Non-invasive cardiac output monitoring in preterm neonates

By

Lizelle Van Wyk

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Promotors:

Professor Johan Smith
Department of Paediatrics and Child Health, Stellenbosch University

Professor Willem-Pieter de Boode
Department of Neonatology, Radboud Institute for Health Sciences, The Netherlands

Professor John Lawrenson
Paediatric Cardiology Unit, Department of Paediatrics and Child Health, Stellenbosch University

DECLARATION

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SUMMARY

Neonatal hemodynamic compromise is linked to numerous adverse neonatal outcomes. Objective, comprehensive, continuous hemodynamic monitoring of the systemic circulation, in conjunction with the pulmonary system, is required to timeously intervene and improve outcomes. Non-invasive cardiac output monitoring utilising bioreactance, a specific type of thoracic electrical biosensing technology (TEBT), may offer such a solution.

The overall aim of this research was to determine the use of bioreactance as a comprehensive, non-invasive cardiac output monitor in preterm neonates (<37 weeks). Research aims included determining (1) agreement (bias and precision) and (2) trending ability of bioreactance. Further aims were to determine the use of bioreactance in monitoring hemodynamic parameters and thoracic fluid content in the transitional period (first 72 hours of life) and during respiratory support in preterm neonates.

In a prospective, observational, longitudinal cohort study, the agreement (accuracy and precision) of bioreactance (BR), as compared to transthoracic echocardiography (TTE), for estimating cardiac output (CO) and stroke volume (SV) in a cohort of stable preterm neonates during the transitional period, was investigated. Bland Altman analyses showed a high bias, indicating poor accuracy, and wide limits of agreement, indicating poor precision, of BR as compared to TTE. A high percentage error indicated non-interchangeability of BR with TTE. Bias was shown to be affected by gestational age, birth weight, continuous positive airway pressure (CPAP), patent ductus arteriosus (PDA) and CO category. Despite a new technology's inaccuracy and lack of absolute number agreement, it could possibly be a valuable trending monitor, if reference values were known.

In the same cohort, the average values for BR-derived hemodynamic parameters (heart rate (HR), blood pressure (BP), SV, CO, total peripheral resistance (TPR)) were described. All parameters were associated with postnatal age. Changes were in line with

expected transitional changes, as described in the literature. BR may therefore be valuable to monitor the transitional period in preterm neonates.

In continued accuracy analysis, the ability of BR, as compared to TTE, to track temporal changes in SV and CO was investigated. Four-quadrant and polar plots were used to assess BR trending ability. Concordance rate was lower than the accepted benchmarks, when using a 5% and 10% exclusion zone. Angular bias was high, radial limits were wide and radial concordance was poor; indicating a poor trending ability. Trending parameters were significantly associated with postnatal age, PDA, and CO category but not gestational age, birth weight or CPAP. BR, as compared to TTE, does not provide good trending analysis of CO and SV and should be used with caution in neonatology to direct therapeutic decisions.

A narrative systematic review was performed to determine the agreement and trending ability of electrical biosensing technology (EBT) in neonates, including the current research. Only thoracic EBT studies, with TTE as comparator, were available for inclusion, up to December 2020. High heterogeneity was apparent in the eligible studies, due to varying gestational and chronological ages, birth weight, disease states, ventilation requirements, inotropic support and surgical intervention, which made meta-analysis impractical. Only agreement studies were available with no studies reporting trending analysis. Effect direction plots were used to report outcome measures (bias, percentage error). Overall, most studies showed that EBT was not interchangeable with TTE. Results remained similar in sub-analyses for preterm vs term neonatal populations, different respiratory support modes, cardiac anomalies and type of TEBT technology.

In a post hoc analysis of the cohort study, BR-derived thoracic fluid content (TFC) parameters were described. TFC, another hemodynamic parameter, may be able to identify pulmonary fluid overload states, that may compromise cardiac function or be the consequence of cardiac dysfunction. Absolute TFC and cumulative TFC change from baseline (TFC and TFCd0, respectively) decreased over the first 72 hours of life. Both TFC and TFCd0 showed significant associations with clinical variables (gestational age,

postnatal age, respiratory support mode). Sub-analyses according to respiratory support type and a pre-and post -intervention analysis was performed. TFC and TFCd0 showed significant pre- and post-intervention differences between respiratory intervention groups (CPAP and CPAP+surfactant). Neither TFC nor TFCd0 were associated with PDA in the transitional period. TFC and TFCd0 may offer the ability to monitor lung fluid during the transitional period in preterm neonates.

In conclusion, the agreement and trending of bioreactance in preterm neonates in the transitional period is questionable. Numerous physiological and interventional parameters influence this. However, on an individual level, BR may be able to monitor hemodynamic parameters, as parameters showed changes in the same direction as described in transitional physiology. Currently, bioreactance should be used with caution in the neonatal population to dictate therapeutic interventions. More research is required before bioreactance can be used at the bedside to replace transthoracic echocardiography.

OPSOMMING

Neonatale hemodinamiese kompromie hou verband met talle nadelige neonatale uitkomste. Objektiewe, omvattende, deurlopende hemodinamiese monitering van die sistemiese sirkulasie, tesame met die pulmonale sisteem, is nodig om betyds in te gryp en die uitkomste te verbeter. Nie-indringende monitering van kardiale omset met behulp van bioreaktansie, 'n spesifieke tipe torakale elektriese biosensietegnologie (TEBT), kan so 'n oplossing bied.

Die algemene doel van hierdie navorsing was om die gebruik van bioreaktansie (BR) as 'n omvattende, nie-indringende kardiale omset monitor in premature pasgeborenes (<37 weke) te bepaal. Navorsingsdoelstellings was die bepaling van (1) ooreenkoms en (2) tydsanalise-vermoë van BR. Verdere doelstellings was om die gebruik van BR te bepaal by die monitering van hemodinamiese parameters en die longvloeistof in die oorgangsperiode (eerste 72 uur van lewe) en tydens respiratoriese ondersteuning van vroeggebore pasgeborenes.

In 'n voornemende, waarnemingsstudie was die ooreenkoms (akkuraatheid en presisie) van bioreaktansie (BR), vergeleke met transtorakale eggokardiografie (TTE), vir die beraming van kardiale omset (KO) en slagvolume (SV) in 'n groep stabiele vroeggebore babas tydens die oorgangstydperk, ondersoek. Bland Altman-ontledings het ‘n hoë vooroordeel, duidend op swak akkuraatheid, en wye grense van ooreenstemming, duidend op swak presisie, getoon. 'n Hoë persentasie fout (>30%) het gedui op die onverwisselbaarheid van BR met TTE. Daar was getoon dat vooroordeel beïnvloed word deur die gestasie, geboortegewig, aanhoudende positiewe druk asemhaling (APDA), patente ductus arteriosus (PDA) en KO-kategorie. Ten spyte van 'n nuwe tegnologie se onakkuraatheid en gebrek aan absolute getal-ooreenstemming, kan dit belangrike 'n neigingsmonitor wees, indien verwysingswaardes bekend is.

In dieselfde groep was die gemiddelde waardes vir BR-afgeleide hemodinamiese parameters (hartspoed, bloeddruk, SV, KO, totale perifere weerstand)beskryf. weerstand) beskryf. Al die parameters was geassosieer met die postnatale ouderdom.

Veranderings was in ooreenstemming met die verwagte oorgangstydperk veranderinge, soos beskryf in die literatuur. BR kan dus waardevol wees om die oorgangsperiode by vroeggebore pasgeborenes te monitor.

In voortgesette akkuraatheidsanalise was die vermoë van BR, in vergelyking met TTE, om tyds veranderinge in SV en KO te meet, ondersoek. Vier-kwadrant- en polêre grafieke was gebruik om BR-tydsanalise-vermoë te bepaal. Die ooreenstemmingskoers was laer as die aanvaarde maatstawwe, met die gebruik van 'n uitsluitingsone van 5% en 10%. Polêre hoek was hoog, radiale grense was wyd en radiale ooreenstemming was swak; alles duidend op 'n swak tydsanalise-vermoë. Tydsanalise-vermoë parameters was beduidend geassosieer met die postnatale ouderdom, PDA en KO kategorie, maar nie gestasie, geboortegewig of APDA nie. BR, in vergelyking met TTE, bied nie goeie tydsanalise-vermoë van KO en SV nie en moet met omsigtigheid in die neonatale tydperk gebruik word om terapeutiese besluite te neem.

'n Beskrywende sistematiese oorsig was uitgevoer om die ooreenkoms en tydsanalise-vermoë van elektriese biosensietegnologie (EBT) in die neonatal populasie te bepaal, insluitend die huidige navorsing. Slegs torakale EBT-studies, met TTE as vergelyker, was beskikbaar vir insluiting. Hoë heterogeniteit was duidelik in die ingeslote studies as gevolg van wisselende swangerskapstyd, kronologiese ouderdomme, geboortegewig, siektetoestande, ventilasievereistes, inotropiese ondersteuning en chirurgiese ingryping, en het meta-analise onprakties gemaak. Slegs ooreenkomsstudies was beskikbaar vir analise, en geen studies het verslag gedoen oor tydsanalise-vermoë nie. Effekrigtingsdiagramme was gebruik om resultate (vooroordeel, persentasie fout) aan te toon. Oor die algemeen,

het die meeste studies getoon dat EBT nie met TTE verwissel kon word nie. Resultate het dieselfde gebly in sub-ontledings vir vroeggebore in vergelyking met volterm babas, verskillende respiratoriese ondersteuningsmodaliteite, hartafwykings en die tipe TEBT-tegnologie.

In 'n post hoc-analise van die kohortstudie, was BR-afgeleide torakale vloeistofinhoud (TVI) parameters beskryf. TVI, nog 'n hemodinamiese parameter, mag pulmonale vloeistofoorladingstate kan identifiseer, wat hartfunksie in gevaar mag stel of die gevolg van hartdisfunksie mag wees. Absolute TVI- en kumulatiewe TVI-verandering vanaf basislyn (onderskeidelik TVI en TVId0) het gedurende die eerste 72 uur van die lewe afgeneem. Beide TVI en TVId0 het beduidende assosiasies getoon met kliniese veranderlikes (gestasie, postnatale ouderdom, en respiratoriese ondersteuningsmodaliteit). Sub-ontledings volgens die tipe respiratoriese ondersteuning en 'n voor- en na-intervensie-analise, was uitgevoer. TVI en TVId0 het beduidende verskille voor- en na- intervensie getoon tussen respiratoriese intervensiegroepe APDA en APDA + surfaktant). Nie TVI of TVId0 was ge-assosieer met ‘n PDA in die oorgangstydperk. TVI en TVId0 mag die vermoë bied om longvloeistof te monitor gedurende die oorgangsperiode by vroeggebore pasgeborenes.

Ten slotte, die akkuraatheid en tydsanalise-vermoë van BR by vroeggebore pasgeborenes is twyfelagtig. Talle fisiologiese en intervensionele aspekte mag dit beïnvloed. Op ‘n individuele vlak, mag BR in staat wees om hemodinamiese parameters te monitor, aangesien BR-parameters veranderinge in dieselfde rigting getoon het, soos beskryf in oorgangsfisiologie. Tans moet bioreaktansie met omsigtigheid in die neonatale populasie gebruik word om terapeutiese intervensies te dikteer. Meer navorsing is nodig voordat bioreaktansie gebruik kan word om transtorakale eggokardiografie te vervang.

DEDICATION

To my parents, who always just smiled patiently when I said I wanted to do another degree. Thank you for always believing in me.

To Prof Smith, without whose support, friendship and mentorship I would not be the neonatologist I am today.

To all the babies that I have had the privilege to look after; they have taught me something new every day.

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CHAPTER 1

Introduction

General introduction

Despite numerous monitoring options, laboratory tests and extensive neonatal cardiovascular physiology knowledge, there remains a significant disconnect between applying technology-derived information and targeted therapeutic interventions to improve neonatal morbidity and mortality. This is especially true regarding neonatal hemodynamic compromise. Adequate assessment of cardio-pulmonary interaction is also challenging. Comprehensive, simultaneous monitoring of hemodynamic parameters and cardio-pulmonary interactions is required, highlighting the need for improved technology.

Maintaining adequate tissue perfusion is a key component of preterm neonatal care[1]. Low cardiac output may cause inadequate perfusion of organs leading to increased morbidity and mortality[2]. Indirect assessment of systemic blood flow (cardiac output) using clinical examination and biochemical parameters is inaccurate[3]. Technology that continuously monitors cardiac output (CO) may be able to detect circulatory compromise, offering opportunities for timely intervention, thereby possibly decreasing morbidity and mortality[4].

Traditional CO monitoring methods are often invasive, not feasible in small neonates and only offer intermittent measurements. Non-invasive monitoring technologies may offer a viable alternative by providing continuous monitoring of numerous hemodynamic parameters[5]. However, for a new technology to be used in clinical practice it needs to be proven accurate, precise, and able to accurately track changes in the parameter of interest[6]. Method comparison research methodology is employed in this regard [7].

Bioreactance (BR) is a novel, non-invasive thoracic electrical biosensing technology (TEBT) that can continuously monitor numerous hemodynamic variables, including

cardiac output (CO), stroke volume (SV), thoracic fluid content (TFC) and total peripheral resistance (TPR).

BR-monitored hemodynamic parameters may assist the neonatal clinician in the early identification of hemodynamic compromise. This may enable an individualized pathophysiological-based management and therapeutic monitoring system, thereby improving neonatal outcome.

This formed the premise of the current research.

Literature Review

Cardiac output in preterm neonates

Adequate systemic perfusion is dependent on an adequate cardiac output (CO). CO, together with blood pressure (BP), is considered a fundamental physiological parameter for diagnosis and guidance of therapy in various neonatal conditions[11]. Maintaining optimal tissue perfusion and oxygenation is of prime concern in neonatal intensive care units (NICU). The hemodynamic physiology of neonates is significantly different from that of the adult or pediatric population, as this population is a heterogeneous mix of gestational and postconceptional ages, with different degrees of cardiovascular maturation[12]. Prevention of hemodynamic compromise is essential as low CO has been associated with oliguria, necrotising enterocolitis, late onset sepsis, retinopathy of prematurity, intraventricular haemorrhage, abnormal electroencephalogram, adverse long-term neurodevelopment, and mortality [2,13–16].

CO is determined by heart rate (HR) and stroke volume (SV) and influenced by systemic vascular resistance (SVR) (Eq 1)[17]. A complex interaction exists between HR, blood flow, SVR and blood pressure (BP) to ensure that metabolic cellular oxygen demand is met [18]. Through Hagen-Poiseuille's law of fluid mechanics, as applied to cardiovascular physiology, the relationship between BP and blood flow is described by:

Pressure gradient (arterial BP – right atrial pressure) = CO x SVR Eq 1

Blood pressure is therefore a hemodynamic dependant variable, with CO and SVR being two major determinants thereof [17]. In hemodynamic compromise, BP may be normal when CO is counterbalanced by changes in SVR. Indirect measures of CO (HR and BP) and indirect measures of cellular oxygenation (arterial oxygen saturation (SpO2)) are inadequate for assessment of neonatal hemodynamic status[1]. Neither CO nor SVR are routinely or continuously measured in neonates.

Due to the multifactorial causes of hemodynamic compromise in neonates(figure 1), comprehensive monitoring of various physiological variables is required to recognise underlying pathophysiology [3,17]. Numerous physiological, pathophysiological, and neonatal management factors may contribute to the potential of developing hemodynamic compromise [19]. It is therefore essential that hemodynamic monitoring takes place and includes the monitoring of, not only conventional parameters of HR and BP, but also CO and SVR. This may be possible with thoracic electrical biosensing technology (TEBT). Bioreactance is one such technology.

Due to cardio-pulmonary interaction, lung fluid may influence cardiac function during the neonatal period or may represent cardiac dysfunction. Failure to clear fetal lung fluid may lead to various forms of respiratory and cardiac compromise[20]. Monitoring of lung fluid may increase the ability to identify respiratory and hemodynamic compromise. Bioreactance is also able to monitor thoracic fluid in conjunction with other hemodynamic parameters.

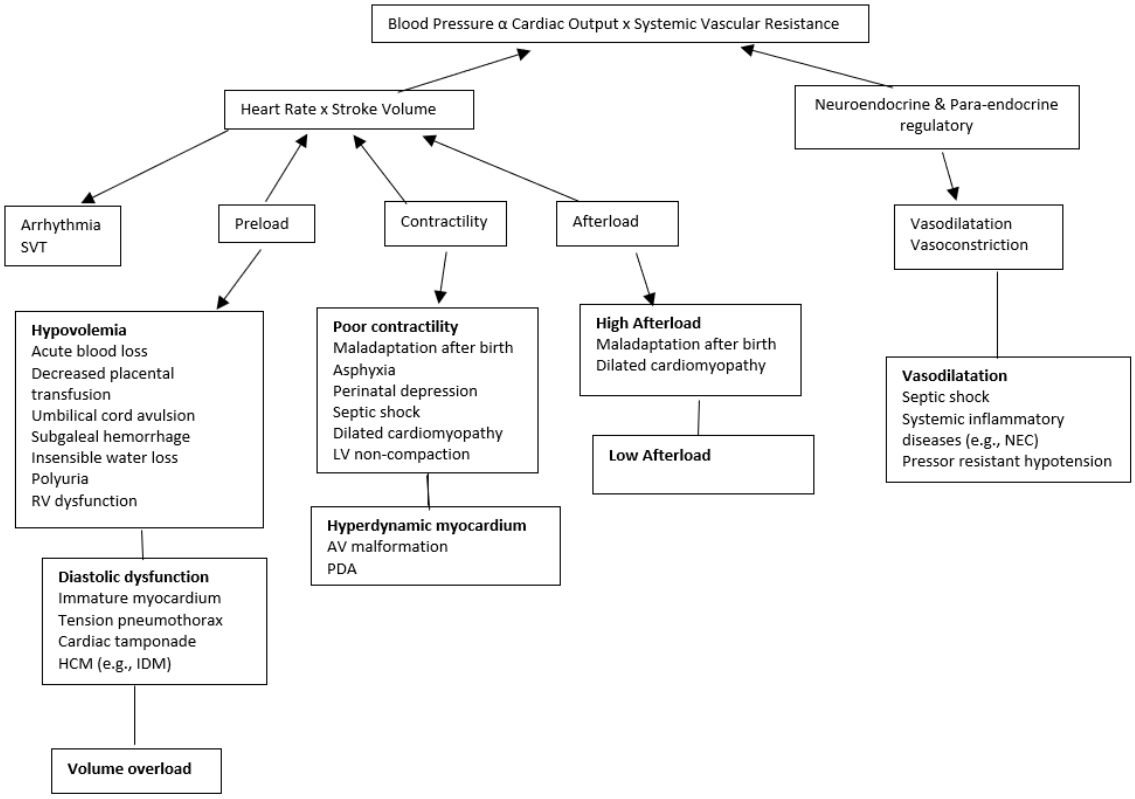
Cardiac output monitoring technology

Numerous hemodynamic monitoring technologies exist, with varying degrees of invasiveness and practicality in neonates. Some still remain in the domain of research only[5].

