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Disertační práce

LOW CARDIAC OUTPUT IN EXTREMELY LOW GESTATION AGE NEONATES AND INTRAVENTRICULAR HAEMORRHAGE

NÍZKÝ SRDEČNÍ VÝDEJ U EXTRÉMNĚ NEZRALÝCH NOVOROZENCŮ A MOZKOVÉ INTRAVENTRIKULÁRNÍ KRVÁCENÍ

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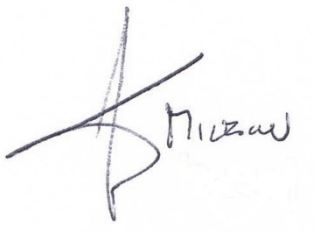

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Abbreviations

BA; Bland-Altman

BP; Blood Pressure

BPD; Bronchopulmonary Dysplasia

CAR; Cerebral Autoregulation

CBF; Cerebral Blood Flow

CLD; Chronic Lung Disease

CO; Cardiac Output

CT; Computed Tomography

CTG; Conservative Treatment Group

CWIUH; Coombe Women and Infants University Hospital

DA; Ductus Arteriosus

DV; Ductus Venosus

DR; Delivery Room

DS; Digital Stethoscope

ECG; Electrocardiography

Echo-CO; Echocardiography Measured Cardiac Output

ELBW; Extremely Low Birth Weight

ETG; Early Treatment Group

FMPAP; Foetal Mean Pulmonary Artery Pressure

FO; Foramen Ovale

GFAP; Glial Fibrillary Acidic Protein

HR; Heart Rate

HUS; Handheld Ultrasound

IVC; Inferior Vena Cava

IVH; Intraventricular Haemorrhage

LA; Left Atrium

LV; Left Ventricle

LVO; Left Ventricular Output

MABP; Mean Arterial Blood Pressure

MRI; Magnetic Resonance Imaging

NCPAP; Nasal Continuous Positive Airway Pressure

NDI; Neurodevelopmental Impairment

NE; Neonatal Encephalopathy

NEC; Necrotising Enterocolitis

NICOM™; Non-invasive Cardiac Output Monitor

NICU; Neonatal Intensive Care Unit

NIRS; Near Infrared Spectroscopy

PDA; Patent Ductus Arteriosus

PFO; Patent Foramen Ovale

PH; Pulmonary Haemorrhage

PICCO; Pulse Index Continuous Cardiac Output

PIVH; Peri-intraventricular Haemorrhage

PEEP; Positive End Expiratory Pressure

PPHN; Persistent Pulmonary Hypertension of the Newborn

PVHI; Peri-Ventricular Haemorrhagic Infarction

PVL; Periventricular Leucomalacia

PVR; Pulmonary Vascular Resistance

RDS; Respiratory Distress Syndrome

REC; Research Ethics Committee

ROC; Receiving Operating Characteristic

ROP; Retinopathy of Prematurity

RA; Right Atrium

RV; Right Ventricle

RVO; Right Ventricular Output

RV-RA; Right Ventricle – Right Atrium

SctO2; Cerebral Mixed Venous Saturation

STG; Symptomatic Treatment Group

SV; Stroke Volume

SVC; Superior Vena Cava

SVR; Systemic Vascular Resistance

TAPSE; Tricuspid Annular Plane Systolic Excursion

TDI; Tissue Doppler Imaging

TH; Therapeutic Hypothermia

tnECHO; Targeted Neonatal Echocardiography

TOST; Two-One-Sided-t-Test

TR; Tricuspid Valve Regurgitation

USCOM; Ultrasonic Cardiac Output Monitor

VLBW; Very Low Birth Weight

VON; Vermont Oxford Network

VTI; Velocity Time Integral

Summary

This thesis is a commented monothematic collection of nine publications addressing cardiovascular assessment in preterm and term infants with a special focus on the immediate postnatal period. At the beginning, it provides a literature review of different modalities of Cardiac Output (CO) measurements in neonates, pathophysiology of Peri-intraventricular Haemorrhage (PIVH) in preterm infants and short review of the neonatal transition with some notes on role of the Patent Ductus Arteriosus (PDA).

The main thesis is then divided into three logical parts. In the first and the main part, CO measurement possibilities in the neonatal period are reviewed and published with bioreactance identified as a novel emerging method of continuous CO assessment. The second study of this part is a prospective, observational cohort study in infants with a birth weight of less than 1250g. The CO was measured by bioreactance between 6 and 48 hours of age. Infants with PIVH and/or Necrotising Enterocolitis (NEC) had significantly lower CO compared to infants without these complications on day one of life. This low CO was then followed by a significant increase on day two of life. The third study is a prospective observational cohort study in near term and term infants undergoing Therapeutic Hypothermia (TH) for diagnosis of Neonatal Encephalopathy (NE). We have demonstrated that the assessment of the hemodynamic status of term infants with NE undergoing TH in addition to cerebral perfusion in a continuous fashion is feasible and reflects the expected hemodynamic changes occurring as a result of TH and rewarming. In our opinion, further studies using bioreactance are warranted in order to help to understand systemic blood flow physiology and pathophysiology in preterm and term infants including the alteration in perfusion leading to adverse outcomes and the response to different treatments currently used to tackle hypotension/hypoperfusion.

In the second part of the main thesis, we review one of the most used and commonly employed methods of echocardiographic CO measurement, Superior Vena Cava (SVC) flow,

with a research study assessing a newly proposed technique of SVC flow measurement and comparing it to the standard validated technique. The study is a prospective, observational cohort study in infants with a birth weight of less than 1250g. Both SVC flow echocardiography measurement techniques yielded clinically equivalent results, although due to poor correlation and agreement they do not seem to be interchangeable. The poor correlation is mostly secondary to the velocity time integral measurements and we would strongly advocate the use of the standard technique. The SVC cross-sectional area had quite satisfactory correlation early after delivery and in fact it seems plausible that the modified technique obtains more stable and accurate values.

In the last part of the thesis, we present a prospective observational study of immediate transition of the cardiovascular system in infants with a birth weight of less than 1000g. There was a significant decrease in pulmonary pressures between 6 and 12 hours of age, however PDA diameter was unchanged over the first 12 hours of life and flow remained bidirectional in almost a quarter of infants, suggesting ongoing transition. In the second small prospective observational study in term infants, we have identified Electrocardiography (ECG) as the quickest method of recording heart rate in the delivery room compared to digital stethoscope and handheld ultrasound. However, the traditional stethoscope remains the quickest method to obtain a heart rate when the time delay in applying ECG leads is taken into consideration. The last two studies are retrospective cohort studies, intimately connected and exploring different management of PDA and ultimately describing the natural history of the PDA in Very Low Birth Weight (VLBW, <1500g) infants. These two studies document the feasibility of conservative treatment of a PDA in VLBW infants. Spontaneous closure of the ductus arteriosus is highly likely in VLBW infants as demonstrated in a large cohort of infants who underwent truly non-interventional conservative PDA management. The rate of permanent ductal patency at discharge is inversely related to the gestational age and birthweight. The

results support the existing data on the feasibility of conservative management without an increase in neonatal morbidity and mortality.

Souhrn

Tato disertační práce je monotematicky zaměřeným souborem devíti původních vědeckých publikací zaměřených na hemodynamiku a možnosti evaluace kardiovaskulárního systému u nedonošených a donošených novorozenců v prvních dnech života při probíhající adaptaci kardiovaskulárního systému na extrauterinní život. Na začátku disertace předkládame literární přehled měření srdečního výdeje (SV) u novorozenců, patofysiologie peri-intaventrikulárního krvácení (PIVH) u nedonošených novorozenců a krátký přehled nejdůležitějších částí kardiovaskulárni adaptace u novorozence s přihlédnutím k roli persistujícího arteriálního duktu (PDA).

Hlavní část disertace je poté rozdělena do tří logicky na sebe navazujících částí. První a hlavní část obsahuje publikovaný systematický přehled měření SV u novorozenců. Tento přehled indentifikoval bioreaktanci jako novou metodu kontinuálního měření SV. Tato metoda byla poté využita v dalších dvou vědeckých publikacích prezentovaných v této části disertace. První je prospektivní, observačni kohortová studie u dětí s porodní hmotností pod 1250g. V této studii jsem měrili SV bioraktancí mezi 6. a 48. hodinou života. Novorozenci s PIVH a nekrotisující enterokolitidou měli první den života signifikantně nižší SV oproti novorozencům bez těchto komplikací. Tento nízký SV byl následován signifikantním zvýšením druhý den života. Druhou studií je prospektivní, observační kohortová studie u lehce nedonošených a donošených novorozenců s diagnózou neonatální encefalopatie (NE) léčených terapeutickou hypotermií (TH). V této studii jsme prokázalí, že pomocí bioreaktance je možné kontinuálně sledovat SV u těchto novorozenců (společně s kontinuálním měřením parametrů mozkové perfúze – metodou ‚near infrared spectroscopy‘). Tato studie ukázala očekávané hemodynamické změny v důsledku TH a postupného ohříváni na konci TH. Dle našeho názoru jsme tímto prokázali nutnost dalších studií využívajících měření SV bioreaktancí, u donošených a nedonošených novorozenců, které by měly přispět k dalšímu pochopení

fysiologie a patofysiologie systemického SV a změn SV vedoucích potencionálně k morbiditě a mortalitě u této skupiny pacientů. Další studie by také mohly přispět k většímu pochopení terapeutických postupů používaných při léčbě hypotenze a hypoperfuse.

Druhá část obsahuje publikovaný systematický přehled jednoho z nejčastěji používaných echokardiografických měření SV u novorozenců, a to průtoku horní dutou žílou (SVC). Po tomto přehledu následuje prospektivní, observační kohortová studie u novorozenců s porodni hmotností pod 1250g. V této studii jsme porovnali nově navrženou metody meření průtoku v SVC s metodou standardní a validovanou. Použitím nové metody jsem získali ekvivalentní výsledky v porovnání s metodou standarní (ekvivalence byla definována jako -20 až +20 ml/kg/min). Nicméně jsme prokázali špatnou korelaci a shodu mezi námi použitými metodami a tyto metody nelze zaměňovat. Špatná korelace byla z větší části důsledkem měření ‘velocity time integral‘ a z tohoto důvodu doporučujeme standardní metodu měření. V krátké době po porodu korelovalo měření plochy SVC celkem dobře mezi oběma metodami a je teoreticky možné, že nová metoda poskytuje stabilnější a přesnější měření, zejména v delším časovém horizontu.

Závěrečná část disertace obsahuje prospektivní, observační kohortovou studii kardiovaskulární adaptace u novorozenců s porodní hmotností pod 1000g. V této práci jsme zdokumentovali signifikantní pokles tlaku v plicní arterii mezi 6. a 12. hodinou života, nicméně průměr PDA zůstal nezměněn a u jedné čtvrtiny zkoumaných novorozenců byl průtok PDA bidirekční, což naznačuje zhoršenou poporodní adaptaci. Ve druhé, prospektivní, observační kohortové studii jsem se zaměřili na způsoby měření srdeční akce u donošených novorozenců na porodním sále. Nejrychlejší ze zkoumaných metod byla elektrokardiografie (EKG) (ve srovnání s digitálním stetoskopem a kompaktním ultrazvukem). Nicméně po započítaní času nutného k aplikaci EKG byl nejrychlejší metodou klasický stetoskop. Poslední dvě studie jsou úzce související retrospektivní kohortové studie zabývající se různými přístupy k léčbě PDA a

popisující fysiologii PDA u novorozenců velmi nízké porodní hmotnosti (VLBW, <1500g). Tyto dvě studie ukazují možnost konzervativního přístupu k terapii PDA u VLBW novorozenců. Tyto studie dále prokázaly, že u většiny VLBW novorozenců dochází ke spontánnímu uzávěru PDA bez nutné terapie. Podíl novorozenců s PDA při propuštění je inverzně závislý na gestačním stáří a porodní hmotnosti. Naše výsledky podporují možnost konzervativního přístup k terapii PDA bez zvýšení novorozenecké mobidity a mortality.

1. Introduction

Monitoring and maintaining adequate cardiac output (CO) is a key component of cardiovascular care in the preterm neonate. Low output states have been associated with a variety of adverse outcomes and there is some evidence that low central blood flow may respond to medical therapy.(1, 2) Immaturity of the cardiovascular system predisposes the preterm neonate to low-flow states and the relative immaturity of other organ systems means that premature infants are vulnerable to organ damage as a result of low flow. The unique anatomy and physiology of preterm infants makes monitoring of CO a difficult process, complicated by the transitional circulation and the presence of shunting.

Abnormal perfusion is recognised as having adverse effects on the preterm neonate with reduced mean arterial blood pressure (MABP) being associated with increased mortality, increased severe intraventricular haemorrhage (IVH) and ischaemic brain lesions.(3) The duration of hypotension also correlates with developmental outcome in Very Low Birth Weight (VLBW; birth weight < 1500g) infants (4) and Extremely Low Birth Weight (ELBW; birth weight <1000g) infants, with treated hypotension they are at risk of hearing loss, motor delay and death.(5) While such derangements in traditional clinical measurements of perfusion clearly have prognostic implications for the neonate, traditional clinical assessment is known to be of limited use in predicting central blood flow within the paediatric population.(6) Blood Pressure (BP) is one of the commonest clinical methods of assessing circulatory status; however, accurate measurement in the preterm population is difficult and there is no consensus definition on hypotension. In addition, BP shows poor correlation with central blood flow (7-12) and is likely to be a late sign of uncompensated low perfusion meaning it is an insensitive sign in early circulatory compromise.

Capillary refill (7, 8, 13), urine output (7) and temperature (7) are similarly unreliable for detection of low perfusion in the preterm neonatal population. While in combination these clinical signs are undoubtedly useful in defining critically unwell infants, they are clearly inadequate as markers of perfusion in the preterm population as they lack sensitivity in the early stages of disease where medical intervention is likely to have the greatest role.

As a result, neonatologists should turn to more objective measurements in assessment of perfusion within this population. The availability of bedside measures of CO such as echocardiography is acknowledged as an important tool for adult and paediatric intensivists in improving outcome.(14) The non-invasive nature of echocardiographic measurements along with the real-time information provided means that they are favoured in the acute setting, and there is evidence that the availability of bedside CO monitoring positively impacts patient care.(14-17) Low central blood flow measurements in preterm infants are associated with a variety of early adverse outcomes including altered electroencephalographic activity, oliguria, hyperkalaemia, Necrotising Enterocolitis (NEC), Retinopathy of Prematurity (ROP), IVH and death.(9, 18-25) Preterm infants with reduction in Left Ventricular Output (LVO) or Right Ventricular Output (RVO) of more than 50% in late-onset sepsis have increased mortality (26), and low central blood flow has been linked to adverse long-term neurodevelopmental outcomes in the preterm population.(20, 27) Low CO is also a common perioperative complication for children with congenital heart disease (28), and is a risk factor for prolonged mechanical ventilation following cardiac surgery (29) and for adverse neurodevelopmental outcome.(28)

Given the implications of reduced central blood flow in the preterm neonate there is a need for a robust, non-invasive and continuous measure of CO within this population. Criteria for the ideal technology have been outlined in previous publications (30), though at present no ideal technology exists to help us to prevent adverse outcomes in preterm neonates.

2. Cardiac Output Measurements

2.1 Traditional Invasive Methods

Due to the availability of newer, less-invasive technologies many of the "gold-standard" invasive techniques used in adult medicine are rarely used in the neonatal population. These methods still merit discussion as they are held by some as the most accurate method of evaluating CO despite their infrequent clinical use and limited data on repeatability within the paediatric population. One of the oldest methods of invasively measuring CO are techniques based on the Fick principle. The Fick principle measures blood flow to an organ (most commonly used to measure systemic blood flow as a whole) based on the idea that the blood flow may be calculated if the amount of a substance taken up by an organ over time is known, and the quantity of the substance can be measured both proximal to and distal to the organ of interest. The classic methodology used Oxygen and stated that CO may be calculated if oxygen consumption, arterial oxygen concentration and venous oxygen concentration are known. Subsequent adaptations of the Fick principle have also used Carbon Dioxide, with animal models suggesting that the methodology may be potentially viable in the neonatal population.(31) The Fick methodology has been used successfully in term neonates (32, 33) and appears to correlate well with other invasive methodologies within the paediatric population.(32) The obvious disadvantages of this methodology are the requirement for arterial and venous lines and the need for accurate breath-by-breath oxygen consumption calculation which is likely to prove difficult in preterm neonates where the commonly used uncuffed endotracheal tubes are likely to make such measurements inaccurate.

Modern thermodilution techniques rely on placement of a specialised catheter within the pulmonary artery with a temperature probe placed distally. The most commonly employed

example is the Swan-Ganz catheter, placement of which has previously been undertaken successfully in the preterm neonatal population.(34) This catheter has a temperature probe at the tip and at a proximal point which lies in the Right Atrium (RA) there is a port through which a cold solution is injected. Following injection of a cold solution into the RA, the catheter tip in the pulmonary artery detects the temperature change relative to the dilution within the blood allowing accurate measurement of CO. The original description of the Swan-Ganz catheter showed that it produced comparable values to dye-dilution with a repeatability of 4.1%.(35) While held as the "gold standard" by many there is a variety of potential pitfalls to the technique.(36, 37) Variations on this technique including trans-pulmonary thermodilution have been developed (38), and are feasible in the paediatric population with high repeatability.(39) Despite evidence of validation in comparison to the Fick methodology in children (33), data in the preterm neonatal population is limited and the technique is seldom used due to technical restraints.

Dye-dilution is based on injection of a dye in the pulmonary artery and measurement of the dye concentration through the peripheral arterial line. If the concentration and volume of dye injected is known, CO is subsequently calculated based on the concentration detected peripherally over time.(40) Experiments in humans have confirmed that the dye-dilution methodology correlates well with the Fick methodology and thermodilution.(41) Modifications of this technique have been utilised in the term neonate to determine CO (42), but similar to thermodilution this has not entered routine practice and has not been examined in the preterm neonatal population.

While there is no true "gold-standard" for CO monitoring in the neonatal population, invasive technologies are considered by many to be the most accurate methodologies for determining CO. Their clinical use in the neonate is rare due to a variety of important limitations. Infection, damage of surrounding tissue and thrombus formation number among

the most serious complications of central catheter placement. Other difficulties arising from use of the techniques include the need for arterial and venous blood sampling and potential volume overload from injection of substrate. As well as the risk of morbidity and technical limitations, catheter placement is a source of discomfort and the measurements of output, while likely accurate, are not continuous.

2.2 Minimally Invasive Techniques

Pulse contour and pulse power analysis make inferences about CO and other central blood flow parameters based on a peripherally measured arterial pulse wave. Both techniques rely on the presence of a peripheral arterial line and these techniques represent two of the most extensively investigated minimally invasive technologies for measuring CO in the adult population. Pulse contour analysis relates the contour of arterial pressure over time to stroke volume and systemic vascular resistance. A mathematical algorithm is then used to calculate CO based on measurements taken from a blood flow sensor within a peripheral artery and a variety of devices such as the FloTrac, Pulse Index Continuous Cardiac Output (PICCO) monitor and the pressure recording analytical method represent variations on this idea.(43) Pulse contour analysis has been used successfully in older children with congenital heart disease (44), but concerns have been raised with regards to its accuracy in relation to traditional methodologies within the paediatric population.(45) Pulse power analysis is a similar technology relying on peripherally obtained arterial measurements to deduce central flow measurements. Pulse power analysis relies on the idea that variations in pulse power detected peripherally are equivalent to stroke volume minus the blood volume sent to the periphery of the body. As the title suggests, the power of the arterial pulsation rather than its contour is used to calculate CO using a mathematical algorithm. Pulse power devices have not been extensively

investigated in paediatric patients to date. While these devices are minimally invasive there is a variety of downsides to using this technology.(46) Changes in systemic resistance and certain cardiac conditions are known to affect the results obtained in adults, and while minimally invasive, certain devices require calibration before use and both methodologies rely on placement of an arterial catheter.

Partial gas rebreathing based on a modification of the Fick principle has emerged as a much less invasive alternative for measuring CO in adults but remains untested in preterm neonates. Ultrasound dilution methodology relies on changes in ultrasound velocity within blood following the injection of body-temperature isotonic saline to calculate CO. It has compared favourably to more traditionally invasive techniques in older children (47, 48), and in vitro work has shown that the technology may be feasible in neonates.(49) Despite some promising results, ultrasound dilution requires placement of arterial and central venous catheters to create an extracorporeal loop and has not been validated in vivo in the neonatal population to date. Lithium dilution is a method of calculating CO where a Lithium Chloride solution is injected through a central venous catheter and a sensor on a peripheral artery measures the lithium concentration over time to estimate CO.(50) Safety and accuracy when compared to thermodilution have been established in a paediatric population including some neonatal patients (51), but this technology has not been evaluated in preterm infants to date.

2.3 Non-invasive Methodologies

2.3.1 Echo-based Left Ventricular Output

LVO measurement by echocardiography represents the outflow of oxygenated blood from the left side of the heart. In the absence of shunting, LVO represents systemic blood flow

and hence cumulative blood flow to all major organs. In theory, changes in LVO reflect changes in blood flow to the periphery of the neonate. LVO is measured according to the following formula:

LVO (mL/kg/min) = [Velocity Time Integral x Cross sectional area (aortic valve) x Heart rate] / Weight (Kg).

Cross sectional area is calculated at the level of the aortic valve using the long parasternal view at the end of systole, and Velocity Time Integral (VTI) is measured using pulse wave Doppler just proximal to the aortic valve in the apical five-chamber view.(52) In experienced hands, LVO represents an easily performed measure of blood flow to the periphery of the baby and as with all echo measurements has the advantage of providing real-time measurements of systemic blood flow facilitating rapid decision-making in the neonatal intensive care unit (NICU). The technique is well-established in the paediatric population and was first described in preterm infants over 30 years ago.(53) Early work showed that LVO correlated well with traditional cardiac catheterisation and thermodilution in term neonates (54), though it is worth noting that infants used in early studies were generally outside the transitional period. Despite these advantages there are several limitations to the use of LVO in the preterm population. LVO calculation relies on calculation of vessel diameter, hence any inaccuracy in measurement will be magnified when vessel diameter is squared during the cross-sectional area calculation.(52) Foremost among the limitations of LVO is the impact of shunting on the LVO measurement (55), with expert guidance stating that LVO does not represent systemic blood flow in the presence of a Patent Ductus Arteriosus (PDA). (56) Since a PDA is present in most preterm neonates the technique has limited value as an isolated measure of systemic perfusion in this population but may be of use in combination with other parameters as a global overview of preterm circulatory status. In addition, like all other echocardiography techniques discussed

below, LVO measurements are not continuous and imaging needs to be repeated over time for best results.

2.3.2 Echo-based Right Ventricular Output

RVO represents another commonly recorded measure of central blood flow. In the absence of shunting, RVO reflects the cumulative inflow of deoxygenated blood and hence venous return. RVO is measured according to the following formula:

RVO (ml/kg/min) = [Velocity Time Integral x Cross sectional area (pulmonary valve) x Heart rate] / Weight (Kg)

Cross sectional area is calculated at the level of the pulmonary valve at the end of systole using an oblique long parasternal view, and VTI is calculated just proximal to the pulmonary valve in the same view.(52) Similar to left ventricular measures, RVO was first described in the neonatal population approximately 30 years ago.(57, 58) Because the reference points used in measurement lie close to the anterior chest and the view for calculating VTI and cross sectional area are the same, RVO is easily measured in the preterm infant. Like all measurements taken with echocardiography, RVO provides results in real-time and is non-invasive. No information is available on the accuracy of RVO in relation to invasive methods in the preterm neonatal population. Similar to LVO, RVO is affected by the presence of shunting, in this case a Patent Foramen Ovale (PFO) or other septal defects lead to inaccuracy in measurement.(55) The issue of inter and intra-observer variation in measurement is also present in RVO measurement with repeatability being similar to measurement of LVO in the term and preterm population.(59) In a recent study by Popat et al. differences in measurement led to significantly different results between users with the majority of the difference being made up by inaccurate measurement of VTI and vessel cross sectional area.(60) Because of the limitations of RVO, the technique

has a limited role in the assessment of the circulatory status of preterm infants. Like other echo techniques the maximal benefit is likely to come from recording RVO along with other complementary echo measurements, with readings repeated over time and ideally taken by the same user to reduce variation.

2.3.3 Superior Vena Cava Flow

Due to the limitations of LVO and RVO measurement within the neonatal population Superior Vena Cava (SVC) flow was developed as an alternative measure of central blood flow which is not affected by the presence of shunting.(61) The flow within the SVC is calculated according to the following formula:

SVC flow (ml/kg/min) = [Velocity Time Integral x (π x (mean SVC diameter)^2 / 4) x Heart rate] / Weight (Kg)

From a low subcostal view, the SVC is identified as it enters the RA and flow within is recorded using pulsed Doppler. The diameter of the vessel is measured via the high parasternal view as the vessel enters the RA. Since its initial description, low SVC flow in the neonatal population has been shown to correlate with a variety of adverse short and long-term outcomes.(8, 9, 18-23, 27, 62) Compared to the other echocardiography-based techniques described, SVC flow has the advantage of being unaffected by shunting and is considered by many to be the most robust echocardiography technique for measurement of central blood flow.(63) Similar to other methodologies discussed however, there are concerns around the repeatability of the technique with studies on inter- and intra-observer variability, showing potential variability of between 1%-102% and 1%-34% respectively.(61, 64, 65) Much of the variability is attributed to probe positioning and differences in SVC diameter measurement (60), which are a particular problem given the compressible nature of the SVC's venous wall.

2.4 Bioreactance and Bioimpedance

At its most basic level the thorax may be seen as a 3D shape with fluid (blood) flowing through it. Depending on the point in the cardiac cycle the amount of fluid in the thorax will vary, for example during systole blood flow through the aorta will increase. Different substances within the chest have different resistances to electrical flow, with blood having lower resistance than soft tissue or bone. Because blood flow changes based on CO between heartbeats, the relative resistance to electrical flow will alter depending on flow through the aorta. Bioimpedance uses this principle to measure CO by passing an electrical signal of known amplitude and frequency between electrodes across the chest and measuring the resistance to flow. With more blood flow in the aorta, the resistance to the passage of electrical signal is lower as calculated by the ratio of voltage to current amplitude. Hence differences in resistance can be used to estimate CO. While traditional bioimpedance is continuous, non-invasive and requires relatively little expertise to perform, it is limited by the interference from electrical noise, the need for exact placement of electrodes for accuracy and concerns over accuracy when compared to more established techniques in the paediatric population.(66) An adaptation of bioimpedance called electrical velocimetry has been suggested by some as improving the accuracy of the technique and has been shown to be feasible in the neonatal population.(67) In addition, CO measurements taken by electrical velocimetry appear to compare favourably with echocardiography measures in children with congenital heart disease (68), term neonates (69) and within the preterm population.(70) Despite these advantages, the bioimpedance-based methodology has not yet been adequately validated in the neonatal population either against traditional invasive methodologies or with regard to clinical outcomes.

Another new methodology based on measures of thoracic electricity conduction is bioreactance, which measures the phase shift of an electrical signal as it passes through tissues and is thought to be less susceptible to noise interference than traditional bioimpedance.(71) Bioreactance relies on the fact that changes in phase shift can only occur in the setting of pulsatile flow and given that the majority of pulsatile flow within the thorax is accounted for by the aorta, phase shift will reflect flow in the aorta and hence CO.(72) Similar to bioimpedance, electrodes are placed on the chest for measurement. In bioreactance, electrodes on the upper and lower chest measure bioreactance on the left and right sides of the chest separately and the results are averaged to determine CO. Despite initial concerns regarding the accuracy of the technique in smaller children (73), bioreactance has been shown to be feasible in both the term and preterm population.(74, 75) There is also evidence that bioreactance has shown some potential to monitor fluid status in postoperative paediatric patients (76) and the bioreactance strongly correlates with CO in term infants with Neonatal Encephalopathy (NE) undergoing Therapeutic Hypothermia (TH).(77) While measurements of LVO by bioreactance have been shown to correlate with echocardiography measurements, bioreactance appears to underestimate CO.(74, 77) Bioreactance is similarly non-invasive to bioimpedance but has the advantage of not being dependant on distance between electrodes and is less affected by electrical “noise”, a common feature in the NICU setting. While bioreactance is widely considered a more robust technique, it has not yet entered routine use in the neonatal population and there are concerns from adult studies regarding its accuracy in low-flow states.

Despite the limitations of both bioimpedance and bioreactance methods, the only existing systematic review and meta-analysis of the accuracy and precision of non-invasive CO techniques in the paediatric population concluded that electrical cardiometry was the most accurate, with other methodologies varying greatly between studies.(78) At present both

techniques are used primarily in a research capacity but represent two of the most promising devices for the non-invasive measurement of CO in the preterm neonate.

2.5 Portable Doppler

Devices such as the Ultrasonic Cardiac Output Monitor (USCOM) monitor measure Doppler flow within the large vessels of the chest transthoracically. The technique relies on external placement of a small Doppler probe, which when angled correctly can measure the flow within the aorta and calculate CO based on an algorithm which uses patient height to estimate cross sectional area. The technique is non-invasive, continuous and easy to learn.(79) The technique has been compared to thermodilution in the paediatric population with results suggesting that the technique was inaccurate for estimation of actual CO measurements.(80) The technique has been used successfully within the preterm neonatal population and shows good correlation with echo measurement of CO (81, 82), though due to the small number of studies in the preterm population there are ongoing concerns about the accuracy of the technique in neonates.(83) One study looking at the repeatability of USCOM has suggested that a variety of factors make measurement easier in younger patients (84), which may favour the technique in the paediatric and neonatal population. Despite promising data from adult patients (85), the only meta-analysis assessing accuracy and precision of non-invasive CO measures in children suggested that Doppler flow techniques are prone to a high percentage error.(78) Oesophageal Doppler is a related technique which is used successfully in the adult population. Because this methodology involves placement of a Doppler probe within the oesophagus to measure flow in the descending aorta it is limited by the size of the child and only used in infants >3kg (86), making it of limited use in the preterm neonatal population.

2.6 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) has safely been used in the preterm neonatal population to derive central blood flow measurements.(87) MRI has been suggested as having improved accuracy and repeatability compared to other techniques for CO measurement in neonates and older children.(88, 89) The obvious disadvantages of MRI are that the technique is slow, expensive, non-continuous, not routinely available to neonatologists and non-portable. The technique has also not yet been compared to traditional invasive techniques in the neonatal population. As a result, MRI is not ideal as a methodology of assessing CO in preterm neonates as it cannot be performed at the bedside to facilitate decision-making in critically unwell infants. Consequently, at present CO from MRI is limited to experimental use but may have a role in the development of future techniques for CO assessment or to improve existing technologies.

2.7 Limitations and Current Situation

Neonatologists currently stand in an unusual position regarding CO monitoring: there are numerous techniques available for the evaluation of CO in the neonatal population, but few have been rigorously validated against the classically held “gold standards”. Fewer still have been validated against clinical outcomes and we are often unsure if intervention to improve the measurements taken is improving the outcome of the infant. Like many aspects of neonatology, rigorous validation of new CO technologies is challenging as the traditionally held best practice, in this case invasive dilution techniques, have themselves been largely extrapolated from adult studies and are of uncertain utility in neonatology. Added to this is the inherent difficulty of defining a “normal range” within the neonatal population, as identifying what

constitutes a “healthy” preterm infant is not easy. The solution may seem obvious to some: designing randomised trials where some infants are assigned to receive a novel investigation and some are not. On the surface this seems easy but there are numerous pitfalls to navigate: the ability to properly blind, the ethics of performing sham studies and the practice of withholding a technology in a group of patients in whom it may be reasonably assumed could potentially benefit from its availability, to name but a few.

None of the technologies described above are perfect, with many suffering limitations unrelated to their lack of validation: namely their practicality and invasiveness in the setting of preterm neonatal care. Of those that are considered most promising within the adult population, many require insertion arterial and venous lines to provide accurate, real-time measurements making them unsuitable as techniques in preterm infants. Among those discussed, echocardiography is likely to represent the best validated and most practical technique at present. Despite its widespread adoption, some have questioned the use of echocardiography in the NICU suggesting that it requires further validation, definition of normal values and guidance on potential therapy before it can be optimally utilised.(90)

Several guidelines have been created to aid in the standardisation of training and image acquisition for neonatologist-performed echocardiography.(56, 91, 92) All echocardiography-based techniques have the advantage of being non-invasive and providing real-time information on blood flow. Echocardiography techniques are among the best-validated in the preterm neonatal population and measurements taken can facilitate bedside decision-making. Notwithstanding these advantages, echocardiography is a non-continuous measure of blood flow and although high-quality images can be obtained, potentially significant issues regarding interobserver variability exist.(60)

2.8 Future Directions

In an editorial regarding CO monitoring in critically ill children, Chang eloquently defined three areas which warrant our focus: designing the ideal technology for CO measurement, recognition of the importance of assessing tissue perfusion and the incorporation of non-medical expertise in the design of computer systems to analyse the increasing volumes of data which we will collect.(93) The design of an ideal technology for CO monitoring will first require us to validate the existing technologies at our disposal. For some technologies such as pulmonary artery thermodilution this is unlikely to be feasible within the preterm neonatal population. Instead, we may need to validate existing technologies more rigorously around clinical outcomes and their ability to positively impact patient care; this in itself raising the question of what outcomes we should ideally be measuring. Concurrent to this we may have to examine novel technologies more rigorously in older children and extrapolate data to the neonatal population before introducing them into practice or exploring them experimentally in premature infants. Regardless of how this is undertaken, we must appreciate that our efforts to validate existing technologies are largely to establish a relative "gold standard" within the neonatal population and that the ideal CO technology is likely to require considerable innovation and is unlikely to be closely related to any technology which is currently in use. Previous discussions on haemodynamic monitoring within the neonatal population have highlighted the importance of comprehensive haemodynamic monitoring integrating computational modelling to assist decision making.(94) This idea is likely to become more important as new technologies allow us to measure cardiovascular parameters which were previously either unmeasurable or wholly unknown. Such incorporation of computer technology should be fostered in conjunction with novel CO measurements, so that as time

passes and we have more information available we can make objective decisions which are most likely to benefit patient care, rather than being overwhelmed by information.

3. Intraventricular Haemorrhage in Preterm Infants

3.1 Pathophysiology

IVH, especially in ELBW infants, is one of the most severe complications of prematurity. IVH usually initiates in the periventricular germinal matrix, the majority of infants would have the haemorrhage within the first week of life.(95) Pathogenesis of the IVH is multifactorial, however there are two main factors playing a role: an intrinsic fragility of the germinal matrix vasculature and disturbances in the Cerebral Blood Flow (CBF).(96)

3.1.1 Fragility of Germinal Matrix

The density and cross-sectional area of the blood vessels are the largest in the human germinal matrix followed by the cerebral cortex and then the white matter for all gestational ages (17–40 weeks of gestation).(97) Blood vessels in the germinal matrix are circular in the coronal section, while vessels in the cerebral cortex and white matter are relatively flat. The rounded contour of the blood vessel in cross-section indicates the immaturity of germinal matrix vasculature.(98) The high vascularity of the germinal matrix enhances the probability of heamorrhage compared to brain regions with low and mature vascularity; however, this does not entirely explain the mechanism of its intrinsic fragility and propensity to heamorrhage.(96)

There is decreased pericytes, density and coverage in the germinal matrix vasculature compared to the cortex or the white matter in human foetuses and premature infants.(99)

Pericytes are cells of microvasculature (capillaries, venules, and arterioles) that wrap around the endothelial cells. They provide stability and structural integrity to the microvasculature.(100) There is also an immaturity of the basal lamina, a key component of the blood-brain barrier, that surrounds pericytes and separates pericytes form astrocyte end-feet endothelium.(101, 102) Its formation and maintenance is assured by the endothelium, astrocytes, and pericytes. This contributes to the structural integrity of vasculature by virtue of its anchoring function.(103) The most striking difference between constituents of the basal lamina in the germinal matrix vasculature compared to the cortex and white matter vasculature in human foetuses and preterm infants are significantly reduced fibronectin levels.(104) Given that polymerization of fibronectin into extracellular matrix controls the stability of the vasculature and that fibronectin null mice exhibit cerebral heamorrhage, deficient fibronectin in the germinal matrix is likely to contribute to the fragility of germinal matrix vasculature and to the immaturity of the basal lamina.(103, 105, 106)

Another contributory factor to the germinal matrix fragility is reduced Glial Fibrillary Acidic Protein (GFAP) expression in the astrocyte end-feet, as GFAP provides structural integrity and mechanical strength to these.(107) The astrocytes contribute to the development of the blood-brain barrier and regulate its function. Specifically, they provide structural integrity and control permeability of the blood-brain barrier.(101, 103) Overall, a scarcity of pericytes, low fibronectin levels in the basal lamina, and reduced GFAP expression in the astrocyte end-feet contributes to the weakness of the germinal matrix blood-brain barrier and to the vulnerability to heamorrhage.

3.1.2 Disturbances in Cerebral Blood Flow

The Cerebral Autoregulation (CAR) concept (CBF and MABP relationship with constant CBF for BP changes within a certain range) represents one of the key aspects of cerebral haemodynamics in a preterm newborn.(108) CAR can be dysfunctional or completely absent (a decrease in MABP causes a decrease in CBF) in critically ill preterm infants and may be associated with increased mortality and brain injury through various pathophysiological mechanisms. These mechanisms include hypoperfusion with hypoxic-ischemic injury, cerebral perfusion fluctuations, hyperperfusion (causing hyperoxia and peroxidation) or reperfusion injury.(109-117) On the contrary, many preterm infants in intensive care units are able to maintain adequate cerebral perfusion at MABP in the range 23 to 40 mmHg or borderline MABP.(118, 119)

3.2 Classification, Incidence and Risk Factors

In 1978 Papile et al. performed Computed Tomography (CT) on 46 consecutive VLBW live-born infants. Twenty of them (46%) had evidence of cerebral IVH. They classified IVH into four grades.(120) With the evolution of the less invasive imaging method, head ultrasound, this classification/scoring system was then adopted by most neonatal units across the globe. Grade 1 IVH actually does not have blood in the ventricles but is restricted to subependymal region/germinal matrix which is seen in the caudothalamic groove. A Grade 2 haemorrhage extends into normal sized ventricles (typically filling less than 50% of the volume of the ventricle). A Grade 3 IVH is heamorrhage distending the ventricles (one or both), and a Grade 4 IVH is bleeding into the substance of the brain (with or without blood in the ventricles). However, there are several problems with the Papile grading, the biggest being the term Grade 4 IVH as these parenchymal echo-densities without intraventricular blood are often not actually bleeds. There is also a high degree of inter-rater variability in their diagnosis and

interpretation.(121) These haemorrhages are often called Peri-Ventricular Haemorrhagic Infarction (PVHI) and a classification scheme was developed in 2006 by Bassan et al..(122) Another type of possible brain injury in preterm infants (and rarely in term neonates) is Periventricular Leucomalacia (PVL). There is obvious overlap between PVHI/grade 4 IVH (as these infants would frequently develop PVL on subsequent scanning) and PVL.(123) However, classic PVL is presumed to be a mostly pre- or perinatal injury caused by hypoxia.(124)

Current data from a large population-based cohort (44 028 infants in the California Perinatal Quality Care Collaborative between 2005 and 2015) by Handley et al. show the rate of any IVH in infants below 32 weeks of gestation at 24.2%. The incidence of severe IVH (Grade 3 and Grade 4 IVH) in the same study was 7.7%.(125) A smaller study by Vogtmann et al. (1782 neonates born at less than 32 weeks of gestation or weighing less than 1500 g at birth from Peri- and Neonatal Survey of the German state of Saxony in the years 2001–2005) reported a very favourable rate of any IVH at 19.9% and rate of severe IVH at 8.5%.(126) These rates did not substantially change during the last two decades.(127) The rate of severe IVH in infants with birth weight between 501 and 1500 g decreased from 9.4% in 2005 to 7.9% in 2014 at Vermont Oxford Network (VON) Member Centers in the United States.(128) The incidence of IVH in all VON centres in 2017 was 25.7% with severe IVH of 7.9% (unpublished data from VON database; infants with birth weight 501-1500g).

The risk of IVH in preterm infants is increased with numerous factors: lower gestational age, lower birth weight, small for gestational age status, preterm premature rupture of membranes, male gender, multiple gestation, certain ethnic group (Afro-American), lack of antenatal steroid therapy, maternal hypertension, maternal chorioamnionitis, vaginal delivery, outborn birth, low Apgar score, delivery room cardiopulmonary resuscitation, surfactant administration, use of catecholamines/low arterial blood pressure at NICU admission, low SVC flow, pneumothorax, hyperglycaemia, hypernatremia, metabolic acidosis, hypercapnia,

hypothermia, thrombocytopenia, red cell transfusion before developing IVH and early onset infection. (9, 21, 23, 125, 129-142) However, these factors are not independent. In a multivariate analysis by Poryo et al, higher gestational age, antenatal steroid therapy and caesarean section without uterine contraction were associated with a lower rate IVH while Respiratory Distress Syndrome (RDS), pneumothorax and use of catecholamines were associated with an increased risk of IVH.(129) A complete course of antenatal corticosteroid therapy was also independently associated with a decreased risk for severe IVH in singleton and in multiple preterm VLBW infants in large cohort of preterm infants reported by Blickstein et al.(143) Multivariate regression analysis of hypernatremia and hyperglycaemia confirmed the independent association of higher risk of IVH with the presence of hypernatremia plus hyperglycaemia, but not with hypernatremia or hyperglycaemia alone.(130) A low five minute Apgar Score, multiple birth, low arterial blood pressure at NICU admission, hypercapnia and absence of any antenatal corticosteroids were found to be significant independent risk factors in the development of IVH in the study by Waitz et al.(137) After stratification by gestational age, antenatal steroid exposure was the only factor associated with a decreased odds of severe IVH for all gestational age subgroups in the large cohort of preterm infants reported by Handley et al..(125) Emerging data suggests IVH of the preterm neonate is a complex disorder with contributions from the genome, however the role of genetic factors in IVH remains unclear.(144, 145)

3.3 Short Term and Long Term Outcomes

Diagnosis of IVH in preterm infants bears an increased risk of adverse outcomes. There is a reduction in cerebral cortical grey matter volume at near-term age in ex-preterm infants with uncomplicated IVH.(146) Current meta-analysis of studies looking at outcomes of

preterm infants (≤ 34 weeks of gestation; studies published between January 2000 and June 2014) reported the pooled unadjusted odds ratios of the primary outcome of death or moderate-severe Neurodevelopmental Impairment (NDI). These were higher with both mild (Grade 1 and 2) (1.48, 95% CI 1.26-1.73; 2 studies) and severe IVH (Grade 3 and 4) (4.72, 4.21-5.31; 3 studies); no studies reported adjusted odds ratios. Among survivors, odds of moderate-severe NDI were higher with mild and severe IVH in both unadjusted (1.75, 1.40-2.20; 3 studies; 3.36, 3.06-3.68; 5 studies) and adjusted (1.39, 1.09-1.77; 3 studies; 2.44, 1.73-3.42; 2 studies) pooled analyses. Adjusted odds of cerebral palsy and cognitive delay were higher with severe but not mild IVH.(147)

Recent population-based cohort study including all very preterm (≤ 30 completed weeks) infants born in the province of Nova Scotia showed association of IVH Grades 2, 3 and 4 with an increased overall mortality, primarily in the neonatal period, and the risk increased with increasing grade of IVH. Grade 4 IVH was significantly associated with an increased risk of disability (relative risk of 2.0), and the disability appeared to be primarily due to cerebral palsy and cognitive impairment. No infants with Grade 1 or 2 IVH developed hydrocephalus, and hydrocephalus and cerebrospinal fluid shunting were not associated with poorer outcomes when controlling for IVH grade.(148) ELBW infants with bilateral 4 IVH compared to those with unilateral Grade 4 IVH have worse neurodevelopmental outcomes. Infants with Grade 1, 2 and 3 IVH have similar outcomes whether they have unilateral or bilateral IVH.(149) Neurodevelopmental dysfunction at school age in ELBW/very preterm survivors varies little with increasing severity of IVH, with the exception of Grade 4 IVH.(150) In agreement with the adjusted odds of cerebral palsy and cognitive delay from meta-analysis by Mukerji et al (147), there were no statistically significant differences in neurodevelopmental outcome at two years of corrected gestational age in a recent retrospective case-control study in very preterm infants with and without low-grade IVH (Grade 1-2).(151) Furthermore, low-grade IVH was

not demonstrated to be an independent risk factor associated with lower outcomes in intelligence, academic achievement or problem behaviour at age three, eight and 18 years in ex-preterm infants.(152)

Looking at the more severe part of IVH spectrum, progressive post-haemorrhagic ventricular dilatation requiring intervention is more likely in infants with a Grade 3 heamorrhage, compared with infants with a Grade 4 heamorrhage.(153) Infants with cystic PVL plus low-grade or high-grade IVH have a higher risk of abnormal neurodevelopmental outcomes than infants with isolated cystic PVL at the age of 24 months. This would be suggestive of different causal pathways.(154)

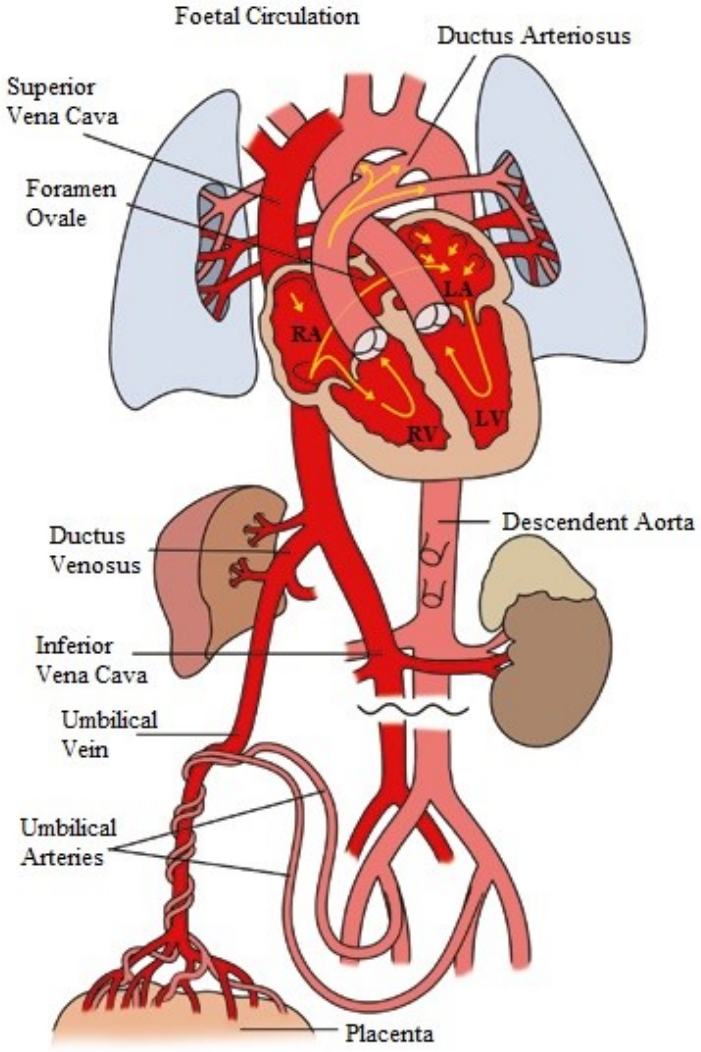
4. Early Neonatal Transition and Role of the Patent Ductus Arteriosus

4.1 Foetal Circulation

There are numerous differences between foetal and postnatal circulation. However, the two most important and distinctive are the presence of the fetoplacental unit as a principal site of gas and metabolic exchanges and parallel circulation where both ventricles work together. Blood enters the placenta via two umbilical arteries and leaves the placenta via umbilical vein.(Figure 1) Absolute placental umbilical flow increases with gestational age, although when normalised for foetal weight it shows moderate decrease during the pregnancy. In the third trimester of the pregnancy the umbilical flow remains between 110 and 125 ml/kg/min.(155) This represents approximately 30% of the overall combined biventricular CO.(156) Relatively oxygen-rich blood from the placenta returns to the heart, either passing through the liver or being shunted directly to the Inferior Vena Cava (IVC) through Ductus

Venosus (DV).(156) Left Atrium (LA) and Left Ventricle (LV) then receive the preferentially highest oxygen saturated blood via DV, IVC and Foramen Ovale (FO).

