⁹ However, LVO measures of less than 150mls/kg/min have been associated with increased morbidity and mortality in preterm infants,^{285,290} When the PDA is closed, this measurement is a good estimate of systemic blood flow and cardiac output (e.g. impaired late left ventricular contractility).²⁹¹

8.6.9 Right ventricular outflow (RVO)

RVO represents the flow of blood returning to the heart and in the absence of shunts, systemic blood flow.^{285,292} RVO is commonly derived from the measurement of the annulus of the pulmonary valve using its hinge points in end systole as reference points. Both the vessel diameter and the VTi are gained from a modified parasternal long axis view of the heart (Figure 8.16).^{186,280,285,286,288,293-296} Again, the repeatability of this technique is good with intra-observer differences in diameter measurements being reported be as low as 4%.²⁸⁶ Once again, this measurement is confounded by shunting across the PFO within the heart. During the transitional circulation the degree of shunting through the PFO is less than the PDA so in theory the RVO should be a more accurate measure of systemic blood flow. It correlates well with SVCF and increases in the first 48 hours of life in preterm infants.^{297,298} Similarly to LVO a measurement of less than 150mls/kg/min or decreases by 50% in septic infants is associated with increased morbidity and mortality.^{222,285,292,299}

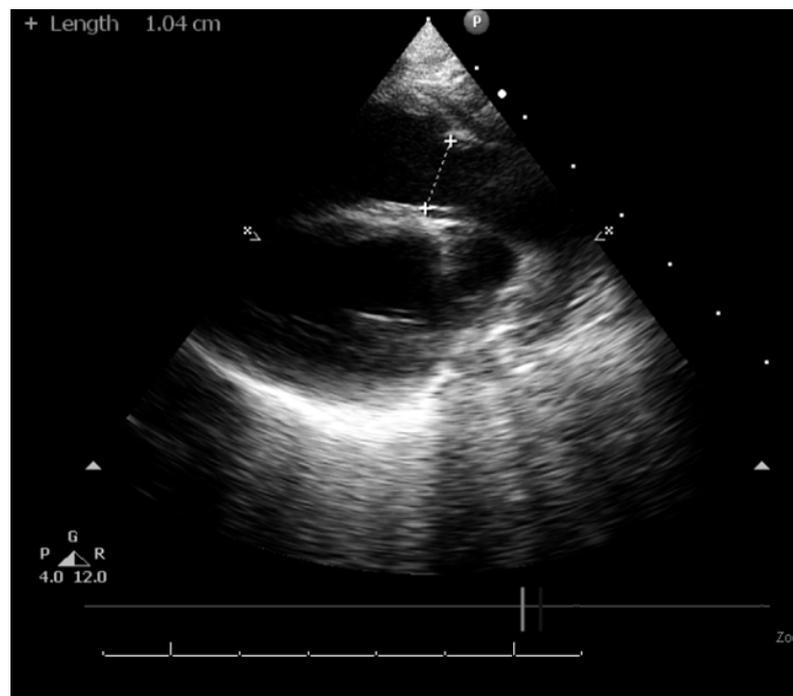


Figure 8.16: Echocardiographic measurement of RVO diameter at the level of the pulmonary valve (white line)

8.6.10 Superior vena cava flow (SVCF)

SVCF has been proposed as a better measure of systemic blood flow because it is unaffected by intra-cardiac shunting.³⁰⁰ The most well researched or “traditional”

method of measuring SVCF involves obtaining VTi measurements from a low subcostal view with pulsed Doppler “sample gates” placed at the junction of the SVC and the right atrium.³⁰⁰ The diameter of the SVC is measured in either B or M-mode in a true sagittal left mid parasternal window (Figure 8.17).³⁰⁰

The interest in this method of measuring systemic blood flow is the association of low SVCF and brain injury. Incidences of low flow may provide insight into the pathophysiology of poor perfusion and brain injury in preterm infants.^{290,300} 80% of blood flow in the superior vena cava returns from the head and neck.³⁰⁰ In preterm infants low superior vena cava flow (less than 42 mls/kg/min) at 5 hours of age is associated with late intraventricular haemorrhage and poor neurodevelopmental outcome.^{254,290} This supports the “perfusion-reperfusion” theory of intraventricular haemorrhage. Low SVCF has also been associated with abnormal cerebral autoregulation.³⁰¹ This biomarker has been the target of two randomised control trials where dobutamine was given with the aim of increasing SVCF and thus preventing adverse long term neurodevelopmental outcomes. Both studies found that dobutamine did significantly increase SVCF but only trends for improved long term outcomes in treated infants were found.^{9,302}

In term infants suffering from HIE, SVCF during the first day of life is significantly reduced when compared to healthy controls (34.5 mls/kg/min compared to 78.5 mls/kg/min).³⁰³ Whilst the clinical use of SVCF has not been established previous research has found that during total body cooling those neonates who had abnormal MRI scans were found to have a significantly higher SVCF than those with normal scans.^{9,127,285,290} This may reflect the loss of cerebral autoregulation in severe cases of HIE, thus increasing cerebral blood flow and SVCF.³⁰⁴

The repeatability of this technique has been questioned, but the intra and inter-observer variability is quoted to be between 8-17% and 14-29% respectively.²⁷⁷ In particular measurements of the SVC diameter are sometimes difficult to capture as an infant’s lungs inflate interfering with the ultrasound images gained. Moreover, due to the lack of muscle within the vessel wall, the cross sectional area might not be truly cylindrical.^{300,305} Furthermore multiple VTi measurements must be taken into account for the variation seen with spontaneous respiration.²⁶⁶ Recent

research has attempted to improve the repeatability of measuring SVCF using modified approaches in measuring both the VTi and diameter of the SVC. For example, Harabor and Fruitman found that measuring SVC VTi, such as through a suprasternal view, may reduce the variability in measurements gained.³⁰⁶ A prospective observational study compared the repeatability of measuring SVCF by the traditional method versus a modified approach where the SVC VTi is measured from a suprasternal view and the area of the SVC via a short axis view. They found that compared to the traditional approach, the modified approach improved both scan–rescan intra-observer and inter-observer analysis–reanalysis repeatability index (37% vs 31% and 31% vs 18% respectively).³⁰⁷ Furthermore the agreement with MRI phased contrast measurements of SVCF was also better with the modified approach to SVCF compared to the traditional approach ($R^2=0.259$ vs 0.775).³⁰⁷ However, the modified methodology of measuring SVCF has only just been developed and has yet to be assessed in interventional studies in neonates.

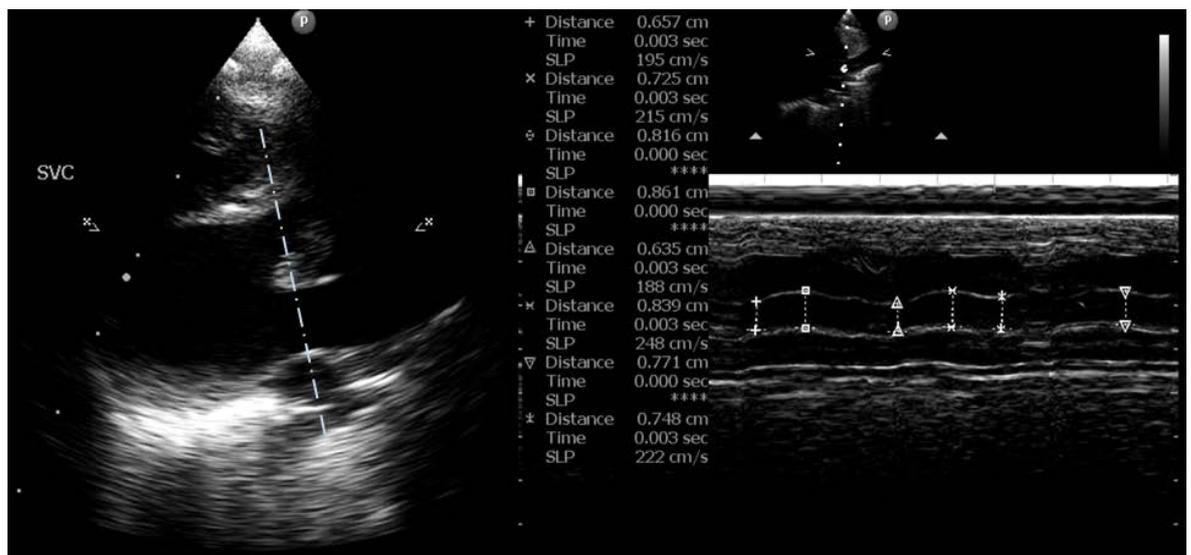


Figure 8.17: Echocardiographic measurement of SVC diameter via M-mode

The role of these measurements of systemic blood flow in the management of the haemodynamically compromised late preterm and term infants, including reference values and their association with morbidity and mortality have yet to be studied.

8.7 Pulse oximetry derived plethysmographic traces

The concept of plethysmographic traces derived from oxygen saturation probes was developed in the 1940s but was not routinely used clinically until the 1970s.³⁰⁸ Similar to NIRS, pulse oximetry is based on Beer-Lambert law. In the case of pulse oximetry, the arterial oxygen saturation is determined from the amount of red and infrared light absorbed by deoxygenated and oxygenated blood in the capillaries.³⁰⁹ With regards to neonates this is determined by a probe placed either side of a capillary bed (e.g. the hand or foot). On one side of the probe there are two light emitting diodes that produce wavelengths of light between 660 to 940 nm. The opposite side of the probe consists of an electrode that detects the intensity of light that travels through the extremity. Therefore, this electrode is detecting the light absorption of the extremity's soft tissue, venous and arterial blood. With each heart beat there is an alteration in light absorption owing to the changes in the volume of arterial blood in the extremity. This is known as the plethysmographic waveform. The arterial oxygen saturations are calculated from the ratio of the transmitted light through the pulsatile tissue component to the transmitted light through the non-pulsatile tissue component. Figure 8.18 provides a graphical depiction of this concept.³¹⁰

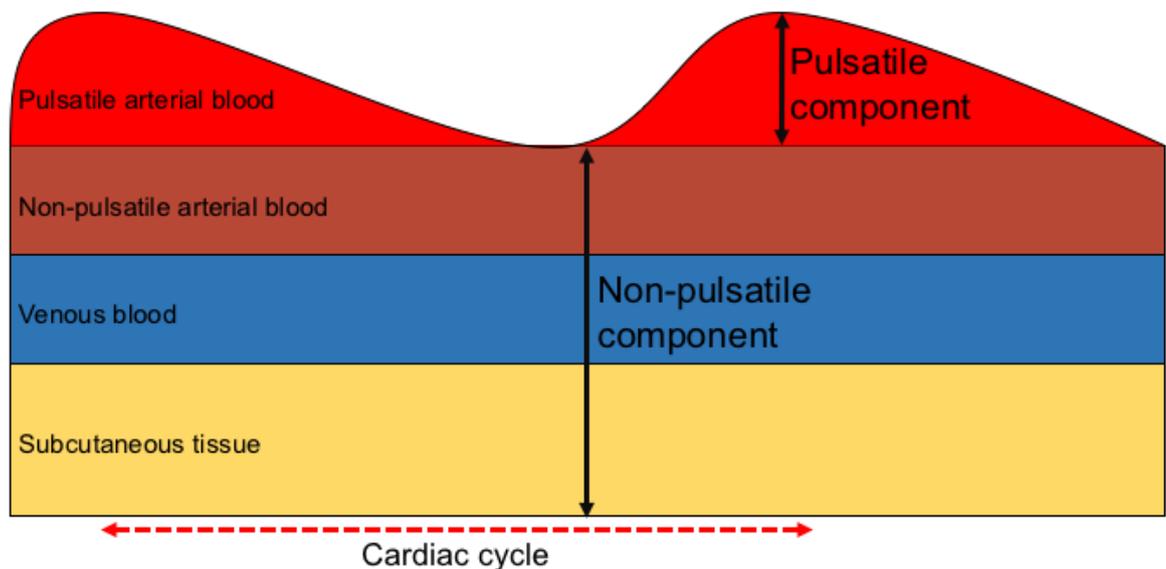


Figure 8.18: Illustration of the path of light from a pulse oximeter as it travels through a periphery

The clinical advantage of developing indices from such technology are that it is already in widespread use and is operator independent.

8.7.1 Physiological factors and clinical plethysmographic indices

The absorbance of infra-red light in a pulse oximeter is affected by the volume of blood present in the extremity where the pulse oximeter is placed. Therefore, during systole when the volume of blood in the capillary bed increases, so does the absorbance of infrared light. The reverse happens during cardiac diastole. Thus alterations in cardiac stroke volume, peripheral vasomotor tone, hypovolaemia and temperature will lead to differences in capillary blood volume and therefore alterations in the pulsatile and non-pulsatile components of the plethysmographic trace.

Changes in the intra-thoracic pressure will also alter the non-pulsatile and pulsatile components of the plethysmographic trace further. During inspiration the pressure in the thoracic cavity becomes negative, increasing venous flow to the heart. The converse happens in expiration. These factors will affect the cardiac output and stroke volume in individuals which, in pathological states such as severe asthma, lead to clinically detectable differences in volume of peripheral pulses during respiration.³¹¹

8.7.1.1 Perfusion index (PI)

PI is a commercially available clinical ratio of the pulsatile and non-pulsatile components of the plethysmographic trace multiplied by 100. Clinical studies have shown that perfusion index can be useful in establishing how unwell a neonate is, predicting low SVCF and detecting congenital heart malformations.³¹²⁻³¹⁵ A potential criticism is that it fails to take into account the respiratory induced variations that one sees in the plethysmographic trace.

8.7.1.2 Pleth variability index (PVI)

PVI is another commercially available clinical plethysmographic value. It uses the same equation as above to calculate the PI, then goes on to calculate the plethysmographic variation that occurs during respiration.

$$PVI = \left(\frac{PI \max - PI \min}{PI \max} \right) \times 100\%$$

Where PI_{max} = maximum PI over the respiratory cycle, and PI_{min} = minimum PI over the respiratory cycle.

Figure 8.19 gives an example of how PVI is calculated from the plethysmographic trace.³¹⁶

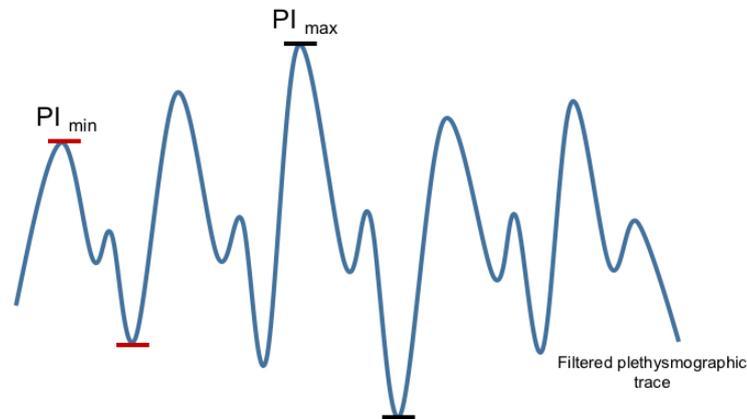


Figure 8.19: Example of pleth variability index (PVI) calculation from a filtered plethysmographic trace

The majority of the studies surrounding PVI explored its accuracy in predicting fluid responsiveness in hypotensive mechanically ventilated adults. A meta-analysis of PVI found a pooled sensitivity of 0.8 and specificity of 0.76 for its ability to predict a positive haemodynamic response to fluid boluses for cardiovascular compromise.³¹⁷

Reference values for PVI in the first day of life in term neonates have been established with a median of 20% (interquartile range of 14 – 24%.) Its values appear to be significantly affected by the behavioural status of the infant. For example, the PVI values are greater in crying or agitated infants. This likely due to the decrease in preload seen with increased inspiration and heart rate of such infants.³¹⁸ Inverse correlations were also found with oxygen saturations.³¹⁸

PVI has also been shown to be predictive of PDA behaviour in premature infants. Vidal *et al.* found that in infants with a PDA who were exhibiting a “growing” or “pulsatile” pattern the PVI values were significantly less than those with PDAs exhibiting “pulmonary hypertension”, “closed” or “closing” patterns.³¹² This is due to the former having greater left to right shunts across the PDA and thereby increasing cardiac preload and reducing PVI values.

Due to its apparent relation to hypovolemia, PVI has been investigated as a tool for predicting an infant's responsiveness to fluids in case of circulatory failure. The majority of studies have reported that PVI values significantly reduce in response to fluid resuscitation and demonstrate a predictive value (up to 0.78 area under the ROC curve) for a positive response to this intervention.³¹⁹⁻³²¹ These findings are presumably due to an increase in the preload.

However, some studies have reported that PVI is not predictive of fluid responsiveness in infants.³²² This may be because of the physiological interactions with respiratory mechanics. PVI may be less accurate in neonates due to their inherent higher chest-wall compliance.³²³ The use of PVI and the changes in response to inotropic therapy therefore need further study. The accuracy of PVI has been questioned by a study in preterm infants that performed a Bland Altman analysis showing only moderate reproducibility with large biases when a saturation probe was placed on different limb sites to calculate PVI in the same neonate.³²⁴ PVI calculation is also dependent on an undisturbed plethysmographic trace not altered through motion artefact.

8.7.1.3 Pulse transit time (PTT)

This is defined as the time it takes for an arterial pulse wave to travel between two sites in the body.³²⁵ In the clinical domain it is the period of time between the R wave on an electrocardiogram (ECG) and a particular point on a concurrently recorded plethysmographic trace derived from a pulse oximeter (Figure 8.20). Thus it is a measurement of the speed it takes for an arterial waveform to travel from the aortic valve to the an extremity.³²⁵

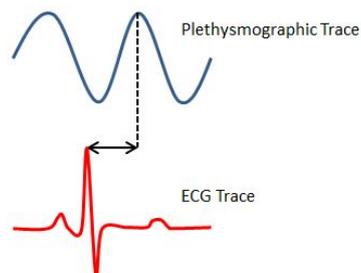


Figure 8.20: An example of a calculation of pulse transit time (PTT) from a concurrent ECG and plethysmographic trace (arrowed line)

The relationship this clinical parameter has to cardiovascular physiology is represented by the Meons-Kortweg equation-

$$PWV = \sqrt{\frac{E \times h}{2 \times p \times r}}$$

Where PWV = pulse wave velocity, E = incremental elastic modulus of a vessel wall, h = wall thickness, p = blood density and r = radius of a blood vessel.

Therefore, PTT (which is inversely proportional to pulse wave velocity) is shortened by vasoconstriction.³²⁵ It is also affected by variations in respiration, as inspiration increases isovolumetric contraction time in the heart and therefore will prolong PTT.³²⁵

The calculation of PTT would be feasible in a neonatal unit as both the ECG and pulse oximetry are used concurrently in those admitted to intensive care. However, data on its use in infants is limited. The majority of studies have been conducted in adults. They have found PTT to correlate negatively with systolic blood pressure ($r^2=-0.39$) and also clinically detect spikes in blood pressure seen with micro-arousals during polysomnography testing.³²⁶⁻³³⁰ A study looking at the use of PTT in infants aged 2-3 months during sleep found non-significant trends for an inverse relationship between PTT and systolic blood pressure.³²⁶

Similar to PVI, PTT can be limited by the quality of the ECG and plethysmographic traces gained.³²⁵ The feasibility of PTT in preterm neonates needs further study. Furthermore, its relationship to other parameters used in haemodynamic monitoring and treatment of neonates has not been assessed.

It should be noted that the prior text refers to commercially available plethysmographic measures of PVI and PTT. Modified versions of both of these measures are used for the clinical studies contained in this thesis and shall be referred to as modified PVI (mPVI) and modified (mPTT) henceforth. This is expanded upon in the clinical studies section of this thesis.

8.8 Management of circulatory failure

Treatment in circulatory failure aims to restore end organ perfusion and prevent irreversible damage. A number of regimens have been recommended in the literature, but the application of these treatments varies greatly between neonatal units.¹⁸⁰ This apparent heterogeneity in the treatment of circulatory failure is likely to be a reflection of the available evidence.⁸⁹

8.8.1 Redistribution of placental blood

This includes either delayed cord clamping or cord milking. The former involves delaying the clamping of the umbilical cord for 30 seconds or more after birth. The latter involves the stripping or milking of blood within the umbilical cord towards the infant after delivery. Both facilitate the increased transfer of blood from the placental to the neonatal circulation. A number of trials in preterm and term infants indicate benefits including fewer blood transfusions, improved SVCF and reduced incidence of intraventricular haemorrhages.³³¹ Its potential to cause or exacerbate jaundice or polycythaemia in newborns is negligible.¹⁸⁸

8.8.2 Permissive hypotension

This is a concept defined as accepting a low blood pressure provided there are no adverse signs of poor perfusion (e.g. normal capillary refill time). A retrospective cohort study (over 4-years) found that in infants hypotensive on GA criteria but with clinical evidence of good perfusion clinical outcome was no different to neonates considered to be normotensive.¹⁷⁹

8.8.3 Fluids and blood products

Meta-analysis of multiple trials has shown that no colloid or crystalloid is superior in the successful treatment of hypotension, mortality or long-term morbidity.³³² There is a consensus that aliquots of 10mls/kg boluses of 0.9% saline are effective and safe in raising blood pressure and cardiac output.^{188,332,333} However there is animal evidence to suggest that rapid infusion of fluids may be harmful.¹⁰⁴ Where circulatory failure is associated with blood loss (e.g. placental abruption, twin to

twin transfusion) it is recommended that packed red cell transfusion of 10-20mg/kg be implemented.³³³

8.8.4 Inotropic therapy

The premise of using pharmacological therapy in order to correct circulatory failure is to induce change in either the myocardium or in the vascular tone in an attempt to normalise end organ perfusion. This is mediated through the actions on adrenergic and dopaminergic receptors. Table 8.5 lists commonly used treatments in circulatory failure.

Drug	Dose Range	Therapeutic Effect
Dopamine	1-20mcg/kg/min	Inotrope, Vasopressor, \uparrow SVR & PVR
Dobutamine	1-20mcg/kg/min	Inotrope, \downarrow SVR & \uparrow CO
Adrenaline	0.5-1.5 mcg/kg/min	Inotrope, Vasopressor, \uparrow SVR
Noradrenaline	20-100 ng/kg/min	Vasopressor, \uparrow SVR
Milrinone	0.35-0.75mcg/kg/min	\uparrow CO, \downarrow SVR
Hydrocortisone	2mg/kg IV Bolus	Uncertain
Vasopressin	0.00003-0.002 units/kg/min	Vasopressor, \uparrow SVR

SVR=Systemic vascular resistance, PVR= Pulmonary vascular resistance, CO= Cardiac output

Table 8.5: Inotropes typically used on neonatal units, their doses and therapeutic effect⁷

Dopamine is the most commonly used inotrope in neonates. It acts on α , β and dopaminergic receptors. It is thought to be primarily a vasoconstrictive agent in premature infants.^{167,333} A Cochrane review found it to be more successful than dobutamine at raising a neonate's blood pressure. However no difference was found between the inotropes with regards to short and long term morbidity or mortality.³³⁴

Dobutamine increases cardiac output through its effect on myocardial β adrenoreceptors. Significant increases in SVCF and RVO has been reported in response to infusions of 10–20mcg/kg/min.^{167,333} Furthermore a number of studies have also shown it decreases systemic and pulmonary vascular resistance.³³⁵ For this reason it might be considered the primary inotrope of choice in the first 24

hours of life. This is because circulatory failure, during this period of time, is attributed to reductions in systemic blood flow due to myocardial dysfunction in response to increasing afterload from the natural increase in systemic vascular resistance during the transitional circulation. In preterm infants low superior vena cava flow (less than 42 mls/kg/min) at 5 hours of age is associated with late intraventricular haemorrhage and poor neurodevelopmental outcome.²⁵⁴ Two randomised control trials hypothesised that giving dobutamine would increase SVCF. Both studies found that dobutamine significantly increased SVCF but only trends for improved long term outcomes in treated infants were found.³³⁵

Adrenaline is believed to produce similar cardiovascular effects to dopamine in the preterm population. One trial found adrenaline to be equal to dopamine in increasing a neonate's blood pressure, though more likely to cause hypoglycaemia, increased myocardial oxygen use, raised lactate levels and arrhythmias.²⁵⁴

Noradrenaline is naturally released either from the adrenal medulla or from sympathetic nerve fibres. It is a powerful vasoconstrictor that also increases myocardial contractility. It has not been studied systematically in the neonatal population.^{9,302}

Milrinone is a selective phosphodiesterase III inhibitor and increases the activation of cyclic adenosine monophosphate and subsequently increases the calcium influx into the myocardium, thereby improving cardiac contractility. It also exhibits pulmonary and systemic vasodilator properties. It has been predominantly been used in the preservation of cardiac output after cardiac surgery and in persistent pulmonary hypertension of the newborn. In randomised controlled trials prophylactic milrinone did not increase cardiac output or SVCF.¹⁶⁷

Hydrocortisone has primarily been used in circulatory failure refractory to inotropic therapy. It is thought to act by up-regulating the number of adrenoreceptors priming a neonate's cardiovascular system to respond to circulating catecholamines. A Cochrane review of its use concluded that it may be as effective as dopamine in increasing a neonates blood pressure.¹⁶⁷ Whilst concerns

about the effect on long term development appear to be unfounded this needs to be assessed in long term studies.³³³

Vasopressin is naturally secreted from the posterior pituitary gland and increases SVR by inducing vasoconstriction in the peripheral vasculature. In circulatory failure associated with sepsis it has been shown to be depleted.³³⁶ The rationale for its use is to increase levels and promote vasoconstriction, but experience and systematic research of its use is limited.^{167,333}

9 Hypothesis & Objectives

9.1 Hypothesis

Based on the background reading the following hypotheses were developed:

- Traditional clinical parameters and examination do not accurately assess circulatory adaptation in late preterm and term neonates who are healthy, receiving intensive care or total body cooling therapy.
- Traditional clinical parameters and examination do not accurately assess circulatory failure in late preterm and term neonates who are receiving intensive care or total body cooling therapy.
- Non-invasive measurement of circulatory status will aid clinicians in the monitoring of circulatory adaptation in late preterm and term neonates who are healthy, receiving intensive care or total body cooling therapy.
- Non-invasive measurement of circulatory status will aid clinicians in the detection and management of circulatory failure in late preterm and term neonates who are receiving intensive care or total body cooling therapy.

9.2 Aims and Objectives

The objectives of this thesis are:

- To produce reference values for SVCF, RVO, modified pulse transit time (mPTT) and modified pleth variability index (mPVI) in late preterm and term neonates who are healthy (NeoAdapt 1), receiving intensive care, (NeoAdapt 2) or total body cooling therapy (NeoAdapt 3).
- To examine the changes in daily values recorded for SVCF, RVO, mPTT and mPVI in late preterm and term neonates who are healthy (NeoAdapt 1), receiving intensive care, (NeoAdapt 2) or total body cooling therapy (NeoAdapt 3).
- To investigate SVCF, RVO, mPTT and mPVI associations with treatment for circulatory failure and early markers of neurodevelopmental outcome in late preterm and term neonates who are receiving intensive care (NeoAdapt 2) or total body cooling therapy (NeoAdapt 3).
- To explore the relationships between for SVCF, RVO, mPTT, mPVI and traditional measurements of circulatory status in late preterm and term

neonates who are healthy (NeoAdapt 1), receiving intensive care, (NeoAdapt 2) or total body cooling therapy (NeoAdapt 3).

- To assess the inter- and intra-observer repeatability of SVCF, RVO, mPTT, and mPVI in in late preterm and term neonates who are healthy (NeoAdapt 1), receiving intensive care, (NeoAdapt 2) or total body cooling therapy (NeoAdapt 3).

10 Methods

This chapter contains a description of each clinical research study design, methodology and results.

10.1 Clinical Studies: Longitudinal and comparative analysis

10.1.1 Study backgrounds

10.1.1.1 NeoAdapt 1: Non-invasive measurements in cardiovascular adaptation of well late preterm and term infants

This study assessed cardiovascular adaptation in healthy late preterm and term infants using traditional bedside, echocardiographic and plethysmographic measurements over the first three days of life. The study aims to provide novel reference values for these assessments but also determine how they change over the transitional circulation in infants considered to be healthy.

10.1.1.2 NeoAdapt 2: Non-invasive measurements of cardiovascular adaptation in severely unwell late preterm and term infants

This study assessed the cardiovascular adaptation in late preterm and term infants who required intensive care using traditional bedside, echocardiographic and plethysmographic measurements over the first three days of life. The study aims to determine how they change during the transitional circulation in infants requiring intensive care. The study will also explore how these assessments of cardiovascular status in a neonate relate to the treatment for circulatory failure but also short term neurological outcomes.

10.1.1.3 NeoAdapt 3: Non-invasive measurements in cardiovascular adaptation of neonates suffering hypoxic ischemic encephalopathy receiving total body cooling treatment

This study assessed the cardiovascular adaptation in term infants suffering from HIE who were receiving total body cooling therapy using traditional bedside, echocardiographic and plethysmographic measurements over the first three days of life. The study aimed to determine how they change over the period of transitional circulation in infants requiring intensive care. The study will also

explore how these assessments of cardiovascular status in a neonate relate to treatment for circulatory failure but also short term neurological outcomes.

10.1.1.4 Interstudy comparisons

The basis of the analysis for this study was to assess whether there is a difference in the cardiovascular adaption of the three studied cohorts according to the research measurements used.

10.1.2 Sample size

Prior to the development of this study, consultation for the proposed sample sizes for each study was performed with Stephanie Goubet, Medical Statistician (CIRU, Brighton & Sussex University Hospitals NHS Trust) and Dr Laurie Smith (Division of Mathematics, School of Computing, Engineering and Mathematics at the University of Brighton) was sought. As there are no reference values for either echocardiographic and plethysmographic measurements in the proposed study populations we were unable to perform power calculations in order to generate the sample size needed to reach a significance where the p-value is ≤ 0.05 or the confidence interval reaches 95%.

Previous studies researching these parameters have reported sample sizes of 13 to 92 infants. The annual number of infants in the eligible group receiving special care on the Trevor Mann Baby Unit is 159 and 3695 infants on the postnatal ward. We anticipated that for the NeoAdapt 1 study we would be able to recruit 50 participants over a two-year period. This meant enrolling 1 patient per week into the study.

The annual number of neonates aged greater 33 weeks GA receiving intensive care on the Trevor Mann Baby Unit is 166. We aimed to recruit 25 babies into the NeoAdapt 2 study. This meant that that over a two-year period 7% of the total number of eligible infants would require consent to the study.

With regard to the NeoAdapt 3 study there has been one previous study which investigated these parameters in infants who received selective head cooling

studied 24 infants.³³⁷ The annual number of infants treated with total body cooling for HIE on the Trevor Mann Baby Unit is 25. We again used a convenience sample from this population in order to recruit as many infants as possible into the study. Whilst this might be considered ambitious the Trevor Mann Baby Unit was part of the TOBY trial for which successful recruitment rates were 64% from the same population.¹¹⁹ It should also be noted after receiving ethical approval there was a requirement for the NeoAdapt 3 study to commence 3 months after the opening of the NeoAdapt 1 and 2 studies.

For all of the NeoAdapt studies we used a convenience sampling method for recruitment.

10.1.3 Inclusion criteria

The NeoAdapt 1 study included infants born later than 33 weeks' GA within 72 hours of birth receiving either routine care on the post-natal ward or special care on the Trevor Mann Baby Unit at the Royal Sussex County Hospital, Brighton.³³⁸

The NeoAdapt 2 study included neonates born older than 33 weeks' GA within 72 hours of birth receiving intensive care on the Trevor Mann Baby Unit at the Royal Sussex County Hospital, Brighton.³³⁸ For the purposes of this study the definition of intensive care was developed from the classification of high dependency and intensive care from the British Association of Perinatal Medicine Categories of Care 2011 documents.³³⁹ Therefore if an infant was admitted to intensive to receive the following types of care they were eligible for the NeoAdapt 2 study:

- Any day where a baby receives any form of mechanical respiratory support
- via a tracheal tube or non-invasive ventilation (e.g. nasal CPAP, SIPAP, BIPAP, HHFNC).
- Presence of an arterial line
- Presence of an umbilical venous, central venous or long line
- Insulin infusion
- Presence of a chest drain
- Exchange transfusion
- Parenteral nutrition

- Continuous infusion of drugs
- Presence of a tracheostomy
- Presence of a urethral or suprapubic catheter
- Presence of NP airway/nasal stent
- Observation of seizures / cerebral function monitoring
- Barrier nursing

The NeoAdapt 3 study included infants born older than 36 weeks' GA within 72 hours of birth receiving cooling therapy for HIE according to criteria set out by the "TOBY Trial" and clinical guidelines from the Trevor Mann Baby Unit at the Royal Sussex County Hospital, Brighton.²³³

10.1.4 Exclusion criteria

For all three NeoAdapt studies infants were excluded if they were considered to be non-viable, had congenital hydrops, cardiovascular malformations, believed to have chromosomal abnormalities or considered for surgical treatment within 72 hours of birth.

10.1.5 Parental consent

Informed written consent was received from parents after the birth of an eligible infant. The principles of the continuous consent process was utilised in order to ensure parents were satisfied in remaining in the studies.³⁴⁰ This involved discussing the study with the parents again throughout the period their child was involved in the study ensuring that they are happy to continue in the study, that they understand what the it entails and that they can withdraw consent at any point.³⁴¹ When informed consent was received 3 copies of the completed consent sheet were made: one placed in the patient notes, one given to the parents and one kept in the trial master file.

10.1.6 Ethical approval and protocol publication

Ethical approval for each study was gained from the City and East National Research Ethics Committee. The protocol for each study was published on the

website Clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT02047916, NCT02051855 and NCT02051894). The study was adopted by the UK Clinical Research Network Study Portfolio (Study ID: 16767, 16826 and 16768).

10.1.7 Demographic and clinical data

Basic demographic and clinical data were obtained from inpatient notes. This included GA (GA), birth weight, whether their birth weight was less than the third centile for their age or small for GA (SGA), 5 minute APGAR score, multiplicity, type of delivery, course of antenatal steroids and principle diagnoses on admission to the neonatal unit. For both the NeoAdapt 2 and 3 studies additional information on risk factors for sepsis and delivery complications was also gained. All principle diagnoses were recorded from the patients notes and were based on clinician's opinions throughout an infant's stay in the neonatal unit.

Additional data were gained from subject notes with regards to treatment (if received) for circulatory failure and respiratory management was gathered for both the NeoAdapt 2 and 3 studies. The Trevor Mann Baby Unit has several clinical guidelines on various aspects of neonatal care of infants included in the three studies. This includes that all pregnancy women between 23-<35 weeks GA considered at risk of preterm birth would be given a course of antenatal steroids.³⁴² With regard to the neonatal cardiovascular management all neonates irrespective of GA at birth should have delayed cord clamping or cord milking at birth. The unit also defines a that an infant should be considered for hypotensive therapy when a MAP is less than an infant's GA in weeks with a treatment algorithm consisting fluid therapy (10-20mls/kg of normal saline) followed by intravenous infusions of dopamine, dobutamine, adrenaline and then hydrocortisone.³⁴³ Red cell blood transfusions at 15-20mls/kg may also be considered as first line therapy in hypotension.³⁴³ Transfusions of red blood cells at the same volume are considered outside of hypotensive treatment when a clinician felt that clinical signs of anaemia were present in a neonate such as tachypnoea, tachycardia or apnoea. If such signs were present and the haemoglobin count was below 110 g/L in the first week of life, 100 g/L in the second week of life or in the third week of life 85 g/L a red cell blood transfusion at 15-20mls/kg could be considered. The threshold for a red cell blood transfusion

decreased if an infant was on any type of respiratory support with haemoglobin count was below 100 g/L in the first week of life, 8.5 g/L in the second week of life or in the third week of life 75 g/L.³⁴⁴

Whilst these guidelines are utilised on the unit, clinical practice varied between clinicians. Furthermore, as this was an observational study the decision to give treatment for circulatory failure was at the discretion of the attending physician. For the purposes of the NeoAdapt 2 and 3 studies infants were considered to be in circulatory failure if they received treatment that was documented in the subject's notes for the purpose of improving haemodynamics parameters.

10.1.8 Research measurements

Enrolled subjects in the NeoAdapt 1 and 2 studies had a set of research measurements performed every 24 hours for the first three days of life. Therefore, a maximum of three sets of research measurements could be performed depending on when an infant was enrolled. For the neonates included in the NeoAdapt 3 study had set of research measurements performed every 24 hours for the first three days of life and one more during or after rewarming phase of total body cooling. Therefore, a maximum of four sets of research measurements could be performed depending on when an infant was enrolled.

10.1.8.1 Traditional bedside assessments

All bedside assessments were performed concurrently with echocardiographic and plethysmographic assessments. Where measurements were missed due to operator error the most recent measurement completed for clinical purposes was used.

Heart rate (HR) and oxygen saturations (SpO₂) were gained from routine monitoring from the infant at the time of research measurements. These monitors included the General Electric Dash 3000TM, 4000TM and 8000iTM monitors (General Electric, USA). For infants on the post-natal ward their HR and SpO₂ were

recorded from the SOMNOscreen™ Plus system (SOMNOmedics GmbH, Germany) used for the plethysmographic assessments.

Capillary refill time (CRT) was assessed on the anterior chest over the lower sternum. The index finger was used to apply sufficient pressure to blanch the skin; countdown to normal skin colour was then timed.

The mean, systolic and diastolic blood pressure (BP) of an infant was measured either invasively via an arterial line or non-invasively using the oscillation methods. These measurements were made using a General Electric Dash 3000™, 4000™ and 8000i™ monitors. An infant's pulse pressure could then be calculated by subtracting diastolic from the systolic BP.

For the NeoAdapt 2 and 3 studies data regarding blood gas parameters of lactate, base excess and pH were recorded. In order to reduce the burden placed on the infant blood gas results taken for clinical purposes closest to the time research measurements were taken was used for all analyses performed. The daily urine output of each neonate was also recorded. The method of recording this measurement was left to the discretion of the clinical team.

10.1.8.2 Plethysmographic assessments

Plethysmographic traces for the calculation of both mPVI and mPTT were performed using the SOMNOscreen™ Plus system (SOMNOmedics GmbH, Germany). For each recording the saturation probe from this system was placed preferentially on the left hand. If this was not possible, then it was placed on either one of the other limbs. Three electrocardiogram (ECG) electrodes were also placed on the chest wall to record a concurrent ECG trace at the time plethysmographic measurement. The typical step-up for this is shown in Figure 10.1. The traces were recorded to a compact flash memory card and subsequently downloaded to a computer.



Figure 10.1: Set up for recording plethysmographic traces using the SOMNOscreen™ Plus system

Once the plethysmographic traces were downloaded mPTT was calculated using the SOMNOmedics™ Domino software (Version 2.6. SOMNOmedics GmbH, Germany, 2013). mPTT was calculated by measuring the time between the R wave on an ECG to the peak on the concurrent plethysmographic trace (Figure 10.2). Prior research has previously measured PTT by measuring the time difference between the R wave on the ECG and at a point 25-50% of the maximum height of a pulse wave of the plethysmographic trace.³²⁵ We decided to use the peak of the plethysmographic pulse wave to try and improve the reliability of the mPTT measurements. Furthermore, a Spearman rank correlation analysis between mPTT calculated using the peak and mPTT calculated using 50% of the height of the plethysmographic trace was 0.91 ($p=0.0008$) therefore indicating excellent associations between the two measures. The mPTT measurements were also normalised (NmPTT) for the heart rate by dividing the resulting mPTT by the time difference between two R waves on the ECG at the time the mPTT calculation was made. For each recording three mPTT and NmPTT measurements were made and averaged.

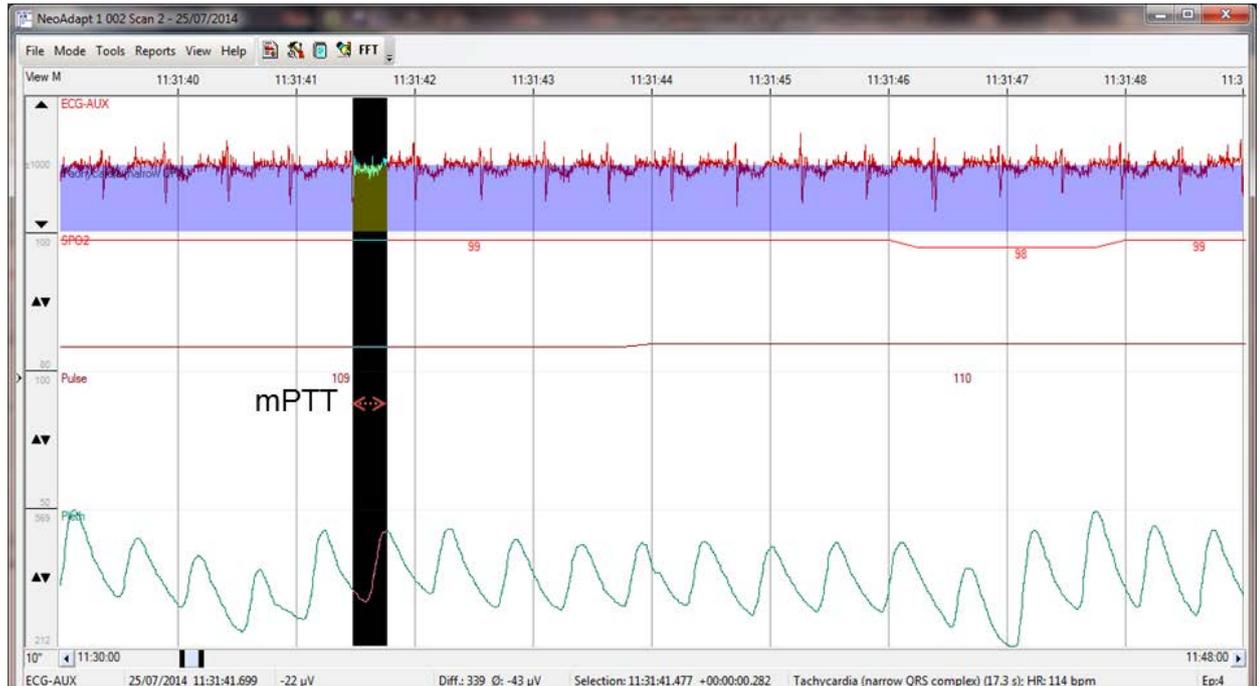


Figure 10.2: Screenshot of mPTT calculation

The mPTT measurements were also transformed (Trans mPTT) using the equation below.

$$\text{Trans mPTT} = \frac{1}{\text{mPTT}}$$

The reason for this measurement is that mPTT measurements are inversely related to the arterial pulse waveform velocity.³²⁹ This is demonstrated in the equation:

$$PWV = \frac{BDC \times H}{PTT}$$

Where PWV = pulse wave velocity, BDC = body correlation factor and H = height.

Pulse waveform velocities have been found to be approximately proportional to systolic blood pressure in adults.³²⁹ Therefore we may expect systolic blood pressure to be proportional to Trans mPTT as height would be a constant for individual infants.

mPVI assessments were calculated from the same plethysmographic recording. The plethysmographic trace required filtering in order to gain traces of the pulse amplitude over the respiratory cycle in order to calculate mPVI. This was performed using MATLAB (Version 8.6.0.267246., The MathWorks Inc., Natick, Massachusetts, USA: The Mathworks Inc., August 2015). Over a respiratory cycle

the maximum pulse amplitude (PA_{max}) and minimum pulse amplitude (PA_{min}) from the filtered plethysmographic trace was selected by the observer. Then the mPVI was calculated using the following equation.

$$mPVI = \left(\frac{PA_{max} - PA_{min}}{PA_{max}} \right) \times 100\%$$

Figure 10.3 provides a screenshot of how mPVI was calculated. For each recording three mPVI measurements were made and averaged.

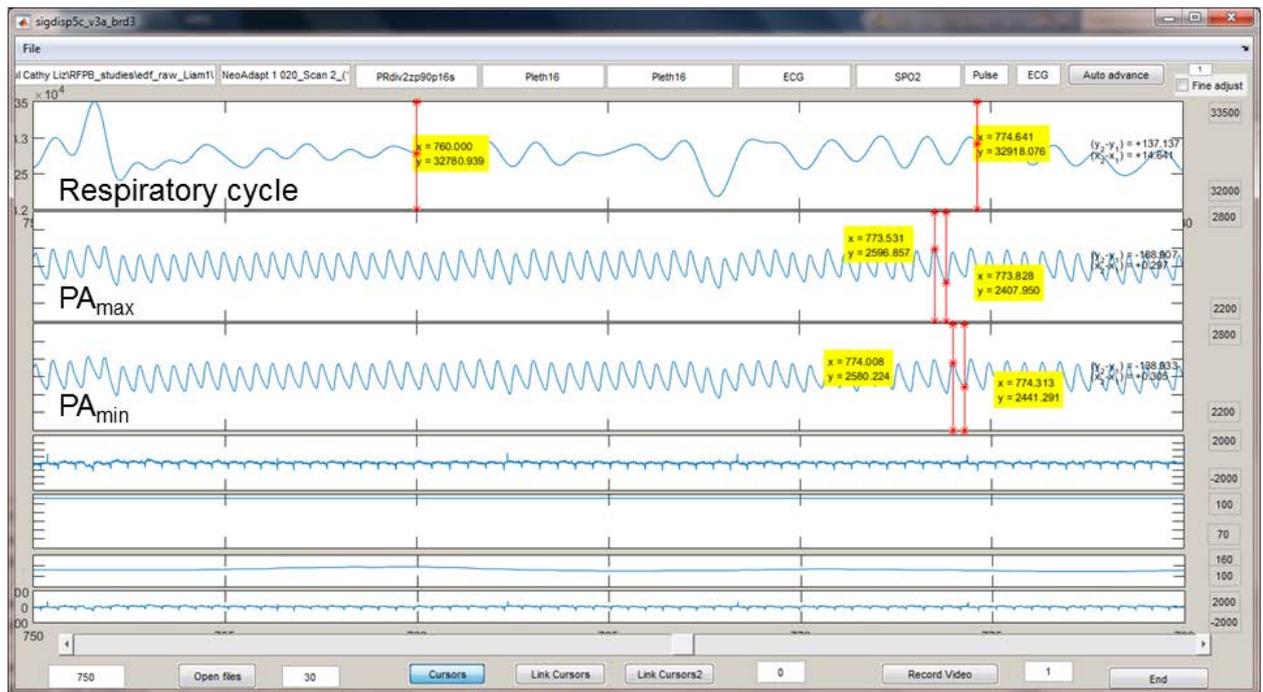


Figure 10.3: Screenshot of mPVI calculation

10.1.8.3 Echocardiographic assessments

SVCF and RVO measurements were acquired using either a HD11 XE (Phillips Healthcare, The Netherlands) or the Sonosite Edge ultrasound machine (Fujifilm Sonosite Inc., Japan). SVCF and RVO measurements were taken according to methods previously described in the literature.^{285,300} SVC VTi measurements are taken from a low subcostal view with pulsed Doppler measurements placed at the junction of the superior vena cava and the right atrium. Up to 10 VTi measurements were taken and averaged to account for respiratory variation seen in SVCF. The diameter of the SVC was measured in either B or M-mode in a true sagittal left mid parasternal window. M-Mode measurements were used preferentially and up to 10 measurements of the maximum and minimum diameter of the SVC were used and averaged. RVO VTi measurements were gained from a

modified parasternal long axis view of the heart. Up to 5 VTi measurements were measured and averaged. The RVO diameter was measured in B-mode from a modified parasternal long axis view using the hinge points of the pulmonary artery.

All diameter and VTi measurements were either performed at the bedside using the inbuilt software on the ultrasound machines or after the examination using Intellispace PACs Enterprise programme (Phillips Healthcare, The Netherlands).

Both SVCF and RVO were calculated using the equation a below:

$$Q = \frac{VTi \times HR \times (\pi \times d^2/4)}{BW}$$

Where Q = blood flow, VTi = volume time integral, HR = heart rate, d = vessel diameter and BW = body weight

10.1.8.4 Cranial ultrasound data

In the NeoAdapt 2 study cranial ultrasound appearances were used as a marker of cerebral injury. The timing of scans were performed according to the preference of the attending physician or unit guidance. The cranial ultrasounds were performed using a HD11 XE Ultrasound machine (Phillips Healthcare, The Netherlands). A standard series of 11 views (6 coronal and 5 sagittal) were taken to assess if any intra-cranial injury had been sustained. The appearances of the cranial ultrasound were then classified into one of three categories: Normal, Mild Brain Injury and Severe Brain Injury. This classification was derived from the consensus of expert opinion within the NEO-Circulation consortium.³⁴⁵ The characteristics of each criterion are outlined below-

- Normal brain scan
 - No cysts
 - No ventricular dilatation
 - No enlargement of extra-cerebral spaces
 - Normal cortical grey matter
 - Normal periventricular white matter (flaring lasting <7 days)³⁴⁶
- Mild brain injury:
 - Grade 1-2 IVH¹⁵⁰

- Persistent pathological non-decreasing flaring at days 7 and 14³⁴⁶
- Abnormal echogenicity at cortical/subcortical region
- Thinning of the corpus callosum
- Ventriculomegaly at term, ventricular index (VI) < 97th centile³⁴⁷
- Enlargement of the 3rd or 4th ventricle
- Severe brain injury:
 - IVH grade 3 (VI>97th centile during the acute phase)¹⁵⁰
 - Post haemorrhagic ventricular dilatation with the VI exceeding the 97th percentile³⁴⁷
 - Parenchymal ischemic/haemorrhagic infarction
 - Periventricular haemorrhagic infarction
 - Local cystic lesions (unilateral)
 - Cystic PVL (bilateral)³⁴⁶
 - Cerebellar haemorrhage / atrophy
 - Cerebral atrophy at term age

10.1.8.5 MRI measurements

In the NeoAdapt 3 study cranial MRI appearances were used as a marker of cerebral injury. Routine care of neonates with HIE on the Trevor Mann Baby Unit involves the acquisition of a brain MRI after the completion of cooling therapy. This was performed on enrolled neonates using the Brighton and Sussex University Hospitals NHS Trust standardised protocol. This comprises-

- T2 weighted turbo spin axial 512 images
- T1 weighted turbo spin axial 512 images
- T2 weighted turbo inversion recovery magnitude coronal images
- T1 weighted echo sagittal images
- T2 weighted echo sagittal images
- Diffuse weighted images

Afterwards the scan was reviewed and reported by a member of the Consultant Radiology staff. The appearance of the MRI images were then classified according to a score derived from Rutherford *et al.*¹⁵⁵

- Normal appearance of the posterior limb of the internal capsule is defined as high signal intensity in one third of the posterior of the internal capsule on T1 weighted images and low signal intensity on T2 images
- Abnormal appearance of the posterior limb of the internal capsule is defined as partial or complete absence of high signal intensity in one third of the posterior of the internal capsule on T1 weighted images and loss of the low signal intensity on T2 images
- Equivocal appearance will be used when asymmetry of signal is found within the posterior limb of the internal capsule.