Invasive techniques –e.g., intermittent pulmonary artery thermodilution and Fick's method via a pulmonary artery catheter– are considered the gold standards for accurately determining CO in the clinical setting [21]. However, in neonates these methods are not feasible[2] as catheters are often too large and the invasiveness of these methods has been questioned in adult medicine[22]. Minimally invasive cardiac output monitoring technologies encompass devices not requiring the insertion of a pulmonary artery catheter – e.g., pulse contour analysis, pulse power analysis, partial carbon dioxide re-breathing and transpulmonary ultrasound dilution (TPUD)[23]. Some of these technologies require the placement of an arterial line (pulse contour and pulse power

analysis) and may need placement of a central venous line for calibration purposes [2]. These technologies have been poorly studied in the neonatal population whilst others are still under development (TPUD [24]).

Figure 1: Determinants of blood pressure and causes of hemodynamic compromise



Adapted from [17]

In response to these dilemmas, non-invasive monitoring technologies were developed, offering fully non-invasive methods of monitoring stroke volume (SV) and CO. Non-invasive CO technologies encompass Doppler ultrasound, cardiac MRI (cMRI), carbon dioxide and inert gas re-breathing and electrical biosensing technologies (EBT). Of these, only EBT can provide continuous hemodynamic monitoring.

Thoracic electrical biosensing technology

The first type of non-invasive cardiac monitoring, rheocardiography, was developed in 1949 by Kedrov[25] but only found popularity in 1966 when Kubicek re-designed it for use in the aerospace industry [26]. Since then, numerous iterations of this technology have become available in the healthcare industry. Various nomenclatures are used –thoracic electrical bioimpedance (TEB), electrical velocimetry (EV), electrical cardiometry (EC), impedance cardiometry, impedance cardiography (ICG), thoracocardiography, bioimpedance (BI), bioreactance (BR) and rheocardiography. Each of these have subtle differences, often with proprietary algorithms which SV and CO are calculated. These technologies have been grouped together under the umbrella term of electrical biosensing technology (EBT).

The underlying principle of EBT is the application of a high frequency, low amplitude electrical current across the thorax (TEBT) or entire body (WBEBT). Different tissues in the body display different resistance to electrical current flow (impedance, Z0), with the primary distribution being to the blood and extracellular fluid[27]. As blood flows through the aorta, there is an increase in impedance in systole and a decrease in diastole. This cyclical change in impedance (ΔZ0) over time (dZ0/dt) corresponds to SV, from which CO can be calculated.

Very few studies have utilised WEBT in neonates [28,29] whilst numerous studies have utilised TEBT. TEBT is divided into 2 broad categories: (1) bioimpedance and (2) bioreactance.

Bioimpedance (BI): In the early phase of development, bioimpedance assumed the chest to be a blood-filled cylinder through which the electrical current flowed and changed with diastole and systole. This model was found to be inaccurate and was update to a truncated cone model and further modified to only consider red blood cell alignment within the aorta during systole and diastole [27]. Despite these updates, bioimpedance was

considered to be too sensitive to external factors, which lead to the development of bioreactance [27].

Bioreactance (BR). In BR, it is assumed that blood flow changes are not only related to changes in impedance (Z0) (as in bioimpedance) but also changes in capacitance (biological tissue's ability to store an electrical current) and inductance (biological tissue's ability to store energy in a non-electrical form) (figure 2a). BR therefore measures phase shift (φ) (time delay between the applied and received electrical signal) of an oscillating current as it traverses the thorax (figure 2b). Technology utilising phase shifts is assumed to be more robust and less susceptible to noise from external factors in comparison to bioimpedance[27].

In BR, thoracic resistance and reactance create a time delay between the applied current and measured voltage, resulting in a phase shift (φ) (the NICOM signal) (figure 2b). The peak rate of change of φ ($d\varphi / dt_{max}$) is proportional to the peak aortic flow (figure 2c). The peak of the QRS complex from the ECG is used to mark the start of each beat, allowing the calculation of ventricular ejection time (VET) (determined from the first zero crossing of the $d\varphi/dt$ signal (beginning of ejection) and the second crossing of the $d\varphi/dt$ signal (end of ejection)). BR uses the following formula to estimate stroke volume (SV) (figure 2d&e):

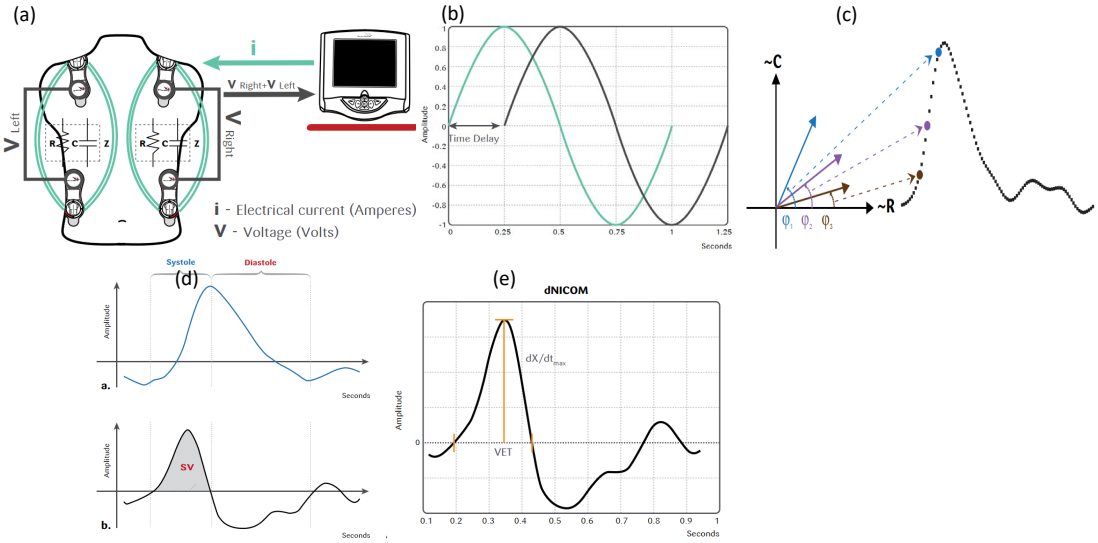
$$SV = C \times VET \times d\varphi / dt_{max} \qquad \text{Equation 2}$$

where C is a constant of proportionality, VET is ventricular ejection time, and $d\varphi / dt_{max}$ is the peak rate of change of the phase shift (φ). As dX/dt is an electrical measurement that is influenced by the transmission of the signal in the thoracic cavity, age and body surface area are considered when calculating SV and CO:

$$CO = f(dX/dt, VET, HR, weight, height, age) \qquad \text{Equation 3}$$

Phase shifts only occur during pulsatile flow. The majority of thoracic pulsatility is from the aorta during systole and diastole, thus ensuring that most of the BR signal is from the aorta and less reliant on other fluid in the thorax[30].

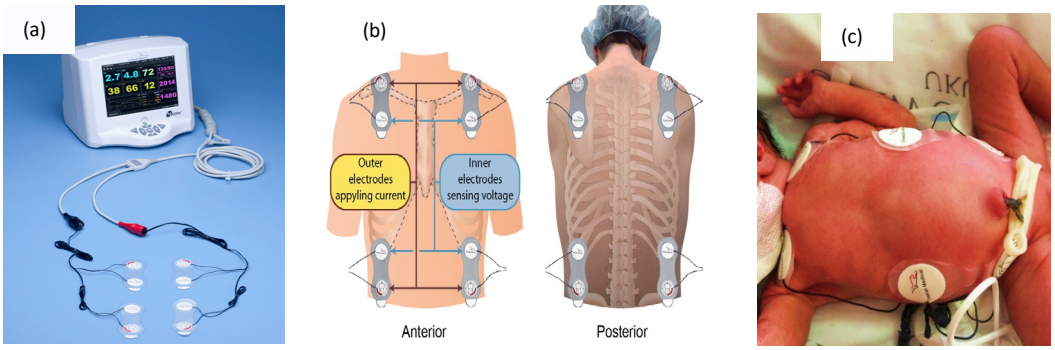
Figure 2: (a) Electrical equivalence of thorax, (b) Time delay translation to phase shift, (c) translation of phase shift to the NICOM signal (dNICOM), (d) calculation of volume from NICOM signal (dNICOM), (e) Mathematical calculation of SV.



(a) R – resistance, C- capacitance, Z – impedance
Adapted from Cheetah Medical "How does it work"

The BR device compromises a high frequency (75kHz) sine wave generator and four dual electrodes that establish an electrical current across the body (figure 3a). Each dual electrode has an outside voltage generator sensor and an inner voltage input amplifier sensor, with 2 dual sensors placed on the right and 2 on the left (figure 3b). Cardiac output measurement signals are generated separately (left and right sets of sensors) with the final cardiac output signal obtained by averaging the two signals. Sensors can be placed anterior or posterior (figure 3b) or can be adapted for neonatal use (figure 3c). Measurements are averaged over 60 seconds and data are provided every minute, continuously.

Figure 3: (a) NICOM Reliant, (b) dual sensor placement in adults and (c) dual sensor placement in neonates



(a) and (b) from "Cheetah NICOM: How does it work". Accessed from http://wiki.med.uottawa.ca/download/attachments/21692680/How+Does+it+Work.pdf?version=1&modificationDate=1387401223000

(c) from the current research

BR provides continuous monitoring of HR, SV, CO, total peripheral resistance (TPR), thoracic fluid content (TFC) and their indices (corrected for body surface) as well as various derivatives (table 1).

Numerous adult non-invasive cardiac output monitoring studies have been performed with systemic reviews showing a lack of accuracy and precision[31,32]. Despite this, various international health care funders have endorsed its use in the diagnosis and management of various adult cardiovascular diseases[33,34], stating that it is cost effective in the diagnosis, management, and follow-up of cardiac and renal related diseases and shock.

Non-invasive cardiac output monitoring in neonates

Simultaneous and continuous measurement of hemodynamic parameters are essential for optimal neonatal care. Written medical records only provide intermittent clinical information. The long intervals at which these assessments are recorded often miss the rapid changes in the hemodynamic status of newborn infants[1].

Table 1: Hemodynamic parameters measured and calculated by bioreactance

Hemodynamic parameter	Unit of measurement	Implication/ Use	Calculation
Cardiac output (CO)	l/min	Blood ejected per minute	CO=SVxHR
Cardiac Index (CI)	l/min/m^2 ml/kg/min	CO corrected for body surface area (BSA) or body weight	CI=CO/BSA CI=CO/weight (kg)
Heart rate (H	Bpm		
Ventricular ejection time (VET)	ms	Time of ventricular ejection beginning at aortic valve opening and ending at valvular closure	
dX/dt		Thoracic bioreactance electrical signal changing with pulsatile volume change during systole & diastole	
SV	ml	Volume ejected per beat	
SV Index (SVI)	ml/min/m^2 ml/kg	SV corrected for BSA or body weight	SVI=SV/BSA SVI= SV/weight (kg)
SV variation (SVV)	%	Calculated variation of SV from minute to minute as an indication of preload responsiveness	
Thoracic fluid content (TFC)	1/Z0 1/Ω	Reflects conductivity of chest cavity and correlates to thoracic fluid content	TFC=1/Z0
Dynamic change of TFC over time (TFCd)	%	Dynamic change of TFC over time – average change over last 10 readings	
TFC change from initiation (TFCd0)	%	Change in TFC from the average of first 5 readings at initiation of study	
Mean arterial pressure (MAP)	mmHg		
Total peripheral resistance (TPR)	mmHg.min/mL	Indication of vasotone	TPR = MAP/CO
TPR Index (TPRI)		TPR corrected for BSA	
Cardiac power (CP)	Watts	Work product generated by heart	CP=CO*MAP/451
Cardiac power index (CPI)		CP indexed to BSA	CPI = CP/BSA
DO_2I (if SpO_2 cable attached)	Oxygen delivery index		DO2I =1.39xHbx(S_PO_2/100)xCIx10

The current standard of non-invasive cardiac output monitoring in neonates is transthoracic echocardiography (TTE). Despite its clinical acceptability and non-invasive, bedside availability, it remains labour intensive, requires extensive training, provides only intermittent measurements of CO and SV, is an expensive technology and measurements are prone to inter- and intra-observer-variability [35].

Non-invasive cardiac output monitors offer the ability to provide non-invasive, objective continuous measurements of various hemodynamic measurements, requires minimal training, easy application of sensors and usability by all levels of medical personnel[36].

Despite the plausibility of this technique, few studies have been performed using TEBT, especially bioreactance, in preterm neonates.

Outline of thesis

Very little research has been performed utilising BR in preterm neonates[8–10]. The main aim of this thesis is to investigate the comprehensive use of bioreactance in preterm neonates (< 37 weeks gestational age) during the transitional phase, i.e., the first 72 hours of life.

In the **first study (chapter 2),** the agreement, in terms of accuracy and precision, of bioreactance in measuring cardiac output and stroke volume, as compared to transthoracic echocardiography-derived cardiac output and stroke volume, is investigated.
The hypothesis is that bioreactance agrees with transthoracic echocardiography for the measurement of cardiac output and stroke volume in preterm neonates.

In the **second study (chapter 3),** bioreactance-derived hemodynamic parameters during the transitional period in preterm neonates are described.

In the **third study (chapter 4)**, the ability of bioreactance to accurately track temporal changes in cardiac output and stroke volume (trending analysis), as compared to transthoracic echocardiography, is investigated.
The hypothesis is that bioreactance is an accurate trend monitor, as compared to transthoracic echocardiography, for cardiac output and stroke volume in preterm neonates.

In the **fourth study (chapter 5)** consists of a systematic review of clinical studies in neonates assessing the agreement and trending ability of thoracic electrical biosensing technologies. This was performed at this stage of the research so as to include the current research.

In the **fifth study (chapter 6)** the observed bioreactance-derived thoracic fluid content in the first 72 hours of life in preterm neonates is described, as well as thoracic fluid content parameters between neonates receiving different respiratory interventions.

The primary hypothesis is that bioreactance-derived thoracic fluid content does not decrease in the transitional period in neonates. The secondary hypothesis is that bioreactance-derived thoracic fluid content parameters do not differ, over time, between neonates receiving different respiratory interventions.

In **chapter 7**, discussion and conclusion are presented.

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CHAPTER 2

Agreement of bioreactance and transthoracic echocardiography in preterm neonates

Van Wyk L, Smith J, Lawrenson J, de Boode W-P. Agreement of cardiac output measurements between bioreactance and transthoracic echocardiography in preterm infants during the transitional phase: a single-centre, prospective study. Neonatology 2020;117(3):271-278. DOI:10.1159/000506203

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Agreement of Cardiac Output Measurements between Bioreactance and Transthoracic Echocardiography in Preterm Infants during the Transitional Phase: A Single-Centre, Prospective Study

Lizelle Van Wyk[a] Johan Smith[a] John Lawrenson[b] Willem Pieter de Boode[c]

[a]Division Neonatology, Department of Paediatrics and Child Health, Stellenbosch University and Tygerberg Children's Hospital, Cape Town, South Africa; [b]Paediatric Cardiology Unit, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; [c]Department of Neonatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, The Netherlands

Keywords
Cardiac output · Bioreactance · Preterm infants · Transition · Echocardiography

Abstract
Introduction: Bioreactance cardiac output (CO) monitors are able to non-invasively and continuously monitor CO. However, as a novel tool to measure CO, it must be proven to be accurate and precise. ***Objective:*** To determine the agreement between CO measured with a bioreactance monitor and transthoracic echocardiography-derived left ventricular output parameters in preterm infants. ***Methods:*** This is a prospective observational study in 63 preterm neonates with non-invasive respiratory support, not requiring inotrope support. The infants underwent continuous bioreactance monitoring of CO and stroke volume (SV) and simultaneous transthoracic echocardiography every 6 h until 72 h of life. ***Results:*** The agreement between bioreactance and transthoracic echocardiography, for both SV and CO, was poor. The percentage error was 67.5% for SV and 71.6% for CO. The mean error was 60.4% for SV and 69.8% for CO. Bias was affected by numerous variables. After correcting for time, CO and SV bias were significantly affected by the presence of an open patent ductus arteriosus and the level of CO. ***Conclusion:*** Bioreactance cannot be considered interchangeable with transthoracic echocardiography to measure CO in preterm infants during the transition phase. Agreement between bioreactance and other CO metrics should be assessed before concluding its accuracy or inaccuracy in neonates.