Figure 1 *– Scheme of Foetal Circulation*
(Adapted from Miletin J. Perzistující ductus arteriosus (PDA). In: Janota J, Stranak Z. Neonatologie, Mladá Fronta 2013, p. 307)



This setting allows for prioritising oxygen delivery to coronary arteries and cerebral circulation. The shunt across DV and FO decreases throughout the pregnancy, as does LVO. The Right Ventricle (RV) receives less saturated blood from the caval veins with SVC dominance. In early pregnancy, 90% of the RVO is shunted through ductus arteriosus (DA) to the systemic circulation.(156) This changes throughout the third trimester with decreasing Pulmonary

Vascular Resistance (PVR) where more proportion of the RVO is directed to lung circulation. However as RV becomes dominant at the end of the pregnancy, with approximately 60% of combined CO produced by the RV, the portion of combined CO going through DA is very similar to that at 20 weeks of gestation.(156) Foetal combined CO distribution is presented in Table 1 (adapted from Wu et. al, 2016).(156)

Table 1 – Combined Cardiac Output (CCO) distribution in foetal life
(Adapted from Wu et al., Transitional Hemodynamics in Preterm Neonates: Clinical Relevance. Pediatrics and Neonatology, Vol. 16, Issue 1, Feb 2016, 7-18.)

	20 weeks of gestation	30 weeks of gestation	40 weeks of gestation
RVO (% of CCO)	53	57	60
LVO (% of CCO)	47	43	40
DA (% of CCO)	40	32	39
FO (% of CCO)	34	18	19
Lungs (% of CCO)	13	25	31

RVO – Right Ventricular Output; LVO - Left Ventricular Output; DA – Ductus Arteriosus; FO – Foramen Ovale

As described above, the key part of the foetal circulation and the parallel pump setting is the existence of FO and DA. As both ventricles are working in parallel, systemic CO in early foetal life is approximately double of the LVO in postnatal life and this is estimated in the range of 470 to 503 ml/kg/min.(157) However, this changes slightly at the end of the foetal period with more flow (up to 30% of combined CO) directed to the pulmonary circulation.

The foetal ventricular pressures are same in the right and left ventricle and similar to those observed in systemic circulation after delivery, as both ventricles contribute to systemic CO. This ventricular pressure increases with gestational age.(158) The mean aortic pressure closely copies the ventricular pressure and, in the same pattern as both ventricles, rises from

28 mm Hg at 20 weeks of gestation to 45 mm Hg at 40 weeks of gestation.(159) The pulmonary artery pressures are increased due to high PVR and estimated Foetal Mean Pulmonary Artery Pressure (FMPAP) decreases with the advancing gestational age. The FMPAP is between 60 and 70 mm Hg before 28 weeks of gestation, decreasing to 40 to 50 mm Hg at term gestation.(160) The atrial mean pressures in foetal life are same throughout the pregnancy at approximately 3 to 4 mm Hg (with LA having slightly lower pressure than RA).(158)

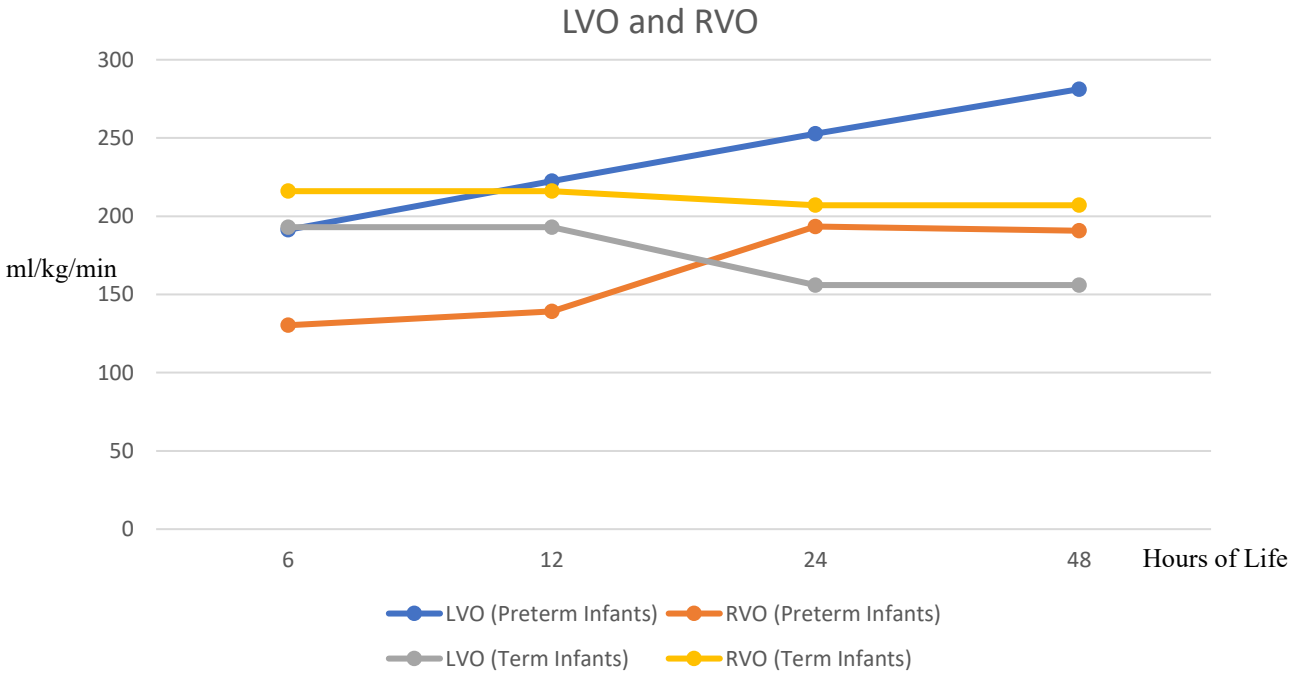
4.2 Postnatal Transition of the Circulation

There are numerous changes immediately following birth. With the first breath and high alveolar and subsequently high blood oxygen content, PVR decreases, initially significantly and later in a more gradual pattern. Echocardiography estimates in healthy term neonates suggest a mean pulmonary blood pressure decline from 63 mm Hg at two hours of age to 34 mm Hg at 24 hours of age and then 25 mm Hg at 72 hours of age.(161) There is a paucity of normative data on pulmonary artery pressure in the preterm population. However, it is documented that in preterm infants, particularly in those affected by early respiratory morbidity, the decrease in pulmonary pressures may be impaired, resulting in pulmonary hypertension.(162, 163) Simultaneously there is an increase in systemic vascular resistance (SVR) as a result of the loss of low-pressure placental vasculature and neuroendocrine changes (increased production of catecholamines, renin, angiotensin and vasopressin). Shortly after delivery, LV becomes the dominant ventricle of the heart. As systemic BP increases, the LA pressure increases and FO would functionally close, however anatomical closure can take up to one year of age.(156) The neonatal circulation thus quickly becomes serial circulation despite early presence of DA, that will functionally close within first 72 hours of age, with anatomical closure during the first two to three weeks of age in healthy term neonates.(164)

This situation is different in the premature population, where the ductal closure may occur up to four to six months of age.(165) The DV typically closes within three to seven days after birth as a result of the decrease in circulating prostaglandins.(164)

The RVO is very stable during the first 48 hours of age in term neonates at approximately 200 ml/kg/min (Figure 2).(166, 167) The LVO decreases somewhat within the first 48 hours, most likely secondary to closing DA (and its disappearing influence on LVO). The LVO is 193 ml/kg/min at six hours of age, decreasing to 156 ml/kg/min between 24 and 48 hours of age (Figure 2).(166, 167) Contrary to the term infants, the LVO and RVO are steadily increasing in preterm infants, most likely due to FO and DA shunting.

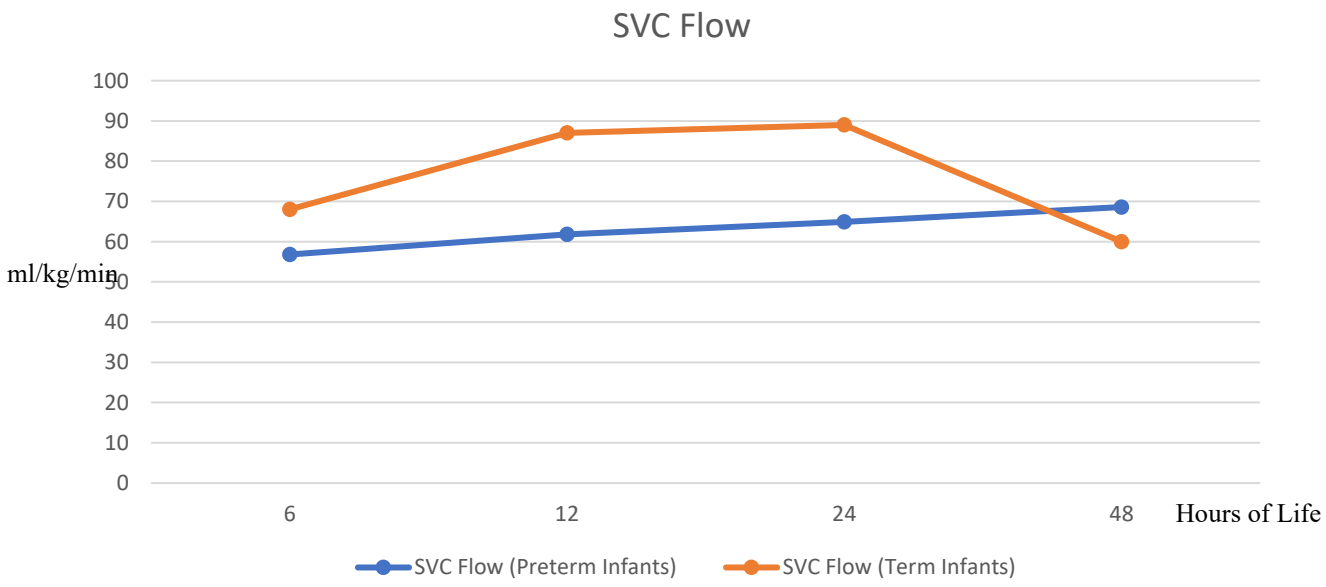
Figure 2 – Left Ventricular Output (LVO) and Right Ventricular Output (RVO) in term and preterm infants within first 48 hours after delivery
(data adapted from Popat H et al. Noninvasive assessment of the early transitional circulation in healthy term infants. Neonatology. 2012;101(3):166-71.; Noori S et al. Transitional changes in cardiac and cerebral hemodynamics in term neonates at birth. J Pediatr. 2012 Jun;160(6):943-8; Sirc J et al. Cerebral tissue oxygenation index, cardiac output and superior vena cava flow in infants with birth weight less than 1250 grams in the first 48 hours of life. Early Hum Dev. 2013 Jul;89(7):449-52.)



LVO – Left Ventricular Output; RVO – Right Ventricular Output

To overcome the issue of shunting through DA and FO and the inability to obtain true systemic blood flow, SVC flow can be used as a surrogate marker of the systemic flow. In term infants SVC flow increases during the first 24 hours of life, however then decreases to 60 ml/kg/min at 48 hours of age (Figure 3).(64) In preterm infants there is a slow, but steady increase in SVC flow during the first 48 hours of life reaching 70 ml/kg/min (Figure 3).(168) This is suggestive of a different transition in preterm infants with lower systemic blood flow in the first 24 hours of age.

Figure 3 – Superior Vena Cava (SVC) flow in term and preterm infants within first 48 hours after delivery
(data adapted from Groves AM et al. Echocardiographic assessment of blood flow volume in the superior vena cava and descending aorta in the newborn infant. Arch Dis Child Fetal Neonatal Ed. 2008 Jan;93(1):F24-8; Sirc J et al. Cerebral tissue oxygenation index, cardiac output and superior vena cava flow in infants with birth weight less than 1250 grams in the first 48 hours of life. Early Hum Dev. 2013 Jul;89(7):449-52.)



Overall, the neonatal heart has fewer myocytes, is more fibrous, and lacks the compliance of its adult counterpart. This is even more pronounced in preterm infants. Cardiac output is dependent on heart rate and a neonatal heart is unable to generate increases in stroke volumes due to their non-compliant ventricle. The sudden increase in afterload after delivery in very

premature infants is the explanation for lower systemic blood flow compared to term infants. Some authors postulated that very preterm infants without any apparent systemic hypotension are in the compensated phase of shock during the transitional period.(24)

4.3 The Role of Patent Ductus Arteriosus in Early Transition

As described previously, during pregnancy the DA is a temporary blood vessel allowing blood to bypass the lungs. The DA is essential for foetal survival, however after birth it should close during the first days of life. This closure is a result of increased saturation of oxygen in the blood and decreasing levels of prostaglandins after delivery. The situation where the DA stays open after birth is called PDA. The incidence of PDA is inversely related to the degree of prematurity and is highest in infants with ELBW, with spontaneous closure of PDA occurring in only 30–35% of ELBW infants by day seven of life.(169)

PDA can have a negative effect on blood flow to vital organs. Data indicates that a large ductal diameter is associated with decreased SVC flow at five hours of postnatal life; however, this effect is no longer observed at 24–48 hours after delivery.(21) This is also documented by differences between LVO/RVO and SVC flow in term and preterm infants (Figure 2 and 3). Well-known early complications of prematurity due to hypoperfusion include IVH, Pulmonary Haemorrhage (PH), and decreased blood flow to the gut leading to NEC. Large, early, haemodynamically significant PDA is particularly associated with higher risk of IVH, PH, NEC and subsequent need for PDA treatment.(170-172) These complications can lead to significant morbidity, and mortality for premature and ELBW babies.

At present, current practice in PDA management varies greatly among institutions.(173) The most common treatment approach consists of medical treatment of haemodynamically significant PDA with Indomethacin and Ibuprofen. Surgical ligation is

considered when medical treatment is unsuccessful. Medical treatment is typically commenced after the first days of life thus lacking the benefits of reduction of early complications.(174) Early prophylactic treatment of PDA has demonstrated a reduction in the rate of early complications, however this has not been shown to influence long term outcomes.(172, 175, 176) The prophylactic nature of some early treatment trials may result in inclusion of many infants whose PDA would close spontaneously, therefore potentially exposing them to iatrogenic adverse effects. There is also the risk of recruitment of sick infants where the PDA has right-to-left flow e.g. in persistent pulmonary hypertension of the newborn (PPHN), where PDA closure may not be beneficial. Therefore, although prophylactic treatment may enable enrolment of a large study population, such trials may not produce the desired outcomes. A targeted approach to early PDA treatment would overcome these issues by focusing only on the group of infants that may potentially benefit most from the intervention.

In recent years there have been randomised trials looking at, and demonstrating the feasibility of, early targeted PDA treatment with Ibuprofen and Indomethacin.(177, 178) Indomethacin and Ibuprofen are prostaglandin inhibitors that promote PDA closure. Both medications have been proven effective in closing PDA, but also potentially harmful in terms of adverse effects including renal impairment and NEC, with no proven effect on long-term outcomes.(171, 179) Kluckow et al. demonstrated the feasibility of early echocardiography targeted treatment of PDA with Indomethacin in extremely preterm infants, showing a significant reduction in PH before 72 hours of life in the treatment group, and a reduction in the need for later treatment of PDA.(177)

A recent systematic review has shown that Paracetamol is an alternative medication to Indomethacin and Ibuprofen with the similar efficacy to treat PDA and fewer gastrointestinal and renal side effects.(180) There is no systematic review of Paracetamol prophylaxis for PDA, however there is a small randomised trial showing the feasibility of the approach.(181)

4.4 Early PDA Treatment

There are over 60 randomised controlled trials in the literature relating to the treatment of PDA. These trials can be divided from the timing perspective as prophylactic, early targeted and delayed treatment. According to the type of treatment, the medical option includes Indomethacin, Ibuprofen and Paracetamol (intravenous or enteral administration) and the ligation option includes surgical or transcatheter closure.

The Cochrane systematic review of prophylactic intravenous Indomethacin included 19 trials with a total of 2872 infants, and most participants were VLBW infants. The largest single trial restricted participation to ELBW infants. The review showed significantly lower incidence of symptomatic PDA and PDA surgical ligation in treated infants. Prophylactic indomethacin also significantly reduced the incidence of any, and also specifically severe, IVH (>grade 2). Meta-analyses found no evidence of an effect on mortality or on a composite of death or severe neurodevelopmental disability assessed at 18 to 36 months of age.(179)

Regarding prophylactic Ibuprofen, the recently updated Cochrane review includes nine trials with 1070 infants. The conclusion of the review was that prophylactic Ibuprofen decreased the risk of PDA on day three or four of life, however the spontaneous closure rate in the control group was 58% by day three to four of life. There was a possible decrease in the risk of grade 3 and/or 4 PIVH in infants receiving prophylactic Ibuprofen, however, there was high quality evidence showing increased risk for oliguria. Low quality evidence from four studies showed that oral Ibuprofen may decrease the risk of PDA but may increase the risk of gastrointestinal bleeding. There was no evidence of a difference for mortality, any Peri-intraventricular Haemorrhage (PIVH), or Chronic Lung Disease (CLD).(171)

There is no systematic review of Paracetamol prophylaxis for PDA. There is a small, randomised trial showing feasibility of the approach as mentioned previously.(181)

The systematic review of prophylactic surgical ligation (within the first 24 hours of life) identified one trial with 84 ELBW infants. Prophylactic surgical ligation of the PDA resulted in a statistically significant reduction of NEC ≥grade II, with a number needed to treat of five. There was no statistically significant difference in mortality or other neonatal morbidities.(172)

A recent meta-analysis of early targeted PDA treatment in VLBW infants and/or infants below 32 weeks of gestation with Ibuprofen or Indomethacin showed that targeted medical treatment did not significantly reduce mortality rates, but it did significantly reduce the overall incidence of developing symptomatic PDA. All seven trials in this review were small and early treatment ranged from three hours of life to 14 days of life, with only two trials targeting PDA within first 24 hours of life. One of these trials was performed in 1988 and included 37 infants overall. The second trial was performed by Kluckow et al. showing a decrease of PH and a trend towards decreased PIVH in infants less than 29 weeks of gestation.(177, 182)

A recent systematic review showed Paracetamol was as effective for PDA closure as Indomethacin/Ibuprofen, with decreased side effects on gastrointestinal and renal systems.(180)

5. Aims and Hypotheses of the Thesis

5.1 Introduction

This thesis is a commented monothematic collection of nine publications addressing cardiovascular assessment in preterm and term infants with a special focus on the immediate postnatal period.

The thesis is divided into three logical parts. In the first and main part, CO measurement possibilities in the neonatal period are reviewed with two studies exploring the usefulness of a novel method of continuous CO measurement, bioreactance, in extremely preterm infants immediately after delivery and then in near term and term infants diagnosed with NE undergoing TH.

In the second part of the thesis, we are reviewing one of the most used and commonly employed methods of echocardiography CO measurement, SVC flow, with a research study assessing a newly proposed technique of SVC flow measurement and comparing it to the standard validated technique.

The third part contains studies related to an assessment of immediate postnatal transition and the role of the PDA. The first study is an echocardiography description of the ELBW infants' transition in the first 12 hours of life. Then we have tested the portable Handheld Ultrasound (HUS) and Digital Stethoscope (DS) as tools for the Heart Rate (HR) assessment immediately after delivery (in term infants). The last two studies are retrospective cohort studies, exploring conservative management of PDA and the natural course of PDA in VLBW infants.

5.2 Main Aims of the Thesis

5.2.1 Part 1 - Cardiac Output Measurement by Bioreactance in Newborn Infants

1. Review and publish current knowledge in relation to CO measurements in preterm infants.
2. To measure continuously CO in preterm infants by bioreactance (Non-Invasive Cardiac Monitor (NICOM^{TM}), Cheetah Medical, USA) in the first 48 hours of life and correlate the low CO with adverse outcomes attributable to poor perfusion, including IVH.
3. To assess the feasibility and reliability of continuous cardiac output monitoring by bioreactance in infants with NE undergoing TH.

5.2.2 Part 2 - Superior Vena Cava Flow Measurements

1. Review and publish current knowledge in relation to echocardiography measurement of SVC flow in preterm infants.
2. To evaluate standard and modified techniques of echocardiography SVC flow measurement in a cohort of extremely preterm neonates in the immediate postnatal period.

5.2.3 Part 3 - Assessment of Early Cardiovascular Status in Newborn Infants and Role of the PDA

1. To measure parameters of cardiopulmonary transition in the first 12 hours of life in ELBW infants and explore relationship to adverse outcomes.
2. To determine if HUS or DS could offer a novel method of quickly and effectively assessing HR in the Delivery Room (DR) in newborn infants.

3. To evaluate three different PDA management approaches in VLBW infants and correlate these with long term outcomes.
4. To document the natural course of DA in a cohort of VLBW infants who underwent conservative PDA management with no medical or surgical intervention.

5.3 Main Hypotheses of the Thesis

5.3.1 Part 1 - Cardiac Output Measurement by Bioreactance in Newborn Infants

1. Extremely preterm infants with adverse outcomes attributable to hypoperfusion (IVH and/or NEC) have lower CO measured by bioreactance (NICOM^{TM}) compared to infants without this adverse outcome.
2. Measurement of CO by bioreactance (NICOM^{TM}) in infants with NE is feasible and can provide a reliable method of CO assessment in this population.

5.3.2 Part 2 - Superior Vena Cava Flow Measurements

1. The modified method of the SVC flow is equivalent to the standard method of the SVC flow in extremely preterm infants in the transitional period (first 36 hours of age)

5.3.3 Part 3 - Assessment of Early Cardiovascular Status in Newborn Infants and Role of PDA

1. Pulmonary pressure significantly drops in ELBW infants between 3 and 12 hours of age.
2. ELBW infants with increased pulmonary pressure at 12 hours of age have increased risk of CLD and/or death before discharge.
3. HUS and DS will provide a quick assessment of the HR in DR in term infants.

4. Conservative management of PDA is a feasible option for VLBW infants.
5. In VLBW infants, the majority of infants close their PDA before discharge home.

6. Main Thesis Part 1

Cardiac Output Measurement by Bioreactance in Newborn Infants

6.1 Review of Current Knowledge in Relation to Cardiac Output Measurements in Preterm Infants

6.1.1 Summary

Maintaining optimal circulatory status is a key component of preterm neonatal care. Low CO in the preterm neonate leads to inadequate perfusion of vital organs and has been linked to a variety of adverse outcomes with heightened acute morbidity and mortality and adverse neurodevelopmental outcomes. Having technology available to monitor CO allows us to detect low-output states and potentially intervene to mitigate the unwanted effects of reduced organ perfusion. There are many technologies available for the monitoring of CO in the preterm neonatal population and, while many act as useful adjuncts to aid clinical decision-making, no technique is perfect. In this review, we discuss the relative merits and limitations of various common methodologies available for monitoring CO in the preterm neonatal population. The ongoing challenges in monitoring CO in the preterm neonate along with current gaps in our knowledge are discussed, with bioreactance identified as one of the most exciting emerging technologies under investigation due to its non-invasive nature and ability to provide continuous measurements. In conclusion, further research should focus on validating existing techniques against clinical outcomes in order to best define those technologies which will impact patient care.

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REVIEW
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Cardiac Output Monitoring in Preterm Infants

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Maintaining optimal circulatory status is a key component of preterm neonatal care. Low-cardiac output (CO) in the preterm neonate leads to inadequate perfusion of vital organs and has been linked to a variety of adverse outcomes with heightened acute morbidity and mortality and adverse neurodevelopmental outcomes. Having technology available to monitor CO allows us to detect low-output states and potentially intervene to mitigate the unwanted effects of reduced organ perfusion. There are many technologies available for the monitoring of CO in the preterm neonatal population and while many act as useful adjuncts to aid clinical decision-making no technique is perfect. In this review, we discuss the relative merits and limitations of various common methodologies available for monitoring CO in the preterm neonatal population. We will discuss the ongoing challenges in monitoring CO in the preterm neonate along with current gaps in our knowledge. We conclude by discussing emerging technologies and areas that warrant further study.

Keywords: preterm, neonate, cardiac output, hemodynamic, monitoring, perfusion

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INTRODUCTION

Monitoring and maintaining adequate cardiac output (CO) is a key component of cardiovascular care in the preterm neonate. Low-output states have been associated with a variety of adverse outcomes and there is some evidence that low-central blood flow may respond to medical therapy (1, 2). Immaturity of the cardiovascular system predisposes the preterm neonate to low-flow states and relative immaturity of other organ systems means that premature infants are vulnerable to organ damage as a result of low flow. The unique anatomy and physiology of preterm infants makes monitoring of CO a difficult process, complicated by the transitional circulation and the presence of shunting.

Abnormal perfusion is recognized as having adverse effects on the preterm neonate with reduced mean arterial pressure being associated with increased mortality, increased severe intraventricular hemorrhage (IVH) and ischemic brain lesions (3). Duration of hypotension also correlates with developmental outcome in very low-birth weight infants (4), and extremely low-birth weight infants with treated hypotension are at risk of hearing loss, motor delay, and death (5). While such

Abbreviations: CO, cardiac output; ELBW, extremely low-birth weight; IVH, intraventricular hemorrhage; LVO, left ventricular output; MRI, magnetic resonance imaging; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; PICCO, pulse index continuous cardiac output; ROP, retinopathy of prematurity; RVO, right ventricular output; SVC, superior vena cava; USCOM, ultrasonic cardiac output monitor; VLBW, very low-birth weight.

derangements in traditional clinical measurements of perfusion clearly have prognostic implications for the neonate, traditional clinical assessment is known to be of limited use in predicting central blood flow within the pediatric population (6). Blood pressure is one of the commonest clinical methods of assessing circulatory status; however, accurate measurement in the preterm population is difficult and there is no consensus definition on hypotension. In addition, blood pressure shows poor correlation with central blood flow (7–12) and is likely to be a late sign of uncompensated low-perfusion meaning it is an insensitive sign in early circulatory compromise. Capillary refill (7, 8, 13), urine output (7), and temperature (8) are similarly unreliable for detection of low perfusion in the preterm neonatal population. While in combination, these clinical signs are undoubtedly useful in defining critically unwell infants they are clearly inadequate as markers of perfusion in the preterm population as they lack sensitivity in the early stages of disease where medical intervention is likely to have the greatest role.

As a result, neonatologists should turn to more objective measurements in assessment of perfusion within this population. The availability of bedside measures of CO such as echocardiography is acknowledged as an important tool for adult and pediatric intensivists in improving outcome (14). The non-invasive nature of echocardiographic measurements along with the real-time information provided means that they are favored in the acute setting, and there is evidence that the availability of bedside CO monitoring positively impacts patient care (14–17). Low-central blood flow measurements in preterm infants are associated with a variety of early adverse outcomes including altered electroencephalographic activity, oliguria, hyperkalaemia, necrotizing enterocolitis, retinopathy of prematurity, IVH, and death (8, 18–25). Preterm infants with reduction in left ventricular output (LVO) or right ventricular output (RVO) of more than 50% in late-onset sepsis have increased mortality (26) and low-central blood flow has been linked to adverse long-term neurodevelopmental outcomes in the preterm population (20, 27). Low CO is also a common perioperative complication for children with congenital heart disease (28), and is a risk factor for prolonged mechanical ventilation following cardiac surgery (29) and for adverse neurodevelopmental outcome (28).

Given the implications of reduced central blood flow in the preterm neonate, there is a need for a robust, non-invasive, and continuous measure of CO within this population. Criteria for an ideal technology have been outlined in previous publications (30), though at present no ideal technology exists.

TRADITIONAL INVASIVE METHODS

Due to the availability of newer, less invasive technologies many of the "gold standard" invasive techniques used in adult medicine are rarely used in the neonatal population. These methods still merit discussion as they are held by some as the most accurate method of evaluating CO despite their infrequent clinical use and limited data on repeatability within the pediatric population. One of the oldest methods of invasively measuring CO are techniques based on the Fick principle. The Fick principle measures blood flow to an organ (most usually used to measure systemic blood flow as a whole) based on the idea that the blood flow may be calculated if the amount of a substance taken up by an organ over time is known, and the quantity of the substance can be measured both proximal to and distal to the organ of interest. The classic methodology used oxygen and stated that CO may be calculated if oxygen consumption, arterial oxygen concentration, and venous oxygen concentration are known. Subsequent adaptations of the Fick principle have also used carbon dioxide, with animal models suggesting that the methodology may be potentially viable in the neonatal population (31). The Fick methodology has been used successfully in term neonates (32, 33) and appears to correlate well with other invasive methodologies within the pediatric population (32). The obvious disadvantages of this methodology are the requirement for arterial and venous lines and the need for accurate breath-by-breath oxygen consumption calculation which is likely to prove difficult in preterm neonates where the commonly used uncuffed endotracheal tubes are likely to make such measurements inaccurate.

Modern thermodilution techniques rely on placement of a specialized catheter within the pulmonary artery with a temperature probe placed distally. The most commonly employed example is the Swan-Ganz catheter, placement of which has previously been undertaken successfully in the preterm neonatal population (34). This catheter has a temperature probe at the tip and at a proximal point which lies in the right atrium there is a port through which a cold solution is injected. Following injection of a cold solution into the right atrium, the catheter tip in the pulmonary artery detects the temperature change relative to the dilution within the blood allowing accurate measurement of CO. The original description of the Swan-Ganz catheter showed that it produced comparable values to dye-dilution with a repeatability of 4.1% (35). While held as the "gold standard" by many there are a variety of potential pitfalls to the technique (36, 37). Variations on this technique including trans pulmonary thermodilution have been developed (38), and are feasible in the pediatric population with high repeatability (39). Despite evidence of validation in comparison with the Fick methodology in children (33), data in the preterm neonatal population is limited, and the technique is seldom used due to technical restraints.

Dye-dilution is based on injection of a dye in the pulmonary artery and measurement of the dye concentration through peripheral arterial line. If the concentration and volume of dye injected is known, CO is subsequently calculated based on the concentration detected peripherally over time (40). Experiments in humans have confirmed that the dye-dilution methodology correlates well with the Fick methodology and thermodilution (41). Modifications of this technique have been utilized in the term neonate to determine CO (42), but similar to thermodilution this has not entered routine practice and has not been examined in the preterm neonatal population.

While there is no true "gold standard" for CO monitoring in the neonatal population, invasive technologies are considered by many to be the most accurate methodologies for determining CO. Their clinical use in the neonate is rare due to a variety of

important limitations. Infection, damage of surrounding tissue, and thrombus formation number among the most serious complications of central catheter placement. Other difficulties arising from use of the techniques include the need for arterial and venous blood sampling and potential volume overload from injection of substrate. As well as the risk of morbidity and technical limitations, catheter placement is a source of discomfort and the measurements of output, while likely accurate, are not continuous.

MINIMALLY INVASIVE TECHNIQUES

Pulse contour and pulse power analysis make inferences about CO and other central blood flow parameters based on a peripherally measured arterial pulse wave. Both techniques rely on the presence of a peripheral arterial line and these techniques represent two of the most extensively investigated minimally invasive technologies for measuring CO in the adult population. Pulse contour analysis relates the contour of arterial pressure over time to stroke volume and systemic vascular resistance. A mathematical algorithm is then used to calculate CO based on measurements taken from a blood flow sensor within a peripheral artery and a variety of devices such as the FloTrac, pulse index continuous cardiac output monitor, and pressure recording analytical method represent variations on this idea (43). Pulse contour analysis has been used successfully in older children with congenital heart disease (44), but concerns have been raised with regards to its accuracy in relation to traditional methodologies within the pediatric population (45). Pulse power analysis is a similar technology relying on peripherally obtained arterial measurements to deduce central flow measurements. Pulse power analysis relies on the idea that variations in pulse power detected peripherally are equivalent to stroke volume minus the blood volume sent to the periphery of the body. As the title suggests, the power of the arterial pulsation rather than its contour is used to calculate CO using a mathematical algorithm. Pulse power devices have not been extensively investigated in pediatric patients to date. While these devices are minimally invasive, there are a variety of downsides to using this technology (46). Changes in systemic resistance and certain cardiac conditions are known to affect the results obtained in adults, and while minimally invasive, certain devices require calibration before use and both methodologies rely on placement of an arterial catheter.

Partial gas rebreathing based on a modification of the Fick principle has emerged as a much less invasive alternative for measuring CO in adults but remains untested in preterm neonates. Ultrasound dilution methodology relies on changes in ultrasound velocity within blood following injection of body-temperature isotonic saline to calculate CO. It has compared favorably to more traditionally invasive techniques in older children (47, 48), and *in vitro* work has shown that the technology may be feasible in neonates (49). Despite some promising results, ultrasound dilution requires placement of arterial and central venous catheters to create and extracorporeal loop and has not been validated *in vivo* in the neonatal population to date. Lithium dilution is a method of calculating CO where a Lithium Chloride solution is injected through a central venous catheter and a sensor on a peripheral artery measures the lithium concentration over time to estimate CO (50). Safety and accuracy when compared with thermodilution have been established in a pediatric population including some neonatal patients (51), but this technology has not been evaluated in preterm infants to date.

NON-INVASIVE METHODOLOGIES

Echo-Based LVO

Left ventricular output measurement by echocardiography represents the outflow of oxygenated blood from the left side of the heart. In the absence of shunting LVO represents systemic blood flow and hence cumulative blood flow to all major organs. In theory, changes in LVO reflect changes in blood flow to the periphery of the neonate. LVO is measured according to the following formula:

$$\mathrm{LVO(mL/kg/min)} = \frac{[\text{Velocity time integral} \times \text{Cross sectional area (aortic valve)} \times \text{Heart rate}]}{\text{Weight (kg)}}$$

Annulus size is measured at one of three locations: between the aortic valve hinges, at the aortic sinus, and at the sinotubular junction using a parasternal long-axis view. It has been suggested that the sinotubular junction may be the most accurate method of measuring diameter (52), however, no gold standard approach exists and most guidance suggests measurement just below the aortic valve (53). Cross-sectional area is calculated at the level of the aortic valve using the long parasternal view at the end of systole, and velocity time integral (VTI) is measured using pulse wave Doppler just proximal to the aortic valve in the apical five-chamber view (54). As with all Doppler techniques, the angle of insonation has potential to effect the accuracy of all echocardiography techniques. This is a particular issue in the measurement of LVO where the angle of insonation is known to be larger on the left outflow tract than on the right (55). Most modern echocardiography equipment incorporate software correction to combat this, however, this correction is not without issues and some clinicians prefer to use the initial uncorrected measurements if the angle of insonation is <20°. In experienced hands, LVO represents an easily performed measure of blood flow to the periphery of the baby and as with all echo measurements has the advantage of providing real-time measurements of systemic blood flow facilitating rapid decision making in the neonatal intensive care unit (NICU). The technique is well-established in the pediatric population and was first described in preterm infants over 30 years ago (56). Early work showed that LVO correlated well with traditional cardiac catheterization and thermodilution in term neonates (57), though it is worth noting that infants used in early studies were generally outside the transitional period. Despite these advantages, there are several limitations to the use of LVO in the preterm population. LVO calculation relies on calculation of vessel diameter, hence any inaccuracy in measurement will be magnified when vessel diameter is squared during the cross-sectional area calculation (54). Doppler-derived

CO measurement in the pediatric population has traditionally been prone to considerable inter- and intra-observer variability (58), however, recent studies on repeatability within the preterm neonatal population are lacking. Studies looking at repeatability in neonates have found that in experienced hands intra-observer variability for LVO can be as low as 3.6% (59), and that inter-observer variability may not differ significantly between users (60). While improved training and technology have undoubtedly lessened the potential bias of measurements between and within users, the potential for such differences cannot be discounted and could contribute to clinically meaningful differences. Foremost among the limitations of LVO in the preterm population is the impact of shunting on the LVO measurement (61), with expert guidance stating that LVO does not represent systemic blood flow in the presence of a patent ductus arteriosus (PDA) (53). Since a PDA is present in most preterm neonates the technique has limited value as an isolated measure of systemic perfusion in this population but may be of use in combination with other parameters as a global overview of preterm circulatory status. It is likely that the greatest precision in functional echocardiographic measurements will come with repeated measures taken by the same experienced user and as discussed elsewhere, functional echocardiography should not rely on a single measurement, but rather on repeated measurements over time to assess changes in circulatory status.

Echo-Based RVO

Right ventricular output represents another commonly recorded measure of central blood flow. In the absence of shunting, RVO reflects the cumulative inflow of deoxygenated blood and hence venous return. RVO is measured according to the following formula:

$$\text{RVO}(\text{mL/kg/min}) = \frac{[\text{Velocity time integral} \times \text{Cross sectional area (at pulmonary valve)} \times \text{Heart rate}]}{\text{Weight (kg)}}$$

Cross-sectional area is calculated at the level of the pulmonary valve at the end of systole using an oblique long parasternal view or short parasternal view, and VTI is calculated just proximal to the pulmonary valve in the same views (54). Measurements of vessel diameter and VTI for RVO have traditionally both been obtained in this manner, however, recently published material has suggested several adaptations to standard right ventricular imaging protocols to address the unique issues in echocardiography within the neonatal population during the transitional period (62). As a result, there will likely be increasing use of additional views such as the right ventricle 3-chamber view in assessing right ventricular outflow and function in future publications. Similar to left ventricular measures, RVO was first described in the neonatal population approximately 30 years ago (63, 64). Because the reference points used in measurement lie close to the anterior chest and the view for calculating VTI and cross-sectional area are the same, RVO is easily measured in the preterm infant. Like all measurements taken with echocardiography, RVO provides results in real-time and is non-invasive. No information is available on the accuracy of RVO in relation to invasive methods in the preterm neonatal population. Similar to LVO, RVO is affected by the presence of shunting, in this case a patent foramen ovale or other septal defects leading to inaccuracy in measurement (61). The issue of inter and intra-observer variation in measurement is also present in RVO measurement with repeatability being similar to measurement of LVO in the term and preterm population (60). In a recent study by Popat et al., differences in measurement led to significantly different results between users with the majority of the difference being made up by inaccurate measurement of VTI and vessel cross-sectional area (65). Because of the limitations of RVO, the technique has a limited role in the assessment of the circulatory status of preterm infants. Similar to other echo techniques, the maximal benefit is likely to come from recording RVO along with other complementary echo measurements, with readings repeated over time and ideally taken by the same user to reduce variation.

Superior Vena Cava (SVC) Flow

Due to the limitations of LVO and RVO measurement within the neonatal population SVC flow was developed as an alternative measure of central blood flow which is not affected by the presence of shunting (66). The flow within the SVC is calculated according to the following formula:

$$\text{SVC flow}(\text{mL/kg/min}) = \frac{[\text{Velocity time integral} \times (\pi \times (\text{Mean SVC diameter}^2/4) \times \text{Heart rate})]}{\text{Weight (kg)}}$$

The diameter of the vessel is measured *via* the high-parasternal view as the vessel enters the right atrium with VTI traditionally calculated from a low-subcostal view as the SVC enters the right atrium (66). Though this is the most common approach, a recent publication suggests that measurement of vessel area from a short axis view and VTI from a suprasternal view may improve repeatability (67). Since its initial description, low-SVC flow in the neonatal population has been shown to correlate with a variety of adverse short- and long-term outcomes (8, 9, 18–23, 27, 68). Compared with the other echocardiography-based techniques described, SVC flow has the advantage of being unaffected by shunting and is considered by many to be the most robust echocardiography technique for measurement of central blood flow (69). Similar to other methodologies discussed, however, there are concerns around the repeatability of the technique with studies on inter- and intra-observer variability, showing potential variability of between 1 and 102% and 1 and 34%, respectively (66, 70, 71). Much of the variability is attributed to probe positioning and differences in SVC diameter measurement (65), which are a particular problem given the compressible nature of the SVC's venous wall.

Bioreactance and Bioimpedance

At its most basic level, the thorax may be seen as a 3D shape with fluid (blood) flowing through it. Depending on the point in the cardiac cycle, the amount of fluid in the thorax will vary, for example, during systole blood flow through the aorta will increase. Different substances within the chest have different resistances to electrical flow, with blood having lower resistance than soft tissue or bone. Because blood flow changes based on CO between heartbeats, the relative resistance to electrical flow will

alter depending on flow through the aorta. Bioimpedance uses this principle to measure CO by passing an electrical signal of known amplitude and frequency between electrodes across the chest and measuring the resistance to flow. With more blood flow in the aorta, the resistance to the passage of electrical signal is lower as calculated by the ratio of voltage to current amplitude. Hence, differences in resistance can be used to estimate CO. While traditional bioimpedance is continuous, non-invasive, and requires relatively little expertise to perform; it is limited by the interference from electrical noise, the need for exact placement of electrodes for accuracy and concerns over accuracy when compared with more established techniques in the pediatric population (72). An adaptation of bioimpedance called electrical velocimetry has been suggested by some as improving the accuracy of the technique and has been shown to be feasible in the neonatal population (73). In addition, CO measurements taken by electrical velocimetry appear to compare favorably with echocardiography measures in children with congenital heart disease (74), term neonates (75), and within the preterm population (76). Despite these advantages, the bioimpedance-based methodology has not yet been adequately validated in the neonatal population either against traditional invasive methodologies or with regard to clinical outcomes.

Another new methodology based on measures of thoracic electricity conduction is bioreactance, which measures the phase shift of an electrical signal as it passes through tissues and is thought to be less susceptible to noise interference than traditional bioimpedance (77). Bioreactance relies on the fact that changes in phase shift can only occur in the setting of pulsatile flow and given that the majority of pulsatile flow within the thorax is accounted for by the aorta, phase shift will reflect flow in the aorta and hence CO (78). Similar to bioimpedance, electrodes are placed on the chest for measurement. In bioreactance electrodes on the upper and lower chest measure bioreactance on the left and right sides of the chest separately and the results are averaged to determine CO. Despite initial concerns regarding the accuracy of the technique in smaller children (79), bioreactance has been shown to be feasible in both the term and preterm population (80, 81). There is also evidence that bioreactance has shown some potential to monitor fluid status in postoperative pediatric patients (82). While measurements of LVO by bioreactance have been shown to correlate with echocardiography measurements, bioreactance appears to underestimates CO (80). Bioreactance is similarly non-invasive to bioimpedance but has the advantage of not being dependant on distance between electrodes and is less affected by electrical "noise," a common feature in the NICU setting. While bioreactance is widely considered a more robust technique, it has not yet entered routine use in the neonatal population and there are concerns from adult studies regarding its accuracy in low-flow states.

Despite the limitations of both bioimpedance and bioreactance methods, the only existing systematic review and meta-analysis of the accuracy and precision of non-invasive CO techniques in the pediatric population concluded that electrical cardiometry was the most accurate, with other methodologies varying greatly between studies (83). At present, both techniques are used primarily in a research capacity but represent two of the most promising devices for the non-invasive measurement of CO in the preterm neonate.

Portable Doppler

Devices such as the ultrasonic cardiac output monitor (USCOM) monitor measure Doppler flow within the large vessels of the chest transthoracically. The technique relies on external placement of a small Doppler probe, which when angled correctly can measure the flow within the aorta and calculate CO based on an algorithm which uses patient height to estimate cross-sectional area. The technique is non-invasive, continuous, and easy to learn (84). The technique has been compared with thermodilution in the pediatric population with results suggesting that the technique was inaccurate for estimation of actual CO measurements (85). The technique has been used successfully within the preterm neonatal population and shows good correlation with echo measurement of CO (59, 86) though due to the small number of studies in the preterm population there are ongoing concerns about the accuracy of the technique in neonates (87). One study looking at the repeatability of USCOM has suggested that a variety of factors make measurement easier in younger patients (88), which may favor the technique in the pediatric and neonatal population. Despite promising data from adult patients (89), the only meta-analysis assessing accuracy and precision of non-invasive CO measures in children suggested that Doppler flow techniques are prone to a high-percentage error (83). Esophageal Doppler is a related technique which is used successfully in the adult population. Because this methodology involves placement of a Doppler probe within the esophagus to measure flow in the descending aorta, it is limited by the size of the child and only used in infants >3 kg (90), making it of limited use in the preterm neonatal population.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging has safely been used in the preterm neonatal population to derive central blood flow measurements (91). MRI has been suggested as having improved accuracy and repeatability compared with other techniques for CO measurement in neonates and older children (92, 93). The obvious disadvantages of MRI are that the technique is slow, expensive, non-continuous, not routinely available to neonatologists, and non-portable. The technique has also not yet been compared with traditional invasive techniques in the neonatal population. As a result, MRI is not ideal as a methodology of assessing CO in preterm neonates as it cannot be performed at the bedside to facilitate decision making in critically unwell infants. Consequently, at present CO from MRI is limited to experimental use but may have a role in the development of future techniques for CO assessment or to improve existing technologies.

EVIDENCE FOR IMPROVED OUTCOME WITH CO MONITORING

As the use of functional echocardiography has increased in the NICU so too have efforts to standardize the quality of imaging obtained in different centers. In addition, there is a limited but increasing body of evidence that monitoring CO in the preterm

population improves outcome. While this article focuses on the use of point of care ultrasound for assessing CO, there are many other ways in which functional echocardiography can be used to improve neonatal care (94). It has been suggested that the availability of CO monitoring such as functional echocardiography can improve the care of both term and preterm infants in a variety of ways (95, 96), though as previously discussed there is only a limited pool of evidence for this to date. Despite this, there is data supporting the role of CO monitoring in clinical decision making and in some cases avoiding unnecessary intervention in the neonatal population (97). Functional echocardiography measurement of LVO allows early detection of cardiorespiratory instability in neonates with PDA ligation (98), a situation which is potentially amenable to medical intervention. Novel functional echocardiography measures also have potential to provide valuable information on myocardial performance following ligation of ductus arteriosus (99). In addition to targeted imaging on the basis of a known circulatory issue, functional echocardiography has also potential to screen preterm infants for asymptomatic but potentially clinically important abnormalities which are not uncommonly uncovered during routine imaging (100, 101).

LIMITATIONS AND CURRENT SITUATION

Neonatologists currently stand in an unusual position with regard to CO monitoring: there are numerous techniques available for the evaluation of CO in the neonatal population but few have been rigorously validated against the classically held "gold standards." Fewer still have been validated against clinical outcomes and we are often unsure if intervention to improve the measurements taken is improving the outcome of the infant. Like many aspects of neonatology, rigorous validation of new CO technologies is challenging as the traditionally held best practice, in this case invasive dilution techniques, have themselves been largely extrapolated from adult studies and are of uncertain utility in neonatology. Added to this is the inherent difficulty of defining a "normal range" within the neonatal population as identifying what constitutes a "healthy" preterm infant is not easy. The solution may seem obvious to some: designing randomized trials where some infants are assigned to receive a novel investigation and some are not. On the surface, this seems easy but there are numerous pitfalls to navigate: the ability to properly blind, the ethics of performing sham studies, and the practice of withholding a technology in a group of patients in whom it may be reasonably assumed could potentially benefit from its availability, to name but a few.

None of the technologies described above are perfect, with many suffering limitations unrelated to their lack of validation: namely their practicality and invasiveness in the setting of preterm neonatal care. Of those that are considered most promising within the adult population, many require insertion of arterial and venous lines to provide accurate, real-time measurements making them unsuitable as techniques in preterm infants. Among those discussed, echocardiography is likely to represent the best validated and most practical technique at present. Despite its widespread adoption, some have questioned the use of echocardiography in the NICU suggesting that it requires further validation, definition of normal values, and guidance on potential therapy before it can be optimally utilized (102). Several guidelines have been created to aid in the standardization of training and image acquisition for neonatologist-performed echocardiography (53, 103, 104). All echocardiography-based techniques have the advantage of being non-invasive and providing real-time information on blood flow. Echocardiography techniques are among the best validated in the preterm neonatal population and measurements taken can facilitate bedside decision making. Notwithstanding these advantages, echocardiography is a non-continuous measure of blood flow and although high-quality images can be obtained, potentially significant issues regarding inter-observer variability exist (65).