10.1.9 NeoAdapt studies schedule of assessments

The timing of research measures for the NeoAdapt 1 study are outlined in Table 10.1.

Research Assessment	Hour of life			
	0-72	0-24	24-48	48-72
Participant enrolment logs	X			
Informed consent	X			
Assess eligibility	X			
Maternal medical history	X			
Perinatal data	X			
Blood pressure measurements	X	X	X	X
CRT	X	X	X	X
Heart rate	X	X	X	X
Plethysmographic traces	X	X	X	X
Echocardiographic traces	X	X	X	X
Neonatal diagnoses/outcomes	X	X	X	X

Table 10.1: NeoAdapt 1 schedule of research assessments

The timing of the research assessments for the NeoAdapt 2 study are outlined in Table 10.2.

Research Assessment	Hour of life				As per clinical team
	0-72	0-24	24-48	48-72	
Informed consent	X				
Assess eligibility	X				
Maternal medical history	X				
Perinatal data	X				
Circulatory failure treatment data	X	X	X	X	
Blood pressure	X	X	X	X	
CRT	X	X	X	X	
Heart rate	X	X	X	X	
Blood gas data	X	X	X	X	
Respiratory support data	X	X	X	X	
Cranial ultrasound data					x
Urine output	X	X	X	X	
Plethysmographic traces	X	X	X	X	
Echocardiographic traces	X	X	X	X	
Neonatal diagnoses/outcomes	X	X	X	X	

Table 10.2: NeoAdapt 2 schedule of research assessments

The timing of the research assessments for the NeoAdapt 3 study are outlined in Table 10.3.

Research Assessment	Hour of life				As per clinical team
	0-72	0-24	24-48	48-72	
Informed consent	X				
Assess eligibility	X				
Maternal medical history	X				
Perinatal data	X				
Circulatory failure treatment data	X	X	X	X	
Blood pressure	X	X	X	X	
CRT	X	X	X	X	
Heart rate	X	X	X	X	
Blood gas data	X	X	X	X	
Respiratory support data	X	X	X	X	
MRI data					X
Urine output	X	X	X	X	
Plethysmographic traces	X	X	X	X	
Echocardiographic traces	X	X	X	X	
Neonatal diagnoses/outcomes	X	X	X	X	

Table 10.3: NeoAdapt 3 schedule of research assessments

10.1.10 Statistical Analysis

For all three NeoAdapt studies the research measurements were analysed within the cohort as a whole. For the NeoAdapt 1 and 2 studies the cohort was then split into two groups; late preterm infants who were aged between 33 to <37 weeks GA, and those aged equal to or greater than of 37 weeks GA, defined as term infants. Pairwise longitudinal analysis of research measures was then performed within the late preterm and term cohorts. Comparative analysis between research measures gained from the late preterm and term cohorts were then performed.

For the NeoAdapt 2 and 3 studies additional analyses involving the comparison of research measures between those who received and did not receive treatment for circulatory failure and those who were found to have sustained brain injuries on cranial ultrasound or MRI imaging and those who did not were performed.

For the interstudy analysis comparisons were made between cohorts of similar GAs. Thus cohorts that included late preterm neonates (33-<37-weeks GA) were compared between the NeoAdapt 1 and NeoAdapt 2 studies. Comparisons between all three studies were performed for term neonates (≥ 37 -weeks GA).

Data is summarised as mean \pm standard deviation or median and interquartile ranges (IQR) where appropriate. Non-parametric tests were used throughout the statistical analysis as multiple research parameters were not normally distributed and could not be easily corrected through transformation. Where paired data were compared the Wilcoxon rank test was used. The Mann Whitney U test was used where comparisons were made using pooled data from 2 cohorts. Kruskal Wallis tests with Dunn's multiple comparison tests were used to compare results between more than 2 cohorts. For categorical data the Chi Squared test was used. Associations between measurements were calculated using the Spearman rank correlations. All of the statistical calculations and graphs were performed using Prism version 6.05 for Windows (GraphPad Software, La Jolla California USA). A p-value < 0.05 was considered statistically significant.

10.2 Clinical Studies: Plethysmographic & echocardiographic measurement repeatability

10.2.1 Study background

The purpose of this study was to assess the repeatability of plethysmographic and echocardiographic assessments within and between observers to see whether they are robust enough to be used in future studies and possibly within the clinical domain. As previously outlined a number of studies have assessed the repeatability of SVCF and RVO in extremely preterm and term neonates.^{286,289,348}

The repeatability of SVCF and RVO in late preterm neonates and infants receiving cooling therapy has yet to be performed. The repeatability of mPVI, mPTT and NmPTT using the methodologies outlined in this thesis has yet to be performed in neonates. The repeatability of commercially available devices that measure PVI has been assessed in neonates under 32 weeks GA.³²⁴ The authors of this study found in stable preterm infants that PVI measurements were poorly reproducible when taken consecutively from the same or different limbs on the same neonate.³²⁴

10.2.2 Plethysmographic measurements

Intra-observer repeatability was performed by one observer (Dr Liam Mahoney). A specific point on a subject's plethysmographic trace was selected by the observer for the calculation of mPVI, mPTT and NmPTT. Each plethysmographic measure was then calculated twice according to the methodologies described previously.

Inter-observer repeatability calculations for plethysmographic traces were performed by two observers (Dr Liam Mahoney & Prof. David Wertheim). Specific points on a subject's plethysmographic trace were selected by both observers for the calculation of mPVI, mPTT and NmPTT. Each observer then independently calculated each measurement according to the methodologies described previously.

10.2.3 Echocardiographic measurements

The intra-observer SVCF and RVO measurements were performed by one observer (Dr Liam Mahoney). SVCF and RVO measurements were performed twice at different time points during a single that echocardiographic assessment of an infant. Inter-observer measurements were taken by two mutually blinded observers (Dr Liam Mahoney and Dr Ramon Fernandez), one immediately after the other from the same participant during an echocardiographic assessment. Again both SVCF and RVO calculations were performed according to the methodology previously described.

10.2.4 Statistical analysis

The repeatability of echocardiographic and plethysmographic measures was assessed using Bland-Altman (BA) plots.³⁴⁹ These plot the difference between two measurements on the y-axis against the mean of the two measurements on the x-axis. The repeatability coefficient was also calculated from the standard deviations between measurements multiplied by 1.96. This is the difference between repeated measures that one would have to see in order for there to be a 95% probability that it did not occur by chance alone.¹⁶² The repeatability index can be further calculated from this by dividing the repeatability coefficient by the mean of all values. This is expressed as a percentage with increasing repeatability index representing poorer repeatability.³⁰⁵ All of the statistical results and graphs were performed using Prism version 6.05 for Windows (GraphPad Software, La Jolla California USA). A p-value <0.05 was considered statistically significant.

11 Results

11.1 Clinical Studies: Longitudinal and comparative analysis

11.1.1 NeoAdapt 1

11.1.1.1 Subjects

A total of 52 infants were recruited. Two subjects were excluded as one was found to have a congenital cardiac malformation on echocardiography. We were unable to record any research measures in the second subject. The recruitment for NeoAdapt 1 is outlined in Figure 11.1

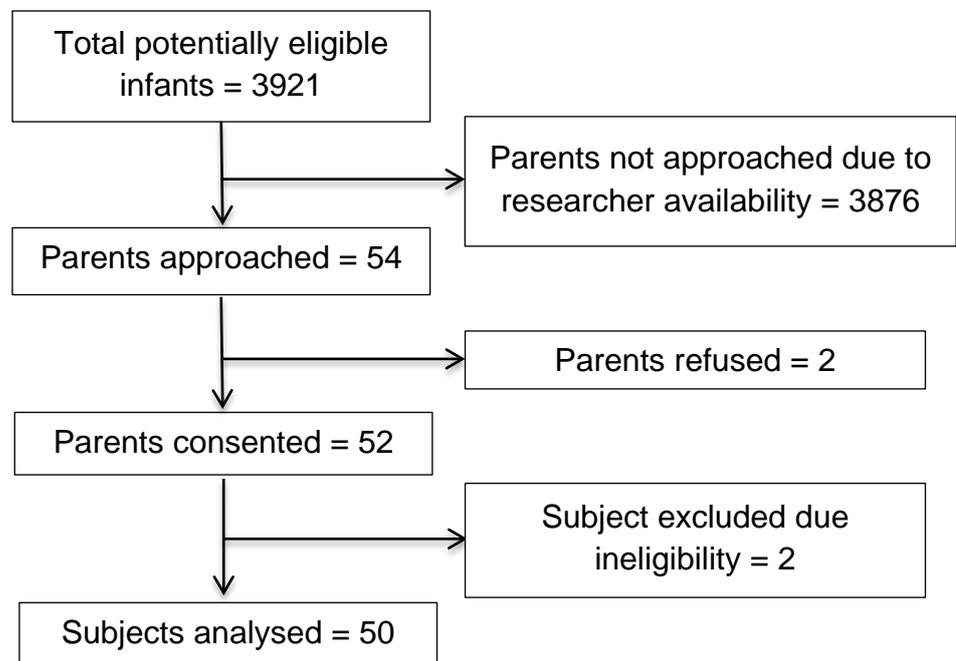


Figure 11.1: NeoAdapt 1 consort diagram

11.1.1.2 Pairwise daily comparisons: Whole cohort

Basic demographic characteristics for this cohort are displayed in Table 11.1. The most common reason for receiving special care was suspected sepsis followed by hypoglycaemia. Table 11.2 shows the daily paired comparisons of research measures. With regards to bedside measurements significant increases were noted in mean and systolic blood pressure over the first three days of life. Similar results were found for diastolic blood pressure, though the increase between day 2 and 3 was not significant. mPVI was the only plethysmographic value found to significantly decrease over the first three days of life. No significant changes were noted in echocardiographic measures, but trends were noted in some parameters.

Non-significant trends for decreases in SVCF, mPTT, and NmPTT were also noted. Non-significant trends for increases in pulse pressure and Trans mPTT were also noted. No trends were found for either RVO or CRT. Significant daily changes in research measures are displayed in Figure 11.2.

NeoAdapt 1 Cohort (n=50)		
GA (weeks)		35 (34-40)
Gender n (%)	<i>Male</i> <i>Female</i>	21 (42) 29 (58)
Birth weight (grams)		2555 (2040-3338)
Small for GA (SGA) (Birth weight <3 rd centile) n (%)	<i>Yes</i> <i>No</i>	4 (8) 46 (92)
5 minute APGAR score		9 ± 1
Multiplicity n (%)	<i>Singleton</i> <i>Twin</i> <i>Triplet</i>	34 (68) 13 (26) 3 (6)
Type of delivery n (%)	<i>Vaginal</i> <i>C-section</i>	21 (42) 29 (58)
Antenatal steroids n (%)	<i>None</i> <i>Incomplete</i> <i>Full</i>	27 (54) 2 (4) 21 (42)
Principle diagnoses n (%)	<i>Respiratory Distress</i> <i>Suspected Sepsis</i> <i>Hypoglycaemia</i> <i>Transient tachypnoea of the newborn (TTN)</i> <i>Jaundice</i> <i>Grade 4 IVH</i> <i>Feeding Problems</i> <i>Respiratory Distress Syndrome</i> <i>Hyponatraemia</i> <i>Congenital Pneumonia</i> <i>Anaemia</i> <i>Bruising</i> <i>Microcephaly</i> <i>Twin to Twin Transfusion</i> <i>None</i>	11 (22) 28 (56) 13 (26) 2 (4) 11 (22) 1 (2) 8 (16) 1 (2) 1 (2) 2 (4) 1 (2) 1 (2) 1 (2) 2 (4) 14 (28)

Table 11.1: Basic demographics of the whole NeoAdapt 1 cohort; data displayed as n (%) or median (IQR)

Bedside Measures	Day 1 (n=30)	Day 2 (n=35)	Day 3 (n=37)	Pairwise Comparisons (p-value)		
				Day 1 Vs 2 (n=24)	Day 2 Vs 3 (n=26)	Day 1 Vs 3 (n=19)
Age taken (hours)	18.5 (12-22)	35 (31-41)	59.5 (53-67)			
Mean BP (mmHg)	39 (36-43)	45 (41-49)	50 (43-61)	0.003*	0.004	<0.0001[‡]
Systolic BP (mmHg)	59 (50-63)	67 (60-72.5)	76 (63-74)	0.047*	0.01	0.0007[‡]
Diastolic BP (mmHg)	30 (26-35)	34 (31-41)	41 (33-49)	0.0003*	ns	<0.0001[‡]
PP (mmHg)	28 (23-34)	29 (23.75-35)	32 (25-40)	ns*	ns	ns [†]
HR (Beat per minute)	129 (122-137)	130 (122-137)	134 (122-137)	ns	ns	ns
CRT (Seconds)	2.0 (1.9-2.3)	2.0 (2-2.3)	2.0 (2-2.3)	ns	ns	ns
Echocardiographic Measures						
SVC VTi (cm)	16.4 (13.8-18.1)	16.3 (13.7-19.0)	15.5 (12.3-18.6)	ns	ns	ns
SVC diameter (cm)	0.45 (0.41-0.50)	0.42 (0.39-0.47)	0.41 (0.49-0.35)	ns	ns	ns
SVCF (mls/kg/min)	137.1 (115.4-173.7)	124.4 (103.4-173.7)	105.0 (85.3-140.7)	ns	ns	ns
RVO VTi (cm)	10.6 (9.2-12.5)	10.7 (9.1-12.3)	9.7 (8.2-12.2)	ns	ns	ns
RVO diameter (cm)	0.79 (0.74-0.86)	0.79 (0.72-0.86)	0.77 (0.69-0.86)	ns	ns	0.009
RVO (mls/kg/min)	257.3 (221.9-318.7)	282.7 (213.0-328.1)	253.7 (188.2-318.4)	ns	ns	ns
Plethysmographic Measures						
SpO2 (%)	99 (96-100)	99 (98-100)	99 (98-100)	ns	ns	ns
mPVI (%)	20.6 (15.8-24.6)	15.3 (12.1-17.9)	9.2 (5.8-12.5)	<0.0001*	<0.0001*	<0.0001[‡]
mPTT (seconds)	0.28 (0.27 – 0.29)	0.28 (0.26-0.31)	0.27 (0.26-0.29)	ns*	ns*	ns [#]
NmPTT	0.63 (0.57-.67)	0.62 (0.57-0.65)	0.62 (0.57-0.67)	ns*	ns*	ns [#]
Trans mPTT	3.5 (3.3-3.7)	3.6 (3.3-3.8)	3.6 (3.5-3.8)	ns*	ns*	ns [#]

*n=23, #n=17, †n=18, ns= not significant

Table 11.2: Daily paired comparisons of research measurements (median, IQR) in the whole NeoAdapt 1 cohort

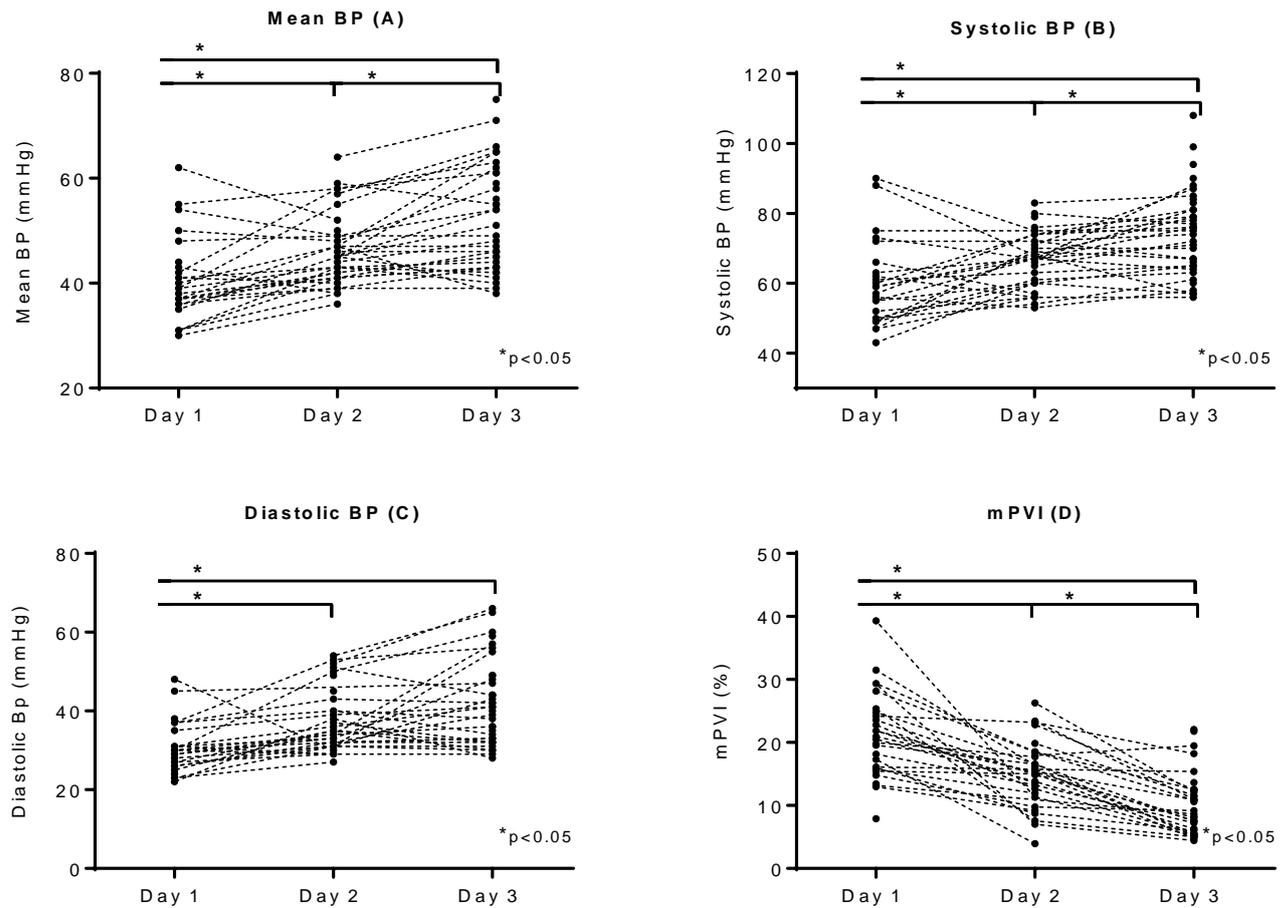


Figure 11.2: Daily paired comparisons of Mean BP (A), Systolic BP (B), Diastolic BP (C) and mPVI (D) in the whole NeoAdapt 1 cohort

Having presented the results for the whole NeoAdapt 1 cohort, the following sections present separately the results gained from late preterm neonates (<37-weeks GA) and term neonates (≥ 37 -weeks GA).

11.1.1.3 Pairwise daily comparisons: Late preterm neonates

Table 11.3 shows significant increases in mean, systolic and diastolic blood pressure were found over the first three days of life. With regards to plethysmographic traces significant decreases in mPVI seen and mPTT were also found, though the latter only between days one and three of life. Non-significant decreases in SVCF were noted with no trends observed for either CRT or RVO. A significant decrease in RVO diameter was noted between day 2 and 3 of life. Significant results are displayed graphically in Figure 11.3.

Bedside Measures	Day 1 (n=21)	Day 2 (n=22)	Day 3 (n=24)	Pairwise Comparisons (p-value)		
				Day 1 Vs 2 (n=19)	Day 2 Vs 3 (n=17)	Day 1 Vs 3 (n=15)
Age taken (hours)	21 (13-23)	40 (34-45)	63 (54-68)			
Mean BP (mmHg)	37 (35-40)	42 (40-45)	45 (42-58)	0.004	0.0501	0.0001*
Systolic BP (mmHg)	56 (49-60)	64 (57-67)	67 (61-81)	0.0051	0.0021	0.0004*
Diastolic BP (mmHg)	29 (25-30)	33 (31-36)	33 (32-44)	<0.0001	ns	0.0004*
PP (mmHg)	28 (22-32)	29 (22-32)	29 (24-33)	ns	ns	ns*
HR (Beat per minute)	132 (121-137)	132 (124-145)	142 (125-150)	ns	ns	ns
CRT (Seconds)	2.0 (1.9-2.3)	2.0 (2.0-2.3)	2.0 (1.8-2.2)	ns	ns	ns
Echocardiographic Measures						
SVC VTi (cm)	16.9 (15.1-18.0)	15.4 (13.6-17.5)	14.7 (12.1-17.5)	ns	ns	ns
SVC diameter (cm)	0.43 (0.40-0.46)	0.41 (0.38-0.44)	0.39 (0.34-0.47)	ns	ns	ns
SVCF (mls/kg/min)	149.1 (128.2-177.8)	132.9 (105.5-166.8)	128.0 (96.8-150.0)	ns	ns	ns
RVO VTi (cm)	10.9 (9.2-12.8)	10.7 (8.9-12.0)	10.3 (8.5-12.5)	ns	ns	ns
RVO diameter (cm)	0.76 (0.71-0.79)	0.74 (0.70-0.80)	0.72 (0.68-0.80)	ns	0.035	ns
RVO (mls/kg/min)	262.8 (240.9-329.4)	296.9 (249.9-368.2)	283.4 (215.9-357.1)	ns	ns	ns
Plethysmographic Measures						
SpO2 (%)	98 (96-100)	98 (96.75-100)	98.5 (98-100)	ns	ns	ns
mPVI (%)	20.5 (15.9-24.5)	15.0 (11.6-18.1) [†]	8.1 (5.5-12.2) [†]	<0.0001	<0.0001*	0.0001*
mPTT (seconds)	0.29 (0.27-0.30)	0.28 (0.26-0.29) [†]	0.27 (0.26-0.29) [†]	ns	ns [†]	0.002⁺
NmPTT	0.65 (0.61-0.68)	0.64 (0.62-0.68) [†]	0.64 (0.61-0.68) [†]	ns	ns [†]	ns ⁺
Trans mPTT	3.4 (3.3-3.6)	3.6 (3.4-3.8) [†]	3.7 (3.5-3.8) [†]	ns	ns [†]	0.008⁺

[†]n=22, *n=15, #n=15, [†]n=14, ⁺n=13, ns= not significant

Table 11.3: Daily paired comparisons of research measurements (median, IQR) in late preterm neonates (NeoAdapt 1)

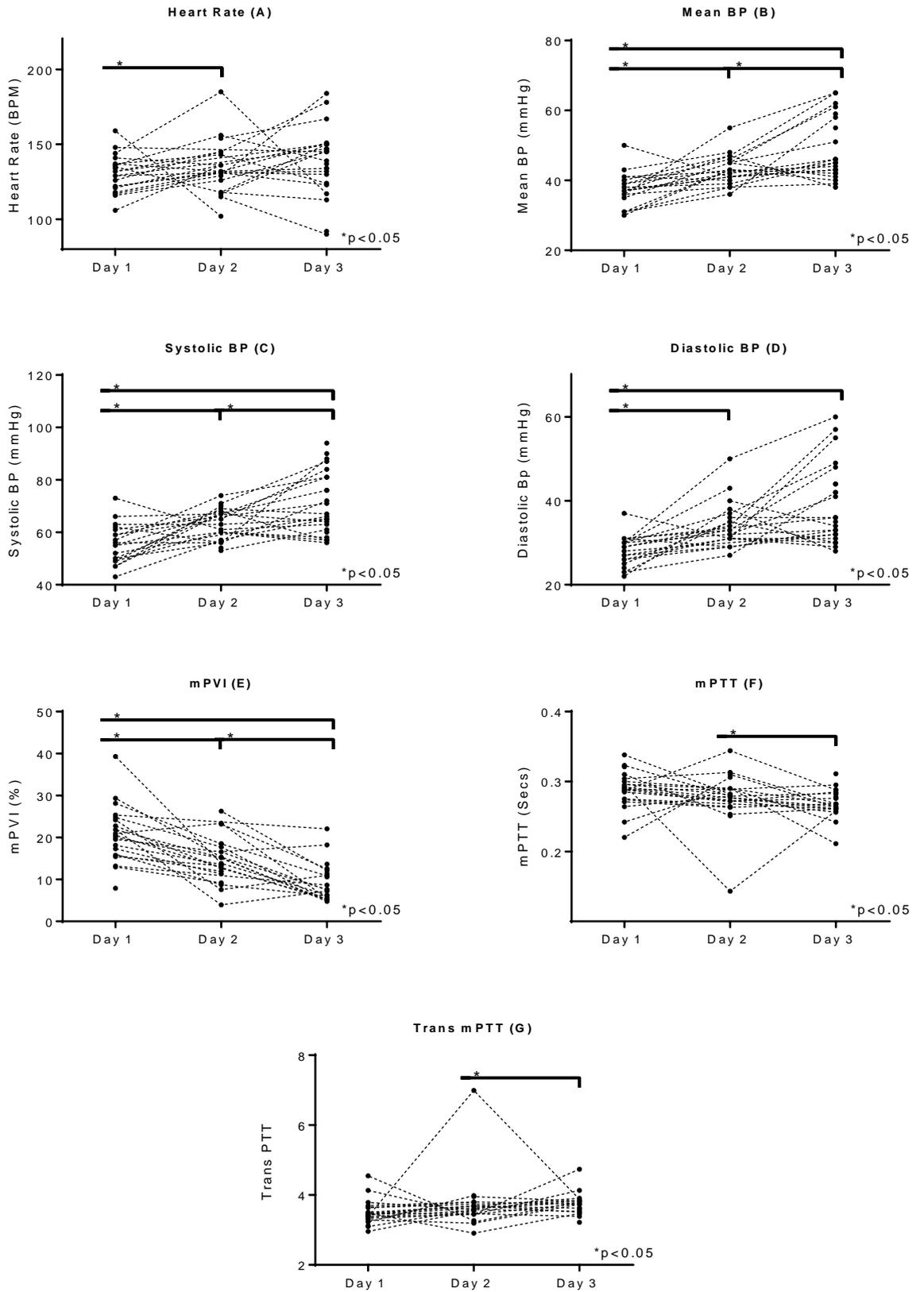


Figure 11.3: Daily paired comparisons of Mean BP (A), Systolic BP (B), Diastolic BP (C), RVO Dimeter, mPVI (E), mPTT (F) and Trans mPTT (G) in late preterm neonates (NeoAdapt 1)

11.1.1.4 Pairwise daily comparisons: Term neonates

Whilst a number of trends were noted in Table 11.4 no significant results were found with the pairwise comparisons of research measures taken within this cohort. With regards to bedside measures trends for increases in mean, systolic and diastolic blood pressure were noted. Non-significant decreases in SVCF and RVO were also found. No trends were noted for plethysmographic traces apart from daily decreases in mPVI values gained which were significant between day 2 and 3 of life.

Bedside Measure	Day 1 (n=9)	Day 2 (n=13)	Day 3 (n=13)	Pairwise Comparisons (p-value)		
				Day 1 Vs 2 (n=5)	Day 2 Vs 3 (n=9)	Day 1 Vs 3 (n=4)
Age taken (hours)	14 (12-20)	33 (28-36)	56 (52.5-60)			
Mean BP (mmHg)	51 (43-57) [†]	51 (47-57) [#]	56 (51-65)	ns ^Δ	ns	ns
Systolic BP (mmHg)	73.5 (61-88) [†]	74 (70-78) [#]	78 (74-84)	ns ^Δ	ns	ns
Diastolic BP (mmHg)	37 (36-46) [†]	42 (32-52) [#]	44 (39-57)	ns ^Δ	ns	ns
PP (mmHg)	33 (23-44) [†]	29 (23-39)	34 (25-42)	ns ^Δ	ns	ns
HR (Beat per minute)	127 (118-137)	119 (105-127)	123 (105-133)	ns	ns	ns
CRT (Seconds)	2 (1.9-2.3)	2 (2.0-2.3)	2.4 (2.0-2.5)	ns	ns	ns
Echocardiographic Measures						
SVC VTi (cm)	17.7 (13.9-21.3)	15.4 (13.6-17.5)	16.6 (12.3-21.5)	ns	ns	ns
SVC diameter (cm)	0.52 (0.45-0.58)	0.46 (0.40-0.58)	0.46 (0.34-0.52)	ns	ns	ns
SVCF (mls/kg/min)	118.4 (89.8-151.5)	115.9 (72.3-125.6)	84.35 (69.4-97.8)	ns	ns	ns
RVO VTi (cm)	10.2 (9.0-11.9)	11.5 (9.3-12.7)	8.9 (7.7-11.5)	ns	ns	ns
RVO diameter (cm)	0.88 (0.84-0.95)	0.89 (0.79-0.96)	0.86 (0.79-0.94)	ns	ns	ns
RVO (mls/kg/min)	221.7 (195.0-319.3)	213.0 (169.5-290.1)	165.1 (142.8-236.5)	ns	ns	ns
Plethysmographic Measures						
SpO2 (%)	100 (96.5-100)	99 (98-100)	98 (97.5-99.5)	ns	ns	ns
mPVI (%)	19.8 (14.8-29.3) [†]	15.8 (14.9-17.9) [*]	10.9 (8.1-15.4) [*]	ns ^Δ	0.02[†]	ns
mPTT (seconds)	0.27 (0.22-0.29) [†]	0.30 (0.24-0.31) [#]	0.28 (0.27-0.29) [#]	ns ^Δ	ns	ns
NmPTT	0.57 (0.52-0.62) [†]	0.55 (0.51-0.63) [#]	0.59 (0.51-0.65) [#]	ns ^Δ	ns	ns
Trans mPTT	3.7 (3.5-4.5) [†]	3.3 (3.2-4.1) [#]	3.5 (3.4-3.7) [#]	ns ^Δ	ns	ns

*n=11, #n=12, †n=8, ‡n=6, Δn=4, ns= not significant

Table 11.4: Daily paired comparisons of research measurements (median, IQR) in term neonates (NeoAdapt 1)

11.1.1.5 Pooled daily comparisons: Late preterm vs. Term cohort

Comparing the demographics of these two groups (Table 11.5) as might be expected, there were more twins in the late preterm cohort and their mothers were more likely to have received antenatal steroids.

Table 11.6 shows that significantly higher mean, systolic and diastolic blood pressures were found in the term cohort. Heart rate was significantly higher in the late preterm infants on day 2 and 3. Capillary refill time was significantly longer in the term cohort on day 3 of life only. Both RVO and SVCF were significantly higher in the late preterm cohort on day 2 and 3. The diameters of these vessels were significantly smaller on days 1 and 2 in this cohort. With regards to plethysmographic data mPTT was longer on day 1 in the late preterm cohort, with it being then being significantly longer in the term cohort on day 3. Conversely Trans mPTT was longer on day 1 in the term cohort, with it being then being significantly longer in the late preterm cohort on day 3. NmPTT was found to be significantly shorter in the term group on days 1 and 2. Significant results are displayed graphically in Figure 11.4 and 11.5.

Variable		Late Preterm Cohort (n=30)	Term Cohort (n=20)	p-value
GA (weeks)		34 (33-35)	40 (39-41)	<0.0001
Gender n (%)	<i>Male</i> <i>Female</i>	9 (30) 21 (70)	12 (54) 8 (46)	0.03
Birth weight (grams)		2150 (1823-2372)	3455 (3190-3581)	<0.0001
SGA n (%)	<i>Yes</i> <i>No</i>	4 (14) 26 (86)	0 (0) 20(100)	ns
APGAR score		9 (8-10)	9 (8-10)	ns
Multiplicity n (%)	<i>Singleton</i> <i>Twin</i> <i>Triplet</i>	14 (46) 13 (44) 3 (10)	20 (100) 0 (0) 0 (0)	0.0004
Type of delivery n (%)	<i>Vaginal</i> <i>C-section</i>	22 (74) 8 (26)	13 (74) 7 (26)	ns
Antenatal steroids n (%)	<i>None</i> <i>Incomplete</i> <i>Full</i>	8 (26) 2 (4) 20 (70)	19 (95) 0 (0) 1 (5)	<0.0001

Table 11.5: Characteristics and comparison of the NeoAdapt 1 participants when split into late preterm and term cohorts; data displayed as median (IQR)

Bedside Measure	Cohort	Day 1	Day 2	Day 3	Cohort Comparisons (p-value)		
					Day 1	Day 2	Day 3
Age taken (hours)	Late preterm	21 (13-23) [‡]	40 (34-45) [*]	63 (54-68.5) [□]	ns	0.019	ns
	Term	14 (12-20) ⁺	33 (28-36) [#]	56 (52.5-60) [#]			
Mean BP (mmHg)	Late preterm	37 (35-40) [‡]	42 (40-45) [*]	45 (42-58) [†]	<0.0001	<0.0001	0.0016
	Term	51 (43-57) [†]	51 (47-57) ^Σ	56 (51-65) [#]			
Systolic BP (mmHg)	Late preterm	56 (49-60) [‡]	64 (57-67) [*]	67 (61-81) [†]	0.0008	<0.0001	0.034
	Term	73 (61-88) [†]	74 (70-78) ^Σ	74 (70-78) [#]			
Diastolic BP (mmHg)	Late preterm	29 (25-30) [‡]	33 (31-36) [*]	29 (24-33) [†]	<0.0001	0.018	0.023
	Term	37 (36-46) [†]	42 (32-52) ^Σ	44 (39-57) [#]			
PP (mmHg)	Late preterm	28 (22-32) [‡]	29 (22-32) [*]	29 (24-33) [†]	ns	ns	ns
	Term	33 (23-44) [†]	29 (23-39) ^Σ	34 (25-42) [#]			
HR (Beat per minute)	Late preterm	132 (121-137) [‡]	132 (124-145) [*]	142 (125-150) [□]	ns	0.0062	0.007
	Term	127 (118-137) ⁺	119 (105-127) [#]	123 (105-133) [#]			
CRT (Seconds)	Late preterm	2 (1.9-2.3) [‡]	2 (2.0-2.3) [*]	2 (1.8-2.2) [□]	ns	ns	0.0158
	Term	2 (1.9-2.3) ⁺	2 (2.0-2.3) [#]	2.4 (2.0-2.5) [#]			
Echocardiographic Measures							
SVC VTi (cm)	Late preterm	16.9 (15.1-18.0) [‡]	15.4 (13.6-17.5) [*]	14.7 (12.1-17.5) [□]	ns	ns	ns
	Term	17.7 (13.9-21.30) ⁺	15.4 (13.6-17.5) [#]	16.6 (12.3-21.5) [#]			
SVC diameter (cm)	Late preterm	0.43 (0.40-0.46) [‡]	0.41 (0.38-0.44) [*]	0.39 (0.34-0.47) [□]	0.0048	0.049	ns
	Term	0.52 (0.45-0.58) ⁺	0.46 (0.40-0.58) [#]	0.46 (0.34-0.52) [#]			
SVCF (mls/kg/min)	Late preterm	149.1 (128.2-177.8) [‡]	132.9 (105.5-166.8) [*]	128.0 (96.8-150.0) [□]	0.054	0.04	0.001
	Term	118.4 (89.8-151.5) ⁺	115.9 (72.27-125.6) [#]	84.3 (69.4-97.8) [#]			

□n=24, †n=23, *n=22, ‡n=21, #n=13, Σn=12, +n=9, †n=6, ns= not significant

Table 11.6: Daily comparisons of research measurements (median, IQR) between late preterm and term neonates (NeoAdapt 1)

Echocardiographic Measures	Cohort	Day 1	Day 2	Day 3	Cohort Comparisons (p-value)		
					Day 1	Day 2	Day 3
RVO VTi (cm)	Late preterm Term	10.9 (9.2-12.8) [‡] 10.2 (9.0-11.9) [†]	10.7 (8.9-12.0) [*] 11.5 (9.3-12.8) [#]	10.3 (8.5-12.5) [□] 8.9 (7.7-11.5) [#]	ns	ns	ns
RVO diameter (cm)	Late preterm Term	0.76 (0.71-0.79) [‡] 0.88 (0.84-0.95) [†]	0.74 (0.70-0.80) [*] 0.89 (0.78-0.96) [#]	0.72 (0.68-0.80) [□] 0.86 (0.79-0.94) [#]	0.0006	0.0004	0.0001
RVO (mls/kg/min)	Late preterm Term	262.8 (240.9-329.4) [‡] 221.7 (195.0-319.3) [†]	296.9 (249.9-368.2) [*] 213.0 (169.5-290.1) [#]	283.4 (215.9-357.1) [□] 165.1 (142.8-236.5) [#]	ns	0.0038	0.0003
Plethysmographic Measures							
SpO2 (%)	Late preterm Term	98 (96-100) [‡] 100 (96-100) [†]	98 (97-100) [*] 99 (98-100) [#]	98.5 (98-100) [□] 98 (97-99) [#]	ns	ns	ns
mPVI (%)	Late preterm Term	20.5 (15.9-24.5) [‡] 19.8 (14.8-29.3) ^Δ	15.0 (11.6-18.1) [‡] 15.8 (14.9-17.9) [∞]	8.13 (5.5-12.2) [*] 10.9 (8.1-15.4) [∞]	ns	ns	ns
mPTT (seconds)	Late preterm Term	0.29 (0.27-0.30) [‡] 0.27 (0.22-0.29) ^Δ	0.28 (0.26-0.29) [‡] 0.30 (0.24-0.31) [∞]	0.27 (0.26-0.29) [*] 0.28 (0.27-0.29) [∞]	0.049	ns	0.036
NmPTT	Late preterm Term	0.65 (0.61-0.68) [‡] 0.57 (0.52-0.62) ^Δ	0.64 (0.62-0.68) [‡] 0.55 (0.51-0.63) [∞]	0.64 (0.61-0.68) [*] 0.59 (0.51-0.65) [∞]	0.035	0.0017	ns
Trans mPTT	Late preterm Term	3.4 (3.3-3.6) [‡] 3.7 (3.5-4.5) ^Δ	3.6 (3.4-3.8) [‡] 3.3 (3.2-4.1) [∞]	3.7 (3.5-3.8) [*] 3.5 (3.4-3.7) [∞]	0.049	ns	0.036

□n=24, †n=23, *n=22, ‡n=21, #n=13, ∑n=12, ∞n=11, †n=9, Δn=7, †n=6, ns= not significant

Table 11.6: Daily comparisons of research measurements (median, IQR) between late preterm and term neonates (NeoAdapt 1)

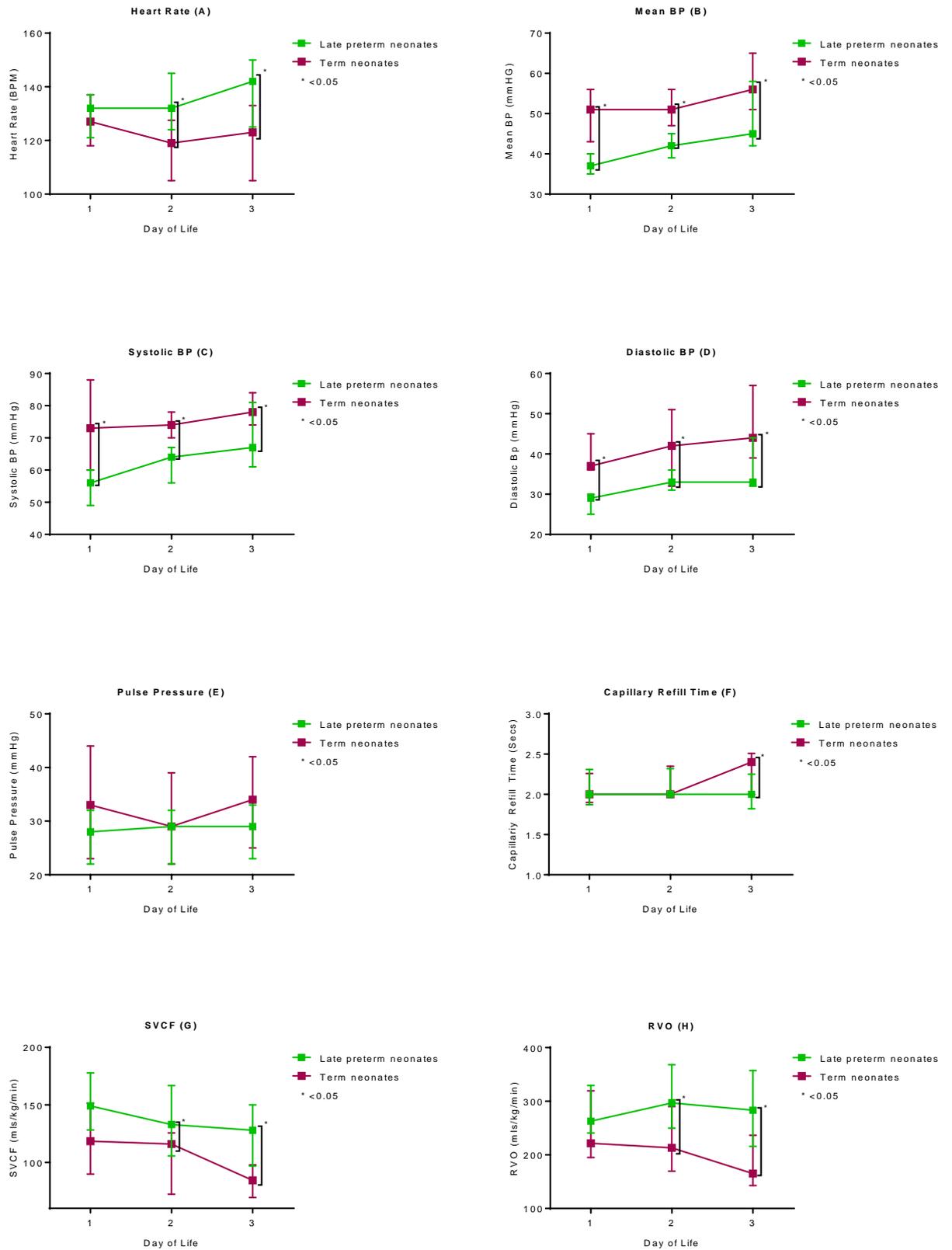


Figure 11.4: Daily comparisons of Heart rate (A), Mean BP (B), Systolic BP (C), Diastolic BP (D), Pulse pressure (E), Capillary refill time (F), SVCF (G) and RVO (H) (median, IQR) between late preterm and term neonates (NeoAdapt 1)

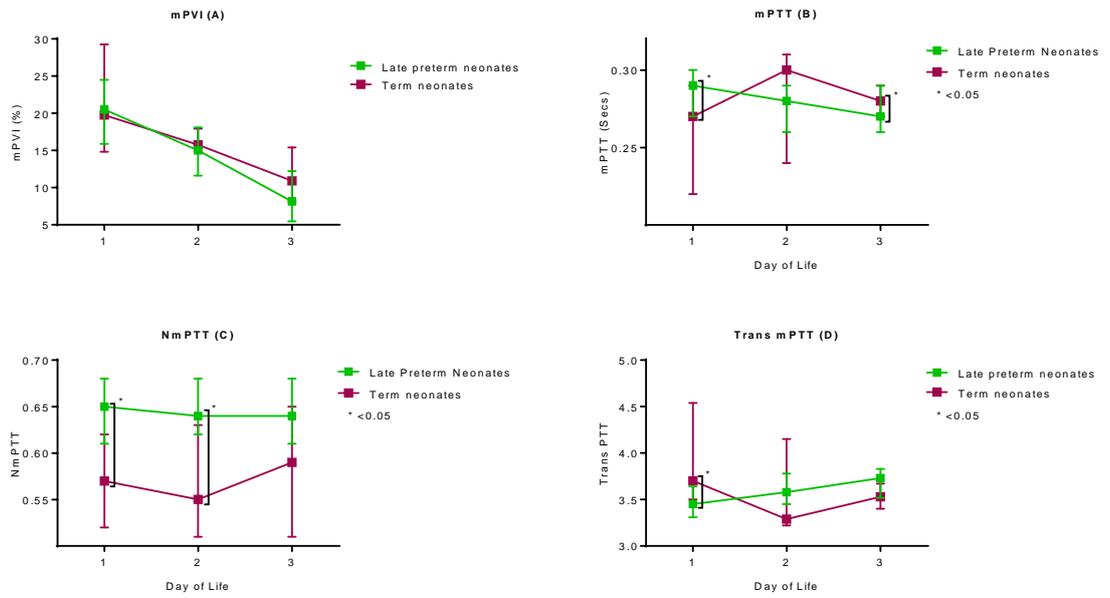


Figure 11.5: Daily comparisons of mPVI (A), mPTT (B), NmPTT (C) and Trans mPTT (D) (median, IQR) between late preterm and term neonates (NeoAdapt 1)

11.1.1.6 Correlations of research measurements

The results of the Spearman rank correlations are displayed in Appendix 1. Many significant relationships were found on individual's days, but none of the associations remained significant on all 3 days.

11.1.2 NeoAdapt 2

11.1.2.1 Subjects

A total of 27 infants were recruited. The recruitment for NeoAdapt 2 is outlined in Figure 11.6. Two subjects were excluded due to congenital cardiac malformations found on echocardiography.

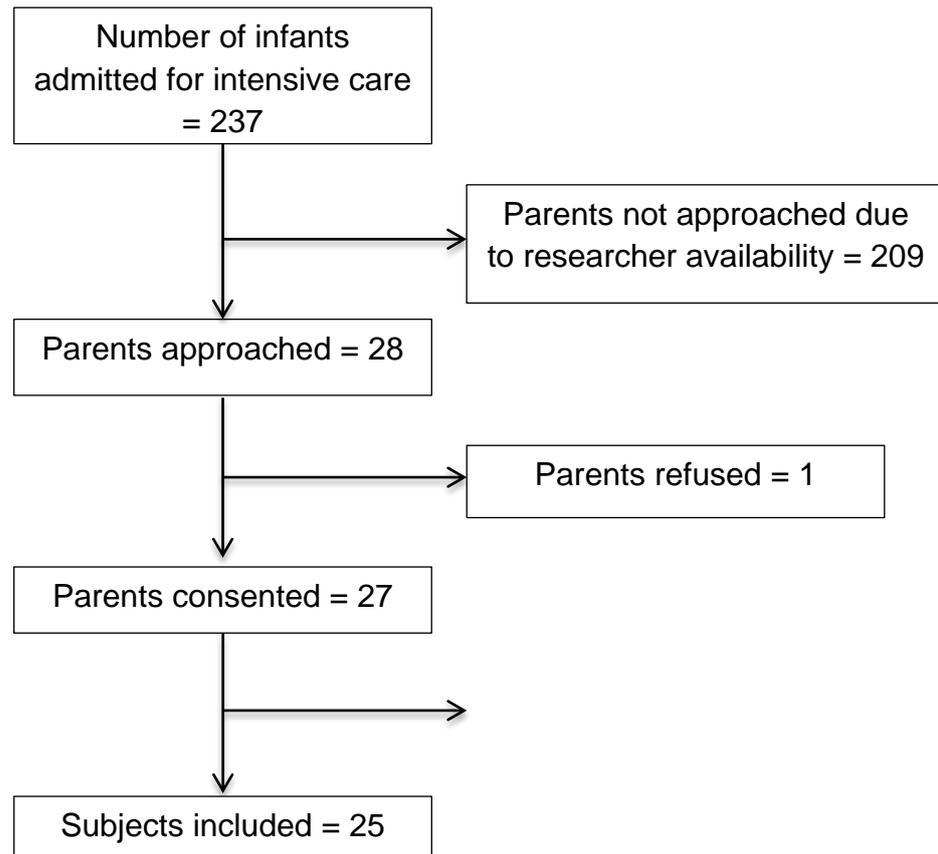


Figure 11.6: NeoAdapt 2 consort diagram

11.1.2.2 Pairwise daily comparisons: Whole cohort

The basic demographic detail for the entire cohort are displayed in Table 11.7. The most common reason for intensive care was suspected sepsis (96%), jaundice and respiratory distress. Table 11.8 displays the daily paired comparisons of research measures. Bedside measures revealed that the MAP increased significantly between days 1 and 3. Systolic blood pressure increased between days 1 and 3 as well as days 2 and 3. With regards to echocardiographic measures SVC VTi decreased significantly between days 1 and 2 as well as on day 2 and 3. No trends were observed for SVCF, RVO or any plethysmographic

trace. Urine output and pH increased significantly between days 1 and 3, with the latter also increasing between day 1 and 2. Base excess became significantly more positive between days 1 and 3. Lactate was found to decrease significantly between day 2 and 3 as well as day 1 and 3. These significant results are displayed graphically in Figure 11.7. Table 11.9 shows that the level of respiratory support decreased over the first three days of life.