Introduction

Bioreactance (BR)-based technology is able to non-invasively and continuously monitor cardiac output (CO) and may be able to monitor hemodynamic status in neonates. There is, however, a paucity of data validating its use in preterm infants.

Two types of non-invasive transthoracic electrical biosensing technology (TEBT) are available: BR and bioimpedance (BI). BR measures phase shift – a technique

Lizelle Van Wyk
Department of Paediatrics and Child Health
Stellenbosch University and Tygerberg Children's Hospital
Francie van Zijl Road, Parow 7530 (South Africa)
lizelle@sun.ac.za

Table 1. Summary of neonatal TEBT versus TTE studies (LVO measurements)

Study	Patients/ paired measurements	TEBT method	Mean reference CO/SV (TTE)	Mean bias (reference – new method)	LOA	Bias%	Error%
LV SV measurements							
Grollmuss [7], 2012	24/240	BI	3.6 mL	0.37 mL	±1.07 mL	7.6	29
Boet [80], 2016	79/451	BI	n/a	–1.1 mL	n/a	n/a	n/a
Blohm [91], 2017	99/291	BI	5.25 mL	–0.7 mL	±1.3 mL	8	41
Weisz [19], 2014	25/75	BR	1.57 mL	0.63 mL	n/a	39	n/a
Total LVO measurements							
Weisz [18], 2012	10/97	BR	484 mL/min	153 mL/min	±112 mL/min	31	23
Noori [102], 2012	20/115	BI	536 mL/min	4 mL/min	±233 mL/min	0.74	43.6
Torigoe [11], 2015	28/81	BI	317 mL/min	–6.3 mL/min	±92 mL/min	2	29
Boet [8], 2016	79/451	BI	n/a	–200 L/min	±350 mL/min	n/a	n/a
Body-weight-indexed LVO measurements							
Song [12], 2014	60/109	BI	218 mL/kg/min	–18.8 mL/kg/min	±132 mL/kg/min	9	60
Boet [13], 2014	28/228	BI	256 mL/kg/min	8.9 mL/kg/min	±63 mL/kg/min	4	25
Weisz [19, 2014	25/75	BR	227 mL/kg/min	n/a	n/a	39	31
Blohm [14], 2014	26/41	BI	n/a	n/a	n/a	39	46
Forman [15], 2017	8/24	BI	121 mL/min/kg	n/a	n/a	27	n/a
Hsu [16], 2017	36/105	BI	252 mL/min/kg	5.3 mL/kg/min	±73 mL/kg/min	2	29

BI, bioimpedance; BR, bioreactance; CO, cardiac output; n/a, not specified in article; LOA, limit of agreement; LV, left ventricular; LVO, left ventricular output; SV, stroke volume; TEBT, thoracic electrical biosensing technology; TTE, transthoracic echocardiography.

that analyses the frequency spectra variation of a delivered oscillating current across the thoracic cavity. BI measures changes in signal amplitude. As such, BR is a refinement of BI, with an improved signal-to-noise ratio, and is not affected by electrode placement, body movement, or respiration. Phase shift signal changes are mathematically equated to stroke volume (SV) and CO [1].

Thermodilution technology, using a pulmonary artery catheter [2], and cardiac MRI [3] are considered the reference standard for CO measurement. However, the invasiveness and size of a pulmonary artery catheter and the impracticality of cardiac MRI for regular, repeated CO measurements impedes their use in neonates. Transthoracic echocardiography (TTE) is the most commonly used non-invasive method to estimate CO in neonatal intensive care units [4] but is dependent on the availability of a trained operator [5].

Most method comparison studies have used BI, with few using BR. The accuracy of BI and BR has been questioned in adults, especially when using TTE as a reference standard [6]. Some paediatric studies have shown acceptable agreement between TEBT and TTE [6]. BI studies in neonates have shown varied results with bias percentage of 0.74–39% and percentage error of 25–60% [7–17]. This may be due to the diversity in patient demographics, illness severities, ventilatory and circulatory support, as well as different underlying TEBT techniques (Table 1). Only 2 neonatal CO method comparison studies have used BR, showing a bias percentage of 31–39% and percentage error of 23–31% as compared to TTE-measured left ventricular output [18, 19].

The objective of the current study was to determine the agreement between CO measured with a BR monitor and TTE-derived left ventricular output parameters (SV and CO) in preterm infants receiving non-invasive respiratory support without the need for inotropic support during the first 72 h of life. It was hypothesized that there would be no difference between BR and TTE-derived measurements of SV and CO.

Methods

Study Design and Setting

A prospective, observational study was performed in the neonatal intensive care service of Tygerberg Hospital (Cape Town, South Africa), a tertiary academic hospital.

Study Population

All preterm infants (<37 weeks' gestational age) admitted to the neonatal service were eligible for enrolment. Infants were excluded if they: (1) required invasive ventilation or inotropic support, (2)

were diagnosed with congenital cardiac defects (except for patent ductus arteriosus [PDA] and patent foramen ovale [PFO]), (3) were diagnosed with severe congenital anomalies, and (4) were not expected to survive the first 72 h. Infants were enrolled within 3 h after delivery.

BR and TTE Methodology

All infants underwent continuous BR monitoring (NICOM Reliant®, Cheetah Medical, MA, USA) until 72 h of life. Sensor size was decreased by cutting the edges of the sensors down to the size of the gel electrode only. Sensors were placed according to the markers for upper and lower sensors. Four sensors were placed over the mid-clavicles and upper back bilaterally, as well as between the 6th and 7th intercostal spaces mid-axillary and stretching down towards the abdomen (Fig. 1). Sensors were only replaced within the 72 h of monitoring if they failed to provide an appropriate signal. SV_{BR} data was accessed directly from the Reliant® and CO_{BR} was calculated as $SV_{BR} \times$ heart rate. Min-to-min data was accessed from the Reliant®.

Echocardiography (TTE) was performed every 6 h for the first 72 h of life in all infants by a single investigator (L.V.W.). The aortic diameter was measured in the long axis parasternal view with zooming in at the level of the aortic valve hinge points. The aortic valve diameter was measured thrice and the average used. It was assumed to remain constant for the 72 h of examination. Aortic velocity time integral (VTI) was averaged over 5 cycles. Calculations from TTE measurements were: $SV_{TTE} = (\pi \times \text{aortic diameter}^2/4) \times \text{VTI}$ and $CO_{TTE} = SV_{TTE} \times$ heart rate.

A Vivid S6 (GE Healthcare, USA) ultrasound machine with a 10-MHz probe was used. BR readings prior to TTE were recorded. Patients with any suspected cardiac anomalies (excluding PDA and PFO) were referred to a paediatric cardiologist for review.

Statistical Analysis

Various data were categorised: gestational (2-week clusters); birth weight (ELBW, VLBW, LBW, >2,500 g); PFO: small (<0.5 mm) or large (≥0.5 mm); PDA (open or closed); CO was classified according to TTE measurements: low (<150 mL/kg/min) or normal (≥150 mL/kg/min). Data are presented as mean ± standard deviation or median (interquartile range) and number (proportion). BR and TTE data indexed to patient weight were used.

Statistical Definitions in CO Method Comparison Studies

Accuracy and precision of BR compared to TTE were analysed using repeated-measurement Bland-Altman analysis [17].

The following definitions were used:

1. Bias: refers to the mean difference between the reference method (TTE) and the new method (BR), calculated as: (TTE – BR). This represents the accuracy or systematic error between the two methods. It is represented by the mean line on the Bland-Altman graph.
2. Limits of agreement: calculated as (LOA = ±1.96 × SD). It refers to the precision (reproducibility/repeatability) of measurements and is estimated by the random error around the bias. This is represented by the ±1.96 SD lines on the Bland-Altman graphs.
3. Bias percentage (bias%) is calculated as bias indexed to the mean CO or SV (bias/mean × 100).
4. Percentage error (error% or PE) refers to the precision of a new method of CO measurement indexed to the mean CO in the study population (error% = ±1.96 × SD/mean CO × 100) [20, 21]. A percentage error of ≤30% is considered clinically acceptable and would indicate interchangeability of BR and TTE [17]. However, this assumes that the precision of the reference method is ±10–20%, which is not the case when using TTE as a reference standard.
5. Mean error (ME) (true precision (TP)) represents the PE of the new method taking into account the imprecision of the reference method, calculated as $\sqrt{((\text{PE-new method})^2 + (\text{PE-reference method})^2)}$, [10]. The interchangeability of two methods of CO monitoring can be assumed when the new method has an equal or better "true" precision than the reference method [17]. Given the error% of TTE of ±30% [22], this means that the combined percentage error of BR and TTE should be <42% ($\sqrt{((30)^2 + (30)^2)}$) to conclude that the two methods have a comparable precision.

Due to clustering of measurements over time, mixed-effect multi-linear regression was used to determine the relationship between bias and time. The time variable (postnatal age in hours) was evaluated with a mixed-effects model. Predictive margins were calculated to determine the effect of time (as a non-linear variable) on bias.

The effect of variables (gestational age, birth weight, postnatal age category, PDA status, CO level, respiratory support mode) on bias was analysed using Student's *t* test or ANOVA, as appropriate. Variables with $p < 0.1$ were included in multivariate regression.

Coefficient of variation (CV = standard deviation/mean × 100%) for BR and TTE was calculated as an expression of each methodology's precision. Acceptable levels of CV are defined as <10% for both TTE and BR [23]. The intraclass correlation coefficient for repeatability of TTE measurements (aorta VTI) was calculated for intra-individual variability.

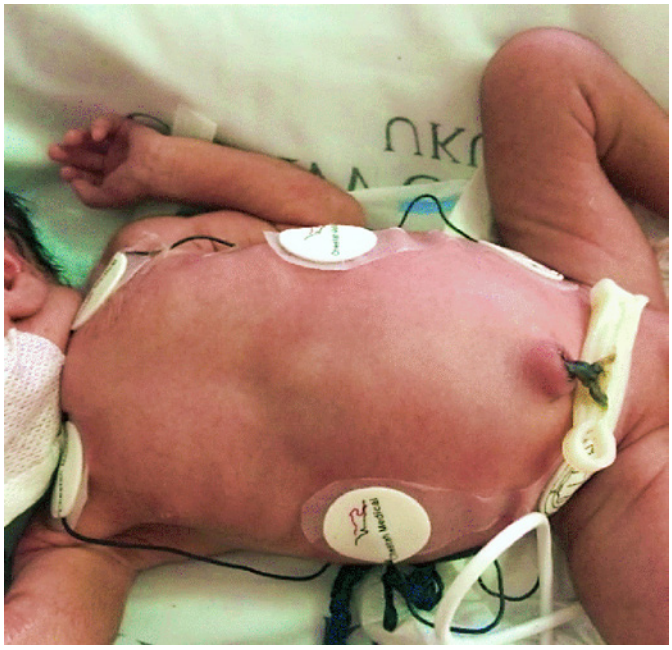

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Fig. 1. NICOM Reliant® sensor placement.

Table 2. Summary of the study parameters

Parameter	*n* = 63
Male	33 (52)
Paired measurements	754
African race	34 (54)
Gestational age, weeks	31.3±2.7
<28 weeks	8 (13)
29–30 weeks	20 (32)
31–32 weeks	12 (19)
33–34 weeks	13 (21)
35–36 weeks	10 (16)
Birthweight, g	1,563±411
Complete antenatal steroids	21 (33)
Caesarean section	51 (81)
Twins	16 (25)
IUGR	5 (8)
EOS[a]	7 (11)
Respiratory support	
None	14 (22)
NPO_2	3 (5)
HFNC	2 (3)
CPAP	44 (70)
PDA	
Closed before 72 h postnatal age	56 (89)
Postnatal age of closure, h	18
SNAPPE-II score	8 (0–15)
Heart rate, bpm	144 (133–154)
Mean non-invasive blood pressure, mm Hg	46 (41–52)

Data are presented as *n* (%), mean ± SD, or median (IQR), as appropriate. CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula (flow 3–6 L); LVO, left ventricular output; NPO2, nasal prong oxygen (flow ≤2L); PDA, patent ductus arteriosus; SNAPPE-II score, score for neonatal acute physiology with perinatal extension II. [a] EOS – defined as CRP >10 mg/L at 12–24 h of postnatal age.

Data were analysed using STATA IC15 (StataCorp (2017), College Station, TX, USA) and MedCalc v18.10 (MedCalc Software bvba (2016), Ostend, Belgium). Statistical significance is defined as a p value <0.05.

Results

Patient Demographics

A total of 89 neonates were enrolled between January 2014 and January 2016 and underwent simultaneous BR and TTE examinations at the specified time points. Four infants were excluded on clinical grounds, namely incorrect gestational age (n = 1) or impaired contractility (requiring invasive ventilation and inotropic support; n = 3). A further 22 patients had to be excluded due to incomplete BR (corrupt and lost data due to BR monitor damage during electricity supply failures). A total of 63 infants (<37 weeks' gestational age) were included in the study (Table 2).

The CV, at specific time points, was within the acceptable limits of <10% (online suppl. Data; for all online suppl. material, see www.karger.com/doi/10.1159/000506203). The intraclass correlation coefficient for aortic VTI measurements showed a good repeatability of measurements (0.89, 95% CI: 0.876; 0.900).

Mean CO was 124.4 mL/kg/min and 105.6 mL/kg/min for CO_{TTE} and CO_{BR}, respectively. Mean SV was 0.87 mL/kg and 0.73 mL/kg for SV_{TTE} and SV_{BR}, respectively. BR underestimated CO and SV as compared to TTE, at all time points (online suppl. data).

Agreement between BR and TTE

Repeated-measurement Bland-Altman graph analysis showed that bias was relatively small (0.13 mL/kg for SV and 18.5 mL/kg/min for CO) but with wide limits of agreement (Fig. 2). The percentage error was 67.5% for SV and 71.6% for CO. The mean error was 60.4 and 69.8% for SV and CO, respectively (online suppl. data).

Effect of Time on Bias during the Transitional Period

Bias was assessed at each time point (3–72 h) (online suppl. data). Mean CO and SV bias decreased over time until 42 h of age (Fig. 3). Repeated-measurement Bland-Altman evaluation showed a decrease in bias of 9 mL/kg/min after 42 h of postnatal age, but with persisting wide limits of agreement (online suppl. data). SV bias showed similar improvement after 42 h of age (online suppl. data).

Other Variables Affecting Bias

CO bias was significantly affected by all variables except birth weight category. Only PDA category (p = 0.000), respiratory support method (p = 0.009), and CO level (p = 0.000) remained significant after multivariate regression with correction for time (online suppl. data).

SV bias was affected by gestational age, postnatal age category, PFO category, PDA category, and CO level but not birthweight category, respiratory support method, or PEEP category. Only CO level (p = 0.000) remained significant after multivariate regression with correction for time (online suppl. data).

Effect of PDA and CPAP

An open PDA doubled the bias for CO and SV, as compared to a closed PDA (online suppl. data). CPAP affected CO bias (p = 0.009) but not SV bias (p = 0.113).

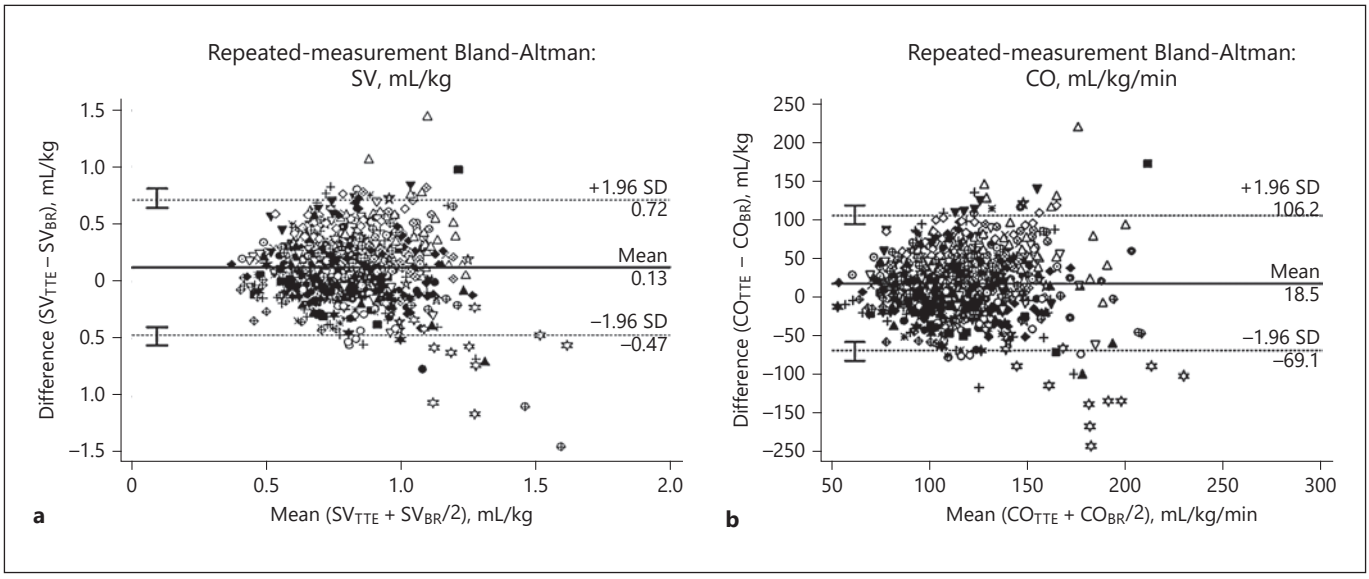

Fig. 2. Repeated-measurement Bland-Altman plots for stroke volume (SV) (**a**) and cardiac output (CO) (**b**).