FUTURE DIRECTIONS

In an editorial regarding CO monitoring in critically ill children, Chang eloquently defined three areas which warrant our focus: designing the ideal technology for CO measurement, recognition of the importance of assessing tissue perfusion, and the incorporation of non-medical expertise in the design of computer systems to analyze the increasing volumes of data which we will collect (105). The design of an ideal technology for CO monitoring will first require us to validate the existing technologies at our disposal. For some technologies such as pulmonary artery thermodilution, this is unlikely to be feasible within the preterm neonatal population. Instead we may need to validate existing technologies more rigorously around clinical outcomes and their ability to positively impact patient care; this in itself raising the question of what outcomes we should ideally be measuring. Concurrent to this, we may have to examine novel technologies more rigorously in older children and extrapolate data to the neonatal population before introducing them into practice or exploring them experimentally in premature infants. Regardless of how this is undertaken, we must appreciate that our efforts to validate existing technologies are largely to establish a relative "gold standard" within the neonatal population and that the ideal CO technology is likely to require considerable innovation and is unlikely to be closely related to any technology which is currently in use. Previous discussions on hemodynamic monitoring within the neonatal population have highlighted the importance of comprehensive hemodynamic monitoring integrating computational modeling to assist decision making (106). This idea is likely to become more important as new technologies allow us to measure cardiovascular parameters which were previously either unmeasurable or wholly unknown. Such incorporation of computer technology should be fostered in conjunction with novel CO measurements, so that as time passes and we have more information available we can make objective decisions which are most likely to benefit patient care, rather than being overwhelmed by information.

CONCLUSION

There are many options available to the neonatologist to monitor CO in the preterm infants but few are well-validated within this population. There are many obstacles to creating the ideal technology to non-invasively monitor preterm CO such as the

lack of a true "gold standard" within the population and the difficulty in defining true gestation-based normal ranges for a novel device. At present, echocardiography is likely to be the most robust technique available to the neonatologist though this requires experience and has a variety of limitations. Bioreactance, electrical velocimetry, and continuous Doppler measurements of CO represent the most exciting technologies under investigation due to their non-invasive nature and ability to provide continuous measurements. In the short-term, research should focus on validating existing techniques against clinical outcomes in order to best define those technologies which will impact patient care. Over the coming decades, there is need for true innovation to produce a CO technology which meets the needs of the preterm neonatal population.

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MM designed the article, performed the literature review, and wrote the article. JM equally designed the article, performed the literature review, and edited article.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a past collaboration with the authors.

6.2 Low Cardiac Output Measured by Bioreactance and Adverse Outcome in Preterm Infants with Birth Weight less than 1250 g

6.2.1 Background

As outlined in the previous chapter, a new continuous non-invasive CO measurement, based on trans-thoracic bioreactance, has become available. Bioreactance measurement of CO has been shown to correlate with LVO detected by echocardiography in healthy term and preterm neonates and in unstable preterm neonates following ductal ligation.(74, 75, 183)

The aim of our study was to correlate CO measurements by bioreactance in the first 48 hours of life with adverse outcomes attributable to hypoperfusion, namely PIVH and NEC in the cohort of infants with birth weight less than 1250g.

6.2.2 Materials and Methods

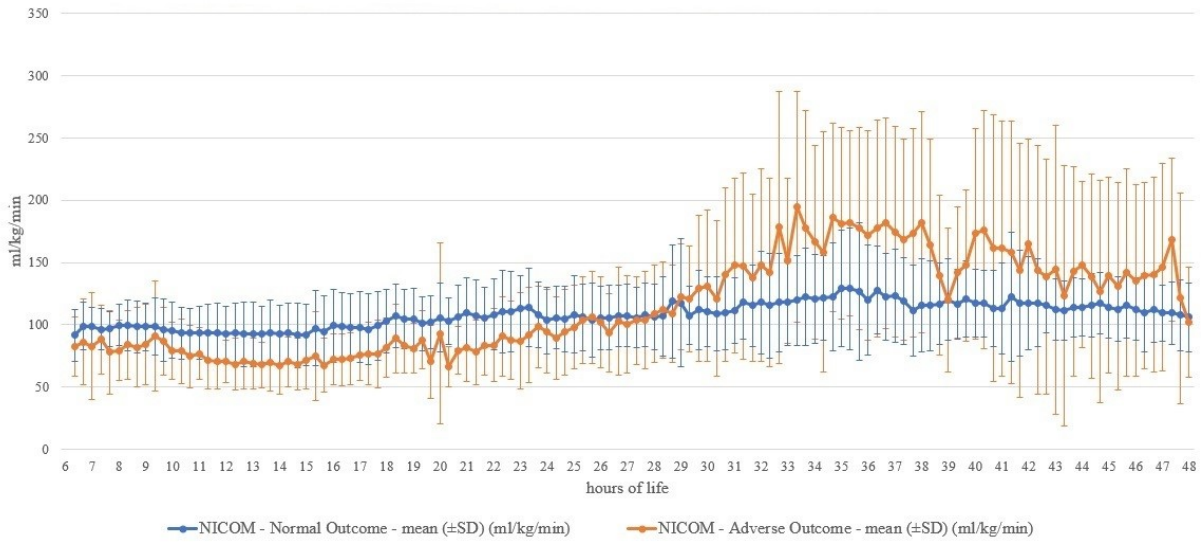
We have designed a prospective observational cohort study in a level III neonatal centre (Coombe Women and Infants University Hospital (CWIUH), Dublin, Ireland). The study was approved by the Research Ethics Committee (REC) in CWIUH (No.23 – 2015). Our inclusion criteria were: birth weight <1250g, less than six hours of age at the time of enrolment, baseline cranial ultrasound free of PIVH ≥grade II and parental consent. Our exclusion criteria were: infants with a major congenital and/or chromosomal anomaly, congenital heart disease other than PDA or PFO diagnosed on the first echocardiography (or earlier), critical status of the infant or decision to provide palliative care. The NICOM^{TM} monitor (Cheetah NICOM^{TM}, Cheetah Medical, USA) was used for bioreactance CO (LVO) measurements between six and 48 hours of age. The CO was expressed as ml/kg/min and recorded for every 60 seconds of the study. The mean CO (ml/kg/min) for every 20 minutes of the study for each participant was then established and used for the outcome calculations. Our primary outcome was the

difference in CO in the first 48 hours between infants with adverse outcomes attributable to hypoperfusion – PIVH ≥grade II and/or NEC ≥grade IIA (184) (Group 1) and those without these outcomes (Group 2). Our secondary outcomes included a description of the CO in infants less than 1250g in the first 48 hours of age and the data in relation to neonatal morbidity including RDS, CLD, defined as respiratory support requirements at 36 weeks of postmenstrual age, ROP ≥Stage II, PDA requiring medical or surgical treatment and mortality before discharge from the hospital. We analysed the data using a PC-based statistics package (StatsDirect version 3.2.10) using the Fisher exact test, Chi^2 test, Student t-test, Mann – Whitney U test and Pearson correlation as appropriate. We have constructed a Receiving Operating Characteristic (ROC) curve for minimal CO between six and 48 hours of age. We considered $p < 0.05$ as statistically significant.

6.2.3 Results

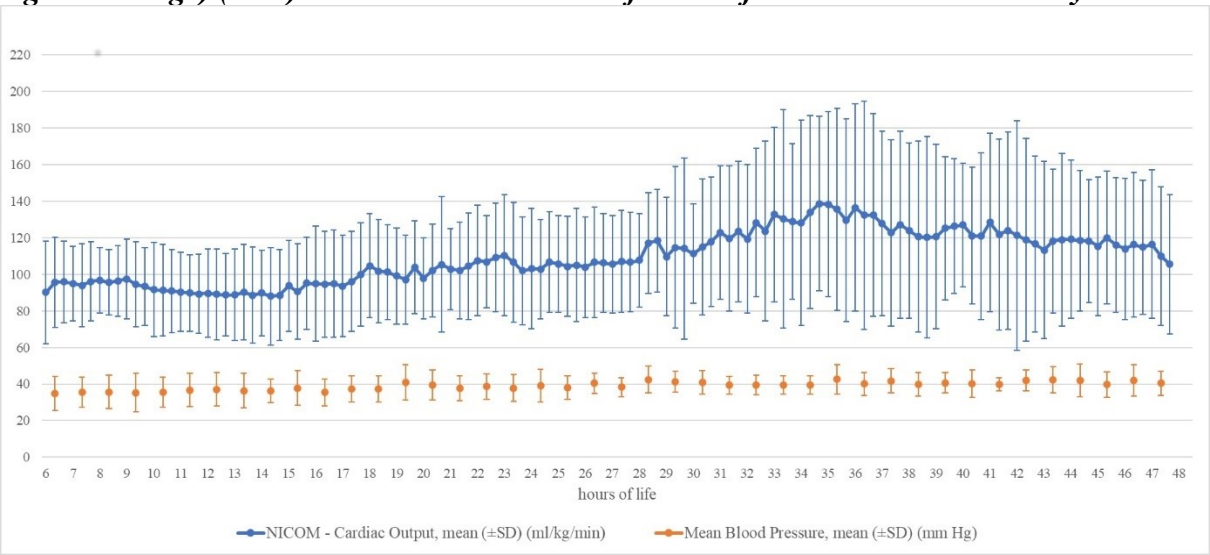
There were 39 infants enrolled in the study. The mean gestational age of the study cohort was 27.5 (±1.8) weeks of gestation and the mean birth weight was 0.95 (±0.15) kg. There were six infants in Group 1. These infants had a significantly lower minimal CO measurement compared to Group 2 (mean 36.7 ml/kg/min vs 64.5 ml/kg/min, $p = 0.0006$). The mean CO in Group 1 was statistically significantly lower at 11, 12, 13, 16 and 19 to 22 hours of age. This was followed by an increase in CO for Group 1, and their output was statistically significantly higher than Group 2 at 33 to 37, 39, 40 and 47 hours of age. (Figure 4).

Figure 4 - Mean cardiac output (ml/kg/min) (±SD) between 6 and 48 hours of age according to predefined adverse outcomes (PIVH/NEC in orange, normal outcome in blue).



The overall cohort CO was rising during the study and the difference between the lowest CO at 14 hours of age and the highest CO at 34 hours of age reached statistical significance (mean 88.0 ml/kg/min vs. 138.7 ml/kg/min respectively, p <0.0001). (Figure 5)

Figure 5 - Mean cardiac output (ml/kg/min – in blue) (±SD) and mean blood pressure (mm Hg – in orange) (±SD) between 6 and 48 hours for all infants enrolled in the study.



There were no other differences in the two groups apart from predefined outcomes and minimal CO.

6.2.4 Conclusions

In conclusion, infants with a birth weight less than 1250g and adverse outcome related to hypoperfusion (PIVH and/or NEC) had significantly lower CO, measured by bioreactance, when compared to infants without these complications. This low CO was then followed by a significant increase on the second day of life. The overall cohort CO was rising during the first 48 hours of life.

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Low cardiac output measured by bioreactance and adverse outcome in preterm infants with birth weight less than 1250 g

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ABSTRACT

Background: Recently a new continuous non-invasive cardiac output measurement, bioreactance, has become available. Bioreactance measurement of cardiac output has been shown to correlate with left ventricular output detected by echocardiography in healthy term and preterm neonates.
Aims: Our aim was to correlate cardiac output measurements by bioreactance in the first 48 h of life with adverse outcomes attributable to hypoperfusion (peri/intraventricular haemorrhage (PIVH) and/or necrotising enterocolitis (NEC)) in the cohort of extremely preterm infants.
Study design: A prospective observational cohort study.
Subjects: Preterm infants with birth weight less than 1250 g.
Outcome measures: Cardiac output was measured between six and 48 h of age by bioreactance. Our primary outcome was a difference in cardiac output between infants with an adverse outcome attributable to hypoperfusion (Group 1), and infants without the predefined adverse outcome (Group 2).
Results: There were 39 infants enrolled in the study. There were six infants in Group 1. These infants had a significantly lower minimal cardiac output measurement compared to Group 2 (mean 36.7 ml/kg/min vs 64.5 ml/kg/min, $p = .0006$). The mean cardiac output in Group 1 was significantly lower on day one of life, followed by a significant increase in cardiac output on day two of life compared to Group 2.
Conclusions: Infants with birth weight less than 1250 g and PIVH and/or NEC had significantly lower cardiac output compared to infants without these complications on day one of life. This low cardiac output was then followed by a significant increase on day two of life.

1. Introduction

Cardiovascular instability with subsequent treatment is a very common complication in extremely preterm infants and most commonly occurs within the first 24 h of life [1,2]. The most used parameter to assess circulatory status is the blood pressure measurement (mean blood pressure). There is some evidence of a correlation between lowest blood pressure measurement in the first 24 h of life and adverse outcomes [3] however low blood pressure alone is not related to adverse long term neurodevelopmental outcome [4]. Moreover antihypotensive therapy exposure itself seems to be associated with an increased risk of death or neurodevelopmental impairment/developmental delay at 18–22 months' corrected gestational age in extremely preterm infants [5].

The uncertainty around blood pressure treatment may be explained by the pathophysiology of low organ perfusion as the organ perfusion is dependent on peripheral vascular resistance, characteristic of arterioles and blood pressure. Hence measurement of organ blood flow would be better to diagnose neonates with cardiovascular compromise. Theoretically, cardiac output would be the most suitable measured

Abbreviations: CLD, chronic lung disease; LVO, left ventricular output; NEC, necrotising enterocolitis; NICU, Neonatal Intensive Care Unit; PDA, patent ductus arteriosus; PIVH, peri/intraventricular haemorrhage; RDS, respiratory distress syndrome; ROC, Receiving Operating Characteristic; ROP, retinopathy of prematurity; SVC, superior vena cava

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parameter. However, in newborn infants, the invasive cardiac output measurement is not technically feasible due to lack of the appropriately sized device. On the other hand, cardiac output can be measured using echocardiography. Such measurement is technically feasible, but in the newborn period quite imprecise as a result of naturally occurring shunts between the systemic and the pulmonary circulation [6]. To overcome this issue, superior vena cava (SVC) flow measurement has been used [7]. Low SVC flow was documented to be a risk factor for death, intraventricular haemorrhage and long term adverse neurodevelopmental outcome [8–10]. However the commonly used SVC flow echocardiography assessment technique has been quite challenging, is not continuous and has important inter and intra observer variability [11].

Recently a new continuous non-invasive cardiac output measurement, based on trans-thoracic bioreactance, has become available. Bioreactance measurement of cardiac output has been shown to correlate with left ventricular output detected by echocardiography in healthy term and preterm neonates, in unstable preterm neonates following ductal ligation and in term neonates with hypoxic ischaemic encephalopathy [12–15].

The aim of our study was to correlate cardiac output measurements by bioreactance in the first 48 h of life with adverse outcomes attributable to hypoperfusion, namely peri/intraventricular haemorrhage (PIVH) and necrotising enterocolitis (NEC) in the cohort of infants with birth weight less than 1250 g.

2. Methods

2.1. Study design

A prospective observational cohort study in a level III neonatal centre (Coombe Women and Infants University Hospital, Dublin, Ireland). The study was approved by the Research Ethics Committee in Coombe Women and Infants University Hospital (No.23 – 2015).

2.2. Participants

Our inclusion criteria were: birth weight $<$ 1250 g, less than 6 h of age at the time of enrolment, baseline cranial ultrasound free of PIVH $\geq$grade II (performed at 6 h of age) and parental consent. Our exclusion criteria were: infants with a major congenital and/or chromosomal anomaly, congenital heart disease other than patent ductus arteriosus or foramen ovale diagnosed on the first echocardiography (or earlier), critical status of the infant or decision to provide palliative care. As we had only one NICOM™ machine at the start of the study, in multiple pregnancies we aimed to enrol first born if eligible unless there was a parental preference for the enrolment. Delayed cord clamping for 40 s was done as a part of the standard care after delivery.

2.3. Measurements

2.3.1. Bioreactance cardiac output measurements

The NICOM™ monitor (Cheetah NICOM™, Cheetah Medical, USA) was used for bioreactance cardiac output (left ventricular output (LVO)) measurements. Bioreactance is the analysis of the variation in the frequency spectra of a delivered oscillating current when it traverses the thoracic cavity. Upper thoracic electrode strips were placed over the mid-clavicles and upper back bilaterally. The lower electrode sensors were placed between the 6th and 7th intercostal spaces extending from the anterior axillary to posterior axillary line in cranio-caudal direction [13,14]. The cardiac output measurements were blinded to the echocardiography providers and the clinical team by covering the screen displaying the values. The monitor was applied just before 6 h of age in order to have the monitor fully functional and providing reliable data at 6 h of age. The monitoring continued up to 48 h of age. The sensors were not replaced during the study unless the leads contact were suboptimal (in that instance re-attachment would be tried first). The stroke volume was measured by the NICOM™ monitor every 60 s, the cardiac output was then calculated using heart rate (measured by NICOM ™ simultaneously with stroke volume) and weight of the infant. The cardiac output was expressed as ml/kg/min and recorded for every 60 s of the study. The mean cardiac output (ml/kg/min) for every 20 min of the study for each participant was then established and used for the outcome calculations.

2.3.2. Functional echocardiography in the study

We performed functional echocardiography at the start of the study (6 h of age or earlier) to establish normal cardiac anatomy. The Phillips CX50 (Philips, Amsterdam, Netherlands) ultrasound system and a sector-array cardiology 12 Hz probe were used. All studies were performed by a neonatologist trained in targeted neonatal echocardiography (JM, JS).

2.3.3. Cranial ultrasound in the study

Point of care ultrasound of the brain was performed at the start of the study to rule out PIVH Grade II or higher [16]. Further cranial ultrasounds were done as a part of the normal clinical care (as per departmental guidelines), for the purpose of the study the highest grade of PIVH diagnosed within the first 28 days was documented. The Phillips CX50 ultrasound system (Philips, Amsterdam, Netherlands) with curved-array 8 Hz probe was used.

2.3.4. Vital function monitoring

Data from patient's bedside monitor and NICOM™ monitor were used to record blood pressure (systolic, diastolic and mean) and heart rate. The blood pressure monitoring was either invasive or non-invasive and the arterial line was not mandated as a part of the study. If the arterial line was available, the blood pressure was recorded hourly. When non-invasive blood pressure was available, this was measured as per attending physician, however at least 6-hourly.

2.4. Outcomes

Our primary outcome was the difference in cardiac output in the first 48 h between infants with adverse outcomes attributable to hypoperfusion – PIVH $\geq$grade II and/or NEC $\geq$ grade IIA [17] and those without these outcomes. Our secondary outcomes included a description of the cardiac output in infants less than 1250 g in the first 48 h of age and the data in relation to neonatal morbidity including respiratory distress syndrome (RDS), chronic lung disease (CLD), defined as respiratory support requirements at 36 weeks of postmenstrual age, retinopathy of prematurity (ROP) $\geq$ Stage II, patent ductus arteriosus (PDA) requiring medical or surgical treatment and mortality before discharge from the hospital. We collected baseline demographic data including gestational age, birth weight, Apgar scores, mode of delivery, antenatal steroid use and data in relation to treatment requirements during the first 48 h of age (ventilation requirements, surfactant use, volumotherapy, inotropic support).

2.5. Statistics

We planned to enrol 40 infants (convenience sample) as previously used in several studies of cardiac output in preterm infants including our own group [10,18]. We analysed the data using a PC-based statistics package (StatsDirect version 3.2.10) using Fisher exact test, Chi^2 test, Student *t*-test, Mann – Whitney *U* test and Pearson correlation as appropriate. We have constructed a Receiving Operating Characteristic (ROC) curve for minimal cardiac output between six and 48 h of age. We considered $p < .05$ as statistically significant.

3. Results

During the study period (January 2016 to July 2017) there were

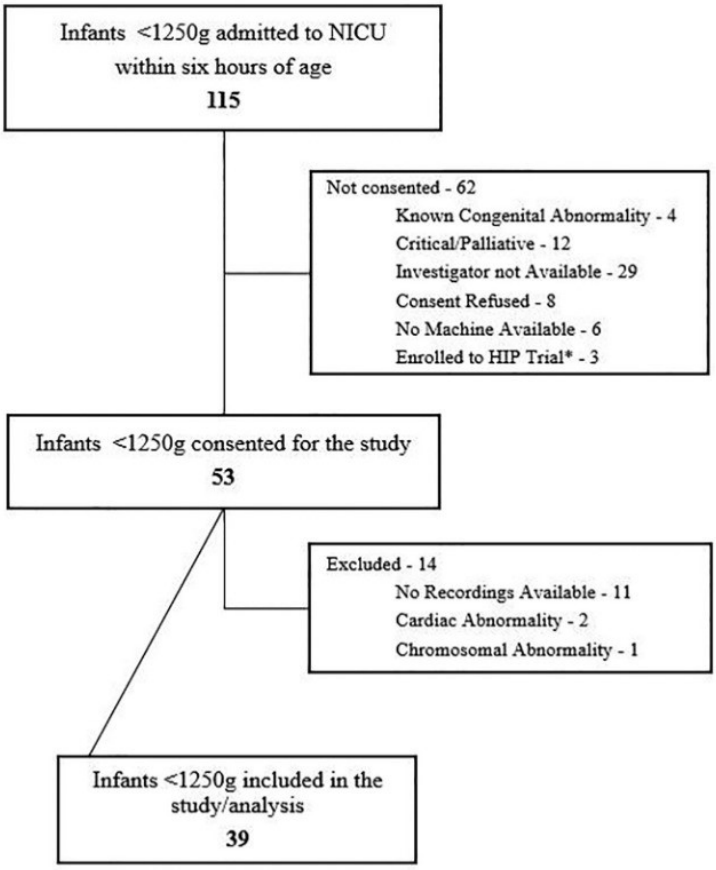

Fig. 1. Flowchart of the enrolment to the study.

115 infants below 1250 g admitted to the Neonatal Intensive Care Unit (NICU) within the first 6 h of life. Sixteen infants fulfilled exclusion criteria and we consented 53 out of 99 eligible infants to the study. A further fourteen infants were excluded, three infants fulfilled exclusion criteria after consenting and in 11 infants the NICOM™ recording was not available for the personnel and/or technical reasons. There were 39 infants included in the final analysis (flow sheet of the study enrolment see Fig. 1).

The mean gestational age of the study cohort was 27.5 (± 1.8) weeks of gestation and the mean birth weight 0.95 (± 0.15) kg. The full description of the study cohort including neonatal morbidity and mortality see Table 1.

There were six infants with predefined adverse outcomes (PIVH and/or NEC) – Group 1. These infants had significantly lower minimal cardiac output measurement compared to infants without the predefined outcome (Group 2) (mean 36.7 ml/kg/min vs. 64.5 ml/kg/min, $p = .0006$). However the overall mean cardiac output between six and 48 h of age did not differ between the groups. The mean cardiac output for Group 1 was lower between six and 24 h of age compared to Group 2, as documented in Fig. 2. This reached statistical significance at 11, 12, 13, 16, 19, 20, 21 and 22 h of age. This was followed by an increase in cardiac output for Group 1 and their output was statistically significantly higher than Group 2 at 33, 34, 35, 36, 37, 39, 40 and 47 h of

Table 1
Demographics, neonatal outcomes and cardiac output of the entire cohort.

n = 39	Values
Gestational age, mean (± SD), weeks	27.5 (1.8)
Birth weight, mean, mean (± SD), kg	0.95 (0.15)
Apgar score 1st minute, median (IQR)	7 (5–9)
Apgar score 5th minute, median (IQR)	9 (8–9)
Completed antenatal steroids, n (%)	33 (85)
Female gender, n (%)	17 (44)
Caesarean section, n (%)	30 (77)
RDS, n (%)	39 (100)
CLD, n (%) (survivors)	5 (13)
ROP (≥grade II), n (%) (survivors)	3 (8)
PDA - medical treatment, n (%)	1 (3)
Early onset sepsis, n (%)	1 (3)
PIVH ≥ grade II, n (%)	3 (8)
NEC ≥ grade IIA, n (%)	3 (8)
Mortality, n (%)	1 (3)
Mean cardiac output (6–48 h of age), mean (± SD), ml/kg/min	110.3 (± 21.0)

SD – Standard Deviation; IQR – Interquartile Range; CLD – Chronic Lung Disease; ROP – Retinopathy of Prematurity; PDA – Patent Ductus Arteriosus; PIVH – Peri/Intraventricular Haemorrhage; NEC – Necrotising Enterocolitis.

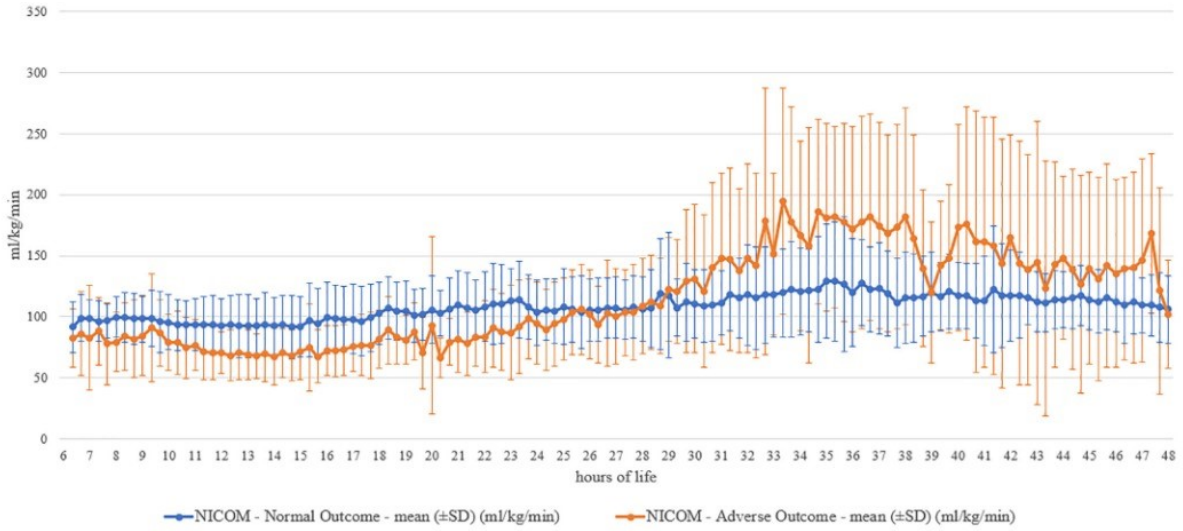

Fig. 2. Mean cardiac output between six and 48 h of age according to predefined adverse outcomes.

age. (Fig. 2).

There were no other differences in the two groups apart from predefined outcomes and minimal cardiac output as summarized in Table 2.

We have constructed the ROC curve, the cut-off point of minimal cardiac output of 31.7 ml/kg/min had 80% positive predictive value, 94% negative predictive value, sensitivity of 67% and specificity of 97% for subsequent PIVH ≥grade II and/or NEC ≥ grade IIA.

The overall cohort cardiac output was rising during the study and the difference between the lowest cardiac output at 14 h of age and the highest cardiac output at 34 h of age reached statistical significance (mean 88.0 ml/kg/min vs. 138.7 ml/kg/min respectively, $p < .0001$). The increase did not, however, reach statistical significance between the start and the end of the study (six and 48 h of age, mean 90.1 ml/kg/min vs. 105.6 ml/kg/min respectively, $p = .11$). The mean blood pressure was consistently rising for the study group between six and 48 h of age and this difference was statistically significant (mean 34.9 mmHg vs. 42.9 mmHg respectively, $p < .0001$). The cardiac output and mean blood pressure for the whole cohort during the study period are plotted in Fig. 3, there was a weak, however significant correlation between them ($r = 0.71$, $p < .0001$).

4. Discussion

In our study, the lowest cardiac output (measured by bioreactance) in infants with subsequent PIVH and NEC was significantly different from the cardiac output in infants without these complications. This would be in agreement with previous studies linking low cardiac output, measured by a surrogate marker (SVC flow) with adverse outcome, including PIVH [9,10]. Pathogenesis of both PIVH and NEC is multifactorial, however one of the definite factors playing a role is the disturbance in the end-organ blood flow [19–21].

Surprisingly the initial lower cardiac output in infants with PIVH and/or NEC was followed by a 'compensatory' increase in the second 24 h that was statistically significant, raising the possibility of ischaemia/reperfusion situation predisposing these infants to subsequent complications.

While the choice of PIVH as an adverse outcome linked to hypoperfusion would be obvious for our study [9,10,19], the choice of NEC might be more controversial. There is no doubt that ischaemic insult coupled with reperfusion injury can lead to intestinal injury [22]. This

Table 2
Demographic variables and outcomes of the groups in relation to predefined outcomes (normal outcome versus combined adverse outcome of PIVH/NEC).

	Adverse outcome (Group 1) n = 6	Normal outcome (Group 2) n = 33	p
Gestation, mean (± SD), weeks	26.5 (± 1.6)	27.7 (± 1.8)	0.15
Birth weight, mean (± SD), g	0.879 (± 0.12)	0.965 (± 0.16)	0.22
Apgar score 1st minute, median (IQR)	7.5 (6.3–8.8)	7 (5–9)	0.46
Apgar score 5th minute, median (IQR)	9 (8.25–9)	8 (8–9)	0.54
Female gender, n (%)	2 (33)	15 (45)	0.68
Caesarean section, n (%)	4 (67)	26 (79)	0.61
Complete antenatal steroids, n (%)	5 (83)	28 (85)	> 0.99
Highest mode of ventilation (1st 48 h of life)	–	–	–
No support, n (%)	0 (0)	0 (0)	0.58
nCPAP, n (%)	5 (83)	24 (73)	
Conventional ventilation, n (%)	1 (17)	9 (27)	
HFOV, n (%)	0 (0)	0 (0)	
Surfactant, n (%)	5 (83)	23 (70)	0.65
Pneumothorax, n (%)	0 (0)	3 (9)	> 0.99
Volumotherapy (1st 48 h of life), n (%)	1 (17)	0 (0)	0.15
Inotropes (1st 48 h of life), n (%)	1 (17)	0 (0)	0.15
CLD, n (%) (survivors)	2 (40)	3 (9)	0.12
ROP (≥grade II), n (%) (survivors)	1 (20)	2 (6)	0.35
PDA - medical treatment, n (%)	0 (0)	1 (3)	> 0.99
Early onset sepsis, n (%)	0 (0)	1 (3)	> 0.99
Mortality, n (%)	1 (17)	0 (0)	0.15
Mean cardiac output (6–48 h of age), mean (± SD), ml/kg/min	118.6 (± 39.7)	108.8 (± 16.2)	0.18
Lowest cardiac output (6–48 h of age), mean (± SD), ml/kg/min	36.7 (± 21.4)	64.5 (± 15.8)	**0.0006**
Lowest MBP (6–48 h of age), mean (± SD), mm Hg	30.5 (± 6.4)	34.7 (± 4.6)	0.06

SD – Standard Deviation; IQR – Interquartile Range; nCPAP – nasal Continuous Positive Airway Pressure; HFOV – High Frequency Oscillatory Ventilation; CLD – Chronic Lung Disease; ROP – Retinopathy of Prematurity; PDA – Patent Ductus Arteriosus; MBP – Mean Blood Pressure. Bold: p < 0.05 was considered statistically significant.

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6.3 Non-invasive Continuous Cardiac Output and Cerebral Perfusion Monitoring in Term Infants with Neonatal Encephalopathy: Assessment of Feasibility and Reliability

6.3.1 Background

Another important group of patients in NICU, where non-invasive hemodynamic monitoring would be potentially useful, are infants with NE undergoing TH. Studies to date assessing the hemodynamic status of infants undergoing TH have used echocardiography which produces discrete, isolated measurements of function and output. The ability to assess CO (including Stroke Volume (SV)), in a continuous, non-invasive manner together with cerebral oxygenation monitoring using Near Infrared Spectroscopy (NIRS) would enable a more detailed assessment of the haemodynamic status in the setting of TH.

6.3.2 Materials and Methods

This was a prospective observational study carried out in the NICUs of the Rotunda Hospital and the CWIUH, Dublin, Ireland. Ethical approval was obtained from the local RECs and written informed consent was obtained from parents of all participants prior to enrolment. All infants were either passively or actively cooled within six hours following birth. Parents were given up to 12 h following the initiation of TH to consider the study. Infants greater than 35 weeks gestation with a diagnosis of NE who underwent TH were all eligible provided they fulfilled two of the following criteria based on the TOBY study (185): Apgar score of ≤5 at 10 min after birth; continued need for endotracheal or mask ventilation at 10 min after birth; acidosis within 60 min of birth (defined as any occurrence of umbilical cord, arterial, or capillary pH <7.00 or a base deficit ≥16 mmol/l); and/or clinical seizures or moderate to severe encephalopathy using the Sarnat grading system.(186) We excluded infants who were unlikely to survive beyond the cooling period. All clinical care decisions including sedation and

inotrope use were left to the discretion of the clinical team. The clinical team was blinded to the NICOM and NIRS measurements. We planned to perform continuous measurements of CO, SV, SVR, HR, BP, Cerebral Mixed Venous Saturation (SctO2) values using NICOM^{TM} and NIRS throughout the cooling and rewarming period and to compare NICOM^{TM} measured CO with echocardiography-measured CO (echo-CO) over three time points (day 1 [10 h of TH], prior to rewarming [70 h of TH], and at the end of the rewarming period [100 h after commencement of TH]). We hypothesized that NICOM^{TM} use in infants with NE is feasible and can provide a reliable method of CO assessment in this population. Continuous data were presented as median (interquartile range) or as means (SD) as appropriate. Categorical data were presented as absolute numbers and proportions. Two group analysis was conducted using the Mann-Whitney U test for continuous variables or the $\chi 2$ test for categorical variables. One-way repeated measures ANOVA was used to assess the change in the hemodynamic measurements with respect to time. Pairwise comparison carried out between two time points (70 and 100 h) and baseline (10 h) was conducted using the Bonferroni adjustment. Two-way repeated measures ANOVA was used to assess the difference in the hemodynamic measurements between two groups (normal vs. abnormal MRI) over time. We compared the two methods of CO measurement using the Bland-Altman (BA) analysis and assessed the correlation between the two methods using Pearson's correlation coefficient. A p value <0.05 was considered significant. SPSS (IBM House, Dublin, Ireland) (IBM version 22) was used to perform the statistical analysis.

6.3.3 Results

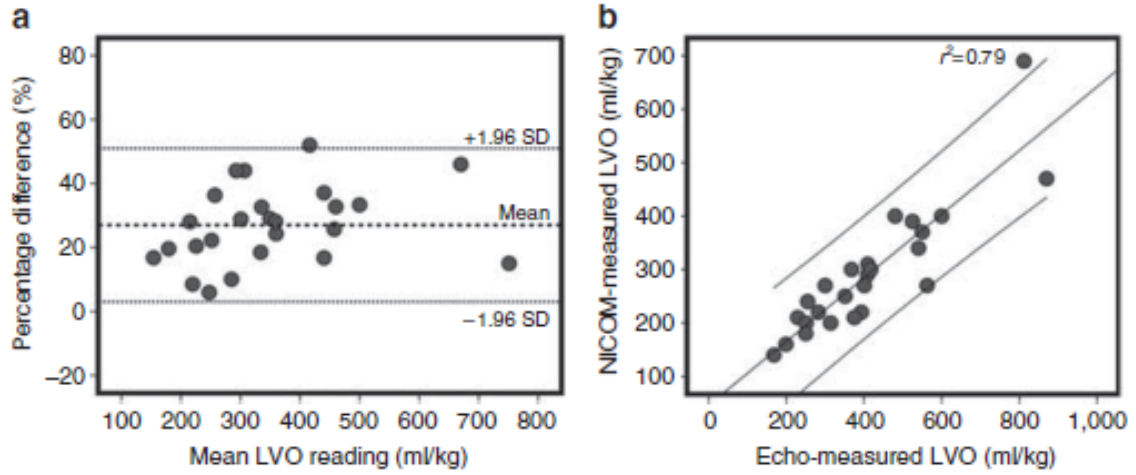
Twenty infants with a median gestation (IQR) of 40 (38.7 – 41.1) weeks were enrolled. There was a strong correlation between NICOM^{TM} and echo-CO ($r^2 = 0.79$, $P < 0.001$).(Figure 6) NICOM^{TM} measured CO was systematically lower than echo-CO with a bias of 27% (limits of

agreement 3–51%).(Figure 6) NICOM^{TM} illustrated lower CO during TH, which increased during rewarming. SctO2 increased over the first 30 h of TH and stayed high for the remainder of the study. There was a rise in SVR over the first 30 h of TH and a decrease during rewarming (all p <0.05). There was no change in mean arterial BP or SV over the study period. HR significantly increased during rewarming. All infants underwent a brain MRI between days 5–10 of life. Ten infants had an abnormal MRI. Infants in the abnormal MRI group had lower CO and SV, and a higher SVR during TH. However, these differences did not reach statistical significance.

6.3.4 Conclusions

We have demonstrated that the assessment of the hemodynamic status of infants with NE undergoing TH in addition to cerebral perfusion in a continuous fashion is feasible and reflects the expected hemodynamic changes occurring as a result of TH and rewarming in infants with NE. Further studies are required to assess NICOM^{TM}'s clinical applicability in this condition in a larger cohort.

Figure 6 - Bland-Altman Analysis (a) and Correlation (b) between echocardiography and non-invasive cardiac output monitoring (NICOM)-measured cardiac output. NICOM and Echo cardiac output (depicted as left ventricular output, LVO) was not indexed to weight for graphical representation.



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Noninvasive continuous cardiac output and cerebral perfusion monitoring in term infants with neonatal encephalopathy: assessment of feasibility and reliability

Eva Forman[1], Colm R. Breatnach[1], Stephanie Ryan[2], Jana Semberova[3], Jan Miletin[3], Adrienne Foran[1] and Afif EL-Khuffash[4]

BACKGROUND: Noninvasive hemodynamic monitoring of infants with neonatal encephalopathy (NE) undergoing therapeutic hypothermia (TH) would be a potentially useful clinical tool. We aimed to assess the feasibility and reliability of noninvasive cardiac output monitoring (NICOM) and near-infrared spectroscopy (NIRS) in this cohort.

METHODS: NICOM and NIRS were commenced to measure cardiac output (CO), systemic vascular resistance (SVR), blood pressure (BP), and cerebral regional oxygen saturations ($SctO_2$) during TH and rewarming. NICOM measures of CO were also compared with simultaneous echocardiography-derived CO (echo-CO).

RESULTS: Twenty infants with a median gestation of 40 weeks were enrolled. There was a strong correlation between NICOM- and echo-CO ($r^2 = 0.79$, $P < 0.001$). NICOM-CO was systematically lower than echo-CO with a bias of 27% (limits of agreement 3–51%). NICOM illustrated lower CO during TH, which increased during rewarming. $SctO_2$ increased over the first 30 h of TH and stayed high for the remainder of the study. There was a rise in SVR over the first 30 h of TH and a decrease during rewarming (all $P < 0.05$).

CONCLUSIONS: Noninvasive hemodynamic assessment of infants with NE is feasible and illustrates potentially important changes. Larger studies are needed to assess the clinical applicability of those methods in this cohort.

Term infants sustaining a hypoxic-ischemic perinatal insult resulting in neonatal encephalopathy (NE) are considered for therapeutic hypothermia (TH) as a neuroprotective measure (1). The effects of TH on cardiac output (CO), systemic vascular resistance (SVR), blood pressure (BP), and cerebral perfusion in this cohort is becoming an area of active research. Several studies have documented impaired myocardial performance (measured conventionally and by speckle tracking echocardiography) and a reduced CO measured by echocardiography in infants with NE undergoing TH when compared to healthy term counterparts (2,3). Animal data suggest that the fall in CO is secondary to a decreased heart rate and stroke volume (SV), accompanied by a concomitant increase in SVR (4–6). The decrease in metabolic demand associated with TH is thought to offset the potential detrimental effect of a low blood flow state in those infants. Near-infrared spectroscopy (NIRS) may also play a role in monitoring cerebral perfusion and oxygen extraction during TH. Recent studies have demonstrated good correlation between NIRS-measured cerebral mixed venous saturation values ($SctO_2$) and cerebral blood flow measured using magnetic resonance imaging (MRI) in infants undergoing TH (7). In addition, NIRS may have a prognostic role in this population (8,9).

However, studies to date assessing the hemodynamic status of infants undergoing TH have used echocardiography which produces discrete, isolated measurements of function and output. The ability to assess CO (including SV), SVR, BP, and heart rate in addition to $SctO_2$ in a continuous, noninvasive manner would enable a more detailed assessment of the interaction of all the above parameters in the setting of TH and NE in real time. Transthoracic bioreactance is a new technique of continuous noninvasive cardiac output monitoring (NICOM) that has demonstrated good reliability against invasive measures of CO in studies involving adults, children, and small animals (10–15). Our group has recently demonstrated the feasibility and reliability of NICOM (NICOM, Cheetah Medical, Portland, OR) compared with echocardiography in stable late-preterm and term neonates, and in premature infants following patent ductus arteriosus (PDA) ligation (16,17). Its application in neonates with NE however remains unexplored.

In this study, we aim to (i) perform continuous measurements of CO, SV, SVR, heart rate, BP, and $SctO_2$ using NICOM and NIRS in infants with NE undergoing TH throughout the cooling and rewarming period; and (ii) compare NICOM-measured CO with echocardiography-measured CO (echo-CO) over three time points. We hypothesized that NICOM use in infants with NE is feasible and can provide a reliable method of CO assessment in this population.

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METHODS

Study Setting, Patient Population, and Clinical Characteristics

This was a prospective observation study carried out in the neonatal intensive care units of the Rotunda Hospital and the Coombe Women and Infants University Hospital, Dublin, Ireland. Ethical approval was obtained from the local Research Ethics Committees and written informed consent was obtained from parents of all participants prior to enrollment. All infants were either passively or actively cooled within six hours following birth. Parents were given up to 12 h following the initiation of TH to consider the study. Infants greater than 35 weeks gestation with a diagnosis of NE who underwent TH were all eligible provided they fulfilled two of the following criteria based on the TOBY study (18): Apgar score of ≤ 5 at 10 min after birth; continued need for endotracheal or mask ventilation at 10 min after birth; acidosis within 60 min of birth (defined as any occurrence of umbilical cord, arterial, or capillary pH <7.00 or a base deficit ≥ 16 mmol/l); and/or clinical seizures or moderate to severe encephalopathy using the Sarnat grading system (19). We excluded infants who were unlikely to survive beyond the cooling period.

All clinical care decisions including sedation and inotrope use were left to the discretion of the clinical team. Clinical characteristics including gestation, birth weight, mode of delivery, Apgar scores, first pH, base excess, and lactate, the need for resuscitation at birth, the use of sedation and inotropes during TH, the presence of seizures, and the use of antiepileptic medication were recorded. The clinical team was blinded to the NICOM and NIRS measurements.

Continuous Hemodynamic Monitoring

We used the NICOM system (Cheetah Medical Inc, MA) which employs transthoracic bioreactance to obtain continuous hemodynamic readings during TH and rewarming (16,17). Bioreactance is the analysis of the variation in the frequency spectra of a delivered oscillating current when it traverses the thoracic cavity. This is obtained by placing four emitting and receiving electrodes in a manner that "boxes" the heart. Each electrode sensor strip consists of two contact points. Upper thoracic electrode strips were placed over the mid-clavicles and upper back bilaterally. The lower electrode sensors are placed between the sixth and seventh intercostal spaces at the mid-axillary line. NICOM measurements of SV and CO are obtained every minute. SVR is calculated by the NICOM system on an hourly basis as the mean BP is manually entered using the following formula: $SVR = (BP \times 80)/CO$ as per the entered algorithm; where BP is the mean arterial pressure.

NIRS monitoring of cerebral mixed venous saturations was performed using the INVOS Somanetics system (Medtronic, MN) and cerebral oximetry neonatal sensors. The sensors were applied to the skull over the frontal lobes at the center of the forehead and secured using clear bandages for the duration of TH and rewarming. NIRS provides continuous $SctO_2$ readings using spatially-resolved spectroscopy (20).

MRI Findings

All enrolled infants underwent a brain MRI on day 5–10 after delivery. A pediatric radiologist who is blinded to NICOM and NIRS results reported and scored the MRI results using the Barkovich criteria (21). This employs a combination five-point score including components of both basal ganglia and watershed patterns of injury. Patients were divided into "normal" (score = 0) and "abnormal" (score = 1–4) neuroimaging groups for the purpose of data analysis.

Echocardiography Measurements

Echocardiograms were performed using the Vivid S6 machine (GE Medical, Milwaukee, WI) and a 7 MHz cardiac multi-frequency probe on infants recruited from the Rotunda Hospital site. After TH initiation, infants underwent echocardiography assessments of CO on day 1 (10 h of TH), prior to rewarming (70 h of TH), and at the end of the rewarming period (100 h after commencement of TH). The 10-h time point was chosen to ensure that all the infants undergoing echocardiography also had NICOM monitoring. The delay in applying NICOM monitoring was to facilitate parental informed consent. The 70-h time point was chosen as the time of maximal cooling duration just prior to rewarming. The 100-h time point represented the completion of rewarming. At the time of the first echocardiogram, the NICOM and echocardiography internal clocks were synchronized. All echocardiograms were performed and analyzed by one investigator (CRB) to avoid inter-rater variability. The investigator was blinded to the NICOM readings during the echocardiogram. The echo-CO was calculated based on previously described methodology (22). At a later date, complete NICOM measurements for each infant were downloaded from the NICOM machine. The NICOM-CO measurements that exactly corresponded to the timed minute of acquisition of the echocardiography data were identified. These NICOM and echocardiography data were compared.

Statistical Analysis

Continuous data were presented as median (interquartile range) or as means (SD) as appropriate. Categorical data were presented as absolute numbers and proportions. Two group analysis was conducted using the Mann-Whitney *U* test for continuous variables or the χ^2 test for categorical variables. One-way repeated measures ANOVA was used to assess the change in the hemodynamic measurements with respect to time. Pairwise comparison carried out

Table 1. Hemodynamic measurements at three time points

	During cooling (10 h)	Pre-rewarming (70 h)	Post-rewarming (100 h)	ANOVA *P*
Temperature (°)	33.4 (0.4)	33.5 (0.1)	36.4 (0.8)[a]	<0.001
NICOM-CO (ml/kg/min)	82 (31)	83 (38)	120 (57)[a]	0.003
Echo-CO (ml/kg/min)	91 (24)	118 (38)	153 (55)[a]	0.001
NICOM/Echo percentage bias (%)	21 (14)	29 (10)	32 (9)	0.14
Cerebral regional O2 saturation (%)	80 (9)	85 (6)[a]	85 (5)[a]	0.005
SVR × 1000 (dynes.sec.cm^{-5})	14.3 (10.1–18.0)	16.0 (12.9–18.4)	11.0 (8.3–14.1)[a]	<0.001
SV (ml)	3.0 (1.4)	3.0 (0.8)	3.5 (1.0)	0.2
Mean BP (mmHg)	45 (5)	50 (6)	50 (5)[a]	0.002
Heart rate	102 (13)	97 (15)	116 (16)[a]	<0.001

ANOVA, analysis of variance; Echo-CO, echocardiography-derived cardiac output; Mean BP, mean blood pressure; NICOM-CO, NICOM-derived cardiac output; SV, stroke volume; SVR, systemic vascular resistance.
Values are presented as means (SD) or medians (IQR). One was ANOVA with repeated measures was used to assess change over time.
[a]*P* value < 0.05 compared to baseline (Bonferroni adjustment).

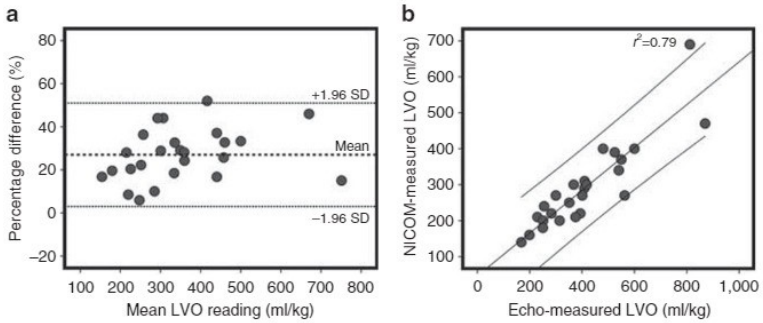

Figure 1. Bland-Altman Analysis (**a**) and Correlation (**b**) between echocardiography and noninvasive cardiac output monitoring (NICOM)-measured cardiac output. NICOM and Echo cardiac output (depicted as left ventricular output, LVO) was not indexed to weight for graphical representation.