NeoAdapt 2 Cohort (n=25)		
GA (weeks)		36 (34-37)
Gender n (%)	<i>Male</i> <i>Female</i>	15 (60) 10 (40)
Birth weight (grams)		2385 (1950-2920)
SGA n (%)	<i>Yes</i> <i>No</i>	1 (4) 24 (96)
APGAR score		9 ± 1
Multiplicity n (%)	<i>Singleton</i> <i>Twin</i>	20 (80) 5 (20)
Type of delivery n (%)	<i>Vaginal</i> <i>C-section</i>	13 (52) 12 (48)
Antenatal steroids n (%)	<i>None</i> <i>Incomplete</i> <i>Full</i>	11 (44) 2 (4) 14 (56)
Sepsis risk factors n (%)	<i>PROM</i> <i>Maternal tachycardia</i> <i>Maternal pyrexia</i> <i>Maternal leucocytosis</i> <i>Fetal tachycardia</i>	4 (16) 0 (0) 1 (4%) 11 (44) 0 (0)
Delivery complications n (%)	<i>None</i> <i>Meconium stained liquor</i> <i>Pathological CTG</i> <i>Antepartum haemorrhage</i> <i>Meconium aspiration</i>	17 (68) 2 (8) 2 (8) 2 (8) 3 (12)
Principle diagnoses n (%)	<i>Respiratory Distress</i> <i>Suspected Sepsis</i> <i>Hypoglycaemia</i> <i>Thrombocytopenia</i> <i>Jaundice</i> <i>TTN</i> <i>Respiratory distress syndrome</i> <i>Seizures</i> <i>Twin to twin transfusion</i> <i>Hyperinsulinaemia</i> <i>Hypophosphatemia</i> <i>Intra-uterine growth restriction</i> <i>Neutropenia</i> <i>Pneumothorax</i> <i>Polycythaemia</i> <i>Persistent pulmonary hypertension</i> <i>Establishing feeds</i>	8 (32) 24 (96) 4 (16) 1 (4) 9 (36) 2 (8) 6 (24) 1 (4) 2 (8) 1(4) 1(4) 4 (16) 1(4) 2 (8) 1(4) 2 (8) 1(4)

Table 11.7: Basic demographics of the whole NeoAdapt 2 cohort; data displayed as n (%) or median (IQR)

Bedside Measure	Day 1 (n=12)	Day 2 (n=21)	Day 3 (n=20)	Pairwise comparisons (p-value)		
				Day 1 Vs 2 (n=12)	Day 2 Vs 3 (n=16)	Day 1 Vs 3 (n=8)
Age taken (hours)	14 (11-21)	36 (31-41)	61 (54-645)			
Mean BP (mmHg)	42 (35-48)	45 (38-51)	47 (42-50)	ns	ns	0.015
Systolic BP (mmHg)	59 (48-66)	64 (59-66)	65 (57-74)	ns	0.045	0.039
Diastolic BP (mmHg)	33 (30-42)	36 (31-42)	38 (34-41)	ns	ns	ns
PP (mmHg)	25 (2-30)	25 (21-30)	25 (21-32)	ns	ns	ns
HR (Beat per minute)	136 (126-143)	137 (121-147)	139 (124-151)	ns	ns	ns
CRT (Seconds)	2.0 (1.7-2.3) [†]	2.0 (1.8-2.2) [*]	2.0 (1.8-2.2)	ns	ns	ns
Echocardiographic Measures						
SVC VTi (cm)	13.1 (9.5-17.8)	16.4(12.8-17.9)	13.4 (11.3-17.1)	ns	0.009	ns
SVC diameter (cm)	0.54 (0.46-0.64)	0.49 (0.41-0.57)	0.43 (0.39-0.51)	ns	ns	ns
SVCF (mls/kg/min)	133.8 (105.6-198.1)	163.6 (112.5-226.9)	137.5 (90.6-174.4)	ns	0.025	ns
RVO VTi (cm)	9.70 (8.92-10.64)	10.09 (8.14-10.99)	10.29 (9.16-12.62)	ns	ns	ns
RVO diameter (cm)	0.82 (0.79-0.87)	0.82 (0.76-0.93)	0.80 (0.72-0.89)	ns	ns	ns
RVO (mls/kg/min)	304.8 (229.6-377.1)	302.4 (258.8-347.3)	323.2 (241.8-368.5)	ns	ns	ns
Plethysmographic Measures						
SpO ₂ (%)	96 (95-99)	98 (94-99)	98 (94-100)	ns	ns	ns
mPVI (%)	18.2 (12.2-20.2)	21.9 (13.9-23.0)	18.8 (8.5-22.2)	ns	ns	ns
mPTT (seconds)	0.30 (0.27-0.32)	0.29 (0.27-0.32)	0.29 (0.26-0.30)	ns	ns	ns
NmPTT	0.65 (0.59-0.82)	0.66 (0.56-0.70)	0.66 (0.56-0.71)	ns	ns	ns
Trans mPTT	3.4 (3.2-3.8)	3.5 (3.3-3.8)	3.5 (3.4-3.8)	ns	ns	ns
Clinical & Biochemical Measures						
Urine output (mls/kg/hr)	0.8 (0.5-1.6) ⁺	1.8 (1.1-5.0) [#]	3.4 (0.9-4.5) [#]	0.031 [†]	ns ^Δ	ns [§]
pH	7.30 (7.21-7.35)	7.38 (7.35-7.40)	7.38 (7.35-7.40)	0.001 [□]	ns [°]	0.0003 [¥]
Base excess (mmol/l)	-1.5 (-5.4-0.37)	-0.4 (-3.3-1.3)	0.35 (-1.78-1.78)	ns [□]	ns [°]	0.047 [¥]
Lactate (mmol/l)	2 (1.3-3.7)	0.9 (1.4-2.7)	1.3 (1.1-1.6)	ns [□]	0.0003 [°]	0.006 [¥]

□n=24, °n=23, ¥n=22 *n=18, +n=12 #n=11, †n=10, §n=6, Δn=5, ns= not significant

Table 11.8: Daily paired comparisons of research measurements (median, IQR) in the whole NeoAdapt 2 cohort

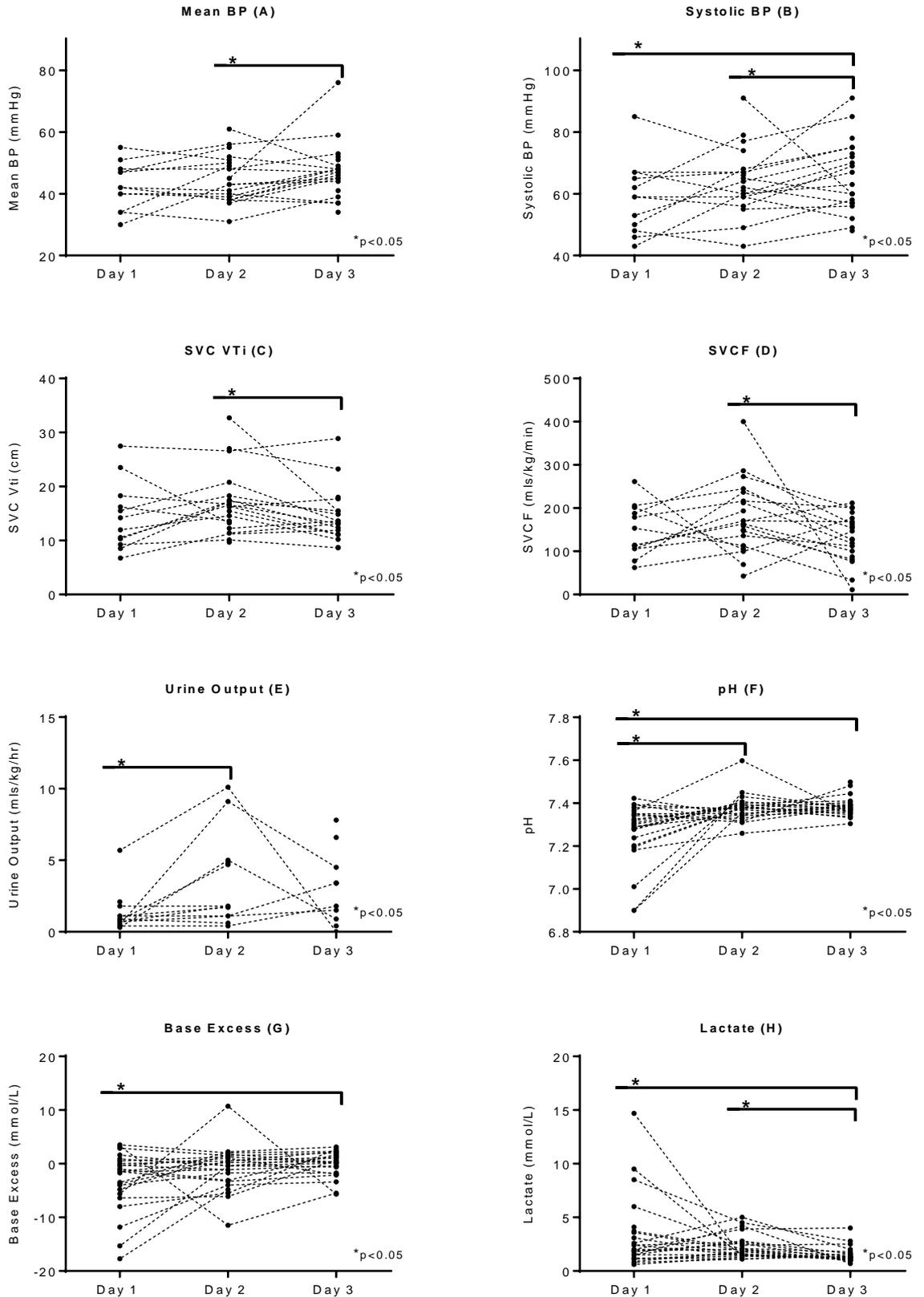


Figure 11.7: Daily paired comparisons of Mean BP (A), Systolic BP (B), SVC VTi (C), SVCF (D), Urine Output (E), pH (F), Base Excess (G) and Lactate (H) in the whole NeoAdapt 2 cohort

Respiratory support	Day 1 (n=25)	Day 2 (n=24)	Day 3 (n=24)	p-value
None n (%)	2 (8)	6 (25)	10 (42)	ns
Humidified high flow nasal cannula (HHFNC) n (%)	16 (64)	16 (66)	13 (54)	
Continuous positive airway pressure (CPAP) n (%)	1 (4)	0 (0)	0 (0)	
Invasive ventilation n (%)	6 (24)	2 (9)	1 (4)	

Table 11.9: Respiratory management of neonates in the NeoAdapt 2 cohort; data displayed as n (%)

Having presented the results for the whole NeoAdapt 2 cohort, the following sections present separately the results gained from late preterm neonates (33- <37-weeks GA) and term neonates (\geq 37-weeks GA).

11.1.2.3 Pairwise daily comparisons: Late preterm neonates

Tables 11.10 and Figure 11.8 shows that in this cohort SVC VT_i, and pH increased significantly between day 1 and 2. Systolic blood pressure increased significantly between day 2 and 3. Significant differences were found between day 2 and 3 for SVC VT_i and lactate. RVO increased non-significantly over the first three days of life. No trends were noted for all other plethysmographic or echocardiographic measures in this cohort. Table 11.11 shows that as for the whole cohort, the level of respiratory support decreased over the first three days of life.

Bedside Measure	Day 1 (n=7)	Day 2 (n=14)	Day 3 (n=15)	Pairwise comparisons (p-value)		
				Day 1 Vs 2 (n=7)	Day 2 Vs 3 (n=12)	Day 1 Vs 3 (n=6)
Age taken (hours)	15 (12-21)	36.5 (34-43.25)	62 (54-65)			
Mean BP (mmHg)	40 (34-42)	43 (39-49)	47 (41-49)	ns	ns	ns
Systolic BP (mmHg)	59 (48-65)	60.5 (58.25-67.25)	67 (56-75)	ns	0.013	ns
Diastolic BP (mmHg)	32 (28-35)	36 (31-44)	38 (34-40)	ns	ns	ns
PP (mmHg)	23 (18-28)	25 (19.75-29)	26 (22-33)	ns	ns	ns
HR (Beat per minute)	136 (129-144)	138 (122-147)	143 (131-155)	ns	ns	ns
CRT (Seconds)	2.18 (1.8-2.5) [#]	2 (2-2.4) ^Δ	2 (1.9-2.3)	ns	ns	ns
Echocardiographic Measures						
SVC VTi (cm)	10.5 (9.2-15.5)	16.3 (11.3-18.9)	13.3 (11.1-15.5)	0.05	0.01	ns
SVC diameter (cm)	0.53 (0.45-0.59)	0.47 (0.41-0.57)	0.41 (0.37-0.47)	ns	ns	ns
SVCF (mls/kg/min)	114.2 (105.5-178.9)	166.9 (130.3-239.0)	146.9 (87.2-190.1)	ns	ns	ns
RVO VTi (cm)	9.4 (9.2-10.5)	10.0 (8.0-10.6)	10.1 (8.7-12.5)	ns	ns	ns
RVO diameter (cm)	0.82 (0.79-0.87)	0.82 (0.76-0.93)	0.80 (0.72-0.89)	ns	ns	ns
RVO (mls/kg/min)	321.5 (265.1-377.1)	333.3 (275.7-352.6)	341.1 (274.1-373.6)	ns	ns	ns
Plethysmographic Measures						
SpO2 (%)	96 (96-98)	98 (94-98.25)	99 (96-100)	ns	ns	ns
mPVI (%)	16.3 (11.2-20.9) [#]	22.2 (16.1-23.2) [¥]	20.7 (11.5-28.2) [□]	ns [#]	ns ^Δ	ns [†]
mPTT (seconds)	0.30 (0.29-0.32) [#]	0.28 (0.26-0.30) [¥]	0.29 (0.26-0.30) [□]	ns [#]	ns ^Δ	ns [†]
NmPTT	0.65 (0.60-0.82) [#]	0.67 (0.55-0.72) [¥]	0.67 (0.57-0.71) [□]	ns [#]	ns ^Δ	ns [†]
Trans mPTT	3.3 (3.1-3.5)	3.5 (3.3-3.9)	3.4 (3.34-3.8)	ns [#]	ns ^Δ	ns [†]
Clinical & Biochemical Measures						
Urine output (mls/kg/hr)	1.1 (0.7-2.1) ⁺	4.75 (1.6-9.3) [#]	3.4 (1.5-6.6) ⁺	ns [†]	ns [†]	ns [#]
pH	7.30 (7.24-7.36)	7.38 (7.24-7.39)	7.37 (7.35-7.39)	0.001[†]	ns [*]	ns [*]
Base excess (mmol/l)	-1 (-4.25-1.25)	-0.4 (-3.2-1.4)	0.1 (-2.1-1.7)	ns [†]	ns [*]	ns [*]
Lactate (mmol/l)	1.5 (1.1-2.8)	1.6 (1.3-2.6)	1.2 (1.0-1.6)	ns [†]	0.01[*]	ns [*]

[†]n=17, ^{*}n=15, [□]n=14, [¥]n=13, ^Δn=11, ⁺n=7, [#]n=6, [†]n=5, ns= not significant

Table 11.10: Daily paired comparisons of research measurements (median, IQR) in late preterm infants (NeoAdapt 2)

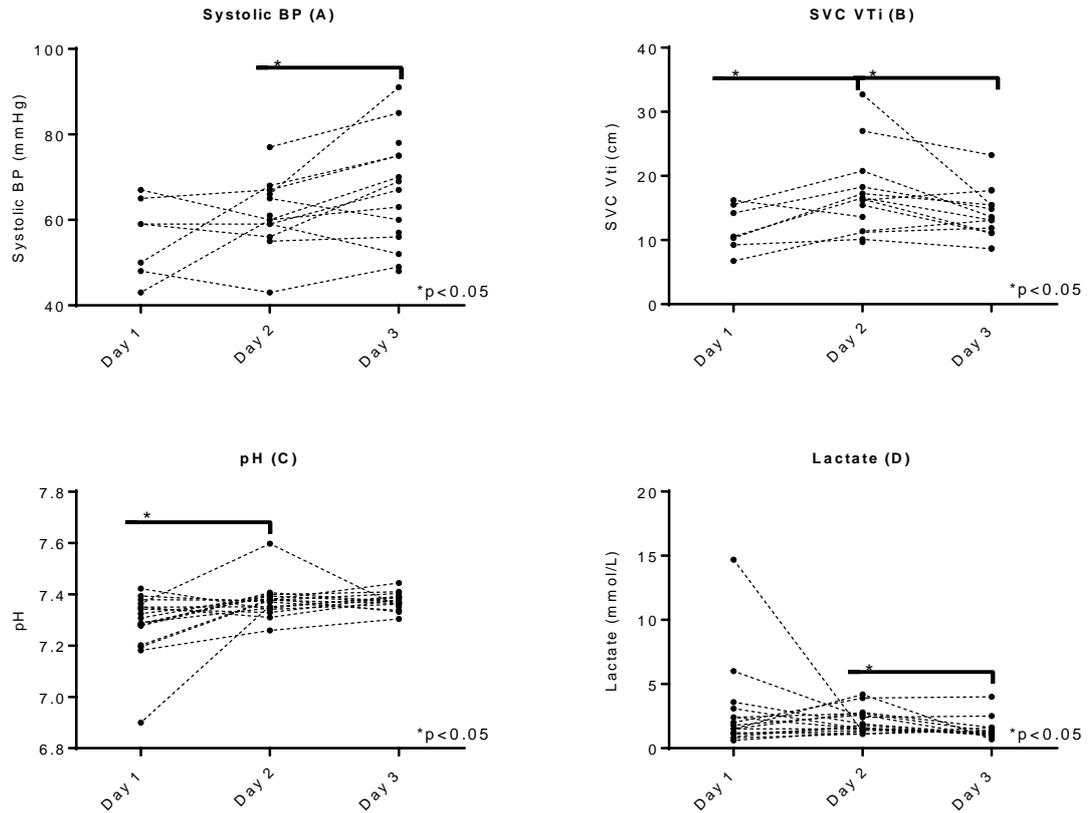


Figure 11.8: Paired daily comparisons of Systolic BP (A), SVC VTi (B), pH (C) and Lactate (D) in late preterm neonates (NeoAdapt 2)

Respiratory support	Day 1 (n=17)	Day 2 (n=17)	Day 3 (n=17)	p-value
None n (%)	1 (6)	4 (24)	6 (35)	ns
Humidified high flow nasal cannula n (%)	11 (64)	12 (70)	11 (65)	
Continuous positive airway pressure n (%)	1 (6)	0 (0)	0 (0)	
Invasive ventilation n (%)	4 (24)	1 (6)	0 (0)	

Table 11.11: Respiratory management of late preterm neonates; data displayed as n (%)

11.1.2.4 Pairwise daily comparisons: Term neonates

As displayed in Table 11.12 pH and base excess increased significantly between days 1 and 2, with the latter also increasing significantly between days 2 and 3. Lactate was found to decrease significantly between days 1 and 3. These results are displayed graphically in Figure 11.9. Many of the pairwise comparisons between days 1 and 3 could not be performed as there were not more than 3

paired measurements. Table 11.13 revealed no significant differences in the ventilation status of neonates over the first three days of life.

Bedside Measure	Day 1 (n=5)	Day 2 (n=7)	Day 3 (n=5)	Pairwise comparisons (p-value)		
				Day 1 Vs 2 (n=5)	Day 2 Vs 3 (n=5)	Day 1 Vs 3 (n=6)
Age taken (hours)	13 (11-21.5)	33 (31-37)	58 (52.5-62.5)			
Mean BP (mmHg)	47 (40.5-53)	50 (37-55)	47 (42-55)	ns	ns	
Systolic BP (mmHg)	62 (49.5-76)	67 (62-79)	60 (57.5-72.5)	ns	ns	
Diastolic BP (mmHg)	42 (36-44.5)	36 (32-41)	41 (35-45.5)	ns	ns	
PP (mmHg)	20 (13.5-31.5)	30 (23-43)	23 (17.5-30)	ns	ns	
HR (Beat per minute)	137 (117.5-155)	134 (111-150)	126 (111-137)	ns	ns	
CRT (Seconds)	1.9 (1.6-2.07)*	1.8 (1.6-2.2)	1.7 (1.3-2.3)	ns	ns	
Echocardiographic Measure						
SVC VTi (cm)	18.3 (10.3-25.5)	16.7 (13.3-17.5)	13.6 (11.3-23.5)	ns	ns	
SVC diameter (cm)	0.64 (0.36-0.69)	0.53 (0.49-0.58)	0.53 (0.49-0.58)	ns	ns	
SVCF (mls/kg/min)	187.9 (84.0-231.5)	147.1 (100.0-212.4)	128.1 (100.0-170.0)	ns	ns	
RVO VTi (cm)	10.5 (6.1-12.3)	10.1 (8.5-11.9)	10.7 (10.2-14.2)	ns	ns	
RVO diameter (cm)	0.83 (0.76-1.01)†	0.83 (0.76-1.03)	0.83 (0.73-0.91)	ns	ns	
RVO (mls/kg/min)	221 (119.4-503.5)†	271.0 (247.8-335.7)	257.5 (216.9-372.1)	ns	ns	
Plethysmographic Measure						
SpO2 (%)	97 (94-99)	98 (95-100)	94 (93-99)	ns	ns	
mPVI (%)	18.3 (15.0-27.2)	16.7 (12.5-22.3)	8.5 (6.6-15.7)	ns	ns*	
mPTT (seconds)	0.30 (0.25-0.33)	0.29 (0.25-0.33)	0.29 (0.23-0.31)	ns	ns*	
NmPTT	0.59 (0.56-0.81)	0.64 (0.61-0.70)	0.52 (0.49-0.68)	ns	ns*	
Trans mPTT	3.4 (3.0-4.0)	3.5 (3.3-3.9)	3.5 (3.2-4.2)	ns	ns*	
Clinical & Biochemical Measures						
Urine output (mls/kg/hr)	0.7 (0.3-1.0)†	1.7 (0.5-3.4)†	2.1 (0.5-3.4)*	ns	ns†	
pH	7.29 (7.01-7.32)□	7.39 (7.36-7.43)¥	7.38 (7.35-7.48)□	0.03 ¥	ns¥	ns ^Δ
Base excess (mmol/l)	-4 (-8.0- -1.7)□	-1.05 (-5.65-0.92)¥	1.2 (-0.6-2.7)	0.03 ¥	ns¥	0.03
Lactate (mmol/l)	3.7 (2.0-4.6)□	2.0 (1.8-4.6)	1.5 (1.3-2.0)	ns¥	ns¥	0.03

□n=7, ¥n=6, †n=5, *n=4, ^Δn=3, ns= not significant

Table 11.12: Paired daily comparisons of research measurements (median, IQR) in term neonates (NeoAdapt 2)

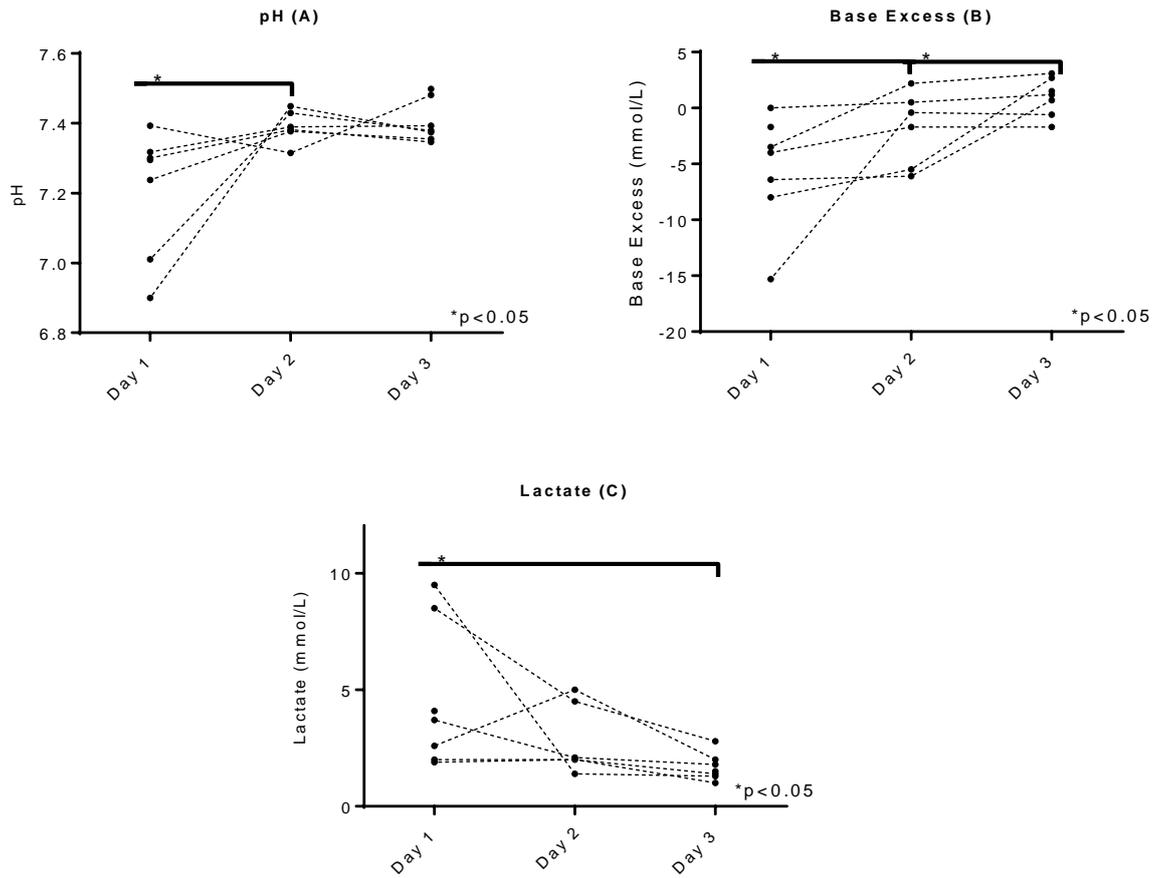


Figure 11.9: Paired daily comparisons of pH (A), Base excess (B) and Lactate (C) in term neonates (NeoAdapt 2)

Respiratory support	Day 1 (n=8)	Day 2 (n=7)	Day 3 (n=7)	p-value
None n (%)	1 (12)	2 (29)	4 (57)	ns
HHFNC n (%)	5 (63)	4 (57)	2 (29)	
CPAP n (%)	0 (0)	0 (0)	0 (0)	
Invasive ventilation n (%)	2 (25)	1 (14)	1 (14)	

Table 11.13: Respiratory management of term neonates; data displayed as n (%)

11.1.2.5 Pooled daily comparisons: Late preterm vs. Term cohort

Table 11.14 shows that GA and birth weight of the term cohort was significantly higher than the late preterm cohort. There were also significantly more males in the term cohort. Significant differences were also noted in the rates of delivery complications between cohorts. Furthermore, antenatal steroid use was

significantly higher in the late preterm cohort. With regards to the research measures Table 11.15 shows that the only significant difference was that lactate on day 1 was significantly higher in the term group. Figures 11.10 and 11.11 display these comparisons graphically. Table 11.16 reveals no difference respiratory management between neonates in the two cohorts.

Variable		Late Preterm Cohort (n=17)	Term Cohort (n=8)	p-value
GA (weeks)		34 (33-36)	39 (37-41)	<0.0001
Gender n (%)	<i>Male</i> <i>Female</i>	9 (53) 8 (47)	6 (75) 2 (25)	0.03
Birth weight (grams)		2200 (1850-2621)	3537 (2435-3834)	0.0008
SGA n (%)	<i>Yes</i> <i>No</i>	0 (0) 17 (100)	1 (14) 7 (86)	ns
APGAR score		9 (7.25-9.75)	9 (5.5-10)	ns
Multiplicity n (%)	<i>Singleton</i> <i>Twin</i>	12 (71) 5 (29)	8 (100) 0 (0)	ns
Type of delivery n (%)	<i>Vaginal</i> <i>C-section</i>	8 (47) 9 (53)	4 (50) 4 (50)	ns
Antenatal steroids n (%)	<i>None</i> <i>Full</i>	5 (29) 12 (71)	6 (75) 2 (25)	0.03
Sepsis risk factors n (%)	<i>PROM</i> <i>Maternal tachycardia</i> <i>Maternal pyrexia</i> <i>Maternal leucocytosis</i> <i>Fetal tachycardia</i>	3 (37) 0 (0) 1 (12) 5 (62) 0 (0)	1 (6) 0 (0) 1 (6) 6 (35) 0 (0)	ns
Delivery complications n (%)	<i>None</i> <i>Meconium stained liquor</i> <i>Pathological CTG</i> <i>Antepartum haemorrhage</i> <i>Meconium aspiration</i>	14 (82) 1 (6) 0 (0) 2 (12) 0 (0)	3 (37) 1 (12) 2 (25) 0 (0) 3 (37)	0.012

Table 11.14: Comparison of basic demographics of the NeoAdapt 2 study participants when split into late preterm and term cohorts; data displayed as n (%) and median (IQR)

Bedside Measure	Cohort	Day 1	Day 2	Day 3	Cohort comparisons (p-value)		
					Day 1	Day 2	Day 3
Hour of life taken (hours)	Late preterm	15 (12-21)*	36.5 (34-43) [□]	62 (54-65) [∞]	ns	ns	ns
	Term	13 (11-21) ⁺	33 (31-37)*	58 (52-62) ⁺			
Mean BP (mmHg)	Late preterm	40 (34-42)*	43 (39) [□]	47 (41-49) [∞]	ns	ns	ns
	Term	47 (40.5-53) ⁺	50 (37-55)*	47 (42-55) ⁺			
Systolic BP (mmHg)	Late preterm	59 (48-65)*	60 (58-67) [□]	67 (56-75) [∞]	ns	ns	ns
	Term	62 (49-76) ⁺	67 (62-79)*	60 (57-72) ⁺			
Diastolic BP (mmHg)	Late preterm	32 (28-35)*	36 (31-44) [□]	38 (34-40) [∞]	ns	ns	ns
	Term	42 (36-44.5) ⁺	36 (32-41)*	41 (35-45) ⁺			
Pulse Pressure (mmHg)	Late preterm	23 (18-28)*	25 (20-29) [□]	26 (22-33) [∞]	ns	ns	ns
	Term	20 (13.5-31.5) ⁺	30 (23-43)*	23 (17-30) ⁺			
HR (Beat per minute)	Late preterm	136 (129-144)*	138.5 (122-147) [□]	143 (131-155) [∞]	ns	ns	ns
	Term	137 (117.5-155) ⁺	134 (111-150)*	126 (111-137) ⁺			
CRT (Seconds)	Late preterm	2.2 (1.8-2.5) [¥]	2 (2-2.4) [#]	2 (1.9-2.3) [∞]	ns	ns	ns
	Term	1.9 (1.6-2.1) [†]	1.8 (1.6-2.2)*	1.7 (1.3-2.3) ⁺			
Echocardiographic Measures							
SVC VTi (cm)	Late preterm	10.6 (9.2-15.5)*	16.3 (11.3-18.9) [□]	13.3 (11.1-15.5) [∞]	ns	ns	ns
	Term	18.3 (10.3-25.5) ⁺	16.7 (13.3-17.5)*	13.6 (11.3-23.5) ⁺			
SVC diameter (cm)	Late preterm	0.53 (0.45-0.59)*	0.47 (0.41-0.57) [□]	0.41 (0.37-0.47) [∞]	ns	ns	ns
	Term	0.64 (0.36-0.69) ⁺	0.53 (0.49-0.58)*	0.53 (0.49-0.58) ⁺			
SVCF (mls/kg/min)	Late preterm	114.2 (105.5-178.9)*	166.9 (130.3-239.0) [□]	146.9 (87.2-190.1) [∞]	ns	ns	ns
	Term	187.9 (84.0-231.5) ⁺	147.1 (100.0-212.4)*	128.1 (100.0-170.0) ⁺			
RVO VTi (cm)	Late preterm	9.4 (9.2-10.5)*	10.0 (8.0-10.6) [□]	10.1 (8.7-12.5) [∞]	ns	ns	ns
	Term	10.5 (6.1-12.3) ⁺	10.1 (8.5-12.0)*	10.7 (10.2-14.1) ⁺			

†n=23, Σn=17, ∞n=15, □n=14, Δn=13, #n=11, *n=7, ¥n=6, +n=5, †n=4, ns= not significant

Table 11.15: Daily comparisons of research measurements (median, IQR) between late preterm and term neonates (NeoAdapt 2)

Echocardiographic Measure	Cohort	Day 1	Day 2	Day 3	Cohort comparisons (p-value)		
					Day 1	Day 2	Day 3
RVO diameter (cm)	Late preterm Term	0.82 (0.79-0.87)* 0.83 (0.76-1.01) [†]	0.82 (0.76-0.93) [□] 0.83 (0.76-1.03)*	0.80 (0.72-0.89) [∞] 0.83 (0.73-0.91) ⁺	ns	ns	ns
RVO (mls/kg/min)	Late preterm Term	321.5 (265.1-377.1)* 221 (119.4-503.5) [†]	333.3 (275.7-352.6) [□] 271.0 (247.8-335.7)*	341.1 (274.1-373.6) [∞] 257.5 (216.9-372.1) ⁺	ns	ns	ns
Plethysmographic Measures							
SpO2 (%)	Late preterm Term	96 (96-98)* 97 (94.5-99.5) ⁺	98 (94-98.25) [□] 98 (95-100)*	99 (96-100) [∞] 94 (93-99) ⁺	ns	ns	ns
mPVI (%)	Late preterm Term	16.3 (11.2-20.9) [¥] 18.3 (15.0-27.2) ⁺	22.2 (16.1-23.2) ^Δ 16.7 (12.5-22.3)*	20.7 (11.5-28.2) [∞] 8.5 (6.6-15.7) ⁺	ns	ns	ns
mPTT (seconds)	Late preterm Term	0.30 (0.29-0.32) [¥] 0.30 (0.25-0.33) ⁺	0.28 (0.26-0.30) ^Δ 0.29 (0.25-0.33)*	0.29 (0.26-0.30) [∞] 0.29 (0.23-0.31) ⁺	ns	ns	ns
NmPTT	Late preterm Term	0.65 (0.60-0.82) [¥] 0.59 (0.56-0.81) ⁺	0.67 (0.55-0.72) ^Δ 0.64 (0.61-0.70)*	0.67 (0.57-0.71) [∞] 0.52 (0.49-0.68) ⁺	ns	ns	ns
Trans mPTT	Late preterm Term	3.3 (3.1-3.5) [¥] 3.4 (3.0-4.0) ⁺	3.5 (3.3-3.9) ^Δ 3.5 (3.3-3.9)*	3.4 (3.3-3.8) [∞] 3.5 (3.2-4.2) ⁺	ns	ns	ns
Clinical & Biochemical Measures							
Urine output (mls/kg/hr)	Late preterm Term	1.1 (0.7-2.1)* 0.7 (0.3-1.0) ⁺	4.48 (1.6-6.6) [¥] 1.7 (0.5-3.4) ⁺	3.4 (1.5-6.6)* 2.1 (0.5-3.4) [†]	ns	ns	ns
pH	Late preterm Term	7.30 (7.24-7.36) [†] 7.29 (7.01-7.32)*	7.38 (7.24-7.39) ^Σ 7.39 (7.36-7.43) [¥]	7.37 (7.35-7.39) [∞] 7.38 (7.35-7.48)*	ns	ns	ns
Base excess (mmol/l)	Late preterm Term	-1 (-4.25-1.25) [†] -4 (-8.0- -1.7)*	-0.4 (-3.2-1.4) ^Σ -1.05 (-5.6-0.9) [¥]	0.1 (-2.1-1.7) [∞] 1.2 (-0.6-2.7)*	ns	ns	ns
Lactate (mmol/l)	Late preterm Term	1.5 (1.1-2.8) [†] 3.7 (2.0-4.6)*	1.6 (1.3-2.65) ^Σ 2.0 (1.8-4.6) [¥]	1.2 (1.0-1.6) [∞] 1.5 (1.3-2.0)*	0.02	ns	ns

[†]n=23, ^Σn=17, [∞]n=15, [□]n=14, ^Δn=13, [#]n=11, *n=7, [¥]n=6, ⁺n=5, [†]n=4, ns= not significant

Table 11.15: Daily comparisons of research measurements (median, IQR) between late preterm and term neonates (NeoAdapt 2)

Respiratory support	Cohort	Day 1	Day 2	Day 3	Cohort comparison (p-value)		
					Day 1	Day 2	Day 3
None n (%)	Late preterm	1 (6)	4 (24)	6 (35)	ns	ns	ns
	Term	1 (0)	2 (29)*	4 (57)*			
Humidified high flow nasal cannula n (%)	Late preterm	11 (64)	12 (70)	11 (65)			
	Term	4 (63)	4 (57)*	2 (29)*			
Continuous positive airway pressure n (%)	Late preterm	1 (6)	0 (0)	0 (0)			
	Term	0 (0)	0 (0)*	0 (0)*			
Invasive ventilation n (%)	Late preterm	4 (24)	1 (6)	0 (0)			
	Term	3 (37)	1 (14)*	1 (14)*			

*n=7

Table 11.16: Comparisons of the respiratory management between neonates' aged late preterm and term neonates; data displayed as n (%)

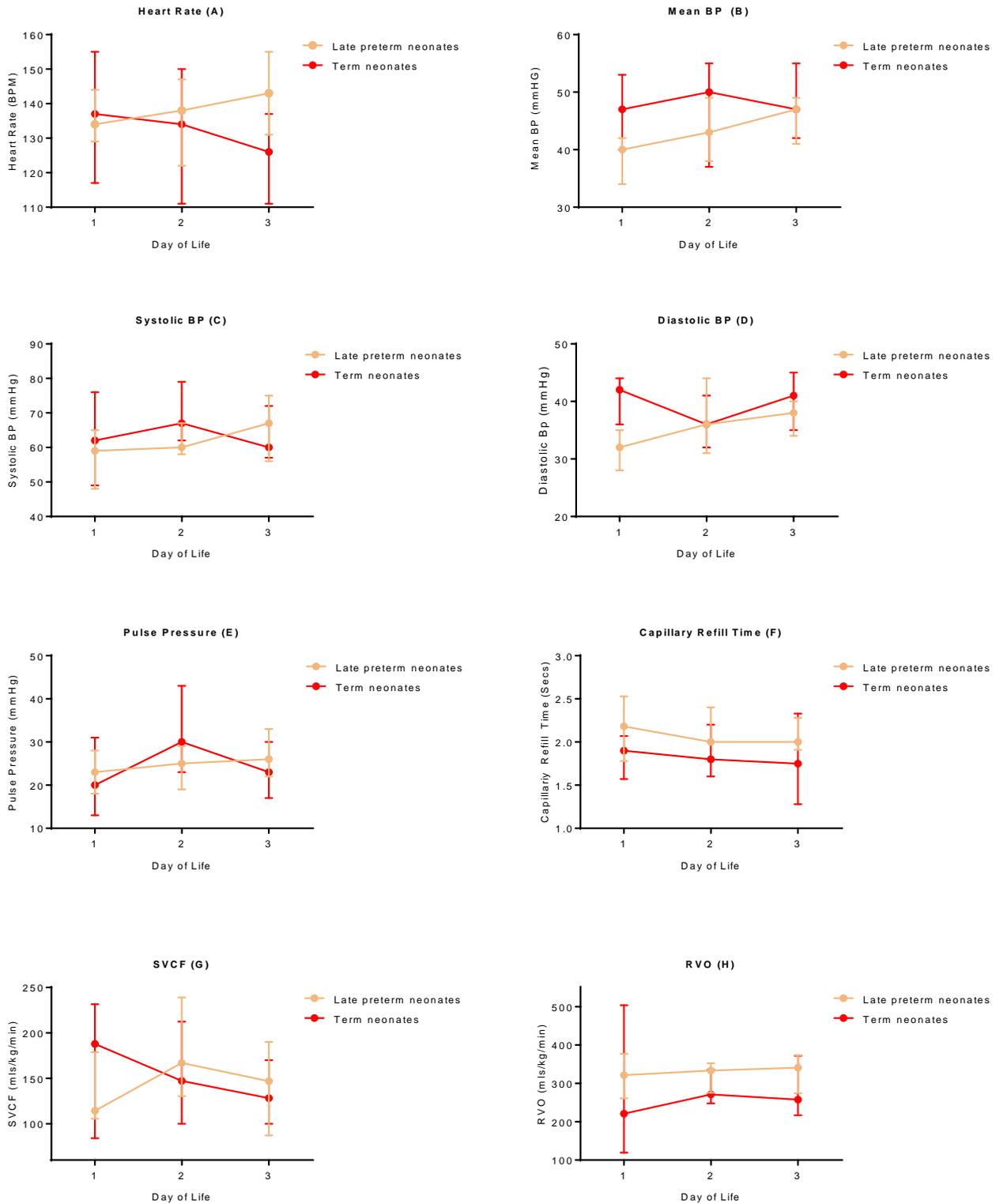


Figure 11.10: Daily comparisons of Heart rate (A), Mean BP (B), Systolic BP (C), Diastolic BP (D), Pulse pressure (E), Capillary refill time (F), SVCF (G) and RVO (H) (median, IQR) in late preterm and term neonates (NeoAdapt 2)

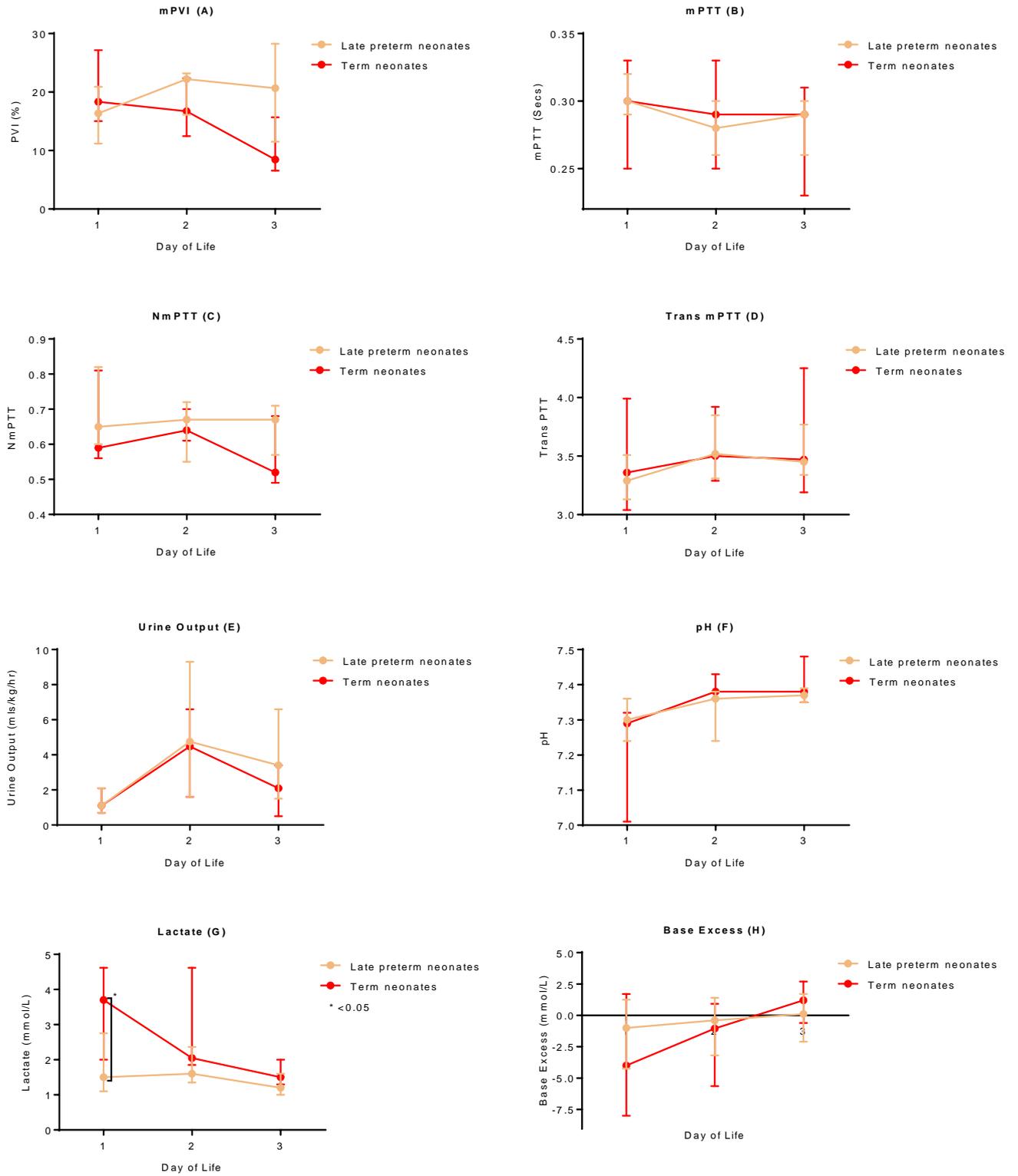


Figure 11.11: Daily comparisons of mPVI (A), mPTT (B), NmPTT (C), Trans mPTT (D), Urine output (E), pH (F), Lactate (G) and Base excess (H) (median, IQR) in late preterm and term neonates (NeoAdapt 2)

11.1.2.6 Comparisons of research measurements in neonates treated and untreated for circulatory failure

A total of 12 infants had research measurements performed on day 1 of life. Only three infants were treated for circulatory failure on day 1 of life. The results of research measures from these infants were compared to nine infants who also had research measurements performed on day 1. The range of treatments received by neonates is displayed in Table 11.17. Those neonates who were treated for circulatory failure were most likely to receive 0.9% saline. Dopamine or dobutamine were the most popular inotropes used. The only significant difference found between the two groups was pulse pressure. As outlined in Table 11.17 no significant difference in the research measures between the two groups. There was also no difference in the degrees of respiratory support received by either group throughout the first three days of life.

Variable		Not Treated (n=9)	Treated (n=3)	p-value
GA (weeks)		37 (36-39)	36 (33-39)	ns
Birth weight (grams)		2750 (2280-3625)	2200 (1600-3020)	ns
5 minute APGAR		10 (8-10)	5 (4-9)	ns
Antenatal steroids n (%)	<i>Full</i> <i>None</i>	6(66) 3(34)	1 (20) 4 (80)	ns
Treatment received n (%)	<i>0.9% Saline</i> <i>Blood products</i> <i>Dopamine</i> <i>Dobutamine</i> <i>Noradrenaline</i> <i>Corticosteroids</i>	0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0)	3 (100) 2 (66) 2 (66) 2 (66) 1 (34) 1 (34)	
Respiratory support n (%)	<i>HHFNC</i> <i>CPAP</i> <i>Invasive</i>	7 (78) 1 (11) 1 (11)	2 (67) 0 (0) 1 (33)	ns
Cranial Ultrasound Appearance n (%)	<i>Normal/Unknown</i> <i>Mild Brain Injury</i>	8 (88) 1 (12)	2 (67) 1 (33)	ns
Mean BP (mmHg)		42 (37-47.5)	42 (34-51)	ns
Systolic BP (mmHg)		62 (54-67)	48 (46-53)	ns
Diastolic BP (mmHg)		32 (29-42.5)	35 (30-42)	ns
PP (mmHg)		23 (20-31)	13 (11-16)	0.009
HR (Beat per minute)		131 (119-140.5)	168 (137-169)	ns
CRT (Seconds)		2 (1.6-2.4)	2*	
SVC VTi (cm)		14.23 (9.42-17.24)	11.99 (9.25-27.48)	ns
SVC Diameter (cm)		0.55 (0.47-0.65)	0.48 (0.23-0.64)	ns
SVCF (mls/kg/min)		114.2 (105.7-203.6)	178.9 (62.2-187.9)	ns
RVO VTi (cm)		10.0 (9.6-10.6) [#]	8.8 (3.4-13.9)	ns
RVO Diameter (cm)		0.84 (0.79-0.96)	0.79 (0.74-0.82)	ns
RVO (mls/kg/min)		293.3 (237.2-368.0) [#]	304.8 (87.9-594.8)	ns
SpO2 (%)		96 (94-98.5)	98 (96-100)	ns
mPVI (%)		17.1 (12.0-19.2)	27.2 (20.2-34.1) ^Δ	ns
mPTT (seconds)		0.27 (0.24-0.30)	0.31 (0.28-0.32) ^Δ	ns
NmPTT		0.65 (0.59-0.81)	0.68 (0.55-0.82) ^Δ	ns
Trans mPTT		3.8 (3.6-4.2)	3.2 (3.1-3.6) ^Δ	ns
Urine output (mls/kg/hr)		0.5 (0.3-0.7) ^Δ	0.7 (0.5-1.1)	ns
pH		7.295 (7.24-7.32)	7.24 (6.9-7.39)	ns
Base excess (mmol/l)		-0.4 (-2.8-1.2)	-3.5 (-8-3.3)	ns
Lactate (mmol/l)		2.4 (1.2-3.9)	2 (1.9-8.5)	ns

[#]n=8, ^Δn=2, *n=1

Table 11.17: Comparison of basic demographics and research measurements in neonates in the NeoAdapt 2 cohort who did and did not receive treatment for circulatory failure; data displayed as n (%) or median (IQR)

11.1.2.7 Comparisons of research measurements in neonates with and without cerebral injury

All infants who suffered cerebral injuries experience mild brain injuries according to our coding system. Table 11.18 shows that no differences were found in the demographic characteristics or research measurements between the two groups. Trends were noted with lower SVCF and RVO in the infants who suffered mild brain cerebral injuries. No other obvious trends were noted in bedside, clinical, biochemical or plethysmographic measures.