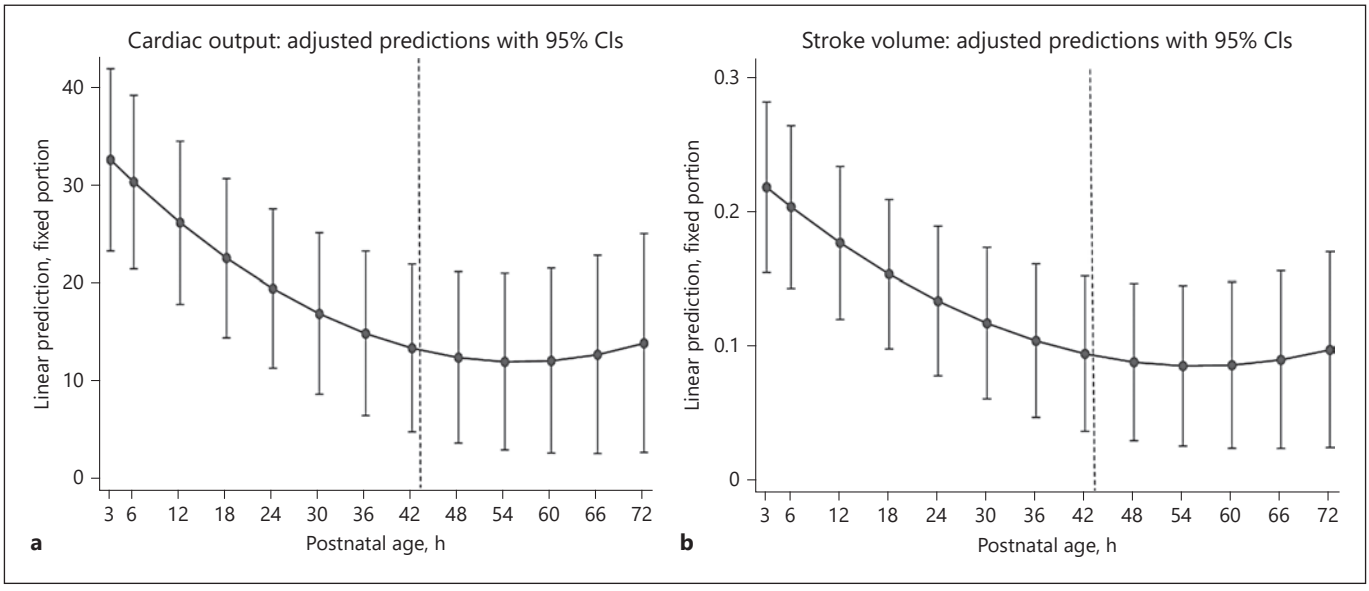

Fig. 3. Postnatal effect on bias change in cardiac output (**a**) and stroke volume (**b**).

Effect of CO Level on Mean Bias

The mean CO and SV bias differed with different levels of CO (online suppl. data). As CO and SV increased, mean bias also increased – as reflected by the angle of the mean and limit of agreement lines in the Bland-Altman graphs (Fig. 4).

Discussion

To the best of our knowledge, we present the largest study analysing the agreement between BR- and TTE-derived CO parameters, encompassing a total of 754 paired measurements. It shows that the two methods do not appear to be interchangeable for CO measurement. Despite relatively small mean bias and bias percentage, the limits

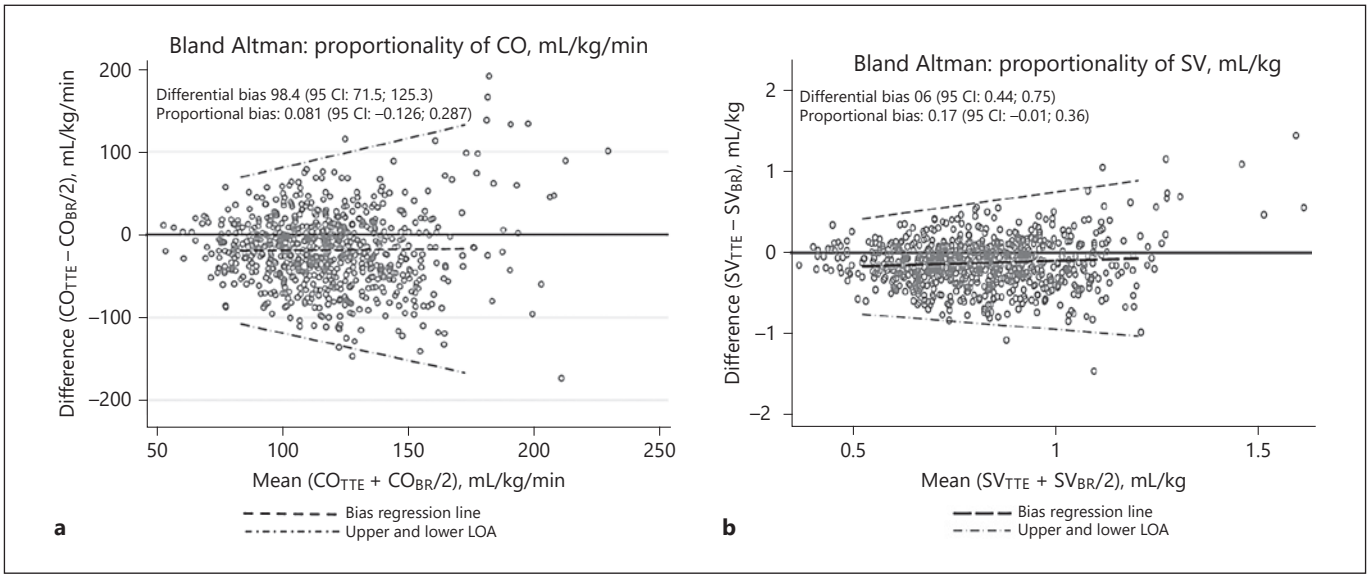

Fig. 4. Proportionality of cardiac output (CO) (**a**) and stroke volume (SV) (**b**).

of agreement are wide with unacceptably high error percentage and mean error. However, postnatal age seems to be a strong influencer on accuracy, possibly explained by the physiological changes of numerous haemodynamic parameters in the transitional period [24].

Accuracy of BR Compared to TTE

In the current study, BR underestimated left ventricular SV and CO. This is similar to observations in other BR studies in neonates [18, 19], as well as neonatal BI studies (Table 1).

The observed error percentages were much higher than the acceptable 30% and double the values found in other neonatal BR method comparison studies [18, 19]. Some neonatal BI method comparison studies have shown error percentages up to 60% [12]. The difference in patient populations and management strategies may contribute to the large variation.

Factors Affecting Bias between BR and TTE

The association between mean bias and postnatal age has not been previously reported. In this study mean CO and SV bias decreased with increasing age, reaching a steady point at 42 h of life. This may be due to the physical maturation over the first 48 h, with most infants in the study population having closed PDAs and decreased CPAP requirements at this age. In this study, after correcting for time, only the level of CO and PDA were shown to affect the accuracy of BR.

The presence of PDA and/or PFO have been shown to have variable effects on bias and precision in TEBT studies [9]. After correcting for time, this study showed that bias decreased significantly with closure of the PDA. This is probably due to the decrease in aortic volume fluctuations, resulting in more stable phase shift signals in BR and improved accuracy.

CPAP has been shown to affect the accuracy of TEBT-TTE measurements [12, 25]. This may be due to CPAP causing an increase in intrathoracic pressure, leading to an increase in the distance between the sensing electrodes and the descending aorta, thereby decreasing impedance measurements [18] and decreasing accuracy. In the current study, CPAP affected the accuracy of CO measurements but not SV. This may be due to the difference in heart rates in the preterm neonates subjected to CPAP compared to those without CPAP (149 ± 18 vs. 141 ± 14, respectively, $p = 0.000$).

Mean bias was influenced by the level of CO. In this study, bias increased significantly in higher CO states (≥150 mL/kg). This finding is consistent with other studies showing increased bias at higher CO and SV ranges [8, 16, 19].

TTE has an error percentage of ±30%, compared to indicator dilution techniques [21], and can therefore not be considered an ideal reference standard. Due to the inaccuracies of TTE, disagreement between TTE and BR may not automatically indicate the need to reject BR as a new method of measuring CO [21]. BR needs to be vali-

dated against more accurate reference technologies, such as indicator dilution or cardiac MRI.

This study has several limitations. Despite the large number of patients recruited, many data (22 patients, potentially an additional 264 paired BR-TTE measurements) were lost due to hospital power supply issues leading to BR monitor damage. Our results were from a single centre in a resource-limited environment. Nevertheless, our study provides insight into real-life practice. Inter-rate variability of TTE parameters was not performed.

It is unclear as to what constitutes acceptable limits of agreement in CO monitors in neonates. This needs further study and should be pre-defined in future TEBT-TTE studies.

Data in this study were collected longitudinally and may require alternative statistical analysis [26]. The data also showed significant proportionality which also complicates statistical analysis [27] and needs to be addressed in further research.

Conclusion

Currently, BR cannot be considered interchangeable with TTE for the measurement of CO in preterm infants during the transition phase. Agreement between BR and other CO metrics should be assessed before concluding its accuracy or inaccuracy in neonates.

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Statement of Ethics

This research was conducted in accordance with the World Medical Association Declaration of Helsinki. The parents of the infants provided written consent. The study was approved by the Human Research Ethics Committee of Stellenbosch University (Cape Town, South Africa).

Disclosure Statement

L. Van Wyk declares that Amayezu Medical provided BR monitors and sensors, but no monetary incentives were provided. W.P. de Boode declares research support from Cheetah Medical.

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Author Contributions

L. Van Wyk: primary investigator, research concept, data acquisition, data analysis, and manuscript preparation and editing. J. Smith, J. Lawrenson, and W.P. de Boode: supervisor, manuscript preparation and editing, and final manuscript approval.

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Supplemental data: Agreement of cardiac output measurements between bioreactance and transthoracic echocardiography in preterm infants during the transitional phase: a single-centre, prospective study

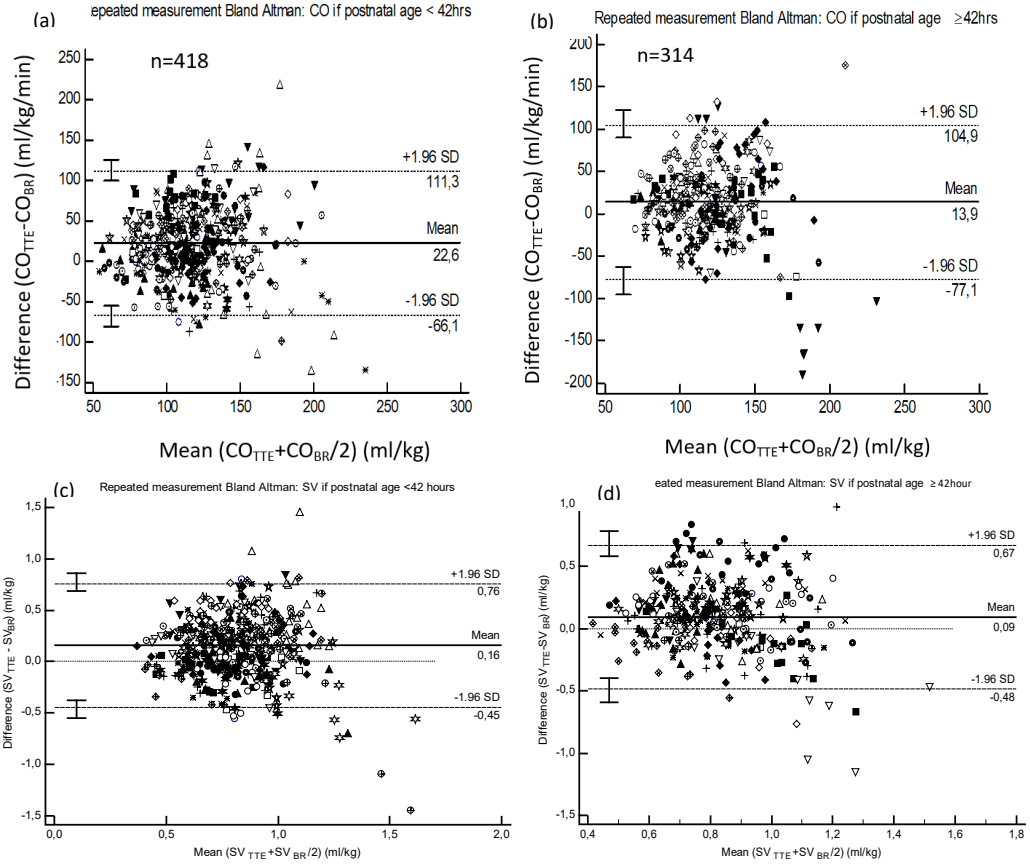
Supplemental data Table S1. Coefficient of variation (%) for TTE (aortic VTI) and BR at specific time points

Patient	Time point 0		Time point: 48hrs		Time point: 72hrs	
	BR	TTE	BR	TTE	BR	TTE
1	4.7	5.6	7.2	3.4	5.3	2
2	5.2	4.9	3.6	9	5.4	1.3
3	12.6	4.9	5.5	11.4	9.9	6.5
4	9.2	3.3	13.1	16.1	10	5.5
5	4.5	9.3	9.8	8.2	7.7	5.6
6	8.1	14.6	6.3	4.9	1.8	8.9
7	7.9	3.9	6.7	7.1	3.1	7.4
8	2.6	6.9	7.5	3.8	4.2	9.8
9	4.7	2.6	3.6	5.8	2.6	5.2
10	10.7	2.5	7.5	11	10.4	8.9
11	3.3	10	2.9	15.4	6.9	7.9
12	2.3	11.3	7.4	7.8	5.9	8.3
13	5.3	12.2	4	4.9	6.9	4.8
14	3.2	21	6.7	7.3	4.8	3.3
15	4.4	5.4	3.5	5.4	9.7	19.1
Mean ±SD (%)	5.91±3.09	7.89±5.20	6.35±2.72	8.10±3.90	6.31 ±2.81	6.97±4.21
p-value	0.213		0.165		0.617	

Supplemental data Table S2. Agreement between BR and TTE_{LVO} derived hemodynamic variables (n=63 patients, 754 repeated measurements)

Measurement	**BR** Median (IQR)	**TTE** Median (IQR)	**Mean (BR+TTE/2)**	**Bias** Mean ±SD	**Limits of agreement** (lower limit; upper limit)	**Bias %**	**Percentage error** (%)	**Mean error** (%)
SV (ml/kg)	0.73 (0.58-0.88)	0.87 (0.74-1.03)	0.80	0.13 ± 0.30	0.72; -0.47	16.3	67.5	60.4
CO (ml/kg/min)	105.6 (85.1-126.2)	124.4 (103.5-149.4)	115.0	18.5 ± 45.5	106.2; -69.1	16.0	71.6	69.8

Supplemental data Figure S1: Stroke volume (a & b) bias and cardiac output (c & d) bias for postnatal age <42hrs and ≥ 42hours



Supplemental data Table S3. Bias at different postnatal ages

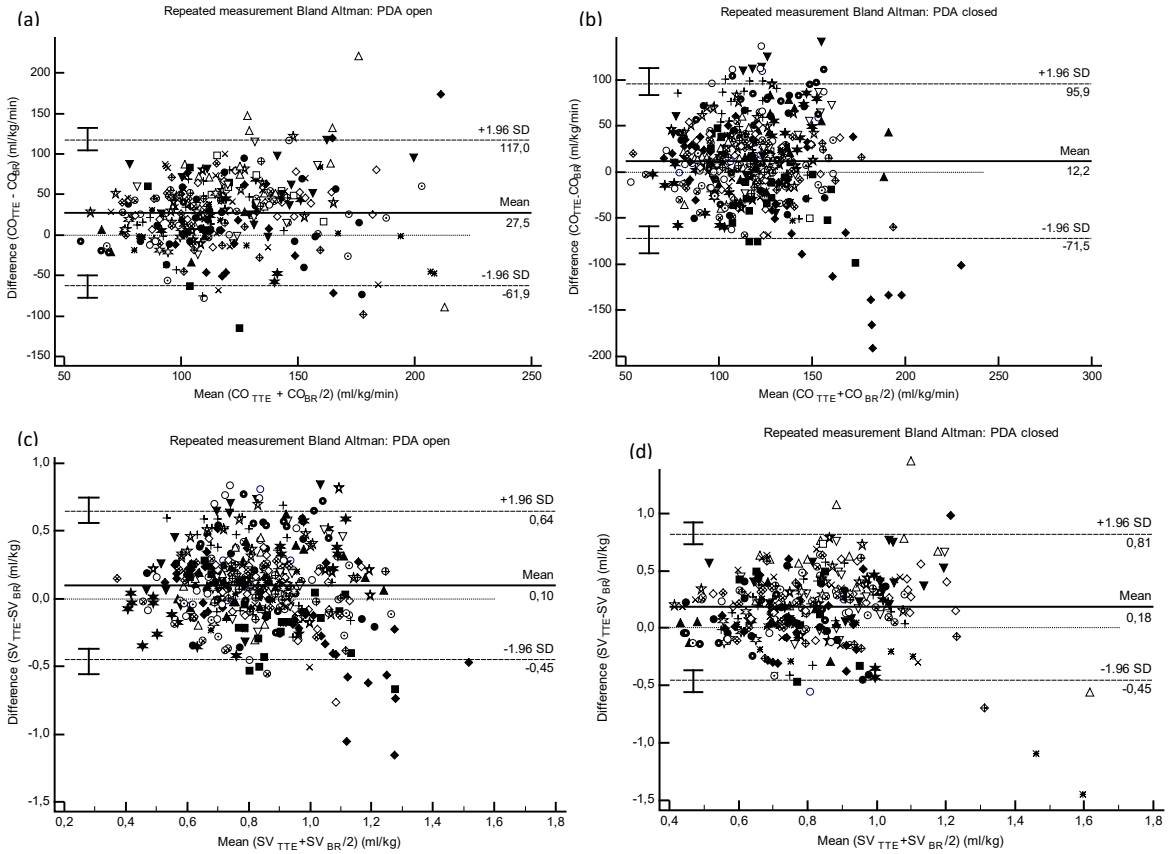
Postnatal age (hrs)	CO Bias (ml/kg/min)	p-value	SV bias (ml/kg)	p-value
3	34.4±48.9		0.23±0.30	
6	28.4±43.2		0.19±0.31	
12	30.4±42.8		0.19±0.28	
18	19.6±39.0		0.12±0.33	
24	18.4±47.1		0.11±0.35	
30	19.7±45.0		0.15±0.29	
36	10.3±40.8	0.018	0.08±0.26	0.050
42	5.6±42.5		0.05±0.27	
48	15.0±39.8		0.11±0.26	
54	16.0±48.1		0.10±0.31	
60	14.4±45.5		0.11±0.26	
66	20.1±40.4		0.14±0.29	
72	10.7±51.5		0.07±0.32	