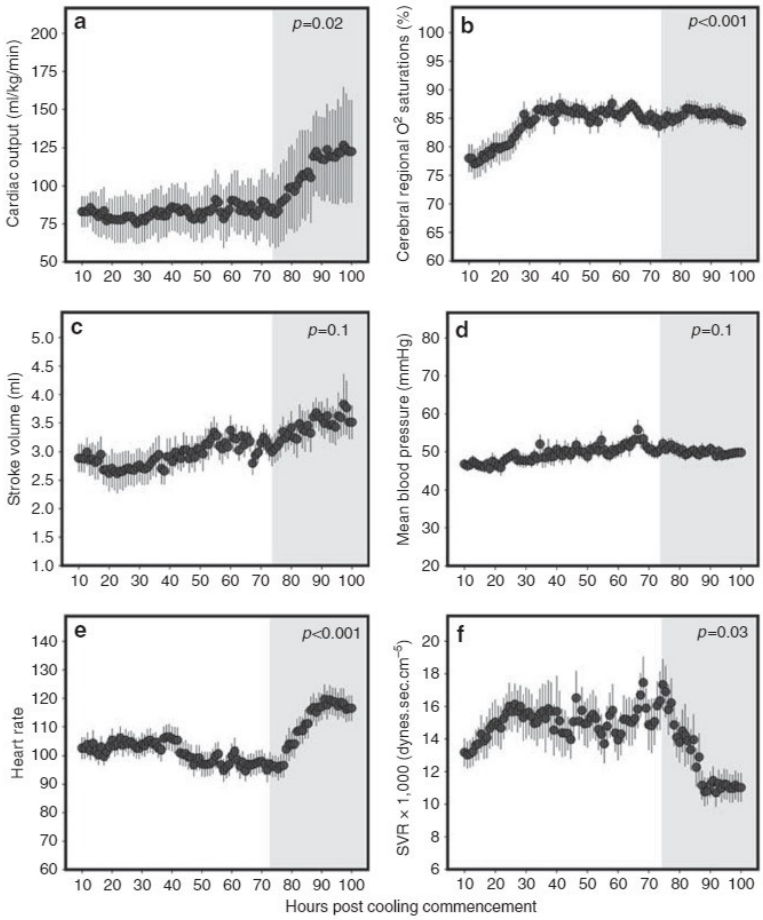

Figure 2. Continuous hemodynamic measurements in the cohort over the study period. Changes in cardiac output (**a**), cerebral regional oxygen saturation (**b**), stroke volume (**c**), mean blood pressure (**d**), heart rate (**e**), and systemic vascular resistance (**f**) are presented. The white area represents the hypothermia phase and the gray area represents the rewarming phase. Values are presented as means (dark gray circles) and the black lines represent the standard error. One-way ANOVA with repeated measures was used to assess the change over time. SVR, systemic vascular resistance.

Table 2. Clinical characteristics of infants with and without an abnormal MRI

	Normal MRI ($n=10$)	Abnormal MRI ($n=10$)	P
Gestation (weeks)	38.7 (38.0–40.1)	38.9 (38.0–39.1)	0.42
Birth weight (kg)	3.53 (3.32–3.90)	3.34 (2.50–4.23)	0.83
Cesarean section	8 (80)	5 (50)	0.35
Male gender	8 (80)	4 (40)	0.17
Outborn	5 (50)	7 (70)	0.65
Apgar Scores			
1 min	0 (0–1)	3 (3–5)	<0.01
5 min	4 (1–5)	4 (2–7)	0.19
10 min	5 (3–9)	7 (5–9)	0.76
Lowest first-hour pH	6.96 (6.89–7.12)	6.90 (6.82–7.01)	0.74
Base excess	−15.8 (−20.4–−12.3)	−14.8 (−19.8–−12.3)	0.58
First lactate (mmol/l)	12.8 (10.4–14.4)	10.9 (9.5–16.6)	0.91
Inotropes	5 (50)	4(40)	1.0
Seizure activity	1 (10)	4 (40)	0.30

MRI, magnetic resonance imaging.
Data are presented as medians (interquartile range) or as count (%).

between two time points (70 and 100 h) and baseline (10 h) was conducted using the Bonferroni adjustment. Two-way repeated measures ANOVA was used to assess the difference in the hemodynamic measurements between two groups (normal vs. abnormal MRI) over time.

A systematic bias of 31 ± 8% between the two methods of CO assessment was demonstrated previously, with NICOM under-reading the echocardiography values (17). Therefore, differences in measurement between the two methods were expressed as a percentage ((echo-CO—NICOM-CO)/echo-CO). We compared the two methods using the Bland-Altman analysis, and assessed the correlation between the two methods using Pearson's correlation coefficient. A P value < 0.05 was considered significant. SPSS (IBM House, Dublin, Ireland) (IBM version 22) was used to perform the statistical analysis.

RESULTS

Over the study period, 27 infants were eligible for inclusion. Three were excluded due to the unavailability of the NICOM monitor, two were unlikely to survive (and subsequently had care redirected to palliation) and two families refused consent. Twenty infants with a median (IQR) gestation of 40.0 (38.7–41.1) weeks and a median birth weight of 3.6 (3.4–4.0) kg were enrolled over an eighteen-month period. Thirteen (65%) were delivered by cesarean section and twelve (60%) were male. Ten (50%) infants were outborn. Their 1, 5, and 10 min Apgar scores were 2 (0–4), 5 (2–7], and 6 (4–9) respectively. The cohort had an admission pH of 6.93 (6.85–7.07), a base excess of −14.9 (−19.3–−11.8), and an initial arterial lactate of 12.8 (9.0–14.8) mmol/l. TH was commenced within 6 h following birth in all infants. All infants were in receipt of either morphine ($n=11$), fentanyl ($n=11$) or midazolam ($n=5$) for sedation during TH. NICOM hemodynamic measurements (CO, SVR, BP, SV, and HR) and NIRS measurements ($SctO_2$) were all commenced within 10 h of TH initiation. During the cooling period, all infants were maintained at a temperature between 33° to 34° centigrade and were rewarmed following 72 h of TH over an 18 h period (**Table 1**).

NICOM and NIRS assessments were feasible in all enrolled infants. Eight infants underwent echocardiography assessments of CO over three time points. NICOM-CO were lower than echo-CO with a bias of 27% (limits of agreement 8–51%). There was a strong correlation between echo-CO and NICOM-CO ($r^2=0.79$, $P<0.001$) (**Figure 1**). The bias between the two methods remained constant throughout the study period with no difference noted between the cooling and rewarming phases. There was an increase in both NICOM-CO and echo-CO following the rewarming period (**Table 1**).

CO was lower during TH and significantly increased during rewarming. $SctO_2$ significantly increased over the first 30 h of TH and stayed higher for the remainder of the study period (**Table 1**, **Figure 2**). There was a significant rise in NICOM-measured SVR over the first 30 h of TH. SVR subsequently decreased during rewarming. There was no change in mean arterial BP or SV over the study period. Heart rate significantly increased during rewarming (**Table 1**, **Figure 2**).

Nine infants received inotropes during the study period. There was no difference in gestation, birth weight, Apgar scores, pH, base excess, or lactate between infants in receipt of inotropes and those without (data not shown). All infants received dopamine, with two infants receiving adrenaline and one infant receiving dobutamine as adjuvant therapy. The median time of commencement was 6 (2–18) h, with a total duration of 49 (23–83) h. The median BP at inotrope commencement was 44 (42–47). There was no significant change in any of the measurements in the 24 h period following the commencement of inotropes (data not shown).

All infants underwent a brain MRI between days 5–10 of age. Ten infants had an abnormal MRI. **Table 2** summarizes the differences in characteristics between infants with and without a normal MRI. There were no significant differences between the two groups with the exception of the 1 min Apgar score which was higher in the abnormal MRI group (**Table 2**). **Figure 3** illustrates the hemodynamic profiles in the two groups. Infants in the abnormal MRI group had lower CO, and SV and a higher SVR during TH. However those differences did not reach statistical significance (**Figure 3**).

DISCUSSION

In this prospective study, we applied a relatively novel method of continuous hemodynamic assessment (NICOM) to infants with NE throughout the cooling and rewarming periods and compared CO measured using this method with that of echocardiography. The use of NICOM and NIRS in this population is feasible as measurements were obtainable in all recruited infants. We did not encounter difficulty in applying the sensors on the infants or maintaining the sensors in place throughout the study period. In addition, those sensors did not impede routine clinical monitoring or care provision to those infants.

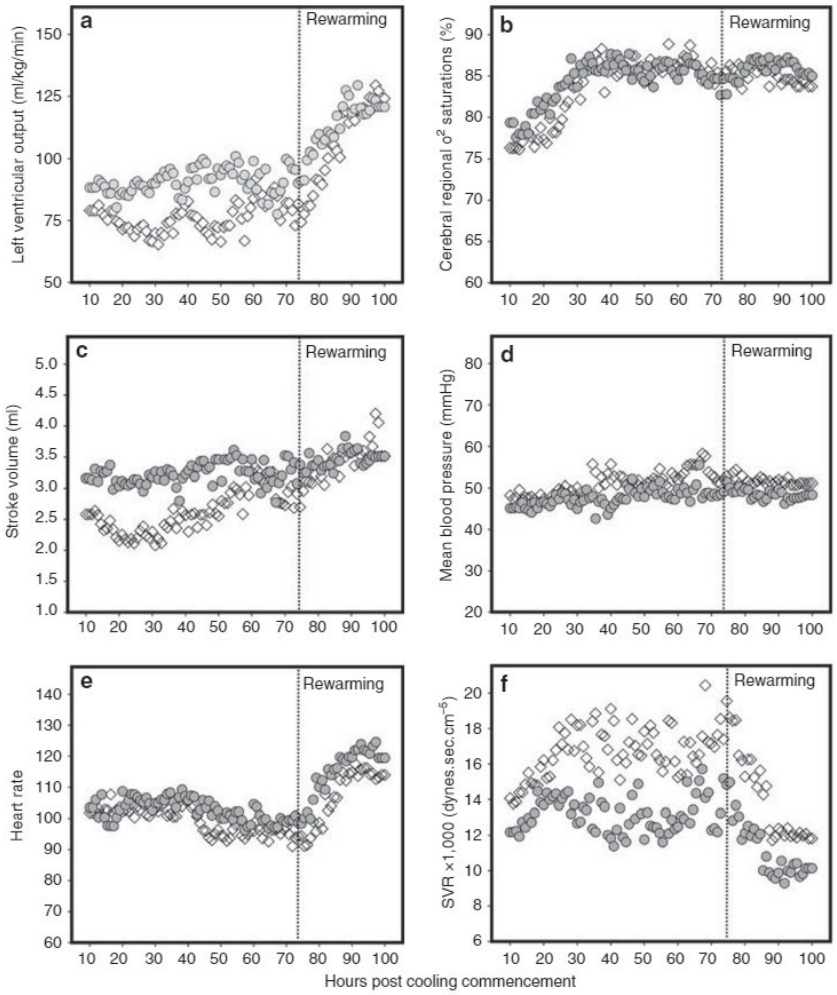

Figure 3. Change in the hemodynamic profile in infants with (white diamonds) and without (gray circles) an abnormal magnetic resonance imaging (MRI). Changes in cardiac output (**a**), cerebral regional oxygen saturation (**b**), stroke volume (**c**), mean blood pressure (**d**), heart rate (**e**), and systemic vascular resistance (**f**) are presented. One-way ANOVA with repeated measures was used to assess the change over time. There was no significant change in any of those measurements between the groups over time (all ANOVA $P > 0.05$). SVR, systemic vascular resistance.

We illustrated that NICOM under-reads echo-CO by an average of 27%; This systematic bias is similar to the bias illustrated by our group in two other patient populations: healthy term and late-preterm infants, and preterm infants following patent ductus arteriosus ligation (16,17). While acknowledging that neither method can be regarded as a gold-standard, we have previously provided a rationale for this systematic bias between the two methods (17). The NICOM algorithm used to estimate aortic diameter size in the neonatal population is extrapolated from adults which may have resulted in the lower NICOM values of CO (23). Conversely, echocardiography may overestimate CO readings as it uses the velocity of blood flowing through the central portion of the aortic root to estimate CO. This may significantly overestimate the true overall velocity of blood flowing through the aortic root as the higher velocity is found in the center of the vessel while flow along the periphery (not measured by echocardiography) is significantly lower (24). We also found that the bias appears to be constant throughout the cooling and rewarming phases with no significant differences between the three NICOM and echocardiography measurement time points. This has important implications as it suggests that body temperature changes do not appear to affect the bioreactance signal properties. Animal studies support these findings. In a study of nine open-chest pigs, where blood flow was controlled with cardiopulmonary bypass, NICOM-CO measurement correlated well with cardiopulmonary bypass measurements ($r = 0.84$) across two blood temperatures (36° and 38°C). Although this temperature

range is different to that in our study, the data suggest the relative lack of effect temperature has on NICOM-CO measurement (23).

We illustrated that NICOM monitoring of infants with NE during TH and rewarming reflects expected hemodynamic changes during this process, adding further support to its reliability in this patient cohort. Left ventricular output is lower during hypothermia and increased during rewarming. This change appears to be driven by changes in heart rate which mirrored the increased CO rather than SV, which increased at a lower rate. There was a rise in SVR during cooling which decreased with rewarming. There was no change in mean BP during the study period. Hypothermia is associated with a reduction in metabolic demand and a resultant fall in CO (25). Adult human data and animal models of TH have previously demonstrated this rise in SVR following the lowering of body temperature (26,27). The rise in SVR may be a contributing mechanism to the maintenance of cerebral perfusion in the cooled neonatal population (28). The early rise in $SctO_2$ seen in our cohort occurring in conjunction with the rising SVR supports this theory. $SctO_2$ remained elevated during rewarming despite a falling SVR. The increase in CO may have maintained cerebral perfusion.

We found that infants with evidence of brain injury seen on MRI had a higher SVR and a lower CO driven by a lower SV rather than heart rate (although none of those differences reached statistical significance, likely due to the small number of subjects). This finding suggests that the more severely affected infants may also have myocardial injury, with an inability to maintain adequate SV in the face of increasing afterload. This relationship warrants further study in a larger cohort to confirm those findings.

The effect of inotropes on the cardiovascular system during TH warrants further study. We found no demonstrable change in CO, mean BP or SVR following the introduction of inotropes in this population. The lack of change may highlight the lack of response to inotropes during TH (26), however, no meaningful conclusions can be drawn from this small sample size and the relatively diverse number of inotropes used in this study.

This study has several limitations: the relative small number of infants may have resulted in missing important differences in the measures between infants with and without brain injury. In addition, the relative delay in applying NICOM (done to facilitate obtaining consent) may have resulted in missing important hemodynamic changes during the early cooling phase. Although NICOM has been validated against echocardiography in neonates (16,17), further work is required to assess its precision and its ability to detect important changes over time. Our study was not powered to assess the effect of other important factors such as sedation, inotrope use, and the presence of seizures on the hemodynamic status of those infants.

CONCLUSION

We have demonstrated that the assessment of the hemodynamic status of infants with NE undergoing TH in addition to cerebral perfusion in a continuous fashion is feasible and reflects the expected hemodynamic changes occurring as a result of TH and rewarming in infants with NE. Further studies are required to assess NICOM's clinical applicability in this condition in a larger cohort.

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6.4 Summary of the Main Findings

From the review of the literature, we have identified non-invasive CO measurement by bioreactance as one of the methods theoretically capable of continuous CO measurement in term and preterm infants in the early neonatal period.

In the first study, the lowest CO (measured by bioreactance) in extremely preterm infants with subsequent PIVH and/or NEC was significantly different from the CO in infants without these complications. The initial lower CO in infants with PIVH and/or NEC in the first 24 hours after delivery was followed by a 'compensatory' increase in the second 24 hours that was statistically significant, raising the possibility of an ischaemia/reperfusion situation predisposing these infants to subsequent complications. There was a moderate, non-significant increase in CO between six and 48 hours of age in the whole cohort of infants enrolled in the study, however the difference between the lowest CO at 14 hours of age and the highest CO at 34 hours of age reached statistical significance.

In addition, in our second study, we have demonstrated that the assessment of the hemodynamic status of term infants with NE undergoing TH in a continuous fashion by bioreactance is feasible and reflects the expected hemodynamic changes occurring as a result of TH and rewarming in infants with NE. We illustrated that NICOM^{TM} underreads echo-CO by an average of 27%. This bias appears to be constant throughout the cooling and rewarming phases with no significant differences between the three NICOM^{TM} and echocardiography measurement time points. This has important implications as it suggests that body temperature changes do not appear to affect the bioreactance signal properties. We have documented haemodynamic changes during TH, LVO was lower during hypothermia and increased during rewarming. This change appears to be driven by changes in HR which mirrored the increased CO rather than SV, which increased at a lower rate. There was a rise in SVR during cooling which decreased with rewarming. There was no change in mean BP during the study period.

We found that infants with evidence of brain injury seen on MRI had a higher SVR and a lower CO driven by a lower SV rather than HR (although none of those differences reached statistical significance, likely due to the small number of subjects). We found no demonstrable change in CO, mean BP or SVR following the introduction of inotropes in this study.

7. Main Thesis Part 2

Superior Vena Cava Flow Measurements

7.1 A review of Superior Vena Cava Flow Measurement in the Neonate by Functional Echocardiography

7.1.1 Summary

Neonatologists have begun using SVC flow as assessed by functional echocardiography to facilitate real-time decision-making on cardiovascular care. This review aims to describe the basis of the technique, summarise the evidence for its use and compare the technique to existing clinical, biochemical and radiological techniques for assessing neonatal circulatory status. Although echocardiographic measurements of SVC flow, like other measures of perfusion, are not perfect, their non-invasive nature and ability to facilitate real-time decision-making means that at present, they remain the most available methodology of monitoring central perfusion in the neonatal population. Ficial et al. have recently published data on a novel approach to imaging SVC flow relying on a short-axis view to directly assess SVC area at the level of the right pulmonary artery, in combination with flow velocity being measured from the suprasternal approach at the level of the right pulmonary artery. Although this approach to measuring flow is not yet widely used, it showed improved repeatability compared to the traditional technique indicating that their approach may represent an improvement on existing methodology.(187)

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REVIEW ARTICLE

A review of superior vena cava flow measurement in the neonate by functional echocardiography

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ABSTRACT

Neonatologists have begun using superior vena cava flow as assessed by functional echocardiography to facilitate real-time decision-making on cardiovascular care. This review aims to describe the basis of the technique, summarise the evidence for its use and compare the technique to existing clinical, biochemical and radiological techniques for assessing neonatal circulatory status.

Conclusion: Although echocardiographic measurements of superior vena cava flow, like other measures of perfusion, are not perfect, their noninvasive nature and ability to facilitate real-time decision-making means that at present, they remain the best available methodology of monitoring central perfusion in the neonatal population.

INTRODUCTION

Assessing cardiovascular status is an important but challenging aspect of care for the ill or preterm newborn (1). Difficulties have arisen in the use of traditional clinical signs as they are imperfect markers of perfusion during the transitional period (2–6). In response to this, functional echocardiography (FE) has grown in popularity as a tool that allows rapid, noninvasive measurement of cardiovascular parameters (7,8). Unlike formal echocardiography performed by cardiology services, FE assesses the function of the circulatory system rather than detailed anatomy to facilitate rapid decision-making based on real-time images of central blood flow (7,8). FE is employed in conjunction with traditional clinical skills, and there is increasing recognition that patients benefit from its availability

Abbreviations

BNP, b-Type natriuretic peptide; BP, Blood pressure; CRT, Capillary refill time; ELBW, Extremely low birth weight; FE, Functional Echocardiography; HFOV, High frequency oscillatory ventilation; IVH, Intraventricular haemorrhage; MRI, Magnetic resonance imaging; NCPAP, Nasal continuous positive airway pressure; NIRS, Near-infrared spectroscopy; PDA, Patent ductus arteriosus; PIVH, Peri/intraventricular haemorrhage; SVC, Superior vena cava; VLBW, Very low birth weight.

Key notes

- Traditional clinical and biochemical markers of perfusion are of limited utility in the neonatal population
- Superior vena cava flow, as assessed by functional echocardiography has emerged as a clinically validated measure of central perfusion in neonates which allows for rapid decision-making based on real-time measures of central perfusion
- Functional echocardiography measures of superior vena cava flow represent the best available methodology of monitoring central perfusion in the neonatal population

(9,10). The presence of the patent foramen ovale and patent ductus arteriosus (PDA), respectively, make measurements of right and left ventricular output inaccurate in the preterm neonate (11,12). The superior vena cava (SVC) is formed by the joining of the brachiocephalic veins, and the majority of blood within the SVC represents return flow from the brain; hence, it has been hypothesised that flow within the SVC is a good surrogate marker of cerebral perfusion (13). FE of SVC flow is unaffected by shunting and has emerged as a useful marker of central perfusion with low SVC flow being linked to a number of adverse outcomes in both the short and longer-term (3,14–19). This study summarises the evidence for the use of SVC flow, the effects of medical interventions and compares its use to that of other available technologies.

TECHNIQUE

Functional Echocardiography measurement of SVC flow was first described by Kluckow and Evans (13), and this remains the most commonly employed method for assessing SVC flow in the neonate. The technique as described initially is outlined below:

Using a low subcostal view for imaging, the SVC is identified as it enters the right atrium and flow within is recorded using pulsed Doppler over 20–30 cardiac cycles. Mean velocities are calculated over 10 consecutive cardiac cycles to minimise variation. The diameter of the vessel is measured in the parasternal long axis by angling the beam sagittally as the vessel enters the right atrium. A 2D image is obtained to measure the internal vessel diameter with the mean of the maximum and minimum diameter being averaged over 3–5 cardiac cycles due to variation through the cardiac cycle. The flow within the SVC is then calculated according to the following formula, with results reported in mL/kg/min:

$$\text{SVC flow} = \Big(\text{Velocity Time Integral} \times \Big(\pi \times \Big(\text{mean SVC diameter}^2/4\Big) \times \text{Heart rate}\Big)\Big)/\text{weight}$$

Most studies assessing SVC flow have chosen this as their methodology with some opting to average vessel diameter from M-mode rather than 2D images for improved accuracy (20,21). Other authors have suggested that the subcostal approach will be limited by gaseous expansion of the bowel and may cause discomfort in a small cohort of neonates and have suggested a suprasternal or high parasternal view, (22) with flow measurements and intraobserver variability from this approach being comparable to those of the abdominal approach (22). Following on from this, Ficial et al. have recently published data on a novel approach to imaging SVC flow relying on a short-axis view to directly assess SVC area at the level of the right pulmonary artery, in combination with flow velocity being measured from the suprasternal approach at the level of the right pulmonary artery (23). Although this approach to measuring flow is not yet widely used, Ficial et al. showed improved repeatability compared to the traditional technique indicating that their approach may represent an improvement on existing methodology.

Large changes occur in the cardiovascular system as the infant adapts to extra-uterine life and multiple FE measurements are often necessary to ensure normal transition. Repeatability of FE measurements is therefore of great importance to document consistency, and since its initial description, measurements of intra- and interobserver repeatability have varied between studies (13,20,24,25). Table 1 displays data on repeatability from published studies. Of note, Lee et al. (25) published data comparing inter- and intraobserver differences in analysis of offline images rather than scan-scan variability and found mean intraobserver variability of 17% (SD 4.7%) as well as significant differences in interobserver variability suggesting that different observers looking at the same image may produce varying results.

Because the technique was pioneered by the group describing the least variability, it is reasonable to conclude that experience with the technique will improve results. Despite this, the data above do show that variability can occur, and while ideally the same person would perform all imaging acquired on an infant, this is unlikely to be feasible in most centres. Concerns have been previously been expressed regarding the adoption of SVC flow measures into routine clinical practice without further validation (26), and the data presented in Table 1 does highlight the potential for varying results especially in the hands of different users. Because of this potential for variability, it is important that centres deciding to adopt the technique adhere to guidelines and standardise image acquisition and interpretation protocols to ensure consistency in data acquisition (26). Furthermore, it is important that clinicians skilled in the technique are aware that new technology is

Table 1 Comparison of repeatability measures of SVC Flow

Year published	Author	Intraobserver variability	Repeatability coefficient	Interobserver variability	Repeatability coefficient
2000	Kluckow and Evans (13)	Median 8.1% (range: 1.3%–32.8%)	N/A	Median 14% (range: 2%–57%)	N/A
2008	Groves et al. (20)	Median 12% (range: 1%–34%)	30 mL/kg/min	Median 56% (range: 1%–102%)	85 mL/kg/min
2012	Sommers et al. (24)	Median 10%	24 mL/kg/min	N/A	N/A

SVC = Superior vena cava.

constantly becoming available to facilitate learning and that online resources of high quality now exist allowing the dissemination of expertise (27).

SUPERIOR VENA CAVA EVIDENCE

Tamura et al. published data on blood velocity in the SVC of neonates in 1998 (28); however, it was only with subsequent publications by Kluckow and Evans that we began to appreciate the utility and reproducibility of SVC flow in predicting morbidity in the neonate (13,14). In 2000, this group described the technique for SVC flow measurement (13) and concurrently published data on the first adverse neonatal outcomes in infants with low SVC flow (14). The latter paper enrolled 126 neonates <30 weeks gestation and took serial measurements of SVC flow, blood pressure (BP) and cranial ultrasounds. They found that SVC flow increased naturally over the first 48 hours of life, was generally lower in those of earlier gestation, was not strongly associated with BP and most importantly that there was a strong association between the presence of low flow in the SVC and the development of late intraventricular haemorrhage (IVH). Interestingly, the study also demonstrated that the haemorrhages that developed did so while SVC flow was improving and not during its nadir and that the median minimum SVC flow correlated with the severity of IVH, as did the number of measurements below normal. These findings supported the idea that late IVH in the setting of hypoperfusion is due to reperfusion injury and that development of severe IVH is not related to the absolute lowest measurement but instead to the duration of time low flow is present. Further evidence has since confirmed the strong association between low SVC flow and the development of late IVH and even death (3,15,16). Indeed, late IVH has been a consistent finding in many of the studies on low SVC flow in preterms or very low birth weight (VLBW) babies with as many as 50% of those with low flow having death or severe IVH as an outcome (4). Many other studies have subsequently linked low SVC flow to a variety of other adverse short-term outcomes including oliguria, hyperkalaemia, retinopathy of prematurity and necrotising enterocolitis (17,18). There has also been a suggestion that SVC flow may have an effect on brain activity as reflected by EEG although evidence is limited at present (29,30). Hunt et al. published three-year developmental outcomes from preterms with low SVC flow after birth and found that the average low flow on day one of life correlated with death and survival with disability (19). A subsequent study published in 2007 showed that preterm neonates who had low SVC flow went on to have significantly poorer outcomes across a range of neurodevelopmental areas as well as overall increased morbidity and mortality (18).

Trends in SVC flow in preterms generally show a natural increase in the first days of life (13,14,20,29–33). However, there is evidence that extremely low birth weight (ELBW) preterms have an initial reduction in SVC flow which is mirrored by changes in cerebral tissue oxygenation suggesting an early period of reduced cerebral perfusion that may not be reflected clinically (33). After the transitional period, there would not appear to be major changes in the SVC flow over the first two weeks of life, with measurements not varying significantly over this period of time (34). The lower limit for SVC flow in the original publication by Kluckow and Evans was determined by the lowest recording obtained in a group of healthy preterm infants at a given time point with values of 30, 34, 42 and 46 mL/kg/min, respectively, at 5, 12, 24 and 48 hours of age (13). These time-dependant cut-offs were used in many of the original papers, but for convenience, more recent publications are adopting a single number below which they are classing all measures as abnormal. Cut-offs adopted for low SVC flow generally range between 40 and 45 mL/kg/min with many opting to use <41 mL/kg/min as their definition as this was the number below which all peri/intraventricular haemorrhage(PIVH) was seen in early publications (14,15). 50 mL/kg/min has also been identified as a cut-off that may have prognostic value in identifying patients who develop late cerebral ischaemic lesions (35). Interestingly, because individual studies have defined their numerical cut-off for low SVC flow differently, defining the incidence of low SVC flow in the preterm population is difficult. This said however cut-offs are usually within a range of 40–55 mL/kg/min and are generally based on the findings of earlier studies (3,4,14,24,30–32,34–44). Table 2 presents data from the last 15 years on the incidence of low SVC flow across published literature, and it is clear that there is great variability between studies. Much of this variability can be explained by the differing patient cohorts included in each study with results likely being dependant on a number of factors including gestational age and baseline morbidity of the infants. An interesting observation is that the incidence of low flow does appear to decrease over time based on the figures presented. The exact reason for this is unclear; however, improved obstetric care, less invasive ventilation of preterm infants and better awareness of the factors contributing to the development of low cerebral blood flow have likely impacted on the favourable change in incidence observed.

Although the majority of work on SVC flow concerns preterm neonates in the transitional period, there is an increasing use of SVC flow in other areas of care for both term and preterm infants including sepsis, PDA management, neonatal encephalopathy and vascular surgery (45–49). SVC flow is used in many centres to monitor the cardiovascular status of term infants with perinatal asphyxia. One study which looked at SVC flow measurements in neonates >35 weeks with perinatal hypoxia showed that short-term outcomes were poorer in those with higher SVC flow after initiation of cooling (47). The authors in this case hypothesised that the higher SVC flow represented poorer cerebral autoregulation in those with worse injury, in this case reflected by Magnetic Resonance Imaging (MRI) changes. A subsequent publication mirrored these findings showing higher prerewarming SVC flow in those neonates developing brain injury on MRI (48).

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Table 2 Incidence of low SVC flow as defined by available studies

Authors	When imaged	Gestation studied	Special cohort	Low SVC cut-off	Incidence
Osborn et al. (3)	<24 hours	<30 weeks		<41 mL/kg/min	34%
Miletin et al. (4)	<24 hours	Mean 27.82 weeks (SD 2.14)	VLBW	<40 mL/kg/min	21%
Kluckow et al. (14)	<24 hours	<30 weeks		Age dependant	38%
Sommers et al. (24)	<108 hours	<32 weeks	Randomised to delayed or immediate clamping	≤45 mL/kg/min	1.96% overall, with 3.8% of the immediate cord clamping group and 0% of the delayed clamping
Shah et al. (30)	<48 hours	<29 weeks		<45 mL/kg/min	20%
Sirc, et al. (31) Sirc et al. (32)	<48 hours	25.9 weeks (SD 1.7)	<1250 g	<41 mL/kg/min	41%
Sloot et al. (34)	DOL 7 + 14	25–32 weeks	After transitional period	Not specified	1.6%
Osborn et al (35)	<24 hours	<29 weeks	Randomised to either HFOV or conventional	<50 mL/kg/min	Overall 34.9%: 48% on HFOV and 20% on conventional ventilation
Moran et al. (36)	<24 hours	25 + 3 weeks to 31 + 5 weeks	VLBW	<40 mL/kg/min	21%
Meyer et al. (37)	<24 hours	<30 weeks	Delayed cord clamping vs. immediate cord clamping	<55 mL/kg/min	33.3% overall, 52.9% in immediate and 7.7% in delayed cord clamping
Osborn et al. (38)	<24 hours	<30 weeks		<41 mL/kg/min	42%
Paradisis et al. (39)	<48 hours	<29 weeks	Patients on Milrinone	<45 mL/kg/min	Overall 24%, with 36% in the lower dosages and 0% in the optimised regimen
Osborn et al. (40)	<24 hours	<30 weeks		<41 mL/kg/min	33.3%
Paradisis et al. (41)	<48 hours	<30 weeks	Randomised to prophylactic Milrinone or placebo	<45 mL/kg/min	Overall 17.8%: 17% in the Milrinone group, 19% in the placebo group
Holberton et al. (42)	<24 hours	<30 weeks		<41 mL/kg/min	3.6%
Takahashi et al. (43)	<72 hours	<32 weeks	VLBW	<40 mL/kg/min	29.6%
Lakkundi et al. (44)	<72 hours	<29 weeks	Early surfactant administration	<45 mL/kg/min	9%

SVC = Superior vena cava; VLBW = Very low birth weight; HFOV = High frequency oscillatory ventilation.

RISK FACTORS FOR LOW SUPERIOR VENA CAVA FLOW

It may be that low SVC flow is not a disease state in itself but merely a reflection of a more systemic insult, hence to better understand the pathophysiology of low SVC flow several studies have identified risk factors for its development. Babies developing low SVC flow are less likely to have completed antenatal steroids and less likely to be born to a mother on antihypertensive medication (38,40). Lower gestational age, larger PDA and failure of early PDA constriction are also known to be risk factors for low flow in the SVC (14,16,38,40). Interestingly, although babies developing low SVC flows are more likely to be of lower birthweight (40), a study performed solely on growth-restricted infants showed that symmetrically small infants had significantly higher SVC flow than those babies who were asymmetrically small (50). This observation may relate more to the nature of foetal growth or the underlying cause of growth restriction rather than birthweight per se, with recent evidence showing that growth-restricted babies have complex changes in the nature of the cardiovascular system (51–54). Higher mean airway pressures and rates of invasive ventilation have been associated with an increased likelihood of having low SVC flow (2,14,38,40); however, mode of invasive ventilation and changes to noninvasive ventilation do not significantly impact on development of low flow (35,55,56).

CLINICAL/BIOCHEMICAL MARKERS OF LOW SUPERIOR VENA CAVA FLOW

It is important to be aware of the evidence around clinical and biochemical markers of low perfusion as they relate to SVC flow as many of these continue to be used in deciding fluid resuscitation and inotropic support. BP is probably the most traditionally used marker of perfusion in the neonate and is the commonest reason for initiating fluid resuscitation and inotropic support, particularly in those of lower gestation and birthweight (57). In their initial publications, Kluckow and Evans reported a weak-positive relationship between BP and SVC flow early in life (3,14). In the former of these publications, a direct study was made regarding the sensitivity and specificity of the most commonly used cut-offs for mean BP in detecting low SVC flow: when gestational age in weeks was used as the cut-off for mean BP, the sensitivity for detecting low SVC flow was 30% with specificity of 88%; when systolic BP <40 mmHg was used, the sensitivity was 76% with specificity of 68%. More recent publications showed no differences in mean BP between those developing low SVC flow and those who did not (2,4), and there is even evidence of an early inverse relationship between the two (5). While the information available on the relationship between BP and cerebral perfusion may seem conflicting, what the evidence likely infers is that if a relationship exists between SVC flow and BP, then it is

unlikely to be strong or directly linear and may be subject to change as the neonatal circulation transitions to extra-uterine life.

Capillary refill time (CRT) is another commonly used measure of neonatal perfusion, and while alone it is a poor predictor of low SVC flow (3), there is an evidence that in combination with SVC flow measures it may improve our ability to predict adverse outcomes (4). Oliguria has been associated with the lowest recorded SVC measurement in the first days of life (17); however, there is now evidence that urinary output does not differ significantly in those developing low SVC flow (4). While differences in central and peripheral temperature measurements have not been shown to be associated with low SVC flow (3), admission temperature was an independent variable associated with low SVC flow in infants <30 weeks gestation (42). One study detected a significant difference in serum lactate concentrations between those with low SVC flow and those without (2). The same publication stated that a serum lactate ≥2.8 mmol/L had a sensitivity of 100% for low SVC flow with specificity of 60%. Combining a serum lactate concentration >4 mmol/L and a CRT of >4 seconds leads to a sensitivity of 50%, specificity of 97%, positive predictive value of 80% and a negative predictive value of 88%. These combined markers are obviously unhelpful as a screening test due to the low sensitivity; however, the high specificity and negative predictive values mean that they may have a role in 'ruling out' low SVC flow if negative. There is no correlation between serum cortisol and low SVC flow in VLBW preterms (58). A potassium rise of greater than 0.12 mmol/L/hour in the initial 12 hours of life can predict low SVC flow with 93% specificity; however, the sensitivity of this rise was poor at only 35% limiting its use in predicting low SVC flow (17). Because low flow in the SVC is a marker of inadequate perfusion, it had been hypothesised that biochemical markers of cardiac dysfunction may be useful indices of low perfusion states; however, data presented by Konig et al. have shown no correlation between low flow in the SVC as measured by echocardiography and either b-type natriuretic peptide (BNP) and N-terminal proBNP (59).

Although clinical and biochemical markers are imperfect at predicting low SVC, in many smaller centres, they may be the only guidance on circulatory status that is available to the treating clinician. Hence, while we must acknowledge that the role of individual biochemical and clinical markers is limited, the majority of these markers have been studied in isolation and their greatest benefit at predicting SVC flow is likely to be in combination to give a more global view of circulatory status.

OTHER METHODOLOGIES

While echocardiography is the most commonly employed and best validated method of assessing central blood flow measures in the neonate, many alternatives methodologies exist. MRI of SVC flow was first described by Groves et al. (60) who were able to obtain high quality images with consistently better repeatability index than those obtained by FE, with subsequent studies confirming this improved repeatability [S61]. Although repeatability was improved, Groves et al. stated that MRI should not be viewed as a replacement for FE and that its main role was likely to be in the experimental setting or indeed to guide new echocardiography techniques rather than supersede them. Ficial et al. subsequently published findings which directly compared echo-derived blood flow measures to those produced by MRI [S62] and suggested that SVC flow measurements by echocardiography were inferior due to poor correlations between the two. Shortly thereafter, Martin Kluckow and Nick Evans published a response to these findings [S63], highlighting that despite improved repeatability MRI remains nonvalidated in the preterm population. They also argued that cardiac MRI has not yet been shown to correspond to any clinical outcomes in neonates and that the images obtained for comparison in the study were separated greatly in time from one another and were therefore unsuitable for comparison. Although it remains to be seen how the use of MRI will progress over time, at present most clinicians would agree that it should be reserved for experimental analyses and to effect improvements in more readily available echocardiography-based technology.

Near-infrared spectroscopy (NIRS) is used to noninvasively measure cerebral flow and has been shown to correlate with adverse neurological outcome in preterm neonates [S64]. Transmission and subsequent absorption of near-infrared light by human tissues can give information on haemoglobin concentration changes, and hence, NIRS has potential to act as a noninvasive monitor of cerebral tissue perfusion. Like echocardiography, NIRS is noninvasive and requires minimal handling of the neonate; one advantage of NIRS however is that it is a continuous measure. Although as mentioned above there is a link between NIRS and cerebral insult in preterm neonates, the published relationships between NIRS and SVC flow from FE are conflicting. Two publications have suggested a positive correlation between NIRS-derived measurements and SVC flow as measured by echocardiography (33,36). A more recent publication however has cast doubt on these findings suggesting that there may be an early negative correlation between SVC flow measurements and NIRS-derived measures of perfusion and that after 12 hours of life, there may be no correlation between the two at all (32). While the exact relationship between SVC flow and NIRS measurements has yet to be defined, it is very likely that the maximal benefit to patients will come from their combined use. Perfusion index (PI) is another methodology with potential for noninvasive monitoring of neonatal circulatory status. PI is based on assessment of pulse strength from the amount of infrared light absorbed at a particular site and is available through certain pulse oximeters meaning that measurements are easily obtained [S65]. PI has been shown to be associated with low SVC flow in the preterm population and may even have potential to predict low flow states (43). Although PI may provide useful insights into the

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neonatal circulatory status, a recent review of the subject concluded that the technique requires further validation before entering routine use [S66]. Flow in the descending aorta is feasible, but its poor repeatability means it has not entered widespread clinical practice (20). Measurements of oxygen extraction on blood from centrally placed vascular catheters can be performed in preterm neonates but has not yet been shown to predict low SVC flow [S67]. Although haemodynamic measurements taken from the middle cerebral artery have been shown to vary with low SVC flow, the small diameter of peripheral vessels limits the accuracy of measurements [S68]. Other newer methods of assessing central blood flow such as continuous-wave Doppler ultrasound measurement of cardiac output and electrical velociometry have been used successfully in neonates, but there is no published data comparing their measurements to those of echocardiographically obtained SVC flow [S69, S70].

EFFECT OF MEDICAL INTERVENTIONS ON SUPERIOR VENA CAVA FLOW

Given the link between low SVC flow and PIVH, several therapeutic interventions, mainly targeting inotropic support of the preterm, have attempted to improve SVC flow. A randomised controlled trial comparing dopamine and dobutamine has suggested that dobutamine produces a significantly higher SVC flow (40); unfortunately, this does not appear to translate into meaningful improvements in clinical outcome (18). Initial work done regarding milrinone as prophylaxis in maintaining SVC flow in very preterm neonates was promising (39) however; subsequent research into its use showed that it lacked efficacy in the prevention of low SVC flow (41). Until recently, there were no trials comparing inotropes to placebo for management of low SVC flow in terms of either improvement in flow parameters or clinical outcome [S71]. Bravo et al. have recently published the first randomised controlled trial comparing active management of low SVC flow with dobutamine to placebo [S72]. Despite being primarily published as a feasibility study and containing significant methodological issues, this trial does represent the first direct comparison of active management of low SVC flow to placebo and shows some evidence of improved short-term outcomes in those actively treated. Another recent publication of note from Bates et al. has suggested that flow in the SVC is not predictive of IVH in ELBW infants who received active management [S73]. While this observation is potentially of great interest, it should be noted that data therein were collected retrospectively and the authors themselves hypothesised that their local standardised treatment of low SVC flow may have resulted in the favourable neurological outcome observed. Taking this in the light of the findings of other studies, it is difficult to comment to what extent active management will improve outcomes in affected infants; however, given the wealth of previous evidence linking low SVC flow to adverse outcomes, it would seem doubtful SVC flow could be dismissed as insensitive for the development of IVH based on this study alone.

Higher mean airway pressure is known to be associated with low SVC flow (2,14,38). However, it could reasonably be suggested that this may simply be as a result of a globally sicker neonate and may not reflect change due to the level of ventilatory support present. Minor alterations in ventilatory support do not greatly alter SVC flow (55), and indeed mode of ventilation may not have a significant impact either (35). Another study suggested that a respiratory approach aimed at avoiding ventilation may lead to higher SVC flow, but as this study did not have a comparison group, it is difficult to ascertain whether this is a meaningful conclusion (44). Several studies have looked at the effects of differences in nasal continuous positive airway pressure(nCPAP) on SVC flow, and these have generally concluded that minor alterations are not of great significance [56, S74].

It has been hypothesised that delaying cord clamping or milking the cord at delivery will increase the circulating blood volume resulting in lower vascular resistance and improved autoregulation of cerebral blood flow. One randomised trial showed that preterm infants with delayed clamping had significantly increased SVC flow at 24 hours when compared to those with immediate clamping (37). A separate study has found that these increases in SVC flow are consistent through the first four days of life meaning that the gains obtained from delaying cord clamping are maintained beyond the early postpartum period (24). Actively milking the umbilical cord at delivery has been shown to similarly improve the flow in the SVC in preterm neonates, and these improvements are mirrored in NIRS measurements of cerebral blood flow taken simultaneously [S75, S76].

Patent ductus arteriosus is common in the preterm population, and previous work has suggested that preterm infants with significant PDA treated with dopamine infusions have higher SVC flow on average [S77]. Despite evidence linking the size and flow pattern at the PDA to SVC flow [S73], we know that attempts to affect early closure of PDAs through the use of indomethacin do not significantly alter the flow in the SVC (16). Fluid restriction is another commonly employed technique in the NICU in infants with PDA in attempt to affect closure of the shunt. Despite its widespread use, there is evidence that this practice may decrease SVC flow by as much as 40% [S78].

CONCLUSION

As evidence continues to be published on the role of echo-derived SVC flow measurements, we continue to gain a more nuanced appreciation of its role in guiding management and predicting outcomes. Methodology for echo-derived measures of SVC flow continue to improve, and it is hoped that new techniques may address some of the issues around repeatability (23, S79). Several excellently designed trials are currently underway in an effort to improve the

haemodynamic care of preterm neonates. The HIP trial is one such study which incorporates FE assessment of SVC flow into their trial design in a subgroup of patients [S80]. Another ongoing trial is being conducted by the Neocirculation group which hopes to guide hypotension therapy and improve our understanding of the pathophysiology of neonatal hypoperfusion states [S81]. It is hoped that on completion of these and other ongoing trials, we will better understand the pathophysiology and management of the neonate with poor central blood flow. Other technologies show great promise in aiding our assessment of neonatal circulatory status, and it is likely that their combined use with echocardiography will improve our understanding of neonatal haemodynamics. To date, our ability to meaningfully increase SVC flow is limited and there is hope that future studies will focus more on prevention of systemic hypoperfusion rather than its treatment once established. Strong evidence linking low SVC flow and adverse outcomes highlights the importance of SVC flow measurements, and although echo-derived measurements of SVC flow are not perfect indices of neonatal perfusion, their noninvasive nature and the ability to facilitate real-time decision-making means that at present they remain the best available methodology of monitoring central perfusion in the neonatal population.

COMPETING INTERESTS
None declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1 References.

7.2 Comparison of Two Techniques of Superior Vena Cava Flow Measurement in Preterm Infants with Birth Weight less than 1250g in the Transitional Period – Prospective Observational Cohort Study

7.2.1 Background

As revealed in our review, SVC flow in neonates measured by the standard approach has been validated by different groups around the world. The modified SVC flow measurement technique was recently suggested.(63) The aim of this study was to evaluate the standard and modified techniques of echocardiography SVC flow measurement in a cohort of extremely preterm neonates in the immediate postnatal period.

7.2.2 Materials and Methods

We designed a prospective, observational cohort study in a level III neonatal centre (CWIUH, Dublin, Ireland). Infants with birth weight less than 1250g were eligible for enrolment. The study was approved by the local REC (No 23-2015) and consent was obtained from all participants. SVC flow was measured by echocardiography using standard and modified methods at 6, 18 and 36 hours of age. Our primary outcome was equivalency (using raw bounds of –20 to +20 ml/kg/min difference between the paired measurements), agreement and correlation between standard and modified methods of the SVC flow measurements. All demographic parameters were expressed using mean (SD), median (IQR) or percentages as appropriate. We have defined SVC flow equivalency using raw bounds of –20 to +20 ml/kg/min difference between the paired measurements and used two-one-sided t-test (TOST) equivalency test with 90% Confidence Intervals. Correlation between the standard and modified methods and their components was calculated using Pearson's correlation coefficient. B-A analysis was used to calculate and visualize the agreement between the standard and

modified SVC flow measurement and their components. A paired-samples t-test was used to compare paired measurements and their components. When the differences between pairs were not normally distributed, we used the Wilcoxon signed-rank test for two sample comparisons. P-values <0.05 were considered statistically significant. The data were analysed by a PC-based statistics software, StatsDirect version 3.2.10 (StatsDirect Ltd, United Kingdom). For equivalency testing, R software (R 4.0.0, The R Foundation, https://www.r-project.org/) was used.