Variable		Unknown or No Cerebral Injury (n=20)	Mild Brain Cerebral Injury (n=5)	p-value
GA (weeks)		36 (34-38)	34 (33-37)	ns
Birth weight (grams)		2325 (1975-3253)	2750 (1395-2920)	ns
5 minute APGAR		9 (6.25-10)	9 (4.5-9.5)	ns
Antenatal steroids n (%)	Full None	11 (55) 9 (45)	3 (60) 2 (40)	ns
Treatment for circulatory failure n (%)	Yes No	4 (66) 16 (84)	2 (34) 3 (16)	ns
Mean BP (mmHg)		45 (39-49) [#]	48 (42-54) [*]	ns
Systolic BP (mmHg)		66 (56-73) [#]	61 (56-73) [*]	ns
Diastolic BP (mmHg)		36 (31-42) [#]	41 (33-42) [*]	ns
Pulse pressure (mmHg)		25 (20-31) [#]	23 (21-35) [*]	ns
HR (Beat per minute)		134 (122-144) [#]	142.5 (137-153) [*]	ns
CRT (Seconds)		2 (1.8-2.2) ^Δ	2.2 (1.9-2.7) [¥]	ns
SVC VTi (cm)		14.6 (11.4-17.3) [#]	14.4 (11.5-17.2) [*]	ns
SVC diameter (cm)		0.49 (0.41-0.58) [#]	0.41 (0.29-0.57) [*]	ns
SVCF (mls/kg/min)		153.4 (112.1-200.9) [#]	126.9 (73.8-191.5) [*]	ns
RVO VTi (cm)		10.4 (9.1-13.4) [#]	10.4 (5.7-10.7) [*]	ns
RVO diameter (cm)		0.82 (0.75-0.89) [#]	0.81 (0.74-0.96) [*]	ns
RVO (mls/kg/min)		330.9 (247.8-351.5) [#]	279.5 (233.7-331.1) [*]	ns
SpO2 (%)		98 (94-99) [#]	98 (95-100) [*]	ns
mPVI (%)		18.3 (11.3-22.3) ^Σ	21.4 (13.4-28.5) [*]	ns
mPTT (seconds)		0.29 (0.27-0.31) ^Σ	0.27 (0.24-0.30) [*]	ns
NmPTT		0.65 (0.56-0.71) ^Σ	0.66 (0.59-0.72) [*]	ns
Trans mPTT		3.4 (3.2-3.8) ^Σ	3.7 (3.3-4.1) [*]	ns
Urine output (mls/kg/hr)		1.5 (0.6-3.4) [†]	3.4 (0.8-5.7) [¥]	ns
pH		7.36 (7.31-7.39) [†]	7.37 (7.31-7.39)	ns
Base excess (mmol/l)		-0.4 (-3.5-0.8) [†]	1.7 (-3.4-2.3)	ns
Lactate (mmol/l)		1.6 (1.3-2.8) [†]	1.6 (1.1-2.4)	ns

[†]n=57, [#]n=43, ^Σn=40, ^Δn=39, [†]n=23, [¥]n=11, ^{*}n=10, [¥]n=9

Table 11.18: Comparison of basic demographics and research measurements in neonates in the NeoAdapt 2 cohort who did and did not suffer cerebral injuries on cranial ultrasound; data displayed as n (%) or median (IQR)

11.1.2.8 Correlations of research measurements

The results of the Spearman rank correlations are displayed in Appendix 1. Many significant relationships were found; however none were consistent across the 3 days. Interesting significant correlations of note were found on day 1 in the 33- <37-week cohort between both mean, systolic and diastolic blood pressure and mPTT ($r = -0.93, -0.87$ and -0.92) and Trans mPTT ($r = 0.93, 0.87$ and 0.93).

11.1.3 NeoAdapt 3

11.1.3.1 Subjects

A total of 15 infants were recruited. One subject was excluded due to congenital cardiac malformations found on echocardiography. Recruitment for the NeoAdapt 3 study is outlined in Figure 11.12.

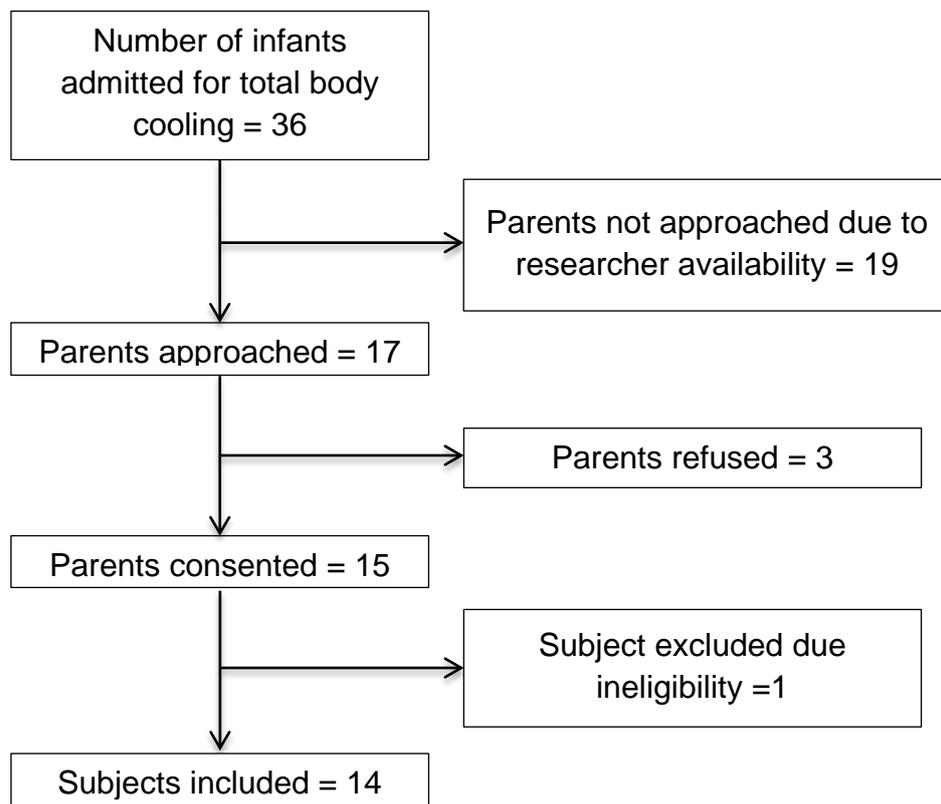


Figure 11.12: NeoAdapt 3 consort diagram

11.1.3.2 Pairwise daily comparisons: Whole cohort

Table 11.19 displays the demographic characteristics of the neonates included in the study. Table 11.20 shows SVC VTi increased significantly between days 1 and 2. CRT also increased significantly between day 2 and 3 of life. RVO diameter significantly decreased between day 3 and when neonates were rewarmed. Trends for increases in SVCF over the first two days of life were seen. Trends for increases in RVO over the first three days of life were seen. Urine output significantly increased between day 1 to day 2 and 3. Pairwise comparisons found lactate to decrease significantly between day 2 and 3, day 1 and 3, or when day 1 or day 2 was compared to the rewarming period. pH significantly increased between days 1 or 3 and the rewarming period. Base excess also became

significantly more positive from day 1 to day 2, 3 and the rewarming period. These significant results are displayed in Figure 11.13. It should be noted that plethysmographic measurements from one subject on day 2 were excluded from the analysis for being an extreme outlier. Bedside measures remained relatively stable throughout the time measurements were taken. No significant differences were seen in the level of respiratory support of cooled neonates over the first three days of life (Table 11.21).

NeoAdapt 3 Cohort (n=14)		
GA (weeks)		40 (38-41)
Gender n (%)	<i>Male</i>	7 (50)
	<i>Female</i>	7 (50)
Birth weight (grams)		3615 (3720-4056)
SGA n (%)	<i>Yes</i>	0 (0)
	<i>No</i>	14 (100)
APGAR Score		5 ± 2
Multiplicity n (%)	<i>Singleton</i>	14 (100)
Type of delivery n (%)	<i>Vaginal</i>	9 (65)
	<i>C-section</i>	5 (35)
Antenatal steroids n (%)	<i>None</i>	14 (100)
Sepsis risk factors n (%)	<i>PROM</i>	0 (0)
	<i>Maternal tachycardia</i>	0 (0)
	<i>Maternal pyrexia</i>	0 (0)
	<i>Maternal leucocytosis</i>	4 (29)
	<i>Fetal tachycardia</i>	0 (0)
Delivery complications n (%)	<i>None</i>	0 (0)
	<i>Antepartum Haemorrhage</i>	1 (7)
	<i>Pathological CTG</i>	5 (35)
	<i>Meconium aspiration</i>	5 (35)
Principle diagnoses n (%)	<i>HIE Grade 1</i>	6 (43)
	<i>HIE Grade 2</i>	7 (50)
	<i>HIE Grade 3</i>	1 (7)
	<i>MAS</i>	4 (28)
	<i>Hypotension</i>	4 (28)
	<i>Hypertension</i>	1 (7)
	<i>Suspected Sepsis</i>	11 (78)
	<i>Hyponatraemia</i>	4 (28)
	<i>Brachial Plexus Injury</i>	1 (7)
	<i>Pneumothorax</i>	1 (7)
	<i>Seizures</i>	7 (50)
	<i>Persistent pulmonary hypertension</i>	1 (7)
	<i>Stridor</i>	1 (7)
	<i>Jaundice</i>	1 (7)
	<i>Hypoglycaemia</i>	1 (7)
	<i>Neonatal coagulopathy</i>	1 (7)
Survival to discharge n (%)	<i>Yes</i>	13 (93)
	<i>No</i>	1 (7)

Table 11.19: Basic demographics of the whole NeoAdapt 3 cohort; data displayed as n (%) or median (IQR)

Bedside Measures	Day 1 (n=5)	Day 2 (n=11)	Day 3 (n=12)	Rewarming (RW) (n=10)	Pairwise Comparisons (p-value)					
					Day 1 Vs 2 (n=5)	Day 2 Vs 3 (n=9)	Day 1 Vs 3 (n=4)	Day 3 Vs RW (n=10)	Day 1 Vs RW (n=3)	Day 2 Vs RW (n=7)
Age taken (hours)	16 (8.5-20.5)	40 (30-44.75)	62 (55.25-67.25)	82.5 (79.5-89.25)						
Mean BP (mmHg)	54 (45-56)	47 (42-51)	47 (44-52)	47 (45-55)	ns	ns	ns	ns	ns	ns
Systolic BP (mmHg)	69 (66-70)	61 (59-69)	62 (58-70)	67 (57-75)	ns	ns	ns	ns	ns	ns
Diastolic BP (mmHg)	43 (36-47)	40 (36-43)	39 (36-43)	38 (35-47)	ns	ns	ns	ns	ns	ns
PP (mmHg)	29 (22-30)	23 (19-25)	25 (20-28)	26 (22-36)	ns	ns	ns	ns	ns	ns
HR (Beat per minute)	92 (76-107)	92 (90-103)	103 (93-116)	107 (100-118)	ns	ns	ns	ns	ns	ns
CRT (Seconds)	2.3 (1.95-3.62)	3.0 (2.6-3.3)	3.2 (2.8-3.6) [‡]	2.4 (2.1-3.5)	ns	0.03	ns	ns [†]	ns	ns
Echocardiographic Measures										
SVC VTi (cm)	8.2 (4.7-14.2)	14.7 (6.8-17.4)	15.0 (10.4-22.1)	14.6 (11.1-17.4)	ns	0.02	ns	ns	ns	ns
SVC diameter (cm)	0.60 (0.49-0.65)	0.59 (0.51-0.64)	0.53 (0.47-0.59)	0.50 (0.46-0.57)	ns	ns	ns	ns	ns	ns
SVCF (mls/kg/min)	65.4 (39.2-94.2)	80.4 (60.4-123.3)	78.1 (60.5-171.5)	106.1 (55.2-138.7)	ns	ns	ns	ns	ns	ns
RVO VTi (cm)	8.6 (5.7-9.2)	9.8 (8.5-11.2)	10.2 (8.5-12.1)	10.4 (8.8-10.9)	ns	ns	ns	ns	ns	ns
RVO diameter (cm)	0.82 (0.80-1.06)	0.87 (0.83-0.99)	0.95 (0.88-1.03)	0.81 (0.75-0.92)	ns	ns	ns	0.009	ns	ns
RVO (mls/kg/min)	155.5 (84.4-201.4)	189.6 (144.5-233.6)	202.2 (155.1-294.5)	167.3 (147.3-202.1)	ns	ns	ns	ns	ns	ns
Plethysmographic Measures										
SpO2 (%)	98 (91-100)	97 (95-99)	98 (97-99)	98 (95-99)	ns	ns	ns	ns	ns	ns
mPVI (%)	16.9 (11.7-25.8)	12.3 (7.7-17.2) [#]	12.9 (7.9-17.3)	13.3 (11.1-16.4)	ns ^Δ	ns [†]	ns	ns	ns	ns
mPTT (seconds)	0.34 (0.28-0.38)	0.35 (0.33-0.36) [#]	0.32 (0.28-0.34)	0.30 (0.26-0.31)	ns ^Δ	ns [†]	ns	ns	ns	ns
NmPTT	0.55 (0.51-0.55)	0.54 (0.47-0.60) [#]	0.59 (0.54-0.61)	0.57 (0.50-0.61)	ns ^Δ	ns [†]	ns	ns	ns	ns
Trans mPTT	2.9 (2.6-3.6)	2.9 (2.8-3.1) [#]	3.1 (3.0-3.5)	3.4 (3.2-3.9)	ns ^Δ	ns [†]	ns	ns	ns	ns
Clinical & Biochemical Measures										
Urine output (mls/kg/hr)	0.7 (0.0-1.9) [□]	3.4 (2.0-8.5) [□]	5.4 (3.8-10.0)	2.1 (1.5-6.5) [*]	0.0001 [□]	ns [‡]	0.0005 [*]	ns [‡]	ns [*]	ns [*]
pH	7.30 (7.18-7.36) [□]	7.35 (7.33-7.37) [□]	7.34 (7.31-7.36) [*]	7.39 (7.34-7.40) [*]	ns [□]	ns [*]	ns [*]	0.004 [*]	0.001 [*]	ns [*]
Base excess (mmol/l)	-3.6 (-9.3- -1.3) [□]	-0.6 (-4.7-2.2) [□]	-0.2 (-2.2-2.0) [*]	0.2 (-1.9-3.4) [*]	0.005 [*]	ns [*]	0.0002 [*]	ns [*]	0.0002 [*]	ns [*]
Lactate (mmol/l)	3.2 (1.4-8.1) [□]	2.3 (1.4-3.0) [□]	1.3 (1.0-2.3) [*]	1.2 (0.8-2.3) [*]	ns [□]	0.002 [*]	0.03 [*]	ns [*]	0.005 [*]	0.02 [*]

□n=14, *n=13, ‡n=12, +n=10, #n=9, †n=8, Δn=4, ns= not significant

Table 11.20: Daily paired comparisons of research measurements (median, IQR) in the NeoAdapt 3 cohort

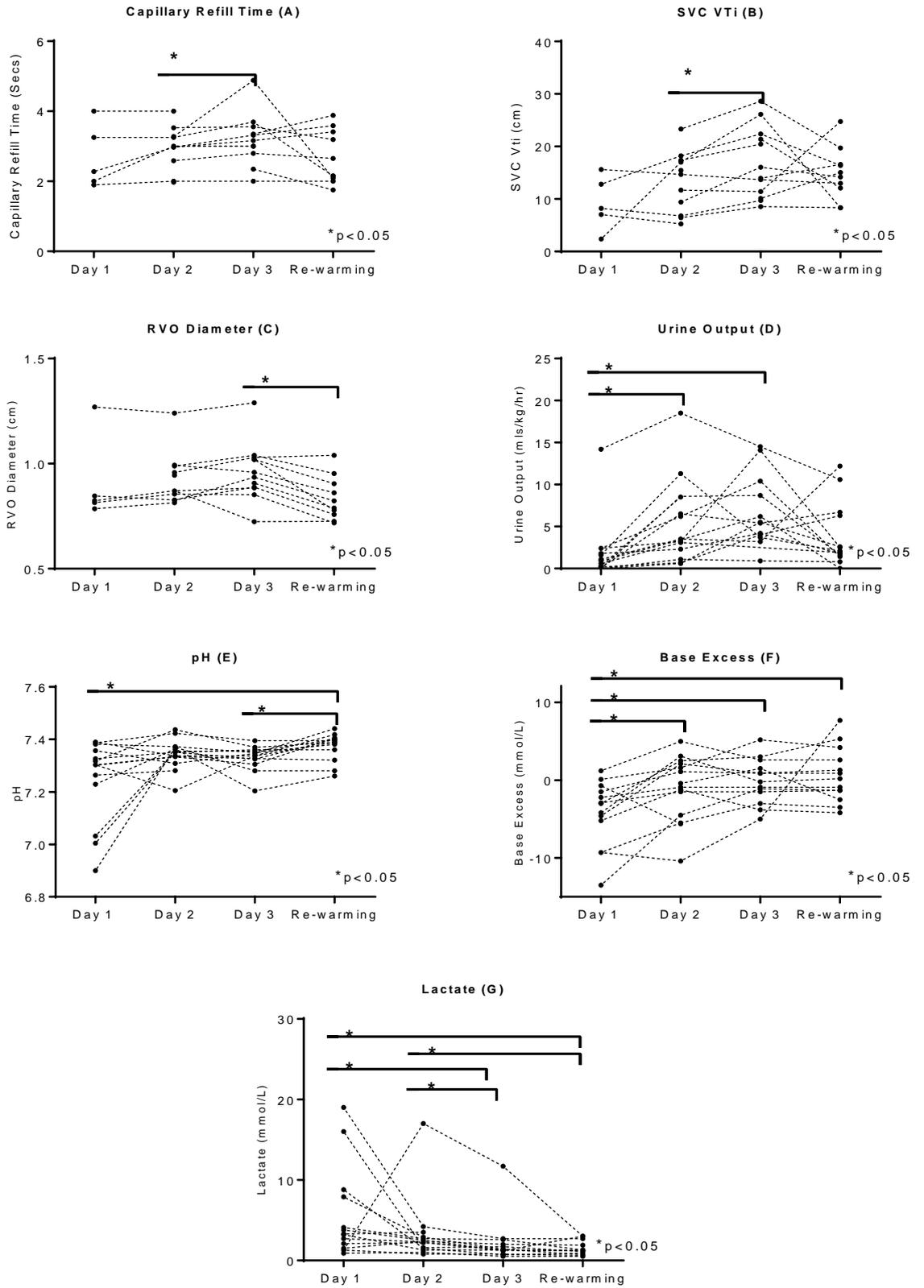


Figure 11.13: Daily paired comparisons of CRT (A), SVC VTi (B), RVO Diameter (C), Urine Output (D), pH (E), Base Excess (F) and Lactate (G) in the NeoAdapt 3 cohort

Respiratory support	Day 1 (n=14)	Day 2 (n=14)	Day 3 (n=13)	Rewarming (n=13)	p-value
None n (%)	5 (36)	4 (29)	4 (31)	4 (31)	ns
Nasal cannula n (%)	2 (14)	1 (7)	1 (8)	0 (0)	
HHFNC n (%)	1 (7)	3 (21)	3 (23)	3 (23)	
Invasive ventilation n (%)	6 (43)	6 (43)	5 (38)	6 (46)	

Table 11.21: Respiratory management of neonates in the NeoAdapt 3 cohort; data displayed as n (%)

11.1.3.3 Comparison of research measurements in treated and untreated neonates for circulatory failure

On day three of life research measures were performed on a total of 12 neonates. Three infants were treated for circulatory failure on day 3 of life. These results were compared to the nine infants who did not receive any treatment day 3 of life. Table 11.22 shows that out of those who received treatment 33% were given blood products and all received inotropic therapy. Those who received treatment were of a significantly lower GA than those who did not. Pooled data showed that those infants who did receive treatment had significantly increased lactate levels (Figure 11.14). Non-significant increases were seen in SVCF and RVO in individuals given treatment for circulatory failure. Plethysmographic data indicated that treated infants showed trends for shorter mPTT and thus longer Trans mPTT. Trends for higher mPVI values were also found in the treated infants.

Variable		Not Treated (n=9)	Treated (n=3)	p-value
GA (weeks)		40 (39-41)	38 (36-39)	0.036
Birth weight (grams)		3700 (3212-4117)	3092 (2795-3995)	ns
5 Minute APGAR		5 (3-7)	4 (2-5)	ns
Antenatal steroids n (%)	<i>Full</i> <i>None</i>	0 (0) 9 (100)	0(0) 3(100)	ns
Treatment Received n (%)	<i>Blood products</i> <i>Dopamine</i> <i>Dobutamine</i> <i>Adrenaline</i>	0 (0) 0 (0) 0 (0) 0 (0)	1 (33) 2 (66) 1 (33) 1 (33)	
Respiratory support n (%)	<i>None</i> <i>HHFNC/Nasal Cannula</i> <i>Invasive</i>	3 (33) 3 (33) 3 (33)	0 (0) 1 (33) 2 (66)	ns
MRI Appearance	<i>Normal</i> <i>Abnormal</i>	7 (78) 2 (22)	2 (67) 1 (33)	ns
Mean BP (mmHg)		47 (43-53)	48 (44-53)	ns
Systolic BP (mmHg)		64 (60-71)	58 (50-66)	ns
Diastolic BP (mmHg)		40 (34-44)	39 (38-43)	ns
PP (mmHg)		27 (23-28)	19 (12-23)	ns
HR (Beat per minute)		99 (91-111)	116 (108-116)	ns
CRT (Seconds)		3.2 (2.5-3.7)	3 (2.8-3.3)	ns
SVC VTi (cm)		13.9 (10.8-24.2)	20.4 (8.6-21.4)	ns
SVC diameter (cm)		0.53 (0.47-57)	0.52 (0.44-0.76)	ns
SVCF (mls/kg/min)		74.2 (57.0-189.1)	135.5 (78.5-152.2)	ns
RVO VTi (cm)		10.7 (6.3-14.0)	9.8 (8.8-11.7)	ns
RVO diameter (cm)		0.91 (0.88-1.03)	0.96 (87-1.03)	ns
RVO (mls/kg/min)		188.8 (144.8-293.8)	223.8 (169.5-318.1)	ns
SpO2 (%)		98 (96-98)	99 (97-99)	ns
mPVI (%)		12.6 (6.8-14.3)	18.2 (7.7-24.6)	ns
mPTT (seconds)		0.32 (0.29-0.34)	0.29 (0.09-0.34)	ns
NmPTT		0.58 (0.51-0.60)	0.61 (0.54-0.68)	ns
Trans mPTT		3.1 (2.9-3.4)	3.5 (3.0-11.1)	ns
Urine output (mls/kg/hr)		5.8 (3.8-12.8) [*]	5.5 (0.9-10.4)	ns
pH		7.35 (7.33-7.36)	7.32 (7.28-7.34)	ns
Base excess (mmol/l)		0.2 (-2.2-1.7)	-0.9 (-5.0-1.5)	ns
Lactate (mmol/l)		1.3 (0.7-1.7)	2.7 (1.7-11.7)	0.03

^{*}n=8, ns= not significant

Table 11.22: Comparison of basic demographics and research measurements in neonates in the NeoAdapt 3 cohort who did and did not receive treatment for circulatory failure; data displayed as n (%) or median (IQR)

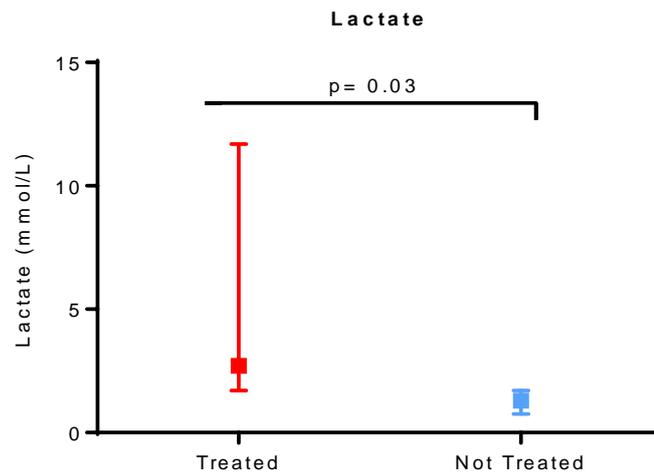


Figure 11.14: Comparisons of lactate (median, IQR) between neonates in the NeoAdapt 3 cohort who did and those who did not receive treatment for circulatory failure

11.1.3.4 Comparison of research measurements in neonates with and without cerebral injury according to MRI appearances

Table 11.23 and Figure 11.15 show that in those neonates with abnormal MRIs blood gases were found to have significantly more acidic blood pH and a more negative base excess. Capillary refill times were also longer in infants who had poor outcomes according to MRI appearances. One subject's plethysmographic measurements were excluded from the analysis due to being an extreme outlier.

Variable		Normal MRI (n=10)	Abnormal MRI (n=4)	p-value
GA (weeks)		41 (39-41)	38 (37-39)	0.02
Birth weight (grams)		3845 (3266-4088)	3416 (2723-4115)	ns
5 Minute APGAR		5 (3-7)	5 (4-7)	ns
Antenatal steroids n (%)	<i>Full</i> <i>None</i>	0 (0) 10 (100)	0(0) 4 (100)	ns
Treatment Received n (%)	<i>0.9% Saline</i> <i>Blood products</i> <i>Dopamine</i> <i>Corticosteroids</i> <i>Dobutamine</i> <i>Adrenaline</i>	1 (10) 5 (50) 2 (20) 0 (0) 1 (10) 1 (10)	3 (75) 3 (75) 2 (50) 1 (25) 0 (0) 0 (0)	ns
Mean BP (mmHg)		48 (44-53) [#]	48 (43-53) ^Δ	ns
Systolic BP (mmHg)		67 (61-71) [#]	60 (64-69) ^Δ	ns
Diastolic BP (mmHg)		41 (38-43) [#]	36 (33-46) ^Δ	ns
PP (mmHg)		26 (22-29) [#]	23 (19-25) ^Δ	ns
HR (Beat per minute)		103 (92-11) [#]	102 (85-108) ^Δ	ns
CRT (Seconds)		2.7 (2.0-3.3) [‡]	3.2 (3.0-3.7) ^Δ	0.009
SVC VTi (cm)		13.7 (8.6-17.0) [#]	16.0 (9.4-18.2) ^Δ	ns
SVC diameter (cm)		0.55 (0.46-0.62) [#]	0.52 (0.49-0.62) ^Δ	ns
SVCF (mls/kg/min)		77.8 (56.4-127.2) [#]	101.1 (61.2-152.2) ^Δ	ns
RVO VTi (cm)		9.8 (8.2-11.1) [#]	9.3 (8.7-10.3) ^Δ	ns
RVO diameter (cm)		0.91 (0.82-1.02) [#]	0.86 (0.78-0.88) ^Δ	ns
RVO (mls/kg/min)		188.1 (149.6-221.4) [#]	160.1 (144.5-202.7) ^Δ	ns
SpO2 (%)		97 (96-99) [#]	98 (96-99) ^Δ	ns
mPVI (%)		13.5 (10.7-18.8) [#]	13.2 (6.8-16.9) [□]	ns
mPTT (seconds)		0.31 (0.29-0.35) [#]	0.31 (0.29-0.35) [□]	ns
NmPTT		0.57 (0.52-0.60) [#]	0.56 (0.54-0.60) [□]	ns
Trans mPTT		3.17 (2.89-3.50) [#]	3.12 (2.86-3.37) [□]	ns
Urine output (mls/kg/hr)		3.55 (1.65-6.65) [†]	2.45 (0.87-4.75) [¥]	ns
pH		7.36 (7.33-7.39) [*]	7.28 (7.25-7.33) [¥]	<0.0001
Base excess (mmol/l)		0.5 (-2.6-2.5) [*]	-3.2 (-5.3 -0.9) [¥]	0.004
Lactate (mmol/l)		1.9 (1.3-2.9) [*]	1.15 (0.7-3.3) [¥]	ns

*n=38, †n=36, #n=27, ‡=23, ¥n=14, Δn=11, □n=9, ns= not significant

Table 11.23: Comparison of basic demographics and research in neonates in the NeoAdapt 3 cohort who were found to have normal and abnormal MRI appearances on the first three days of life; data displayed as n (%) or median (IQR)

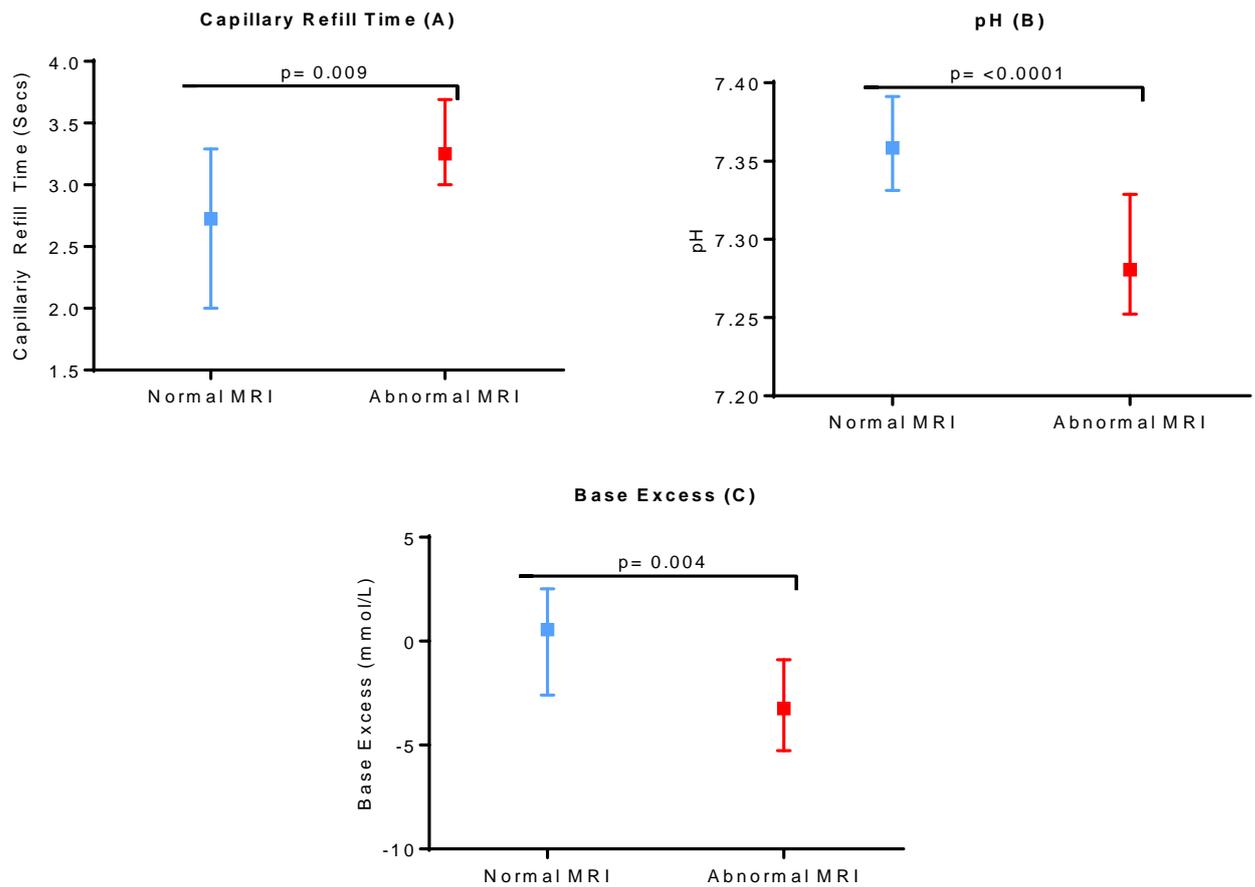


Figure 11.15: Comparisons of Capillary refill time (A), pH (B) and Base excess (C) (median, IQR) in neonates in the NeoAdapt 3 cohort with normal and abnormal MRI appearances

11.1.3.5 Correlations of research measurements

The results of the Spearman rank correlations are displayed in appendix 1. Many significant relationships were found; however none were consistent over the time research measurements were performed.

11.1.4 Inter-study comparisons

11.1.4.1 NeoAdapt 1 vs. NeoAdapt 2: Late preterm neonates

A total of 47 infants aged between 33 to <37 weeks GA were included. This included a total of 30 neonates from the NeoAdapt 1 cohort and 17 from the NeoAdapt 2 cohort. The characteristics of these cohorts are displayed in Table 11.24. No significant difference was noted between these two preterm cohorts with regard to baseline characteristics. Table 11.25 shows that on the first day of life diastolic blood pressure, SVC diameter and RVO diameter were significantly lower than in infants in the healthy NeoAdapt 1 cohort compared to the sick NeoAdapt 2 cohort. RVO diameter was again significantly smaller in healthy cohort compared to infants receiving intensive care on day 2 of life. mPVI was also significantly reduced in the NeoAdapt 1 cohort compared to the NeoAdapt 2 cohort on day 2 too. On day 3 CRT, mPTT and mPVI was significantly reduced in the NeoAdapt 1 cohort compared to the NeoAdapt 2 cohort. Trans mPTT was significantly longer in the NeoAdapt 1 cohort compared to the NeoAdapt 2 cohort on day 3. These comparisons are displayed in Figure 11.16 and 11.17.

Variable		NeoAdapt 1 (n=30)	NeoAdapt 2 (n=17)	p-value
GA (weeks)		34 (33-35)	34 (33.5-36)	ns
Gender n (%)	<i>Male</i>	9 (30)	9 (53)	ns
	<i>Female</i>	21 (70)	8 (47)	
Birth weight (grams)		2150 (1823-2372)	2200 (1850-2621)	ns
SGA) n (%)	<i>Yes</i>	4 (14)	0 (0)	ns
	<i>No</i>	26 (86)	17 (100)	
APGAR score		9 (8-10)	9 (5-10)	ns
Multiplicity n (%)	<i>Singleton</i>	14 (46)	12 (71)	ns
	<i>Twin</i>	13 (44)	5 (29)	
	<i>Triplet</i>	3 (10)	0 (0)	
Type of delivery n (%)	<i>Vaginal</i>	22 (74)	8 (47)	ns
	<i>C-section</i>	8 (26)	9 (53)	
Antenatal steroids n (%)	<i>None</i>	8 (26)	5 (29)	ns
	<i>Incomplete</i>	2 (4)	0 (0)	
	<i>Full</i>	20 (70)	12 (71)	

Table 11.24: Comparison of basic demographics between the NeoAdapt 1 and 2 late preterm cohorts; data displayed as n (%) and median (IQR)

Bedside Measure	Cohort	Day 1	Day 2	Day 3	Comparisons (p-value)		
					Day 1	Day 2	Day 3
Age taken (hours)	NeoAdapt 1	21 (13-23) [‡]	40.5 (34-45) [*]	63 (54-68.5) [□]	ns	ns	ns
	NeoAdapt 2	15 (12-21) [△]	36 (34-43) [#]	62 (54-65) ⁺			
Mean BP (mmHg)	NeoAdapt 1	37 (35-40) [‡]	42.5 (40-45) [*]	45 (42-58) ^Σ	ns	ns	ns
	NeoAdapt 2	40 (34-42) [△]	43 (39-49) [#]	47 (41-49) ⁺			
Systolic BP (mmHg)	NeoAdapt 1	56 (49-60) [‡]	64 (57-67) [*]	67 (61-81) ^Σ	ns	ns	ns
	NeoAdapt 2	59 (48-65) [△]	60 (58-67)	67 (56-75) ⁺			
Diastolic BP (mmHg)	NeoAdapt 1	29 (25-30) [‡]	33 (31-36) [*]	29 (24-33) ^Σ	0.03	ns	ns
	NeoAdapt 2	32 (28-35) [△]	36 (31-44) [#]	38 (34-40) ⁺			
PP (mmHg)	NeoAdapt 1	28 (22-32) [‡]	29 (22-32) [*]	29 (24-33) ^Σ	ns	ns	ns
	NeoAdapt 2	23 (18-28) [△]	25 (20-29) [#]	26 (22-33) ⁺			
HR (Beat per minute)	NeoAdapt 1	132 (121-137) [‡]	132 (124-145) [*]	142 (125-150) [□]	ns	ns	ns
	NeoAdapt 2	136 (129-144) [△]	138 (122-147) [#]	143 (131-155) ⁺			
CRT (Seconds)	NeoAdapt 1	2.0 (1.9-2.3) [‡]	2.0 (2.0-2.3) [*]	2.0 (1.8-2.2) [□]	ns	ns	0.016
	NeoAdapt 2	2.2 (1.8-2.5) [†]	2.0 (2.0-2.4) [#]	2.0 (1.9-2.3) ⁺			
Echocardiographic Measures							
SVC VTi (cm)	NeoAdapt 1	16.9 (15.1-18.0) [‡]	15.4 (13.6-17.5) [*]	14.7 (12.1-17.5) [□]	0.002	ns	ns
	NeoAdapt 2	10.5 (9.2-15.5) [△]	16.3 (11.3-18.9) [#]	13.3 (11.1-15.5) ⁺			
SVC diameter (cm)	NeoAdapt 1	0.43 (0.40-0.46) [‡]	0.41 (0.38-0.44) [*]	0.39 (0.34-0.47) [□]	0.026	ns	ns
	NeoAdapt 2	0.53 (0.45-0.59) [△]	0.47 (0.41-0.57) [#]	0.41 (0.37-0.47) ⁺			
SVCF (mls/kg/min)	NeoAdapt 1	149.1 (128.2-177.8) [‡]	132.9 (105.5-166.8) [*]	128.0 (96.8-150.0) [□]	ns	ns	ns
	NeoAdapt 2	114.2 (105.5-178.9) [△]	166.9 (130.3-239.0) [#]	146.9 (87.2-190.1) ⁺			

□n=24, Σn=23 *n=22, ‡n=21, +n=15, #n=14, △n=7, †n=6, ns= not significant

Table 11.25: Daily comparisons of research measurements (median, IQR) between the NeoAdapt 1 and 2 late preterm cohorts

	Cohort	Day 1	Day 2	Day 3	Comparisons (p-value)		
					Day 1	Day 2	Day 3
RVO VTi (cm)	NeoAdapt 1	10.9 (9.2-12.8) [¥]	10.7 (8.9-12.00) [*]	10.3 (8.5-12.5) [□]	ns	ns	ns
	NeoAdapt 2	9.4 (9.2-10.5) [△]	10.0 (8.0-10.6) [#]	10.1 (8.7-12.5) ⁺			
RVO diameter (cm)	NeoAdapt 1	0.76 (0.71-0.79) [¥]	0.74 (0.70-0.80) [*]	0.72 (0.68-0.80) [□]	0.008	0.018	ns
	NeoAdapt 2	0.82 (0.79-0.87) [△]	0.82 (0.76-0.93) [#]	0.80 (0.72-0.89) ⁺			
RVO (mls/kg/min)	NeoAdapt 1	262.8 (240.9-329.4) [¥]	296.9 (249.9-368.2) [*]	283.4 (215.9-357.1) [□]	ns	ns	ns
	NeoAdapt 2	321.5 (265.1-377.1) [△]	333.3 (275.7-352.6) [#]	341.1 (274.1-373.6) ⁺			
Plethysmographic Measures							
SpO ₂ (%)	NeoAdapt 1	98 (96-100) [¥]	98 (96.75-100) [*]	98.5 (98-100) [□]	ns	ns	ns
	NeoAdapt 2	96 (96-98) [△]	98 (94-98) [#]	99 (96-100) ⁺			
mPVI (%)	NeoAdapt 1	20.5 (15.9-24.5)	15.0 (11.6-18.1)	8.1 (5.5-12.2) [†]	ns	0.03	0.0005
	NeoAdapt 2	16.3 (11.2-20.9) [†]	22.2 (16.1-23.2) [‡]	20.7 (11.5-28.2) [#]			
mPTT (seconds)	NeoAdapt 1	0.29 (0.27-0.30) [¥]	0.28 (0.26-0.29) [¥]	0.27 (0.26-0.29) [*]	ns	ns	0.04
	NeoAdapt 2	0.30 (0.29-0.32) [†]	0.28 (0.26-0.30) [‡]	0.29 (0.26-0.30) [#]			
NmPTT	NeoAdapt 1	0.65 (0.61-0.68) [¥]	0.64 (0.62-0.68) [¥]	0.64 (0.61-0.68) [*]	ns	ns	ns
	NeoAdapt 2	0.65 (0.60-0.82) [†]	0.67 (0.55-0.72) [‡]	0.67 (0.57-0.71) [#]			
Trans mPTT	NeoAdapt 1	3.4 (3.3-3.6) [¥]	3.6 (3.4-3.8) [¥]	3.7 (3.5-3.8) [*]	ns	ns	0.04
	NeoAdapt 2	3.3 (3.1-3.5) [†]	3.5 (3.3-3.9) [‡]	3.4 (3.3-3.8) [#]			

□n=24, *n=22, ¥n=21, †n=15, #n=14, ‡n=13, △n=7, †n=6, ns= not significant

Table 11.25: Daily comparisons of research measurements (median, IQR) between the NeoAdapt 1 and 2 late preterm cohorts

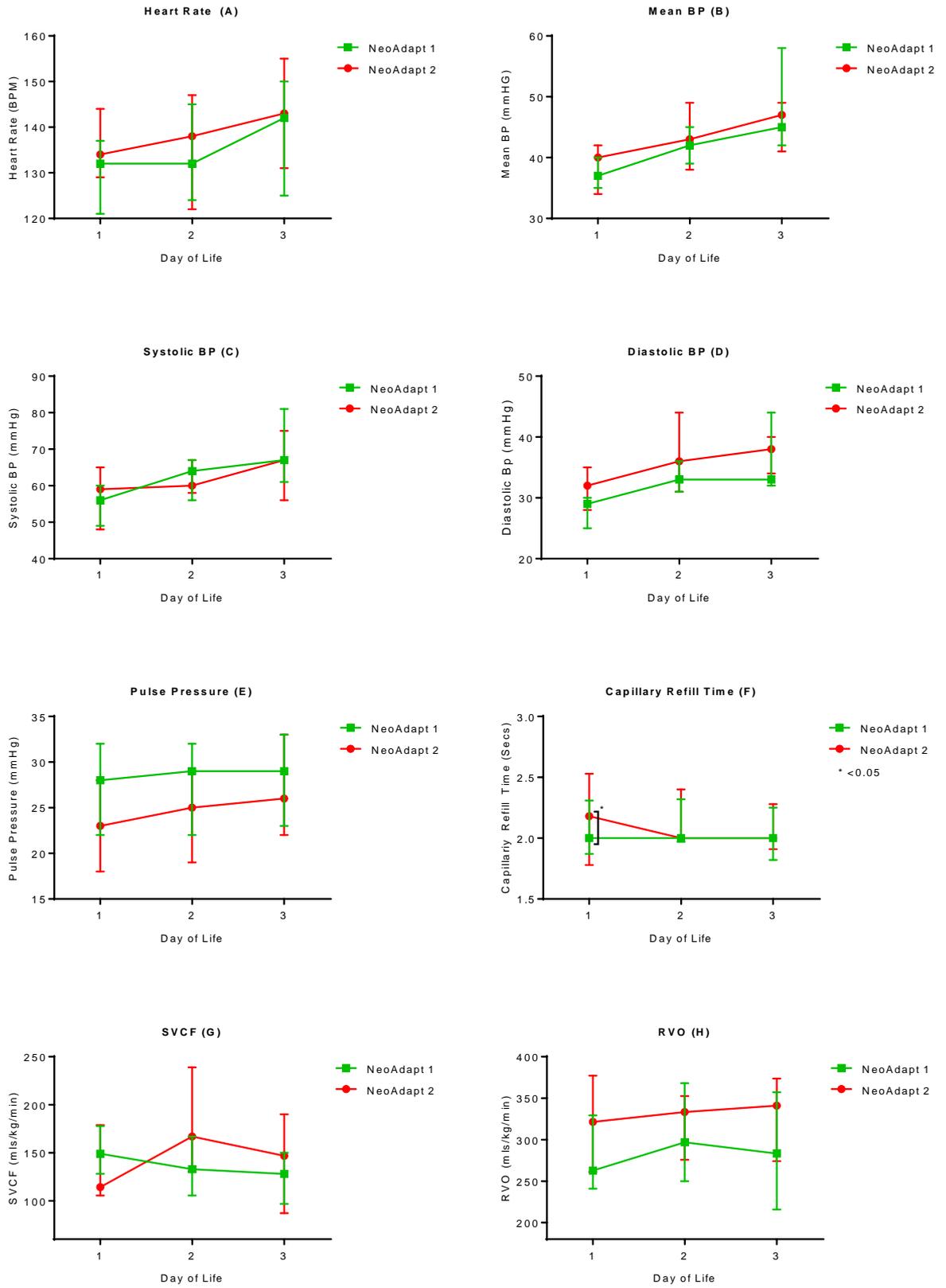


Figure 11.16: Daily comparisons of Heart rate (A), Mean BP (B), Systolic BP (C), Diastolic BP (D), Pulse pressure (E), Capillary refill time (F), SVCF (G) and RVO (H) (median, IQR) between the NeoAdapt 1 and 2 late preterm cohorts

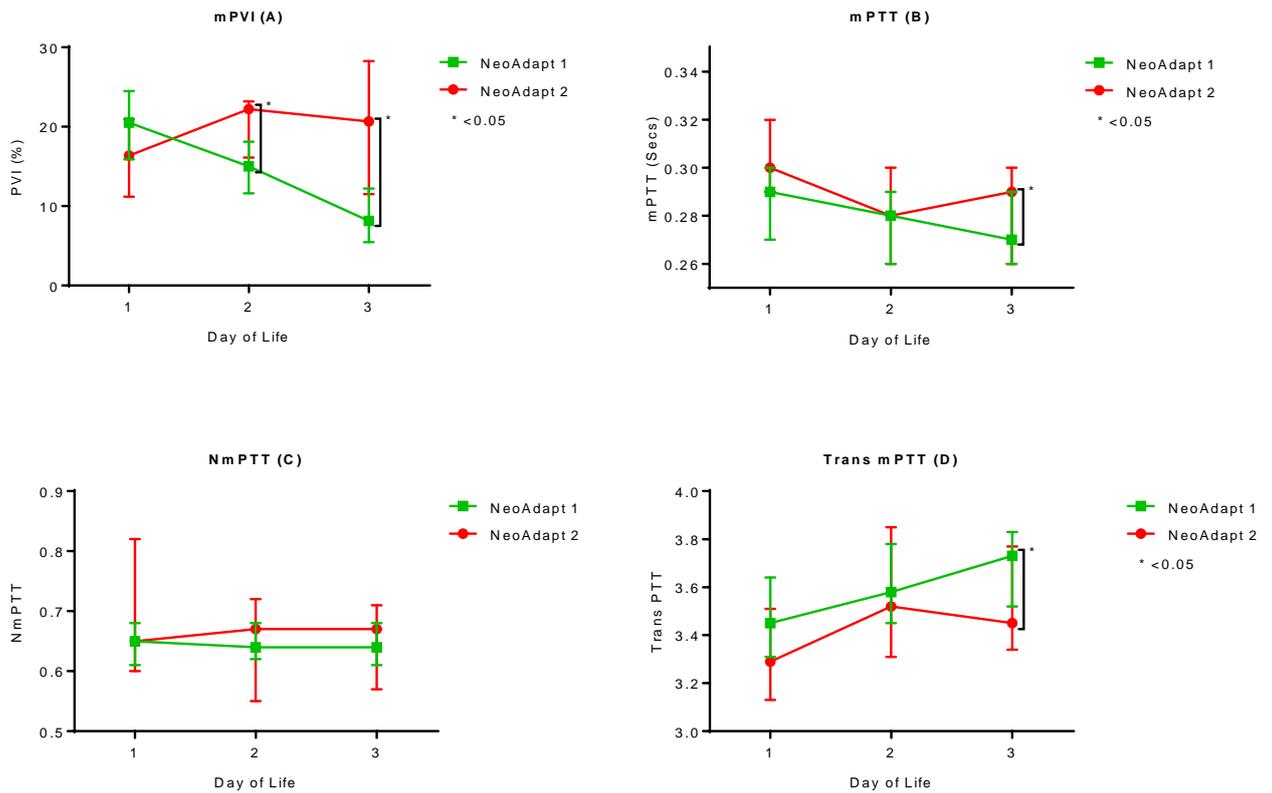


Figure 11.17: Daily comparisons of mPVI (A), mPTT (B), NmPTT (C) and Trans mPTT (D) (median, IQR) between the NeoAdapt 1 and 2 late preterm cohorts

11.1.4.2 NeoAdapt 1 vs. NeoAdapt 2 vs. NeoAdapt 3: Term infants

Results were compared between the 3 NeoAdapt studies involving all term infants (≥ 37 -weeks GA). The basic demographic details of the 42 included infants are displayed in Table 11.26. The APGAR scores were significantly lower in the cooled infants compared to the other two cohorts. There were no other differences between each of the other baseline characteristics.

With regard to bedside measures Table 11.27 and Figure 11.18 show that the heart rate was significantly different between the three groups throughout the three days. When looking at the post-hoc tests the heart rate was significantly reduced in the cooled infants compared to the other two groups. The systolic blood pressure was significantly different between the three cohorts on day 2 and 3. Dunns multiple comparison (post hoc) tests showed that systolic blood pressure was significantly higher in healthy neonates when compared to cooled neonates on both days. On day 3 healthy infants systolic blood pressure was significantly

higher compared to infants requiring intensive care. MAP was significantly different between the three groups on day 3 of life. The post hoc tests revealed that it was significantly higher in healthy infants compared to those who were cooled. ANOVA analysis revealed pulse pressure was significantly different between the three cohorts on day 3 of life. CRT was significantly different between the three groups on day 2 & 3. Multiple comparisons revealed that the CRT was shorter in neonates receiving intensive care when compared to cooled neonates on days 2 and 3.