Supplemental data Table S4. Univariate and multivariate analysis of variables affecting bias of body-weight indexed cardiac output and stroke volume bias

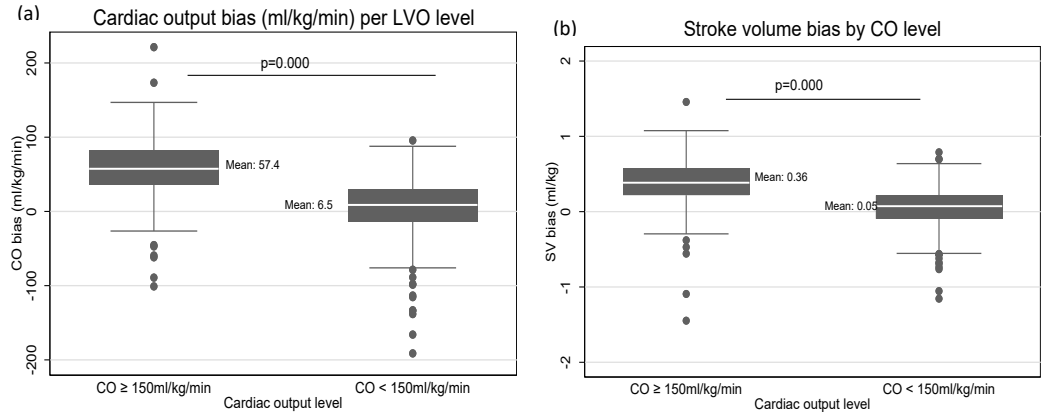
Variable	Category	n	CO bias (ml/kg/min)	Uni-p#	Multi-p##	Bias SV (ml/min)	Uni-p#	Multi-p##
Gestational age category	< 28 weeks	95	24.2±39.1	0.000	0.698	0.15±0.24	0.000	0.375
	29-30 weeks	225	22.7±42.9			0.14±0.31		
	31-32 weeks	155	33.4±40.5			0.23±0.27		
	33-34 weeks	152	-2.3±53.9			0.02±0.34		
	35-36 weeks*	126	16.1±34.4			0.11±0.24		
Birth weight category	≤1000g	57	26.5±47.3	0.088	0.769	0.15±0.30	0.490	na
	1001-1500g	271	22.7±40.7			0.15±0.29		
	1501-2500g	413	15.8±47.1			0.12±0.30		
	≥2501g*	13	7.0±28.6			0.05±0.20		
Postnatal age category	0-24hrs*	304	26.3±44.5	0.000	0.536	0.17±0.32	0.009	0.200
	25-48hrs	232	12.8±42.1			0.10±0.27		
	49-72hrs	218	15.2±46.5			0.11±0.29		
PFO Category	<0.5*	240	33.4±44.7	0.017	Excluded$	0.23±0.29	0.042	Excluded$
	≥0.5	19	7.5±50.1			0.09±0.30		
PDA category	Closed*	442	12.5±44.6	0.000	0.042	0.10±0.29	0.000	0.015
	Open	304	28.7±43.7			0.18±031		
CO category	<150ml/kg/min	570	6.5±37.6	0.000	0.000	0.05±0.25	0.000	0.000
	≥150ml/kg/min*	184	57.4±43.3			0.36±0.32		
Respiratory support method	None*	419	15.7±43.7	0.026	0.009	0.11±0.28	0.113	na
	CPAP	335	23.0±45.8			0.15±0.32		
PEEP category	≤5cmH2O	329	23.2±44.3	0.034	Excluded$$	0.15±0.31	0.101	na
	>5cmH2O	20	0.8±64.3			0.03±0.39		

Data as mean ±SD,
*Reference category
Univariate regression p-value; ## multivariate regression p-value
$ Excluded due to large portion missing data; $$ due excluded to interaction variable with RS support method
CO – cardiac output; na – not applicable (univariate p>0.1); PDA – patent ductus arteriosus; PEEP – positive end expiratory pressure; PFO – patent foramen ovale; SV – stroke volume

Supplemental data Figure S2. Cardiac output (a&b) and stroke volume (c&d) bias for open and closed PDA



Supplemental data Figure S3. Cardiac output(a) and stroke volume (b) bias per LVO category



CHAPTER 3

Bioreactance-derived hemodynamic parameters in the transitional phase in preterm neonates

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ORIGINAL RESEARCH

Bioreactance-derived haemodynamic parameters in the transitional phase in preterm neonates: a longitudinal study

Lizelle Van Wyk[1] · Johan Smith[1] · John Lawrenson[2] · Carl J. Lombard[3,4] · Willem Pieter de Boode[5]

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Abstract

Bioreactance (BR) is a novel, non-invasive technology that is able to provide minute-to-minute monitoring of cardiac output and additional haemodynamic variables. This study aimed to determine the values for BR-derived haemodynamic variables in stable preterm neonates during the transitional period. A prospective observational study was performed in a group of stable preterm (< 37 weeks) infants in the neonatal service of Tygerberg Children's Hospital, Cape Town, South Africa. All infants underwent continuous bioreactance (BR) monitoring until 72 h of life. Sixty three preterm infants with a mean gestational age of 31 weeks and mean birth weight of 1563 g were enrolled. Summary data and time series graphs were drawn for BR-derived heart rate, non-invasive blood pressure, stroke volume, cardiac output and total peripheral resistance index. All haemodynamic parameters were significantly associated with postnatal age, after correction for clinical variables (gestational age, birth weight, respiratory support mode). To our knowledge, this is the first paper to present longitudinal BR-derived haemodynamic variable data in a cohort of stable preterm infants, not requiring invasive ventilation or inotropic support, during the first 72 h of life. Bioreactance-derived haemodynamic monitoring is non-invasive and offers the ability to simultaneously monitor numerous haemodynamic parameters of global systemic blood flow. Moreover, it may provide insight into transitional physiology and its pathophysiology.

Keywords Bioreactance · Transition · Haemodynamics · Preterm · Longitudinal

1 Introduction

Indirect measures of cardiac output, such as heart rate (HR) and blood pressure (BP), are inadequate for assessment of neonatal haemodynamics [1]. A complex interaction exists between HR, blood flow, total peripheral vascular resistance (TPR) and BP to ensure that metabolic cellular oxygen demand is met [2]. Comprehensive monitoring of physiological variables is therefore required during the transitional period given the risk of maladaptation to extra-uterine life. Simultaneous and continuous assessment of haemodynamic parameters is essential for optimal care. Written or electronic medical records only provide intermittent clinical information at long intervals which is inadequate to depict the often rapid changes in the haemodynamic status of newborn infants [1]. Numerous medical interventions as well as physiological changes in this period are known to affect the newborn's haemodynamic wellbeing [2].

Bioreactance (BR), a novel, non-invasive technology, utilises non-invasively delivered oscillating current across the thoracic cavity to mathematically calculate stroke volume

✉ Lizelle Van Wyk
lizelle@sun.ac.za

1 Division Neonatology, Dept. Pediatrics & Child Health, Stellenbosch University and Tygerberg Children's Hospital, Cape Town, South Africa

2 Pediatric Cardiology Unit, Dept. Pediatrics & Child Health, Stellenbosch University, Cape Town, South Africa

3 Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University, Cape Town, South Africa

4 Biostatistics Unit, South African Medical Research Council, Cape Town, South Africa

5 Division of Neonatology, Dept. of Perinatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, The Netherlands

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(SV) and cardiac output (CO) [3]. It is able to provide minute-to-minute monitoring of HR, SV, CO, TPR and other haemodynamic variables. Normative BR-derived haemodynamic data may be able to describe a neonate's haemodynamic status. BR's ability to provide minute-to-minute data may provide (patho)physiological insights into the rapidly changing haemodynamics of the transitional phase of newborn infants [4].

Non-invasive cardiac output monitors, including BR, have the advantage of being fully non-invasive and low cost. BR has advantages above bioimpedance, including less interference from patient movement, electrical noise, lead placement, respiratory effort and body-mass index due to a higher signal to noise ratio [5]. However, disadvantages are the possible effect of electrocautery during surgery [6] and the contradictory evidence regarding accuracy [7]. Despite these variable results regarding accuracy and precision, thoracic electrical biosensing technology (TEBT), encompassing bioimpedance (BI) and bioreactance (BR), is used to monitor CO in numerous clinical and research environments, in neonates, children and adults [8]. In neonatology, BR is increasingly used to monitor cardiac output [9], ductal persistency (7), thoracic fluid content [10], haemodynamic changes during blood transfusion [11] and low CO in adverse neonatal outcomes [12].

Normative data for bioimpedance (BI)-derived haemodynamic variables have been published [13], showing an association with neonatal maturity [14]. BR, however, differs from BI: BR measures electrical phase shift as an oscillating current traverses the thorax, whereas BI measures impedance changes only [15]. As such, BR is considered more robust than BI [15].

No data on BR-derived haemodynamic parameters in preterm infants are available. We aimed to determine longitudinal values of various bioreactance-derived haemodynamic parameters during the first 72 h of life in a stable cohort of preterm (< 37 weeks) infants.

2 Methodology

2.1 Study design and setting

A prospective observational, longitudinal study was performed in the neonatal service of Tygerberg Children's Hospital, Cape Town, South Africa, between December 2016 and July 2017.

2.2 Study population

All preterm infants (< 37 weeks gestational age) admitted to the neonatal service were eligible for enrolment. Infants with antenatally or postnatally diagnosed congenital cardiac defects [except for patent ductus arteriosus (PDA) and patent foramen ovale (PFO)], severe congenital anomalies and infants not expected to survive the first 72 h of life, were excluded. Infants requiring invasive ventilation or inotropic support were also excluded. Infants were enrolled within 3 h after delivery.

The study was performed in a group of stable preterm infants. All infants received standard non-invasive respiratory support {flow driver nasal continuous positive airway pressure (nCPAP) [5–6 cm H_20 PEEP (peak end expiratory pressure)] and surfactant via less invasive surfactant administration, as required}, peripheral intravenous lines, peripheral saturation monitoring. Enteral nutrition (breastmilk only) was started as available and no central lines were placed. All infants were cared for in servo-controlled thermal environments (radiant warmer or incubator). nCPAP was weaned at the discretion of the attending medical personnel. Preterm infants were not routinely screened for a PDA (screening occurred when an infant was considered symptomatic) and therefore no infant received pharmaceutical treatment for a PDA.

The University of Stellenbosch granted ethical approval (N13/04/053). All parents provided written consent.

2.3 Bioreactance monitoring

All infants underwent continuous bioreactance (BR) monitoring (NICOM® Reliant, Cheetah Medical, Massachusetts) until 72 h of life. Sensors were placed as per manufacturer's specifications. Sensor size was decreased by cutting the edges of the sensors down to the size of the gel electrode only.

Studied haemodynamic parameters included: HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), stroke volume (SV), cardiac output (CO) and total peripheral resistance index (TPRI). Non-invasive blood pressure (NIBP) and HR were monitored by the BR monitor. The appropriate size BP cuff was placed on a lower limb (due to the placement of peripheral intravenous lines on the upper limbs). NIBP was set to be measured every 30 min for the 72 h of monitoring.

NICOM reliant measures CO, calculated as HR x SV, as litres/ minute, accurate to only 1 decimal point. For this study, CO was calculated offline using the measured SV (in mL expressed with 2 decimal points) and HR to obtain CO as millilitre/ min for optimal accuracy in this neonatal population.

Postnatal age (PNA) measurements of all haemodynamic parameters were recorded at the initiation of the study (within 3 h of delivery) and at every 6 h of life. Time-point specific haemodynamic parameters were recorded at the specific time point and were not averaged. All haemodynamic parameters were recorded off-line.

2.4 Statistical analysis

Data are presented as mean ± standard deviation and number (proportion). BR-derived haemodynamic parameters were calculated according to patient weight (CO and SV) or according to body surface area (TPR).

Categorical indicators for gestational age (< 28, 29–30, 31–32, 33–34, 35–36 weeks gestational age) and birth weight [extremely low birth weight (ELBW) < 1000 g, very low birth weight (VLBW) 1001–1500 g and low birth weight (LBW) 1501–2500 g] were derived. Respiratory support mode was classified as continuous positive pressure (CPAP) [for infants receiving nCPAP and high flow nasal cannula (HFNC) at 3-6 l flow] and no CPAP (for infants receiving no respiratory support and nasal prong oxygen at 1–2 l flow).

Time series graphs were constructed for all variables over the first 72 h of life, using the mean value of each haemodynamic parameter at each time point. Repeated measurement analysis of variance (ANOVA) was performed to determine the association between the different BR-derived haemodynamic parameters and all variables [postnatal age (PNA), gender, gestational age (GA) and birth weight (BW)], separately. If ANOVA was significant ($p < 0.05$), post-hoc pairwise comparison of means analysis, with Bonferonni correction, was performed to determine between-group differences. A linear mixed effects regression was performed to determine the fixed effects of PNA and clinical variables on all haemodynamic parameters with the participant as the random effect to account for the repeated measure. A linear time effect model was specified for the random effect with an unstructured covariance matrix.

Data were analysed using STATA IC15 (StataCorp, 2017, College Station, TX, USA) and MedCalc v18.10 (Medcalc Software bvba, 2016, Ostend, Belgium). Statistical significance was defined as a p-value < 0.05, apart from Bonferonni corrections ($p < 0.006$).

Results are reported according to STROBE guidelines.

3 Results

Seventy-nine infants were enrolled in the study. Power disruptions at the hospital led to machine failures and corrupted data, thereby leading to incomplete data sets in 16 patients. After excluding these 16 patients, 63 were included in the study. Patient demographics are shown in Table 1.

Table 1 Study patient demographics

Parameter		n = 63
Male, n (%)		33 (52)
Gestational age (weeks), mean ± SD		31.3 ± 2.7
Gestational age category	≤ 28 weeks, n (%)	8 (13)
	29–30 weeks, n (%)	20 (32)
	31–32 weeks, n (%)	12 (19)
	33–34 weeks, n (%)	13 (20)
	35–36 weeks, n (%)	10 (16)
Birthweight (grams), mean ± SD		1563 ± 411
Birth weight category	ELBW (≤ 1000 g), n (%)	5 (8)
	VLBW (1001–1500 g), n (%)	24 (38)
	LBW (1501–2500 g), n (%)	33 (52)
	> 2500 g, n (%)	1 (2)
Complete course antenatal steroids, n (%)		21 (33)
Cesarean section, n (%)		51 (81)
Respiratory support mode	None, n (%)	14 (22)
	NPO_2, n (%)	3 (5)
	HFNC, n (%)	2 (3)
	nCPAP, n (%)	44 (70)
	PEEP (cm H_2O), mean ± SD	4.0 ± 0.9
PDA	Spontaneous closure before 72 h postnatal age, n (%)	56 (89)
EOS, n (%)		7(11)
SNAPPE-II score, mean ± SD		11.4 ± 13.2
Number BR measurements		754

BR bioreactance, *nCPAP* nasal continuous positive airway pressure, *ELBW* extremely low birth weight, *HFNC* high flow nasal cannula (3–6 l flow), *LBW* low birth weight, *NPO_2* nasal prong oxygen (≤ 2 l flow), *PDA* patent ductus arteriosus, *PEEP* peak end expiratory pressure, *SNAPPE-II* Score for neonatal acute physiology with perinatal extension-II, *VLBW* very low birth weight

3.1 Effect of postnatal age on BR-derived haemodynamic variables

Summary data, for the whole study cohort, of all BR-derived haemodynamic variables, at each postnatal age (PNA) time point, are shown in Table 2.

Time-series graphs, using time-point mean values, for the first 72 h of life, were constructed for all haemodynamic parameters (Fig. 1). Time was significantly associated with all haemodynamic parameters: HR ($p = 0.002$), SBP, DBP, MBP, CO, SV, TPRI (all $p < 0.001$). HR, SV and CO showed initial decreasing values up to 12–18 h with increasing values up to 72 h of life. TPRI showed initial increasing values until 12 h of age followed by decreasing values up to 24 h of age and then relative stabilisation. SBP, DBP, MBP showed increasing values over the first 54 h of life, followed by stabilisation.

3.2 Effect of gestational age on BR-derived haemodynamic parameters over the first 72 h of life

Summary data for all BR-derived haemodynamic parameters, for gestational age categories, are shown in Table 3. Gestational age (GA) was significantly associated with all haemodynamic parameters, except SBP. NIBP showed no between-GA group differences but significant between-GA group differences existed for HR, SV, CO and TPRI (online resource).

3.3 Effect of birth weight on BR-derived haemodynamic parameters

Summary data for all BR-derived haemodynamic parameters, for birth weight categories, are shown in Table 4. Birth weight (BW) was significantly associated with all haemodynamic parameters. Between-group differences existed for LBW vs VLBW, and LBW vs ELBW but not VLBW vs ELBW for most haemodynamic parameters (online resource).