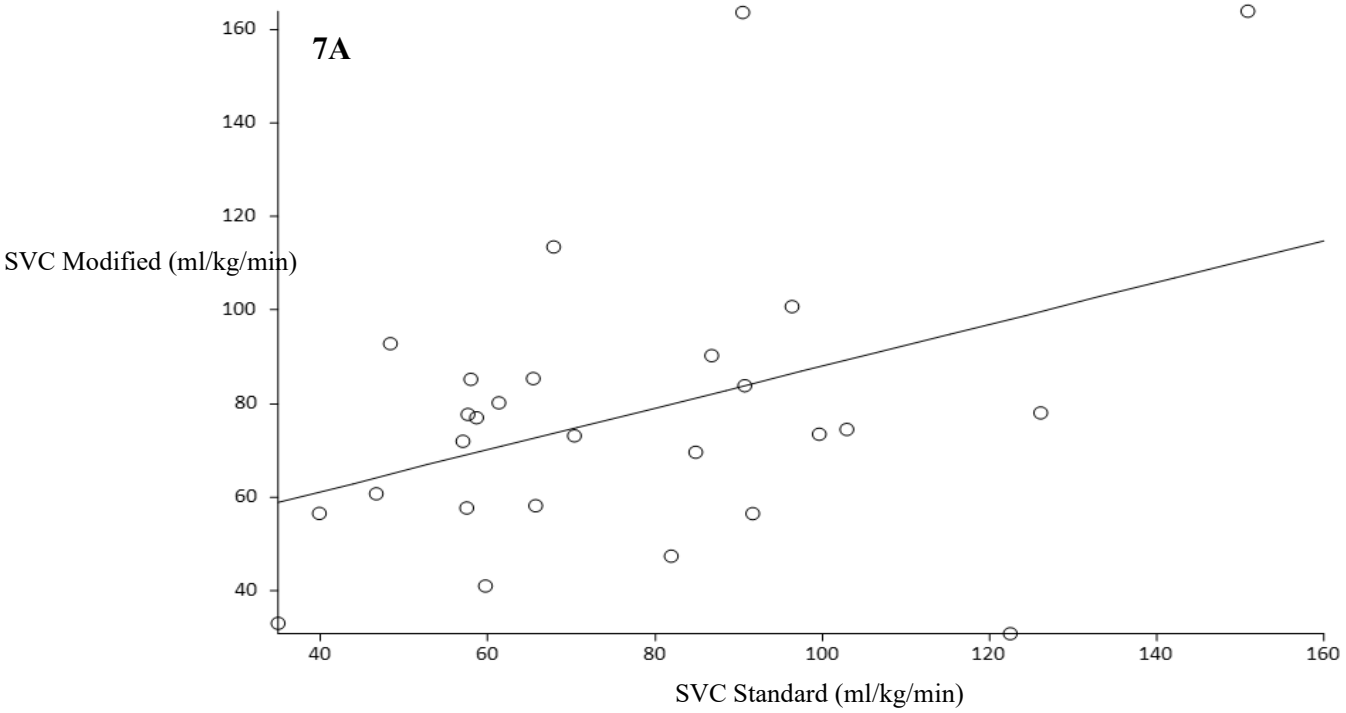
7.2.3 Results

Thirty-nine infants fulfilled the inclusion criteria. The mean gestational age of the cohort was 27.4 (SD 2.1) weeks of postmenstrual age, the mean birth weight was 0.95 kg (SD 0.2). The measurements at 6 and 36 hours of age were statistically significantly equivalent as defined in the design of the study (p =0.003 and p =0.004 respectively; raw bounds -20 to 20 ml/kg/min). At 6 hours of age, the correlation between the standard and modified methods of SVC flow was statistically significant (r =0.39, p =0.04). The mean difference between the measurements was –0.8 ml/kg/min with 95% limits of agreement of -65.0 to 63.4 ml/kg/min. (Figure 7AB) At 18 hours of age, the two methods did not significantly correlate (r =0.09, p =0.64). The mean difference between the measurements was +9.5 ml/kg/min, with 95% limits of agreement of -79.6. to 98.7 ml/kg/min. (Figure 8AB) At 36 hours of age the methods did not significantly correlate (r =0.17, p =0.35). The mean difference between the measurements was –2.2 ml/kg/min with 95% limits of agreement -73.4. to 69.1 ml/kg/min. (Figure 9AB)

7.2.4 Conclusions

Both SVC flow echocardiography measurement techniques yielded clinically equivalent results, although due to wide limits of agreement and poor correlation they do not seem to be interchangeable.

Figure 7-A Correlation between Standard and Modified Superior Vena Cava (SVC) Flow measurement at six hours of age
Figure 7-B Agreement between Standard and Modified Superior Vena Cava (SVC) Flow measurement at six hours of age with Mean Difference and 95% Limits of Agreement



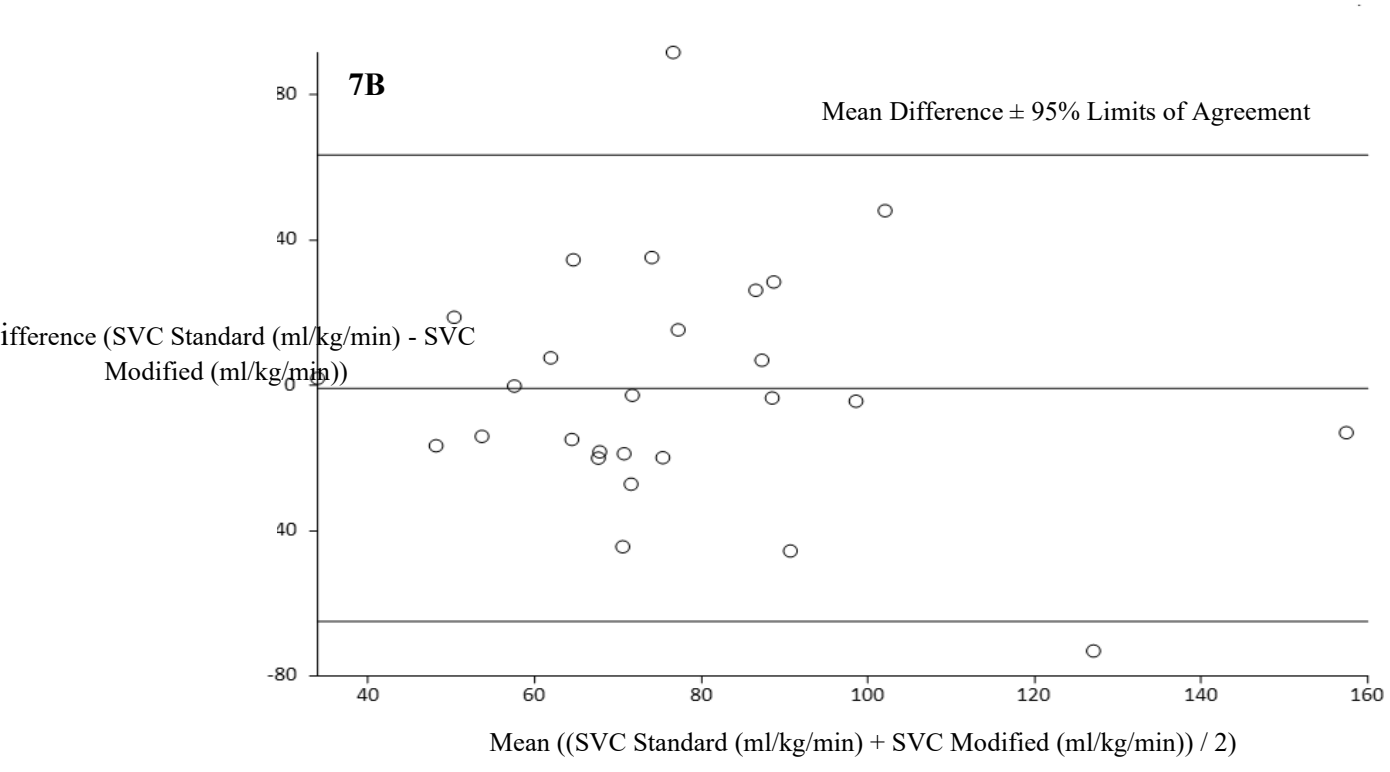
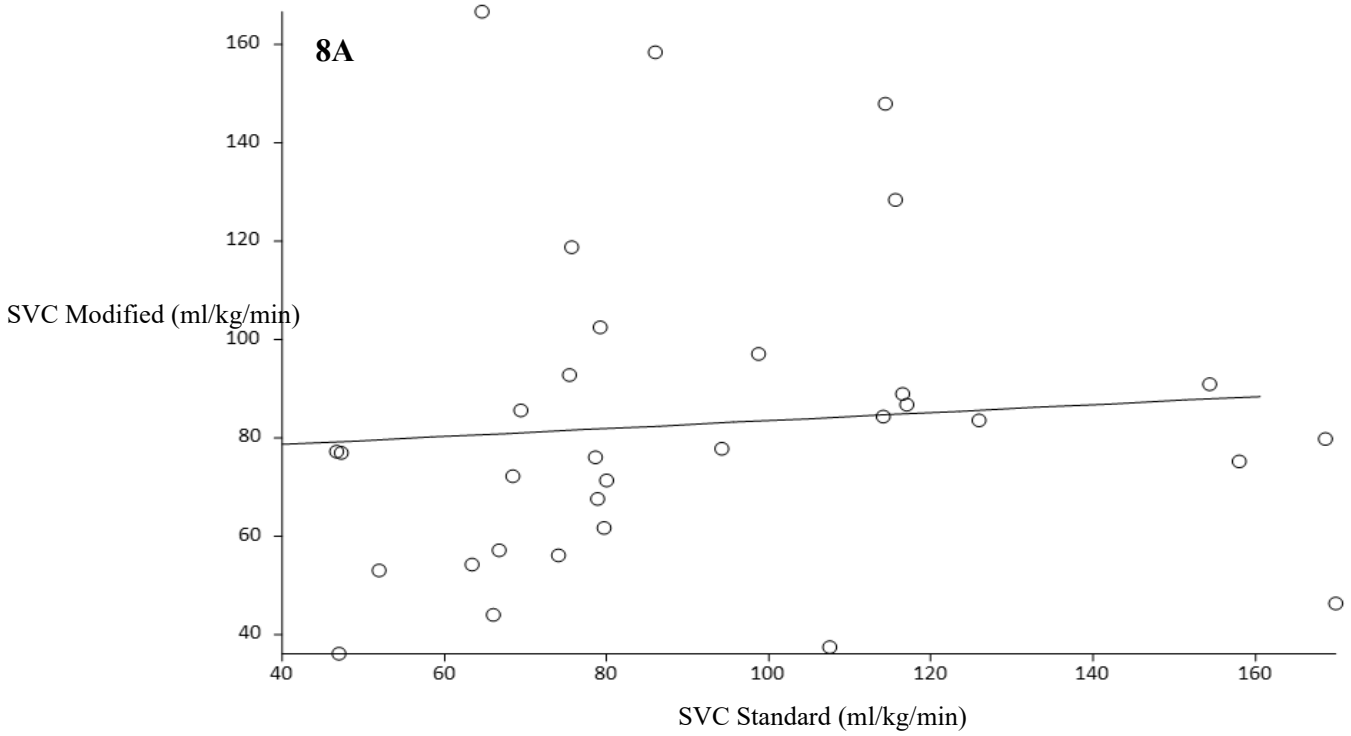


Figure 8-A Correlation between Standard and Modified Superior Vena Cava (SVC) Flow measurement at 18 hours of age
Figure 8-B Agreement between Standard and Modified Superior Vena Cava (SVC) Flow measurement at 18 hours of age with Mean Difference and 95% Limits of Agreement



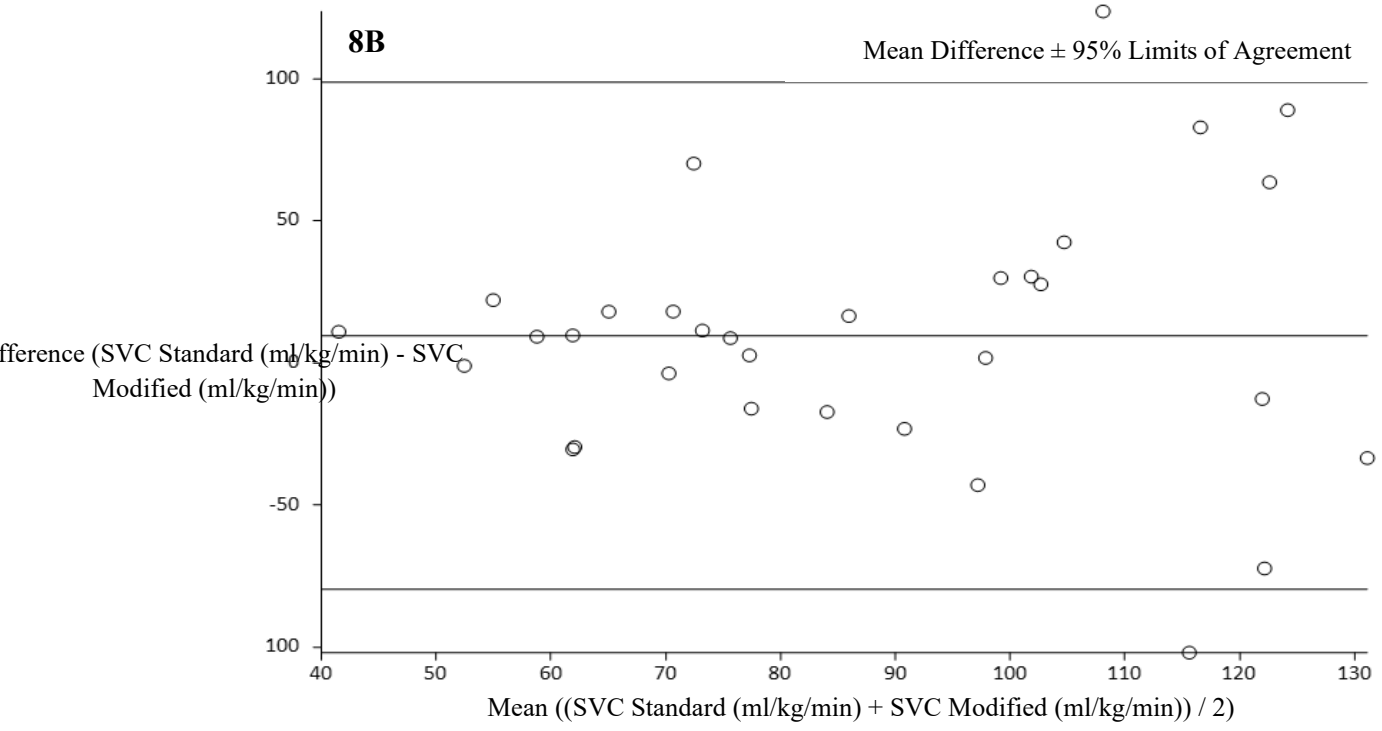
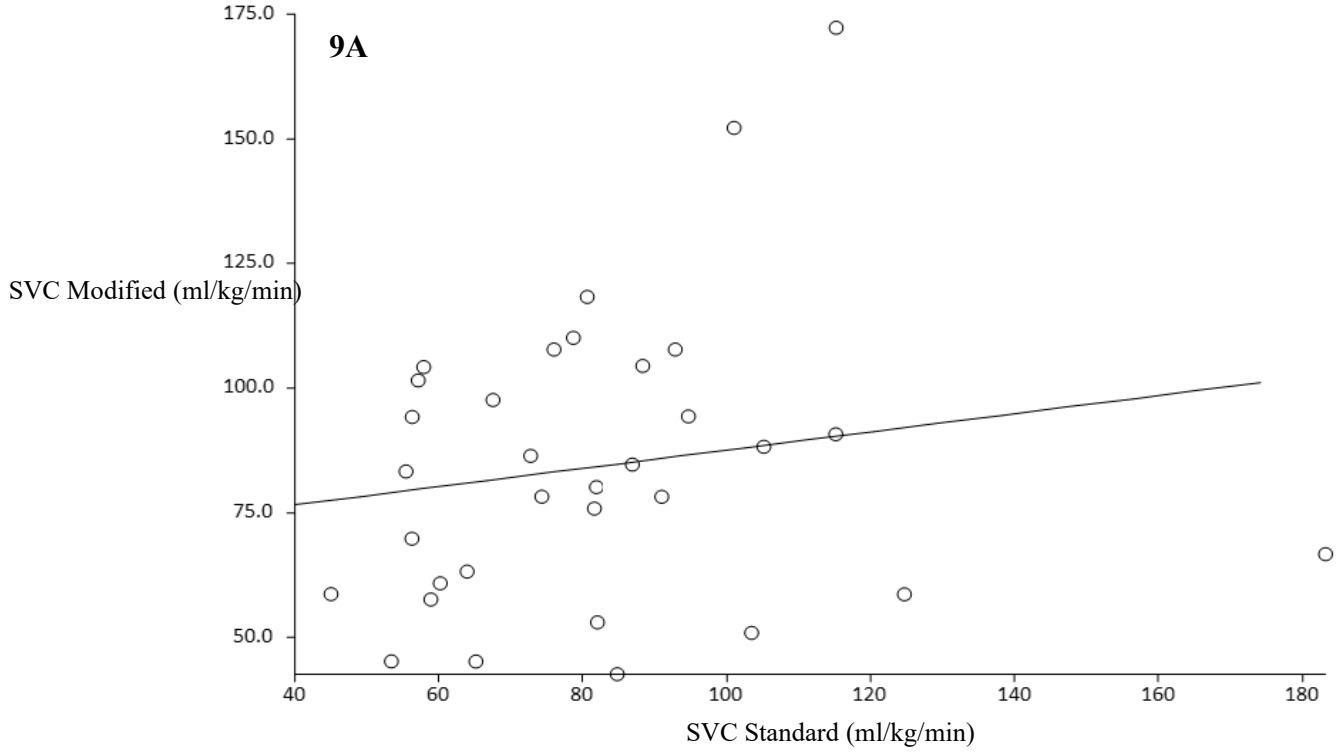
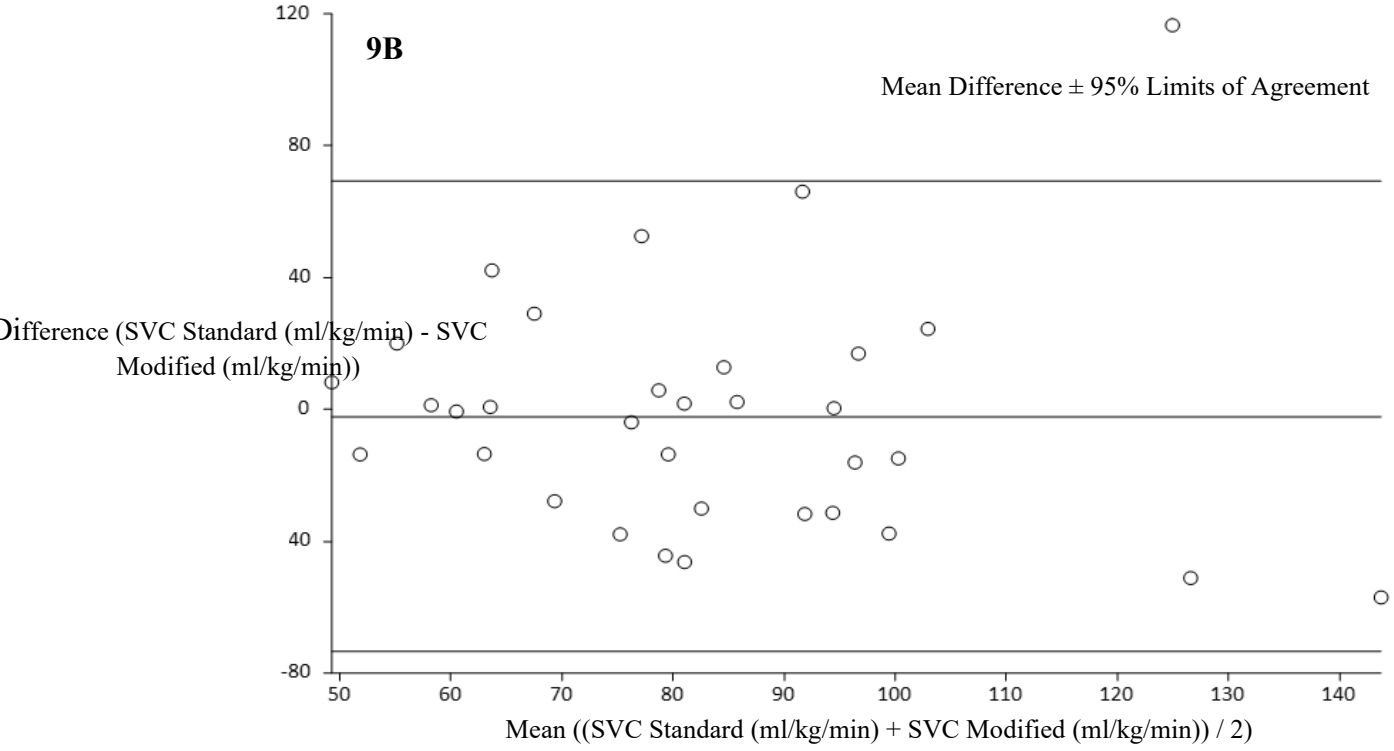


Figure 9-A Correlation between Standard and Modified Superior Vena Cava (SVC) Flow measurement at 36 hours of age
Figure 9-B Agreement between Standard and Modified Superior Vena Cava (SVC) Flow measurement at 36 hours of age with Mean Difference and 95% Limits of Agreement





frontiers

Comparison of Two Techniques of Superior Vena Cava Flow Measurement in Preterm Infants with Birth Weight less than 1250g in the Transitional Period - Prospective Observational Cohort Study

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Comparison of Two Techniques of Superior Vena Cava Flow Measurement in Preterm Infants with Birth Weight less than 1250g in the Transitional Period – Prospective Observational Cohort Study

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Introduction

Invasive measurement of cardiac output, currently employed in adult and paediatric intensive care medicine, is not technically feasible in preterm infants due to lack of appropriately sized devices.(1) Therefore, the cardiac output measured by echocardiography, together with the other echocardiography markers of cardiac function, has gained a lot of attention amongst neonatal practitioners over the last 20 years.(2) Such measurement is technically feasible, non-invasive, and well-tolerated, but in the newborn period and even more in premature infants it is quite imprecise as a result of naturally occurring shunts between the systemic and pulmonary circulation – patent ductus arteriosus and foramen ovale. The effect of the ductal shunt on left ventricular output, and of atrial shunts on right ventricular output, can cause either of these measurements to overestimate the real systemic blood flow by up to 100%.(3-5)

To overcome this issue, a Superior Vena Cava (SVC) flow measurement technique has been developed in preterm infants. SVC flow is independent of the shunts and 80% of SVC flow consists of blood return from cerebral circulation and can be a surrogate marker of systemic blood flow.(5) Low SVC flow, measured by the standard approach described by Kluckow et al., has been associated with increased risk of intraventricular haemorrhage (IVH) and adverse neurodevelopmental outcomes. Hyperkalaemia has also been observed.(6-9) A relationship between amplitude-integrated electroencephalography and SVC flow has been reported.(10) The technique became a standard approach to SVC flow measurement and was validated by different groups around the world. Furthermore this technique would be considered standard approach to SVC flow measurement by expert consensus.(11) The velocity time integral (VTI) is measured from a subxiphoid trace, and a parasternal view in a true sagittal plane is used to measure the diameter of the SVC using 2D or M-mode imaging and then the SVC area is calculated.(5, 12) The standard SVC flow echocardiography assessment technique has been somewhat challenging and has high intra-observer variability (median ranging between 8% and

12%) and inter-observer variability (median 14% to 56%) in different studies.(5, 13, 14) However, with highly experienced operators, the median inter-observer variability was as low as 6%.(15, 16)

Ficial et al. demonstrated poor correlation between standard SVC flow measurement and MRI SVC flow assessment. The modified SVC flow measurement technique was suggested by the same group, firstly using measurement of SVC area from an axial view and applying 50% reduction to stroke distance to compensate for overestimation by the subxiphoid approach.(17) Subsequently, the modified approach included VTI measured from the suprasternal view.(18) This modified measurement offered an improvement in accuracy and repeatability in a study by Ficial et al.. (19)

However, both reports using modified approach of SVC flow were done mostly on infants beyond 48 hours of age and on infants with gestation varying from extreme prematurity to term gestation.

The aim of our study was to evaluate the standard and modified techniques of echocardiography SVC flow measurement in a cohort of extremely preterm infants in the immediate postnatal period. We aimed to describe equivalency, correlation and agreement between the two techniques, and variability of components of the calculations in infants born below 1250g at six, 18 and 36 hours of age.

Material and Methods

This was a prospective, single centre, observational study in Coombe Women and Infants University Hospital (CWIUH), Dublin, Ireland (level III perinatal centre). The enrolment period was planned for 18 months (January 2016 to June 2017). The study was approved by the Research Ethics Committee in CWIUH (No.23-2015).

Participants

Inclusion criteria for the study were: birth weight <1250g, age less than 36 hours at the time of enrolment, baseline cranial ultrasound free of IVH ≥grade II (performed before first echocardiography), parental consent and presence of a researcher capable of SVC flow measurements (JM, JS). Infants with major congenital and/or chromosomal anomalies (including congenital heart diseases other than patent ductus arteriosus or foramen ovale) were excluded from participation, as were infants where the decision by the attending physician was to provide palliative and/or comfort care only.

Measurements

All infants were planned to have a cranial ultrasound just prior to the first echocardiography assessment to rule out any intracranial abnormality and/or IVH. The normal anatomy of the heart was established at the first echocardiography. Infants enrolled in the study had standard and modified SVC flow measurements at 6, 18 and 36 hours of age. We allowed for infants to be enrolled to the study at any time before 36 hours of age to have at least one paired measurement, however we aimed for enrolment before six hours of age where possible. All echocardiography measurements were done by one of two researchers (JM, JS) trained in both methods of SVC flow measurements. All paired studies were done by the same investigator.

Echocardiography

Evaluations were performed by Phillips CX50 (Philips, Amsterdam, Netherlands) echocardiography system with the sector 12Hz cardiology probe. All studies were archived and reviewed later to assess quality and accuracy of data acquisition. All measurements were done off-line after finishing the study. Standard views were obtained at the first echocardiography to confirm normal heart anatomy.(11)

SVC flow measurement - standard method (5)

SVC diameter was assessed using parasternal long axis view with the beam in a true sagittal plane and angled to the right of the ascending aorta. M–mode was used for measurements of minimal and maximal diameter during the cardiac cycle. Diameters were measured at the point where the SVC starts to open up into the right atrium. Diameter measurements were averaged from three cardiac cycles and the sweep setting of the machine was 100mm/second. Diameter was measured in centimetres (cm) for further calculations and was averaged from all six measurements (three minimal and three maximal diameters).

Velocity Time Integral (VTI) was measured using low subcostal view. The SVC flow was identified by angling the beam anteriorly and by using colour Doppler. The angle of insonation was minimized by manoeuvring the transducer inferiorly, without software corrections. The SVC flow was measured by pulsed wave (PW) Doppler at the junction of the SVC and the right atrium. A representative sample of at least 20 cycles was obtained at the pre-set sweep of 100mm/s. The mean velocity of blood flow was calculated from the integral of the Doppler velocity tracings and was averaged from five consecutive cardiac cycles. SVC VTI was expressed in cm. Forward flow was positively integrated and any retrograde flow was negatively integrated.

The heart rate was recorded by the ECG leads. If this was not possible, images obtained for SVC VTI were used and the heart rate was measured from the intervals between the cardiac cycles. Birth weight of the patient was used for all calculations.

Calculation of the SVC flow = (SVC VTI × (π × (mean SVC diameter^2/4) × heart rate)/body weight. The resulting figure has been expressed in ml/kg/min.

SVC flow measurement - modified method (17, 18)

SVC area was assessed directly from the axial/short axis view. B-mode images were obtained, and we traced maximum and minimum cross-sectional SVC area in three consecutive heart cycles. SVC area was then averaged from all measurements, expressed in cm^2.

VTI was measured from the high midline/up to suprasternal or parasternal view as needed, to imagine the SVC as close as possible to its junction with the right atrium and distal from the azygos confluence. The aim was to ensure the smallest possible angle between the Doppler beam and the vessel axis. The SVC flow was visualized with colour Doppler imaging and measured by PW Doppler. A representative sample of at least 20 cycles was obtained at the pre-set sweep of 100mm/s. The mean velocity of blood flow was calculated from the integral of the Doppler velocity tracings and was averaged from five consecutive cardiac cycles. SVC VTI was expressed in cm. Any forward flow was positively integrated and any retrograde flow was negatively integrated. The angle correction was allowed when the angle between the SVC at the point of measure and the ultrasound beam was greater than 15°, but better avoided.

The heart rate was recorded by the ECG leads. In case this was not possible, images obtained for SVC VTI were used and the heart rate was measured from the intervals between the cardiac cycles. Birth weight of the patient was used for all calculations.

Calculation of the SVC flow = (SVC VTI × SVC area × heart rate)/body weight. The resulting figure was expressed in ml/kg/min.

Cranial ultrasound

Bedside cranial ultrasound was performed by an investigator trained to perform this procedure at the time of enrolment. The aim of the ultrasound was only to rule out any major intracranial abnormality including IVH ≥grade II. Phillips CX50 (Philips, Amsterdam, Netherlands) ultrasound system with a curved 8Hz probe was used.

Results of the SVC flow measurements were recorded after 36 hours of age on pre-specified pro-forma sheet together with basic demographic parameters: gestational age, birth weight, Apgar scores, gender and timings of all SVC flow measurements in the study (planned for 6, 18 and 36 hours of age).

Pro-forma sheets were collected in the study folder in neonatal intensive care unit (NICU) and then pseudo-anonymised and stored electronically in Excel sheet (Microsoft Excel, USA) for the statistical analysis in the password protected computer.

Outcomes

Our primary outcome was equivalency, correlation and agreement between standard and modified method of the SVC flow measurement. Our secondary outcome was correlation and agreement between components of the SVC flow calculation, namely SVC VTI, SVC cross-sectional area and heart rate.

Statistics

All demographic parameters were expressed using mean (SD), median (IQR) or percentages as appropriate. We have defined SVC flow equivalency using raw bounds of –20 to +20 ml/kg/min difference between the paired measurements and used two-one-sided t-test (TOST) equivalency test with 90% Confidence Intervals. Correlation between the standard and modified methods and their components was calculated using Pearson's correlation coefficient. Bland-Altman (B-A) analysis was used to calculate and visualize the agreement between the standard and modified SVC flow measurement and their components. The agreement limits are demonstrated as a 95% confidence interval (95% CI = mean ± 1.96 standard deviations), where the ideal agreement difference between measurements is zero. Paired-samples t-test was used to compare paired measurements and their components. When the differences between

pairs were not normally distributed, we used the Wilcoxon signed-rank test for two sample comparisons. P-values <0.05 were considered statistically significant.

The data were analysed by PC-based statistics software, StatsDirect version 3.2.10 (StatsDirect Ltd, United Kingdom). For equivalency testing, R software (R 4.0.0, The R Foundation, https://www.r-project.org/) was used.

Results

We enrolled 39 infants between January 2016 and July 2017 who fulfilled inclusion criteria and had at least one pair of SVC flow measurements (at 6, 18 and/or 36 hours of age). The mean gestational age of the cohort was 27.4 (SD 2.1) weeks of postmenstrual age, the mean birth weight was 0.95 kg (SD 0.2). The median Apgar score at 1st minute was 7 (IQR 5, 9) and median Apgar score at 5th minute was 9 (IQR 8, 9). There were 23 (59%) females in the cohort. The mean time (SD) of the measurements was 7.8 (1.3) hours for six hours of age, 19.3 (1.8) hours for 18 hours of age and 37.7 (2.7) hours for 36 hours of age.

The number of paired measurements for the standard and modified approach of SVC flow were 27 at six hours of age, 32 at 18 hours of age and 33 at 36 hours of age.

The measurements at six and 36 hours of age were equivalent as defined in the design of the study (raw bounds -20 to 20 ml/kg/min). The SVC flow at three different time points as measured by standard and modified method is presented in Table 1.

At six hours of age, the standard SVC flow method had statistically significant correlation with the modified method, however this correlation was weak (r =0.39, p =0.04). The mean difference (bias) between the measurements was –0.8 ml/kg/min with 95% limits of agreement -65.0 to 63.4 ml/kg/min. (Figure 1AB, Table 2, Table 3). The heart rate correlated strongly and significantly between the two methods at this time point. Area of the SVC correlated significantly between the methods. There was also weak, but statistically significant correlation for a VTI at six hours of age between both methods.(Table 2) The mean of differences, median

of differences and 95% limits of agreement for the area of the SVC, VTI and heart rate for six hours of age are included in Table 3.

At 18 hours of age, the standard SVC flow method did not significantly correlate with the modified method (r =0.09, p =0.64). The mean difference (bias) between the measurements was +9.5 ml/kg/min, with 95% limits of agreement -79.6. to 98.7 ml/kg/min. (Figure 2, Table 2, Table 3). Heart rate correlated strongly and significantly between both methods at this time point. Area of the SVC had statistically significant correlation at 18 hours of age. The VTI did not correlate at this time point.(Table 2) The mean of differences, median of differences and 95% limits of agreement for the area of the SVC, VTI and heart rate for 18 hours of age are included in Table 3.

At 36 hours of age, the standard SVC flow method did not significantly correlate with the modified method (r =0.17, p =0.35). The mean difference (bias) between the measurements was –2.2 ml/kg/min with 95% limits of agreement -73.4. to 69.1 ml/kg/min. (Figure 3, Table 2, Table 3). Heart rate correlated strongly and significantly between both methods at this time point. Area of the SVC and VTI did not correlate at this time point.(Table 2) The mean of differences, median of differences and 95% limits of agreement for the area of the SVC, VTI and heart rate for 36 hours of age are included in Table 3.

Discussion

The standard and modified methods have yielded clinically equivalent results at 6 and 36 hours of age as defined in the design of the study. There was no statistically significant difference between the mean SVC flow for the cohort measured by either technique at any of the three time points. However, the SVC flow measurements correlated significantly only at six hours of age. Interestingly, the mean differences (bias) between the two techniques were much

smaller in our study (-0.8, 9.5 and -2.2 ml/kg/min respectively) compared to only other report comparing these two techniques, 19 ml/kg/min in the study by Ficial et al..(19)

Despite clinically equivalent results, the agreement between the two methods was not satisfactory in our opinion, with very wide agreement limits at all three time points and as such we would not deem the two methods interchangeable.

Not surprisingly there was a strong, statistically significant correlation between the heart rate data at all time points as both SVC measurement techniques were done in immediate succession and the heart rate measurements are not related to the echocardiography technique.

SVC area correlated strongly and statistically significantly between the methods at six hours of age. This correlation weakened with time, however was still statistically significant at 18 hours of age. We would speculate from our own experience and the experience of others that the measurement of SVC flow and namely the parasternal diameter of the vessel, is more difficult to carry out and less accurate over time after delivery.(20) SVC area assessed by standard technique obtained consistently lower values compared with the modified technique with mean difference ranging from 1.8 to 2.9 mm^2. This finding would be in agreement with finding of Ficial et al., albeit their mean difference was somewhat higher (4 mm^2). When SVC area by echocardiography measurement was tested against phase contrast cardiac MRI measurement, both echocardiography techniques underestimated MRI data.(17, 19) We would agree with speculation that MRI area measurement is likely to be superior in accurately obtaining the cross sectional area of the vessel.(16) As highlighted above, there was a reasonable correlation between the two echocardiography methods in SVC cross sectional area estimation, and suprasternal access might be preferable as it is most likely better reflecting the true cross sectional area and seems easier to obtain after 24-48 hours of age.

SVC VTI correlated statistically significantly between both techniques only at six hours of age and the correlation weakened with time. The standard method consistently produced higher

values compared with the modified technique, and the mean difference was very similar across the three time points (3.1, 3.0, 3.1 cm respectively). This would be similar to mean difference in VTI's as previously reported (4.3 cm and 0.67 cm by Ficial et al. and Harabor et al. respectively).(18, 19) We would speculate that the lower difference published by Harabor is a result of very frequent angle correction use in their study. We predefined criteria for the use of angle correction (to use only when the angle between the SVC at the point of measure and the ultrasound beam was greater than 15°) and we were successful in obtaining images without any need for this correction. Ficial et al. did not allow for angle correction in their study, thus their results are comparable with and similar to ours. In contrast to cross sectional area measurement, where MRI seems to be superior, we believe that in preterm infants with higher heart rates, MRI significantly underestimates true maximum velocity secondary to the relative low frame rate (20 images per cardiac cycle) compared with the current generation echocardiography machines (commonly >50 images per cardiac cycle).(16, 21) Thus the standard echocardiography technique would be most likely to reflect true VTI.

Our study is a first report of head to head comparison of two techniques of SVC flow measurements in the main population of interest, extremely preterm infants immediately after delivery. All paired measurements were done by the same investigator to eliminate inter-observer variability.

There are some limitations to our observations. Firstly our cohort of infants was relatively small (39 infants), albeit this represents substantial cohort of the most vulnerable preterm infants. We did not calculate intra-observer variability for this study. However all measurements were done by operators with vast experience in functional neonatal echocardiography and SVC measurements. Also, as there is a lack of gold standard, we can only compare variabilities of the two techniques without comparing them to a gold standard.

In summary, both SVC flow echocardiography measurement techniques yielded clinically equivalent results, although due to poor correlation and agreement they do not seem to be interchangeable. The poor correlation is mostly secondary to the VTI measurements and we would strongly advocate use of the standard technique. The SVC cross-sectional area had quite satisfactory correlation early after delivery and in fact it seems plausible that the modified technique obtains more stable and accurate values. We would recommend that future studies use modified cross sectional area measurement together with standard SVC VTI measurements and correlate these with clinically relevant outcomes, and indeed with any future gold standard cardiac output measurement, in extremely premature babies in the transitional period after birth.

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Disclosure Statement: The authors declare that they have no conflict of interest

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Table 1 – Superior Vena Cava (SVC) flow at three different time points and TOST (two-one-sided t-tests) equivalency test (raw bounds -20 to 20 ml/kg/min)

	Standard Method Mean (SD) Median (IQR)	Modified Method Mean (SD) Median (IQR)	TOST Equivalency p (for raw bounds -20 to 20 ml/kg/min) (90% Confidence Interval – ml/kg/min)
SVC 6 hours of age (ml/kg/min)	76.8 (27.7) 67.9 (57.8, 91.2)	77.6 (31.5) 74.5 (57.9, 85.3)	0.003 (-11.6 to 10.0)
SVC 18 hours of age (ml/kg/min)	92.3 (34.9) 79.5 (68.0, 114.7)	82.8 (32.4) 77.4 (60.5, 91.3)	0.1 (-4.1 to 23.1)
SVC 36 hours of age (ml/kg/min)	82.2 (27.1) 80.6 (60.2, 92.9)	84.3 (29.3) 83.3 (60.8, 101.5)	0.004 (-12.8 to 8.6)

Table 2 – Correlation coefficients for standard Superior Vena Cava (SVC) flow measurement method and modified method, including all measurements used for the calculation of SVC flow for three time points.

	r (r^2)	p
6 hours of age, n =27		
SVC flow	0.39 (0.15)	0.04
- Heart Rate	*0.72 (0.52)*	*< 0.0001*
- Velocity Time Integral	*0.54 (0.29)*	*0.003*
- SVC area	*0.70 (0.49)*	*< 0.0001*
18 hours of age, n =32		
SVC flow	0.09 (0.008)	0.64
- Heart Rate	*0.75 (0.56)*	*< 0.0001*
- Velocity Time Integral	*0.28 (0.08)*	*0.12*
- SVC area	*0.53 (0.28)*	*0.002*
36 hours of age, n =33		
SVC flow	0.17 (0.03)	0.35
- Heart Rate	*0.70 (0.49)*	*< 0.0001*
- Velocity Time Integral	*0.24 (0.06)*	*0.17*
- SVC area	*0.30 (0.09)*	*0.09*

Table 3 – Mean and median difference (bias) between the standard and modified method of superior vena cava (SVC) flow measurement with p values (paired-t or Wilcoxon's ranked signed rank test as appropriate) and 95% Limits of Agreement, including cross sectional area of SVC, Velocity Time Integral (VTI) and heart rate at all three time points

	Mean of Differences (SD) Median of Differences (IQR)	*p*	95% Limits of Agreement
6 Hours of age			
SVC Flow Standard vs. SVC Flow Modified method (ml/kg/min)	-0.80 (32.7) -3.46 (-18.6, 17.0)	0.90	-65.0 to 63.4
VTI Standard vs. VTI Modified method (cm)	*3.1 (2.4)* *2.5 (1.5, 4.0)*	*< 0.0001*	*- 1.7 to 7.9*
SVC area Standard vs. Modified method (cm^2)	*-0.029 (0.020)* *-0.031 (-0.038, -0.022)*	*< 0.0001*	*-0.068 to 0.009*
SVC heart rate Standard vs. Modified method (beats /min)	*1.9 (10.5)* *0 (-3.5, 9)*	*0.35*	*-18.6 to 22.5*
18 Hours of age			
SVC Flow Standard vs. SVC Flow Modified method (ml/kg/min)	9.52 (45.5) 9.48 (-16.4, 28.2)	0.25	- 79.6 to 98.7
VTI Standard vs. VTI Modified method (cm)	3.0 (3.2) 3.1 (0.5, 4.6)	*< 0.0001*	*- 3.2 to 9.2*
SVC area Standard vs. Modified method (cm^2)	-0.018 (0.021) -0.014 (-0.031, -0.005)	*< 0.0001*	*-0.060 to 0.023*
SVC heart rate Standard vs. Modified method (beats /min)	1.7 (8.9) 2.5 (-3, 8)	*0.30*	*-15.8 to 19.1*
36 hours of age			
SVC Flow Standard vs. SVC Flow Modified method (ml/kg/min)	-2.15 (36.4) -0.64 (-30.1, 12.8)	*0.46*	- 73.4 to 69.1
VTI Standard vs. VTI Modified method (cm)	3.1 (3.1) 2.8 (1.4, 4.5)	*< 0.0001*	- 3.0 to 9.3
SVC Area Standard vs. Modified method (cm^2)	-0.028 (0.022) -0.033 (-0.040, -0.019)	*< 0.0001*	-0.072 to 0.016
SVC heart rate Standard vs. Modified method (beats /min)	2.5 (10.8) 3 (-4, 7)	*0.18*	-18.6 to 23.6

Figure Legends

Figure 1

1-A Correlation between Standard and Modified Superior Vena Cava (SVC) Flow measurement at six hours of age

1-B Agreement between Standard and Modified Superior Vena Cava (SVC) Flow measurement at six hours of age with Mean Difference and 95% Limits of Agreement

Figure 2

Agreement between Standard and Modified Superior Vena Cava (SVC) Flow measurement at 18 hours of age with Mean Difference and 95% Limits of Agreement

Figure 3

Agreement between Standard and Modified Superior Vena Cava (SVC) Flow measurement at 36 hours of age with Mean Difference and 95% Limits of Agreement

Figure 1

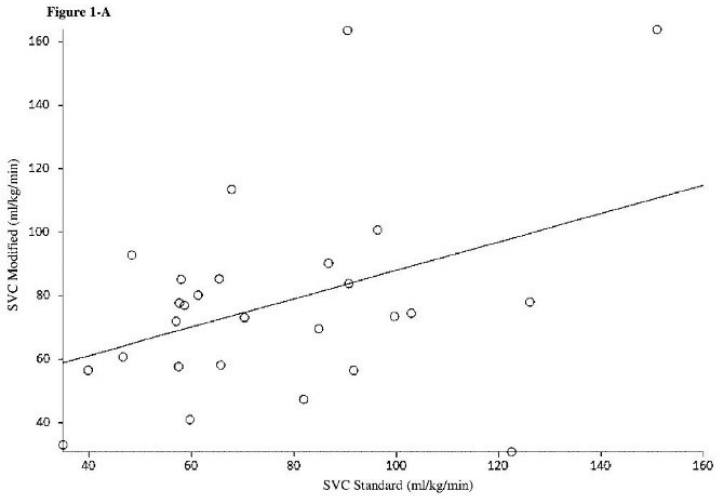


Figure 1-A
SVC Modified (ml/kg/min)
SVC Standard (ml/kg/min)
160
140
120
100
80
60
40
40
60
80
100
120
140
160

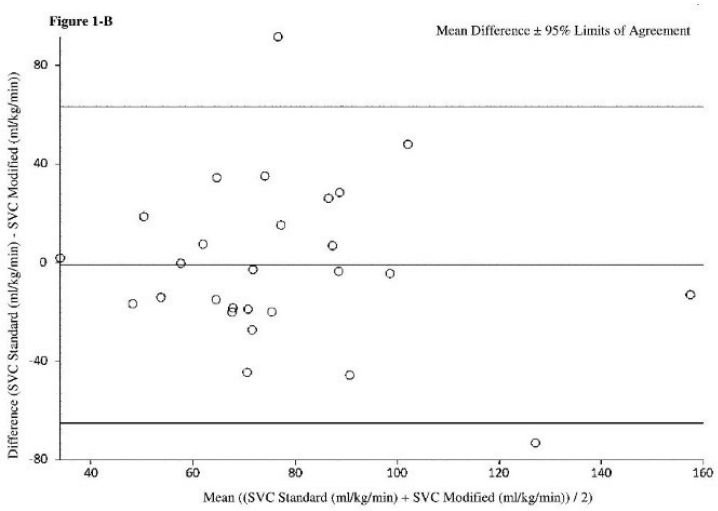


Figure 1-B
Mean Difference ± 95% Limits of Agreement
Difference (SVC Standard (ml/kg/min) - SVC Modified (ml/kg/min))
Mean ((SVC Standard (ml/kg/min) + SVC Modified (ml/kg/min)) / 2)
80
40
0
-40
-80
40
60
80
100
120
140
160

Figure 2

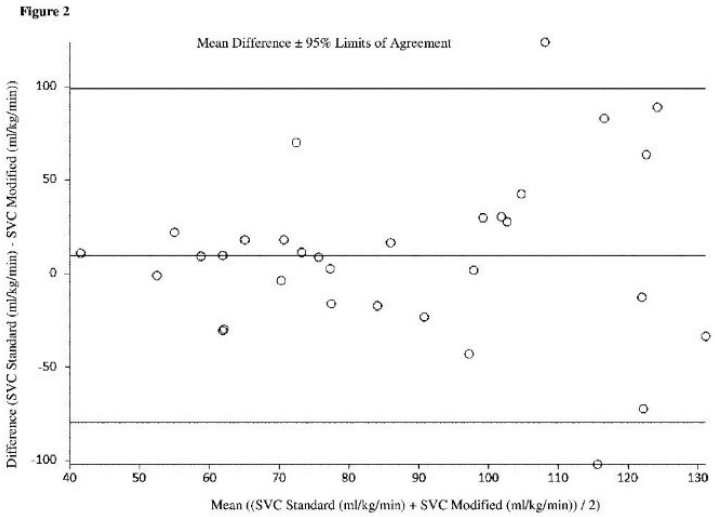
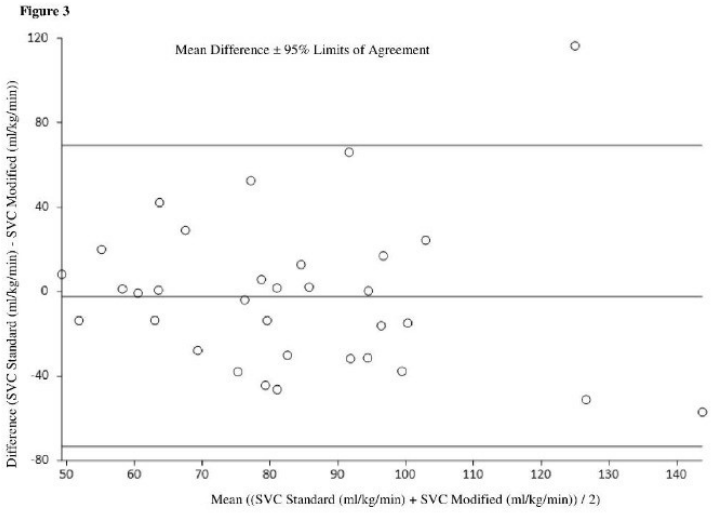


Figure 3



7.3 Summary of the Main Findings

As evidence continues to be published on the role of echocardiography derived SVC flow measurements, we continue to gain a more nuanced appreciation of its role in guiding management and predicting outcomes. Methodologies for echocardiography derived measures of SVC flow continue to improve, and it is hoped that new techniques may address some of the issues around repeatability.(88, 187)

In our study, the new modified measurement of SVC flow yielded clinically equivalent results (as defined in the design of the study - raw bounds of –20 to +20 ml/kg/min difference between the paired measurements) to the standard method of SVC flow measurement at 6 and 36 hours of age in the cohort of extremely preterm infants. There was no statistically significant difference between the mean SVC flow for the cohort measured by either technique at any of the three time points (6, 18 and 36 hours of age). However, the SVC flow measurements correlated significantly only at 6 hours of age. The mean differences (bias) between the two techniques were small from the clinical perspective (-0.8, +9.5 and -2.2 ml/kg/min respectively). Despite clinically equivalent results, the agreement between the two methods was not satisfactory, with very wide agreement limits at all three time points and as such we would not deem the two methods interchangeable. There was a strong, statistically significant correlation between the heart rate data at all time points as both SVC measurement techniques were done in immediate succession and the heart rate measurements are not related to the echocardiography technique. SVC area correlated strongly and statistically significantly between the methods at 6 hours of age. This correlation weakened with time, however was still statistically significant at 18 hours of age. SVC area assessed by the standard technique obtained consistently lower values compared to the modified technique with mean difference ranging from 1.8 to 2.9 mm^2. SVC VTI correlated statistically significantly between both techniques only at 6 hours of age and the correlation weakened with time. The standard method

consistently produced higher values compared with the modified technique, and the mean difference was very similar across the three time points (3.1, 3.0, 3.1 cm respectively).