Analysis of echocardiographic measures revealed that SVCF was significantly different between the three groups on day 1, being lowest in cooled infants. RVO was significantly different between the three groups on day 2. Post hoc tests revealed that it was significantly lower in the cooled neonates compared those receiving intensive care.

Comparisons of plethysmographic traces indicate that mPTT and Trans mPTT were significantly different between the three groups on days 2 and 3. Multiple comparisons showed that mPTT was shorter in neonates who were healthy or receiving intensive care when compared to those receiving total body cooling on day 2 of life. Post hoc tests showed that mPTT was only significantly shorter in healthy neonates and those receiving total body cooling care on day three of life. With regard to Trans mPTT the same significant differences between the two groups were noted, however the relationships were reversed. NmPTT was significantly different between the three groups on day 2 of life with post hoc analysis showing that NmPTT was significantly shorter in healthy and cooled infants when compared to neonates receiving intensive care. These results are displayed graphically in Figure 11.19.

Out of the clinical and biochemical measurements (Table 11.27 and Figure 11.19) compared between neonates in the NeoAdapt 2 and 3 cohort urine output was significantly higher in cooled neonates compared to unwell neonates on day 3 of life. pH was significantly lower in cooled infants on day 2 and 3 of life. Only statistically significant differences in respiratory support received by neonates was noted on day 1 between the two cohorts (Table 11.28).

Variable		Cohort			p-value	Pairwise Comparison (adjusted p value)		
		NeoAdapt 1 (A) (n=20)	NeoAdapt 2 (B) (n=8)	NeoAdapt 3 (C) (n=14)		A vs B	A vs C	B vs C
GA (weeks)		40 (39-41)	39 (37-41)	40 (39-41)	ns	ns	ns	ns
Gender	<i>Male</i>	12 (54)	6 (75)	6 (46)	ns			
	<i>Female</i>	8 (46)	2 (25)	7 (54)				
Birth weight (grams)		3455 (3190-3581)	3537 (2435-3834)	3720 (3100-4056)	ns	ns	ns	ns
Multiplicity	<i>Singleton</i>	20 (100)	8 (100)	14 (100)				
SGA n (%)	<i>Yes</i>	0 (0)	1 (14)	0 (0)	ns			
	<i>No</i>	20 (100)	7 (86)	14 (100)				
APGAR score		9 (8-10)	9 (7-10)	5 (4-7)	<0.0001	ns	<0.0001	0.009
Type of delivery	<i>Vaginal</i>	13 (65)	4 (50)	9 (65)	ns			
	<i>C-Section</i>	7 (3)	4 (50)	5 (35)				
Antenatal steroids	<i>None</i>	19 (95)	6 (75)	14 (100)	ns			
	<i>Complete</i>	1 (5)	2 (25)	0 (0)				

Table 11.26: Comparison of basic demographics between the NeoAdapt 1, 2 & 3 term cohorts; data displayed as n (%) and median (IQR)

Bedside Measures	Day	NeoAdapt 1 (A)	NeoAdapt 2 (B)	NeoAdapt 3 (C)	p-value	Pairwise Comparison (adjusted p value)		
						A vs B	A vs C	B vs C
Hour of life taken (hours)	Day 1	14 (12-20) [‡]	13 (11-21) [†]	16 (8-20) [†]	ns	ns	ns	ns
	Day 2	33 (28-36) ⁺	33 (31-37) ^Δ	37 (30-45) [□]	ns	ns	ns	ns
	Day 3	56 (52-60) ⁺	58 (52-62) [†]	63 (55-68) [*]	ns	ns	ns	ns
Mean BP (mmHg)	Day 1	51 (43-57) [¥]	47 (40-53) [†]	54 (45-56) [†]	ns	ns	ns	ns
	Day 2	51 (47-57) [*]	50 (37-55) ^Δ	47 (42-51) [□]	ns	ns	ns	ns
	Day 3	56 (51-65) ⁺	47 (42-55) [†]	47 (44-52) [*]	0.01	ns	0.02	ns
Systolic BP (mmHg)	Day 1	73 (61-88) [¥]	62 (49-76) [†]	69 (66-70) [†]	ns	ns	ns	ns
	Day 2	74 (70-78) [*]	67 (62-79) ^Δ	61 (59-69) [□]	0.01	ns	0.01	ns
	Day 3	74 (70-78) ⁺	60 (57-72) [†]	62 (58-70) [*]	0.0008	0.02	0.002	ns
Diastolic BP (mmHg)	Day 1	37 (36-46) [¥]	42 (36-44) [†]	43 (36-47) [†]	ns	ns	ns	ns
	Day 2	42.5 (32-52) [*]	36 (32-41) ^Δ	40 (36-43) [□]	ns	ns	ns	ns
	Day 3	44 (39-57) ⁺	41 (35-45) [†]	39 (35-43) [*]	ns	ns	ns	ns
PP (mmHg)	Day 1	33 (23-44) [¥]	20 (13-31) [†]	29 (22-30) [†]	ns	ns	ns	ns
	Day 2	29 (23-39) [*]	30 (23-43) ^Δ	23 (19-25) [□]	ns	ns	ns	ns
	Day 3	34 (25-42) ⁺	23 (17-30) [†]	25 (20-28) [*]	0.04	ns	ns	ns
HR (Beat per minute)	Day 1	127 (118-137) [‡]	137 (117-155) [†]	92 (76-107) [†]	0.008	ns	0.01	0.007
	Day 2	119 (105) ⁺	134 (111-150) ^Δ	92 (90-103) [□]	0.0008	ns	0.03	0.0009
	Day 3	123 (105-133) ⁺	126 (111-137) [†]	103 (93-116) [*]	0.004	ns	0.01	0.03
CRT (Seconds)	Day 1	2 (1.9-2.3) [‡]	1.9 (1.6-2.1) ^Σ	2.3 (1.9-3.6) [†]	ns	ns	ns	ns
	Day 2	2 (2.0-2.3) ⁺	1.8 (1.6-2.2) ^Δ	3.0 (2.6-3.3) [#]	0.003	ns	0.03	0.003
	Day 3	2.4 (2.0-2.5) ⁺	1.7 (1.3-2.3) [†]	3.2 (2.8-3.6) [*]	0.001	ns	0.03	0.002

[†]n=13, ^{*}n=12, [□]n=11, [#]n=10, [‡]n=9, ^Δn=7, [¥]n=6, [†]n=5, ^Σ=4, ns= not significant

Table 11.27: Comparisons of research measurements (median, IQR) between the NeoAdapt 1, 2 and 3 term cohorts

Echocardiographic Measures	Day	NeoAdapt 1 (A)	NeoAdapt 2 (B)	NeoAdapt 3 (C)	p-value	Pairwise Comparison (adjusted p value)		
						A vs B	A vs C	B vs C
SVC VTi (cm)	Day 1	17.7 (13.9-21.3) [‡]	18.3 (10.3-25.5) [†]	8.2 (4.8-14.2) [†]	ns	ns	ns	ns
	Day 2	15.4 (13.6-17.5) ⁺	16.7 (13.3-17.5) ^Δ	14.7 (6. 8-17.4) [□]	ns	ns	ns	ns
	Day 3	16.6 (12.3-21.5) ⁺	13.6 (11.3-23.4) [†]	15.0 (10.4-22.1) [*]	ns	ns	ns	ns
SVC diameter (cm)	Day 1	0.52 (0.45-0.58) [‡]	0.64 (0.36-0.69) [†]	0.60 (0.49-0.65) [†]	ns	ns	ns	ns
	Day 2	0.46 (0.40-0.58) ⁺	0.53 (0.49-0.58) ^Δ	0.59 (0.51-0.64) [□]	ns	ns	ns	ns
	Day 3	0.46 (0.34-0.52) ⁺	0.53 (0.49-0.58) [†]	0.53 (0.47-0.59) [*]	ns	ns	ns	ns
SVCF (mls/kg/min)	Day 1	118.4 (89.8-151.5) [‡]	187.9 (84.0-231.5) [†]	65.4 (39.2-94.2) [†]	0.04	ns	ns	ns
	Day 2	115.9 (72.3-125.6) ⁺	147.1 (100.0-212.4) ^Δ	80.4 (60.4-123.3) [□]	ns	ns	ns	ns
	Day 3	84.3 (69.4-97.8) ⁺	128.1 (100.0-170.0) [†]	78.1 (60.5-171.5) [*]	ns	ns	ns	ns
RVO VTi (cm)	Day 1	10.2 (9.0-11.9) [‡]	10.5 (6.1-12.3) ^Σ	8.6 (5.7-9.2) [†]	ns	ns	ns	ns
	Day 2	11.5 (9.3-12.7) ⁺	10.1 (8.5-11.9) ^Δ	9.79 (8.5-11.2) [□]	ns	ns	ns	ns
	Day 3	8.9 (7.7-11.5) ⁺	10.7 (10.2-14.2) [†]	10.2 (8.5-12.1) [*]	ns	ns	ns	ns
RVO diameter (cm)	Day 1	0.88 (0.84-0.95) [‡]	0.83 (0.76-1.01) ^Σ	0.82 (0.80-1.06) [†]	ns	ns	ns	ns
	Day 2	0.89 (0.78-0.96) ⁺	0.83 (0.76-1.03) ^Δ	0.87 (0.83-0.99) [□]	ns	ns	ns	ns
	Day 3	0.86 (0.79-0.94) ⁺	0.83 (0.73-0.91) [†]	0.95 (0.88-1.03) [*]	ns	ns	ns	ns
RVO (mls/kg/min)	Day 1	221.7 (195.0-319.3) [‡]	221 (119.4-503.5) ^Σ	155.5 (84.43-201.4) [†]	ns	ns	ns	ns
	Day 2	213.0 (169.5-290.1) ⁺	271.0 (247.8-335.7) ^Δ	189.6 (144.5-233.6) [□]	0.009	ns	ns	0.006
	Day 3	165.1 (142.8-236.5) ⁺	257.5 (216.9-372.1) [†]	202.2 (155.1-294.5) [*]	ns	ns	ns	ns

⁺n=13, ^{*}n=12, [□]n=11, [#]n=10, [‡]n=9, [∞]=8, ^Δn=7, [¥]n=6, [†]n=5, ^Σ=4, ns= not significant

Table 11.27: Comparisons of research measurements (median, IQR) between the NeoAdapt 1, 2 and 3 term cohorts

Plethysmographic Measure	Day	NeoAdapt 1 (A)	NeoAdapt 2 (B)	NeoAdapt 3 (C)	p-value	Pairwise Comparison (adjusted p value)		
						A vs B	A vs C	B vs C
SpO2 (%)	Day 1	100 (96-100) [‡]	97 (94-99) [†]	98 (91-100) [†]	ns	ns	ns	ns
	Day 2	99 (98-100) ⁺	98 (95-100) ^Δ	97 (95-99) [□]	ns	ns	ns	ns
	Day 3	98 (97-99) ⁺	94 (93-99) [†]	98 (97-99) [*]	ns	ns	ns	ns
mPVI (%)	Day 1	19.8 (14.8-29.3) ^Δ	18.3 (15.0-27.2) [†]	16.9 (11.8-25.8) [†]	ns	ns	ns	ns
	Day 2	15.8 (14.9-17.9) [□]	16.7 (12.5-22.3) ^Δ	12.4 (9.7-17.5) [‡]	ns	ns	ns	ns
	Day 3	10.9 (8.1-15.4) [□]	8.5 (6.6-15.7) [†]	12.9 (7.9-17.4) [*]	ns	ns	ns	ns
mPTT	Day 1	0.27 (0.22-0.29) ^Δ	0.30 (0.25-0.33) [†]	0.34 (0.28-0.38) [†]	ns	ns	ns	ns
	Day 2	0.30 (0.24-0.31) [*]	0.29 (0.25-0.33) ^Δ	0.35 (0.33-0.36) [‡]	0.008	ns	0.02	0.03
	Day 3	0.28 (0.27-0.29) [*]	0.29 (0.23-0.31) [†]	0.32 (0.28-0.34) [*]	0.04	ns	0.05	ns
NmPTT	Day 1	0.57 (0.52-0.62) ^Δ	0.59 (0.56-0.81) [†]	0.55 (0.51-0.55) [†]	ns	ns	ns	ns
	Day 2	0.55 (0.51-0.63) [*]	0.64 (0.61-0.70) ^Δ	0.54 (0.52-0.60) [‡]	0.02	0.04	ns	0.04
	Day 3	0.59 (0.51-0.65) [*]	0.52 (0.49-0.68) [†]	0.59 (0.54-0.61) [*]	ns	ns	ns	ns
Trans mPTT	Day 1	3.7 (3.5-4.5) [†]	3.4 (3.0-4.0) [†]	2.9 (2.6-3.6) [†]	ns	ns	ns	ns
	Day 2	3.3 (3.2-4.1) [*]	3.5 (3.3-3.9) ^Δ	2.9 (2.8-3.1) [‡]	0.008	ns	0.02	0.03
	Day 3	3.5 (3.4-3.7) [*]	3.5 (3.2-4.2) [†]	3.1 (2.9-3.5) [*]	0.04	ns	0.05	ns

⁺n=13, ^{*}n=12, [□]n=11, [#]n=10, [‡]n=9, [∞]n=8, ^Δn=7, [¥]n=6, [†]n=5, ^Σn=4, ns= not significant

Table 11.27: Comparisons of research measurements (median, IQR) between the NeoAdapt 1, 2 and 3 term cohorts

Clinical & Biochemical Measures	Day	NeoAdapt 2	NeoAdapt 3	p-value
Urine output (mls/kg/hr)	Day 1	0.7 (0.3-1.00) ⁺	0.75 (0.0-1.9)*	ns
	Day 2	1.7 (0.5-3.4) ⁺	3.4 (2.0-8.5)*	ns
	Day 3	2.5 (0.5-3.4) ^Δ	5.4 (3.7-8.7) [¥]	0.01
pH	Day 1	7.29 (7.01-7.32) [‡]	7.30 (7.18-7.36)*	ns
	Day 2	7.39 (7.36-7.43) ^Δ	7.35 (7.33-7.37)*	0.05
	Day 3	7.38 (7.35-7.48) [‡]	7.35 (7.31-7.36) [#]	0.006
Base excess (mmol/l)	Day 1	-4.0 (-8.0- -1.7) [‡]	-3.6 (-9.3- -1.3)*	ns
	Day 2	-1.0 (-5.6-0.9) ^Δ	-0.6 (-4.7-2.2)*	ns
	Day 3	1.2 (-0.6-2.7) [‡]	-0.2 (-2.2-2.0) [#]	ns
Lactate (mmol/l)	Day 1	3.7 (2.0-4.6) [‡]	3.2 (1.4-8.1)*	ns
	Day 2	2.0 (1.8-4.6) ^Δ	2.3 (1.4-3.0)*	ns
	Day 3	1.5 (1.3-2.0) [‡]	1.30 (1.0-2.3) [#]	ns

*n=14, #n=13, ¥n=12, ‡n=7, Δn=6, +n=5, ns= not significant

Table 11.28: Comparisons clinical and biochemical (median, IQR) measurements between the NeoAdapt 2 and 3 term cohorts

Respiratory support	Cohort	Day 1	Day 2	Day 3	Cohort comparison (p-value)		
					Day 1	Day 2	Day 3
None n (%)	NeoAdapt 2	1 (12)	2 (29)*	4 (57)*	0.04	ns	ns
	NeoAdapt 3	5 (36)	4 (29)	4 (31) [#]			
Nasal cannula	NeoAdapt 2	0 (0)	0 (0)*	0 (0)*			
	NeoAdapt 3	2 (14)	1 (7)	1 (8) [#]			
HFFNC n (%)	NeoAdapt 2	5 (63)	4 (57)*	2 (29)*			
	NeoAdapt 3	1 (7)	3 (21)	3 (23) [#]			
Invasive ventilation n (%)	NeoAdapt 2	2 (25)	1 (14)*	1 (14)*			
	NeoAdapt 3	6 (43)	6 (43)	5 (38) [#]			

[#]n=13, *n=7

Table 11.29: Comparisons of respiratory management between the NeoAdapt 2 and 3 term cohorts; data displayed as n (%)

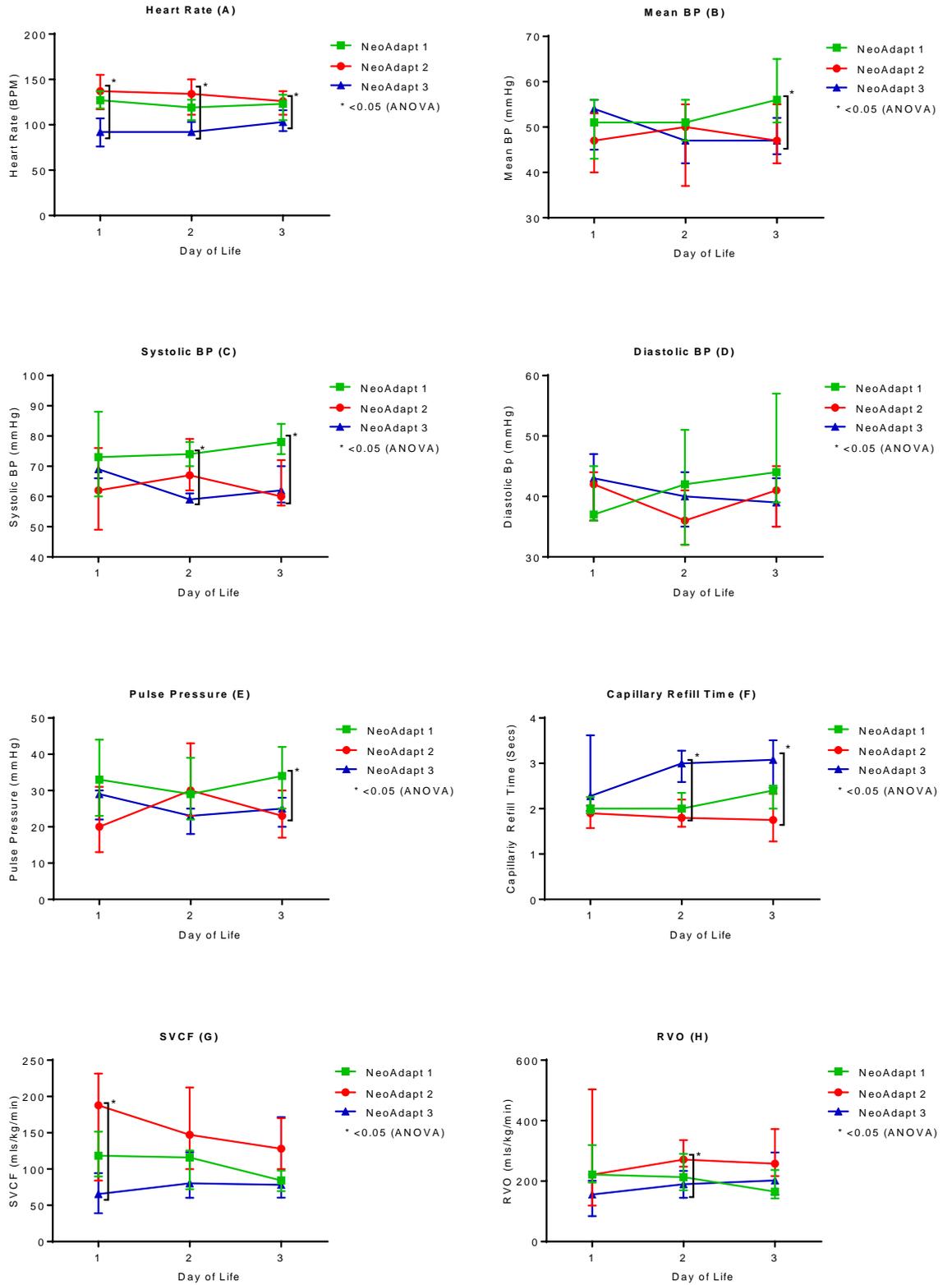


Figure 11.18: Daily ANOVA comparisons of Heart rate (A), Mean BP (B), Systolic BP (C), Diastolic BP (D), Pulse pressure (E), Capillary refill time (F), SVCF (G) and RVO (H) between neonates the NeoAdapt 1, 2 and 3 term cohorts

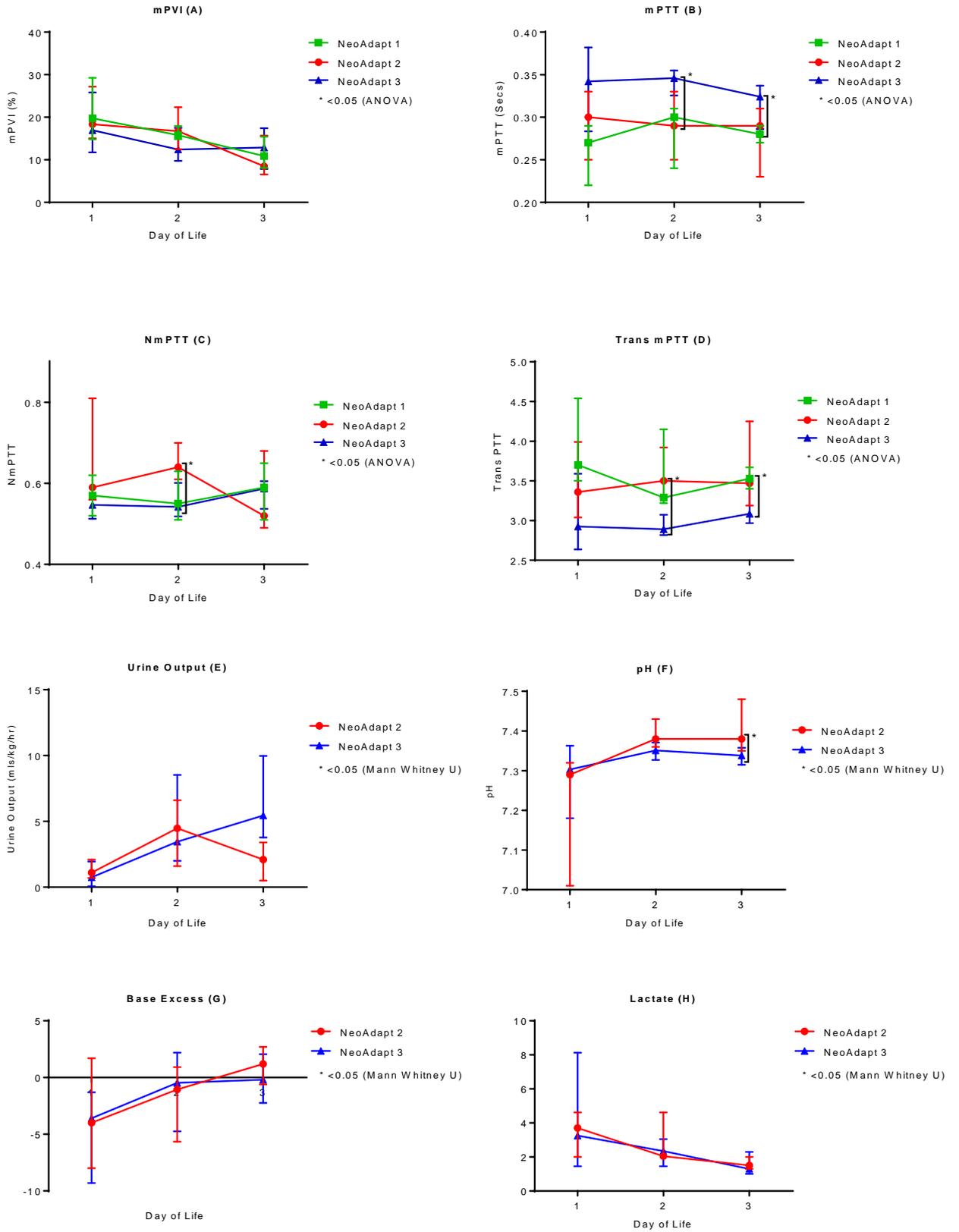


Figure 11.19: Daily comparisons of mPVI (A), mPTT (B), NmPTT (C), Trans mPTT (D), Urine output (E), pH (F), Base excess (G) and Lactate (H) between neonates in the NeoAdapt 1, 2 and 3 term cohorts

11.2 Clinical Studies: Plethysmographic & echocardiographic measurement repeatability

11.2.1 Plethysmographic measurements

The demographic details of subjects included in the intra- and inter-observer repeatability calculations are outlined in Table 11.30. The repeatability for all the plethysmographic measurements whether performed within or between observers, was excellent (Table 11.31). The least repeatable measure was the inter-observer repeatability of mPVI (13.21%), with the BA plots indicating greater spread (poorer repeatability) at lower mPVI values (Fig 11.20), both for inter- and intra-observer comparisons.

Measure	Mean GA Weeks (Range)	Mean Birth weight Grams (Range)	Mean Age at Recording Hours (Range)
Intra-observer plethysmographic repeatability subject characteristics			
mPTT (Secs)	36 (33-42)	2742 (1550-4430)	36 (5-84)
NmPTT	36 (33-41)	2718 (1550-4366)	36 (5-84)
mPVI (%)	36 (33-41)	2655 (1150-4430)	36 (5-84)
Intra-observer plethysmographic repeatability subject characteristics			
mPTT (Secs)	36 (33-41)	2605 (1560-4240)	39 (5-93)
NmPTT	36 (33-41)	2605 (1560-4240)	39 (5-93)
mPVI (%)	36 (33-41)	2602 (1560-4240)	38 (5-84)

Table 11.30: Intra- and Inter-observer repeatability subject characteristics

Measure	n	Mean bias	Standard deviation of bias	95% Limits of Agreement (LOA)	Repeatability Coefficient (RC)	Repeatability Index (RI)
Intra-observer plethysmographic trace repeatability analysis						
mPTT (Secs)	87	-0.0005	0.004	-0.009, 0.008	0.01	3%
NmPTT	87	-0.0003	0.01	-0.02, 0.02	0.02	3%
mPVI (%)	90	-0.09	0.59	-1.25, 1.06	1.16	5%
Inter-observer plethysmographic trace repeatability analysis						
mPTT (Secs)	53	-0.005	0.01	-0.03, 0.03	0.03	9%
NmPTT	53	-0.01	0.02	-0.05, 0.03	0.42	7%
mPVI (%)	55	0.24	1.38	-2.47, 2.95	2.71	13%

Table 11.31: Intra- and Inter- observer plethysmographic trace repeatability analysis

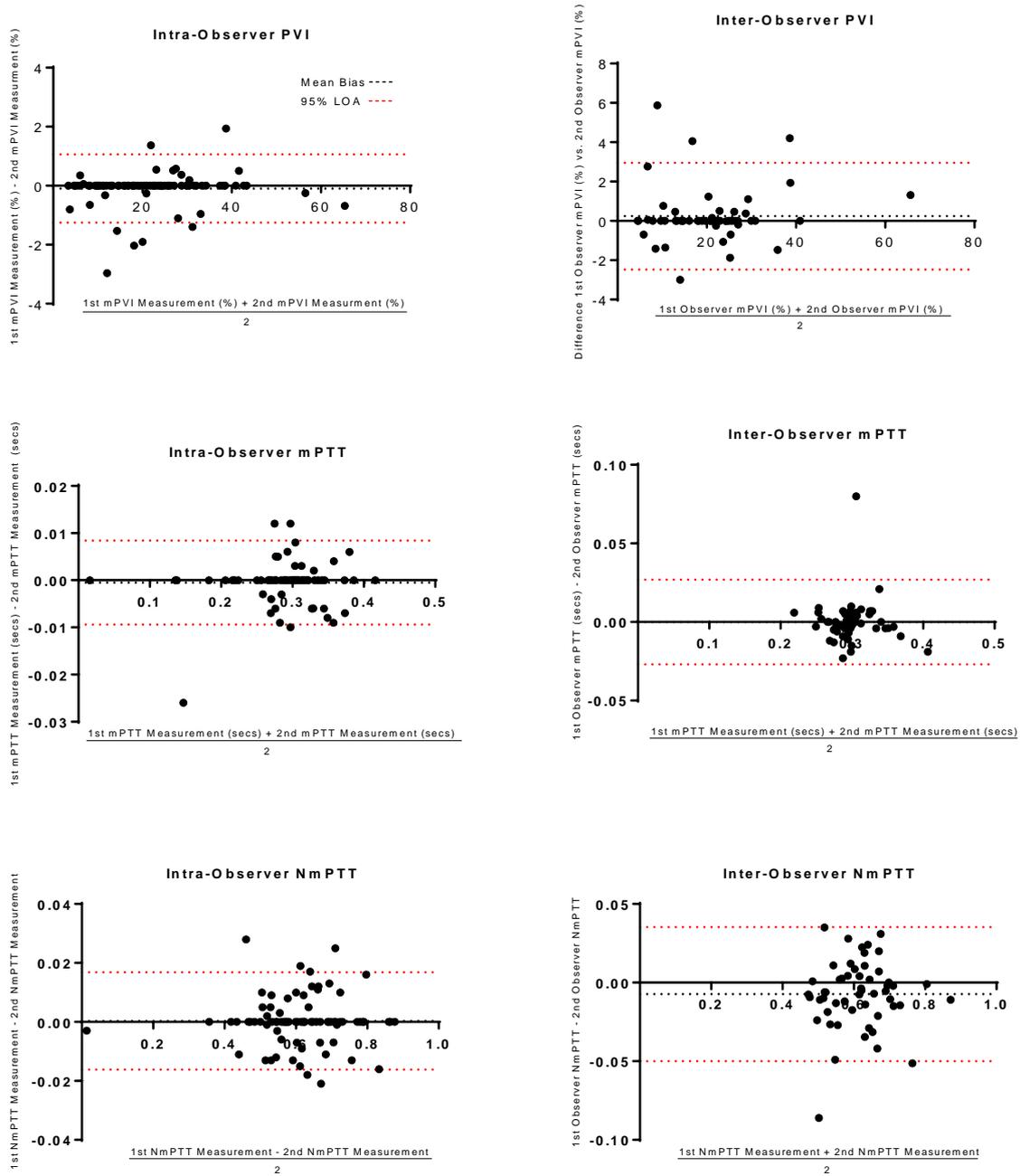


Figure 11.20: Bland-Altman plots of intra- and inter-observer repeatability of plethysmographic traces

11.2.2 Echocardiographic measurements

The demographic details of the subjects included in the intra- and inter-observer reliability are outlined in Table 11.32. It should be noted that a total of 8 recordings were excluded from the intra-observer echocardiographic reliability analysis due to poor image acquisition or problems in accessing images.

Mean GA Weeks (Range)	Mean birth weight Grams (Range)	Mean age at recording Hours (Range)
Intra-observer echocardiographic repeatability subject characteristics		
37 (33-42)	3010 (1650-4430)	38 (9-93)
Inter-observer echocardiographic repeatability subject characteristics		
36 (33-41)	2628 (1120-4430)	32 (5-71)

Table 11.32: Echocardiographic Intra- and Inter observer repeatability subject characteristics

Table 11.33, Figure 11.21 and Figure 11.22 shows that the repeatability index of both intra- and inter-observer SVC diameter measurements was higher than corresponding SVC VTi measurements. With regards to RVO measurements both intra- and inter-observer RVO diameter measurements was lower than the corresponding RVO VTi measurements. As might be expected, the repeatability indices of both of the final flow measurements (SVCF and RVO) are higher than those of each of their contributing diameter and velocity measurements. Furthermore, the repeatability index of RVO diameter and VTi were less than that of SVCF. These results are therefore responsible for the overall intra- and inter-observer repeatability of SVCF being higher than RVO (40% and 64% vs 26% and 49% respectively).

Intra-observer echocardiographic repeatability analysis						
Measure	n	Mean Bias	SD of Bias	95% LOA	RC	RI
SVC diameter (cm)	56	-0.01	0.08	-0.17, 0.15	0.16	33%
SVC VTi (cm)	57	0.27	2.41	-4.45, 4.99	4.70	30%
SVCF (mls/kg/min)	56	-0.52	25.3	-50.1, 49.1	49.6	41%
RVO diameter (cm)	54	0.005	0.08	-0.07, 0.08	0.16	19%
RVO VTi (cm)	54	-0.13	1.20	-2.49, 2.22	2.35	23%
RVO (mls/kg/min)	54	2.70	36.2	-68.3, 73.7	70.9	31%
Inter-observer echocardiographic repeatability analysis						
SVC diameter (cm)	24	0.04	0.07	-0.10, 0.19	0.15	33%
SVC VTi (cm)	25	15.6	2.37	-5.78, 3.49	4.63	30%
SVCF (mls/kg/min)	24	13.0	40.3	-66.1, 92.0	79.1	63%
RVO diameter (cm)	25	0.03	0.08	-0.13, 0.19	0.16	21%
RVO VTi (cm)	25	0.58	1.36	-2.1, 3.2	2.66	26%
RVO (mls/kg/min)	25	24.7	62.8	-98.4, 147.8	123.1	51%

Table 11.33: Intra- and inter-observer echocardiographic measurement repeatability analysis

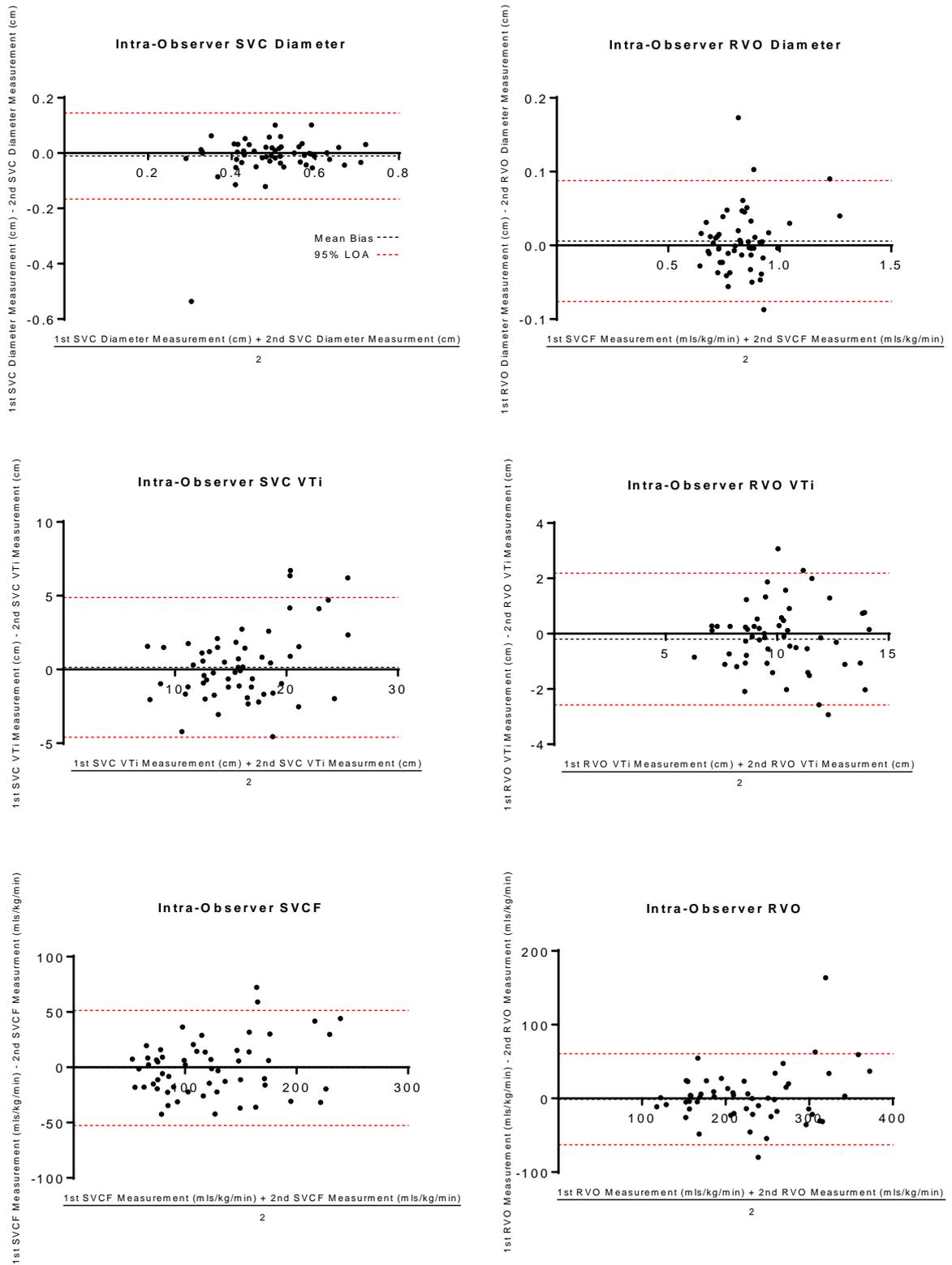


Figure 11.21: Bland-Altman plots of intra-observer repeatability of echocardiographic measurements

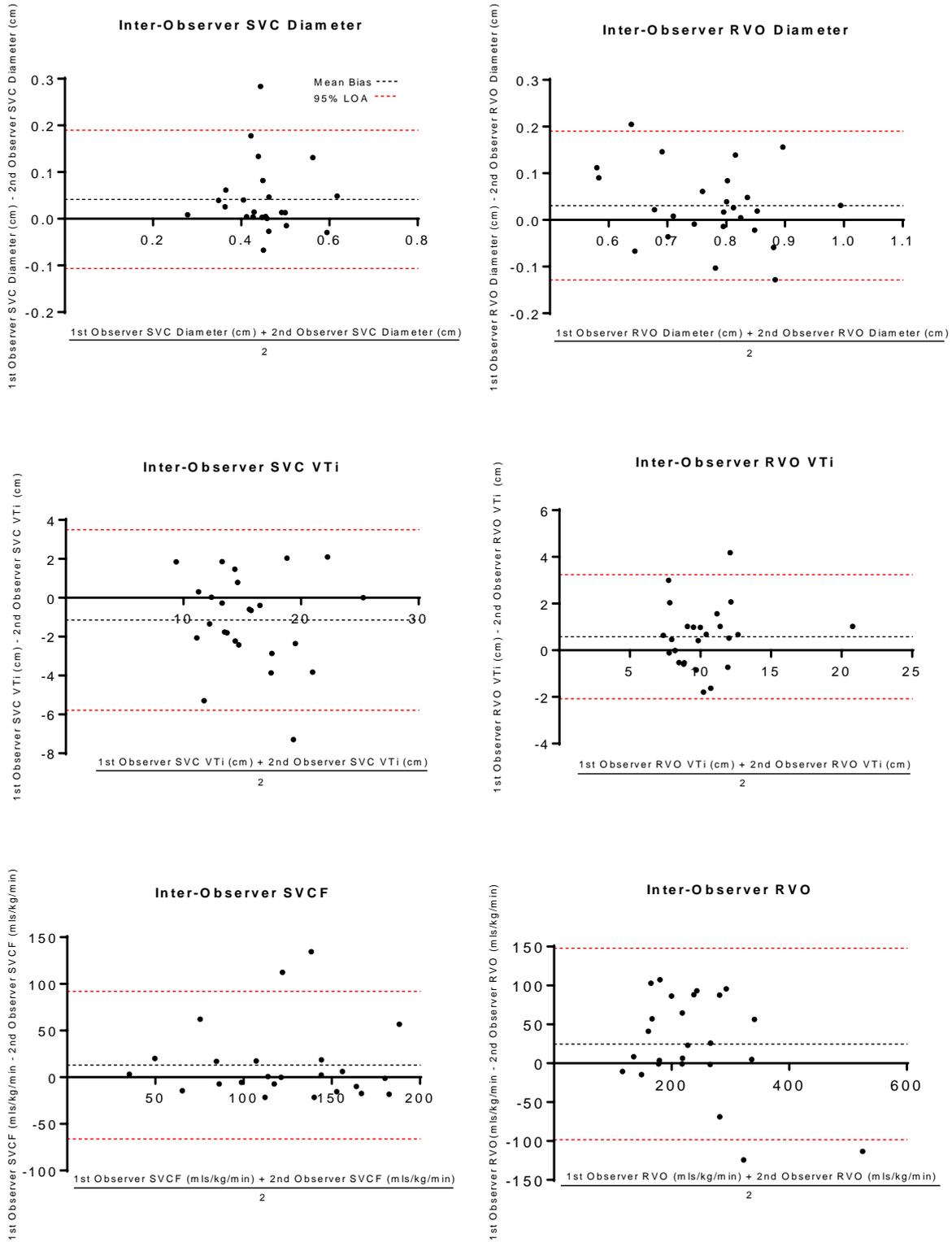


Figure 11.22: Bland-Altman plots of inter-observer repeatability of echocardiographic measurements

11.3 Summary of findings

Below is a summary of the significant results found in each of the clinical studies performed.

11.3.1 NeoAdapt 1

The longitudinal analysis of the whole cohort revealed increases in measures of blood pressure and decreases in mPVI. When the cohort was split according to GA, over the first three days of life infants of late prematurity exhibited increases in measures of blood pressure with concurrent significant decreases in mPTT and mPVI. No differences are seen any research measurement in term infants over the first three days of life apart from an isolated decrease in mPVI between day 2 and 3 of life.

When comparisons of research measurements were made between these two cohorts, infants of late prematurity were found to have higher measurements of systemic blood flow, heart rate, and lower measurements of blood pressure. They were also found to have significantly longer mPTT on day 1 of life, with NmPTT also being significantly longer on day 1 and 2 of life.

11.3.2 NeoAdapt 2

Longitudinal analysis of the whole cohort showed significant increases in measures of blood pressure over the first three days of life, with decreases in SVCF between day 2 and 3. Significant improvements (i.e. measurements returned to normal ranges) in pH, lactate, base excess and urine output were also seen over the first three days of life

Pairwise comparisons in late preterm infants revealed increases in systolic blood pressure between day 2 and 3 of life with concurrent improvement in pH and lactate. The same analysis in term infants revealed improvements and normalisation in pH, base excess and lactate over the first three days of life.

When research measurements were compared between these cohort's lactate, on day 1, was found to be higher in term neonates compared to late preterm infants.

When considering the effect of treatment for circulatory failure on research measures a reduced pulse pressure was found in those infants who received treatment for circulatory failure.

No differences were found with regards to research measures in those infants who were found to have cerebral injuries on cranial ultrasound and compared with those who remained injury free.

11.3.3 NeoAdapt 3

Over the first three days of life longitudinal analysis revealed significant increases in capillary refill time as well as improvements in base excess, lactate, pH and urine output.

Those infants who did receive treatment for circulatory failure were found to have significantly increased lactate levels.

Significantly differences in research measures were found in infants who were found to have normal vs. abnormal MRI brain scans.

11.3.4 Interstudy comparisons

Late preterm infants who are considered to be healthy when compared to those requiring intensive care, were found to have significantly reduced values for mPTT and mPVI on day 2 to 3 of life.

Comparisons of research measurements were performed between term neonates considered to be healthy, requiring intensive care and those receiving total body cooling. Significant differences in heart rate, blood pressure, SVCF, RVO, pH and measures of mPTT were found with cooled infants exhibiting reduced values for many of these measures.

11.3.5 Variability analysis

The repeatability and variability of plethysmographic traces was excellent whether performed by the same or different operator. Echocardiographic measures of systemic blood flow displayed poorer measures of repeatability and variability, although these values were better when sequential measures were performed by the same operator.

12 Discussion

These are the first set of studies that use novel non-invasive biomarkers to assess cardiovascular adaptation and circulatory failure in late preterm and term neonates. The strengths of this thesis include the provision of novel reference values for these echocardiographic and plethysmographic biomarkers. Furthermore, it also describes distinct patterns of cardiovascular adaptation depending on a neonate's GA or pathologies encountered.

12.1 NeoAdapt 1

12.1.1 Cardiovascular adaptation: whole cohort

Examining the NeoAdapt 1 cohort as a whole the natural increase in SVR that occurs in normal cardiovascular adaptation after birth is represented by increase in mean, systolic and diastolic blood pressure over the first three days of life. This increase is in keeping with what has been found previously within the literature.¹⁶⁷ When looking at the cardiovascular system as an analogue of Ohm's law in order for blood pressure to increase despite falls in cardiac output or systemic blood flow there must be an increase in SVR. For this reason, the observed increase in blood pressure is a result of increases in SVR as there were trends for decreases in SVCF. This decrease is explained by the natural diuresis seen in the 24-72 hours of life leading to a reduction in the blood volume of a neonate, which in turn reduces both the diameter of the pliable SVC and SVCF.^{300,305,350} No particular trend for RVO was noted over the first three days of life:- previous literature investigating RVO over the first 48 hours in healthy term infants exhibit similar findings.³⁵¹

Interestingly despite this increase in SVR, and thus peripheral vasoconstriction, there were no changes in the capillary refill time. One might expect an increase in the capillary refill time. These observations may relate to the operator dependent nature of this measurement.¹⁸⁸ However this is should have been minimised in the presented study as the same observer performed the observation on each of the infants.

With regard to plethysmographic traces only significant decreases were noted in mPVI when paired comparisons were performed in the whole cohort.

Physiologically this measure is affected by preload on the heart and also lung distension or expansion.³²³ As these infants did not receive any fluids to increase preload and in view of the natural diuresis that occurs in neonates over the first days of life, it is likely that this observation is due to increasing lung expansion and increasing lung compliance. The median value for mPVI in spontaneous breathing neonates was 20.6% which is similar to that quoted for commercially available PVI measurement devices from a similar cohort of 242 term newborns on the first day of life.³¹⁸

Measurements of pulse transit time did not change throughout the first three days of life. These are novel data and this measurement has not been investigated in newborn term and late preterm infants. A study by Galland *et al.* found that mean measure of pulse transit time was either 0.139 or 0.140 seconds depending on the sleep state in 20 infants aged greater than 9 weeks.³²⁶ The reference values (median of 0.281 seconds over the first three days of life) gained in our study indicate that the pulse transit time may not be as short in newborn infants. In the context of transitional circulation this could be due to the natural increase in SVR not having been established. It must be noted that the pulse transit time was measured at the base of the plethysmographic trace in the study by Galland *et al.*³²⁶ Therefore the pulse transit time measurements are likely to be shorter due to this discrepancy.

12.1.2 Cardiovascular adaptation: Late preterm vs. Term infants

The results of these studies challenge the assumption that cardiovascular adaptation occurs in the same manner in all infants aged above 33 weeks. When the NeoAdapt 1 cohort of infants is divided according to GA (33-<37-weeks and ≥37-weeks GA) it indicates that cardiovascular adaptation occurs differently in each group. Infants aged <37-weeks GA exhibit significant daily increases in mean, systolic and diastolic blood pressure. This is coupled with significant decreases seen in mPTT and lengthening of Trans mPTT between days two and three of life. Such significant changes are not seen in the ≥37-week cohort, which may indicate that the natural cardiovascular adaptations occur early and rapidly in term infants, but later and more gradually in neonates <37-weeks. Both blood pressure and measures of pulse transit time are affected by vessel diameter and therefore the changes seen in both measures represent an increase in SVR over

the first three day of life. The fact that these increases are not seen in the ≥ 37 -week cohort could mean that the SVR increases within the first day in these infants. Explanations for this difference include that due to a reduced number of adrenoceptors seen in younger preterm infants at birth their vasculature is less responsive to the surges in catecholamines seen at birth.³⁸

Similarly, the significant decrease seen in mPVI in the < 37 -week cohort over the first three days of life is not reflected in the ≥ 37 -week cohort, although a significant decrease in mPVI is noted between day 2 and 3 of life. Due to the natural diuresis, preload would be expected to decrease over the first three days of life in both groups. The difference in mPVI between the cohorts is likely to reflect differences in respiratory mechanics. A study of 85 infants comparing the lung function of term and late-preterm infants found that the latter group had less compliant (i.e. stiffer) lungs at birth.³⁵² This reduced compliance leads to greater changes in intrathoracic pressure with each breath. Thus increasing mPVI in this cohort on day 1, which then decreased by day 3 of life as lung compliance increases.