3.4 Effect of respiratory support mode on BR-derived haemodynamic variables

Most neonates required CPAP (nCPAP and HFNC) at the start of the study (73%), whereas by 72 h, only 25.3% of neonates still required CPAP. The mean PEEP supplied by nCPAP was 4 ± 1 cm H_20 with all neonates receiving HFNC at 3–6 l. Summary data for all BR-derived haemodynamic variables, for respiratory support mode, are shown in Table 5. Respiratory support mode was significantly associated with all variables except SV and TPRI (Table 5).

3.5 Effects of multiple clinical variables on haemodynamic parameters

After multivariate regression, including PNA and clinical factors (gestational age, birth weight, respiratory support mode), PNA remained a significant factor for all variables (HR, SBP, DBP, MBP, SV, CO) except TPRI (Table 6). Birth weight category remained significant only for HR. Gestational age category had no significant association with any haemodynamic variable. CPAP remained significant only for CO.

4 Discussion

To our knowledge, this is the first paper to present longitudinal bioreactance-derived haemodynamic parameter data in a cohort of stable preterm infants, not requiring invasive ventilation or inotropic support, during the first 72 h of life (transitional period).

Average haemodynamic parameter values differed from those of other TEBT methodologies [14]. This may be related to the inherent differences in the technology underlying BI and BR [15]. In BI, blood flow is assumed to only change the body's resistance whereas in BR, blood flow is stated to change the body's resistance, capacitance and inductance [15]. Anatomical assumptions regarding the thorax also differ: BI assumes that the thorax is a fluid-filled cylinder or truncated cone, whereas BR assumes the thorax is an electrical circuit with a resistor and capacitor. In BI, SV is estimated from the assessed changes in voltage [ie changes in resistance (Z_0) in electrical current flow over time due to aortic blood flow] are measured (ratio of the amplitudes of the applied and injected signals). In BR, SV is estimated from the relative phase shift, as determined by the values of resistance and capacitance {amplitude (magnitude of impedance) and phase [direction of impedance (Z_0)]}. In BI, the instantaneous rate of change in Z_0 is related to aortic blood flow and SV is proportional to the maximal rate of change of Z_0 (dZ_0/dt_{max}) and the ventricular ejection time (VET). In BR, the peak rate of change of the phase shift ($d\varphi/dt_{max}$) is proportional to the peak aortic flow from which SV is calculated: $SV = C \times VET \times d\varphi/dt_{max}$, where C is the constant of proportionality [15]. In BI, electrodes are applied at the base of the neck (thoracic inlet) and costal margins (thoracic outlet) and measurements are sensitive the electrode placement. In BR, 2 pairs of dual-electrode sensors are placed on each side of the thorax, which are stated not to be sensitive to placement [15]. VET is also determined differently by each methodology. In BI, VET is determined by the distance between QRS complexes. In BR, VET is

Table 2 Average values for bioreactance-derived haemodynamic parameters (mean ± SD) for the first 72 h of life in 63 preterm infants (< 37 weeks' gestation)

PNA Hours	n	HR bpm	SBP mmHg	DBP mmHg	MBP mmHg	SV ml/kg	CO ml/kg/min	TPRI dyne.s.cm^{-5}.m^2
All	754	145 ± 16	62 ± 9	41 ± 7	48 ± 7.8	0.75 ± 0.24	108 ± 35	3328 ± 1209
3	60	146 ± 12	59 ± 8	35 ± 8	41.9 ± 8	0.75 ± 0.22	110 ± 31	2791 ± 916
6	61	143 ± 11	59 ± 8	38 ± 7	45 ± 7	0.65 ± 0.19	93 ± 26	3635 ± 1353
12	61	143 ± 15	61 ± 8	39 ± 8	46 ± 7	0.62 ± 0.23	88 ± 29	3945 ± 1722
18	61	141 ± 16	61 ± 8	40 ± 6	47 ± 6	0.74 ± 0.29	103 ± 33	3375 ± 1124
24	61	141 ± 16	61 ± 7	40 ± 6	47 ± 6	0.79 ± 0.29	111 ± 36	3101 ± 948
30	63	143 ± 15	62 ± 6	40 ± 6	47 ± 6	0.79 ± 0.21	112 ± 31	3117 ± 1050
36	63	146 ± 18	63 ± 9	42 ± 8	49 ± 7	0.82 ± 0.23	120 ± 39	3147 ± 1147
42	59	143 ± 15	64 ± 8	43 ± 8	50 ± 8	0.81 ± 0.23	117 ± 37	3212 ± 1035
48	60	145 ± 15	64 ± 9	42 ± 7	50 ± 7	0.76 ± 0.24	110 ± 36	3316 ± 1102
54	56	147 ± 15	65 ± 9	42 ± 8	50 ± 8	0.77 ± 0.24	112 ± 32	3345 ± 1147
60	56	152 ± 17	67 ± 8	43 ± 7	51 ± 7	0.74 ± 0.22	112 ± 34	3398 ± 1054
66	55	150 ± 17	66 ± 8	43 ± 8	51 ± 7	0.72 ± 0.23	107 ± 29	3636 ± 1441
72	58	148 ± 15	65 ± 7	42 ± 6	49 ± 6	0.78 ± 0.27	115 ± 39	3269 ± 1134
ANOVA		0.002	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

CO cardiac output, *DBP* diastolic blood pressure, *HR* heart rate, *MBP* mean blood pressure, *PNA* postnatal age, *SBP* systolic blood pressure, *SV* stroke volume, *TPRI* total peripheral resistance index

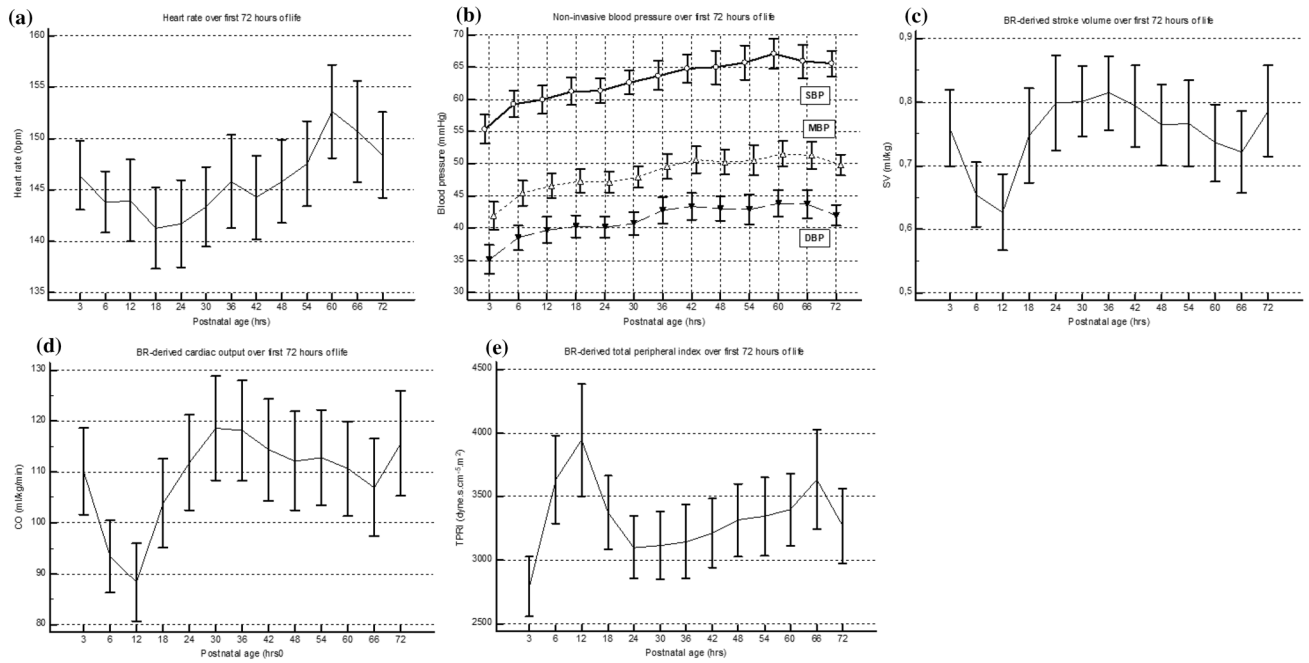

Fig. 1 Time series graphs for BR-derived haemodynamic parameters (mean values) over first 72 h of life in 63 preterm infants (< 37 weeks' gestation) **a** HR, **b** NIBP, **c** SV, **d** CO, **e** TPRI

determined by BR (first and second zero crossing of the dφ/d*t* signal) and electrocardiographic signals (peak of the QRS complex) [15]. Due to these differences, it is important to have "normal" values specifically for BR-derived haemodynamic parameters for a population, since BI and BR should not be considered interchangeable.

Reference values are defined as typical ranges of results seen in a healthy reference population whereas clinical decision limits are values above or below which a significant risk exists for an adverse outcome [16]. Reference ranges vary for various populations and subpopulations due to a difference in physiology and these physiological changes require a partitioning of reference values [16]. This study presents values for various bioreactance-determined haemodynamic parameters during the first 72 h in relatively stable preterm infants. Data are presented

according to PNA, gestational age categories, birth weight categories and respiratory support mode, which may allow for haemodynamic parameter comparison in similar gestational age or birth weight categories, as these are known to affect numerous outcomes in neonates. This population however cannot be assumed to be a healthy population but does represent the more stable infants of these gestational age groups as no neonate required invasive ventilation or inotropic support within the first 72 h of life.

Although the accuracy for TEBT technology has been questioned, this inaccuracy does not necessarily translate into the inability to use such a monitor [8]. However, longitudinal studies require trending analysis, and no such studies exist for BI or BR in neonates.

In this study, all BR-derived haemodynamic variables (NIBP, HR, CO, SV, TPRI) showed significant changes within the first 72 h of life with variable influence of gestational age, birth weight and respiratory support mode.

HR was associated with PNA and BW category, decreasing over the first 18 h of life followed by an increase to approximately 60 h of life. NIBP (SBP, DBP and MBP) was associated with PNA and seemed to stabilise around 54 h of

Table 3 Average values of bioreactance-derived haemodynamic parameters (mean ± SD) over the first 72 h of life for gestational age category

GA category Weeks	n	HR bpm	SBP mmHg	DBP mmHg	MBP mmHg	SV ml/kg	CO ml/kg/min	TPRI dyne.s.cm^{-5}.m^2
All	754	145 ± 16	62 ± 9	41 ± 7	48 ± 7.8	0.75 ± 0.24	108 ± 35	3328 ± 1209
≤ 28	95	158 ± 17	62 ± 9	39 ± 7	47 ± 7	0.80 ± 0.20	105 ± 33	3698 ± 1244
29–30	225	146 ± 14	61 ± 9	40 ± 8	47 ± 8	0.88 ± 0.29	107 ± 32	3432 ± 1296
31–32	155	144 ± 16	63 ± 8	41 ± 7	48 ± 7	0.66 ± 0.20	94 ± 26	3702 ± 1251
33–34	153	140 ± 14	63 ± 8	42 ± 6	49 ± 6	0.73 ± 0.24	124 ± 45	2872 ± 838
35–36	126	140 ± 13	64 ± 10	42 ± 9	49 ± 8	0.66 ± 0.19	111 ± 25	2947 ± 1073
ANOVA		**< 0.001**	0.082	**0.004**	**0.011**	**< 0.001**	**< 0.001**	**< 0.001**

Bold values indicate significant p-value ($p < 0.05$)

CO cardiac output, *DBP* diastolic blood pressure, *HR* heart rate, *MBP* mean blood pressure, *n* number of measurements, *SBP* systolic blood pressure, *SV* stroke volume, *TPRI* total peripheral resistance index

Table 4 Average values for bioreactance-derived haemodynamic parameters (mean ± SD) over the first 72 h of life for birth weight category

Birth weight category	n	HR bpm	SBP mmHg	DBP mmHg	MBP mmHg	SV ml/kg	CO ml/kg/min	TPRI dyne.s.cm^{-5}.m^2
All	741	145 ± 16	62 ± 9	41 ± 8	48 ± 8	0.74 ± 0.24	108 ± 36	3350 ± 1206
ELBW	57	166 ± 16	63 ± 8	39 ± 8	47 ± 8	0.66 ± 0.20	110 ± 35	3779 ± 1337
VLBW	284	148 ± 15	61 ± 8	40 ± 8	47 ± 7	0.69 ± 0.23	101 ± 32	3633 ± 1306
LBW	400	141 ± 13	63 ± 9	42 ± 7	49 ± 7	0.79 ± 0.24	112 ± 36	3107 ± 1058
ANOVA		**< 0.001**	**0.002**	**< 0.001**	**0.001**	**< 0.001**	**< 0.001**	**< 0.001**

Bold values indicate significant p-value ($p < 0.05$)

CO cardiac output, *DBP* diastolic blood pressure, *ELBW* extremely low birth weight, *GA* gestational age, *HR* heart rate, *MBP* mean blood pressure, *LBW* low birth weight, *SBP* systolic blood pressure, *SV* stroke volume, *TPRI* total peripheral resistance index, *VLBW* very low birth weight

Table 5 Bioreactance-derived hemodynamic variable reference ranges for respiratory support mode

	n	HR bpm	SBP mmHg	DBP mmHg	MBP mmHg	SV ml/kg	CO ml/kg/min	TPRI dyne.s.cm^{-5}.m^2
All	754	145 ± 16	62 ± 9	41 ± 7	48 ± 7.8	0.75 ± 0.24	108 ± 35	3308 ± 1193
No CPAP	397	142 ± 14	64 ± 8	42 ± 7	49 ± 7	0.75 ± 0.21	106 ± 29	3322 ± 1166
CPAP	357	148 ± 17	60 ± 9	39 ± 8	46 ± 8	0.75 ± 0.28	112 ± 42	3292 ± 3164
ANOVA		**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	0.893	**0.026**	0.731

Bold values indicate significant p-value ($p < 0.05$)

CO cardiac output, *CPAP* continuous positive airway pressure, *DBP* diastolic blood pressure, *HR* heart rate, *MBP* mean blood pressure, *n* number of measurements, *SBP* systolic blood pressure, *SV* stroke volume, *TPRI* total peripheral resistance index

Table 6 Effect of PNA and clinical variables on BR-derived hemodynamic variables

Variable	HR	SBP	DBP	MBP	SV	CO	TPRI
	p-value						
Time	**0.002**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**0.011**	0.273
Gestational age category	0.471	0.561	0.426	0.486	0.670	0.805	0.482
Birth weight category	**< 0.001**	0.855	0.521	0.611	0.124	0.477	0.111
CPAP	0.718	0.726	0.837	0.952	na	**0.043**	na

Bold values indicate significant p-value ($p < 0.05$)

BW birth weight, *CPAP* continuous positive airway pressure, *CO* cardiac output, *DBP* diastolic blood pressure, *GA* gestational age, *HR* heart rate, *MBP* mean blood pressure, *na* not applicable, *SBP* systolic blood pressure, *SV* stroke volume, *TPRI* total peripheral resistance

age. CO was associated with PNA and respiratory support mode, whereas SV was associated with PNA only. CO and SV decreased in the first 12 h followed by an increase up to 36 h, with stabilisation seeming to occur at 42 h of age. TPRI, not associated with any clinical variable, increased from birth to 12 h of age and then decreased to 24 h of age, with a slower increase again up to 72 h of life. CPAP requirement decreased over the first 72 h of life with most neonates requiring low PEEP. CPAP showed an effect on HR and CO but not SV nor TPRI.

Cardiac function and vascular tone are maintained by a complex interaction of neural, hormonal and metabolic mechanisms and reflex pathways. This is further influenced by the medulla and its sympathetic and parasympathetic autonomic nervous system (ANS). Preterm infants have an immature ANS [17]. Baroreflexes, vagal innervation and chemoreflexes mature with increasing postmenstrual age [18]. CO is determined by an interaction between total peripheral resistance (TPR) and BP. Oxygen delivery is dependent on an adequate cardiac output, apart from total oxygen content of blood.

Heart rate is under ANS control. Various factors are known to affect sympathetic and parasympathetic control of HR in neonates, including genetic characteristics, blood pressure and oxygenation, postmenstrual age, gender, nutritional status (SGA), sleep, breathing pattern and artificial ventilation support [19]. Normal HR in premature infants is stated to be 100–200 bpm [20] but is dependent on gestational and postmenstrual age [20]. Numerous routine neonatal management factors are known to affect HR: respiratory support requirements [21], thermoregulation [22], and various drugs, such as methylxantines [23] and various inotropes [24]. nCPAP has been suggested to increase HR due to a reduction in parasympathetic control with no change in the sympathetic efferent control [25]. Prematurity is associated with immature parasympathetic activity, indicated by a higher resting HR. Studies in lamb models and term infants suggest rapid maturation of ANS, involved in HR regulation, over the first 3–4 days of life [19]. However, maturation of the chronotropic regulation of heart rate seems to occur only at 38 weeks postconceptional age [19].

Blood pressure gradient is the driving force behind blood movement through the vasculature according to Poiseuille's equation [26]. Systemic BP is therefore the dependant variable between the two independent variables of CO and TPR. Gestational age, postmenstrual age, maternal steroids, delayed cord clamping and artificial ventilation are known to affect neonatal BP [27]. The spontaneous increase of blood pressure over the first few days of life is well known, whilst what constitutes neonatal hypotension is controversial [28]. As post menstrual age increases, preterm infants show an increase in parasympathetic modulation of HR but decreased sympathetic modulation of BP [29]. Compared to term infants, preterm infants show lower sympathetic modulation of BP and higher BP variability related to respiratory-mediated changes [29]. Blood pressure in term infants has been shown to increase over the first 24 h after birth followed by a slower rise up to 72 h of age [30] In this study, NIBP appeared to continue to increase over the entire 72 h of life although slower after approximately 54 h of age. Due to the interaction of systemic blood flow and TPR, any factor affecting these variables may negatively impact BP.