8. Main Thesis Part 3

Assessment of Early Cardiovascular Status in Newborn Infants and Role of the PDA

8.1 Postnatal Adaptation of Pulmonary Circulation in Extremely Low Birth Weight Infants - Prospective Observational Trial

8.1.1 Background

A reduction in pulmonary arterial pressure is an important part of neonatal cardiopulmonary transition after birth. In most healthy term newborn infants, the pressure drop in the pulmonary artery is rapid and achieves normal values within the first 48 hours of life.(188) Our primary objective was to describe early cardiopulmonary transition within the first 12 hours of life in ELBW infants using targeted neonatal echocardiography (tnECHO). The secondary objective of the study was to correlate markers of delayed early transition with short-term pulmonary outcomes.

8.1.2 Materials and Methods

We have designed a prospective observational cohort study. ELBW infants born between November 2012 and May 2014 were eligible for enrolment. The study was carried out in a single level III perinatal centre (CWIUH, Dublin, Ireland). The hospital REC approved the study (Approval 13-2012). TnECHO was performed at three, six and 12 hours of life. The mandatory parameters for assessment within all the measurements were the tricuspid valve regurgitation (TR) jet velocity, and DA patency, diameter and flow direction. Outcome data including common neonatal morbidities and mortality, as defined by VON

(https://public.vtoxford.org/), were obtained by a retrospective chart review. The primary aim of our study was to describe changes in the Right Ventricle – Right Atrium (RV–RA) gradient measured by TR jet in ELBW infants, together with PDA flow and diameter, to characterize cardiopulmonary transition. Our secondary outcome was to assess risk factors for a combined outcome of Bronchopulmonary Dysplasia (BPD) (defined as O_2 and/or ventilation requirements at 36 weeks of postmenstrual age) and/or death before discharge, using measured variables and the patient's clinical data. We planned to enrol a convenience sample of 50 ELBW infants. Descriptive statistics were used for all the demographic and outcome variables of interest using frequency distribution and percentage for nominal variables. Mean and standard deviation (SD) were used for normally distributed data, while non-normally distributed data was summarised using median and interquartile range (IQR). A paired t-test was used when comparing RV–RA gradient between three, six and 12 hours of age. A student t-test and Mann-Whitney U-test were used as appropriate to compare two cohorts of interest. We used simple logistic regression to identify variables associated significantly with our pre-defined adverse outcome. The identified variables were then used for our multiple logistic regression model, with the combined outcome of BPD and/or death as a dependent variable. Where the independent variables were collinear, only one of them was used. Logistic regression results were summarized using odds ratios and 95% confidence intervals. P-values <0.05 were considered statistically significant. Data analysed by the StatsDirect v.3.2.10 software (StatsDirect Ltd, UK).

8.1.3 Results

Fifty-one infants were enrolled in the study. The mean gestational age (SD) of the enrolled infants was 26.2 (1.8) weeks and mean birth weight (SD) was 783 (142)g. Forty-six (90%) infants survived until discharge and the predefined outcome of BPD and/or death occurred in

21 (41%) infants. PDA remained open in all infants throughout the first 12 hours of life and there were no significant changes in the mean PDA diameter within this timeframe, ranging from 2.2mm to 2mm at three and 12 hours respectively. PDA remained bidirectional at 12 hours of age in almost one quarter of infants suggesting ongoing transition. TR jet and corresponding RV-RA gradient values decreased over time as expected. Using only the data where TR was present, we have shown a significant drop in the RV-RA gradient from 20.7 to 16.5mmHg between six and 12 hours of age (p =0.004, Figure 10). Using simple logistic regression with BPD and/or death as the dependent variable we tested all the demographic, echocardiographic and ventilation support parameters. Significantly associated parameters were then tested for collinearity and the non-collinear ones were further tested in the multiple logistic regression model. In the multiple logistic regression model using gestational age (birth weight collinear), Apgar at 5th minute (Apgar at 1st minute collinear), mechanical ventilation at 12 hours (mechanical ventilation at three and six hours collinear) and RV – RA gradient at 12 hours, only mechanical ventilation at 12 hours of age was independently predictive of the adverse outcome of BPD and/or Death (Table 2).

8.1.4 Conclusions

We have described cardiopulmonary transition over the first 12 hours of age in 51 ELBW infants. There was a significant decrease in pulmonary pressures at 12 hours of age, however DA flow remained bidirectional in almost a quarter of infants, suggesting ongoing transition. In the multiple logistic regression model, only mechanical ventilation at 12 hours of age was independently predictive of the adverse outcome.

Figure 10 - Box-whisker plot (mean, SD, min, max) of Right Ventricle – Right Atrium (RV-RA) gradient (cases with TR jet measurable only).

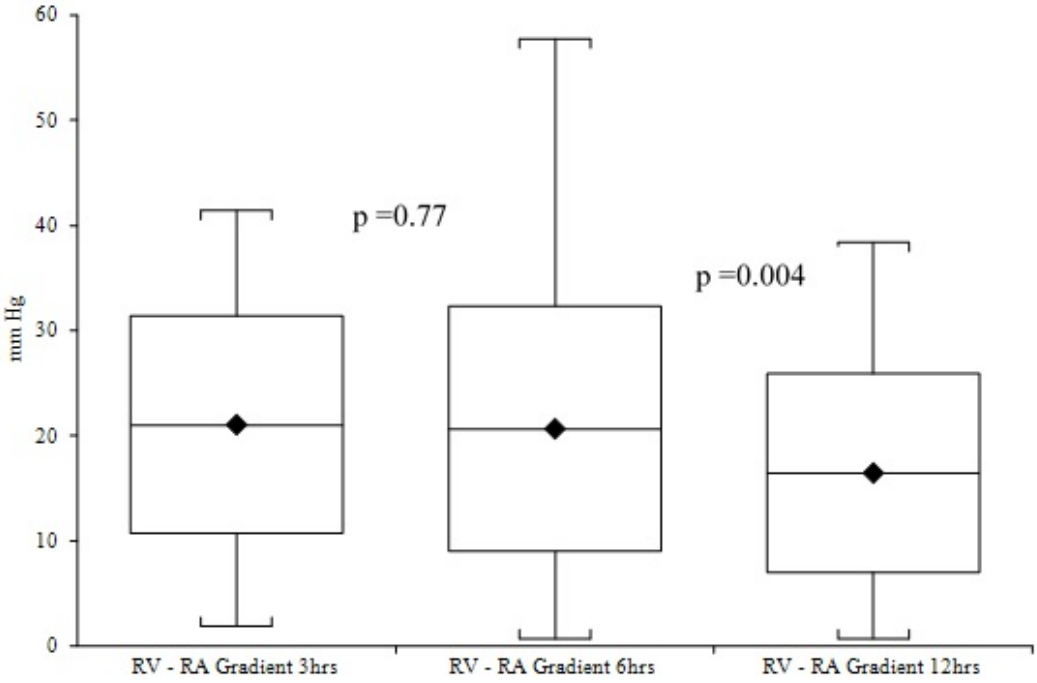


Table 2 - Multiple Logistic Regression Model – Gestational Age, 5th minute Apgar score, Mechanical Ventilation at 12 hours of Age and Right Ventricle – Right Atrium (RV–RA) Gradient at 12 hours of Age (BPD and/or Death as the Dependent Variable)

Variable	OR (95% CI)	p
Gestational Age	0.64 (0.34 – 1.19)	0.16
Apgar 5th Minute	0.61 (0.26 – 1.43)	0.25
RV–RA Gradient 12hrs	1.05 (0.95 – 1.16)	0.33
Mechanical Ventilation 12hrs	**7.92 (1.38 – 45.6)**	**0.021**

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Keywords:	Mortality, Neonatology

Postnatal Adaptation of Pulmonary Circulation in Extremely Low Birth Weight Infants - Prospective Observational Trial

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Word Count: 2477

Keywords: ELBW infant, Pulmonary pressure, Neonatal transition, Bronchopulmonary dysplasia, Mortality

Abstract

Objective

To measure parameters of cardiopulmonary transition in the first 12 hours of life in Extremely Low Birth Weight (ELBW; < 1000g) infants and explore relationship to combined outcome of Bronchopulmonary Dysplasia (BPD) and/or Death

Design

Prospective observational cohort study

Setting

Level III neonatal centre

Patients

All inborn ELBW infants

Interventions

Targeted neonatal echocardiography performed at three, six and 12 hours of age. The size and flow pattern in the Ductus Arteriosus (DA), the Tricuspid Regurgitation jet and the corresponding Right Ventricle – Right Atrium (RV–RA) pressure gradients were assessed.

Main Outcome Measures

Primary outcome of the study was description of RV–RA gradient and DA transition in the first 12 hours of life. Secondary outcome involved assessment of the relationship between the transition data and combined outcome of BPD and/or death.

Results

Fifty-one ELBW infants were enrolled. A significant drop in RV-RA gradient was documented (20.7 to 16.5 mm Hg, p =0.004) between six and 12 hours of age. All infants had a DA present on all measurements, with 12 infants still having bidirectional DA flow at 12 hours of age. In

the multiple logistic regression model only mechanical ventilation at 12 hours of age was predictive of the predefined adverse outcome (OR 7.92, p =0.021).

Conclusions

We have described cardiopulmonary transition over the first 12 hours of age in 51 ELBW infants. There was a significant decrease in pulmonary pressures at 12 hours of age, however DA flow remained bidirectional in almost a quarter of infants, suggesting ongoing transition.

Background

A reduction in pulmonary arterial pressure is an important part of neonatal cardiopulmonary transition after birth. In most healthy term newborn infants, the pressure drop in the pulmonary artery is rapid and achieves normal values within the first 48 hours of life.[1] There is a paucity of normative data on transition in the preterm population. However, it is documented that in preterm infants, particularly in those affected by early respiratory morbidity, the decrease in pulmonary pressures may be impaired, resulting in pulmonary hypertension.[2 3] Studies have shown an association between pulmonary hypertension documented in the early neonatal period and bronchopulmonary dysplasia (BPD)[4-7] and in-hospital mortality in preterm infants.[5-7] Early pulmonary hypertension in preterm newborns also appears to be associated with late respiratory outcomes in childhood.[8] Our primary objective was to describe early cardiopulmonary transition within the first 12 hours of life in Extremely Low Birth Weight (ELBW; birth weight less than 1000g) infants using targeted neonatal echocardiography (tnECHO). The secondary objective of the study was to correlate markers of delayed early transition with short-term pulmonary outcomes.

Methods

This was a prospective observational cohort study. ELBW infants born between November 2012 and May 2014 were eligible for enrolment. The study was carried out in a single level III perinatal centre (Coombe Women and Infants University Hospital, Dublin, Ireland). The hospital Research Ethics Committee approved the study (Approval 13-2012).

The primary aim of our study was to describe changes in Right Ventricle – Right Atrium (RV–RA) gradient measured by tricuspid valve regurgitation (TR) jet in ELBW infants, together with Patent Ductus Arteriosus (PDA) flow and diameter, to characterize cardiopulmonary transition. Our secondary outcome was to assess risk factors for a combined outcome of BPD

(defined as O_2 and/or ventilation requirements at 36 weeks of postmenstrual age) and/or death before discharge, using measured variables and patient's clinical data.

Inclusion criteria were birth weight below 1000g, admission to the neonatal intensive care unit, and parental consent. Due to the inability to obtain the written consent in a timely manner in outborn infants, only inborn infants were included. Exclusion criteria were known congenital malformation or congenital heart disease apart from PDA and/or Patent Foramen Ovale (PFO), requirement for inhaled Nitric Oxide (iNO) within the first three hours of life, infants unlikely to survive the first 12 hours of life, and decision to provide palliative care only. Parents of eligible infants were approached, and consent was obtained prior to delivery or within the first three hours after the delivery.

TnECHO was performed at three, six and 12 hours of life. Point-of-care cranial ultrasound was also performed at the first time point. All echocardiography studies were performed using Phillips CX50 ultrasound (Koninklijke Phillips N.V., Amsterdam, Netherlands) with sector array transducer S12-4. All three clinicians (JP, JS, JM) performing the tnECHO were adequately trained and experienced. Structural normality of the heart was established by the first echocardiography assessment in addition to the measurements related to the cardiopulmonary transition and pulmonary hypertension. The two assessments at six and 12 hours were primarily focused on the latter. Well-established international guidelines for neonatologist performed tnECHO were followed, however the scans were strictly limited to 10 minutes in duration to minimize the disturbance of the infants.[9] The mandatory parameters for assessment within all the measurements were the TR jet velocity, and ductus arteriosus patency, diameter and flow direction. In circumstances where the TR jet was not obviously present and therefore could not be measured, the TR jet velocity value was entered as zero. Baseline demographic data including antenatal steroids use, gestational age, birth weight, gender and Apgar scores were recorded at the time of enrolment. Outcome data including common

neonatal morbidities and mortality, as defined by Vermont Oxford Network (https://public.vtoxford.org/), were obtained by a retrospective chart review.

We planned to enrol a convenience sample of 50 ELBW infants. Data was entered into Microsoft Excel 365 (Office 365, Microsoft, USA) and analysed by the StatsDirect v.3.2.10 software (StatsDirect Ltd, UK). Descriptive statistics were used for all the demographic and outcome variables of interest using frequency distribution and percentage for nominal variables. Mean and standard deviation (SD) were used for normally distributed data, while non-normally distributed data was summarised using median and interquartile range (IQR). Paired t-test was used when comparing RV–RA gradient between three, six and 12 hours of age. Student t-test and Mann-Whitney U-test were used as appropriate to compare two cohorts of interest. We used simple logistic regression to identify variables associated significantly with our pre-defined adverse outcome. The identified variables were then used for our multiple logistic regression model, with the combined outcome of BPD and/or death as a dependent variable. Where the independent variables were collinear, only one of them was used. Logistic regression results were summarized using odds ratios and 95% confidence intervals. P-values <0.05 were considered statistically significant.

Results

Eighty-seven ELBW infants were born within the study period. Of those, 72 infants fulfilled the eligibility criteria and 51 infants were enrolled in the study (Figure 1). The mean gestational age of the enrolled infants was 26.2 weeks and mean birth weight was 783g. Forty-six (90%) infants survived until discharge and the predefined outcome of BPD and/or death occurred in 21 (41%) infants. The demographic description of the enrolled cohort, tnECHO measurements of interest, and clinical outcomes for the entire cohort are presented in Table 1.

Table 1
Demographic characteristics of the cohort, targeted neonatal echocardiography measurements and clinical outcomes.

n =51	
GA, mean (SD), weeks	26.2 (1.8)
Male n, (%)	20 (39)
Apgar 1st median (IQR)	5 (4, 7)
Apgar 5th median (IQR)	8 (7, 9)
Antenatal Steroids, n (%)	46 (90)
Surfactant, n (%)	36 (71)
Birth Weight, mean (SD), g	783 (142)
Vaginal Delivery, n (%)	11 (22)
PDA Diameter 3 hours, mean (SD), mm	2.2 (0.5)
PDA Diameter 6 hours, mean (SD), mm	2.1 (0.4)
PDA Diameter 12 hours, mean (SD), mm	2.0 (0.3)
Bidirectional PDA flow 3 hours, n (%)	25 (49)
Bidirectional PDA flow 6 hours, n (%)	21 (41)
Bidirectional PDA flow 12 hours, n (%)	12 (24)
TR jet 3 hours, mean (SD), m/s	2.1 (0.7)
TR jet 6 hours, mean (SD), m/s	2.1 (0.8)
TR jet 12 hours, mean (SD), m/s	1.8 (0.8)
RV-RA gradient 3 hours, mean (SD), mm Hg	20.2 (10.9)
RV-RA gradient 6 hours, mean (SD), mm Hg	20.3 (11.9)
RV-RA gradient 12 hours, mean (SD), mm Hg	15.5 (10.0)
FiO2 requirements 3 hours, median (IQR)	21 (21, 30)
FiO2 requirements 6 hours, median (IQR)	21 (21, 26.5)
FiO2 requirements 12 hours, median (IQR)	21 (21, 24.5)
Mechanical Ventilation at 3 hours, n (%)	30 (59)
Mechanical Ventilation at 6 hours, n (%)	23 (45)

Mechanical Ventilation at 12 hours, n (%)	21 (41)
Inotropic Support at 3 hours, n (%)	1 (2)
Inotropic Support at 6 hours, n (%)	4 (8)
Inotropic Support at 12 hours, n (%)	5 (10)
RDS, n (%)	51 (100)
iNO (after three hours of age), n (%)*	6 (12)
EOS (BC confirmed), n (%)	1 (2)
Inotropic Support 1st 3 days, n (%)	11 (22)
LOS (BC confirmed), n (%)	11 (22)
Severe IVH (grade ≥2), n (%)	10 (20)
cPVL, n (%)	0 (0)
NEC (grade ≥2A), n (%)	6 (12)
PDA treated medically, n (%)	11 (22)
PDA treated surgically, n (%)	2 (4)
ROP (grade >2) survivors (n =46), n (%)	4 (9)
BPD 28 days, survivors (n =47), n (%)	40 (85)
BPD 36/40, survivors (n= 46), n (%)	16 (35)
BPD or death, n (%)	21 (41)
Survival to discharge, n (%)	46 (90)

* all started outside of the first 12 hours except 1 infant
PDA – Patent Ductus Arteriosus; TR – Tricuspid Regurgitation; RV-RA – Right Ventricle / Right Atrium; RDS – Respiratory Distress Syndrome; iNO – inhaled Nitric Oxide; EOS – Early Onset Sepsis; BC – Blood Culture; LOS – Late Onset Sepsis; IVH – Intraventricular Haemorrhage; cPVL – cystic Periventricular Leucomalacia; NEC – Necrotising Enterocolitis; ROP – Retinopathy of Prematurity; BPD – Bronchopulmonary Dysplasia;

PDA remained open in all infants throughout the first 12 hours of life and there were no significant changes in the mean PDA diameter within this timeframe, ranging from 2.2mm to 2mm at three and 12 hours respectively (Table 1). PDA remained bidirectional at 12 hours of age in almost one quarter of infants suggesting ongoing transition.

TR jet and corresponding RV-RA gradient values decreased over time as expected (Table 1). At each tnECHO measurement time point there were infants where TR was not present. There

were two such measurements at three hours, one at six hours and three at 12 hours of life. Using only the data where TR was present we have shown a significant drop in RV-RA gradient from 20.7 to 16.5mmHg between six and 12 hours of age (p =0.004, Figure 2).

We compared the demographic, echocardiographic and ventilation support data between the two group of infants, those with or without the predefined adverse outcome of BPD and/or death. Comparison of the parameters between the groups is shown in Table 2.

Table 2
Secondary Analysis of parameters in the first 12 hours of age in infants with combined outcome of bronchopulmonary dysplasia (BPD) at 36 weeks of postmenstrual age and/or Death versus infants without this predefined outcome.

	BPD/Death (n =21)	No BPD/Death (n =30)	p
Gestational age, mean (SD), weeks	25.1 (1.5)	27.0 (1.6)	< 0.0001
Birth weight, mean (SD), g	690 (131)	849 (112)	< 0.0001
Male, n (%)	7 (33%)	13 (43%)	0.57
Apgar 1st min, median (IQR)	4 (3, 6)	6 (5, 8)	0.0002
Apgar 5th min, median (IQR)	7 (6, 8)	8 (8, 9)	0.0002
Completed Antenatal Steroids, n (%)	20 (95)	26 (87)	0.39
Surfactant, n (%)	19 (90)	17 (57)	0.012
Vaginal Delivery, n (%)	5 (24)	6 (20)	0.74
PDA Diameter at 3hrs, mean (SD), mm	2.2 (0.6)	2.2 (0.4)	0.91
PDA Diameter at 6hrs, mean (SD), mm	2.0 (0.3)	2.2 (0.4)	0.13
PDA Diameter at 12 hrs, mean (SD), mm	2.0 (0.3)	2.0 (0.4)	0.92
Bidirectional PDA 3hrs, n (%)	12 (57)	13 (43)	0.40
Bidirectional PDA 6hrs, n (%)	11 (52)	10 (33)	0.25
Bidirectional PDA 12hrs, n (%)	6 (29)	6 (20)	0.52
RV-RA Gradient 3hrs, mean (SD), mm Hg	19.7 (10.6)	20.6 (11.4)	0.79
RV-RA Gradient 6hrs, mean (SD), mm Hg	21.2 (10.2)	19.6 (13.1)	0.63
RV-RA gradient 12hrs, mean (SD), mm Hg	19.5 (8.3)	12.7 (10.2)	0.014
FiO_2 3hrs, median (IQR)	22 (21, 30)	21 (21, 26.8)	0.35
FiO_2 6hrs, median (IQR)	21 (21, 30)	21 (21, 25)	0.48

FiO_2 12hrs, median (IQR)	24 (21, 30)	21 (21, 21)	0.027
Mechanical Ventilation 3hrs, n (%)	19 (90)	11 (37)	0.0001
Mechanical Ventilation 6hrs, n (%)	16 (76)	7 (23)	0.0004
Mechanical Ventilation 12hrs, n (%)	17 (81)	4 (13)	< 0.0001
Inotropes 3hrs, n (%)	1 (5)	0 (0)	0.41
Inotropes 6hrs, n (%)	3 (14)	1 (3)	0.29
Inotropes 12hrs, n (%)	4 (19)	1 (3)	0.15
iNO after 12hrs, n (%)	6 (29)	0 (0)	0.003

PDA – Patent Ductus Arteriosus; TR – Tricuspid Regurgitation; RV-RA – Right Ventricle-Right Atrium; RDS – Respiratory Distress Syndrome; iNO – inhaled Nitric Oxide; EOS – Early Onset Sepsis; BC – Blood Culture; LOS – Late Onset Sepsis; IVH – Intraventricular Haemorrhage; cPVL – cystic Periventricular Leucomalacia; NEC – Necrotising Enterocolitis; ROP – Retinopathy of Prematurity

Using simple logistic regression with BPD and/or death as the dependent variable we tested all the demographic, echocardiographic and ventilation support parameters. Data are presented as Odds Ratios (95% Confidence Intervals) with the respective p values. From the demographic and clinical parameters (gestational age, birth weight, sex, Apgar scores at 1st and 5th minute, surfactant administration, mode of delivery), gestational age [0.42 (0.25 – 0.71), p=0.0011], birth weight [0.99 (0.98 – 0.995), p=0.0006], Apgar score at 1st minute [0.50 (0.33 – 0.76), p=0.0013], Apgar score at 5th minute [0.34 (0.18 – 0.67), p=0.0017], and surfactant administration [7.26 (1.43 – 36.94), p=0.017] were significantly associated with the predefined outcome. From the echocardiography parameters tested (PDA diameter, PDA bidirectional flow, and RV-RA gradient, all at three, six, 12 hours), only the RV-RA gradient at 12 hours was significantly associated with BPD and/or death [1.08 (1.01 – 1.15), p=0.019]. From the ventilation support parameters (FiO_2 at three, six and 12 hours, mechanical ventilation at three, six and 12 hours), those significantly associated with BPD and/or death were mechanical ventilation at three [16.41 (3.20 – 84.20), p=0.0008], six [10.51 (2.83 – 39.09), p=0.0004] and

12 hours of age [27.63 (6.07 – 125.65), p<0.0001]. Significantly associated parameters were tested for collinearity and the non-collinear ones were further tested in the multiple logistic regression model. In the multiple logistic regression model using gestational age (birth weight collinear), Apgar at 5th minute (Apgar at 1st minute collinear), mechanical ventilation at 12 hours (mechanical ventilation at three and six hours collinear) and RV – RA gradient at 12 hours, only mechanical ventilation at 12 hours of age was independently predictive of the adverse outcome of BPD and/or Death (Table 3).

Table 3
Multiple Logistic Regression Model – Gestational Age, 5th minute Apgar score, Mechanical Ventilation at 12 hours of Age and Right Ventricle – Right Atrium (RV–RA) Gradient at 12 hours of Age (BPD and/or Death as the Dependent Variable)

Variable	OR (95% CI)	p
Gestational Age	0.64 (0.34 – 1.19)	0.16
Apgar 5th Minute	0.61 (0.26 – 1.43)	0.25
RV–RA Gradient 12hrs	1.05 (0.95 – 1.16)	0.33
Mechanical Ventilation 12hrs	7.92 (1.38 – 45.6)	0.021

Discussion

We have documented a significant drop in pulmonary artery pressures based on RV-RA gradient measurements between six and 12 hours of age. PDA diameter was unchanged over the first 12 hours of life, however, we observed that PDA flow remained bidirectional (right-to-left flow more than 30% of the cycle) in 24% of infants at 12 hours of age, suggesting ongoing transition.

The available normative data on early cardiopulmonary transition within first 24 hours in infants with ELBW are scarce. A study by Seppänen et al. presented serial measurements of pulmonary artery pressures at two, 12, 24 up to 72 hours of age in a group of healthy preterm neonates (mean GA 31.7 weeks, mean BW 1860g) and neonates with respiratory distress

syndrome (RDS) (mean GA 29.9 weeks, mean BW 1605g).[2] They also documented a significant drop in pulmonary artery pressures within the first hours (between two and 12 hours) of life, however the pressure values were in general higher than those we have observed, starting at around 50mm Hg in the healthy preterm group and 55mm Hg in the RDS group at two hours, and dropping to 35mm Hg and 50mm Hg respectively at 12 hours of age. RV-RA gradient measurements were 5mm Hg lower as the investigators estimated RA pressure to be 5mmHg. On the other hand, they were not able to detect a measurable TR jet in 30% of infants with RDS and in 50% healthy preterm infants after two hours, suggesting quickly progressing transition in those infants. They have observed bidirectional PDA at 12 hours in 40% of the infants with RDS and 11% of the healthy preterm infants respectively. The difference in pulmonary pressure estimates as compared with our results could be due to the different population characteristics and high percentage of infants with no TR jet. In the study by Seppänen et al., all infants enrolled received a bolus of normal saline and dopamine infusion, which could contribute to increased pulmonary vasoconstriction and therefore elevate pulmonary artery pressure. Another study by Schmitz et al. evaluated pulmonary pressures in healthy preterm infants (mean GA 31.9 weeks, mean BW 1709g) and preterm infants with severe RDS (mean GA 28.4, mean BW 1061g) within the first 24 hours of life and then daily thereafter, until day four of life.[1] They observed RV-RA gradients within the first 24 hours to be below 20mmHg in 50% of healthy preterm infants but only 25% of infants with RDS, again suggesting increased pulmonary pressures in the 'sicker' infants. Using the cut-off value of 30 mmHg, 90.9% of the healthy preterm infants and 75% of infants with RDS had RV-RA gradients below this value. They did not observe any correlation between RV-RA gradients and gestational age or birth weight using linear regression analysis.

Both of these studies measuring early pulmonary pressures investigated slightly different populations in a different epoch of neonatology. Recent studies investigating a similar

population to ours (infants less than 29 weeks of gestation), present echocardiographic assessment of cardiopulmonary transition at different, slightly later, timeframes, therefore are not directly comparable.[6 10] However, in healthy preterm infants below 29 weeks of gestation, James et al. documented bidirectional PDA at a median of 10 hours of age in 35% of infants, with a median diameter of 2.4mm, similarly to our findings.[10] Mizra et al. described delayed cardiopulmonary adaptation (defined as pulmonary artery pressures more than a half of systemic systolic pressure at 72-96 hours) in 55% of the subjects of their cohort of infants below 29 weeks of gestation.[6] They concluded that delayed cardiopulmonary adaptation is an independent risk factor for death or BPD using multivariate logistic regression

Birth weight, fraction of inspired oxygen and pulmonary artery pressure at 24 hours of age were shown to be independent predictors of chronic lung disease in another study investigating neonatal transition.[11] In our study only mechanical ventilation at 12 hours of age was independently predictive of the adverse outcome. However, we have documented a significant difference in RV-RA gradient measurements at 12 hours of age between the group of infants who had the primary outcome of BPD/death and those who did not. This prompts the question of whether we could influence the outcomes by altering these variables.

Optimal delivery room management and gentle/minimally invasive ventilation practices are well described and established.[12] Routine use of iNO to decrease pulmonary pressures in preterm infants with respiratory disease does not seem to improve survival without BPD.[13] Rescue iNO treatment in very sick preterm infants with impaired oxygenation does not seem to be effective either.[13] There is, however, paucity of information on using targeted strategies to decrease pulmonary pressures in preterm infants, particularly those needing mechanical ventilation, based on echocardiography parameters.[14 15]

Considering that almost a quarter of ELBW infants enrolled in our study had bidirectional PDA at 12 hours of age, there may be potential adverse effects if PDA closure is attempted in these

infants at this time, e.g. prophylactic early PDA treatment, as such closure could cause the infant to deteriorate clinically. This further underscores the importance of point-of-care echocardiography and an individual/targeted approach in the haemodynamic management of preterm newborns.

The main strength of this study is that we were able to recruit a large cohort of the most vulnerable preterm infants within first three hours of life. All infants enrolled had all three measurements carried out on tnECHO at three, six and 12 hours of life (unless they did not survive to the particular time points).

However, we chose to implement only the most common and easily reproducible echocardiography parameters of pulmonary pressures assessment for the sake of minimal manipulation and disturbance of the infants under assessment. More echocardiography measurements are available to assess complex right heart performance, for example Tissue Doppler Imaging (TDI) and strain rate as quantitative markers of RV function, or other RV specific markers like Tricuspid Annular Plane Systolic Excursion (TAPSE).[16]

Conclusion

We have described cardiopulmonary transition over the first 12 hours of life in 51 ELBW infants using targeted neonatal echocardiography. The PDA diameter was unchanged over the first 12 hours of life. PDA flow remained bidirectional in almost a quarter of infants at 12 hours of age, suggesting ongoing transition. There was a significant decrease in pulmonary pressures between six and 12 hours of age. Pulmonary pressures at 12 hours of age were also significantly higher in the group of infants who had later developed BPD and/or died, in comparison with those who did not. However, in the multiple logistic regression model only mechanical ventilation at 12 hours of age was independently predictive of the adverse outcome. These findings could help to address the need for more normative data on early cardiopulmonary

transition in the most vulnerable preterm infants. Our data could be also helpful in designing and performing interventional randomised controlled trials concerning early cardiopulmonary transition.

Competing Interests: None

Source of Funding: None

Contributors: Dr Jana Semberova contributed substantially to design, enrolment, measurements in the study and data collection. She drafted the initial and final version of the manuscript. Dr Purna contributed substantially to design, enrolment, measurements in the study and data collection and reviewed and revised the manuscript. Dr Ó Catháin contributed to data collection and analysis. She reviewed and revised the manuscript. Prof. Miletin conceptualized and designed the study and contributed substantially to enrolment, measurements in the study and data analysis. He reviewed and revised the manuscript critically for important intellectual content. All the authors approved the final manuscript as submitted. They agree to be accountable for all aspects of the work.

What is already known on this topic

- Preterm infants, particularly those with respiratory morbidity, are at risk of impaired transition resulting in pulmonary hypertension.
- Early pulmonary hypertension is associated with neonatal morbidity and mortality.
- There is a lack of normative data on early cardiopulmonary transition in preterm infants.

What this study adds

- We have documented echocardiography parameters of cardiopulmonary transition during the first 12 hours of life in a substantive cohort of Extremely Low Birth Weight Infants.
- Pulmonary pressures decreased significantly at 12 hours of age in the cohort studied, however remained higher in infants who later developed bronchopulmonary dysplasia and/or died.
- In the multiple logistic regression model only mechanical ventilation at 12 hours of age was predictive of such adverse outcomes.

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Figure legends

Figure 1

Number of eligible infants and subsequent study flow chart

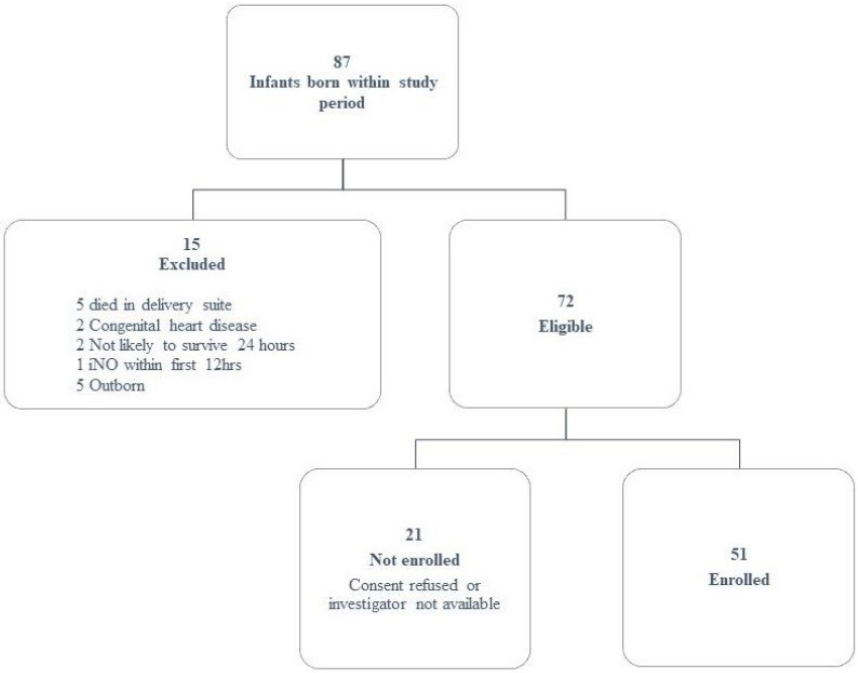
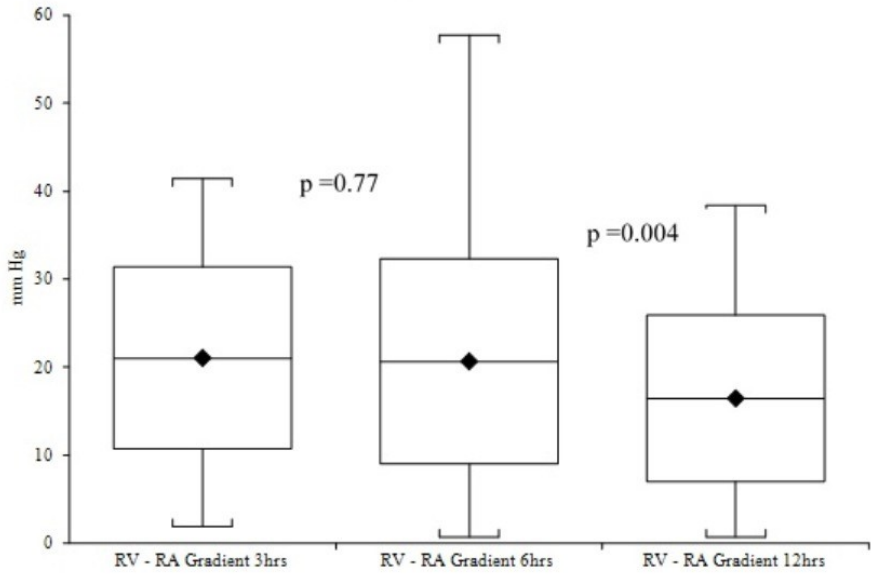


Figure 2

Box-whisker plot (mean, SD, min, max) of Right Ventricle – Right Atrium (RV-RA) gradient (cases with TR jet measurable only).



8.2 Assessment of Neonatal Heart Rate Immediately after Birth Using Digital Stethoscope, Handheld Ultrasound and Electrocardiography: an Observational Cohort Study

8.2.1 Background

The extent and initiation of cardiopulmonary resuscitation of neonates in the DR is largely guided by neonatal HR. This is usually assessed after birth initially by stethoscope auscultation, and then for ongoing monitoring Electrocardiography (ECG) is the standard of care. This is based on the recommendations from the 2015 International Liaison Committee on Resuscitation who noted that ECG was more accurate and efficient compared to pulse oximetry in detecting and monitoring HR in neonates in the delivery suite.(189-191) Ultrasound has previously been used to assess HR in neonates, but not in the delivery suite immediately after birth.(192) Our aim was to determine the time to achieve first HR after delivery by HUS, DS and ECG, and compare these to traditional stethoscope auscultation, and observe the differences in HR achieved.

8.2.2 Materials and Methods

This was an observational prospective cohort study. Ethical approval was granted by the REC at the CWIUH (Study No.10-2016). Women who were planned for elective caesarean sections were recruited and consented prior to delivery at antenatal clinic visits. This study was carried out between January and July 2017. Two physicians attended each delivery, one assessed the HR by stethoscope auscultation and the second assessed the HR using either HUS (Mortara, Signos RT Personal Ultrasound), DS (Littmann 3200, 3M, US) or ECG (IntelliVue MP5, Philips, Netherlands)). The time at which the infant was placed on the resuscitaire and the time the device was fully placed on the infant were recorded. The time to achieve first HR and the

HR recorded was noted, then when both modalities were recording, a simultaneous HR was recorded.

8.2.3 Results

Sixty infants were recruited in total (twenty in each modality group). The mean birth weight (±SD) of the cohort was 3.46kg (±0.43) and mean gestational age was 38.8 (±0.83) weeks of gestation. There was no significant difference between group baseline characteristics. The median time from birth to first HR, and from device application to first HR with each device are outlined in Table 3. There was no reading of HR in seven (35%) infants in DS group (no HR displayed three minutes following device application), and these were excluded from statistical analysis.

Table 3 – Results of the HR Assessment Study

Device	Median time from birth to Heart Rate (seconds)	Median time from device application to Heart Rate (seconds)	Failure to obtain heart rate, n (%)
Handheld Ultrasound	113.5	28	0 (0%)
Stethoscope	90	15	0 (0%)
	p=0.0007	p=0.002	
Digital Stethoscope	120	45	7 (35%)
Stethoscope	96	11	0 (0%)
	p=0.19	p=0.005	
Electrocardiography	98	13	0 (0%)
Stethoscope	85	13	0 (0%)
	p=0.002	p=0.74	

The mean difference between stethoscope and ECG in the HR recorded was -10 bpm (p=0.024), between stethoscope and HUS +5 bpm (p=0.4) and between stethoscope and DS +27 bpm (p=0.061).

8.2.4 Conclusions

ECG was the quickest method of obtaining HR in the delivery room in our study groups. DS was unreliable, often not displaying a HR. HUS is possibly more useful for assessing adequate cardiac contractility.

LETTER

Assessment of neonatal heart rate immediately after birth using digital stethoscope, handheld ultrasound and electrocardiography: an observational cohort study

The extent and initiation of cardiopulmonary resuscitation of neonates in the delivery room are largely guided by neonatal heart rate (HR), with current guidelines recommending the use of ECG for HR monitoring during resuscitation.[1–3] Our aim was to determine if handheld ultrasound (HUS) or digital stethoscope (DS) could offer a novel method of quickly and effectively assessing HR in the delivery suite.

Two physicians attended each delivery, one assessed the HR by stethoscope auscultation and the second assessed the HR using either HUS (Mortara, Signos RT Personal Ultrasound), DS (Littmann 3200, 3M, USA) or ECG (IntelliVue MP5, Philips, The Netherlands). The time to achieve first HR and the HR recorded were noted, then when both modalities were recording a simultaneous HR was recorded. Each physician was blinded to the others recording modality during assessment.

Sixty infants were recruited in total (20 in each modality group). There was no significant difference between group baseline characteristics (table 1). All infants had Apgar score ≥8 at 5 min of age. The median times from birth to first HR and from device application to first HR with each device are outlined in table 2.

The mean difference between stethoscope and ECG in the HR recorded was −10 beats per minute (bpm) (p=0.024), between stethoscope and HUS +5 bpm (p=0.4), and between stethoscope and DS +27 bpm (p=0.061).

We found that the DS used in our study was unreliable at measuring HR in the delivery room, frequently not displaying any HR or displaying an HR significantly lower than the auscultated HR. However, it should be highlighted that all infants assessed in our study were vigorous and often crying, which have been found previously to affect DS recording.[4]

It was noted that our ability to record HR on the HUS was limited by the fact that it is difficult to visually count contractions, especially at HR over 100 bpm. While an exact number of beats per minute was challenging to obtain, we could however appreciate cardiac contractility readily which would be valuable in neonatal resuscitation.

We conclude that ECG was the quickest method of recording HR in the delivery room compared with DS and HUS in our study. However, the traditional stethoscope remained the quickest method to obtain an HR when the time delay in applying ECG leads is taken into consideration.

Table 2 Time to achieve neonatal heart rate in delivery suite by various modalities

Device	Median time from birth to heart rate (IQR) (s)	Median time from device application to heart rate (IQR) (s)	Failure to obtain heart rate, n (%)
Handheld ultrasound	114 (94–120)	28 (17–43)	0 (0)
Stethoscope	90 (84–106)	15 (10–20)	0 (0)
	P=0.0007	P=0.002	
Digital stethoscope	120 (112–180)	45 (17–74)	7 (35)
Stethoscope	96 (86–110)	11 (8–15)	0 (0)
	P=0.19	P=0.005	
ECG	98 (90–111)	13 (10–17)	0 (0)
Stethoscope	85 (77–94)	13 (8–19)	0 (0)
	P=0.002	P=0.74	

Table 1 Infant characteristics

	ECG (n=20)	HUS (n=20)	DS (n=20)	All groups (n=60)	P values*
Birth weight in kg (mean±SD)	3.49±0.43	3.41±0.43	3.51±0.42	3.47±0.42	0.59
Gestation in weeks (mean±SD)	38.8±0.7	38.8±0.8	38.9±0.7	38.8±0.72	0.84

*Analysis of variance of between-group variation.
DS, digital stethoscope; HUS, handheld ultrasound.

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Contributors Project design: JS and RK conceptualised the idea for the project, and JS, RK, JM and BPT designed the study. Ethics proposal was submitted by JS, BPT, RK and JM. The mothers of the infants involved in the study were consented by NOC and BPT. Patient and staff information leaflets were produced and circulated by BPT. Data on the infants involved in the study were collected by BPT, NOC, JS, JM, AB and EC. This involved attending deliveries in advance, gathering data from patient charts, and recording the heart rate by stethoscope or relevant research device (ECG, handheld ultrasound or digital stethoscope). Data were analysed by JM and BPT. Drafting the article and critical revision of the article were carried out by BPT, JS and JM. Final approval of the version to be published was completed by all authors (BPT, JS, RK, EC, AB, NOC and JM).

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8.3 A Conservative Treatment of Patent Ductus Arteriosus in Very Low Birth Weight Infants

8.3.1 Background

Early studies have found an association between PDA and BPD (193), prolonged ventilation (194), mortality (195), PH (174), severe RDS (196), NEC (197), IVH (198) and death (199). A significant left to right shunt is believed to cause pulmonary over-circulation associated with respiratory complications, and systemic hypo-perfusion with resultant reduced cerebral and gut blood flow. Due to these associations, many neonatal units have pursued a policy of active medical and surgical treatment of patients in whom PDA is identified. The timing of the treatment remains controversial. There are numerous options from prophylactic treatment, early targeted treatment, late (symptomatic) treatment to no treatment at all. Three different approaches were used between 2004 and 2011 in CWIUH (level III neonatal centre). The aim of our retrospective study was to assess short term outcomes of infants treated conservatively (minimal medical and/or surgical treatment of the PDA) and compare these results to infants managed by early echocardiography targeted PDA treatment or managed by a symptomatic approach.

8.3.2 Materials and Methods

This was a single centre study carried out in the CWIUH, Dublin, Ireland. The study was a retrospective time series cohort of three groups of VLBW infants born between 2004 and 2011. Data were obtained by chart review and the study was approved by the hospital REC. We compared three different epochs of the PDA management:

Cohort 1 - Symptomatic Treatment Group (STG) - neonates hospitalized in the NICU between January 2004 and June 2006 were included. In this period only neonates with clinical signs of

PDA (continuous murmur, high volume pulses, hyperdynamic precordium, wide pulse pressure and respiratory deterioration) were echocardiographically evaluated by the attending cardiologist. The decision to treat (Ibuprofen) was based on the confirmation of haemodynamically significant PDA.

Cohort 2 - Early Treatment Group (ETG) - from November 2006 to September 2007 an early targeted echocardiography approach with possible treatment of PDA was used. Infants born in this period underwent echocardiographic evaluation within the first 48 hours of life. The echocardiographic study determined the presence, Doppler flow pattern and haemodynamic significance of the PDA. Infants with significant PDA received an early course of Ibuprofen. A PDA was considered significant if larger than 2 mm in diameter.

Cohort 3 - Conservative Treatment Group (CTG) - infants born between April 2010 and February 2011 were included. All infants <1500g born during this period were screened for the presence of PDA on day seven of life. There was a high threshold for a medical treatment of the PDA. Conservative management included high positive end expiratory pressure (PEEP) (at least 5cm H_2O) on either mechanical ventilation or nasal continuous positive airway pressure (NCPAP) support, and mild fluid restriction (130-150mls/kg/day). All infants with PDA were followed up with weekly echocardiography until the PDA closed.

The primary outcome of the study was a rate of PDA treatment in the three groups – medical treatment with Ibuprofen and surgical ligation. Secondary outcomes included mortality and the following morbidities: RDS, CLD (defined as oxygen dependency or ventilator support at 36 weeks of gestation), NEC requiring surgical intervention, IVH grade 3 or more and/or cystic PVL. We analysed the data using a PC-based statistics package (StatsDirect version 2.7.8) using the unpaired t-test, Mann–Whitney U test and Fisher exact test as appropriate, $p<0.05$ was considered significant.

8.3.3 Results

There were 230 VLBW infants admitted in the era of STG, of whom 52 patients (23%) were clinically identified having a PDA. There was 69 VLBW infants admitted in the era of ETG, 52 infants were diagnosed with a PDA. There was 72 VLBW infants admitted in the era of CTG of whom 70 neonates were screened on day 7 of life and 34 were diagnosed with a PDA. Only 15% of babies diagnosed with PDA in the CTG received medical treatment (Ibuprofen), a significantly lower proportion compared to other groups; STG 62% (p=0.0001) and ETG 48% (p=0.002). There was a statistically significant difference in the rate of surgical ligation in infants diagnosed with PDA; 0% in CTG vs. 21% in STG (p=0.003) and 19% in ETG (p=0.005) respectively. There was no difference in mortality between the three groups of infants diagnosed with PDA. There was a statistically significant difference in the incidence of CLD in survivors; CTG vs. STG, 18% vs. 51% (p=0.003) and in CTG vs. ETG; 18% vs. 46% (p=0.02). PDA was diagnosed earliest in ETG, followed by STG and CTG as expected. The rest of the short-term outcomes remained similar between the three groups. Overall medical treatment rate in the STG era was 14% vs. 36% in the ETG and 7% in the CTG, overall ligation rate in the STG era was 5% vs. 14% in the ETG and 0% in the CTG era.

8.3.4 Conclusions

In this study we have shown that conservative treatment of PDA in VLBW infants was a feasible option and future randomized trials of conservative management were warranted.

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A conservative treatment of patent ductus arteriosus in very low birth weight infants

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ABSTRACT

Background: Treatment of the patent ductus arteriosus (PDA) in the preterm infant remains contentious. There are numerous options of the PDA management from early targeted treatment, late (symptomatic) treatment to no treatment at all.
Aims: To evaluate a three different PDA management approaches in very low birth weight (VLBW) infants.
Study design: A retrospective observational time series study of three cohorts of VLBW infants born between 2004 and 2011.
Subjects: Infants in Symptomatic Treatment Group (STG) were echocardiographically evaluated when clinical signs suggestive of a PDA were present and treated if a haemodynamically significant PDA was confirmed. Early Targeted Group (ETG) underwent echocardiography within the first 48 h and infants received ibuprofen if a large PDA was present. Conservative Treatment Group (CTG) was screened by echocardiography on day seven of life; patients with PDA were managed with increased positive end expiratory pressure and fluid restriction as a first line intervention.
Outcomes: The primary outcome was medical and surgical treatment in the three time periods. Secondary outcomes included mortality, severe periventricular and intraventricular haemorrhage, respiratory distress syndrome and chronic lung disease.
Results: There were 138 infants diagnosed with PDA; 52 infants in STG, 52 infants in ETG and 34 infants in CTG. Ibuprofen therapy and ligation were less frequent in CTG. There was significantly decreased incidence of chronic lung disease in CTG compared to STG (18% vs. 51%; $p = 0.003$) and to ETG (18% vs. 46%; $p = 0.02$). There was no difference in the other short term outcomes.
Conclusion: Conservative treatment of persistent ductus arteriosus in VLBW infants is a feasible option and future randomized trials of conservative management are warranted.