Table 12.1 and Figure 12.1 compares the values for systemic blood flow gained in the NeoAdapt 1 to those of previously studied cohorts.²⁷⁸

SVCF (mls/kg/min)			
Cohort	<24 Hours	24-48 Hours	>48 Hours
Term Infants ³⁵³	68 (32-166)	89 (54–167)	60 (41–167)
NeoAdapt 1 (≥ 37 -weeks GA)	118 (89-151)	115 (72 -125)	84 (69-97)
Preterm (< 29 -weeks GA) ³⁵⁴	81 \pm 26	96 \pm 26	106 \pm 30
NeoAdapt 1 (33- < 37 -weeks GA)	149 (128-177)	132 (105-166.)	128 (96-150)
RVO (mls/kg/min)			
Term Infants ^{351,355}	216 (122-338)	207 \pm 47	-
NeoAdapt 1 (≥ 37 -weeks GA)	221 (195-319)	213 (169-290)	165 (142-236)
Preterm (< 29 -weeks GA) ³⁵⁴	264 \pm 90	312 \pm 83	360 \pm 112
NeoAdapt 1 (33- < 37 -weeks GA)	262 (240-329)	296 (249-368)	283 (215-357)

Table 12.1: Daily systemic blood flow values in the NeoAdapt 1 study compared with previous literature; data displayed as mean (standard deviation) or median (IQR)

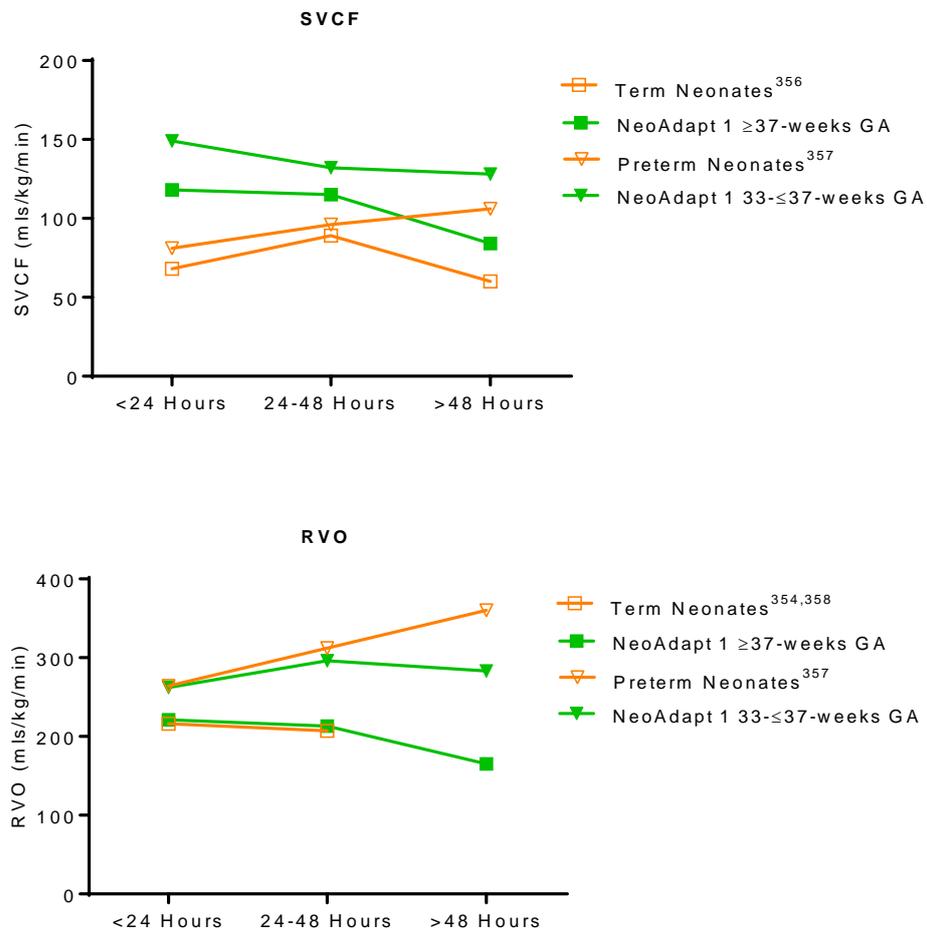


Figure 12.1: Measures of systemic blood flow in the NeoAdapt 1 study compared to previous literature

Late preterm neonates aged 33-<37-weeks exhibited significantly higher measures of SVCF over the transitional circulation compared to studies in term (n=13) and preterm infants less than 29 weeks (n=68);^{353,354} these are novel values for infants aged between 33-<37-weeks GA. These findings, coupled with the longer mPTT and NmPTT values, indicate that in late preterm neonates SVR increases more gradually than term infants. Therefore, in order to compensate for this reduced SVR late preterm neonates increase their systemic blood flow as a compensatory mechanism in order to maintain adequate end organ perfusion. Heart rate was also significantly higher in the 33-<37-week cohort compared to the ≥37-week cohort and is likely to be part of the mechanism for achieving the higher measure of systemic blood flow in this cohort. This supports prior research that

found no significant differences in echocardiographic markers of myocardial contractility (mean velocity of fiber shortening and end systolic wall stress) in 22 preterm and 23 term infants thus indicating that cardiac output in neonates is dependent on heart rate.^{93,94} It should be noted that the discrepancy in SVCF could be due to the timing of the assessment. In the NeoAdapt 1 study the median time for SVCF assessment was at 14 hours of age compared to around 5 hours in the study by Groves *et al.* in 13 healthy term neonates which is typically the time when the nadir in systemic blood flow is seen.^{300,353}

Figure 12.1 shows that the measurements for RVO in both the NeoAdapt cohorts aged ≥ 37 -weeks exhibit trends similar to those previously quoted in term infants.^{351,355} RVO is similar in neonates aged 33- <37 -weeks and <29 weeks GA until day three of life. The increased values for RVO seen on day three of life in neonates <29 weeks could be due to the increased shunting of blood through the PFO that occurs in this cohort increasing preload on the right ventricular and thus RVO.³⁵⁶

12.1.3 Correlation analysis

With regards to the Spearman rank correlations, none of these were consistent across each population or time period studied. It is important to note that there was no correlation between any measure of blood pressure and any measurement of mPTT. Previously studies have described such a relationship in infants and adults.³²⁵ The lack of such a finding may be due to rapidly changing nature of the neonate's circulation. However, it might be expected that positive correlations between these two biomarkers would have been observed. No correlation was found between SVCF and RVO. Such a finding was not present in any of the populations studied. Whilst previous research has found correlations between these measures, they were only found in preterm infants between 6 to 12 hours of life.^{297,298} In these studies at 24 hours no such correlation was observed. The median age 21 hours for all echocardiographic measures in the NeoAdapt 1 cohort could account for these results. Furthermore one study in 40 low birth weight neonates at 19 hours of age found no correlation between SCVF and RVO, attributing the lack of correlation to the shunting that is seen at atrial level influencing RVO.³⁵⁷

12.2 NeoAdapt 2

12.2.1 Cardiovascular adaptation

Similarly, to the healthy neonates, in those requiring intensive care the mean and systolic blood pressure increased in the whole cohort over the first three days of life. Presumably this is due to increases in SVR. However, we did not see the same shortening of measures of mPTT and NmPTT (and thus lengthening of Trans mPTT) that one may expect with increases in SVR. However, as the SVCF decreases between day 2 and 3 thus it would appear to suggest that the increase in SVR must be responsible for the resulting increase in blood pressure. Interestingly when the cohorts are split into according to GA the only significant difference was that in neonates aged <37-weeks GA systolic blood pressure increased between day 2 to 3 of life. No significant differences were found in longitudinal analysis of the ≥37-weeks GA cohort. When both research measures were compared between cohorts only lactate was found to be significantly higher day 1 in neonates ≥37-weeks.

Studies in term and premature neonates have shown that higher initial lactate levels are prognostic of poor outcomes in neonates.^{217,358} Our results indicate that the more mature cohort perhaps was sicker at birth. However, with a lack of differences between the cohorts for the performed research measurements this would indicate that there was no difference in cardiovascular adaptation between the cohorts.

One reason for the lack of a difference in the measures of SVR between the cohorts could be the fact the majority were admitted with sepsis (92%). The increase in hydrogen ions in an increasingly acidic environment that sepsis promotes activates the potassium ATP channels in vascular smooth muscle promoting vasodilation.³⁵⁹ Endothelial release of nitric oxide through inflammatory cytokines and tumour necrosis factor alpha and depletion in vasopressin will also contribute to this vasodilation.^{360,361} Thus neonates in the NeoAdapt 2 cohort will need to increase systemic blood flow in order to maintain end organ perfusion. The novel daily median SVCF and RVO values gained for all of the cohorts are higher than that quoted in the literature for healthy term infants and those less than 29 weeks GA (Table 12.2 and Figure 12.2).²⁷⁸ A study by de Waal and Evans found both SVCF and RVO to be increased in preterm infants (<29 weeks GA)

with sepsis at 72 hours of age.²⁹⁹ A similar study in 52 neonates with a median age of 31 weeks found increased RVO flows (386mls/kg/min) at 96 hours of age.³⁶² Interestingly the study by de Waal found SVR to be reduced in these infants, which may explain why measures of pulse transit time, in or infants, did not shorten during the first three days of life.

SVCF (mls/kg/min)					
Cohorts	<24 Hours	24-48 Hours	>48 Hours	>72 Hours	96 hours
Healthy Term ³⁵³	68 (32-166)	89 (54-167)	60 (41-167)	-	-
Preterm (<29 weeks GA) ³⁵⁴	81 ± 26	96 ± 26	106 ± 30	-	-
Septic Preterm (<29 weeks GA) ²⁹⁹	-	-	-	104 ± 39	-
NeoAdapt 2 (≥37-weeks GA)	187 (84-231)	147 (99-212)	128 (99-170)	-	-
NeoAdapt 2 (33-<37-weeks GA)	114 (105-178)	166 (130-239)	146 (87-190)	-	-
RVO (mls/kg/min)					
Healthy Term ^{351,355}	216 (122-338)	207 ± 47	-	-	-
Preterm (<29 weeks GA) ³⁵⁴	264 ± 90	312 ± 83	360 ± 112	-	-
Septic Preterm (<29 weeks GA) ²⁹⁹	-	-	-	441±164	-
Septic Preterm (31 weeks GA) ³⁶²	-	-	-	-	386 (204-393)
NeoAdapt 2 (≥37-weeks GA)	221 (119-503)	271 (247-335)	257 (216-372)	-	-
NeoAdapt 2 (33-<37-weeks GA)	321 (265-337)	333 (275-352)	341 (274-373)	-	-

Table 12.2: Comparison of measurements of systemic blood flow in healthy and neonates with sepsis; data displayed as mean (standard deviation) or median (IQR)

When looking at the pairwise comparisons of RVO values they did not change throughout the study period. The study by de Waal found that in infants who did not subsequently survive RVO decreased by up to 50%.²⁹⁹ Given that all of the included infants in the NeoAdapt 2 study survived during study period suggests they were all able to increase and maintain their cardiac output throughout the transitional circulation complicated by infection.

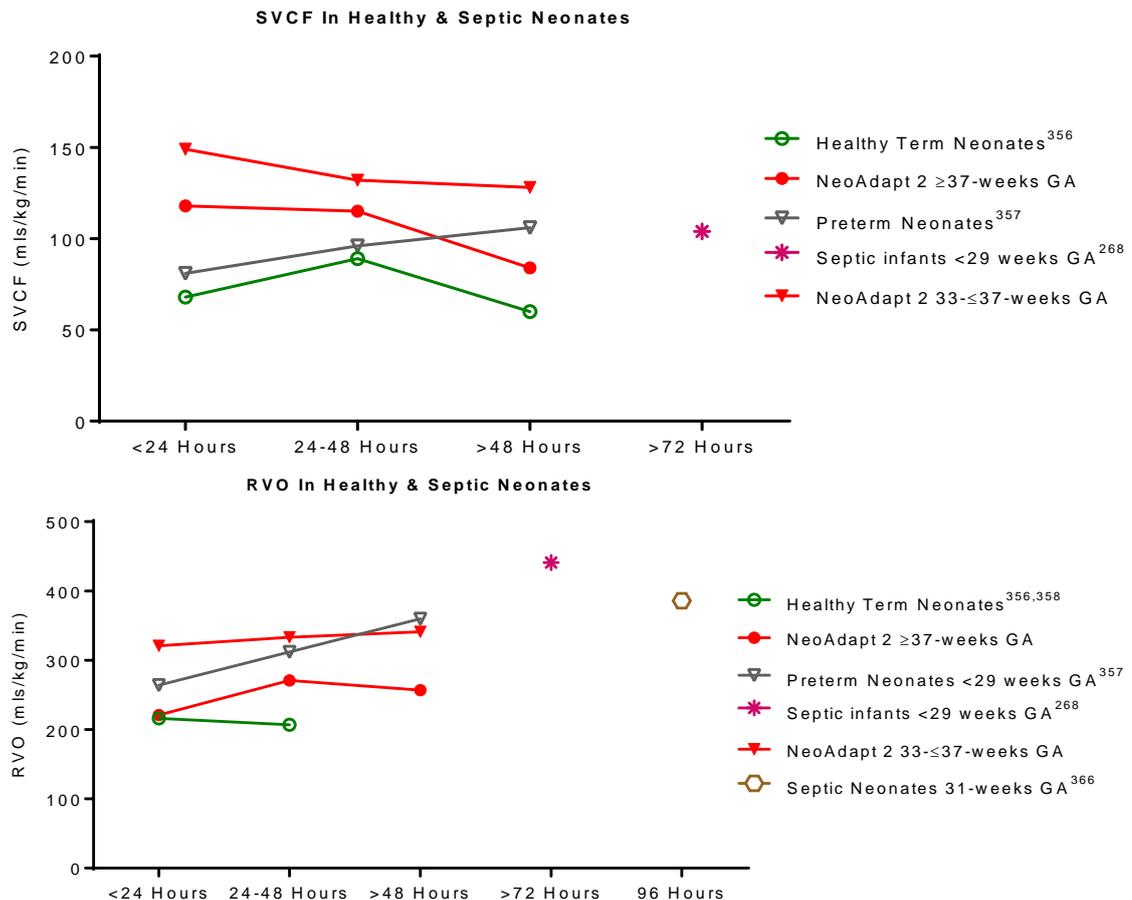


Figure 12.2: Measures of systemic blood flow from the NeoAdapt 2 cohort compared to previous literature

With regards to clinical and biochemical measures urine output significantly increases over the first three days of life reflecting the natural neonatal diuresis.³⁰⁵ pH, base excess and lactate all significantly improved over this time period, reflecting the natural improvement in perfusion and renal function over the 3 days of life.

12.2.2 Treatment for circulatory failure

The pulse pressure was significantly reduced in neonates who received treatment for circulatory failure. Pulse pressure is reduced by either a decrease in stroke volume or increased wall compliance in the aorta. As trends for increased SVCF and RVO were also found in this group, the compliance of the large arterial vessels must increase in response to treatment for circulatory failure. This is backed up by animal research showing that the compliance of the aorta increases during cardiovascular treatment such as dobutamine.^{363,364} It is an interesting

finding which could indicate that pulse pressure may provide information on the behaviour of the large vessels in the arterial tree during circulatory failure.

Trends for higher mPVI values were found in the treated group. Prior research has found that PVI decreases in response to fluid therapy.³¹⁹⁻³²¹ The discrepancy found in the presented data may be due to the fact that different treatment regimens were used on infants for circulatory failure. It could also be the influence of the respiratory system on mPVI. For example, it is possible that those infants who received treatment may have less compliant lungs leading to greater swings in transthoracic pressure and thus higher mPVI values.

It is important to note that these were pooled results from research measures on the first day of life as very few infants (n=2) were given any kind of treatment for circulatory failure after 24 hours of life. This may make the comparisons between the two groups inappropriate to make interpretations. Despite this trends for those infants treated with either fluids or inotropes having higher measures of systemic blood flow indicating that these treatments may have an effect on neonatal haemodynamics.^{92,302,362}

12.2.3 Neurological outcomes: Cranial ultrasound studies

There were no significant differences in the demographics or research measurements between infants who were found to have cerebral injuries on cranial ultrasound and those who did not. However, this may be difficult to infer as not all infants had cerebral ultrasound scans: this was at the discretion of the attending clinician. Interestingly there was no difference in rates of treatment with fluids or inotropes and cerebral ultrasound appearance. Whilst based on low numbers, this is similar to previous research that has yet to find that fluids or inotropes have an effect on neonatal outcomes.^{332,334} Whilst trends for lower measures of SVCF in neonates found to have cerebral injuries (median value 126.9 mls/kg/min) they were nowhere near the pathological levels seen in the preliminary studies performed in preterm infants (<41 mls/kg/min).³⁰⁰ It may also be that the other types of injuries, such as white matter injuries implicated in septic neonates, may not be readily detected on cranial ultrasound.^{365,366}

12.2.4 Correlation analysis

With regard to correlations between biomarkers, significant associations were found between mPTT and systolic & mean BP in the 33-<37-week group on day one. Such findings are consistent with previous studies looking at these association in infants aged as young as 9 weeks and adults.³²⁶⁻³³⁰ However this finding was not sustained through the three days that the measurements were made.

12.3 NeoAdapt 3

12.3.1 Cardiovascular adaptation

In neonates receiving total body cooling bedside parameters did not change throughout this intervention, and this reflects previous research findings.¹²¹ No changes were seen with regards to pulse transit time measurements in cooled infants. The effect of cooling therapy induces vasoconstriction and promotes increased vessel tone.¹²¹ All of the plethysmographic measures over the first three days of life were taken when infants were at therapeutic cooling temperature (33-34°C). Therefore, sustained increases in SVR would be expected throughout the time research measurements were made explaining such findings.

SVCF increased over the duration of cooling therapy. Kumagai *et al.* found similar increases in SVCF over this period of time in infants treated with selective head cooling for HIE.³³⁷ The median values gained for daily SVCF are similar to that quoted by Hochwald *et al.*^{304,337} Kumagai *et al.* SVCF values (Table 12.3 and Figure 12.3) were higher and might be accounted for by these infants having selective head cooling, thus decreasing the effects of cooling on cardiac output and on SVCF.¹²¹ Significantly lower values for SVCF were found in a study by Seghal *et al.* (34.5mls/kg/min) however these measurements were taken at 3-10 hours of age.³⁰³ This may have occurred during the nadir of blood flow seen at that time of life or represent reduced cerebral blood flow seen in the first phase of hypoxic injuries in neonates with HIE. RVO showed an increasing trend during our study period and represents novel values for this biomarker in the first three days of life in this population. The median values gained in our study on the first day of life (155.5mls/kg/min) were higher than the measurements taken by Seghal *et al.* (108mls/kg/min).³⁰³ This is likely to be a result of the timing of the measurements too. The median age for echocardiographic measurements was 16 hours of life in

our study. Thus the higher values for RVO may represent an improvement of cardiac function after the initial hypoxic injury represented in Seghal *et al.*'s results.³⁰³

SVCF (mls/kg/min)				
Cohort	<24 Hours	24-48 Hours	>48 Hours	>72 Hours
Seghal <i>et al.</i> ²⁷²	29 (13-96)			-
Kumagai <i>et al.</i> ³⁰⁶	79 ± 50	125 ± 55	130 ± 53	123 ± 50
Hochwald <i>et al.</i> ²⁷³	-	-	62 ± 16	90 ± 15
NeoAdapt 3	65 (39-94)	80 (60-123)	78 (60-171)	106 (55-138)
RVO (mls/kg/min)				
Seghal <i>et al.</i> ²⁷²	108 (45-246)			
NeoAdapt 3	155 (84-201)	189 (144-223)	188 (155-294)	167 (147-202)

Table 12.3: Measurements of systemic blood flow in cooled infants suffering from HIE; data displayed as mean (standard deviation) or median (IQR)

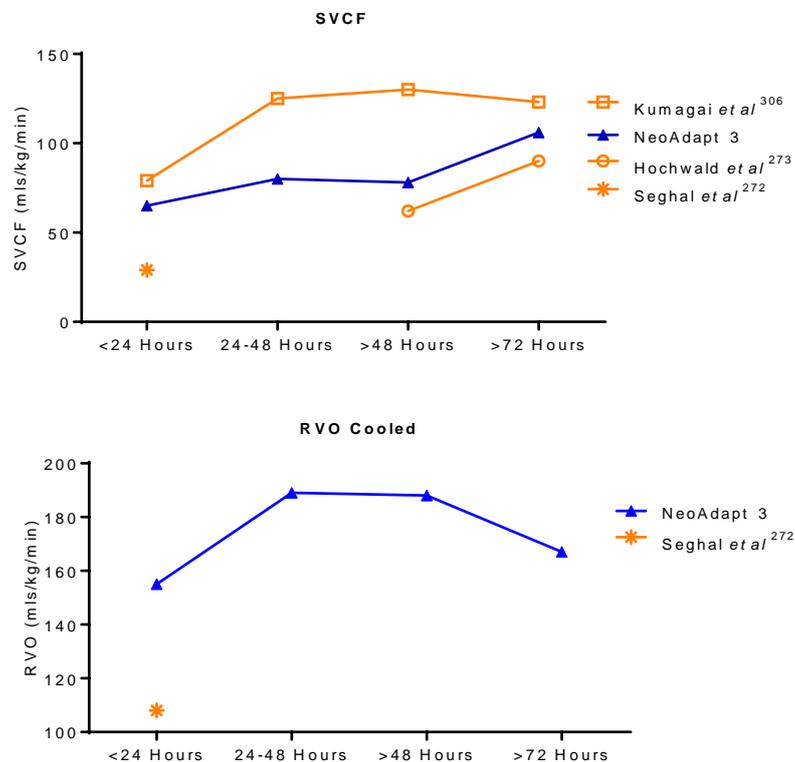


Figure 12.3: Comparison of measures of systemic blood flow in cooled infants suffering from HIE

Significant differences in RVO diameter was noted between day 3 of life and the rewarming phase of treatment. This was associated with a non-significant reduction in RVO. Cooling therapy is known to increase pulmonary vascular

resistance.³⁶⁷⁻³⁶⁹ Therefore during rewarming as pulmonary vascular resistance reduces the decreases in RVO diameter and thus RVO output may reflect the decreasing afterload on the right ventricle. Trends for increases in heart rate increased were noted.¹²² This is likely to be due to a reduction in the effect of cooling on slowing the depolarisation of the sino-atrial node and increasing the conduction of electrical impulses through the myocardium.^{121,370}

Urine output increases during the cooling period. This is likely to be due to a combination of a recovery from hypoxia induced kidney injury and also the natural physiological diuresis. Base excess, pH and lactate all improved over the first three days of life. This again presumably represents the recovery of the neonate from the hypoxic injury sustained at birth through improved end organ perfusion.

12.3.2 Treatment for circulatory failure

When comparing those infants who did and did not receive treatment for circulatory failure, the former had worse lactate levels. However, the median values for each cohort were 1.3 and 2.7, thus difference between these levels are likely to represent a statistical anomaly. Interestingly trends for shorter measures of pulse transit time were noted in the treated group, this is possibly due to the However, given the small numbers of infants included in this analysis all of the findings must be interpreted with caution.

12.3.3 Neurological outcomes: MRI studies

Infants with poor short term neurological outcomes, as defined by MRI appearance, had lower blood gas pH, base excess and longer capillary refill times over the first three days of life. Presumably the worsening pH and base excess reflect worse hypoxic injury and increased ischemia to end organs. It was noted that there was a non-significant trend for lower SVCF values in the normal MRI group compared to the abnormal group (Figure 12.4). Two previous studies noted that SVCF was also higher in those infants who had abnormal MRI findings.^{304,337} This finding represents a more severe HIE injury as the cerebral autoregulation may have been disrupted, increasing cerebral blood flow and thus SVCF. However, given the low numbers of infants included in the presented study such conclusions could be considered questionable.

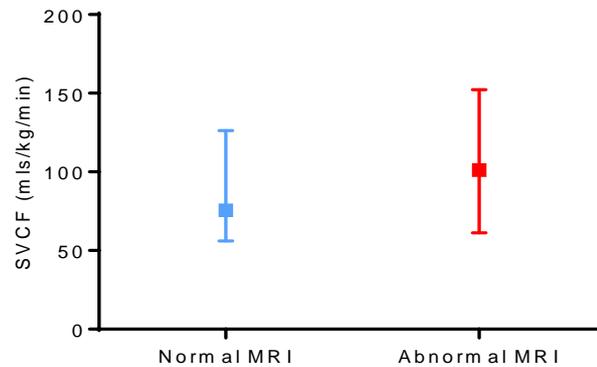


Figure 12.4: SVCF in infants with normal and abnormal MRI appearances (median, IQR)

12.4 Inter-study comparisons

When comparing research measurements between cohorts the presumptions about the different cardiovascular adaptation of each group of neonates appear to be supported.

12.4.1 Late preterm neonates

Measures of pulse transit time were significantly shorter on day 3 of life in well neonates compared to those requiring intensive care. This may be because the majority of infants in the NeoAdapt 2 cohort were septic and the release of inflammatory interleukins meant that the peripheral vasculature remained dilated in this cohort throughout the three days of life.³⁷¹ This is likely to be responsible for the trends for increased SVCF and RVO in the NeoAdapt 2 cohort as these neonates increased systemic blood flow to ensure end organ perfusion despite persisting vasodilation. It also indicates that whilst considered immature the myocardium of these infants was able to increase their contractility to respond to this pathological state.^{9,211} mPVI was found to be significantly reduced in the NeoAdapt 1 compared to NeoAdapt 2 cohort on day 2 and 3 of life. This may be due to the increased likelihood for the infants in the NeoAdapt 2 needing a variety of respiratory support (Table 11.11). This would therefore contribute to the variability of the blood volume within the thoracic cavity and therefore mPVI. The fact that some infants in the NeoAdapt 2 study also received fluid therapy, (which would tend to increase preload and hence reduce mPVI) indicates that mPVI is more likely to be a measure of lung expansion.

12.4.2 Term neonates

When comparing infants ≥ 37 -weeks GA the mean and systolic blood pressure was higher in the healthy cohort compared to neonates receiving intensive care or cooling with these difference becoming significant on day 2 and 3. The mPTT is shorter in healthy neonates and those receiving intensive care compared to cooled neonates. This is somewhat unexpected as it is known that cooling causes peripheral vasoconstriction, which should increase pulse transit times. However total body cooling results in the shifting of fluid from the intra- to the extra-vascular space in the periphery. This is a result of cooling causing increased hydrostatic pressure and permeability of the capillary vessels.^{121,372} This combined with reduced lymphatic and venous return results in haemoconcentration in the capillary vessels with increased blood viscosity. The increased viscosity of the blood will result in reduced blood flow in the periphery and therefore increase the measures of pulse transit time.^{121,372} This is supported by a study in 7 term infants receiving selective head cooling where reduced peripheral microvascular flow, as measured by side field dark imaging, was found when compared to control subjects.³⁷³ These changes are reflected clinically by prolonged capillary refill time in cooled neonates compared with the other cohorts.

The heart rate was significantly different between the three cohorts, and was slowest in cooled neonates. This is due to the effect on cooling of the depolarisation of the myocardium in those infants that are cooled.³⁷⁴ Also cooling increases relaxation time and ventricular stiffness increases.¹²¹ These alterations in myocardial function combined with the effect of the hypoxic injury will be responsible for the significant reduction in SVCF and RVO on day 1 and 2 of life, respectively, between the three cohorts. Hypothermia also reduces cerebral blood flow.¹²¹ As previously mentioned SVCF is thought to be representative of up to 80% of cerebral blood flow. Therefore, the reduction in SVCF is also due to the effect that the total body cooling has on the cerebral perfusion.

12.5 Variability of plethysmographic and echocardiographic measures

12.5.1 Plethysmographic measures

The repeatability of the values gained from plethysmographic traces was much better than those gained for echocardiographic measurements. This is because they are operator independent in terms of their recording. The greatest degree of

variation was seen with regard to mPVI measurements. This is likely to be due to interpretations about where the peaks and troughs on the filtered plethysmographic traces are gained. Whilst these indices could potentially be useful clinically they are currently time consuming and would be difficult to perform by the bedside. However, these problems could be overcome by developing specific software to analyse in real time. As mentioned previously there is a commercially available PVI measurement that is in clinical use which provides a constant measure of PVI. However the repeatability and variability of this device in neonates has been questioned.³²⁴ Automated PTT measurement has also already been incorporated into equipment for polysomnography and could be adapted for use in neonatal intensive care.

12.5.2 Echocardiographic measures

The intra- and inter-observer repeatability index of SVC was 41% and 62% respectively, which is similar to previously quoted values (31%, 53% & 104%), indicating reasonable repeatability of this technique.^{186,300,305,353} Similar to previous research the greatest degree of variability in SVCF appeared to be contributed by intra- and inter-observer diameter measurements. This likely to be due to the difficulty of acquiring good images of the SVC vessel in a sagittal plane due to interference by the expanding lungs. This is of particular importance as the diameter measurement is squared during the calculation of systemic blood flow.

The 19% intra-observer variability for RVO diameter gained in our study is much greater than previous research (3.9%).²⁸⁶ Interestingly both the intra- and inter-observer (23% and 25% respectively) repeatability index measurement of RVO VTi were similar to that of RVO diameter. A previous study found that measuring RVO VTi through a long axis position lead to significant differences in the RVO values gained.²⁸⁶ Thus in our analysis both components of RVO calculation appear equally responsible for the intra- and inter-observer repeatability index values (31% and 51%) observed. The improved repeatability for RVO compared to SVCF is likely to be due to RVO being less affected by respiratory movements interfering with either the echocardiographic window for diameter measurements or the VTI waveforms gained. The variability may have been improved in this study by measuring RVO VTi in a short axis plane as previous research has found this to be the most repeatable way to measure VTi.²⁸⁶

Overall the repeatability of the echocardiographic measures of blood flow ranged from poor to moderate. One of the concerning results is the inter-observer repeatability coefficient results for RVO and SVCF (123 and 79 ml/kg/min respectively). These are values that are too large for them to be considered a reliable measure of systemic blood flow in the clinical domain. These values decrease somewhat for intra-observer repeatability and thus our results support the notion that the same observer should perform sequential measurements in order to reduce variability.¹⁶² It should be noted that whilst both of the observers in this study are experienced in neonatal echocardiography, both SVCF and RVO are relatively new techniques for both clinicians. This lack of experience may in part explain for the high values of repeatability seen in this study.

12.6 Limitations of the presented studies

The use of non-parametric tests and the fact that no reference values exist for the research measurements used in the presented studies made power calculations difficult and reduced the strength of the results presented. Furthermore, due to the nature of the care of this cohort of infant's pairwise comparisons were difficult to achieve as many infants were discharged from hospital within the study period. Whilst the correlation matrixes (Appendix 1) show many significant correlations between the biomarkers used in this study, it should be noted that with the number performed and a p-value of ≤ 0.05 being considered significant, many of the relationships may occur by chance. However it is disappointing that measures of pulse transit time do not correlate to measures of blood pressure constantly as they have been reported in the literature.^{325,326}

Another limitation of the study is the oversight not to include other haematological and cardiovascular research parameters in the analysis that may have produced interesting findings. For example, data was collected about neonate's haemoglobin levels during their stay on the neonatal unit but was not included in the analysis. It would have been a simple parameter to incorporate, and an interesting one as research has shown the influence of increasing haemoglobin through blood transfusions alters parameters such as such RVO.²²⁵

A potential limitation for the NeoAdapt 2 is the broad the inclusion criteria used. It

may have skewed the data gained from the study as the population of neonates sampled from is likely to have been wide-spread. Whilst technically all the neonates required some sort of specialised neonatal care, the intensity of that care could differ greatly between included neonates. A stricter inclusion criterion perhaps including an illness scoring system, such as the SNAPPE-II score, to determine eligibility would have helped narrow the population included.^{375,376} This would not only mean that the population of neonates would have been more defined but also the results from the study could perhaps be more robust and generalisable to that specific cohort of neonates.

84% of blood pressure measurements where recorded were taken by oscillatory methods, this being the most inaccurate way of measuring blood pressure.¹⁷⁰ Whilst the reported results are in keeping with the existing literature, consideration should be given to the fact that some of the insignificant results presented may be due to use of the oscillatory method of measuring blood pressure.¹⁷⁰ In future studies, the use of doppler or plethysmographic methods of measuring blood pressure could be utilised when invasive methods are deemed to be inappropriate.^{193,194}

It is important to acknowledge that the poor repeatability for both RVO and SVCF in the population studied may affect robustness of the values gained. With the high repeatability index for both measures of systemic blood flow, RVO and SVCF may might be considered imprecise methods of assessing true systemic blood flow in a neonate. The inaccuracy of these assessments is mitigated in the presented studies to a certain extent by SVCF and RVO being measured by the same researcher on each individual neonate, however it does raise the question as to whether it is clinically appropriate to use them as measures of blood flow.

It was difficult to determine relationships between research measures and short term assessment of neurological outcomes. Prior research has found that the association between low SVCF and cerebral injury occurs the nadir of SVCF seen between 4-8 hours of life.³⁰⁰ Consent for participation was received from all of the infants after they were born, thus most of the echocardiographic studies were performed after this time period. This could have been ameliorated by the use of antenatal consent. However, many of these infants were unexpected admissions

to intensive care making the use of antenatal consent difficult. In addition, being a tertiary unit meant that many of the infant's receiving total body cooling were born in outlying hospitals so that a number of hours had elapsed from birth and admission to the unit. This also meant that many parents of these neonates were also not available in order for the research team to receive informed consent. The observational nature of the studies meant that the research measures were taken in some instances before, in other instances during or after an intervention for circulatory failure, making inference of their effect on the biomarkers studied difficult. It is imperative to therefore outline that any significant results produced from the analysis in the circulatory failure and cerebral injury comparison studies need to be interpreted with extreme caution due to the low numbers of infants included and are likely to represent chance findings.

13 Conclusion

This is the first set of studies to explore the cardiovascular adaptation in late preterm and term neonates who are considered to be well, receiving intensive care or total body cooling. As well as providing novel insights into the cardiovascular adaptation of each cohort, they provide reference values for echocardiographic studies of systemic blood flow and novel plethysmographic measures of cardiovascular status. Whilst the repeatability of these measures ranges from poor to excellent, both are feasible in these cohorts in the neonatal setting.

13.1.1 Clinical implications and future research

Healthy late pre-term neonates' cardiovascular systems adapt differently to term neonates. The pairwise decreases in measures of mPTT indicate that SVR increases gradually over the first three days of life in these infants. This coupled with the increases in measures of systemic blood flow indicates that late preterm infants preferentially increase cardiac output to ensure end organ perfusion when compared to term infants. As outlined previously these infants, despite not being obviously unwell, are at an increased risk of neurodevelopmental problems. In theory the delayed cardiovascular adaptation could lead to a reduction in cerebral blood flow, failure of cerebral autoregulation and subsequent ischemia to vulnerable areas of a neonate's brain. It would be interesting and important for future research should incorporate widely research measurements of cerebral blood flow or oxygenation, such as NIRS, in order to determine whether this abnormal cardiovascular adaptation may lead to under-perfusion or reduced oxygenation to the brain in this population of neonates.

The results from this study indicate that echocardiographic measures of systemic blood flow are of clinical importance in detecting and elucidating the mechanism of circulatory failure, in particular in septic infants. From the set of conducted studies, it appears that the reduced measures of pulse transit time indicate that the natural increase in SVR is impeded in infants throughout the transitional circulation. All of the sick infants included in the NeoAdapt 2 study, the majority suffering from sepsis, were able to increase their systemic blood flow in order to maintain adequate organ perfusion. The monitoring of systemic blood flow in these cohorts is therefore important as its reduction may indicate circulatory failure which is

associated with increased mortality.²⁹⁹ It would be important to explore measures of RVO and SVCF in term and late preterm infants in greater numbers as it would be important to confirm whether reduced values (<150mls/kg/min) are still associated with increase morbidity and mortality.²⁹⁹

In the context of total body cooling the trend that increased values of SVCF over the transitional circulation being associated with abnormal MRI findings is interesting. It suggests that SVCF may be a potentially act as a marker cerebral blood flow and potentially could be useful in the prediction of MRI outcomes in neonates suffering from HIE. However, there are already a number of well researched clinical tools such as cerebral functional monitoring and MRI which are already in widespread use and are predictive of long term neurodevelopmental outcomes in neonates suffering from HIE. One potential advantage of SVCF is that it could offer a bedside measure that could be a target for treatment in these infants. For example studies could develop interventions that actively reduce SVCF in order to reduce cerebral blood flow and perhaps secondary energy failure injuries that occur in HIE.¹⁴⁷

The repeatability of echocardiographic measures ranged from moderate, RI of 26% for intra-observer repeatability for RVO, to poor, RI of 64% for inter-observer repeatability for SVCF. To improve the robustness of echocardiographic measures of systemic blood flow further research should investigate the use of repeated measurements of stroke volume combined with pre-defined median weight corrected measurements of vessel diameter in order to improve their repeatability.³⁷⁷ The fact that VTi is more repeatable and that it is not squared during the calculation of systemic blood flow means that the repeatability of these echocardiographic biomarkers would improve. However this approach does ignore the finding that the diameter of the SVC changes over the first three days of life.³⁰⁵ There is also a suggestion that novel ways of exploring SVC VTi and diameter, such as through a suprasternal and parasternal view respectively, may reduce variability.^{306,307} Future studies should explore this to see if it improves the repeatability of SVCF. Furthermore this highlights, with the increasing use of ultrasound in the neonatal setting, the importance of the development of structured training programmes for neonatal echocardiography.^{378,379}

The described studies show that it is feasible to perform plethysmographic measurements in this cohort and that they may give new information on the behaviours of the cardiovascular adaptation of a neonate such as pulse transit time representing SVR. These measures, when manually calculated, appear robust and repeatable, with the RI ranging from 3-13%. The results of the studies do question the role of mPVI in the monitoring of circulatory adaptation. Prior research has found that it is useful in the assessment of preload in infants. It must be noted in these studies that infants were all ventilated, therefore the respiratory components of mPVI was controlled for.^{317,319,322} From the set of conducted studies in this thesis it appears that mPVI was unaffected by treatment that may affect preload. Furthermore, we found longitudinal pairwise decreases in mPVI over the first three days of life when preload on the heart would have decreased due to the neonatal diuresis. This is contrary to previous research findings where mPVI has been found to decrease in response to increasing preload.^{317,319,322} Therefore, one may conclude that in neonates where respiratory function is not controlled for, mPVI may potentially be a non-invasive measure of respiratory adaptation, pathology or physiology. Thus future exploration of mPVI should include the correlation to measures of lung functions such as functional residual capacity, lung and respiratory system compliance. Moreover, future studies should incorporate the use of the plethysmographic measures outlined in the study to further explore how they change during therapeutic interventions. If found to be a good clinical measure of treatment effect or clinical outcome then refinement of these measures including automated forms would provide clinicians with potentially constant measures of lung inflation, SVR and preload on the heart.

With regards to the use of MAP the pairwise daily increases in late preterm neonates indicate that it appears to be representative of the changes in SVR that are seen in neonatal adaptation. This is similar to previous research findings blood pressure increased over the first three days of life.¹⁶⁷ Therefore it could be presumed that when such daily increases are not seen in neonates that the natural increases in SVR are not occurring. Thus blood pressure in units where access to echocardiography is limited could be utilised to monitor SVR in this cohort of infants.

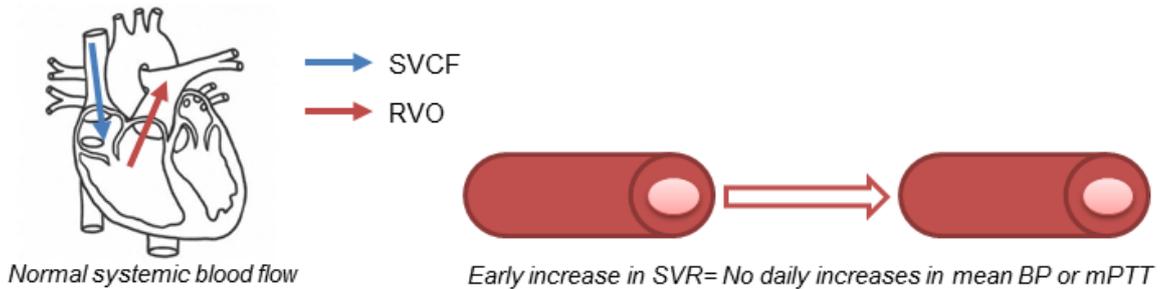
Whilst only low numbers were included in the cardiovascular treatment comparative analysis, pulse pressure appears to be affected by cardiovascular treatment. This measure is simple to calculate, has yet to be explored in therapeutic studies and may warrant further exploration.¹⁹⁹ However, the physiology that underlies this parameter is complicated in neonates with GA affecting the degree of elastin in arterial walls and therefore their compliance.³⁸⁰ Physiological aspects of the measure need to be considered when interpreting the effect on this parameter in designing future studies.

With regards to the other bedside, biochemical and clinical measures of haemodynamic status some significant results are observed. For example, pH, lactate and capillary refill time are worse in cooled babies with abnormal MRIs. However, the majority of the results indicate that most of these biomarkers are non-specific measures of the underlying physiological processes involved in circulatory adaptation and failure. This should not halt their use in future studies. For example in a recent study in 126 preterm infants monitored for circulatory failure it was found that lactate greater than 4 at 12 hours of life showed an odds ratio of 5.5 (confidence interval 1.3-23.0; $p < 0.019$) for predicting death.²¹⁹ Therefore further research into these biomarkers are needed as they are widely available and may aid clinicians in the management of circulatory failure in resource poor settings.

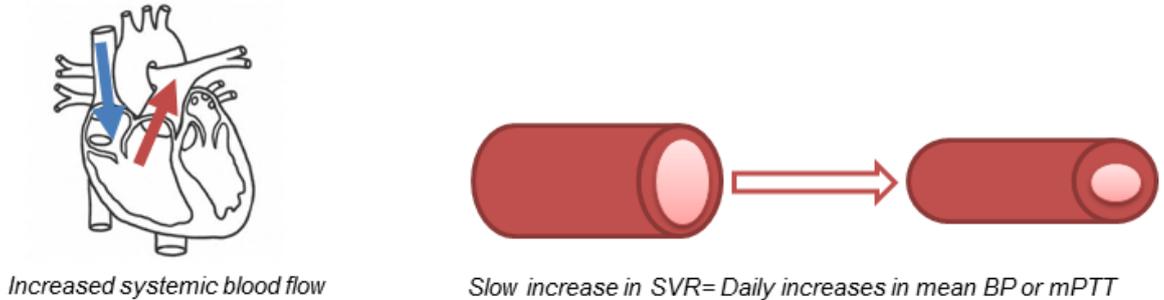
13.1.2 Summary

The results outlined in this thesis indicate that the cardiovascular adaptation of infants is highly variable depending on GA and the pathologies encountered by that neonate. The data provided indicates that the various cohorts' cardiovascular systems adapt distinctly. This is summarised in Figure 13.1.

Healthy neonates >37 weeks gestational age



Healthy neonates <37 weeks gestational age & those requiring intensive care



Neonates requiring total body cooling

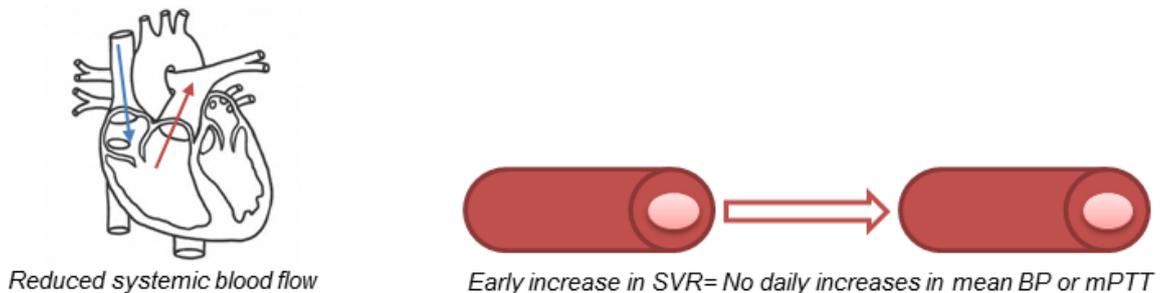


Figure 13.1: Summary of cardiovascular adaption

The presented studies show that cardiovascular adaption of apparently well late preterm infants is different from older neonates. Whether this has pathophysiological links with the increased risk of adverse neurodevelopmental outcomes in this cohort requires further exploration. The presented studies show that the echocardiographic and plethysmographic measurements are possible in these cohorts of neonates, but exhibiting widely varying degrees of repeatability. These biomarkers appear to monitor non-invasively the physiological processes that occur during the transitional neonatal circulation. Thus they provide the potential for clinicians to apply targeted pragmatic pathophysiology based treatments regimes for neonates with circulatory failure until an evidence base develops from well-designed interventional studies.

14 Appendices

14.1 Spearman rank correlations

Correlation matrixes using non-parametric spearman rank tests were performed for each cohort studied in the NeoAdapt 1, 2 and 3 studies. In the NeoAdapt 1 study all 16 variables were correlated with each other, whereas in the NeoAdapt 2 and 3 studies 19 variables could be correlated with each other.

As outlined previously in the results and discussion sections of this thesis many significant results can be seen in all of the correlation matrixes. However, none of the relationships are consistent over the three days' where measurements were taken from neonates irrespective of the of the population studied.