Cardiac output, or systemic blood flow, is directly related to BP and inversely related to TPR [26]. CO is regulated by various autonomic, endocrine, paracrine and autocrine regulators [31]. Despite the long-held belief that neonates can only increase CO by increasing HR, studies have shown that CO also increases secondary to increased SV, whereas BP and HR remain stable or decrease [32]. SV and CO have been shown to increase shortly after birth, to approximately 1 h after birth, due to an increase in pulmonary blood flow and increased pulmonary venous return, followed by a steady decrease until 24 h age [33]. CO and SV have been shown to decrease over the first 72–96 h of life in healthy term infants [34] as well as VLBW infants [35]. The preterm infant is capable of modulating SV. However, due to an intrinsic diastolic dysfunction, an increase in HR could further shorten end-diastolic ventricular filling time, thereby decreasing SV and compromising CO [32]. Echocardiography and

bioimpedance studies have shown that CO and SV are dependent on gestational age and postmenstrual age [12, 31, 33]. In this study, only PNA was shown to affect CO and SV, possibly due to the stable nature of the cohort.

In this study, CO was influenced by CPAP. Studies evaluating the effect of nCPAP on central blood flow are conflicting [36]. Studies utilising PEEP in excess of 10cmH_2O have been shown to decrease CO and SV [37], whereas studies utilising PEEP less than 8cmH_20 showed no effect on CO [38]. It would seem that the most commonly used PEEP levels (5–8 cm H2O) in neonatology do not affect neonatal haemodynamics, even in the presence of lung disease [25, 36, 39, 40]. However, in this study, CO but not SV, was affected by CPAP, suggesting that CO changes were related to the change in HR (CO = SV × HR).

Vascular tone is regulated by autonomic nervous system, endocrine, paracrine and autocrine regulatory factors. The postmenstrual TPR increase is initiated by the removal of the placenta and continued by neuroendocrine changes [41]. Avoiding any sudden increase in TPR is important due to the difficulty of the preterm infant's immature myocardium to overcome the increased afterload [32]. TPR has been shown to decrease over the first 3 days of life and then stabilise in term infants [42]. Adult studies have shown possible higher vasodilated states and lower sympathetic responses in females [43]. Normal TPRI is stated as 1970–2390 dyne.cm^{-5}.m^2.

In this study, SV and CO showed a decreasing trend over the first 12 h of life followed by a gradual increase up to 36 h and stabilisation at 42 h. TPRI showed an increase over the first 12 h followed by a decrease up to 24 h with only minimal changes up to 72 h of life and then stabilisation. This may suggest that the decrease in CO and SV is due to the increase in TPRI. HR showed a decreasing trend over the first 18 h with a subsequent increase again up to 18 h of age. NIBP showed a continuous increase with some stabilisation at 54 h of age. The coincidental decrease in SV and CO with an increase in TPRI and no significant increase in BP would seem to indicate that the reason for the drop in CO is secondary to increased TPRI. This is probably related to the neonate's disconnection from the placenta as well as the release of various vasoactive factors [44]. These vasoactive substances stabilise at various time points, which may account for the varying effects on SV, CO, BP, HR and TPR [45].

Individual clinical variables have been shown to have a poor ability to detect haemodynamic compromise [46] with significant subjectivity and poor reproducibility [47]. Monitoring BP and CO alone is insufficient in the critically ill neonate. If TPR is too low, perfusion pressure (BP) may drop below a critical level thereby compromising cellular oxygen provision despite an adequate CO. Conversely, if TPR is too high, CO and tissue perfusion may also decrease, despite a perceived adequate BP[23]. Identification of an abnormal TPR could help identify the cause of haemodynamic instability (vasodilated vs vasoconstricted state) as well as possibly determine which inotropic support may be indicated/considered. Although monitoring of BP, HR, CO and TPR may indicate global oxygen delivery, it may still not be sufficient in determining end-organ oxygen delivery.

4.1 Limitations

Despite the large measurement sample size (n = 753), the study population was small (n = 63). The study population consisted of relatively stable neonates not requiring invasive ventilation or inotropic support. This does not allow for extrapolation of our observations to other sicker neonates. Although haemodynamic changes were observed as physiologically expected, further research is required before adopting this novel monitoring method into routine practice given the small study population.

Blood pressure was measured non-invasively in this study, which is known to be less accurate than arterial blood pressure [48]. Lower limb BP was measured due to intravenous line placement in upper limbs, which may not be equivalent to pre-ductal upper limb blood pressure measurements [49]. This represents a limitation in this study but also represents real life clinical practice in non-invasive management strategies of neonates in our institution.

5 Conclusion

Bioreactance-derived haemodynamic monitoring is non-invasive and offers the ability to simultaneously monitor numerous haemodynamic parameters of global systemic blood flow. It may provide insight into the cause of haemodynamic instability in neonates during the transitional period.

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Data availability All data are available upon request from corresponding author and available on SUNScholarData.

Declarations

Conflict of interest L Van Wyk declares that Amayezu Medical, South Africa, provided bioreactance monitors and sensors, but no monetary incentives were provided. WP de Boode declares research support by Cheetah Medical. Neither Amayezu Medical nor Cheetah Medical had any input into research design, statistical analysis or manuscript editing.

Ethical approval Research was conducted in accordance with the World Medical Association Declaration of Helsinki. Research was approved by the Human Research Ethics Committee of the Stellenbosch University, Cape Town, South Africa.

Consent to participate Parents of all study participants (neonates) provided written, informed consent.

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Supplemental data for article: Bioreactance-derived hemodynamic parameters in the transitional phase in preterm neonates

Supplemental data Table 1: Gestational age category between-group differences for hemodynamic variables: ANOVA and pairwise comparison p-values

GA category (weeks)	HR	SBP	DBP	MBP	SV	CO	TPRI
	p-value*						
Overall ANOVA	**<0.001**	0.082	**0.004**	0.011	**<0.001**	**<0.001**	**<0.001**
≤28 vs 29-30	0.999	0.717	0.998	0.950	0.036	0.024	0.982
≤28 vs 31-32	0.110	0.949	0.987	0.941	**<0.001**	**0.001**	**<0.001**
≤28 vs 33-34	**0.002**	0.063	0.069	0.032	0.097	0.866	**0.001**
≤28 vs 35-36	**<0.001**	0.560	0.045	0.117	**<0.001**	0.922	**<0.001**
29-30 vs 31-32	0.042	0.980	1.000	1.000	**<0.001**	**<0.001**	**<0.001**
29-30 vs 33-34	**<0.001**	0.658	0.115	0.173	**<0.001**	**<0.001**	**<0.001**
29-30 vs 35--36	**<0.001**	0.995	0.073	0.364	**<0.001**	0.011	**<0.001**
31-32 vs 33-34	0.717	0.276	0.178	0.178	0.020	**0.003**	0.163
31-32 vs 35-36	**0.000**	0.898	0.108	0.374	0.999	0.011	1.000
33-35 vs 35-36	**0.000**	0.948	0.956	1.000	0.142	0.995	0.322

*Bonferonni correction: p<0.006 significant (0.05/8 groups)
CI – cardiac index; CO – cardiac output; DBP – diastolic blood pressure; GA – gestational age; HR – heart rate; MBP – mean blood pressure; SBP – systolic blood pressure; SV – stroke volume; TPRI – total peripheral resistance index

Supplemental data Table 2: Birth weight category between-group differences for hemodynamic variables: ANOVA and pairwise comparison p-values

Birth weight category	HR	SBP	DBP	MBP	SV	CO	TPRI
	p-value*						
Overall ANOVA	**<0.001**	**0.002**	**<0.001**	**0.001**	**<0.001**	**<0.001**	**<0.001**
LBW vs VLBW	**<0.001**	**0.002**	**0.004**	**0.002**	**<0.001**	**0.002**	**<0.001**
LBW vs ELBW	**<0.001**	0.898	0.027	0.129	**<0.001**	0.790	**<0.001**
VLBW vs ELBW	**<0.001**	0.316	0.730	1.000	0.505	0.034	0.663

Bonferroni correction: p<0.006 significant (0.05/8 groups)
CO – cardiac output; DBP – diastolic blood pressure; ELBW – extremely low birth weight ; GA – gestational age; HR – heart rate; MBP – mean blood pressure; LBW – low birth weight ; SBP – systolic blood pressure; SV – stroke volume; TPRI – total peripheral resistance index; VLBW – very low birth weight

CHAPTER 4

Trending ability of bioreactance in preterm infants

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Bioreactance Cardiac Output Trending Ability in Preterm Infants: A Single Centre, Longitudinal Study

Lizelle Van Wyk[a] Johan Smith[a] John Lawrenson[b] Carl J. Lombard[c, d] Willem-Pieter de Boode[e]

[a]Division Neonatology, Department of Paediatrics and Child Health, Stellenbosch University and Tygerberg Children's Hospital, Cape Town, South Africa; [b]Paediatric Cardiology Unit, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; [c]Division of Epidemiology and Biostatistics, Department of Global Health Stellenbosch University, Cape Town, South Africa; [d]Biostatistics Unit, South African Medical Research Council, Cape Town, South Africa; [e]Division of Neonatology, Department of Perinatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, The Netherlands

Keywords
Bioreactance · Cardiac output · Trending · Echocardiography · Preterm

Abstract

Introduction: It is unknown whether bioreactance (BR) can accurately track cardiac output (CO) changes in preterm neonates. ***Methods:*** A prospective observational longitudinal study was performed in stable preterm infants (<37 weeks) during the first 72 h of life. Stroke volume (SV) and CO, as measured by BR and transthoracic echocardiography, were compared. ***Results:*** The mean gestational age (GA) was 31.3 weeks and mean birth weight (BW) was 1,563 g. Overall, 690 measurements were analysed for trending ability by 4-quadrant and polar plots. For non-weight-indexed measurements, 377 (54.6%) lay outside the 5% exclusion zone, the concordance rate was poor (77.2%) with a high mean angular bias (28.6°), wide limits of agreement and a poor angular concordance rate (17.4%). Neither GA, BW nor respiratory support mode affected trending data. Patent ductus arteriosus, postnatal age, and CO level had variable effects on trending data. Trending data for 5 and 10% exclusion zones were also compared. ***Conclusion:*** The ability of BR to track changes in CO is not interchangeable with CO changes as measured by echocardiography. BR, as a trend monitor for changes in CO or SV to determine clinical decisions around interventions in neonatology, should be used with caution.

Introduction

Thoracic electrical biosensing technology (TEBT), encompassing bioimpedance and bioreactance (BR), can provide continuous hemodynamic measurements. Continuous monitoring of cardiac output (CO) may allow for timely detection of circulatory failure and subsequently appropriate initiation of tailored therapy, which may improve patient outcomes [1].

For TEBT to be clinically reliable, it needs to be able to detect CO changes (trending ability) in the same magni-

karger@karger.com
www.karger.com/neo

Correspondence to:
Lizelle Van Wyk, lizelle@sun.ac.za

Table 1. Summary of adult and paediatric CO trending [6–14]

Reference	Study population	*N*	Study/reference technology	Mean CO/CI	Exclusion zone*	Four quadrant concordance rate*, %	Angular bias*, °	Polar concordance*, %	Radial LOA*, °
Adult trending studies									
Kober [6]	Adult, ovarian cytoreductive surgery	15	BR/TPTD	2.62 L/min/m^2	0.5 L/min/m^2	ND	23.4	ND	ND
Lorne [7]	Adult surgery	22	BI/TEE	4.85 L/min	10%	ND	−7.2	86–100	−38; 24
Huang [8]	Adult abdominal surgery	28	BI/USCOM	3.35 L/min/m^2	0.5 L/min	76.3–94.7	ND	ND	ND
Han [9]	Adult liver transplant	15	BR/PATD	8.25 L/min	15%	54.8	ND	ND	ND
Cox et al. [10]	Adult cardiac surgery	50	BI/PATD	2.0 L/min/m^2	15%	55	−12	66%	−55; 51
Mutoh [11]	Adult subarachnoid haemorrhage	18	BI/TPTD	3.75 L/min/m^2	15%	90–91	+17	72–75	±37–40
Magliocca [12]	Adult liver transplant	19	BI/PATD	4.5 L/min	0.75 L/min	100	ND	ND	ND
Feng [13]	Pregnancy (caesarean section delivery)	20	BI/TTE	6.35 L/min	0.75 L/min	85	ND	ND	ND
Paediatric trending studies									
Lee [14]	Paediatric cardiac surgery	29	BR/TEE	Varied	None	ND	NS	Approx 20–65%	ND

BR, bioreactance; BI, bioimpedance; CI, cardiac index; ND, not done; NS, not stated; PATD, pulmonary artery thermodilution; TEE, transesophageal echocardiography; TPTD, transpulmonary thermodilution; USCOM, ultrasound CO monitor; CO, cardiac output; LOA, limits of agreement. * The reader is directed to the methodology section for the explanation of these statistical terms regarding trend ability.

tude and direction as the reference standard method [2]. The trending ability of a TEBT monitor is important for diagnosis and monitoring the effect of therapeutic interventions.

BR , a type of TEBT, measures the phase shift of an oscillating current, which is applied across the thoracic cavity. This phase shift represents the change in resistance and reactance of the applied current and is used mathematically to calculate stroke volume (SV) and CO [3].

A new device should be proven to be accurate and precise [4]. If a new device fails to provide accurate measurements, it may still be useful as a trending monitor [5]. Trend analysis is performed using 4 quadrant and polar plots. In the 4-quadrant plot, differences in sequential measurements between the 2 evaluated technologies are plotted and correlation can be assessed (i.e., concordance). However, the direction and magnitude cannot be assessed with this plot and therefore polar plots are used, where each difference in sequential change is converted into a polar coordinate [2].

TEBT, compared to various reference methods, has shown varying levels of trending accuracy in adult studies and a single paediatric study, generally not meeting the stated statistical criteria for good trending ability (Table 1). No data exist for CO or SV trending in neonates.

This study aimed to determine the trending ability of a BR CO monitor in comparison to transthoracic echocardiography (TTE) in a stable cohort of preterm infants, not requiring invasive ventilation or cardiovascular support.

Materials and Methods

A prospective observational study was performed in the neonatal highcare service of the tertiary academic hospital, Tygerberg Hospital, Cape Town, South Africa. This study was a continuation of the previously published cohort [15]. In short, all preterm infants (<37 weeks GA) admitted to the neonatal service were eligible for enrolment. Infants were excluded if they: (1) required invasive ventilation or cardiovascular (i.e, inotrope) support, (2) were diagnosed with congenital cardiac defects (except for patent ductus arteriosus [PDA] and patent foramen ovale), (3) were diagnosed with severe congenital anomalies, or (4) were not expected to survive the first 72 h. Infants were enrolled within 3 h after delivery.

The University of Stellenbosch granted ethical approval (N13/04/053). All parents provided written consent.

BR and TTE Methodology

All infants underwent continuous thoracic BR monitoring (NICOM® Reliant; Cheetah Medical, MA, USA) until 72 h of life, as previously described [15]. In short: 4 sensors were placed over the mid-clavicles and upper back bilaterally, as well as between the 6th and 7th intercostal spaces mid-axillary, stretching down to-

wards the abdomen. The Reliant records measurements every minute. SV-BR data was accessed directly from the Reliant® and CO-BR was calculated as SV-BR × heart rate.

Echocardiography (TTE) was performed within 3 h after birth and then every 6 h of life for the first 72 h of life in all infants by a single investigator (LVW), blinded to the BR measurements. A Vivid S6 (GE Healthcare, Chicago, IL, USA) ultrasound machine with 10 MHz probe was used. TTE was performed in accordance with published neonatologist performed echocardiography guidelines [16]. In short, aortic diameter was measured thrice at the level of the aortic valve in the long axis parasternal view, averaged and assumed to remain constant for the 72 h of examination. Aortic velocity time integral (VTI) was averaged over 5 cycles. Calculations from TTE measurements were SV-TTE = (π × aortic diameter^2/4) × VTI and CO-TTE = SV-TTE × heart rate. Patients with any suspected cardiac anomalies (excluding PDA and patent foramen ovale) were referred to a paediatric cardiologist for review.

The internal clocks of the Reliant and ultrasound machine were synchronized prior to initiation of each study. BR readings immediately prior to TTE were recorded with no averaging applied. All readings (Reliant and TTE) were recorded and analysed off-line after completion of the study.

Statistical Methods

Trend analysis involves changes in CO (ΔCO) and SV (ΔSV), calculated as the difference in sequential measurements (i.e., measurement N_2–N_1) for TTE and BR [17].

The following statistical analysis was performed:

1. Four-quadrant plots [2, 18] analysis were used to assess the correlation between ΔCO (SV)-TTE and ΔCO (SV)-BR.

Visual inspection of the 4-quadrant scatter plot indicates concordance and discordance of direction of change in sequential measurements: data in the upper right quadrant equating to concordant increases in CO(SV) of TTE and BR, and the lower left quadrant concordant decreases. Discordant measurements (i.e., decrease in one measurement with increase in other measurement) will appear in the upper left or lower right quadrants. This allows for calculation of the concordance rate: (data points in concordant quadrants/all data points) × 100%. Good trending is defined as a concordance rate >95%, marginal as 90–95%, and poor concordance rate as <90% [2]. Measurements with equal changes will lie on the line of equity (45° diagonal line).