1. Introduction

Early studies have found an association between patent ductus arteriosus (PDA) and brochopulmonary dysplasia (BPD) [1], prolonged ventilation [2], mortality [3], pulmonary haemorrhage [4], severe respiratory distress syndrome (RDS) [5], necrotizing enterocolitis (NEC) [6], intraventricular haemorrhage (IVH) [7] and death [8]. A significant left to right shunt is believed to cause pulmonary over-circulation associated with respiratory complications, and systemic hypo-perfusion with resultant reduced cerebral and gut blood flow. Due to these associations, many neonatal units have pursued a policy of active medical and surgical treatment of patients in whom PDA is identified. More than 30% of preterm infants born before 32 weeks have a PDA that fails to close after birth [9].

Medical treatment with either indomethacin or ibuprofen, and surgical closure with PDA ligation, has been the mainstay in the management of PDA. All these treatments have recognized complications and

Abbreviations: VLBW, very low birth weight; PDA, patent ductus arteriosus; STG, symptomatic treatment group; ETG, early treatment group; CTG, conservative treatment group; BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome; NEC, necrotising enterocolitis; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; NCPAP, nasal continuous positive airway pressure; cPVL, cystic periventricular leucomalacia.

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careful assessment of which babies may require treatment is vital. Ibuprofen has been associated with fewer side effects than indomethacin [10–11].

The timing of the treatment remains controversial. There are numerous options from prophylactic treatment, early targeted treatment, late (symptomatic) treatment to no treatment at all. A conservative approach to PDA management was shown to be feasible in a prospective study by Vanhaesebrouck et al. [12]. This included adjustment of ventilation parameters (inspiratory time as low as 0.35 s and PEEP as high as 4.5 mbar) and fluid restriction (130 ml/kg/day beyond day three) [12]. Following the diagnosis of a PDA the decision to treat has therefore become more problematic [13].

In our institution three different approaches were used between 2004 and 2011. The aim of our retrospective study was to assess short term outcomes of infants treated conservatively and compare these results to infants managed by early targeted echocardiography or managed by a symptomatic approach.

2. Methods

This was a single centre study carried out in the Coombe Women and Infants University Hospital, Dublin, Ireland, which is standalone maternity hospital with approximately 8500 deliveries a year and 120 infants below 1500 g admitted to neonatal intensive care unit (NICU). The study was a retrospective time series cohort of three groups of Very Low Birth Weight (VLBW) infants born between 2004 and 2011. Data were obtained by chart review and the study was approved by the hospital Research Ethics Committee.

All echocardiography studies were performed by Phillips HD11XE ultrasound machine with phased sector ultrasound transducers (S 12-4 and/or S 8-3) incorporating color flow, pulsed wave Doppler and continuous wave Doppler with adaptive Doppler technology. A complete two-dimensional echocardiography examination was performed and structural normality of the heart was established on the first measurement. Measurements done obligatory in all groups were diameter of the patent ductus arteriosus and assessment of the Doppler flow pattern. Baseline demographic data including antenatal steroids use, gestational age, birth weight, gender and Apgar scores were recorded.

2.1. Cohort 1 - Symptomatic Treatment Group (STG)

Neonates hospitalized in the NICU between January 2004 and June 2006 were included. In this period only neonates with clinical signs of PDA (continuous murmur, high volume pulses, hyperdynamic precordium, wide pulse pressure and respiratory deterioration) were echocardiographically evaluated by the attending cardiologist. The decision to treat (Ibuprofen) was based on the confirmation of haemodynamically significant PDA (based mainly on the signs of the left cardiac volume overload). Infants with persisting or new PDA related symptoms after the treatment had echocardiographic re-evaluation. PDA ligation was an option following failed medical treatment. All echocardiography studies in this group were done by a cardiologist who also contributed to the treatment decision.

2.2. Cohort 2 - Early Treatment Group (ETG)

From November 2006 to September 2007 early targeted echocardiography approach with possible treatment of PDA was used. Infants born in this period underwent echocardiographic evaluation within the first 48 h of life. The echocardiographic study determined the presence, Doppler flow pattern and haemodynamic significance of the PDA.

Infants with significant PDA received an early course of Ibuprofen (10 mg/kg intravenously followed by two further doses of 5 mg/kg every 24 h) within the first three to five days of life. A PDA was considered significant if larger than 2 mm in diameter on color flow Doppler with or without clinical PDA related symptoms. PDA ligation was considered following failed medical treatment. All early targeted studies in this cohort were done by a neonatologist trained in functional echocardiography and were consulted with a cardiologist if required. Re-evaluations were done by the attending cardiologist.

2.3. Cohort 3 - Conservative Treatment Group (CTG)

Infants born between April 2010 and February 2011 were included. All infants < 1500 g born during this period were screened for the presence of PDA on day seven of life. There was a high threshold for a medical treatment of the PDA. Conservative management included high positive end expiratory pressure (PEEP) (at least 5 cm H_2O) on either mechanical ventilation or nasal continuous positive airway pressure (NCPAP) support, and mild fluid restriction (130–150 mls/kg/day). Any medical treatment (Ibuprofen) was discussed and if initiated, effect of the treatment was evaluated after each dose. All infants with PDA were followed up with weekly echocardiography until the PDA closed. Neonatologists trained in functional echocardiography did all initial studies and also follow up studies. If there were signs of a haemodynamically significant PDA (diameter >2 mm, increased left atrium to aorta ratio > 1.5 and evidence of reduced splanchnic Doppler flow), a cardiology opinion was obtained.

The primary outcome of the study was a rate of PDA treatment in the three groups – medical treatment with Ibuprofen and surgical ligation. Secondary outcomes included mortality and the following morbidities: RDS, chronic lung disease (CLD) (defined as oxygen dependency or ventilator support at 36 weeks of gestation), NEC requiring surgical intervention, IVH grade III or more and/or cystic periventricular leukomalacia (cPVL). We analyzed the data using a PC-based statistics package (StatsDirect version 2.7.8) using unpaired *t*-test, Mann–Whitney *U* test and Fisher exact test as appropriate, $p < 0.05$ was considered significant.

3. Results

There were 230 VLBW infants admitted in the era of STG, of whom 52 patients (23%) were clinically identified having a PDA. There was 69 VLBW infants admitted in the era of ETG, 52 infants were diagnosed with a PDA. There was 72 VLBW infants admitted in the era of CTG of whom 70 neonates were screened on day seven of life and 34 were diagnosed with a PDA (Fig. 1). There was no statistical difference in the mean gestational age, birth weight and Apgar scores between the three cohorts. The usage of antenatal steroids was statistically significantly lower in STG compared to ETG group. There was significantly less males in ETG compared to STG; 29% vs. 50% ($p = 0.04$). A significant proportion of babies in the CTG had a PDA with a diameter >2 mm at the time of diagnosis (Table 1).

Only 15% of babies diagnosed with PDA in the CTG received medical treatment (Ibuprofen), a significantly lower proportion compared to other groups; STG 62% ($p = 0.0001$) and ETG 48% ($p = 0.002$). There was a statistically significant difference in the rate of surgical ligation in infants diagnosed with PDA; 0% in CTG vs. 21% in STG ($p = 0.003$) and 19% in ETG ($p = 0.005$) respectively. There was no difference in mortality between the three groups of infants diagnosed with PDA. There was a statistically significant difference in the incidence of chronic lung disease in survivors; CTG vs. STG, 18% vs. 51% ($p = 0.003$) and in CTG vs. ETG; 18% vs. 46% ($p = 0.02$). PDA was diagnosed earliest in ETG, followed by STG and CTG as expected (Table 2). The rest of the short term outcomes remained similar between the three groups (Table 2).

All infants except one (who subsequently demonstrated spontaneous closure within three months post discharge) in CTG were discharged home with closed PDA. The short term or long term side effects of the medical treatment were not evaluated. Overall medical treatment and overall ligation rate were lowest in the CTG group (Table 3).

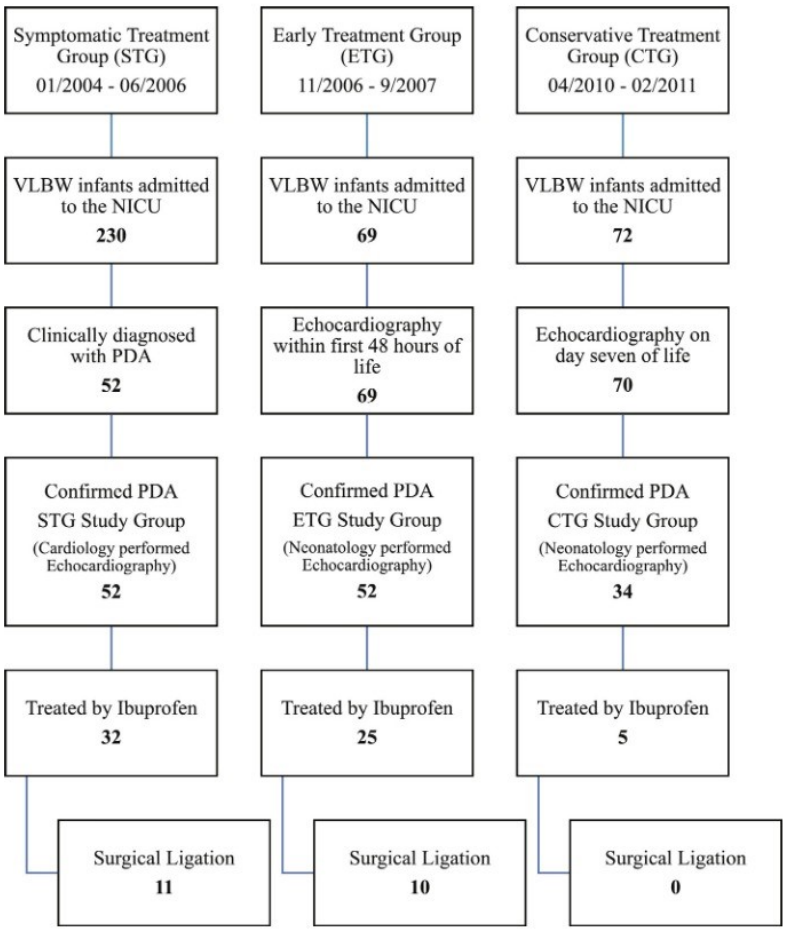

Fig. 1. Overall number of very low birth weight (VLBW) infants admitted to Neonatal intensive care unit (NICU) in the three time periods, infants diagnosed with patent ductus arteriosus (PDA) with subsequent medical and/or surgical treatment (flow chart of the study).

Table 1
Demographic parameters of VLBW infants diagnosed with PDA.

	Symptomatic treatment group	Early treatment group	Conservative treatment group	p values
Number of patients	52	52	34	
Gestational age (weeks) mean (±SD)	27.5 (±1.9)	27.9 (±2.0)	27.4 (±2.7)	NS
Birth weight (kg) mean (±SD)	1.01 (±0.28)	1.04 (±0.27)	1.01 (±0.25)	NS
Male (%)	50[1,3]	29[2,3]	47[1,2]	$p = 0.83^1$ $p = 0.11^2$ **$p = 0.04^3$**
Antenatal steroids (%)	71[1,3]	96[2,3]	88[1,2]	$p = 0.11^1$ $p = 0.20^2$ **$p = 0.0009^3$**
Apgar score 1st min – median (range)	7 (2 to 9)[1,3]	6 (1 to 9)[2,3]	6 (1 to 9)[1,2]	$p = 0.13^1$ $p = 0.88^2$ $p = 0.07^3$
Apgar score 5th min – median (range)	8 (2 to 10)[1,3]	9 (3 to 10)[2,3]	9 (3 to 10)[1,2]	$p = 0.32^1$ $p = 0.48^2$ $p = 0.88^3$
PDA > 2 mm at the time of diagnosis (%)	38[1,3]	40[2,3]	62[1,2]	**$p = 0.047^1$** $p = 0.077^2$ $p > 0.99^3$

Bold values indicate significance at $p < 0.05$.

Table 2
Short term outcomes of infants diagnosed with PDA.

	Symptomatic treatment group (n = 52)	Early treatment group (n = 52)	Conservative treatment group (n = 34)	p values
Day of life of PDA diagnosis – median (range)	3 (1–21)[1,3]	2 (1–7)[2,3]	7*[1,2]	**p < 0.0001[1]** **p < 0.0001[2]** **p = 0.0002[3]**
Ibuprofen treatment (%)	62[1,3]	48[2,3]	15[1,2]	**p < 0.0001[1]** **p = 0.002[2]** p = 0.24[3]
PDA ligation (%)	21[1,3]	19[2,3]	0[1,2]	**p = 0.003[1]** **p = 0.005[2]** p > 0.99[3]
Respiratory distress syndrome (%)	94	96	100	NS
CLD (36/40) survivors (%)	51[1,3]	46[2,3]	18[1,2]	**p = 0.003[1]** **p = 0.02[2]** p = 0.69[3]
Surgical NEC (%)	7.7	7.7	6	NS
IVH grade III–IV/cPVL (%)	15	12	9	NS
Survival (%)	98	92	97	NS

* All infants diagnosed on day 7 of life.

4. Discussion

These three eras describe the natural history of the PDA in VLBW infants. Screening all VLBW infants in the first 48 h shows that approximately 75% of all VLBW infants have a PDA on echocardiography, reducing to <50% by one week of life. These findings would be in agreement with the previous report documenting spontaneous closure of PDA in 44% of infants below 32 weeks of gestation before day seven of life [14]. This spontaneous closure rate is probably lower in extremely low birth weight infants (34%) [15] and also in extremely low gestational age newborns (24%) [16]. There is little published information on very low birth weight infants presenting with clinically symptomatic PDA. In our STG, 23% (52 out of 230 live born infants) presented with presumed clinical signs of a PDA, but in whom <40% had a PDA > 2 mm on color flow Doppler, suggestive of a haemodynamically significant ductus. On weekly echocardiography follow up in CTG we documented PDA closure in all babies except three before day 70 of life (Fig. 2). Only one patient was discharged home with PDA and the closure was documented echocardiographically at three month post discharge. This could be an observation of natural course of the PDA and the conservative measures described previously might prevent progression of a ductus to haemodynamically and clinically significant shunting. However this does not represent solely spontaneous closure as Ibuprofen was used in some newborns in the CTG.

It is not surprising that in our study infants diagnosed with PDA in STG received most proactive treatment from the three groups as these infants were already showing clinical signs of a symptomatic PDA. However there was no significant difference to ETG in terms of treating the diagnosed PDA. CTG infants received significantly less Ibuprofen therapy and ligation (in fact there was no ligation in CTG group). Infants diagnosed with PDA in the CTG did have better outcome for chronic lung disease (oxygen requirement and/or respiratory support at 36 weeks postmenstrual age) compared to the treatment groups, despite this group having a higher proportion of babies with PDA >2 mm in diameter at the time of diagnosis. We speculate this could be partially due to less aggressive treatment of PDA, less ibuprofen therapy and less surgical ligation. The other observed short term outcomes did not significantly differ between the groups.

There are some potential benefits of early treatment with cyclooxygenase inhibitors which represent rationale for ETG management. Prophylactic administration of indomethacin reduces the incidence of patent ductus arteriosus, severe intraventricular haemorrhage, severe early pulmonary haemorrhage and the need for surgical ligation; however it did not improve the rate of survival without neurosensory impairment at 18 months of age [17–18]. Prophylactic and also early targeted indomethacin can reduce risk of severe pulmonary haemorrhage and potentially improve outcome at 18 months of age [19–20].

Unfortunately, most PDA treatment information from randomized controlled trials is related to the PDA closure and timing of the treatment and do not address the key question of whether a PDA should be treated in neonatal period at all [21]. Recent meta-analyses did not find any significant long term benefit of any particular approach to the treatment of PDA [22–23]. Medical and surgical therapy has also well recognized adverse effects. PDA ligation has been associated with CLD and poor neurodevelopmental outcome [24–26]. An increased risk of

Table 3
Overall medical and surgical treatment in the three time eras.

	Symptomatic treatment group era (n = 230)	Early treatment group era (n = 69)	Conservative treatment group era (n = 72)	p values
Ibuprofen treatment (%)	14[1,3]	36[2,3]	7[1,2]	p = 0.15[1] **p < 0.0001[2]** **p < 0.0001[3]**
PDA ligation (%)	5[1,3]	14[2,3]	0[1,2]	p = 0.07[1] **p = 0.0006[2]** **p = 0.01[3]**

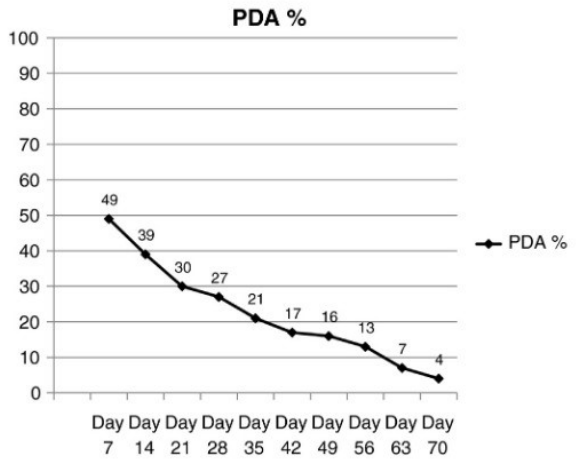

Fig. 2. Percentage of very low birth weight (VLBW) infants with the patent ductus arteriosus (PDA) in the conservative treatment group (CTG) in the first 70 days of life (screened on day seven of life, n = 70).

pulmonary hypertension, increased incidence of NEC and higher risk of CLD has been linked with ibuprofen [27–28]. Ibuprofen is widely used for PDA treatment as it is associated with lower risk of oliguria compared to indomethacin [11]. Therefore, conservative approach to PDA seems to be one of the options.

We acknowledge many obvious limitations to our retrospective cohort study. The results may be influenced by overall improvement in neonatal intensive care management over the years. This included mainly introduction of non-invasive ventilation as a primary ventilation mode even for the most immature infants, adoption of the minimal ventilation strategy, mild changes in fluid and nutrition management - lower initial daily fluid volumes and increase in protein and calories intake. These changes occurred mainly before year 2006, therefore the differences in overall management were probably minimal between ETG and CTG. Also the obstetricians' approach changed gradually over the years towards being more proactive. The use of antenatal steroids was indeed lowest in the most historical group (STG) and this can have negative effect on some of the short term outcomes; mortality, RDS, IVH, NEC [29]. However this should not influence chronic lung disease rate in survivors [30].

We did have a relatively small number of subjects in our study, although we included all patients admitted in the three periods diagnosed with PDA. There was also possible selection bias in the STG and CTG as these groups potentially missed early neonatal deaths occurring prior to PDA diagnosis. This could be reflected in non-significant difference in overall mortality among the groups (8% in ETG vs. 2% in STG and 3% in CTG). However, there was only one neonatal death before day 7 of life in CTG group which occurred within two hours post delivery secondary to fulminant early onset sepsis. There were no deaths prior to PDA screening documented in ETG. Since only 23% of infants in STG had echocardiography performed it is difficult to calculate deaths occurring prior to PDA diagnosis. However, median time of the PDA diagnosis was 3 days. There were 10 deaths identified within the first three days of life in 230 infants born in the STG era. Another potential bias was in STG as the initial diagnosis was made clinically with subsequent cardiology evaluation with possibility of missing infants with small, non-significant PDAs. The diagnostic criteria were not uniform among the cohorts and neither were the decision to treat criteria. In STG, the presumed clinical signs of PDA probably contributed significantly to the treatment decision since only 38% of infants had PDA larger than 2 mm on echocardiogram and 62% were treated. In the CTG era, the situation was completely different with 62% of infants having PDA larger than 2 mm and 15% treated. The PDA significance echocardiographic markers also differed among the groups and the individual management decisions are difficult to trace retrospectively.

We conclude that conservative treatment of a PDA in VLBW infants seems to be a feasible approach to PDA management. Future randomized controlled trials are warranted comparing conservative management to other approaches, with consideration not only of short term outcome measures but also long term neurodevelopmental outcome.

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Conflicts of interest

None declared.

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8.4 Spontaneous Closure of Patent Ductus Arteriosus in Infants ≤1500 g

8.4.1 Background

PDA remains a challenging issue in VLBW infants and its management varies widely. The aim of this study was to document the 'natural' course of DA in a cohort of VLBW infants who underwent conservative PDA management with no medical or surgical intervention and was a logical following of the previous study where we documented feasibility of conservative approach to PDA treatment.

8.4.2 Materials and Methods

We have retrospectively analysed data from a routine serial targeted echocardiography follow-up of VLBW infants admitted to two level three neonatal intensive care units, the Institute for the Care of Mother and Child, Prague, Czech Republic, and the CWIUH, Dublin, Ireland. A PDA targeted point-of-care echocardiography follow-up had been in place in both units prior to the start of the data collection. Data from the period of February 2012 - June 2013 in Prague and June 2013 – June 2014 in Dublin were analysed. The respective RECs approved the use of the data in each institution. Participating units have similar policies and philosophy with regards to ventilation, nutrition, hemodynamic management and indications for discharge. The units also share the same conservative approach to PDA with a very high threshold for treatment. All VLBW infants without congenital malformations or chromosomal anomalies were eligible. Infants with congenital heart disease other than PDA and/or PFO were excluded as well as infants with acquired heart disease not related to PDA (infectious endocarditis, myocardial infarction, twin-to-twin transfusion syndrome) and infants with incomplete inpatient follow up. Infants who died during the study period were excluded from the primary analysis. Demographic information was collected for every infant: gestation at birth, birth

weight, sex, antenatal steroid exposure, multiple gestation and documented intrauterine growth restriction (birth weight <10th percentile). Clinical outcome data included survival to discharge, PDA medical treatment, surgical ligation or catheter device closure, BPD defined as oxygen requirement at 36 weeks postmenstrual age, IVH grade 3 and 4, PVL, NEC grade ≥IIb, ROP stage ≥3. The diagnoses were defined according to the VON.(200) The data was gathered up to 12 months of age, sourced from the infant's general practitioner and/or cardiologist. The primary outcome was to document the time of the closure or permanent patency of the DA in a large cohort of VLBW infants who did not receive medical or surgical treatment and therefore document the 'natural history' of PDA. The secondary outcome was to compare the demographics and the outcomes of infants who achieved spontaneous PDA closure during the hospital stay to those who did not. Data were analysed using Mann-Whitney, Chi-Square or Fisher's Exact test as appropriate. The incidence proportion of ductal patency was analysed with the Kaplan-Meier model for different gestational age and weight groups. Bonferroni correction was used for multiple comparisons among the groups. We used forward stepwise Cox regression to examine variables predictive of PDA patency. Cox regression is a method for investigating the effect of several variables upon the time a specified event takes to happen (PDA patency at the discharge from the hospital in our study). Hazard ratio yielded from Cox regression is then expressing the ratio of hazard (probability) rates that are one unit apart (e.g. one gestational week). Infants who received medical or surgical treatment were not included in the Kaplan-Meier model or in the regression analysis. Statistical analysis was executed using the IBM SPSS Statistics 24.0.0.0 software (IBM Corp., Armonk, NY).

8.4.3 Results

Two hundred and eighty infants received truly conservative PDA management. In 237 (85%) of non-treated infants, PDA closed prior to hospital discharge. Forward stepwise Cox

regression revealed that the gestational age was the strongest predictor of ductus closure (P<0.0001, Hazard Ratio 1.28, 95%CI 1.20 – 1.36). The Kaplan-Meier model was used to document the incidence proportion of PDA closure over time for different gestational age groups – median time to ductal closure (95%CI) was: 71 (51-91); 13 (0-34); 8 (7-9); 6 (4-8) days in <26+0; 26+0-27+6; 28+0-29+6; >30 weeks respectively (Figure 11) and birth weight groups - median (95%CI): 48 (9-87); 22 (6-38); 9 (6-12); 8 (7-9) days in <750; 750-999; 1000-1249; 1250-1500g respectively (Figure 12). No statistically significant relationship was found between PDA closure prior to discharge and neonatal morbidities.

8.4.4 Conclusions

The likelihood of PDA spontaneous closure in VLBW infants is extremely high. These findings provide a platform for future placebo-controlled trials focused on the smallest and youngest infants.

Figure 11 - Prevalence of ductal patency stratified by birth weight over time prior to discharge. Horizontal line: 50% closure. + Censored cases, discharged before closure.

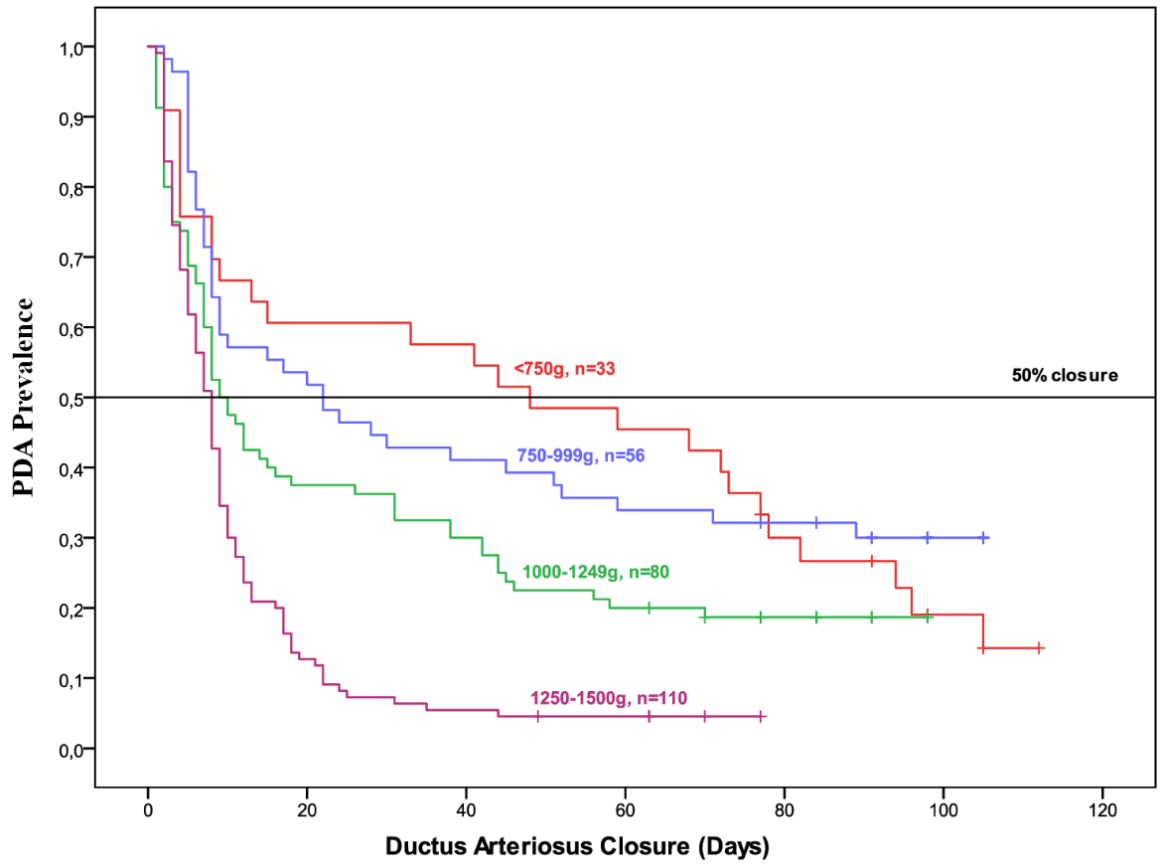
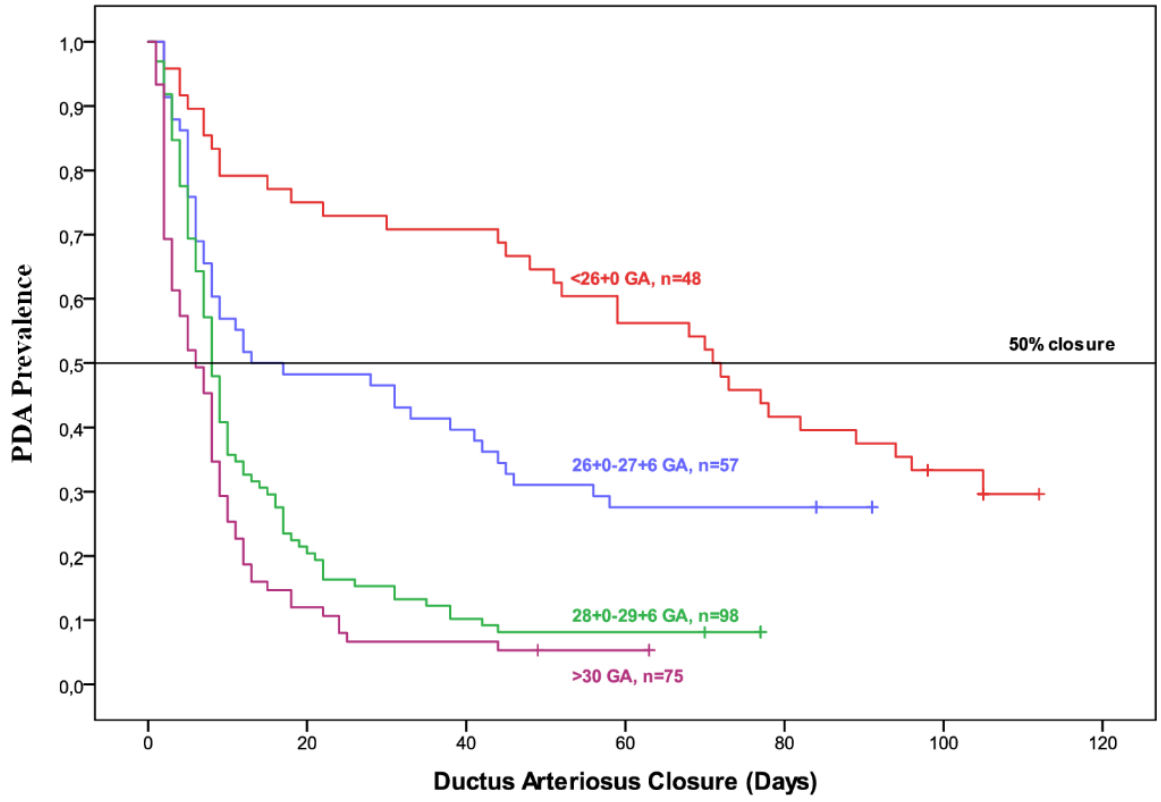


Figure 12 - Prevalence of ductal patency stratified by gestational age over time prior to discharge. Horizontal line: 50% closure. + Censored cases, discharged before closure. GA, gestational age.



Spontaneous Closure of Patent Ductus Arteriosus in Infants ≤1500 g

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abstract

OBJECTIVES: Patent ductus arteriosus (PDA) remains a challenging issue in very low birth weight (VLBW) infants, and its management varies widely. Our aim in this study was to document the natural course of ductus arteriosus in a cohort of VLBW infants who underwent conservative PDA management with no medical or surgical intervention.

METHODS: A retrospective cohort study conducted in 2 European level-3 neonatal units.

RESULTS: A total of 368 VLBW infants were born within the study period. Two hundred and ninety-seven infants were free of congenital malformations or heart defects and survived to hospital discharge. Out of those, 280 infants received truly conservative PDA management. In 237 (85%) of nontreated infants, the PDA closed before hospital discharge. The Kaplan-Meier model was used to document the incidence proportion of PDA closure over time for different gestational age groups. The median time to ductal closure was 71, 13, 8, and 6 days in <26+0, 26+0 to 27+6, 28+0 to 29+6, and ≥30 weeks, respectively. For different birth weight groups, the median was 48, 22, 9, and 8 days in infants weighing <750, 750 to 999, 1000 to 1249, and 1250 to 1500 g, respectively. No statistically significant relationship was found between PDA closure before hospital discharge and neonatal morbidities.

CONCLUSIONS: The likelihood of PDA spontaneous closure in VLBW infants is extremely high. We provide in our findings a platform for future placebo-controlled trials focused on the smallest and youngest infants.

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Dr Semberova designed the study, contributed substantially to the echocardiography, demographic, and outcome data acquisition and analysis, and drafted the initial manuscript; Dr Sirc designed the study, contributed substantially to the echocardiography, demographic, and outcome data acquisition and analysis, and reviewed and revised the manuscript; Dr Miletin conceptualized and designed the study, contributed to data collection and analysis, and reviewed and revised the manuscript critically for important intellectual content; Dr Kucera contributed substantially to the study concept and design and echocardiography data acquisition and analysis, and reviewed and revised the manuscript critically for important intellectual content; Drs Berka and Sebkova contributed substantially to the echocardiography and demographic data acquisition and critically reviewed and revised the manuscript; Dr O'Sullivan contributed substantially to the demographic and outcome data collection (particularly the postdischarge outcomes) and analysis and reviewed the manuscript; Dr Franklin contributed substantially to the study design, supervised the echocardiography data collection, and reviewed and revised the manuscript; Dr Stranak supervised the conduct of the study, contributed substantially to the study design, coordinated the data analysis, and reviewed and revised the manuscript critically for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: The management of patent ductus arteriosus in very low birth weight infants remains controversial. Spontaneous closure occurs frequently, and therefore many infants might receive unnecessary treatment. Data from small cohort studies suggest that noninterventional management is a feasible option.

WHAT THIS STUDY ADDS: Spontaneous closure of ductus arteriosus is extremely prevalent in very low birth weight infants. Infants born before 26 weeks and <750 g have significantly higher rates of patent ductus arteriosus at hospital discharge. Future studies should focus on this population.

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Patent ductus arteriosus (PDA) is a common issue in preterm neonates. It has been associated with an increased risk of short- and long-term complications, mainly bronchopulmonary dysplasia (BPD), chronic lung disease (CLD), and necrotizing enterocolitis (NEC).[1] However, the causality of this relationship has never been established.[2] Practices in PDA management vary greatly among institutions,[3] ranging widely from universal prophylactic treatment through selective treatment on the basis of different criteria to no treatment at all.

Despite the physiologic plausibility of PDA adverse effects (such as pulmonary overcirculation and systemic hypoperfusion), researchers on PDA medical treatment have failed to show a significant decrease in PDA-associated complications or any long-term benefit apart from the PDA closure itself.[4–6] The only beneficial treatment strategy seems to be prophylactic indomethacin, which decreases the rate of intraventricular hemorrhage (IVH) and severe early pulmonary hemorrhage, although this also has not translated into the improvement of long-term outcomes.[7,8] Such an approach exposes a large number of infants to unnecessary medication and carries the risk of adverse effects, especially if given together with steroids.[9–11] Surgical PDA ligation does not carry any long-term benefits either,[2] and it has been associated with adverse outcomes.[12,13] Early targeted treatment according to echocardiographic criteria within the first hours of life seems to be a promising approach. This method reduces pulmonary hemorrhages and trends toward IVH reduction without exposing the entire population to the treatment.[14]

Evidence exists that some infants might theoretically benefit from PDA closure[14]; however, the indication and mode of such treatment is uncertain at the moment. Also, spontaneous PDA closure occurs in a significant number of premature infants.[15,16] Therefore, a noninterventional, conservative approach to PDA management seems to be one of the options.[17,18] Until further evidence for treatment type, timing, and initiation criteria is available, we have adopted such an approach with a high threshold for any type of treatment and regular point-of-care echocardiography (ECHO) follow-up.

Our aim is to present the data on the "natural" course of PDA before hospital discharge in a large retrospective cohort of very low birth weight (VLBW) infants with a birth weight (BW) ≤1500 g who underwent conservative PDA management. A secondary outcome of this study is the comparison of selected neonatal morbidities between patients with closed and permanent PDA.

METHODS

Study Design

We have retrospectively analyzed data from a routine serial-targeted ECHO follow-up of VLBW infants admitted to 2 European level-3 NICUs: the Institute for the Care of Mother and Child, Prague, Czech Republic (center 1), and the Coombe Women and Infants University Hospital, Dublin, Ireland (center 2). PDA-targeted point-of-care ECHO follow-up had been in place in both units before the start of the data collection. Data from the period of February 2012–June 2013 in center 1 and June 2013–June 2014 in center 2 were analyzed. The respective research ethics committees approved the use of the data in each institution. Informed consent was not required because of the retrospective nature of the study.

Participating units have similar policies and philosophies with regards to ventilation, nutrition, hemodynamic management, and indications for hospital discharge. The units also share the same conservative approach to PDA, with a high threshold for treatment.

All VLBW infants without congenital malformations or chromosomal anomalies were eligible. Infants with congenital heart disease other than PDA and/or patent foramen ovale were excluded, as well as infants with acquired heart disease not related to PDA (such as infectious endocarditis, myocardial infarction, and twin-to-twin transfusion syndrome) and infants with incomplete inpatient follow-up. Infants who died during the study period were excluded from the primary analysis.

Functional ECHO and PDA Treatment

Targeted ECHO was performed within the first week of life followed by serial examinations in 1 to 2 weekly intervals until documented ductal closure or hospital discharge. All the clinicians performing the point-of-care ECHO assessment underwent appropriate training and were experienced with the technique. In both centers, the ultrasound assessment was performed by using a Phillips CX50 Ultrasound System with S8-3 broadband sector array or S12-4 sector array transducer (Phillips, Andover, MA).

The first ECHO examination focused not only on the ductal parameters but also on the heart anatomy. Follow-up scans were focused mainly on the PDA presence and the parameters of ductal significance, which included diameter, flow pattern, maximum and minimum flow velocities, left atrium-to-aorta ratio, presence of mitral insufficiency, flow in the abdominal aorta or celiac artery, and end-diastolic flow in the left pulmonary artery.[19,20] Ductal closure was defined as an absence of identifiable flow in the ductus arteriosus (DA) by using color Doppler. DA closure was always reaffirmed after 2 weeks. All

of the parameters were recorded into the infant's documentation and were available for clinical decisions. For the purpose of this article, only the information on ductal patency was used.

The decision to treat and the mode of therapy remained at the discretion of the attending physician and were based on the clinical and echocardiographic features attributable to the PDA.

Data Collection

The following demographic information was collected for every infant: gestation at birth, BW, sex, antenatal steroid (ANS) exposure, multiple gestation, and documented intrauterine growth restriction (IUGR) (BW <10th percentile). Clinical outcome data included survival to hospital discharge, PDA medical treatment, surgical ligation or catheter device closure, BPD (defined as oxygen requirement at 36 weeks postmenstrual age), IVH grades III and IV, periventricular leucomalacia (PVL), NEC grades ≥IIb, and retinopathy of prematurity (ROP) stages ≥III. The diagnoses were defined according to the Vermont Oxford Network.[21] The definition of early- and late-onset sepsis was based on the criteria proposed by Chiesa et al,[22] which is that neonates with positive blood culture results and clinical signs of infection, and/or neonates with negative blood culture results, clinical signs of infection, and a positive laboratory sepsis screen were considered as having sepsis.

Clinical data on infants discharged from the hospital with an open PDA focused on further management, which included ligation, device closure, and a follow-up plan. The data were gathered up to 12 months of age and sourced from the infant's general practitioner and/or cardiologist.

Outcomes

The primary outcome was the documentation of the time of the closure or permanent patency of the PDA in a large cohort of VLBW infants who did not receive medical or surgical treatment and therefore document the "natural history" of PDA. The secondary outcome was the comparison of the demographics and the outcomes of infants who achieved spontaneous PDA closure during the hospital stay with those who did not.

Statistical Analysis

Data were analyzed by using a Mann–Whitney *U* test, a χ^2, or a Fisher's exact test as appropriate. The incidence proportion of ductal patency was analyzed with the Kaplan-Meier model for different gestational age (GA) and weight groups. The Bonferroni correction was used for multiple comparisons among the groups. We used forward stepwise Cox regression to examine variables predictive of PDA patency; the tested variables were GA, BW, sex, multiple pregnancy, ANS, and IUGR. Cox regression is a method for investigating the effect of several variables on the time it takes for a specified event to happen (in our study, PDA patency at discharge from the hospital). The hazard ratio yielded from Cox regression is then expressing the ratio of hazard (probability) rates that are 1 U apart (eg, 1 gestational week). Infants who received medical or surgical treatment were not included in the Kaplan-Meier model or in the regression analysis. Statistical analysis was executed by using the IBM SPSS Statistics 24.0.0.0 software (IBM Corp, Armonk, NY).

RESULTS

In total, 368 VLBW infants were born within the study periods; 242 in center 1 and 126 in center 2. Seventy-one infants were excluded (Fig 1). Data on 297 VLBW infants (study group) were eligible for analysis. The mean weight and GA in the study group were 1112 ± 269 g and 29 ± 2 weeks, respectively. Forty-eight percent were boys, 42% were from multiple pregnancies, 17% were small for GA, and 89% were partially or fully exposed to ANSs.

PDA-Treated Patients

Out of the 297 infants in the study group, 17 infants received PDA treatment, 14 received medical treatment, 1 had PDA ligation performed later, and 3 additional infants were selected for PDA ligation without previous medical therapy. PDA closed in 6 infants receiving medical treatment, but remained open in another 7 infants.

Conservative PDA Management

Two hundred and eighty infants continued to be managed in a truly conservative manner. In 237 (85%) of them, PDA closed before hospital discharge. The Kaplan-Meier model revealed the incidence proportion of PDA closure over time for different GAs. For this group, the median (95% confidence interval [CI]) was 71 (51–91) days in <26+0 GA, 13 (0–34) days in 26+0 to 27+6 GA, 8 (7–9) days in 28+0 to 29+6 GA, and 6 (4–8) days in ≥30 GA. For BW groups, the median (95% CI) was 48 (9–87) days in <750 g; 22 (6–38) days in 750 to 999 g; 9 (6–12) days in 1000 to 1249 g; and 8 (7–9) days in 1250 to 1500 g (Figs 2 and 3). A statistically significant difference was found between the medians of ductal closure among infants born <27+6 and >28+0 GA and among infants <1250 g and >1250 g (Table 1).

Forward stepwise Cox regression revealed that the GA was the only significant predictor of ductus closure ($P < .0001$, hazard ratio 1.28, 95% CI 1.20–1.36) when all variables in the model were used. However, because GA and BW were significantly correlating and collinear ($r^2 = 0.54$, $P < .0001$), we tested

for GA and BW separately with the following additional tested variables: sex, multiple pregnancy, ANSs, and IUGR. Without including GA, BW became a statistically significant predictor of the ductus closure ($P < .0001$, hazard ratio 1.002, 95% CI 1.001–1.002). In the model excluding the BW, GA was the only statistically significant predictor of the ductus closure ($P < .0001$, hazard ratio 1.29, 95% CI 1.21–1.38), as expected. Sex, multiple pregnancy, ANSs, and IUGR were not statistically significant predictors in either model.

Comparison of Infants With Closed and Open PDA at Hospital Discharge

In conducting the univariate analysis, we found no statistically significant difference in severe neonatal morbidities (BPD, IVH grades III and IV, PVL, NEC grades ≥IIb, and ROP stages ≥III) between the infants who achieved spontaneous PDA closure and those whose PDA remained open in the truly conservative group (Table 2).

However, when infants who underwent treatment were included in the comparison, a statistically significant difference was found not only between the GA and the BW but also in the incidence of severe IVH: 2 (1%) infants in the PDA closure group vs 4 infants (8%) in the PDA nonclosure group ($P = .008$).

Follow-up After Hospital Discharge

Spontaneous PDA closure occurred in 24 (56%) out of 43 patients discharged from the hospital with ductus patency without previous medical treatment. Six patients were lost to outpatient follow-up. We cross-checked data for these 6 patients with the only cardiothoracic or cardiac center in each country (Our Ladies Children's Hospital, Crumlin, Dublin, Ireland, and University Hospital Motol, Prague, Czech Republic), and none of them underwent surgical intervention or presented with

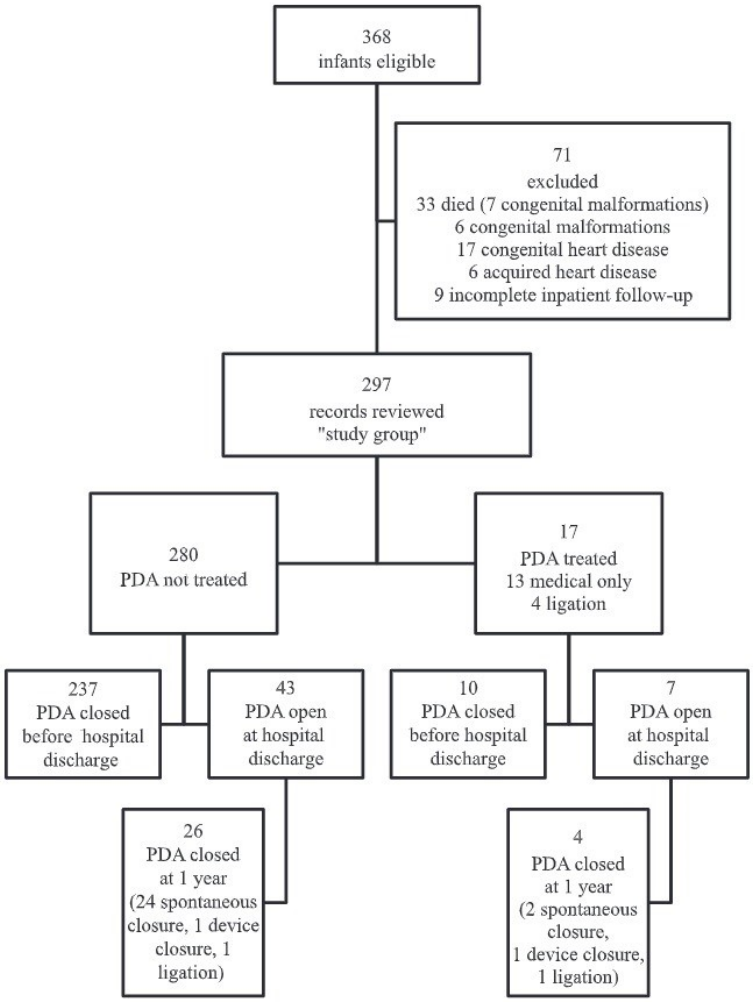

FIGURE 1
Overall number of eligible infants identified with subsequent flowchart of the study.

cardiac failure. Only 2 infants underwent artificial postdischarge closure, 1 by surgical ligation and 1 by percutaneous catheter device closure. In 11 infants, PDA remained open but nonsignificant 1 year after hospital discharge. Seven infants were discharged from the hospital with open PDA after failed medical treatment. Out of those, 2 experienced spontaneous postdischarge closure, 1 underwent surgical ligation, and 1 underwent percutaneous catheter device closure; PDA remained open in 3 of them after 1 year postdischarge. Overall, PDA was closed in 261 infants (93%) at the age of 12 months.

Neonatal Mortality

The overall mortality among infants eligible for the study was 9% (33 out of 368). Seven patients died because of serious congenital malformations. Twenty-six remaining infants died before hospital discharge; 19 died within the first 7 days, and 7 died later. The mean weight and GA were significantly lower than the study

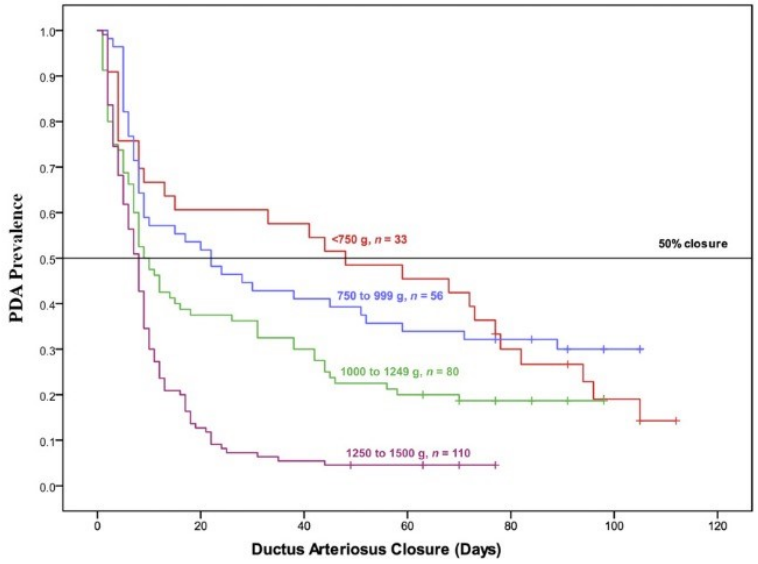

FIGURE 2
Prevalence of ductal patency stratified by BW over time before hospital discharge. The horizontal line represents 50% closure. The plus sign signifies censored patients who were discharged from the hospital before closure.