14.1.1 NeoAdapt 1- Whole cohort day 1

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/m in)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/m in)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT
Heart Rate (BPM)																
Mean BP (mmHg)	-0.33															
Systolic BP (mmHg)	-0.22	0.93*														
Diastolic BP (mmHg)	-0.24	0.86*	0.71*													
PP (mmHg)	-0.16	0.60*	0.82*	0.24												
CRT (Secs)	0.24	0.26	0.22	0.29	0.13											
SVC Diameter (cm)	0.08	0.49*	0.47*	0.55*	0.22	0.14										
SVC VTi (cm)	-0.08	-0.03	0.04	-0.16	0.19	0.22	-0.52*									
SVCF (mls/kg/min)	0.29	-0.14	0.04	-0.18	0.19	0.24	0.24	0.16								
RVO Diameter (cm)	-0.02	0.36	0.30	0.36*	0.13	-0.06	0.21	-0.05	-0.41*							
RVO VTi (cm)	-0.22	-0.29	-0.23	-0.27	-0.05	-0.22	-0.12	0.32	0.21	-0.19						
RVO (mls/kg/min)	0.07	-0.41*	-0.33	-0.44	-0.10	-0.18	-0.44	0.25*	0.22	0.01	0.64*					
mPVI (%)	0.07	-0.08	0.01	-0.002	0.03	-0.10	-0.03	-0.02	-0.03	-0.21	-0.20	-0.20				
mPTT (Secs)	0.19	-0.20	-0.24	-0.22	-0.16	-0.11	0.12	-0.09	0.14	-0.04	-0.05	0.14	-0.35			
NmPTT	0.37*	-0.24	-0.26	-0.10	-0.24	0.10	-0.16	0.05	0.27	0.005	-0.05	0.41*	-0.17	0.47*		
Trans mPTT	-0.19	0.20	0.24	0.22	0.16	0.11	-0.12	0.09	-0.14	0.04	0.05	-0.14	0.35	-1.00	-0.47*	

*p<0.05

14.1.2 NeoAdapt 1- Whole cohort day 2

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/m in)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/m in)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT
Heart Rate (BPM)																
Mean BP (mmHg)	-0.45*															
Systolic BP (mmHg)	-0.45*	0.79*														
Diastolic BP (mmHg)	-0.11	0.75*	0.40*													
PP (mmHg)	-0.28	-0.01	0.48*	-0.50*												
CRT (Secs)	-0.13	0.08	-0.13	0.25	-0.28											
SVC Diameter (cm)	-0.13	-0.03	0.11	-0.17	0.22	-0.01										
SVC VTi (cm)	0.06	0.23	0.11	0.24	-0.20	0.12	-0.14									
SVCF (mls/kg/min)	0.58*	-0.43*	-0.46*	-0.19	-0.13	0.15	0.27	0.38*								
RVO Diameter (cm)	-0.22	0.38*	0.59*	0.05	0.38*	-0.28	0.27	0.41*	-0.15							
RVO VTi (cm)	-0.31	0.03	0.17	-0.16	0.30	-0.35*	0.09	0.17	-0.01	0.26						
RVO (mls/kg/min)	0.34*	-0.37*	-0.24	-0.37*	0.25	-0.40*	-0.20	0.13	0.39*	0.07	0.56*					
mPVI (%)	-0.16	0.20	0.07	0.20	-0.09	-0.13	-0.11	0.19	0.04	-0.01	0.33	0.11				
mPTT (Secs)	-0.09	0.02	0.23	-0.06	0.12	-0.34	-0.10	-0.23	-0.49	0.39*	-0.18	-0.16	-0.16			
NmPTT	0.53*	-0.46*	-0.54*	-0.20	-0.26	0.02	-0.28	-0.09	0.24	-0.37	-0.49*	0.12	-0.32	0.21		
Trans mPTT	0.09	-0.02	-0.23	0.03	-0.12	0.34	0.10	0.23	0.49	-0.39*	0.18	0.16	0.16	-1.00	-0.21	

*p=<0.05

14.1.3 NeoAdapt 1- Whole cohort day 3

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/m in)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/m in)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT
Heart Rate (BPM)																
Mean BP (mmHg)	-0.37*															
Systolic BP (mmHg)	-0.18	0.81*														
Diastolic BP (mmHg)	-0.28	0.87*	0.68*													
PP (mmHg)	-0.01	0.06	0.51*	-0.23												
CRT (Secs)	-0.08	0.26	0.18	0.13	0.06											
SVC Diameter (cm)	-0.27	0.10	0.08	0.09	0.08	0.08										
SVC VTi (cm)	-0.06	-0.13	-0.24	-0.18	-0.10	-0.02	-0.51*									
SVCF (mls/kg/min)	0.20	-0.49*	-0.47*	-0.46*	-0.09	-0.15	0.17	0.30								
RVO Diameter (cm)	-0.34*	0.20	0.10	0.06	0.11	0.01	0.25	0.21	-0.31							
RVO VTi (cm)	0.34*	-0.27	-0.12	-0.22	0.01	-0.25	0.12	-0.17	0.15	-0.17						
RVO (mls/kg/min)	0.59*	-0.41*	-0.39*	-0.36*	-0.15	-0.41*	-0.29	0.08	0.28	-0.17	0.69*					
mPVI (%)	-0.08	0.24	0.15	0.24	-0.07	-0.04	-0.48*	0.21	-0.37*	-0.004	-0.16	-0.02				
mPTT (Secs)	-0.56*	0.45*	0.43*	0.28	0.20	0.21	0.24	-0.14	-0.28	0.33	-0.30	-0.53*	-0.06			
NmPTT	0.26	0.16	0.25	0.29	-0.05	0.07	-0.09	-0.09	0.17	-0.30	-0.14	0.09	0.10	-0.09		
Trans mPTT	0.56*	-0.45*	-0.43*	-0.28	-0.20	-0.21	-0.24	0.14	0.28	-0.33	0.30	0.53*	0.06	-1.000	0.09	

*p<0.05

14.1.4 NeoAdapt 1- Late preterm cohort day 1

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/m in)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/m in)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT
Heart Rate (BPM)																
Mean BP (mmHg)	-0.16															
Systolic BP (mmHg)	-0.005	0.87*														
Diastolic BP (mmHg)	-0.04	0.72*	0.50													
PP (mmHg)	0.07	0.63*	0.89*	0.09												
CRT (Secs)	0.38	0.37	0.30	0.44*	0.17											
SVC Diameter (cm)	0.05	0.55*	0.52*	0.64	0.33	0.29										
SVC VTi (cm)	0.07	-0.07	-0.01	-0.27*	0.05	0.08	-0.34									
SVCF (mls/kg/min)	0.13	0.24	0.46	0.21	0.40	0.17	0.47*	0.15								
RVO Diameter (cm)	0.25	0.03	0.02	-0.05	0.07	0.01	-0.10	0.22	-0.11							
RVO VTi (cm)	-0.50	-0.29	-0.22	-0.22	-0.20	-0.40	-0.16	0.34	0.10	-0.11						
RVO (mls/kg/min)	-0.31	-0.19	-0.09	-0.24	-0.01	-0.35	-0.28	0.23	0.12	0.34	0.71*					
mPVI (%)	0.25	-0.24	-0.07	-0.12	-0.04	-0.05	-0.01	0.02	0.13	-0.48*	-0.03	-0.23				
mPTT (Secs)	-0.02	0.03	-0.06	-0.01	-0.002	-0.11	0.27	-0.10	-0.14	0.39	-0.09	0.12	-0.52*			
NmPTT	0.29	-0.08	-0.13	0.20	-0.18	0.07	0.26	-0.09	0.13	0.38	-0.13	0.07	-0.09	0.58*		
Trans mPTT	0.02	-0.03	0.06	0.01	0.002	0.11	-0.27	0.10	0.14	-0.39	0.09	-0.12	0.52	-1.00	-0.58*	

*p<0.05

14.1.5 NeoAdapt 1- Late preterm cohort day 2

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/m in)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/m in)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT
Heart Rate (BPM)																
Mean BP (mmHg)	-0.52*															
Systolic BP (mmHg)	-0.46*	0.74*														
Diastolic BP (mmHg)	-0.10	0.69*	0.27													
PP (mmHg)	-0.27	0.20	0.72*	-0.37												
CRT (Secs)	-0.04	0.08	-0.09	0.29	-0.32											
SVC Diameter (cm)	-0.13	-0.19	0.09	-0.30	0.29	-0.42										
SVC VTi (cm)	0.38	-0.05	-0.28	0.33	-0.41	0.18	-0.28									
SVCF (mls/kg/min)	0.71*	-0.38	-0.49*	0.08	-0.40	0.26	0.29	0.53*								
RVO Diameter (cm)	0.04	0.006	0.10	-0.12	0.18	-0.24	-0.01	0.43	-0.04							
RVO VTi (cm)	-0.04	-0.12	0.14	-0.24	0.35	-0.65*	-0.10	-0.04	-0.09	0.30						
RVO (mls/kg/min)	0.20	-0.15	0.11	-0.27	0.39	-0.65*	-0.28	0.18	0.14	0.51*	0.82*					
mPVI (%)	-0.26	0.19	-0.05	0.31	-0.14	0.10	-0.24	0.13	0.08	-0.22	0.20	0.08				
mPTT (Secs)	-0.27	0.005	0.14	-0.25	0.28	-0.30	-0.13	-0.07	-0.50*	0.55*	0.25	0.23	-0.14			
NmPTT	0.31	-0.13	-0.19	-0.04	-0.200	0.04	-0.26	0.24	0.03	0.11	-0.45*	-0.16	-0.36	0.38		
Trans mPTT	0.27	-0.005	-0.14	0.25	-0.28	0.30	0.13	0.07	0.50*	-0.55*	-0.25	-0.23	0.14	-1.00	-0.38	

*p<0.05

14.1.6 NeoAdapt 1- Late preterm cohort day 3

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/m in)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/m in)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT
Heart Rate (BPM)																
Mean BP (mmHg)	-0.45*															
Systolic BP (mmHg)	-0.24	0.80*														
Diastolic BP (mmHg)	-0.24	0.79*	0.67*													
PP (mmHg)	-0.06	0.15	0.53*	-0.23												
CRT (Secs)	0.19	0.07	-0.07	-0.16	0.09											
SVC Diameter (cm)	0.23	-0.08	0.18	-0.15	0.37	0.29										
SVC VTi (cm)	0.05	-0.18	-0.30	-0.14	-0.20	-0.09	-0.44*									
SVCF (mls/kg/min)	0.18	-0.21	-0.37	-0.26	-0.14	0.34	0.24	0.55*								
RVO Diameter (cm)	-0.18	-0.07	0.03	-0.19	0.22	-0.24	0.47*	-0.08	-0.14							
RVO VTi (cm)	0.36	-0.15	-0.004	-0.05	0.02	-0.05	0.12	-0.29	-0.02	-0.06						
RVO (mls/kg/min)	0.55*	-0.21	-0.16	-0.10	-0.15	0.005	-0.18	0.05	0.08	0.15	0.75*					
mPVI (%)	-0.14	0.21	0.10	0.31	-0.19	-0.20	-0.61*	0.30	-0.18	-0.28	-0.18	-0.09				
mPTT (Secs)	-0.61*	0.45*	0.46*	0.18	0.38	0.02	0.04	-0.12	-0.38	0.34	-0.34	-0.40	0.04			
NmPTT	0.05	0.32	0.28	0.45*	-0.17	0.16	-0.04	0.25	0.20	0.08	-0.16	0.06	0.12	0.02		
Trans mPTT	0.61	-0.45*	-0.46*	-0.18	-0.38	-0.02	-0.04	0.12	0.38	-0.34	0.34	0.40	-0.04	-1.00	-0.02	

*p=<0.05

14.1.7 NeoAdapt 1- Term cohort day 1

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/m in)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/m in)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT
Heart Rate (BPM)																
Mean BP (mmHg)	-0.60															
Systolic BP (mmHg)	-0.49	0.94*														
Diastolic BP (mmHg)	-0.23	0.64	0.49													
PP (mmHg)	-0.38	0.70	0.87*	0.01												
CRT (Secs)	0.07	-0.06	0.03	-0.09	0.18											
SVC Diameter (cm)	-0.24	0.37*	0.37	0.51	0.22	0.63										
SVC VTi (cm)	-0.45	0.71	0.77	0.67	0.58	0.55	-0.70*									
SVCF (mls/kg/min)	0.67	-0.43	-0.14	-0.29	0.12	0.47	0.63	-0.22								
RVO Diameter (cm)	-0.73	0.43	0.14	0.58	-0.20	0.07	-0.43	0.42	-0.67							
RVO VTi (cm)	0.45	0.77	0.89*	0.46	0.78	0.24	-0.07	0.17	0.55	-0.53						
RVO (mls/kg/min)	0.38	0.71	0.60	0.75	0.29	0.29	-0.37	0.22	0.22	-0.02	0.68*					
mPVI (%)	-0.55	0.09	0.03	0.12	-0.06	-0.19	-0.32	0.04	-0.54	0.29	-0.57	-0.21				
mPTT (Secs)	0.66	-0.67	-0.47	-0.27	-0.31	-0.02	0.14	-0.07	0.27	-0.56	-0.31	-0.42	0.26			
NmPTT	0.50	-0.26	-0.37	-0.06	-0.38	0.45	-0.18	0.11	0.04	0.14	-0.14	0.29	-0.46	0.14		
Trans mPTT	-0.66	0.68	0.47	0.27	0.31	0.02	-0.14	0.07	-0.27	0.56	0.31	0.41	-0.26	-1.00*	-0.14	

*p=<0.05

14.1.8 NeoAdapt 1- Term cohort day 2

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/m in)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/m in)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT
Heart Rate (BPM)																
Mean BP (mmHg)	0.45															
Systolic BP (mmHg)	0.12	0.52														
Diastolic BP (mmHg)	0.45	0.78*	0.23													
PP (mmHg)	-0.26	-0.54	0.28	-0.80*												
CRT (Secs)	-0.17	0.16	-0.33	0.16	-0.30											
SVC Diameter (cm)	-0.28	-0.46	0.33	-0.56	0.89*	-0.30										
SVC VTi (cm)	-0.05	0.05	0.05	-0.19	0.06	0.09	-0.21									
SVCF (mls/kg/min)	0.14	-0.06	0.16	-0.25	0.49	-0.04	0.50	0.43								
RVO Diameter (cm)	-0.02	-0.36	0.34	-0.60*	0.76*	-0.50	0.40	0.34	0.41							
RVO VTi (cm)	-0.61*	0.07	0.04	-0.04	0.08	0.23	0.20	0.34	0.32	0.09						
RVO (mls/kg/min)	0.01	0.21	0.15	-0.01	0.21	0.03	0.27	0.36	0.75*	0.43	0.64*					
mPVI (%)	0.11	0.21	0.22	0.10	0.05	-0.57	0.06	-0.06	0.14	0.16	0.51	0.38				
mPTT (Secs)	0.28	-0.04	0.26	0.07	-0.09	-0.53	-0.07	-0.25	-0.55	0.18	-0.78*	-0.61*	-0.21			
NmPTT	0.27	-0.16	-0.49	0.08	-0.34	-0.06	-0.12	0.01	-0.07	-0.45	-0.56	-0.45	-0.37	0.18		
Trans mPTT	-0.28	0.04	-0.26	-0.07	0.09	0.52	0.07	0.25	0.55	-0.18	0.78*	0.61*	0.21	-1.00*	-0.18	

*p<0.05

14.1.9 NeoAdapt 1- Term cohort day 3

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/m in)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/m in)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT
Heart Rate (BPM)																
Mean BP (mmHg)	0.36															
Systolic BP (mmHg)	0.38	0.69*														
Diastolic BP (mmHg)	0.19	0.93*	0.47													
PP (mmHg)	0.23	-0.12	0.48	-0.39												
CRT (Secs)	-0.18	0.12	0.16	0.32	-0.20											
SVC Diameter (cm)	-0.42	0.12	0.00	0.22	-0.17	-0.05										
SVC VTi (cm)	-0.01	-0.45	-0.18	-0.49	0.07	0.01	-0.71									
SVCF (mls/kg/min)	-0.22	-0.39	-0.01	-0.49	0.13	-0.14	0.30	0.20								
RVO Diameter (cm)	-0.20	-0.36	-0.52	-0.33	-0.10	-0.46	-0.18	0.55	-0.01							
RVO VTi (cm)	-0.07	-0.34	-0.09	-0.37	0.11	-0.45	0.30	-0.03	0.21	0.11						
RVO (mls/kg/min)	0.28	-0.10	-0.12	-0.20	-0.01	-0.64*	-0.33	0.42	-0.10	0.55	0.60*					
mPVI (%)	0.40	0.12	0.17	0.12	0.17	-0.03	-0.52	0.01	-0.73*	-0.02	-0.01	0.26				
mPTT (Secs)	-0.37	0.13	0.05	0.19	-0.26	0.11	0.50	-0.45	0.40	-0.47	-0.09	-0.47	-0.54			
NmPTT	0.27	0.62*	0.63*	0.55	0.18	0.27	-0.08	-0.57	-0.46	-0.75*	-0.27	-0.27	0.31	0.21		
Trans mPTT	0.37	-0.13	-0.05	-0.13	0.26	-0.11	-0.50	0.45	-0.40	0.47	0.09	0.47	0.54	-1.00*	-0.21	

*p<0.05

14.1.10 NeoAdapt 2- Whole cohort day 1

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	0.72*																			
Systolic BP (mmHg)	0.92*	0.74*																		
Diastolic BP (mmHg)	0.14	0.70*	0.10																	
PP (mmHg)	0.14	-0.30	0.08																	
CRT (Secs)	-0.29	-0.57	-0.42	-0.27	0.24															
SVC Diameter (cm)	0.42	0.49	0.59*	0.27	-0.26	-0.06														
SVC VTi (cm)	-0.01	-0.05	0.04	-0.34	0.15	-0.41	-0.27													
SVC (mls/kg/min)	-0.25	0.03	-0.02	0.02	-0.10	-0.25	0.47	0.37												
RVO Diameter (cm)	0.45	0.66	0.54	0.48	-0.14	-0.58	0.41	-0.16	-0.03											
RVO VTi (cm)	0.44	0.22	0.32	-0.36	0.68	-0.10	-0.43	0.68	0.000	0.09										
RVO (mls/kg/min)	-0.69*	-0.45	-0.66	0.05	0.18	0.47	-0.13	-0.23	0.364	-0.24	-0.04									
mPVI (%)	-0.17	-0.61	-0.34	-0.63*	0.34	-0.05	-0.57	0.28	-0.32	-0.18	0.77	0.08								
mPTT (Secs)	-0.03	-0.31	-0.37	-0.49	0.71	0.50	-0.43	0.14	-0.14	-0.49	0.10	0.37	0.54							
NmPTT	-0.07	-0.23	-0.19	-0.03	0.60	0.03	-0.44	0.43	-0.03	0.16	0.43	0.11	0.25	-0.03						
Trans mPTT	0.18	0.20	0.26	-0.04	0.11	0.06	-0.07	-0.32	-0.24	-0.12	-0.09	-0.04	-0.25	0.37	-0.52					
Urine Output (mls/kg/hr)	0.46	-0.10	0.06	-0.41	0.15	0.87	-0.97*	0.20	-0.82	-0.63	0.20	-0.32	0.63	-0.21	0.32	0.32				
pH	-0.06	0.10	0.02	0.34	-0.01	-0.08	0.24	-0.56	0.03	0.68*	-0.02	0.33	-0.30	-0.37	0.11	0.04	-0.01			
Base Excess (mmol/l)	-0.23	-0.18	-0.29	0.09	-0.02	0.50	-0.19	-0.49	-0.30	-0.18	-0.21	0.10	-0.41	-0.42	0.12	0.05	0.07	0.28		
Lactate (mmol/l)	0.23	0.18	0.43	-0.10	0.05	-0.05	0.68	0.17	0.60*	0.14	0.21	0.11	-0.06	0.00	-0.30	0.06	-0.38	-0.32	-0.68*	

*p<0.05

14.1.11 NeoAdapt 2- Whole cohort day 2

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	0.71*																			
Systolic BP (mmHg)	0.80*	0.49*																		
Diastolic BP (mmHg)	-0.16	0.42*	-0.52*																	
PP (mmHg)	-0.01	-0.08	0.18	-0.29																
CRT (Secs)	0.29	0.04	0.17	-0.05	0.06															
SVC Diameter (cm)	-0.19	0.11	-0.19	0.26	-0.19	-0.07														
SVC VTi (cm)	-0.08	-0.09	-0.22	0.13	-0.18	-0.04	-0.10													
SVC (mls/kg/min)	-0.43	-0.27	-0.33	-0.03	0.11	-0.04	0.61*	0.19												
RVO Diameter (cm)	-0.15	0.15	-0.26	0.44*	-0.18	0.06	0.34	0.08	-0.005											
RVO VTi (cm)	-0.01	-0.21	-0.04	-0.13	-0.29	-0.22	-0.04	0.10	-0.17	-0.09										
RVO (mls/kg/min)	-0.38	-0.41	-0.27	-0.17	0.25	0.03	0.14	-0.24	0.36	0.32	0.24									
mPVI (%)	-0.29	-0.08	-0.04	-0.03	0.21	0.24	0.18	0.04	0.31	0.28	-0.38	0.19								
mPTT (Secs)	0.22	0.02	0.27	-0.17	0.21	-0.12	0.04	0.24	-0.13	0.05	0.17	-0.12	-0.17							
NmPTT	-0.26	-0.15	-0.29	0.08	0.30	0.08	0.23	-0.21	0.29	-0.09	0.04	0.22	0.12	0.30						
Trans mPTT	0.24	0.04	0.13	-0.17	0.08	0.16	0.02	-0.16	-0.29	0.49*	-0.16	0.11	-0.19	0.02	-0.16					
Urine Output (mls/kg/hr)	0.06	-0.26	0.04	-0.41	-0.02	0.70	0.04	-0.48	0.01	0.01	-0.13	0.11	0.61	-0.08	0.35	0.32				
pH	0.43	0.20	0.16	0.10	-0.40	0.40	0.16	-0.03	-0.09	0.03	0.35	-0.03	-0.35	-0.34	-0.17	0.19	-0.16			
Base Excess (mmol/l)	0.56*	0.48*	0.40	0.01	0.05	0.35	-0.35	0.11	-0.17	-0.08	0.15	-0.06	-0.26	-0.38	-0.43	0.09	-0.36	0.31		
Lactate (mmol/l)	-0.25	-0.16	-0.04	-0.21	0.14	-0.32	0.39	0.21	0.42	-0.19	0.13	-0.05	-0.07	0.18	-0.05	-0.25	-0.23	-0.22	-0.21	

*p<0.05

14.1.12 NeoAdapt 2- Whole cohort day 3

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	0.81*																			
Systolic BP (mmHg)	0.83*	0.54*																		
Diastolic BP (mmHg)	0.31	0.68*	-0.09																	
PP (mmHg)	0.28	0.06	0.20	-0.16																
CRT (Secs)	0.08	0.02	0.10	-0.12	0.33															
SVC Diameter (cm)	0.13	-0.20	0.31	-0.12	-0.10	-0.21														
SVC VTi (cm)	0.16	0.16	0.15	0.26	-0.06	-0.16	-0.08													
SVC (mls/kg/min)	0.01	-0.32	0.07	-0.11	0.34	-0.34	0.51*	0.34												
RVO Diameter (cm)	0.18	0.49	-0.26	0.49	0.07	0.08	-0.61	*-0.10	-0.64*											
RVO VTi (cm)	0.13	-0.10	0.18	-0.10	0.16	0.09	0.44	-0.07	0.17	-0.07										
RVO (mls/kg/min)	-0.09	-0.19	-0.11	0.09	0.33	0.08	0.38	-0.11	0.56*	-0.27	0.45*									
mPVI (%)	-0.28	-0.20	-0.34	0.14	0.23	0.51*	-0.23	0.06	0.01	-0.19	-0.04	0.32								
mPTT (Secs)	0.34	0.46	0.19	0.42	-0.25	0.07	-0.03	-0.16	-0.38	0.34	0.28	0.13	0.22							
NmPTT	0.12	0.39	0.005	0.51*	0.13	0.22	-0.23	0.16	-0.07	0.15	-0.56*	-0.18	0.33	0.004						
Trans mPTT	0.08	-0.20	-0.06	-0.24	0.14	-0.38	0.16	-0.27	0.36	-0.18	0.35	0.30	-0.20	0.03	-0.62*					
Urine Output (mls/kg/hr)	0.68	0.29	0.59	-0.44	0.55	-0.24	-0.06	-0.14	0.04	0.02	-0.37	-0.17	-0.70	0.02	-0.11	0.51				
pH	-0.14	-0.01	-0.12	0.09	-0.51*	-0.07	-0.08	0.08	-0.43	-0.01	-0.35	-0.55*	0.04	0.31	0.07	-0.21	-0.13			
Base Excess (mmol/l)	0.11	0.24	0.09	0.13	-0.18	-0.13	-0.13	0.07	-0.25	-0.28	-0.02	-0.23	-0.28	0.15	-0.13	0.08	-0.10	0.30		
Lactate (mmol/l)	-0.41	-0.58*	-0.15	-0.53	-0.07	0.12	0.36	-0.36	0.17	-0.05	0.25	0.32	-0.12	-0.20	-0.37	-0.08	0.07	-0.04	-0.21	

*p<0.05

14.1.13 NeoAdapt 2- Late preterm cohort day 1

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	0.55																			
Systolic BP (mmHg)	0.07	0.66																		
Diastolic BP (mmHg)	0.74	0.95*	0.52																	
PP (mmHg)	-0.29	0.24	0.85*	0.07																
CRT (Secs)	-0.03	0.20	-0.09	0.20	-0.26															
SVC Diameter (cm)	0.39	0.45	-0.11	0.54	-0.21	0.83														
SVC VTi (cm)	-0.57	-0.62	-0.05	-0.76*	0.32	-0.49	-0.57													
SVC (mls/kg/min)	0.04	-0.11	-0.14	-0.16	0.07	-0.37	0.29	0.54												
RVO Diameter (cm)	0.68	0.11	0.22	0.24	0.11	-0.54	-0.27	0.05	0.11											
RVO VTi (cm)	-0.54	-0.02	0.27	-0.09	0.43	0.89	0.21	-0.04	-0.25	-0.61										
RVO (mls/kg/min)	0.29	-0.27	-0.09	-0.13	-0.04	0.03	-0.07	0.29	0.21	0.50	0.04									
mPVI (%)	0.03	-0.70	-0.64	-0.58	-0.66	-0.54	-0.83	0.26	-0.09	0.31	-0.77	0.31								
mPTT (Secs)	-0.43	-0.93*	-0.87*	-0.92*	-0.54	-0.26	-0.43	0.71	0.49	-0.09	-0.31	0.49	0.66							
NmPTT	0.49	-0.12	-0.06	-0.02	0.20	-0.43	-0.26	0.54	0.66	0.77	-0.49	0.83	0.26	0.37						
Trans mPTT	0.43	0.93*	0.87*	0.93*	0.54	0.26	0.43	-0.71	-0.49	0.09	0.31	-0.49	-0.66	-1.00*	-0.37					
Urine Output (mls/kg/hr)																				
pH	0.86*	0.24	-0.18	0.41	-0.43	-0.09	0.29	-0.18	0.36	0.67	-0.61	0.57	0.26	0.14	0.83	-0.14	-0.29			
Base Excess (mmol/l)	0.04	0.47	-0.13	0.43	-0.43	0.71	0.57	-0.61	-0.21	-0.67	0.21	-0.46	-0.43	-0.31	-0.83	0.31	-0.71	0.22		
Lactate (mmol/l)	0.43	0.09	-0.05	0.26	0.02	0.55	0.68	-0.20	0.36	0.20	0.27	0.60	-0.41	-0.06	0.41	0.06	0.04	-0.23	-0.51*	

*p<0.05

14.1.14 NeoAdapt 2- Late preterm cohort day 2

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	0.004																			
Systolic BP (mmHg)	0.01	0.84*																		
Diastolic BP (mmHg)	0.38	0.76*	0.47																	
PP (mmHg)	-0.49	-0.20	0.17	-0.74*																
CRT (Secs)	-0.05	0.16	0.10	0.11	0.01															
SVC Diameter (cm)	-0.20	-0.05	-0.08	-0.08	-0.06	0.28														
SVC VTi (cm)	-0.33	-0.25	-0.06	-0.45	0.45	-0.30	-0.04													
SVC (mls/kg/min)	-0.08	-0.30	-0.24	-0.22	-0.06	-0.02	0.67*	0.45												
RVO Diameter (cm)	0.08	-0.45	-0.22	-0.57*	0.29	-0.09	0.30	0.08	0.38											
RVO VTi (cm)	-0.34	-0.13	-0.15	-0.13	0.16	-0.14	0.002	-0.002	-0.11	0.13										
RVO (mls/kg/min)	0.32	-0.33	-0.24	-0.19	-0.05	-0.01	0.05	-0.33	0.04	0.78*	0.34									
mPVI (%)	0.39	-0.40	-0.16	-0.06	-0.23	-0.24	0.09	-0.02	0.41	0.09	-0.29	0.10								
mPTT (Secs)	-0.11	-0.01	0.10	0.07	0.25	-0.06	-0.39	0.29	-0.12	-0.67*	0.18	-0.57*	0.26							
NmPTT	0.22	-0.10	-0.11	-0.05	-0.02	0.26	0.18	-0.03	-0.09	0.11	0.24	0.02	0.03	-0.10						
Trans mPTT	0.11	0.01	-0.10	-0.07	-0.25	0.06	0.39	-0.29	0.12	0.67*	-0.18	0.57*	-0.26	-1.00*	0.10					
Urine Output (mls/kg/hr)	0.50	-0.50	-0.50	-0.50	-0.50		0.50	-0.50	0.50	0.50	-1.00	0.50	1.00	-0.50	0.50	0.50				
pH	-0.55*	0.21	0.00	0.06	0.09	0.19	0.45	-0.09	0.11	-0.02	0.44	0.10	-0.44	-0.02	-0.13	0.02	-0.03			
Base Excess (mmol/l)	-0.18	0.49	0.67*	0.22	0.21	0.16	-0.13	0.07	-0.02	0.05	0.23	0.11	-0.19	0.15	-0.43	-0.15	-0.89*	0.15		
Lactate (mmol/l)	0.12	-0.05	-0.07	0.19	-0.37	-0.12	0.26	0.22	0.39	-0.15	-0.13	-0.23	-0.01	0.01	-0.27	-0.01	0.26	-0.18	0.03	

*p<0.05

14.1.15 NeoAdapt 2- Late preterm cohort day 3

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	0.38																			
Systolic BP (mmHg)	0.08	0.82*																		
Diastolic BP (mmHg)	0.41	0.82*	0.54*																	
PP (mmHg)	-0.32	0.38	0.67*	0.03																
CRT (Secs)	0.30	0.13	0.05	0.09	-0.15															
SVC Diameter (cm)	0.09	0.15	-0.25	0.41	-0.11	-0.09														
SVC VTi (cm)	-0.09	-0.13	-0.01	-0.15	0.28	-0.31	-0.04													
SVC (mls/kg/min)	0.28	-0.07	-0.46	0.19	-0.30	-0.36	0.67*	0.37												
RVO Diameter (cm)	-0.21	0.34	0.47	0.36	0.54	-0.06	0.34	0.20	0.04											
RVO VTi (cm)	0.47	0.34	0.06	0.31	0.03	0.45	0.39	0.10	0.19	-0.03										
RVO (mls/kg/min)	0.20	0.18	-0.10	0.37	0.03	0.15	0.75*	0.19	0.58*	0.48	0.58									
mPVI (%)	-0.02	-0.23	-0.14	-0.33	0.34	0.36	-0.01	0.28	0.07	-0.03	0.20	0.31								
mPTT (Secs)	-0.15	-0.27	0.18	-0.23	0.32	0.13	-0.23	0.21	-0.32	0.36	-0.25	-0.12	0.26							
NmPTT	-0.05	0.13	0.40	0.08	0.52	-0.21	-0.21	0.16	-0.05	0.29	-0.38	-0.27	0.23	0.56						
Trans mPTT	0.15	0.27	-0.18	0.23	-0.32	-0.13	0.23	-0.21	0.32	-0.36	0.25	0.12	-0.26	-1.00*	-0.56*					
Urine Output (mls/kg/hr)	-0.14	-0.71	-0.66	-0.26	-0.70	-0.14	0.09	-0.71	0.26	-0.14	-0.43	0.26	-0.60	-0.26	-0.60	0.26				
pH	-0.48	-0.32	-0.12	-0.35	0.08	0.05	-0.24	-0.11	-0.43	-0.14	-0.55	-0.39*	0.38	0.13	0.16	-0.13	-0.39			
Base Excess (mmol/l)	-0.06	0.03	0.29	-0.15	0.24	0.17	-0.38	-0.04	-0.46	0.17	-0.31	-0.30	0.10	0.21	0.26	-0.21	-0.43	0.55*		
Lactate (mmol/l)	0.21	-0.36	-0.53	-0.07	-0.66*	0.32	0.28	-0.23	0.34	-0.02	0.05	0.45	0.03	0.22	-0.33	-0.22	0.89*	-0.21	-0.34	

*p<0.05

14.1.16 NeoAdapt 2- Term cohort day 1

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	-0.20																			
Systolic BP (mmHg)	-0.70	0.67																		
Diastolic BP (mmHg)	-0.56	0.50	0.87																	
PP (mmHg)	-0.90	0.36	0.90	0.72																
CRT (Secs)	0.60	-0.63	-0.80	-1.00	-0.80															
SVC Diameter (cm)	-0.70	0.36	0.80	0.46	0.90	-0.40														
SVC VTi (cm)	0.90	-0.05	-0.40	-0.15	-0.70	0.00	-0.60													
SVC (mls/kg/min)	-0.10	-0.56	0.10	0.10	0.30	0.00	0.40	0.00												
RVO Diameter (cm)	-0.80	0.80	1.00	0.80	0.80	-0.50	0.80	-0.40	0.00											
RVO VTi (cm)	-0.30	-0.87*	-0.30	-0.20	0.10	0.40	0.00	-0.40	0.60	-0.40										
RVO (mls/kg/min)	-0.40	-0.40	-0.20	-0.40	0.40	1.00	0.40	-0.80	0.40	-0.20	0.80									
mPVI (%)	0.80	-0.10	-0.80	-0.82	-0.90	1.00	-0.70	0.50	-0.50	-0.60	-0.30	-0.20								
mPTT (Secs)	0.10	0.56	0.50	0.20	0.30	-0.20	0.60	0.20	0.20	0.80	-0.60	-0.40	-0.10							
NmPTT	0.70	0.36	0.00	0.15	-0.40	-0.40	-0.30	0.90	-0.10	0.20	-0.70	-1.00	0.30	0.50						
Trans mPTT	-0.10	-0.56	-0.50	-0.20	-0.30	0.20	-0.60	-0.20	-0.20	-0.80	0.60	0.40	0.10	-1.00*	-0.50					
Urine Output (mls/kg/hr)	0.50	0.50	-0.50	0.00	-1.00		-1.00	0.50	-1.00		-0.50		1.00	-0.50	0.50	0.50				
pH	-1.00*	0.20	0.70	0.56	0.90	-0.60	0.70	-0.90	0.10	0.80	0.30	0.40	-0.80	-0.10	-0.70	0.10	-0.30			
Base Excess (mmol/l)	-0.20	0.31	0.30	0.67	0.10	-0.80	-0.30	0.10	-0.40	0.40	-0.20	-0.80	-0.30	-0.40	0.20	0.40	0.80	0.18		
Lactate (mmol/l)	0.00	-0.72	-0.20	-0.31	0.10	0.60	0.30	-0.10	0.90	-0.40	0.70	0.80	-0.20	0.10	-0.30	-0.10	-0.90	-0.14	-0.68	

*p<0.05

14.1.17 NeoAdapt 2- Term cohort day 2

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	0.04																			
Systolic BP (mmHg)	-0.11	0.29																		
Diastolic BP (mmHg)	-0.16	0.96*	0.32																	
PP (mmHg)	0.05	-0.39	0.68	-0.43																
CRT (Secs)	0.12	0.63	0.16	0.54	-0.11															
SVC Diameter (cm)	0.05	-0.50	0.29	-0.46	0.68	-0.14														
SVC VTi (cm)	0.18	0.43	-0.57	0.32	-0.61	0.27	-0.286													
SVC (mls/kg/min)	0.40	-0.64	-0.21	-0.61	0.18	-0.32	0.643	-0.286												
RVO Diameter (cm)	-0.70	0.14	0.50	0.21	0.43	0.20	0.286	-0.071	-0.500											
RVO VTi (cm)	0.04	0.14	-0.71	0.21	-0.93*	-0.09	-0.464	0.429	0.179	-0.607										
RVO (mls/kg/min)	0.25	-0.14	-0.29	-0.07	-0.29	0.18	0.286	-0.071	0.750	-0.500	0.536									
mPVI (%)	-0.36	-0.11	-0.11	-0.14	0.21	0.47	0.321	0.250	-0.179	0.643	-0.357	-0.107								
mPTT (Secs)	0.13	-0.68	-0.18	-0.61	0.25	-0.18	0.750	-0.321	0.929	-0.214	0.071	0.750	0.143							
NmPTT	0.34	-0.71	0.07	-0.75	0.61	-0.07	0.643	-0.571	0.750	-0.214	-0.357	0.429	0.143	0.786						
Trans mPTT	-0.13	0.68	0.18	0.61	-0.25	0.18	-0.750	0.321	-0.929*	0.214	-0.071	-0.750	-0.143	-1.000*	-0.786*					
Urine Output (mls/kg/hr)	-0.30	0.20	0.00	0.20	-0.10	0.70	-0.600	-0.200	-0.300	0.000	-0.100	-0.100	0.400	-0.100	0.300	0.100				
pH	0.26	0.89	0.43	0.89*	-0.09	0.77	-0.486	0.143	-0.600	0.200	-0.257	-0.257	0.029	-0.600	-0.429	0.600	0.500			
Base Excess (mmol/l)	0.60	0.71	0.60	0.71	0.09	0.43	-0.371	-0.086	-0.314	-0.086	-0.257	-0.143	-0.486	-0.543	-0.257	0.543	0.200	0.829		
Lactate (mmol/l)	-0.06	-0.58	-0.75	-0.58	-0.41	-0.41	0.377	0.406	0.522	-0.348	0.638	0.406	0.116	0.522	0.145	-0.522	-0.667	-0.812*	-0.812*	

*p<0.05

14.1.18 NeoAdapt 2- Term cohort day 3

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	0.50																			
Systolic BP (mmHg)	0.40	0.80																		
Diastolic BP (mmHg)	0.70	0.90	0.60																	
PP (mmHg)	0.10	0.20	0.70	-0.10																
CRT (Secs)	-0.10	0.30	0.30	0.40	-0.20															
SVC Diameter (cm)	-1.00	-0.50	-0.40	-0.70	-0.10	0.10														
SVC VTi (cm)	0.50	1.00*	0.80	0.90	0.20	0.30	-0.50													
SVC (mls/kg/min)	0.70	0.40	0.50	0.30	0.60	-0.60	-0.70	0.40												
RVO Diameter (cm)	-0.60	0.30	0.00	0.10	-0.30	0.30	0.60	0.30	-0.50											
RVO VTi (cm)	-0.20	-0.90	-0.90	-0.70	-0.40	-0.50	0.20	-0.90	-0.20	-0.40										
RVO (mls/kg/min)	0.50	-0.50	-0.40	-0.20	-0.10	-0.40	-0.50	-0.50	0.30	-0.90	0.70									
mPVI (%)	0.20	-0.10	-0.50	0.30	-0.90	0.40	-0.20	-0.10	-0.50	0.00	0.30	0.30								
mPTT (Secs)	-0.30	0.40	0.50	0.30	0.10	0.90	0.30	0.40	-0.50	0.50	-0.70	-0.70	0.00							
NmPTT	0.30	0.60	0.90	0.50	0.60	0.60	-0.30	0.60	0.20	-0.10	-0.80	-0.30	-0.30	0.70						
Trans mPTT	0.30	-0.40	-0.50	-0.30	-0.10	-0.90	-0.30	-0.40	0.50	-0.50	0.70	0.70	0.00	-1.00*	-0.70					
Urine Output (mls/kg/hr)	0.95	0.10	0.32	0.10	0.32	-0.74	-0.95*	0.10	0.95	-0.95*	0.21	0.74	-0.32	-0.74	0.32	0.74				
pH	-0.60	0.30	0.30	-0.10	0.30	0.00	0.60	0.30	-0.10	0.80	-0.50	-0.90	-0.60	0.40	0.10	-0.40	-0.74			
Base Excess (mmol/l)	0.70	0.40	0.50	0.30	0.60	-0.60	-0.70	0.40	1.00*	-0.50	-0.20	0.30	-0.50	-0.50	0.20	0.50	0.95	-0.32		
Lactate (mmol/l)	-0.70	-0.90	-0.60	-1.00	0.10	-0.40	0.70	-0.90	-0.30	-0.10	0.70	0.20	-0.30	-0.30	-0.50	0.30	-0.10	0.18	-0.14	

*p<0.05

14.1.19 NeoAdapt 3- Whole cohort day 1

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	0.20																			
Systolic BP (mmHg)	0.67	0.46																		
Diastolic BP (mmHg)	1.00*	0.20	0.67																	
PP (mmHg)	-0.97*	-0.05	-0.53	-0.97*																
CRT (Secs)	0.90	-0.10	0.36	0.90	-0.97*															
SVC Diameter (cm)	0.70	-0.30	0.67	0.70	-0.67	0.60														
SVC VTi (cm)	-0.30	0.70	-0.20	-0.30	0.41	-0.50	-0.70													
SVC (mls/kg/min)	0.00	0.90	0.05	0.00	0.10	-0.20	-0.60	0.90												
RVO Diameter (cm)	-0.30	0.20	0.41	-0.30	0.36	-0.40	0.00	-0.20	-0.10											
RVO VTi (cm)	-0.10	0.50	-0.36	-0.10	0.15	-0.20	-0.60	0.90	0.80	-0.60										
RVO (mls/kg/min)	0.10	0.90	0.62	0.10	0.10	-0.30	-0.10	0.60	0.70	0.40	0.30									
mPVI (%)	-0.60	-0.50	-0.87*	-0.60	0.41	-0.20	-0.60	-0.10	-0.20	-0.10	0.00	-0.70								
mPTT (Secs)	-0.10	-0.90	-0.62	-0.10	-0.10	0.30	0.10	-0.60	-0.70	-0.40	-0.30	-1.00*	0.70							
NmPTT	-0.10	0.10	-0.46	-0.10	-0.05	0.20	-0.60	0.10	0.30	-0.10	0.20	-0.30	0.70	0.30						
Trans mPTT	0.10	0.90	0.62	0.10	0.10	-0.30	-0.10	0.60	0.70	0.40	0.30	1.00	-0.70	-1.00*	-0.30					
Urine Output (mls/kg/hr)	-0.40	0.60	-0.05	-0.40	0.56	-0.70	-0.50	0.90	0.70	0.00	0.70	0.70	-0.30	-0.70	-0.30	0.70				
pH	-0.90	-0.50	-0.67	-0.90	0.87	-0.80	-0.40	0.10	-0.30	0.10	0.00	-0.30	0.50	0.30	-0.20	-0.30	0.26			
Base Excess (mmol/l)	-0.40	-0.60	-0.67	-0.40	0.36	-0.30	-0.10	0.10	-0.30	-0.60	0.30	-0.50	0.30	0.50	-0.30	-0.50	0.15	0.37		
Lactate (mmol/l)	-0.10	-0.40	0.41	-0.10	0.15	-0.20	0.60	-0.60	-0.70	0.60	-0.80	0.00	-0.30	0.00	-0.70	0.00	-0.68	-0.32	-0.11	

*p<0.05

14.1.20 NeoAdapt 3- Whole cohort day 2

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	-0.23																			
Systolic BP (mmHg)	0.78*	0.01																		
Diastolic BP (mmHg)	0.97*	-0.05	0.78*																	
PP (mmHg)	0.58	0.06	0.83*	0.46																
CRT (Secs)	0.18	-0.36	-0.25	-0.19	-0.15															
SVC Diameter (cm)	0.27	0.15	0.43	0.19	0.18	0.15														
SVC VTi (cm)	-0.44	-0.13	-0.35	-0.36	-0.07	-0.29	-0.73*													
SVC (mls/kg/min)	-0.04	-0.10	0.13	-0.01	0.24	-0.07	0.16	0.44												
RVO Diameter (cm)	-0.25	0.16	-0.38	-0.22	-0.66*	0.09	0.16	-0.34	-0.48											
RVO VTi (cm)	-0.39	0.02	0.07	-0.05	-0.02	-0.70*	-0.13	0.42	0.40	0.01										
RVO (mls/kg/min)	-0.27	-0.40	-0.21	-0.18	-0.40	-0.15	0.11	-0.18	-0.15	0.55	0.42									
mPVI (%)	-0.17	0.25	0.36	-0.23	0.56	-0.02	0.38	0.20	0.63	-0.18	0.58	-0.05								
mPTT (Secs)	0.13	-0.31	0.47	0.41	0.51	-0.59	-0.63	0.70	0.17	-0.60	0.58	-0.18	0.03							
NmPTT	0.04	-0.41	0.26	-0.40	0.39	0.23	0.53	-0.13	0.15	0.05	0.10	0.28	0.52	-0.37						
Trans mPTT	-0.13	0.31	-0.47	-0.41	-0.51	0.59	0.63	-0.70*	-0.17	0.60	-0.58	0.18	-0.03	-1.00*	0.37					
Urine Output (mls/kg/hr)	0.45	-0.11	0.63*	0.20	0.67*	-0.11	0.31	-0.41	-0.31	-0.17	-0.03	0.11	0.25	0.00	0.70*	0.00				
pH	0.15	-0.71	-0.04	-0.12	-0.07	-0.10	-0.36	0.34	-0.16	0.08	0.31	0.30	-0.07	0.23	0.48	-0.23	0.19			
Base Excess (mmol/l)	0.01	-0.30	0.25	0.16	0.13	-0.54	-0.41	0.41	-0.14	-0.08	0.52	0.10	-0.03	0.68	0.15	-0.68*	0.23	0.63*		
Lactate (mmol/l)	0.10	-0.13	0.23	0.10	0.07	-0.20	0.55	-0.28	0.26	-0.25	0.07	0.28	-0.15	-0.12	0.33	0.12	0.17	-0.10	0.07	

*p<0.05

14.1.21 NeoAdapt 3- Whole cohort day 3

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	0.14																			
Systolic BP (mmHg)	0.64*	0.03																		
Diastolic BP (mmHg)	0.91*	0.26	0.73*																	
PP (mmHg)	0.10	-0.37	0.75*	0.16																
CRT (Secs)	-0.33	-0.24	-0.64*	-0.38	-0.55															
SVC Diameter (cm)	0.23	0.41	0.14	0.24	-0.14	0.11														
SVC VTi (cm)	-0.73*	0.02	-0.50	-0.62	-0.21	0.43	-0.19													
SVC (mls/kg/min)	-0.49	0.57	-0.36	-0.38	-0.29	0.19	0.41	0.70*												
RVO Diameter (cm)	0.82	0.16	0.50	0.78*	-0.08	0.01	0.29	-0.69*	-0.54											
RVO VTi (cm)	0.63*	-0.06	0.55	0.50	0.39	-0.68*	0.10	-0.85*	-0.54	0.38										
RVO (mls/kg/min)	0.28	-0.13	0.16	0.26	0.10	-0.52	-0.34	-0.34	-0.33	-0.01	0.62*									
mPVI (%)	-0.12	0.46	0.09	-0.03	-0.02	-0.10	0.29	0.00	0.28	0.09	-0.22	-0.41								
mPTT (Secs)	-0.09	-0.34	0.14	-0.22	0.36	-0.18	0.08	0.00	-0.08	-0.16	0.15	-0.20	0.18							
NmPTT	0.14	0.59*	0.11	0.20	-0.05	-0.41	-0.30	0.08	0.20	-0.05	-0.07	-0.05	0.30	-0.07						
Trans mPTT	0.09	0.34	-0.14	0.22	-0.36	0.18	-0.08	0.00	0.08	0.16	-0.15	0.20	-0.18	-1.00*	0.07					
Urine Output (mls/kg/hr)	-0.03	-0.39	0.32	-0.04	0.52	-0.40	-0.34	-0.34	-0.53	0.07	0.34	0.30	0.24	0.19	-0.13	-0.19				
pH	0.16	0.05	0.49	0.36	0.30	-0.23	0.15	-0.26	-0.22	0.36	0.22	-0.10	0.32	0.38	0.00	-0.38	0.38			
Base Excess (mmol/l)	-0.34	0.17	0.08	-0.05	0.16	-0.30	-0.23	0.41	0.26	-0.28	-0.41	-0.23	0.48	0.29	0.47	-0.29	-0.03	0.27		
Lactate (mmol/l)	0.22	0.71*	0.12	0.25	-0.21	-0.37	0.23	0.04	0.46	0.02	0.10	0.25	0.48	0.02	0.55	-0.02	0.06	0.16	0.14	

*p<0.05

14.1.22 NeoAdapt 3- Whole cohort rewarming

Variables	Heart Rate (BPM)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PP (mmHg)	CRT (Secs)	SVC Diameter (cm)	SVC VTi (cm)	SVCF (mls/kg/min)	RVO Diameter (cm)	RVO VTi (cm)	RVO (mls/kg/min)	mPVI (%)	mPTT (Secs)	NmPTT	Trans mPTT	Urine Output (mls/kg/hr)	pH	Base Excess (mmol/l)	
Heart Rate (BPM)																				
Mean BP (mmHg)	0.12																			
Systolic BP (mmHg)	0.08	0.22																		
Diastolic BP (mmHg)	0.90*	0.07	0.14																	
PP (mmHg)	0.39	0.33	0.42	0.01																
CRT (Secs)	-0.12	-0.11	0.17	0.05	-0.11															
SVC Diameter (cm)	0.26	-0.15	0.62	0.39	-0.05	0.14														
SVC VTi (cm)	0.52	0.58	-0.26	0.47	0.11	-0.30	-0.06													
SVC (mls/kg/min)	0.50	0.29	-0.14	0.66*	-0.33	-0.08	0.41	0.70*												
RVO Diameter (cm)	0.66*	-0.23	0.40	0.86*	-0.21	0.15	0.54	0.25	0.48											
RVO VTi (cm)	0.19	0.03	0.33	0.16	0.08	-0.63	0.09	-0.02	0.03	0.11										
RVO (mls/kg/min)	0.62	0.18	0.19	0.71*	-0.15	-0.48	0.43	0.43	0.74*	0.51	0.58									
mPVI (%)	0.45	-0.61	0.09	0.35	0.15	-0.13	0.39	0.01	0.08	0.49	0.33	0.21								
mPTT (Secs)	-0.07	-0.36	0.75*	0.13	-0.10	0.78*	0.54	-0.54	-0.19	0.39	-0.25	-0.26	0.20							
NmPTT	-0.12	0.68*	0.67	-0.02	0.15	0.29	0.37	0.09	0.21	-0.11	0.05	0.10	-0.41	0.30						
Trans mPTT	0.07	0.36	-0.74*	-0.13	0.10	-0.78	-0.54	0.51	0.19	-0.39	0.25	0.26	-0.20	-1.00*	-0.30					
Urine Output (mls/kg/hr)	-0.64*	0.01	-0.36	-0.69*	-0.22	-0.05	-0.28	-0.11	-0.14	-0.70*	-0.04	-0.33	-0.15	-0.18	0.16	0.18				
pH	0.34	-0.69*	0.02	0.33	-0.07	-0.14	0.25	-0.06	0.04	0.54	0.07	0.14	0.70*	0.06	-0.72*	-0.06	-0.37			
Base Excess (mmol/l)	0.34	-0.40	0.44	0.15	0.54	0.02	0.42	-0.40	-0.24	0.15	0.35	0.07	0.67*	0.34	-0.07	-0.34	-0.27	0.46		
Lactate (mmol/l)	0.44	-0.25	0.31	0.25	0.59	0.14	0.26	-0.34	-0.20	0.13	0.26	0.08	0.49	0.29	-0.05	-0.29	-0.51	0.35	0.81*	

*p<0.05

14.2 NeoAdapt 1 study documentation

14.2.1 Sponsorship approval letter

Brighton and Sussex 
University Hospitals
NHS Trust

10 December 2013

Research & Development Directorate
Royal Sussex County Hospital
Eastern Road
Brighton
BN2 5BE

Dr Liam Mahoney
Clinical Research Fellow - Paediatrics
Royal Alexandra Children's Hospital
Royal Sussex County Hospital
Eastern Road
Brighton
BN2 5BE

Sponsorship Enquiries: Amanda Geel
Telephone: 01273 696955 ext. 3538
E-mail: sponsorship.approvals@bsuh.nhs.uk

Dear Dr Mahoney

Full Study Title: NeoAdapt 1: Study of circulatory adaptation of newborn infants after birth.
R&D Ref No. : IRAS 145159
REC Ref: Not yet applied

I am writing to confirm that the Trust is willing to take on the role of Research Sponsor for the duration of the study.

Your project has been allocated the following reference: **IRAS 145159**.
Please quote this on all future correspondence.

1. Conditions of Approval

Please note that you cannot commence this study until you have been given a favourable opinion or approval from:

- Research Ethics Committee (REC)
- BSUH R&D Approvals: (R&D.Approvals@bsuh.nhs.uk)

2. Project Amendments

Should you wish to amend the project in any way, you will need to apply to the Sponsorship Committee for approval before submitting the application to REC and relevant authorities.

Approval of amendments will be conditional upon a financial and legal risk assessment.

3. Indemnity

The study will be indemnified by the Trust in accordance with Health Service Guidance 96(48): *NHS Indemnity - Arrangements for Handling Clinical Negligence Claims against NHS staff*.

4. ICH-GCP Monitoring

The Trust has a duty to ensure that all research that it sponsors is conducted in accordance with applicable legislation, such as the Research Governance Framework; ICH-GCP standards and the Medicines for Human Use (Clinical Trials) Regulations 2004.

The R&D Department is responsible for the monitoring of the study.

Your project has been assessed as:

- **Low Risk** – No monitoring plan will be put in place. However, the Trust undertakes random audits. If your project is selected you will be given six weeks notice to prepare all documentation for inspection.

5. Annual Progress Report and End of Study Report

Please note that you must provide a brief annual progress and end of study report to the Sponsorship Committee and the Ethics Committee.

I wish you luck with your project.

Yours sincerely



Scott Harfield
Head of Research & Development

14.2.2 Research ethics committee approval letter


Health Research Authority
NRES Committee London - City & East
 Bristol Research Ethics Committee Centre
 Whitefriars
 Level 3, Block B
 Lewins Mead
 Bristol
 BS1 2NT
 Telephone: 01173421386
 Facsimile: 01173420445

23 April 2014

Dr Liam Mahoney
 Level 6, Room 601
 Royal Alexandra Children's Hospital
 Eastern Road, Brighton
 BN2 5BE

Dear Dr Mahoney

Study title:	NeoAdapt 1 Study: Study of circulatory adaptation in newborn infants after birth
REC reference:	14/LO/0317
Protocol number:	NEOADAPT 1
IRAS project ID:	145159

Thank you for your letter of 21 March 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Mr Rajat Khullar, nrescommittee.london-cityandeast@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management

permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Advertisement - Parents Poster NeoAdapt 1	1	02 December 2013
Advertisement - Staff Poster NeoAdapt 1	1	02 December 2013
Covering Letter		11 February 2014
Investigator CV		18 December 2013
Letter from Sponsor		10 December 2013
Other: Supervisor CV - Paul Seddon		31 January 2014
Other: Supervisor CV - Heike Rabe		18 December 2013
Participant Consent Form: Antenatal Consent form NeoAdapt 1	1	02 December 2013
Participant Consent Form: Consent Form - NeoAdapt1	2	21 March 2014
Antenatal Information Sheet NeoAdapt 1	2	21 March 2014
Parent Information Sheet -NeoAdapt1	2	21 March 2014
Protocol - NeoAdapt1	2	21 March 2014
REC application		11 February 2014
Response to Request for Further Information		21 March 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

14/LO/0317

Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

With the Committee's best wishes for the success of this project.