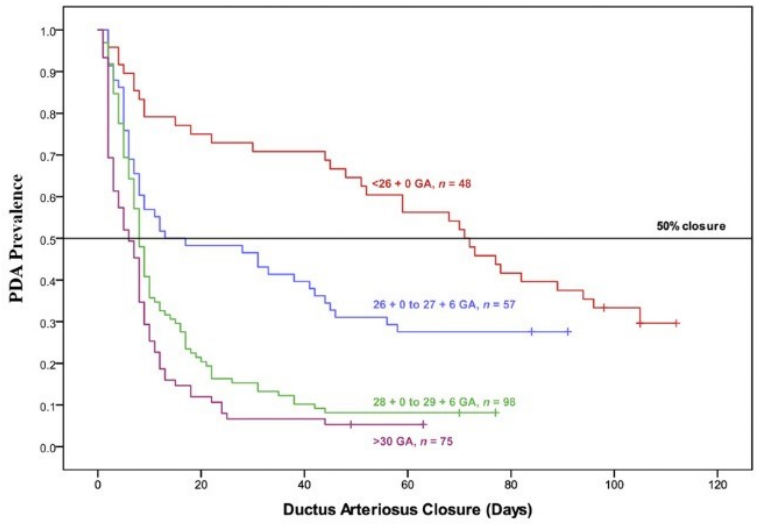

FIGURE 3
Prevalence of ductal patency stratified by GA over time before hospital discharge. The horizontal line represents 50% closure. The plus sign signifies censored patients who were discharged from the hospital before closure.

group (789 ± 256 g and 25.5 ± 2 weeks, respectively, $P < .0001$). The incidence of IVH and NEC was also significantly higher in comparison with survivors (52% vs 2% and 26% vs 1%, respectively, $P < .0001$). However, the main cause of death was early- or late-onset infection in 10 infants followed by severe IVH (which influenced further management of already critically ill infants) in 7 patients and NEC in 5 patients. Pulmonary hemorrhage occurred in 4 infants, and in 1 infant it was stated to be the main cause of death. Ten out of 19 infants who died before 7 days of age had a point-of-care ECHO done, and all of them had documented PDA. None of them was medically treated. Out of 7 infants who died after day 7, 3 of them had NEC stated as the cause of death. Six out of these 7 infants died with open PDA, and 2 of them were previously medically treated for the same without any positive result.

The overall results of the infants eligible for the study in comparison with the data from the Vermont Oxford Network are available in Table 3.

DISCUSSION

The data represent the true "natural history" of PDA derived from a robust retrospective cohort of VLBW infants who underwent noninterventional, conservative management. The likelihood of spontaneous closure before hospital discharge is age- and weight-dependent as documented in the Kaplan-Meier figures. Although the rate of spontaneous closure differs significantly among some of the weight and GA categories, spontaneous closure before hospital discharge occurs in the majority of even the youngest and smallest infants, specifically those with a GA <26 weeks' gestation (68%) and a BW <750 g (76%).

We have excluded the deceased infants from the analysis. However, out of 26 infants who died, 16 had a recorded cause of death that could be potentially related to PDA: IVH ($n = 7$), NEC ($n = 5$), and pulmonary hemorrhage either associated with IVH or alone ($n = 4$). Ten infants who died before 7 days of age had point-of-care ECHO done, and all of them had documented PDA; none of them were medically treated for PDA. We could speculate that the outcome of some deceased infants could be

influenced by early PDA treatment. However, the criteria for such treatment remain currently unclear.

There were no differences in morbidities in nontreated infants. The absence of a statistically significant difference between the groups may just be a consequence of a sample size insufficient to detect differences in those low-incidence morbidities, but it may also be that as morbidity rates have declined in recent years, these conditions may have become dissociated from historical risk indicators such as PDA. When including the treated infants in our study group in the univariate analysis, a significant difference in the incidence of severe IVH becomes apparent between the infants whose PDA closed and those whose remained open until hospital discharge. We suppose that the failed treatment itself has no causal relationship to the severe IVH because no infant received early treatment; all treatments were administered beyond day 3 of life. This result could reflect the fact that the overall "sickest" infants would have persistent PDA despite treatment.

Our data are in agreement with other published studies presenting conservative PDA management.[17,18] The mean closure date in our group of infants <26 weeks GA occurred later than in the cohort recently presented by Sung et al,[18] and the rate of infants discharged from the hospital with open PDA was higher in our group (32% and 5%, respectively). This difference could probably be explained by different fluid management. Sung et al[18] practiced significant fluid restriction with an average fluid intake of 107 ± 20 to 115 ± 21 mL/kg per day between days 7 and 28. In our study, fluid restriction was not routinely applied and diuretics were not used in either participating center. However, the rate of CLD in infants of GA 23 to 26 weeks was similar in both cohorts (34.5% in our cohort as compared with 38%).[18]

TABLE 1 Comparison of Spontaneous DA Closure Time Among Different BW and GA Groups (Statistical Significance $P < .05$)

$N = 280$	Time to Ductal Closure (d), Median (95% CI) IQR [Q1, Q3] SE of the Median (Kaplan-Meier)	Pairwise Comparison Between the Groups, *P*, Mantel-Cox Log Rank Test	Adjusted *P* Value for Multiple Comparisons (Bonferroni Correction)
≤750 g[a]	48 (9–87)	—	—
	[8, 94]	.700[b]	>.999[b]
	20	.058[c]	.347[c]
		<.001[d]	<.001[d]
751–1000 g[b]	22 (6–38)	.700[a]	>.999[a]
	[7, NA]	—	—
	8	.042[c]	.255[c]
		<.001[d]	<.001[d]
1001–1250 g[c]	9 (6–12)	.058[a]	.347[a]
	[3, 44]	.042[b]	.255[b]
	2	—	—
		<.001[d]	.002[d]
1251–1500 g[d]	8 (7–9)	<.001[a]	<.001[a]
	[3, 12]	<.001[b]	<.001[b]
	1	<.001[c]	.002[c]
		—	—
<26+0 GA[e]	71 (51–91)	—	—
	[18, NA]	.028[f]	.169[f]
	10	<.001[g]	<.001[g]
		<.001[h]	<.001[h]
26+0–27+6 GA[f]	13 (0–34)	.028[e]	.169[e]
	[6, NA]	—	—
	11	.001[g]	.003[g]
		<.001[h]	<.001[h]
28+0–29+6 GA[g]	8 (7–9)	<.001[e]	<.001[e]
	[5, 17]	.001[f]	.003[f]
	1	—	—
		.027[h]	.164[h]
>30 GA[h]	9 (4–8)	<.001[e]	<.001[e]
	[2, 11]	<.001[f]	<.001[f]
	1	.027[g]	.164[g]
		—	—

P value is a result of comparison of the BW and GA groups labeled a, b, c, d and e, f, g, h, respectively. NA, not applicable (because Q3 was outside of the inpatient stay); IQR, interquartile range; Q1, 25th percentile; Q3, 75th percentile.

TABLE 2 Comparison of Demographics and Clinical Outcomes of VLBW Infants With and Without Spontaneous PDA Closure Before Hospital Discharge

	PDA Closure Group ($n = 237$)	PDA Nonclosure Group ($n = 43$)	*P*
GA, wk, mean ± SD	29.2 ± 2.3	27.5 ± 2.0	.0001
Birth wt, g, mean ± SD	1145 ± 264	1004 ± 239	.001
ANSs, *n* (%)	215 (91)	37 (86)	.404
Multiple pregnancy, *n* (%)	99 (42)	19 (45)	.867
Sex: M/F	50, 50	44, 56	.510
IUGR, *n* (%)	41 (17)	6 (14)	.665
Severe IVH (grade III and IV), *n* (%)	2 (1)	2 (5)	.113
PVL, *n* (%)	4 (2)	1 (2)	.573
BPD, *n* (%)	24 (10)	8 (19)	.123
NEC grade ≥IIb, *n* (%)	2 (1)	1 (2)	.395
ROP stage ≥III, *n* (%)	4 (2)	0 (0)	>.999

Infants with natural course of DA only, $n = 280$.

The overall mortality and the rate of significant neonatal morbidities in our cohort compare favorably to large databases, including centers with different PDA management policies. The results of this large

TABLE 3 Comparison of the Neonatal Outcomes of All the Infants Eligible for the Study (BW ≤1500 g) Including Deaths and Congenital Anomalies to the Vermont-Oxford Network (BW 401–1500 g or GA From 22 Weeks, 0 Days to 29 Weeks, 6 Days)

	Eligible Infants (n = 368)	Vermont-Oxford Network 2013 (n = 60 562)
Mortality (%) [Q1, Q3]	9.0	14.6 [9.0, 18.4]
CLD (%) [Q1, Q3]	14.6	24.5 [10.5, 30.7]
Severe IVH (grade III and IV) (%) [Q1, Q3]	5.0	8.1 [3.5, 10.6]
PVL (%) [Q1, Q3]	2.4	2.9 [0.0, 4.1]
NEC ≥IIb (%) [Q1, Q3]	3.6	4.6 [0.0, 6.5]
Severe ROP (stage ≥III) (%) [Q1, Q3]	2.4	6.2 [0.0, 8.3]

cohort of infants who underwent truly noninterventional management might encourage further placebo-controlled studies by demonstrating the relative safety of the conservative approach.

Spontaneous PDA closure postdischarge in early infancy is frequently documented,[23] and our results are in agreement. In circumstances where cardiology feels that invasive closure is indicated, the occlusive device appears to be the modality of choice, as it is a much less invasive procedure than surgical ligation. Because a late medical PDA treatment is less effective[6] and indications for late PDA treatment are unclear, it might be beneficial to await early infancy before a closure decision.

The results need to be interpreted cautiously because of the retrospective nature of this study. We acknowledge other obvious limitations. Although the echocardiographic studies were conducted in the first week of life and then regularly in 1 to 2 weekly intervals, the days differ among the infants. The decision to treat was not uniform and sometimes difficult to retrospectively elucidate. The parameters of PDA echocardiographic or clinical significance were not accounted for in the data analysis. Also, the hospital discharge policy might differ significantly among institutions. We have therefore calculated the rate of PDA closure at 36 weeks postmenstrual age. The total closure rate in the truly conservative group of 280 infants at 36 weeks postmenstrual age was 83% as opposed to 85% at hospital discharge.

CONCLUSIONS

Spontaneous closure of the PDA is likely in VLBW infants, as demonstrated in a large cohort of infants who underwent truly noninterventional, conservative PDA management. The rate of permanent ductal patency at hospital discharge is inversely related to GA and BW. The results support the existing data on the feasibility of conservative management without an increase in neonatal morbidity and mortality. However, it is physiologically plausible that some infants might benefit from PDA treatment. The criteria for which infants will benefit from the treatment are not currently defined. Such criteria could be determined through randomised controlled trials and our data on infants managed conservatively provides a platform for future placebo-controlled research, as it has demonstrated the safety of the use of a placebo arm for such trials.

ABBREVIATIONS

ANS: antenatal steroid
BPD: bronchopulmonary dysplasia
BW: birth weight
CI: confidence interval
CLD: chronic lung disease
DA: ductus arteriosus
ECHO: echocardiography
GA: gestational age
IUGR: intrauterine growth restriction
IVH: intraventricular hemorrhage
NEC: necrotizing enterocolitis
PDA: patent ductus arteriosus
PVL: periventricular leucomalacia
ROP: retinopathy of prematurity
VLBW: very low birth weight

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8.5 Summary of the Main Findings

In the first study we have described cardiopulmonary transition over the first 12 hours of life in 51 ELBW infants using tnECHO. We have documented a significant drop in pulmonary artery pressures based on RV-RA gradient measurements between six and 12 hours of age. PDA diameter was unchanged over the first 12 hours of life, however, we observed that PDA flow remained bidirectional (right-to-left flow more than 30% of the cycle) in 24% of infants at 12 hours of age, suggesting ongoing transition. In our study only mechanical ventilation at 12 hours of age was independently predictive of the adverse outcome. However, we have documented a significant difference in RV-RA gradient measurements at 12 hours of age between the group of infants who had the primary outcome of BPD/death and those who did not.

In the second study we found that the DS was unreliable at measuring HR in the DR, frequently not displaying any HR, or displaying a HR significantly lower than the auscultated HR. We noted that our ability to record a HR on the HUS was limited by the fact that it was difficult to visually count contractions, especially at HRs over 100 bpm. While an exact number of beats per minute was challenging to obtain, we could however appreciate cardiac contractility readily which would be valuable in neonatal resuscitation. The quickest method of recording HR in the delivery room was ECG compared to DS and HUS. However, the traditional stethoscope remained the quickest method to obtain a HR when the time delay in applying ECG leads is taken into consideration.

In the third study we reported results of three different approaches to PDA management in VLBW infants. In our study infants diagnosed with PDA in STG received the most proactive treatment from the three groups as these infants were already showing clinical signs of a symptomatic PDA. However, there was no significant difference to ETG in terms of treating the diagnosed PDA. CTG infants received significantly less Ibuprofen therapy and surgical

ligation (in fact there was no ligation in the CTG group). Infants diagnosed with PDA in the CTG did have better outcome for CLD (oxygen requirement and/or respiratory support at 36 weeks postmenstrual age) compared to the treatment groups, despite this group having a higher proportion of babies with PDA more than 2 mm in diameter at the time of diagnosis. The other observed short-term outcomes did not significantly differ between the groups. Conservative treatment of a PDA in VLBW infants seems to be a feasible approach to PDA management.

In the last study we have reported the 'natural' course of PDA derived from a robust retrospective cohort of VLBW infants who underwent non-interventional conservative management. The likelihood of spontaneous closure before hospital discharge is age and weight dependent as documented in the Kaplan-Meier figures (Figure 11 and 12). Although the rate of spontaneous closure differs significantly among some of the weight and gestational age categories, spontaneous closure before discharge occurs in the majority of even the youngest and smallest infants, those with a gestational age below 26 weeks of gestation (68%) and birth weight below 750g (76%). There were no differences in morbidities in non-treated infants. The overall mortality (including all infant born in the observed period) and the rate of significant neonatal morbidities in our cohort compares favourably to large databases including centres with different PDA management policies.

9. Thesis Discussion and Conclusions

A common theme of this thesis is exploration of the cardiovascular status of extremely preterm infants after delivery with employment of novel methods of cardiovascular status assessment and role of the PDA in the transition and short term and long-term outcomes.

In the main study of the thesis, we have used bioreactance to observe CO changes in the cohort of extremely preterm infants undergoing postnatal transition and we hypothesise that infants with adverse outcome attributable to hypoperfusion would have lower cardiac output in the first 24 hours after delivery. We further explored the usefulness of continuous CO monitoring in the cohort of term infants diagnosed with NE undergoing TH. We speculated that bioreactance would be a reliable method to follow cardiovascular changes observed during TH with tnECHO and that the bioreactance might play a role in the management and improvement of the outcome.

In the second part of the thesis, we compared a novel method of SVC flow measurement with the currently used and validated standard method. Our aim was to explore where these methods differ or indeed if they are equal for the use in day-to-day neonatal practice in the infants of main interest, extremely preterm infants after delivery.

In the last part of the thesis, we described immediate transition of the cardiovascular system in ELBW infants by tnECHO. We hypothesised that a substantial number of the most vulnerable infants might have a delayed transition with PPHN, and this might transpire to adverse long term pulmonary outcomes (particularly CLD/BPD). We have also planned to observe PDA characteristics early after delivery and then in two follow up studies we have explored conservative management of the PDA with short term and long-term outcomes. Finally, we have tested the role of HUS and DS in the immediate assessment of the HR in the DR (in well term infants).

The lowest CO (measured by bioreactance) in infants with birth weight less than 1250g with subsequent PIVH and NEC was significantly different from the cardiac output in infants without these complications. This would be in agreement with previous studies linking low CO, measured by a surrogate marker (SVC flow) with adverse outcome, including PIVH.(9, 21) Pathogenesis of both PIVH and NEC is multifactorial, however one of the definite factors playing a role is the disturbance in the end-organ blood flow. (96, 201, 202) The initial lower CO in infants with PIVH and/or NEC was followed by a 'compensatory' increase in the second 24 hours that was statistically significant, raising the possibility of an ischaemia/reperfusion situation predisposing these infants to subsequent complications. While the choice of PIVH as an adverse outcome linked to hypoperfusion would be obvious for our study (9, 21, 96), the choice of NEC might be more controversial. There is no doubt that ischaemic insult coupled with reperfusion injury can lead to intestinal injury.(203) This mechanism is considered a leading factor in the development of NEC in infants with congenital heart disease secondary to diminished systemic blood flow.(204) This might also be valid for infants' post perinatal asphyxia.(205) However the situation in extremely preterm infant seems to be different with epidemiologic evidence suggesting that the most common form of NEC is not primarily triggered by a hypoxic-ischemic event, but rather by microbial and inflammatory processes.(201) However there is enough evidence that early hypoperfusion and hypotension are predisposing factors for developing NEC even in preterm infants.(206) Circulatory disturbance resulting from a PDA is a leading factor for low systemic blood flow in preterm infants and early prophylactic ligation was shown to significantly reduce the incidence of NEC.(207, 208) The complication of NEC is used as either a primary and/or secondary outcome of studies of early PDA treatment at the moment, hypothesising improved systemic blood flow.(178, 209) The measured COs in both groups and the entire cohort were much lower than the LVO measured by echocardiography in a similar cohort of patients by Sirc et al (mean

190, 222, 252, and 281 ml/kg/min at six, 12, 24 and 48 hours of age respectively).(168) There are two possible explanations for this observation. Firstly the NICOM^{TM} monitor has been consistently underestimating echocardiography LVO measurements.(74, 75, 210) Secondly the limitation of echocardiography LVO is the impact of shunting on the LVO measurement (55), with expert guidance stating that LVO does not represent systemic blood flow in the presence of a PDA.(56) Since a PDA was present in all but one infant in our study (at six hours of age), the LVO measured by echocardiography would have very limited value in our cohort. CO in our study was similar to CO measured by bioreactance between six and 72 hours of age in well preterm infants by Van Wyk et al. (mean CO 105.6 ml/kg/min in their study compared to 110.3 ml/kg/min for our entire cohort, with 108.8 ml/kg/min for normal outcome group and 118.6 ml/kg/min for adverse outcome group) despite our cohort being significantly more preterm (mean 27.5 vs. 31.3 weeks of gestation) with lower birth weights (mean 0.95 vs. 1.56 kg).(210) Therefore, while we are lacking a gold standard for the measurement of the CO/systemic blood flow in preterm infants, we would speculate that the bioreactance might be reflecting systemic blood flow/CO patterns more realistically than LVO measured by echocardiography. In fact, the moderate, non-significant increase in CO between six and 48 hours of age would be consistent with a statistically non-significant increase in SVC flow (61, 168) rather than a significant increase in LVO as measured by echocardiography.(168) In our opinion the continuous data measured by bioreactance can offer an advantage over echocardiographically SVC obtained data as these can fail to appropriately pick up the infants with low output and possible adverse consequences.(211) We recognize that there are some limitations to our main study, mainly small sample size with only six infants in the group with a predefined adverse outcome.

In the second study using bioreactance in term infants undergoing TH for NE, we illustrated that NICOM^{TM} under-reads echo-CO by an average of 27%. This systematic bias is

similar to the bias illustrated in two other patient populations: healthy term and late-preterm infants, and preterm infants following PDA ligation.(74, 75) A rationale for this systemic bias between the two methods have been provided previously.(74) The NICOM^{TM} algorithm used to estimate aortic diameter size in the neonatal population is extrapolated from adults which may have resulted in the lower NICOM^{TM} values of CO.(72) Conversely, echocardiography may overestimate CO readings as it uses the velocity of blood flowing through the central portion of the aortic root to estimate CO. This may significantly overestimate the true overall velocity of blood flowing through the aortic root as the higher velocity is found in the center of the vessel while flow along the periphery (not measured by echocardiography) is significantly lower.(212) We also found that the bias appears to be constant throughout the cooling and rewarming phases with no significant differences between the three NICOM^{TM} and echocardiography measurement time points. This has important implications as it suggests that body temperature changes do not appear to affect the bioreactance signal properties. Animal studies support these findings. In a study of nine open chest pigs, where blood flow was controlled with cardiopulmonary bypass, NICOM^{TM} measured CO correlated well with cardiopulmonary bypass measurements (r=0.84) across two blood temperatures (36° and 38°C). Although this temperature range is different to that in our study, the data suggest the relative lack of effect temperature has on NICOM^{TM} measured CO.(72) We illustrated that NICOM^{TM} monitoring of infants with NE during TH and rewarming reflects expected hemodynamic changes during this process, adding further support to its reliability in this patient cohort. LVO is lower during hypothermia and increased during rewarming. This change appears to be driven by changes in HR which mirrored the increased CO rather than SV, which increased at a lower rate. There was a rise in SVR during cooling which decreased with rewarming. There was no change in mean BP during the study period. Hypothermia is associated with a reduction in metabolic demand and a resultant fall in CO.(213) Adult human

data and animal models of TH have previously demonstrated this rise in SVR following the lowering of body temperature.(214, 215) The rise in SVR may be a contributing mechanism to the maintenance of cerebral perfusion in the cooled neonatal population.(216) The early rise in SctO2 seen in our cohort occurring in conjunction with the rising SVR supports this theory. SctO2 remained elevated during rewarming despite a falling SVR. The increase in CO may have maintained cerebral perfusion. We found that infants with evidence of brain injury seen on MRI had a higher SVR and a lower CO driven by a lower SV rather than HR (although none of those differences reached statistical significance, likely due to the small number of subjects). This finding suggests that the more severely affected infants may also have myocardial injury, with an inability to maintain adequate SV in the face of increasing afterload. We found no demonstrable change in CO, mean BP or SVR following the introduction of inotropes in this population. The lack of change may highlight the lack of response to inotropes during TH (214), however, no meaningful conclusions can be drawn from our small sample size and the relatively diverse number of inotropes used in this study. Our study has several limitations: the relatively small number of infants may have resulted in missing important differences in the measures between infants with and without brain injury. In addition, the relative delay in applying NICOM^{TM} (done to facilitate obtaining consent) may have resulted in missing important hemodynamic changes during the early cooling phase.

Conclusions Part 1

Infants with birth weight less than 1250g and PIVH and/or NEC had significantly lower cardiac output (measured by bioreactance) compared to infants without these complications on day one of life. This low CO was then followed by a significant increase on day two of life. We have demonstrated that the assessment of the hemodynamic status of term infants with NE undergoing TH in addition to cerebral perfusion in a continuous fashion is feasible and reflects

the expected hemodynamic changes occurring as a result of TH and rewarming in infants with NE. Further studies using bioreactance are warranted, in our opinion, to help to understand systemic blood flow physiology and pathophysiology in preterm and term infants including the alteration in perfusion leading to adverse outcomes and the response to different treatments currently used to tackle hypotension/hypoperfusion.

The standard and modified methods of SVC flow measurements have yielded clinically equivalent results at six and 36 hours of age (defined as raw bounds of -20 to +20 ml/kg/min) in infants with birth weight less than 1250g. There was no statistically significant difference between the mean SVC flow for the cohort measured by either technique at any of the three time points (6, 18 and 36 hours of age). However, the SVC flow measurements correlated significantly only at six hours of age. Interestingly, the mean differences (bias) between the two techniques were much smaller in our study (-0.8, +9.5 and -2.2 ml/kg/min respectively) compared to the only other report comparing these two techniques, 19 ml/kg/min in the study by Ficial et al..(187) Despite clinically equivalent results, the agreement between the two methods was not satisfactory in our opinion, with very wide agreement limits at all three time points and as such we would not deem the two methods interchangeable. Unsurprisingly, there was a strong, statistically significant correlation between the HR data at all time points as both SVC measurement techniques were done in immediate succession and the HR measurements are not related to the echocardiography technique. SVC area correlated strongly and statistically significantly between the methods at six hours of age. This correlation weakened with time, however was still statistically significant at 18 hours of age. We would speculate from our own experience and the experience of others that the measurement of SVC flow and namely the parasternal diameter of the vessel, is more difficult to carry out and less accurate over time after delivery.(217) SVC area assessed by standard technique obtained consistently

lower values compared with the modified technique with mean difference ranging from 1.8 to 2.9 mm^2. This finding would be in agreement with the finding of Ficial et al., albeit their mean difference was somewhat higher (4 mm^2). When SVC area by echocardiography measurement was tested against phase contrast cardiac MRI measurement, both echocardiography techniques underestimated MRI data.(88, 187) We would agree with the speculation that MRI area measurement is likely to be superior in accurately obtaining the cross sectional area of the vessel.(218) As highlighted above, there was a reasonable correlation between the two echocardiography methods in SVC cross sectional area estimation, and suprasternal access might be preferable as it most likely better reflects the true cross sectional area and seems easier to obtain after 24-48 hours of age. SVC VTI correlated statistically significantly between both techniques only at six hours of age and the correlation weakened with time. The standard method consistently produced higher values compared with the modified technique, and the mean difference was very similar across the three time points (3.1, 3.0, 3.1 cm respectively). This would be similar to mean difference in VTI's as previously reported (4.3 cm and 0.67 cm by Ficial et al. and Harabor et al. respectively).(187, 219) We would speculate that the lower difference published by Harabor is a result of very frequent angle correction use in their study. We predefined criteria for the use of angle correction (to use only when the angle between the SVC at the point of measure and the ultrasound beam was greater than 15°) and we were successful in obtaining images without any need for this correction. Ficial et al. did not allow for angle correction in their study, thus their results are comparable with and similar to ours. In contrast to cross sectional area measurement, where MRI seems to be superior, we believe that in preterm infants with higher heart rates, MRI significantly underestimates true maximum velocity secondary to the relative low frame rate (20 images per cardiac cycle) compared with the current generation echocardiography machines (commonly >50 images per cardiac cycle).(218, 220) Thus the standard echocardiography technique would be most likely to reflect

true VTI. There are some limitations of our study, our cohort of infants was relatively small (39 infants), albeit this represents substantial cohort of the most vulnerable preterm infants. We did not calculate intra-observer variability for this study. However, all measurements were done by operators with vast experience in functional neonatal echocardiography and SVC measurements. Also, as there is a lack of gold standard, we can only compare variabilities of the two techniques without comparing them to a gold standard.

Conclusions Part 2

Both SVC flow echocardiography measurement techniques yielded clinically equivalent results, although due to poor correlation and agreement they do not seem to be interchangeable. The poor correlation is mostly secondary to the VTI measurements and we would strongly advocate use of the standard technique. The SVC cross-sectional area had quite satisfactory correlation early after delivery and in fact it seems plausible that the modified technique obtains more stable and accurate values. We would recommend that future studies use modified cross sectional area measurement together with standard SVC VTI measurements and correlate these with clinically relevant outcomes, and indeed with any future gold standard CO measurement, in extremely premature babies in the transitional period after birth.

In the last part of the thesis, we have documented a significant drop in pulmonary artery pressures based on RV-RA gradient measurements between six and 12 hours of age in ELBW infants. PDA diameter was unchanged over the first 12 hours of life, however, we observed that PDA flow remained bidirectional (right-to-left flow more than 30% of the cycle) in 24% of infants at 12 hours of age, suggesting ongoing transition. The available normative data on early cardiopulmonary transition within first 24 hours in infants with ELBW are scarce. A study by Seppänen et al. presented serial measurements of pulmonary artery pressures at two,

12, 24 up to 72 hours of age in a group of healthy preterm neonates (mean gestational age 31.7 weeks, mean birth weight 1860g) and neonates with RDS (mean gestational age 29.9 weeks, mean birth weight 1605g).(162) They also documented a significant drop in pulmonary artery pressures within the first hours (between two and 12 hours) of life, however the pressure values were in general higher than those we have observed, starting at around 50mm Hg in the healthy preterm group and 55mm Hg in the RDS group at two hours, and dropping to 35mm Hg and 50mm Hg respectively at 12 hours of age. RV-RA gradient measurements were 5mm Hg lower as the investigators estimated RA pressure to be 5mmHg. On the other hand, they were not able to detect a measurable TR jet in 30% of infants with RDS and in 50% healthy preterm infants after two hours, suggesting quickly progressing transition in those infants. They have observed bidirectional PDA at 12 hours in 40% of the infants with RDS and 11% of the healthy preterm infants respectively. The difference in pulmonary pressure estimates as compared with our results could be due to the different population characteristics and high percentage of infants with no TR jet. In the study by Seppänen et al., all infants enrolled received a bolus of normal saline and dopamine infusion, which could contribute to increased pulmonary vasoconstriction and therefore elevate pulmonary artery pressure. Another study by Schmitz et al. evaluated pulmonary pressures in healthy preterm infants (mean gestational age 31.9 weeks, mean birth weight 1709g) and preterm infants with severe RDS (mean gestational age 28.4 weeks, mean birth weight 1061g) within the first 24 hours of life and then daily thereafter, until day four of life.(188) They observed RV-RA gradients within the first 24 hours to be below 20mmHg in 50% of healthy preterm infants but only 25% of infants with RDS, again suggesting increased pulmonary pressures in the ‘sicker’ infants. Using the cut-off value of 30 mmHg, 90.9% of the healthy preterm infants and 75% of infants with RDS had RV-RA gradients below this value. They did not observe any correlation between RV-RA gradients and gestational age or birth weight using linear regression analysis. Both studies measuring early pulmonary pressures

investigated slightly different populations in a different epoch of neonatology. Recent studies investigating a similar population to ours (infants less than 29 weeks of gestation), present echocardiographic assessment of cardiopulmonary transition at different, slightly later, timeframes, therefore are not directly comparable.(221, 222) However, in healthy preterm infants below 29 weeks of gestation, James et al. documented bidirectional PDA at a median of 10 hours of age in 35% of infants, with a median diameter of 2.4mm, similarly to our findings.(222) Mizra et al. described delayed cardiopulmonary adaptation (defined as pulmonary artery pressures more than a half of systemic systolic pressure at 72-96 hours) in 55% of the subjects of their cohort of infants below 29 weeks of gestation.(221) They concluded that delayed cardiopulmonary adaptation is an independent risk factor for death or BPD using multivariate logistic regression. Birth weight, a fraction of inspired oxygen and pulmonary artery pressure at 24 hours of age were shown to be independent predictors of CLD in another study investigating neonatal transition.(223) In our study only mechanical ventilation at 12 hours of age was independently predictive of the adverse outcome. However, we have documented a significant difference in RV-RA gradient measurements at 12 hours of age between the group of infants who had the primary outcome of BPD/death and those who did not. Considering that almost a quarter of ELBW infants enrolled in our study had bidirectional PDA at 12 hours of age, there may be potential adverse effects if PDA closure is attempted in these infants at this time, e.g. prophylactic early PDA treatment, as such closure could cause the infant to deteriorate clinically. This further underscores the importance of point-of-care echocardiography and an individual/targeted approach in the haemodynamic management of preterm newborns. The main strength of this study is that we were able to recruit a large cohort of the most vulnerable preterm infants within the first three hours of life. All infants enrolled had all three measurements carried out on tnECHO at three, six and 12 hours of life (unless they did not survive to the particular time points). However, we chose to

implement only the most common and easily reproducible echocardiography parameters of pulmonary pressures assessment for the sake of minimal manipulation and disturbance of the infants under assessment. More echocardiography measurements are available to assess complex right heart performance, for example Tissue Doppler Imaging (TDI) and strain rate as quantitative markers of right ventricular function, or other right ventricle specific markers like Tricuspid Annular Plane Systolic Excursion (TAPSE).(224)

In the small prospective observational study of the heart assessment in DR in term infants, we found that the DS used in our study was unreliable at measuring heart rate, frequently not displaying any HR, or displaying a HR significantly lower than the auscultated HR. However, it should be highlighted that all infants assessed in our study were vigorous and often crying which has been found previously to affect DS recording.(225) It is of course possible that in a resuscitation scenario where the infant is usually quiet and still that DS could be more reliable. It was noted that our ability to record a HR on the HUS was limited by the fact that it is difficult to visually count contractions, especially at HRs over 100 bpm. We noted that the images we obtained were not high quality and perhaps a higher-resolution ultrasound would be more useful. While an exact number of beats per minute was challenging to obtain, we could however appreciate cardiac contractility readily which would be valuable in neonatal resuscitation.

The last two studies are intimately connected and exploring different management of PDA and ultimately describing the natural history of the PDA in VLBW infants. Screening all VLBW infants in the first 48 hours shows that approximately 75% of all VLBW infants have a PDA on echocardiography, reducing to less than 50% by one week of life. These findings would be in agreement with the previous report documenting spontaneous closure of PDA in 44% of infants below 32 weeks of gestation before day seven of life.(226) Previously this spontaneous closure rate was reported lower in ELBW infants (34%) (227) and also in

extremely low gestational age newborns (24%) (228). We addressed this in our data from the last study that represent the true ‘natural history’ of PDA derived from a robust retrospective cohort of VLBW infants who underwent non-interventional conservative management. The likelihood of spontaneous closure before hospital discharge is age and weight dependent as documented in the Kaplan-Meier figures. Although the rate of spontaneous closure differs significantly among some of the weight and gestational age categories, spontaneous closure before discharge occurs in the majority of even the youngest and smallest infants, those with a gestational age below 26 weeks of gestation (68%) and birth weight below 750g (76%). Our data is in agreement with other published studies presenting conservative PDA management.(229, 230) The mean closure date in our group of infants below 26 weeks gestational age occurred later then in the cohort recently presented by Sung et al. and the rate of infants discharged with open PDA was higher in our group (32% and 5% respectively). This difference could probably be explained by different fluid management. Sung et al. practiced significant fluid restriction with average fluid intake of 107±20 -115±21ml/kg/d between days 7-28 while in both centers participating in our study fluid restriction was not routinely applied and diuretics were not used. However, the rate of CLD in infants of gestational age 23-26 weeks was similar in both cohorts, 34.5% in our cohort as compared to 38%.(230)

There is little published information on VLBW infants presenting with clinically symptomatic PDA. In our STG, 23% (52 out of 230 live born infants) presented with presumed clinical signs of a PDA, but in whom less than 40% had a PDA > 2mm on color flow Doppler, suggestive of a haemodynamically significant ductus. It is not surprising that in our study infants diagnosed with PDA in STG received the most proactive treatment from the three groups as these infants were already showing presumed clinical signs of a symptomatic PDA. However, there was no significant difference to ETG in terms of treating the diagnosed PDA. CTG infants received significantly less Ibuprofen therapy and surgical ligation (in fact there

was no ligation in CTG group). Infants diagnosed with PDA in the CTG did have better outcome for CLD (oxygen requirement and/or respiratory support at 36 weeks postmenstrual age) compared to the treatment groups, despite this group having a higher proportion of babies with PDA more than 2 mm in diameter at the time of diagnosis. We speculate this could be partially due to less aggressive treatment of PDA, less Ibuprofen therapy and less surgical ligation. The other observed short-term outcomes did not significantly differ between the groups. We acknowledge many obvious limitations to the three-epoch study. The results may be influenced by overall improvement in neonatal intensive care management over the years. This mainly included the introduction of non-invasive ventilation as a primary ventilation mode even for the most immature infants, adoption of the minimal ventilation strategy, mild changes in fluid and nutrition management - lower initial daily fluid volumes and increase in protein and calories intake. These changes occurred mainly before year 2006, therefore the differences in overall management were probably minimal between ETG and CTG. Also, the obstetricians' approach changed gradually over the years towards being more proactive. The use of antenatal steroids was indeed lowest in the most historical group (STG) and this can have negative effect on some of the short term outcomes; mortality, RDS, IVH, NEC.(231) However this should not influence CLD rate in survivors.(232) We did have a relatively small number of subjects in our study, although we included all patients admitted in the three periods diagnosed with PDA. There was also possible selection bias in the STG and CTG as these groups potentially missed early neonatal deaths occurring prior to PDA diagnosis. This could be reflected in non-significant difference in overall mortality among the groups (8% in ETG vs. 2% in STG and 3% in CTG). However, there was only one neonatal death before day seven of life in CTG group which occurred within two hours post delivery secondary to fulminant early onset sepsis. There were no deaths prior to PDA screening documented in ETG. Since only 23% of infants in STG had echocardiography performed it is difficult to calculate deaths occurring prior to

PDA diagnosis. However, median time of the PDA diagnosis was three days. There were 10 deaths identified within the first three days of life in 230 infants born in the STG era. Another potential bias was in STG as the initial diagnosis was made clinically with subsequent cardiology evaluation with possibility of missing infants with small, non-significant PDAs. The diagnostic criteria were not uniform among the cohorts and neither were the decision to treat criteria. In STG, the presumed clinical signs of PDA probably contributed significantly to the treatment decision since only 38% of infants had PDA larger than 2 mm on echocardiogram and 62% were treated. In the CTG era, the situation was completely different with 62% of infants having PDA larger than 2mm and 15% treated. The PDA significance echocardiographic markers also differed among the groups and the individual management decisions were difficult to trace retrospectively.

We have tried to address some limitations of the previous study in our last study. We have excluded the deceased infants from the analysis. However, out of 26 infants who died, 16 had a recorded cause of death which could be potentially related to PDA – IVH (n=7), NEC (n=5) and PH either associated with IVH or alone (n=4). Ten infants who died before seven days of age had point-of-care echo done and all of them had documented open PDA, none of them was medically treated for PDA. We could speculate that the outcome of some deceased infants could be influenced by early PDA treatment. However, the criteria for such treatment remain currently unclear. There were no differences in morbidities in non-treated infants. Absence of a statistically significant difference between groups may just be a consequence of a sample size insufficient to detect differences in those low-incidence morbidities, but it may also be that as morbidity rates have declined in recent years these conditions may have become dissociated from historical risk indicators, such as PDA. When including the treated infants in our Study group into the univariate analysis, a significant difference in the incidence of severe IVH becomes apparent between the infants, whose PDA closed and those whose remained open

until discharge. We suppose that the failed treatment itself has no causal relationship to the severe IVH since no infant received early treatment, all the treatment was administered beyond day three of life. This result could reflect the fact that the overall “sickest” infants would have a persistent PDA despite treatment. The overall mortality and the rate of significant neonatal morbidities in our cohort compares favorably to large databases including centers with different PDA management policies. The results of this large cohort of infants who underwent truly non-interventional management might encourage further placebo-controlled studies by demonstrating the relative safety of the conservative approach. Spontaneous PDA closure post discharge in early infancy is frequently documented (233) and our results are in agreement. In case invasive closure is indicated by the cardiologist, occlusive device seems to be a modality of choice due to the much less invasive nature as compared to surgical ligation. Since a late medical PDA treatment is less effective and indications for late PDA treatment are very unclear, it might be beneficial to await early infancy before a closure decision.(234) The results need to be interpreted again cautiously due to the retrospective nature of this study. We acknowledge other obvious limitations. Even though the echocardiographic studies were carried out in the first week of life and then regularly in 1-2 weekly intervals, the days differ among the infants. The decision to treat was not uniform and sometimes difficult to retrospectively elucidate. The parameters of PDA echocardiographic or clinical significance were not accounted for in the data analysis. Also, the discharge policy might differ significantly among institutions. We have therefore calculated the rate of PDA closure at 36 weeks postmenstrual age. The total closure rate in the truly conservative group of 280 infants at 36 weeks postmenstrual age was 83% as opposed to 85% at discharge.

Conclusions Part 3

We have described cardiopulmonary transition over the first 12 hours of life in 51 ELBW infants using tnECHO. The PDA diameter was unchanged over the first 12 hours of life. PDA flow remained bidirectional in almost a quarter of infants at 12 hours of age, suggesting ongoing transition. There was a significant decrease in pulmonary pressures between six and 12 hours of age. Pulmonary pressures at 12 hours of age were also significantly higher in the group of infants who had later developed BPD and/or died, in comparison with those who did not. However, in the multiple logistic regression model only mechanical ventilation at 12 hours of age was independently predictive of the adverse outcome. These findings could help to address the need for more normative data on early cardiopulmonary transition in the most vulnerable preterm infants. Our data could also be helpful in designing and performing interventional randomised controlled trials concerning early cardiopulmonary transition including PDA management together with further studies from the Part 3 of the thesis.

ECG is the quickest method of recording HR in the delivery room compared to DS and HUS. However, the traditional stethoscope remains the quickest method to obtain a HR when the time delay in applying ECG leads is taken into consideration. Further investigations of the accuracy of HUS and DS by directly comparing to ECG are warranted.

A conservative treatment of a PDA in VLBW infants seems to be a feasible approach to PDA management. Spontaneous closure of the DA is highly likely in VLBW infants as demonstrated in a large cohort of infants who underwent truly non-interventional conservative PDA management. The rate of permanent ductal patency at discharge is inversely related to the gestational age and birthweight. The results support the existing data on the feasibility of conservative management without an increase in neonatal morbidity and mortality. However, it is physiologically plausible that some infants might benefit from PDA treatment, even though

the criteria for a beneficial treatment are not currently defined. Such criteria are needed and the data on infants managed conservatively provide a platform for future, placebo-controlled research, demonstrating safety for the placebo arm of the trials.

10. Impact Statements

1. Extremely preterm infants with PIVH and/or NEC had a lower minimal CO measured by bioreactance in the first 48 hours of age.
2. Extremely preterm infants with subsequent PIVH and/or NEC had a lower mean CO measured by bioreactance on day one of life, this was followed by a significantly increased mean CO on day two of life.
3. This thesis includes the first description of continuous measurements of CO by bioreactance in extremely preterm infants in the transition period.
4. We have demonstrated that the assessment of the hemodynamic status of infants with NE undergoing TH in addition to cerebral perfusion in a continuous fashion is feasible and reflects the expected hemodynamic changes occurring as a result of TH and rewarming in infants with NE.
5. Further studies using bioreactance are warranted to help to understand systemic blood flow physiology and pathophysiology in preterm and term infants.
6. This thesis has the first comparison of two echocardiography methods of SVC flow measurement in extremely premature infants.
7. The modified method of SVC flow measurement was equivalent to the standard approach, however the two techniques had very wide limits of agreement and poor correlation and they are not interchangeable.
8. Implementation of modified cross-sectional area of SVC to the standard SVC flow measurement seems justifiable for future studies.
9. We have documented echocardiography parameters of cardiopulmonary transition during the first 12 hours of life in a substantive cohort of ELBW infants.
10. Pulmonary pressures decreased significantly at 12 hours of age in ELBW infants, however remained higher in infants who later developed BPD and/or died.

11. In the multiple regression model only mechanical ventilation at 12 hours of age was predictive of the adverse outcome of BPD and/or death in ELBW infants.
12. ECG was the quickest method of recording HR in the delivery room compared to DS and HUS in well term infants immediately after delivery.
13. The traditional stethoscope remained the quickest method to obtain a HR in DR when the time delay in applying ECG leads was taken into consideration.
14. A minimally invasive approach trying to avoid medical and surgical treatment of PDA seems to be a feasible option for VLBW infants.
15. Infants receiving minimally invasive management of PDA had the lowest rate of CLD as compared to two other cohorts undergoing a high rate of medical and/or surgical treatment of PDA, no difference in other short-term outcomes was observed.
16. Spontaneous closure of ductus arteriosus was extremely prevalent in the large cohort of VLBW infants.
17. We have documented the ‘natural’ course of PDA in VLBW infants.
18. Infants born before 26 weeks and below 750g have a significantly higher rate of PDA at discharge. Further studies should focus on this distinct population.

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12. Publications of the Author

12.1 Publications Thesis Is Based on

a) In Journals with Recognised Impact Factor

1. **Miletin J**, Stranak Z, O Cathain N, Janota J, Semberova J. Comparison of Two Techniques of Superior Vena Cava Flow Measurement in Preterm Infants with Birth Weight less than 1250g in the Transitional Period – Prospective Observational Cohort Study. Front Pediatr 2021 (Accepted, in Publication). ***IF 2.6***
2. Semberova J, Purna JR, O Cathain N, **Miletin J**. Postnatal Adaptation of Pulmonary Circulation in Extremely Low Birth Weight Infants - Prospective Observational Trial. Arch Dis Child Fetal Neonatal Ed 2021 (Submitted, in peer review). ***IF 5.4***
3. **Miletin J**, Semberova J, Martin AM, Janota J, Stranak Z. Low cardiac output measured by bioreactance and adverse outcome in preterm infants with birth weight less than 1250 g. Early Hum Dev. 2020 Oct;149:105153. doi: 10.1016/j.earlhumdev.2020.105153. Epub 2020 Aug 9. PMID: 32799033. ***IF 2.0***
4. Treston BP, Semberova J, Kernan R, Crothers E, Branagan A, O'Cathain N, **Miletin J**. Assessment of neonatal heart rate immediately after birth using digital stethoscope, handheld ultrasound and electrocardiography: an observational cohort study. Arch Dis Child Fetal Neonatal Ed. 2019 Mar;104(2):F227. ***IF 5.4***
5. McGovern M, **Miletin J**. Cardiac Output Monitoring in Preterm Infants. Front Pediatr. 2018 Apr 3;6:84. ***IF 2.6***

6. Forman E, Breatnach CR, Ryan S, Semberova J, **Miletin J**, Foran A, El-Khuffash A. Noninvasive continuous cardiac output and cerebral perfusion monitoring in term infants with neonatal encephalopathy: assessment of feasibility and reliability. Pediatr Res 2017 Nov;82(5):789-795. ***IF 2.7***
7. Semberova J, Sirc J, **Miletin J**, Kucera J, Berka I, Sebkova S, O'Sullivan S, Franklin O, Stranak Z. Spontaneous closure of patent ductus arteriosus in infants ≤1500 g. Pediatrics 2017 Aug;140(2). pii: e20164258. ***IF 5.4***
8. Letshwiti JB, Semberova J, Pichova K, Dempsey EM, Franklin OM, **Miletin J**. A conservative treatment of patent ductus arteriosus in very low birth weight infants. Early Hum Dev 2017 Jan;104:45-49. ***IF 2.0***
9. McGovern M, **Miletin J**. A review of superior vena cava flow measurement in the neonate by functional echocardiography. Acta Paediatr. 2017 Jan;106(1):22-29. Review. ***IF 2.1***

b) In Journals Without Recognised Impact Factor

none

12.2 Publications Related to the Thesis

a) In journals with Recognised Impact Factor

1. **Miletin J**. Near infrared spectroscopy and preterm infants-ready for routine use? J Perinatol. 2017 Oct;37(10):1069. ***IF 1.8***
2. Sirc J, Dempsey EM, **Miletin J**. Cerebral tissue oxygenation index, cardiac output and superior vena cava flow in infants with birth weight less than 1250 grams in the first 48 hours of life. Early Hum Dev. 2013 Jul;89(7):449-52. ***IF 2.0***

3. **Miletin J**, Pichova K, Doyle S, Dempsey EM: Relationship between Cortisol Concentrations, Blood Pressure, Superior Vena Cava Flow and Illness Severity Scores in VLBW Infant. J Perinatol. 2010 Aug;30(8):522-6. Epub 2010 Mar 25. ***IF 1.8***
4. **Miletin J**, Pichova K, Dempsey EM: Bedside detection of low systemic flow in the very low birth weight infant on day 1 of life. Eur J Pediatr. 2009 Jul; 168(7): 809-13. Epub 2008 Sep 26. ***IF 2.3***
5. Moran M, **Miletin J**, Pichova K, Dempsey EM: Cerebral tissue oxygenation index and superior vena cava blood flow in the very low birth weight infant. Acta Paediatr. 2009 Jan; 98(1): 43-6. Epub 2008 Oct 6. ***IF 2.1***
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b) In Journals without Recognised Impact Factor

none