Yours sincerely



pp Professor Arthur T. Tucker
Chair

Email: nrescommittee.london-cityandeast@nhs.net

Enclosures: *List of names and professions of members
who were present at the meeting and those who submitted written
comments*

*"After ethical review – guidance for
researchers"*

Copy to: *Dr Heike Rabe, Brighton & Sussex Medical School
Mr Scott Harfield, Brighton & Sussex University Hospitals NHS Trust*

14.2.3 Antenatal parent information sheet



NeoAdapt 1

A study of circulatory adaptation of newborn infants after birth

ANTENATAL PARENT INFORMATION SHEET TO BE USED BEFORE THE BIRTH OF A CHILD

Dear Parents/Carers,

We would like to inform you about a study in this hospital for babies who may be cared for on the postnatal ward or on the Trevor Mann Baby Unit.

This leaflet gives you information about a research study called NeoAdapt 1. We are doing this study because we want to look at ways to help improve the treatment of babies. Many other parents are receiving this information. Please take time to read this leaflet and feel free to ask a doctor or other member of the research team to explain this study in more detail, now or at any other time.

Why am I being approached?

We are approaching you because your baby may be born at more than 33 weeks gestational age (up to 7 weeks early) and may be cared for on the postnatal ward or in the Trevor Mann Baby Unit at this hospital.

Summary of the project

When babies are born, the way their heart pumps blood around the body changes from one relying on the placenta to one that is self sufficient. Studies in premature babies have shown that this change does not always happen quickly after birth and can prevent the baby getting an adequate blood supply their vital organs. This is very important as research has shown that if we ensure a baby has a good blood supply then this can help prevent problems with a child's later development. The problem we face is that we are not sure of the best way to measure blood supply in babies admitted to the neonatal intensive care unit.

In this project we will investigate different ways of checking blood supply in healthy babies on the postnatal ward and babies admitted to our hospital neonatal unit for special care.

This study is also being used as part of an educational PhD project that Dr Liam Mahoney is undertaking at Brighton & Sussex Medical School.

What questions are we trying to address?

Doctors need to be able to assess how good a baby's blood supply is, but there is no agreement as to how we should do this. Our study aims to increase the amount of information available to doctors so they can better assess the blood supply in a baby.

What is the purpose of the study?



Research has shown that perhaps measuring the blood flow through a large vein connected to your baby's heart is maybe a good way of assessing blood supply in an infant. This measurement is known as a superior vena cava flow assessment and is done with an ultrasound machine, much like the scans that were used to look at your baby when they are in the womb. A small study of very premature infants showed that a low superior vena cava flow measurement was also associated with poor long term development of a baby. However superior vena cava flow in older babies has not been investigated in detail before. We would like to measure the superior vena cava flow in these babies in order fill this knowledge gap.

Research in adults has shown that measurement of an individual's blood oxygen level using an oxygen saturation monitor can give useful information an individual's blood flow. This measurement is known as the pleth variability index. We would also like to measure this in healthy newborn infants as this may also be useful.

What would being in the study mean for my baby?

If your baby is going to be on the postnatal ward, as well as having the usual baby checks we would also like to perform some additional observations such as measuring your baby's heart rate, oxygen saturations, capillary refill time and blood pressure. If your baby is on the Trevor Mann Baby Unit receiving special care they would have these measurements performed routinely as part of the care they receive. In addition to these we would like to perform a superior vena cava flow assessment using an ultrasound machine. At the same time we would also like to measure your baby's pleth variability index. This involves placing a small sensor the size of a small plaster on their hand or foot for the duration of the scan. These are both painless procedures that are well tolerated by babies. All together these measurements should take around 30 minutes in total to complete. We would like to perform these assessments them once a day for a maximum of three days.

We realise that having a baby is an exciting event, but can also be a stressful time. To help improve the study we would like to perform these extra measurements on three occasions. However if we can perform these set of measurements once that would help very much in learning new information about how best to treat unwell babies.

Regardless of where you baby is being looked after, being included in this study will not change the care they receive on the postnatal ward or the Trevor Mann Baby Unit.

Thank you for taking the time to read this leaflet. If you want to discuss anything about the study or get more information please ask your doctor or contact one of the team members below.

Thank you

Name and contact details of local contacts

Dr Liam Mahoney Clinical Research Fellow in Paediatrics Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 2317	PD Dr Heike Rabe Senior Lecturer/Honorary Consultant Neonatologist Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 4195 or 2409
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14.2.4 Parent information sheet

NeoAdapt 1

A study of circulatory adaptation of newborn infants after birth

PARENT INFORMATION SHEET

TO BE USED AFTER THE BIRTH OF A CHILD

Dear Parents,

We think it is important that you know about a study in this hospital for babies who are being cared for on the postnatal ward or the Trevor Mann Baby Unit.

This leaflet gives you information about a research study called NeoAdapt 1. We are doing this study because we want to look at ways to improve the treatment of babies who are admitted to the neonatal intensive care unit. Many other parents are receiving this information. Please take time to read this leaflet and feel free to ask a doctor or other member of the research team to explain this study in more detail, now or at any other time.

Why am I being approached?

We are approaching you because your baby was born aged at more than 33 weeks gestational age (up to 7 weeks early) and is being cared for on the postnatal ward or the Trevor Mann Baby Unit at this hospital.

Summary of the project

When babies are born, the way their heart pumps blood around the body changes from one relying on the placenta to one that is self sufficient. Studies in premature babies have shown that this change does not always happen quickly after birth and can prevent the baby getting an adequate blood supply their vital organs. This is very important as research has shown that if we ensure a baby has a good blood supply then this can help prevent problems with a child's later development. The problem we face is that we are not sure of the best way to measure blood supply in babies admitted to the neonatal intensive care unit.

In this project we are going to investigate different ways of checking blood supply in healthy babies on the postnatal ward and babies admitted to our hospital neonatal unit for special care.

This leaflet explains what being involved in the study would mean for you and your baby. After reading this leaflet and discussing the study with your doctor, if you agree to participate we will ask you to sign a consent form.

This study is also being used as part of an educational PhD project that Dr Liam Mahoney is undertaking at Brighton & Sussex Medical School.



What questions are we trying to address?

Babies born prematurely may not have developed a strong blood supply as their heart muscles are still growing. Older babies, whilst having a stronger heart, may have a medical condition which leads to the heart not pumping properly. These problems can interfere with the blood supply to the brain and other organs resulting in the baby needing a lot of medical care. Doctors need to be able to assess how good the blood supply is, but there is no agreement as to how we should do this. Babies born admitted to intensive care are connected to monitoring devices, which look at the functioning of the heart and the brain. Some people measure blood pressure, others use scanners to visualise the heart and brain. In this study we are going to compare these different methods – and some new ones – so that we can get agreement as to the most useful way of measuring blood flow in a baby.

What is the purpose of the study?

Research has shown that measuring the blood flow through a large vein called the superior vena cava (SVC flow assessment) may be a good way of assessing blood supply in an infant. This measurement is done with an ultrasound machine, much like the scans that were used to look at your baby when they are in the womb. SVC flow assessment has not been researched in babies like yours. We would like to measure the SVC flow in your baby to find out more information about this.

Research in adults has shown that measurement of an individual's blood oxygen level using an oxygen saturation monitor can give useful information an individual's blood flow. This measurement is known as the pleth variability index. We would also like to measure this in newborn infants as this may also be useful.

What does it mean for my baby?

If your baby is going to be on the postnatal ward, as well as having the usual baby checks we would also like to perform some additional observations such as measuring your baby's heart rate, oxygen saturations, capillary refill time and blood pressure. If your baby is on the Trevor Mann Baby Unit receiving special care they would have these measurements performed routinely as part of the care they receive. In addition to these we would like to perform a superior vena cava flow assessment using an ultrasound machine. At the same time we would also like to measure your baby's pleth variability index. This involves placing a small sensor the size of a small plaster on their hand or foot for the duration of the scan. These are both painless procedures that are well tolerated by babies. All together these measurements should take around 30 minutes in total to complete. We would like to perform these assessments them once a day for a maximum of three days.

We realise that having a baby is an exciting event, but can also be a stressful time. To help improve the study we would like to perform these extra measurements on three occasions. However if we can perform these set of measurements once that would help very much in learning new



information about how best to treat unwell babies.

If you decide to be a part of the study you will be regularly updated about the results gained from these measurements. It is important to point out that regardless of where your baby is being looked after, being included in this study will not change the care they receive.

As mentioned previously if you decide to include your baby into this study they will have an ultrasound scan of their heart. Babies will not always have such a scan whilst on the neonatal unit. Rarely this scan may show a problem or defect with your baby's heart which is not known. If this is the case then your baby will be reviewed by a Consultant doctor. We will arrange any necessary treatment required for your baby.

A member of the research team will check regularly throughout the time your baby is part of the study that you are happy to continue participating in it. This is something called "continuous consent" and is to ensure that you have regular opportunities to ask questions about the study.

What will happen to the results of the research?

At the end of the study the results will be published in an international journal. A copy of the full journal article can be requested from the local contacts below. You and your baby will not be identified in any report or publication arising from the study.

Who is organising and funding the research?

The research team on Trevor Mann Baby Unit are organising the research. The European Commission is providing some of the funding for the study to be carried out.

Who has reviewed the study?

This study has been looked at by an independent group of people (the National Ethics Research Committees), who protect the safety, rights, wellbeing and dignity of participants. The committee has also checked that we are giving you enough information so you can make an informed decision about taking part in the study.

What will happen if I don't want to be part of the study anymore?

You are free to leave the study at any point without giving any reason. It will in no way affect the care your baby receives on the postnatal ward or the Trevor Mann Baby Unit.

Who are my contact persons?

If you wish to discuss any aspect of the study you can contact us using the details below. You can also talk to the consultant taking care of your baby on the ward. The research team can always be contacted by phone: 01273 696955 extension 2317. The research team want to thank you for taking the time to read this information sheet. If you would like to make a complaint you can contact the Patient Advice and Liaison Service on 01273 696955 extension



4029/4588 or by email at pals@bsuh.nhs.uk.

Name and contact details of local contact

<p>Dr Liam Mahoney Clinical Research Fellow in Paediatrics Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 2317</p>	<p>PD Dr Heike Rabe Senior Lecturer/Honorary Consultant Neonatologist Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 4195 or 2409</p>
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14.2.5 Consent form

NeoAdapt 1

 A study of circulatory adaptation of
 newborn infants after birth

Please complete in black ballpoint pen

To be used after the birth of a child

CONSENT FORM

Short Title: NeoAdapt 1

Name of Researcher: Dr Liam Mahoney

Name of Infant:

Name of Parent:

 Patient Study Number:

Please initial all boxes

1. I confirm that I have read and understand the information sheet (Version 3. Dated 29/05/2013) for the above study and have had the opportunity to ask questions which have been answered satisfactorily.
2. I understand that participation of my baby in this study is voluntary and that I am free to withdraw my baby from the study at any time, without reason, without the medical care or legal rights of my baby being affected.
3. I understand that the information obtained during the conduct of this study is confidential, and my baby's data will be treated accordingly.
4. I understand that relevant sections of my baby's medical notes and data collected during the study may be looked at by individuals from the Research Departments at Brighton and Sussex University Hospitals NHS Trust and from regulatory authorities, where it is relevant to my baby taking part in this research. I give permission for these individuals to have access to my baby's records.
5. I agree to my baby taking part in the above study.

 Name of Parent/Guardian

 Date

 Signature

 Name of Person receiving consent

 Date

 Signature

1 for parent; 1 for site file; 1 to be kept with hospital notes

14.2.6 Staff poster



NeoAdapt 1- Staff Poster

A study of circulatory adaptation of newborn infants after birth

Inclusion Criteria:

- Neonates >33 weeks gestational age
- Postnatal age <72 hours
- Parental informed consent
- Receiving special care on TMBU
- Receiving routine care on the postnatal ward

Exclusion Criteria:

- Non-viability;
- Congenital hydrops
- Malformations likely to affect cardiovascular adaptation
- Surgery planned within 72 hours of birth
- Chromosomal anomalies
- Informed consent form (ICF) not signed
- Suspected Sepsis

Procedure:

- Infant enrolled into the study on TMBU will have regular routine observation within the NICU. They will also have echos & pleth traces at 24 hourly intervals for 30 minutes.
- Infant enrolled into the study on the postnatal ward will have routine observations, echos and pleth traces at 24 hourly intervals for 30 minutes.

Primary Outcomes:

- Novel reference values for superior vena cava flow & pleth traces in babies >33 weeks
- The association of superior vena cava flow & pleth trace values to other parameters that assess circulatory status in babies >33 weeks

Co-ordination & Funding:

This single-centre study is co-ordinated from the Trevor Mann Baby Unit in the Brighton & Sussex University Hospitals NHS Trust.

Funding is provided by the European Commission Seventh Framework Programme and the Rockinghorse Charity.

Further Information:

For further information about the study please contact the site investigator:

Principal Investigator: Dr Liam Mahoney
ext: 2317

Supervisors: PD Dr Heike Rabe & Dr Paul Seddon
ext: 4296

Staff Poster Version 1 (02/12/2013)

14.3 NeoAdapt 2 study documentation

14.3.1 Sponsorship approval letter

Brighton and Sussex 
University Hospitals
NHS Trust

21 January 2014

Dr Liam Mahoney
Clinical Research Fellow - Paediatrics
Royal Alexandra Children's Hospital
BSUH NHS Trust
Eastern Road
Brighton
BN2 5BE

Research & Development Directorate
Royal Sussex County Hospital
Eastern Road
Brighton
BN2 5BE

Sponsorship Enquiries: Amanda Geel
Telephone: 01273 696955 ext. 3538
E-mail: sponsorship.approvals@bsuh.nhs.uk

Dear Dr Mahoney

Full Study Title: An observational study investigating novel biomarkers in the evaluation and treatment of neonatal circulatory insufficiency in infant older than 33 weeks gestation. (NeoAdapt 2)

R&D Number: IRAS: 145205

REC Ref: Not yet applied

I am writing to confirm that the Trust is willing to take on the role of Research Sponsor for the duration of the study.

Your project has been allocated the following reference: **IRAS 145205**.
Please quote this on all future correspondence.

1. Conditions of Approval

Please note that you cannot commence this study until you have been given a favourable opinion or approval from:

- Research Ethics Committee (REC).
- BSUH R&D Approvals: (R&D.Approvals@bsuh.nhs.uk)

2. Project Amendments

Should you wish to amend the project in any way, you will need to apply to the Sponsorship Committee for approval before submitting the application to REC and relevant authorities.

Approval of amendments will be conditional upon a financial and legal risk assessment.

3. Indemnity

The study will be indemnified by the Trust in accordance with Health Service Guidance 96(48): *NHS Indemnity - Arrangements for Handling Clinical Negligence Claims against NHS staff*.

4. ICH-GCP Monitoring

The Trust has a duty to ensure that all research that it sponsors is conducted in accordance with applicable legislation, such as the Research Governance Framework; ICH-GCP standards and the Medicines for Human Use (Clinical Trials) Regulations 2004.

The R&D Department is responsible for the monitoring of the study.

Your project has been assessed as:

- **Low Risk** – No monitoring plan will be put in place. However, the Trust undertakes random audits. If your project is selected you will be given six weeks notice to prepare all documentation for inspection.

5. Annual Progress Report and End of Study Report

Please note that you must provide a brief annual progress and end of study report to the Sponsorship Committee and the Ethics Committee.

I wish you luck with your project.

Yours sincerely



Scott Harfield
Head of Research & Development

14.3.2 Research ethics committee approval


Health Research Authority
 NRES Committee London - City & East
 Bristol Research Ethics Committee Centre
 Whitefriars
 Level 3, Block B
 Lewins Mead
 Bristol
 BS1 2NT
 Telephone: 01173421386
 Facsimile: 01173420445

23 April 2014

Dr Liam Mahoney
 Level 6, Room 601
 Royal Alexandra Children's Hospital
 Eastern Road, Brighton
 BN2 5BE

Dear Dr Mahoney

Study title: NeoAdapt 2: An observational study investigating novel biomarkers in the evaluation and treatment of neonatal circulatory insufficiency in infants older than 33 weeks gestational age

REC reference: 14/LO/0318

Protocol number: NEOADAPT 2

IRAS project ID: 145205

Thank you for your letter of 31 March 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Mr Rajat Khullar, nrescommittee.london-cityandeast@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Advertisement - Parents poster- Neo Adapt 2	1	02 December 2013
Advertisement - Staff Poster- Neo Adapt 2	1	18 December 2013
Covering Letter		01 January 2014
Investigator CV		18 December 2012
Letter from Sponsor		21 January 2014
Other: Supervisor CV - Paul Seddon		31 January 2014
Other: Supervisor CV - Heike Rabe		
Antenatal Consent Form Neo Adapt 2	1	18 December 2012
Participant Consent Form - New Adapt 2	2	21 March 2014
Antenatal information Sheet- Neo Adapt 2	1	18 December 2012
Parent Information Sheet - New Adapt 2	2	21 March 2014
Protocol - Neo Adapt 2	2	31 March 2014
REC application		05 February 2014
Response to Request for Further Information		21 March 2014
Generic Antenatal Parental Information Sheet	1	21 March 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

14/LO/0318	Please quote this number on all correspondence
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We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

With the Committee's best wishes for the success of this project.

Yours sincerely



pp Professor Arthur T. Tucker
Chair

Email: nrescommittee.london-cityandeast@nhs.net

*Enclosures: List of names and professions of members
who were present at the meeting and those who submitted written
comments*

*"After ethical review – guidance for
researchers"*

*Copy to: Dr Heike Rabe, Brighton & Sussex Medical School
Mr Scott Harfield, Brighton & Sussex University Hospitals NHS Trust*

14.3.3 Antenatal parent information sheet



NeoAdapt 2

An observational study investigating novel biomarkers in the evaluation and treatment of neonatal circulatory insufficiency in infants older than 33 weeks gestational age

TO BE USED BEFORE THE BIRTH OF A CHILD
ANTENATAL PARENT INFORMATION SHEET

Dear Parents,

We think it is important that you know about a study in this hospital for babies admitted to neonatal unit. Your doctor or midwife may have explained that your baby requires admission to the Trevor Mann Baby Unit as they may be delivered too early (before due-date).

We are doing this study because we want to look at ways to improve the treatment of babies admitted to the Trevor Mann Baby Unit. Please take time to read this leaflet and feel free to ask a doctor or other member of the research team to explain this study in more detail, now or at any other time.

Why am I being approached?

We are approaching you because your baby may be born after 33 weeks gestational age (up to 7 weeks early) and may be cared for in Trevor Mann Baby Unit.

Summary of the study

During the period immediately after birth a baby's circulation needs to quickly adapt to living outside the womb. Babies born too early hearts may not be pumping an adequate supply of blood to important parts of the body. This can lead to a baby requiring lots of medical treatment. The purpose of NeoAdapt 2 is to observe and document the way in which a baby's blood supply is assessed and treated on the Trevor Mann Baby Unit in Brighton.

We want to look at two new methods of assessing a baby's blood supply. One is called superior vena cava flow and the other is the pleth variability index. These non-invasive techniques have not been extensively investigated in infants. This study will provide more knowledge on how these new methods may help doctors decide how to treat poor blood flow in babies.

The study is also particularly interested in investigating the use of a drug called dobutamine which is sometimes used to improve a baby's blood supply. This drug has been commonly used in newborn babies in the UK and around the world for many years. This study will gather information on how dobutamine is processed by the baby's body and will help us design larger studies to see how it is best used in babies.

This study is also being used as part of a PhD that Dr Liam Mahoney is undertaking at Brighton & Sussex Medical School.

What would being in the study mean for my baby?



Following discussion with the neonatal unit team, and if you agree to your baby taking part in the study, you will be asked to sign a consent form. Your baby will then be monitored on the Trevor Mann Baby as is routinely done with all preterm babies.

As well as having routine observations that any other baby admitted to the neonatal intensive care unit would have, your baby will have two extra specific measurements once a day for the first three days of their lives. The first measurement is a superior vena cava flow assessment using an ultrasound machine. At the same time we would also like to measure your baby's pleth variability index. This involves placing a small sensor the size of a small plaster on their hand or foot for the duration of the scan. These are both painless procedures that are well tolerated by babies. All together these measurements should take around 30 minutes in total to complete. We would like to perform these assessments once a day for a maximum of three days.

If your doctor's feel there is a problem with your babies blood supply your baby will receive the treatment that the team considers appropriate, which may or may not include the use of drugs such as dobutamine. If your baby receives dobutamine to help their blood supply we would like to take a maximum of 2 small blood samples (4 drops of blood). This will help us investigate how babies process this drug. To minimise the distress this may cause to your baby, blood sampling will be conducted, if possible from a catheter to avoid extra pain or when the attending doctors or nurses are performing blood tests for clinical purposes. This may not always be possible however and will mean your baby will have a blood test for the research study. The samples will be taken once whilst your baby is being given the drug dobutamine and once after they having finished receiving it.

We realise that having a baby is an exciting event, but can also be a stressful time. To help improve the study we would like to perform these extra measurements on three occasions. However if we can perform these set of measurements once that would help very much in learning new information about how best to treat unwell babies.

Regardless of where your baby is being looked after, being included in this study will not change the care they receive on the postnatal ward or the Trevor Mann Baby Unit.

Thank you for taking the time to read this leaflet. If you want to discuss anything about the study or get more information please ask your doctor. They may be able to help you. If not they will contact one of the team members below.

Name and contact details of local contact

<p>Dr Liam Mahoney Clinical Research Fellow in Paediatrics Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 2317</p>	<p>PD Dr Heike Rabe Senior Lecturer/Honorary Consultant Neonatologist Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 4195 or 2409</p>
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14.3.4 Parent information sheet



NeoAdapt 2

An observational study investigating novel biomarkers in the evaluation and treatment of neonatal circulatory insufficiency in infants older than 33 weeks gestational age

TO BE USED AFTER THE BIRTH OF A CHILD PARENT INFORMATION SHEET

Dear Parents,

We think it is important that you know about a study in this hospital for babies admitted to the Trevor Mann Baby Unit in our hospital.

This leaflet gives you information about a research study called NeoAdapt 2. We are doing this study because we want to look at ways to improve the treatment of babies who are admitted to the neonatal. Please take time to read this leaflet and feel free to ask a doctor or other member of the research team to explain this study in more detail, now or at any other time.

Why am I being approached?

We are approaching you because your baby was born after 33 weeks gestational age (up to 7 weeks early and is being care for on Trevor Mann Baby Unit).

Summary of the project

Studies in premature babies have shown us that getting an adequate blood supply to a baby's organs in the first hours after birth is very important. In particular, the later development of the child is likely to be improved if we can improve this blood supply. The problem we face is that we are not sure of the best way to measure blood supply in babies admitted to the neonatal intensive care unit. Sometimes infants are given drugs to improve their blood supply. However another challenge is that we do not yet know which drug is best for improving a baby's blood supply.

In this project we are going to investigate different ways of checking a baby's blood supply. We are also interested in observing all babies who may need treatment for their blood supply regardless of which drug (if any) they may need. We will pay special attention to a drug called dobutamine which is used in some babies to improve their blood supply.

This study is also being used as part of educational PhD project that Dr Liam Mahoney is undertaking at Brighton & Sussex Medical School.

What questions are we trying to address?

Babies born prematurely may not have developed a strong blood supply as their heart muscles are still growing and need to adapt to life outside the womb. This can interfere with the blood supply to the brain and other organs resulting in the baby needing a lot of medical care. Doctors need to assess how good the blood supply is, but there is no agreement as to how we should do this.

Babies admitted to the intensive care unit are connected to monitoring devices that look at the



functioning of the heart and the brain. There are a variety of methods used such as measuring blood pressure, scanning babies' hearts to calculating how much urine a baby is producing. In this study we are going to compare many different methods – and some new ones – so that we can get agreement as to the most useful way of measuring blood flow in a baby.

What is the current standard treatment for circulation problems after birth?

Whichever method of measuring blood supply is being used, if the medical team decide that there is a problem then they will most probably give a drug into the baby that will boost blood supply and so improve the chances of a good outcome. Three drugs are used in the UK: dopamine, dobutamine and adrenaline. Sometimes more than one drug is needed.

The drug that particularly interests us is dobutamine which is used all over the world to help babies whose blood supply is a worry. There are some small studies showing that these drugs can help babies, but we need more evidence from projects such as this one.

What is the purpose of the study?

Research has shown that measuring the blood flow through a large vein called the superior vena cava (SVC flow assessment) may be a good way of assessing blood supply in an infant. This measurement is done with an ultrasound machine, much like the scans that were used to look at your baby when they are in the womb. SVC flow assessment has not been researched in less premature babies like yours. We would like to measure the SVC flow in your baby to find out more information about this.

Research in adults has shown that measurement of an individual's blood oxygen level using an oxygen saturation monitor can give useful information an individual's blood flow. This measurement is known as the pleth variability index. We would also like to measure this in newborn infants as this may also be useful.

Whilst dobutamine has been used for many years we do not have any information on how babies process this drug. We would like to learn more about this by investigating this drug in babies who receive them whilst on the Trevor Mann Baby Unit.

What does it mean for my baby?

Following discussion with the neonatal unit team, and if you agree to your baby taking part in the study, you will be asked to sign a consent form. Your baby will then be monitored on the Trevor Mann Baby as it is routinely done with all preterm babies.

As well as having routine observations that any other baby admitted to the neonatal intensive care unit would have your baby will have two extra specific measurements once a day for the first three days of their lives. The first measurement is a superior vena cava flow assessment using an ultrasound machine. At the same time we would also like to measure your baby's pleth variability index. This involves placing a small sensor the size of a small plaster on their hand or foot for the duration of the scan. These are both painless procedures that are well tolerated by babies. All



together these measurements should take around 30 minutes in total to complete. We would like to perform these assessments them once a day for a maximum of three days.

If you decide to be a part of the study you will be regularly updated about the results gained from these measurements. As mentioned before there is very little research looking into SVC flow assessment and pleth variability index so it will be difficult for the research team to say how the values gained from these tests may relate to your babies health. It is important to point out that regardless of where you baby is being looked after, being included in this study will not change the care they receive.

If your doctors decide that your baby needs treatment to improve their blood supply then the medical team will want to treat them in the same way as any other baby. If your baby receives dobutamine to help their blood supply we would like to take a maximum of 2 extra blood samples (4 drops of blood) to check how it is handled by the baby's body. To minimise the distress this may cause to your baby, blood sampling will be conducted, if possible from a catheter to avoid extra pain or when the attending doctors or nurses are performing blood tests for clinical purposes. This may not always be possible however and will mean your baby will have a blood test for research purposes. These blood samples will be taken once whilst your baby is being given the drug dobutamine and once after they having finished receiving it.

A member of the research team will check regularly throughout the time your baby is part of the study that you are happy to continue participating in it. This is something called "continuous consent" and is to ensure that you have regular opportunities to ask questions about the study.

What will happen to the results of the research?

At the end of the study the results will be published in an international journal. A copy of the full journal article can be requested from the local contacts below. You and your baby will not be identified in any report or publication arising from the study.

Who is organising and funding the research?

The research team on Trevor Mann Baby Unit are organising the research. The European Commission Seventh Framework and the Rockinghorse Charity is providing some of the funding for the study to be carried out.

Who has reviewed the study?

This study has been looked at by an independent group of people (the National Research Ethics Committees), who protect the safety, rights, wellbeing and dignity of participants. The committee has also checked that we are giving you sufficient information to make an informed decision about taking part.



What will happen if I don't want to be part of the study anymore?

You are free to leave the study at any point without giving any reason for this. It will in no way affect the care your baby receives on the postnatal ward or the Trevor Mann Baby Unit.

Who are my contact persons?

If you wish to discuss any aspect of the study you can contact us using the details below. You can also talk to the consultant taking care of your baby on the ward. The research team can always be contacted by phone: 01273 696955 extension 2317. If you would like to make a complaint you can contact the Patient Advice and Liaison Service on 01273 696955 extension 4029/4588 or by email at pals@bsuh.nhs.uk.

The research team want to thank you for taking the time to read this information sheet.

Name and contact details of local contact

<p>Dr Liam Mahoney Clinical Research Fellow in Paediatrics Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 2317</p>	<p>PD Dr Heike Rabe Senior Lecturer/Honorary Consultant Neonatologist Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 4195 or 2409</p>
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14.3.5 Consent form



NeoAdapt 2

An observational study investigating novel biomarkers in the evaluation and treatment of neonatal circulatory insufficiency in infants older than 33 weeks gestational age

Please complete in black ballpoint pen

To be used after the birth of a child

CONSENT FORM

Short Title: NeoAdapt 2

Name of Researcher: Dr Liam Mahoney

Name of Infant:

Name of Parent:

Patient Study Number:

Please initial all boxes

1. I confirm that I have read and understand the information sheet (Version 2. Dated 21/03/2014) for the above study and have had the opportunity to ask questions which have been answered satisfactorily.
2. I understand that participation of my baby in this study is voluntary and that I am free to withdraw my baby from the study at any time, without reason, without the medical care or legal rights of my baby being affected.
3. I understand that the information obtained during the conduct of this study is confidential, and my baby's data will be treated accordingly.
4. I understand that my baby may have an extra blood test which is for the purposes of the research study.
5. I understand that relevant sections of my baby's medical notes and data collected during the study may be looked at by individuals from the Research Departments at Brighton and Sussex University Hospitals NHS Trust and from regulatory authorities, where it is relevant to my baby taking part in this research. I give permission for these individuals to have access to my baby's records.
6. I agree to my baby taking part in the above study.

Name of Parent/Guardian

Date

Signature

Name of Person receiving consent

Date

Signature

1 for parent; 1 for site file; 1 to be kept with hospital notes

14.3.6 Staff poster



NeoAdapt2- Staff Poster

An observational study investigating novel biomarkers in the evaluation and treatment of neonatal circulatory insufficiency in infants older than 33 weeks gestational age

Inclusion Criteria:

- Neonates >33 weeks gestational age
- Postnatal age <72 hours
- Parental informed consent
- Receiving intensive care on TMBU

Exclusion Criteria:

- Non-viability;
- Congenital hydrops
- Malformations likely to affect cardiovascular adaptation
- Surgery planned within 72 hours of birth
- Chromosomal anomalies
- Informed consent form (ICF) not signed

Primary Outcomes:

- Novel values for superior SVCF & PVI in babies >33 weeks
- The association of SVCF & PVI values to other parameters that assess circulatory status
- To investigate how dobutamine or dopamine treatment may alter SVCF & PVI in neonates >33 weeks
- To obtain specific pharmacokinetic and pharmacodynamic data for dobutamine and dopamine in neonates >33 weeks

Procedure:

- Infant enrolled into the study on TMBU will have regular routine observation within the NICU. They will also have echos for superior vena cava flows (SVCF) & pleth traces (PVI) at 24 hourly intervals for 30 minutes.
- Recording of treatment strategies for circulatory insufficiency and their relation to changes biomarkers for circulatory assessment
- If an infant is commenced on dobutamine they will have a maximum of two blood samples taken for pharmacokinetic studies

Co-ordination & Funding:

This single-centre study is co-ordinated from the Brighton & Sussex University Hospitals NHS Trust.

Funding is provided by the European Commission Seventh Framework Programme and the Rockinghorse Charity.

Further Information:

For further information about the study please contact the site investigator:

Principal Investigator: Dr Liam Mahoney ext. 2317
Supervisors: PD Dr Heike Rabe & Dr Paul Seddon ext. 4296

TMBU Poster Version 1 (18/12/2013)

14.4 NeoAdapt 3 study documentation

14.4.1 Sponsorship approval letter

Brighton and Sussex 
University Hospitals
NHS Trust

Research & Development Directorate
Royal Sussex County Hospital
Eastern Road
Brighton
BN2 5BE

Sponsorship Enquiries: Amanda Geel
Telephone: 01273 696955 ext. 3538
E-mail: sponsorship.approvals@bsuh.nhs.uk

21 January 2014

Dr Liam Mahoney
Clinical Research Fellow - Paediatrics
Royal Alexandra Children's Hospital
BSUH NHS Trust
Eastern Road
Brighton
BN2 5BE

Dear Dr Mahoney

Full Study Title: An observational study investigating novel biomarkers in the evaluation and treatment of neonatal circulatory insufficiency infants suffering from Hypoxic Ischemic Encephalopathy. (NeoAdapt 3).

R&D Number: IRAS: 145271

REC Ref: Not yet applied

I am writing to confirm that the Trust is willing to take on the role of Research Sponsor for the duration of the study.

Your project has been allocated the following reference: **IRAS 145271**.
Please quote this on all future correspondence.

1. Conditions of Approval

Please note that you cannot commence this study until you have been given a favourable opinion or approval from:

- Research Ethics Committee (REC).
- BSUH R&D Approvals: (R&D.Approvals@bsuh.nhs.uk)

2. Project Amendments

Should you wish to amend the project in any way, you will need to apply to the Sponsorship Committee for approval before submitting the application to REC and relevant authorities.

Approval of amendments will be conditional upon a financial and legal risk assessment.

3. Indemnity

The study will be indemnified by the Trust in accordance with Health Service Guidance 96(48): *NHS Indemnity - Arrangements for Handling Clinical Negligence Claims against NHS staff.*

4. ICH-GCP Monitoring

The Trust has a duty to ensure that all research that it sponsors is conducted in accordance with applicable legislation, such as the Research Governance Framework; ICH-GCP standards and the Medicines for Human Use (Clinical Trials) Regulations 2004.

The R&D Department is responsible for the monitoring of the study.

Your project has been assessed as:

- **Low Risk** – No monitoring plan will be put in place. However, the Trust undertakes random audits. If your project is selected you will be given six weeks notice to prepare all documentation for inspection.

5. Annual Progress Report and End of Study Report

Please note that you must provide a brief annual progress and end of study report to the Sponsorship Committee and the Ethics Committee.

I wish you luck with your project.

Yours sincerely



Scott Harfield
Head of Research & Development

14.4.2 Ethics committee approval letter


Health Research Authority
 NRES Committee London - City & East
 Bristol Research Ethics Committee Centre
 Whitefriars
 Level 3, Block B
 Lewins Mead
 Bristol
 BS1 2NT
 Telephone: 01173421386
 Facsimile: 01173420445

23 April 2014

Dr Liam Mahoney
 Clinical Research Fellow in Paediatrics
 Brighton & Sussex Medical School
 Level 6, Room 601
 Royal Alexandra Children's Hospital
 Eastern Road, Brighton
 BN2 5BE

Dear Dr Mahoney

Study title:	NeoAdapt Study 3: An observational study investigating novel biomarkers in the evaluation and treatment of neonatal circulatory insufficiency in infants suffering from Hypoxic Ischemic Encephalopathy
REC reference:	14/LO/0319
Protocol number:	NEOADAPT 3
IRAS project ID:	145271

Thank you for your letter of 31 March 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Mr Rajat Khullar, nrescommittee.london-cityandeast@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publicly accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Advertisement - Parents Poster Neo-Adapt 3	1	02 December 2013
Advertisement - Staff Poster- Neo-Adapt 3	1	18 December 2013
Covering Letter		01 January 2014
Investigator CV		11 December 2013
Letter from Sponsor		21 January 2014
Other: Supervisor Summary CV - Heike Rabe		18 December 2013
Other: Supervisor Summary CV - Paul Seddon		
Consent Form - Neo adapt 3	2	21 March 2014
Parent Information Sheet-Neo adapt 3	2	21 March 2014
Protocol - Neo adapt 3	2	31 March 2014
REC application		31 January 2014
Response to Request for Further Information		21 March 2014
Generic Antenatal Parental Info sheet	1.0	21 March 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

14/LO/0319	Please quote this number on all correspondence
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We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

With the Committee's best wishes for the success of this project.

Yours sincerely



pp Professor Arthur T. Tucker
Chair

Email: nrescommittee.london-cityandeast@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

*Copy to: Dr Heike Rabe
Mr Scott Harfield, Brighton & Sussex University Hospitals NHS Trust*

14.4.3 Parent information sheet

NeoAdapt 3

An observational study investigating novel biomarkers in the evaluation and treatment of neonatal circulatory insufficiency in infants suffering from Hypoxic Ischemic Encephalopathy

PARENT INFORMATION SHEET

Dear Parents,

We know that your baby is unwell and that this is an extremely stressful time for you. It may not seem like the best time to think about taking part in a research study but we would like to talk to you about a study in this hospital for babies admitted with hypoxic ischemic encephalopathy (HIE). We would like to give you the opportunity to be informed about and possibly take part in this study.

This leaflet gives you information about a research study called NeoAdapt 3. Other parents in your situation are receiving this information. Please take time to read this leaflet and feel free to ask a member of the research team to explain this study in more detail, now or at any other time.

Why am I being approached?

We are approaching you as your baby has been admitted to the Trevor Mann Baby Unit for cooling therapy.

Summary of the study

Your baby is being treated with total body cooling therapy. This has been shown to sometimes improve babies long term outcomes who are suffering from HIE. We know that babies with HIE can have problems with how their heart pumps blood to vital organs. In addition we also know that cooling therapy can also alter how a baby's heart pumps. This can influence a babies overall blood supply. Doctors need to be able to assess how good this blood supply is, but there is no agreement as to how best to do this.

Doctors use a variety of ways to assess blood supply such as measuring blood pressure, scanning babies' hearts to looking at a variety of blood tests. In this study we are going to compare many different methods – and some new ones – so that we can get agreement as to the most useful way of measuring blood flow in a baby.

Sometimes infants are given drugs to improve their blood supply. In babies who receive cooling therapy the way that they break down drugs is changed and can increase or decrease the amount of drug we think they receive. Information gathered from this study will help us to increase the knowledge that we have about how to give drugs properly to babies receiving total body cooling therapy.

This study is also being used as part of educational PhD project that Dr Liam Mahoney is undertaking at Brighton & Sussex Medical School.



What is the current standard treatment for circulation problems after birth?

Whichever method of measuring blood supply is being used, if the medical team decide that there is a problem then they will probably give a drug to your baby that will improve their blood supply and so help improve outcome. Three drugs are used in the UK: dopamine, dobutamine and adrenaline. Sometimes more than one drug is needed.

The drug dobutamine particularly interest us and is currently used all over the world to help babies whose blood supply is inadequate. There are some small studies showing that this drug can help babies, but we need more evidence from projects such as this one.

What is the purpose of the study?

Research has shown that measuring the blood flow through a large vein connected to your baby's heart is maybe a good way of assessing blood supply in an infant. This measurement is known as a superior vena cava flow assessment and is done with an ultrasound machine, much like the scans that were used to look at your baby when they are in the womb. A small study of very premature infants showed that a low superior vena cava flow measurement was also associated with poor long term development of a baby. However superior vena cava flow in babies receiving cooling therapy has not been very well researched. We would like to measure the superior vena cava flow in these babies in order to find out more information about this.

Research in adults has shown that measurement of an individual's blood oxygen level using an oxygen saturation monitor can give useful information an individual's blood flow. This measurement is known as the pleth variability index. We would also like to measure this as this may be useful in assessing a baby's blood supply.

Total body cooling therapy for hypoxic ischemic encephalopathy has been used routinely for a few years in the UK. Research has shown that it may interfere with how babies process drugs. We would like to investigate how the drug dobutamine is processed by babies receiving cooling therapy. This will give important information about how best to use this drug in treating a baby's blood supply.

What does it mean for my baby?

Your baby will receive the same care that all babies who are admitted to the Trevor Mann Baby Unit with Hypoxic Ischemic Encephalopathy. Typically babies with hypoxic ischemic encephalopathy are treated with total body cooling for the first 72 hours of their life. They also will have routine observations and scans that any other baby admitted to neonatal intensive care would have.

As well as having routine observations your baby will have two extra specific measurements once a day for the first three days they receive cooling therapy and once after this treatment has ended. The first measurement is a superior vena cava flow assessment using an ultrasound machine. At the same time we would also like to measure your baby's pleth variability index. This involves placing a small sensor the size of a small plaster on their hand or foot for the duration of the scan. These are both painless procedures that are well tolerated by babies. All together these measurements should take around 30 minutes in total to complete.



If you decide to be a part of the study you will be regularly updated about the results gained from these measurements. As mentioned before there is very little research looking into SVC flow assessment and pleth variability index so it will be difficult for the research team to say how the values gained from these tests may relate to your babies health. It is important to point out that regardless of where your baby is being looked after, being included in this study will not change the care they receive.

If your doctors decide that your baby needs treatment to improve their blood supply then the medical team will want to treat them in the same way as any other baby. If your baby receives dobutamine to help their blood supply we would like to take a maximum of 2 small blood samples (4 drops of blood) to check how it is handled by the baby's body. To minimise the distress this may cause to your baby, blood sampling will be conducted, if possible from a catheter to avoid extra pain or when the attending doctors or nurses are performing blood tests for clinical purposes. This may not always be possible however and will mean your baby may have a blood test for the research study. The blood samples will be taken once whilst your baby is being given the drug dobutamine and once after they having finished receiving it.

As mentioned previously if you decide to include your baby into this study they will have an ultrasound scan of their heart. Babies will not always have such a scan whilst on the neonatal unit. Rarely this scan may show a problem or defect with your baby's heart which is not known. If this is the case then your baby will be reviewed by a Consultant doctor. We will arrange any necessary treatment required for your baby.

If you decide to be a part of the study you will be regularly updated about the results gained from these measurements. Also a member of the research team will check regularly throughout the time your baby is part of the study that you are happy to continue participating in it. This is something called "continuous consent" and is to ensure that you have regular opportunities to ask questions about the study.

What will happen to the results of the research?

At the end of the study the results will be published in an international journal. A copy of the full journal article can be requested from the local contacts below. You and your baby will not be identified in any report or publication arising from the study.

Who is organising and funding the research?

The research team on Trevor Mann Baby Unit are organising the research. The European Commission is providing some of the funding for the study to be carried out.

Who has reviewed the study?

This study has been looked at by an independent group of people (the National Research Ethics Committees), who protect the safety, rights, wellbeing and dignity of participants. The committee has also checked that we are giving you sufficient information to make an informed decision about taking part.



What will happen if I don't want to be part of the study anymore?

You are free to leave the study at any point without giving any reason for this. It will in no way affect the care your baby receives on the Trevor Mann Baby Unit.

Who are my contact persons?

If you wish to discuss any aspect of the study you can contact us using the details below. You can also talk to the consultant taking care of your baby on the ward. The research team can always be contacted by phone: 01273 696955 extension 2317. The research team want to thank you for taking the time to read this information sheet. If you would like to make a complaint you can contact the Patient Advice and Liaison Service on 01273 696955 extension 4029/4588 or by email at pals@bsuh.nhs.uk.

Name and contact details of local contact

<p>Dr Liam Mahoney Clinical Research Fellow in Paediatrics Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 2317</p>	<p>PD Dr Heike Rabe Senior Lecturer/Honorary Consultant Neonatologist Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 4195 or 2409</p>
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14.4.4 Consent form

NeoAdapt 3

An observational study investigating novel biomarkers in the evaluation and treatment of neonatal circulatory insufficiency in infants suffering from Hypoxic Ischemic Encephalopathy

Please complete in black ballpoint pen

CONSENT FORM

Short Title: NeoAdapt 3

Name of Researcher: Dr Liam Mahoney

Name of Infant:

Name of Parent:

Patient Study Number:

Please initial all boxes

1. I confirm that I have read and understand the information sheet (Version 3. Dated 29/05/2014) for the above study and have had the opportunity to ask questions which have been answered satisfactorily.
2. I understand that participation of my baby in this study is voluntary and that I am free to withdraw my baby from the study at any time, without reason, without the medical care or legal rights of my baby being affected.
3. I understand that the information obtained during the conduct of this study is confidential, and my baby's data will be treated accordingly.
4. I understand that my baby may have an extra blood test which is for the purposes of the research study.
5. I understand that relevant sections of my baby's medical notes and data collected during the study may be looked at by individuals from the Research Departments at Brighton and Sussex University Hospitals NHS Trust and from regulatory authorities, where it is relevant to my baby taking part in this research. I give permission for these individuals to have access to my baby's records.
6. I agree to my baby taking part in the above study.

 Name of Parent/Guardian

 Date

 Signature

 Name of Person receiving consent

 Date

 Signature

1 for parent; 1 for site file; 1 to be kept with hospital notes

Page 1 - Version 2 (21/03/14)

14.4.5 Staff poster



NeoAdapt 3- Staff Poster

An observational study investigating novel biomarkers in the evaluation and treatment of neonatal circulatory insufficiency in infants suffering from Hypoxic Ischemic Encephalopathy

Inclusion Criteria:

- Neonates \geq 36 weeks gestational age
- Postnatal age <72 hours
- Parental informed consent
- Admitted to NICU for total body cooling

Exclusion Criteria:

- Non-viability
- Congenital hydrops
- Malformations likely to affect cardiovascular adaptation
- Surgery planned within 72 hours of birth
- Chromosomal anomalies
- Informed consent form (ICF) not signed

Procedure:

- Infant enrolled into the study on TMBU will have regular routine observation within the NICU. They will also have echos for superior vena cava flows (SVCF) & pleth traces (PVI) at 24 hourly intervals for 30 minutes.
- Recording of treatment strategies for circulatory insufficiency and their relation to changes biomarkers for circulatory assessment
- If an infant is commenced on dobutamine they will have a maximum of two blood samples taken for pharmacokinetic studies

Primary Outcomes:

- Novel values for superior SVCF & PVI in cooled babies with HIE
- The association of SVCF & PVI values to other parameters that assess circulatory status
- To investigate how dobutamine or dopamine treatment may alter SVCF & PVI in cooled babies with HIE
- To obtain specific pharmacokinetic and pharmacodynamic data for dobutamine and dopamine in cooled babies with HIE

Co-ordination & Funding:

This single-centre study is co-ordinated from the Brighton & Sussex University Hospitals NHS Trust.

Funding is provided by the European Commission Seventh Framework Programme and the Rockinghorse Charity.

Further Information:

For further information about the study please contact the site investigator (details below):

Principal Investigator: Dr Liam Mahoney
Supervisors: PD Dr Heike Rabe & Dr Paul Seddon

TMBU Poster Version 1 (18/12/2013)

14.5 Generic study documentation

14.5.1 Generic parent information sheet






NeoAdapt Studies

Dear Parents/Carers,

Thank you for taking the time to read about the NeoAdapt Studies.

The Trevor Mann Baby Unit and the Post-natal ward at the Royal Sussex County Hospital are conducting a set of studies looking at how best to measure and treat blood flow in babies admitted to the neonatal unit and the postnatal ward.

In these studies we want to look at babies who are either-

- Born older than 33 weeks
- Admitted to the Neonatal unit for cooling therapy

The study involves measuring your baby's vital signs such as their heart rate and blood pressure. It also involves two extra measurements; one known as a superior vena cava flow assessment and one called the pleth variability index. These measurements are done using an ultrasound machine scanner (much like the scan you had to look at your baby in the womb) and by placing a small sensor the size of a small plaster on their hand or foot for the duration of the scan. These are both painless procedures that are well tolerated by babies.



Ultrasound Machine Sensor



Pleth Variability Index Sensor

All together these measurements should take around 30 minutes in total to complete. If your bay is on the post natal ward or the neonatal unit we would like to perform these assessments a maximum of once a day over three days. If your baby is receiving cooling therapy these measurements will be repeated once a day over four days.

Thank you

Name and contact details of local contacts

Dr Liam Mahoney Clinical Research Fellow in Paediatrics Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 2317	PD Dr Heike Rabe Senior Lecturer/Honorary Consultant Neonatologist Trevor Mann Baby Unit Royal Sussex County Hospital Eastern Road Brighton BN2 5BE Tel: 01273 696955 ext 4195 or 2409
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14.5.2 Generic parent poster

Brighton and Sussex
University Hospitals
NHS Trust



brighton and sussex
medical school
TEN YEARS OF SUCCESS

neocirculation
an international network of research
dedicated to exploring and improving
the neonatal circulation



Dear Parents and Guardians,

The Trevor Mann Baby Unit is taking part in set of research studies

'NeoAdapt'

Please take a minute to read the information below as we may ask
your permission for your baby to take part in these studies



In these studies we are looking at how best to measure blood flow in
babies. This will provide doctors with more knowledge on how to
treat poor blood flow in babies.

To help us we would like to recruit babies who are either-

- Born older than 33 weeks
- Babies who are receiving cooling therapy

For any queries contact the study team:

Dr Liam Mahoney, Clinical Research Fellow. Ext:2317

PD Dr Heike Rabe, Senior Lecturer/Honorary Consultant Neonatologist

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16 Publications

1. Mahoney L, Shah G, Crook D, Rojas-Anaya H, Rabe H. A Literature Review of the Pharmacokinetics and Pharmacodynamics of Dobutamine in Neonates. *Pediatric Cardiology*. 2016;37(1):14-23.
2. L. Mahoney, D. Wertheim, J.R. Fernandez Alvarez, N. Aiton, H. Rojas-Anaya, P. Seddon, H. Rabe. Novel non-invasive measurements in the assessment of normal cardio-vascular adaptation in term & near term infants. *Journal of Pediatric and Neonatal Individualized Medicine*. 2015;4(2):e040207.
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