2. Polar plot analysis [2] is an extension of the 4-quadrant plot where each data point (BR vs. TTE) is addressed by an angle (representing the direction of change) and a radius (representing the magnitude of change). The following were calculated from the polar plot analysis:

   2.1.Angular bias: the average angle between all polar data points and the polar axis (0°). Good trending ability is defined as an angular bias ≤ ±5° [17].

   2.2.Radial limits of agreement (LOA): the radial sector containing 95% of data points (mean angular bias ±1.96SD). Acceptable radial LOA is defined as < ±30°. However, different radii represent different levels of trending ability: good trending ±27–37°, moderate trending ±37–45°, and poor trending >±45° [17].

   2.3.Angular concordance rate: the percentage of data points within the ±30° radial LOA zone. Good trending ability is defined as an angular concordance rate >92% [17].

Data at the centre of polar plots represent very small changes in sequential measurements of ΔCO or ΔSV and are considered to be statistical noise. As such these values may not contribute to, or even disturb, trend analysis [17] and are considered clinically insignificant and irrelevant [18]. This has led to the creation of exclusion zones which eliminate these less predictive data points [2]. Exclusion zones in adult studies vary between ≤5 and 15% of ΔCO or ΔSV [19, 20]. Definitions for exclusion zones for neonatal studies have, to our knowledge, not been defined. For this study, 5 and 10% exclusion zones were chosen based on neonatal animal CO method comparison studies (≤10%) [21, 22]. Average normal CO and SV were used to calculate exclusion zones, that is, CO 150–350 mL/kg/min [23] and 229–534 mL/min [24, 25] and SV 1.63 mL/kg and 2.97 mL [26] (calculations detailed in online suppl. Table S1; see www.karger.com/doi/10.1159/000518656 for all online suppl. material). Both weight-indexed (WI) (birth weight [BW]) and non-WI (NWI) measurements for SV and CO were used for analysis.

Sub-analyses were performed on parameters that could possibly affect CO: CO level, open versus closed PDA and respiratory support mode (CPAP vs. no respiratory support), as well as general neonatal factors (postnatal age [PNA], GA, BW). CO was classified according to TTE measurements: low (<150 mL/kg/min) or normal (≥150 mL/kg/min).

Data are reported as mean ± standard deviation, median (IQR), and number (proportion), as appropriate. *T* tests and χ^2 for differences between groups were performed, as appropriate. Repeated measurement analysis of variance (ANOVA) was performed to determine the association between the different trending data outcomes and all clinical variables (PNA, GA, and BW), respiratory support mode, PDA and CO level). If ANOVA was significant ($p < 0.05$), post hoc pairwise comparison of means analysis, with Bonferonni correction, was performed to determine between-group differences. A linear mixed-effects regression was performed to determine the fixed effects of significant clinical variables on trending data, per haemodynamic variable, with the participant as the random effect to account for the repeated measures. A linear time effect model was specified for the random effect with an unstructured covariance matrix.

Data management (for polar plot data calculation [2]) was performed using Excel (Office 2010; Microsoft, Seattle, WA, USA). Statistical analysis was performed using STATA IC 15.1 (StataCorp, College Station, TX, USA). Polar plots were constructed using MedCalc® Statistical Software v19.7.2 (MedCalc Software Ltd., Ostend, Belgium). Results were reported according to STROBE guidelines [27].

Results

Seventy-nine infants were enrolled in the study. Power disruptions at the hospital led to machine failures and corrupted data, thereby leading to incomplete data sets in 16 patients. After excluding these 16 patients, 63 (<37 weeks GA) infants were included in the study (Table 2). BR consistently underestimated SV and CO over the first 72 h of life, compared to TTE (Fig. 1).

Table 2. Study population demographics

Parameter	*N* = 63
Male, *n* (%)	33 (52)
Paired measurements, *n*	754
African race, *n* (%)	34 (54)
GA, weeks, (mean ± SD)	31.3±2.7
<28 weeks, *n* (%)	8 (13)
29–30 weeks, *n* (%)	20 (32)
31–32 weeks, *n* (%)	12 (19)
33–34 weeks, *n* (%)	13 (21)
35–36 weeks, *n* (%)	10 (16)
Birth weight, g (mean ± SD)	1,563±411
Complete antenatal steroids, *n* (%)	21 (33)
Caesarean section, *n* (%)	51 (81)
Twins, *n* (%)	16 (25)
IUGR[#], *n* (%)	5 (8)
EOS*, *n* (%)	7 (11)
Respiratory support, *n* (%)	
None	14 (22)
NPO_2	3 (5)
HFNC	2 (3)
CPAP	44 (70)
PDA	
Closed before 72 h PNA, *n* (%)	56 (89)
PNA of closure, h, median (IQR)	18 (12–30)
SNAPPE-II score, median (IQR)	8 (0–15)
CO-TTE (mean ± SD)[##]	
mL/kg/min	127.70±34.40
mL/min	200.02±73.11
CO-BR (mean ± SD)	
mL/kg/min	108.74±34.97
mL/min	172.90±77.6
SV-TTE (mean ± SD)	
mL/kg	0.88±0.22
mL	1.47±0.53
SV-BR (mean ± SD)	
mL/kg	0.75±0.24
mL	1.21±0.57

BR, bioreactance; CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula (3–6 L flow); NPO_2, nasal prong oxygen (≤2 L flow); PDA, patent ductus arteriosus; PNA, postnatal age; SNAPPE-II score, score for neonatal acute physiology with perinatal extension II; TTE, transthoracic echocardiography; HR, heart rate; VTI, velocity time integral; GA, gestational age; BW, birth weight. [#] IUGR defined as BW <10th centile for GA. * EOS, defined as a CRP >10 mmol/L at 12–24 h of postnatal age. [##] CO-TTE calculations: Average aorta CSA 0.47 cm^2, average aorta VTI 7.97 cm and average HR 145 bpm.

SV Trending Ability

Trending ability was assessed in 690 NWI measurements of which 353 (51.1%) were outside the 5% exclusion zone (i.e., ΔSV changes ≤5% of mean SV were excluded). The 4-quadrant plot showed a poor concordance rate (58.0%) (no exclusion zone) which improved to 77.8%, with application of a 5% exclusion zone (Fig. 2a).

Angular bias was 16.4° (no exclusion zone) and worsened to 30.3° with application of the 5% exclusion zone. Radial LOA were very wide, irrespective of exclusion zone (Fig. 2b; online suppl. Table S1). Angular concordance rate (within 30°) was 15.0% (no exclusion zone) and increased slightly to 17.8% with application of the 5% exclusion zone (online suppl. Table S1).

Cardiac Output Trending Ability

Trending ability was assessed in 690 NWI measurements of which 377 (54.6%) were outside the 5% exclusion zone (i.e., ΔCO changes ≤5% of mean CO were excluded). The 4-quadrant plot showed a poor concordance rate (57.2%) (no exclusion zone) which improved to 77.2%, with application of a 5% exclusion zone (Fig. 2c).

Angular bias was 16.7° (no exclusion zone) and worsened to 28.6° with application of the 5% exclusion zone. Radial LOA were very wide, irrespective of exclusion zone (Fig. 2d; online suppl. Table S1). Angular concordance rate was 14.4% (no exclusion zone) and increased slightly to 17.4% with application of the 5% exclusion zone (online suppl. Table S1).

No significant differences existed in trending data (concordance rate, angular bias nor angular concordance rate) between WI or NWI hemodynamic variables (online suppl. Table S1). When using 5 or 10% exclusion zones, significant differences existed for SV and CO concordance rate and angular bias but not angular concordance rate (online suppl. Table S2).

Clinical Variables Influencing Trending Ability

Very few clinical variables showed a statistically significant effect on trending data (Table 3). Only PDA affected SV concordance and angular bias.

CO concordance rate was not statistically affected by any clinical variable. SV concordance rate was affected by PDA (Table 3).

CO angular bias was not statistically affected by any clinical variable. SV angular bias was affected by PDA (Table 3).

SV concordance rate was significantly affected by PNA, PDA and CO level. CO angular concordance rate was significantly affected by PNA and CO level (Table 3). After correction for multiple comparisons, SV and CO angular concordance rate were only affected by CO level with no other clinical parameters reaching statistical significance (Table 3).

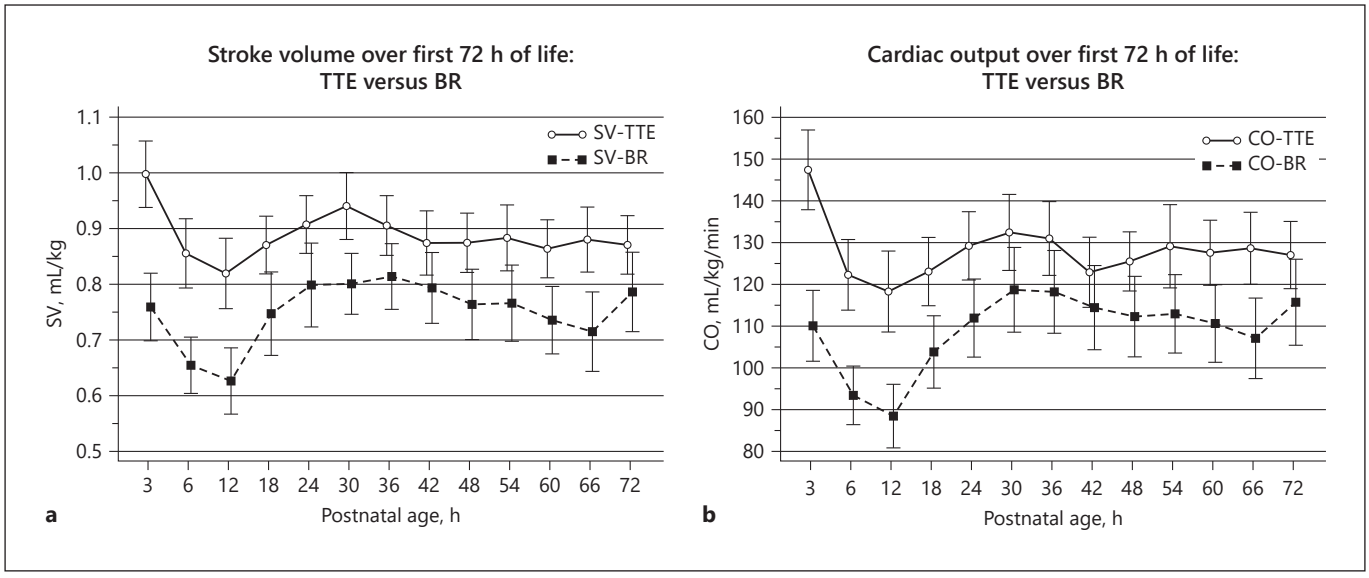


Fig. 1. SV and CO over time for TTE and BR (mean values).

SV concordance rate decreased 8.8% ($p = 0.020$) with removal of CPAP. CO angular concordance rate increased 7.4% between a low (<150 mL/kg) CO and a normal CO (≥150 mL/kg) ($p = 0.017$), whilst SV angular concordance rate increased 11.3% ($p < 0.001$). No other between group differences were apparent for other trending data (online suppl. Table S3).

Discussion

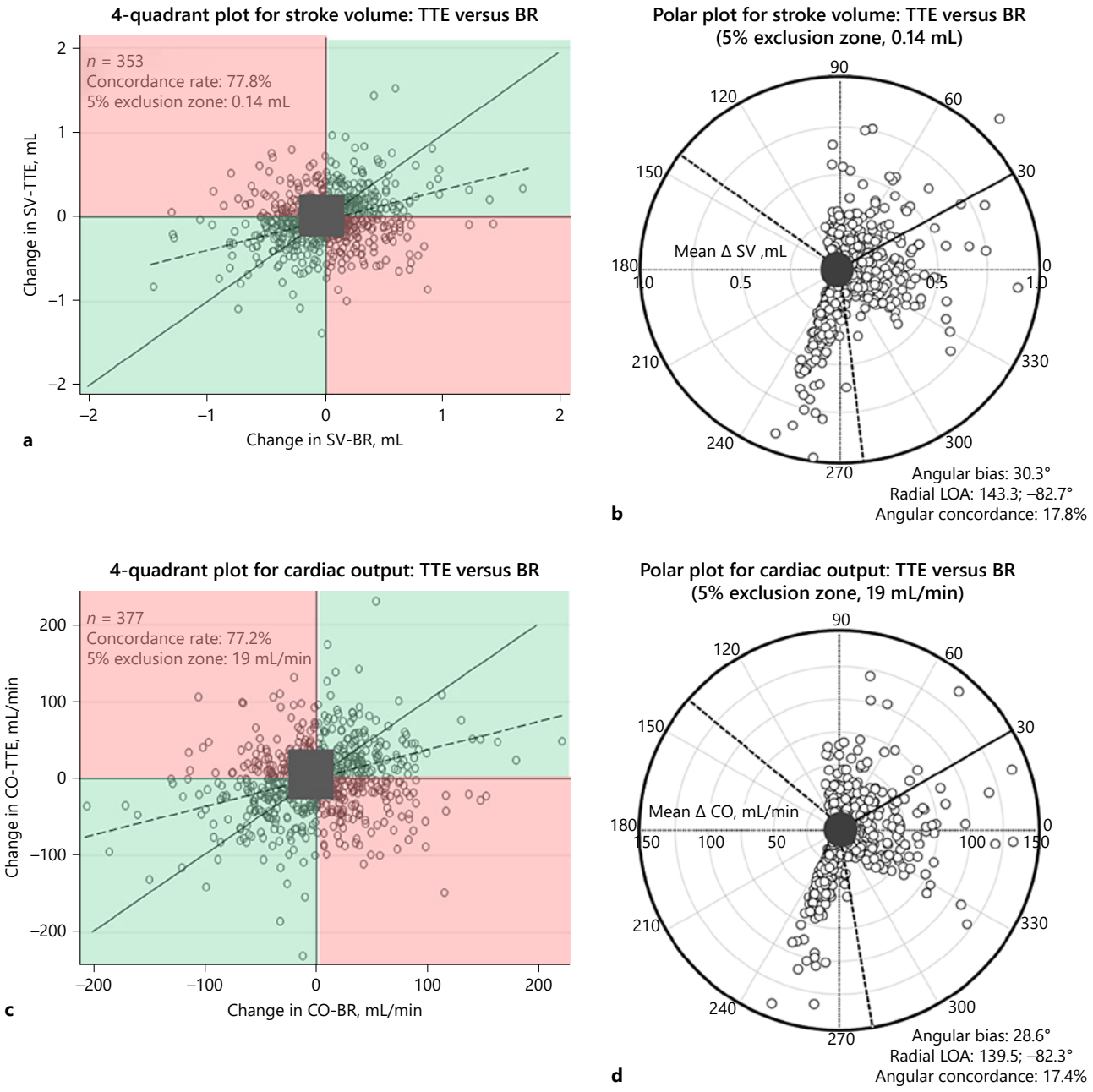
This is the first neonatal study to determine the ability of BR to accurately track CO and SV changes in a population of stable preterm infants. Results showed a poor trending ability for both CO and SV, as compared to TTE.

In the current study, the concordance rate was lower than the minimally accepted 90% for moderate trending ability [2]. This study's mean angular bias was much higher than the acceptable ±5° for good trending [17]. Radial LOA for this study were wide and exceeded the accepted radial LOA (<±30°). Angular concordance rate in this study was very poor. All trending data were worse than in adult studies (Table 1) with no paediatric studies with which to compare data [28]. The interaction between neonatal transitional physiology and the requirement of respiratory support may play a role in these discrepancies. Respiratory support may increase the air interface between the sensors and heart, thereby decreasing BR signal accuracy [29]. A PDA, an integral part of transitional physiology, due to its proximity to the aorta, may decrease the aortic blood flow-only signal detection, contributing to BR signal inaccuracy [30].

Contrary to CO accuracy studies, this study could show no association between trending data and GA [15] and BW [26]. Adult studies have shown that BMI affected trending ability [31]. In the current study, trending data were not influenced by CPAP, possibly due to the low PEEP applied. CPAP with PEEP <8 cm H_2O has not been shown to adversely affect CO [32]. This study showed poorer trending ability in neonates with a low CO level, similar to the poor trending shown in adults with a low cardiac index [33, 34].

Closure of the PDA showed insignificant worsening of the polar angle but no effect on the concordance and angular concordance rate. The reason for this is unknown but may be associated with the change in CO after PDA closure.

In trending method comparison studies, a priori exclusion zones should be established [17]. These have not been established in neonates. In adult medicine, exclusion zones are based on 10% (or 15%) of a normal CO of 5L/min. However, "normal" CO in neonatology is unknown and is simply described as a range of 150–350 mL/kg/min [23]. As such, it is difficult to determine a single CO (or SV) cut-off value upon which to base an exclusion zone. In this study, exclusion zones were chosen based on animal studies [21, 22] and extrapolated from adult percentage values (5 and 10%) but results showed significant



Color version available online

Fig. 2. 4-Quadrant plots and polar plots for SV (**a**, **b**) and CO (**c**, **d**). Scatter plot (**a**, **c**) graphs showing sequential changes in BR and TTE plotted along the line of identity ($y = x$). Data in upper left and lower right quadrant (red shaded areas) represent BR changes in the opposite direction of TTE changes, and data in upper right and lower left quadrant (green shaded areas) represent BR changes in same direction as TTE changes. Solid black line represents line of identity with dashed line the regression line. Solid grey squares represent the exclusion zones. Polar plots (**b**, **d**) showing sequential mean changes in BR and TTE plotted along polar co-ordinates. Solid black line represents mean polar angle and dashed lines represent the angular LOA. Solid grey circles represent the exclusion zones. SV, stroke volume; LOA, limits of agreement BR, bioreactance; TTE, transthoracic echocardiography.

Table 3. Association between clinical parameters and trending data (*p* value*)

Clinical variables	Concordance rate		Angular bias		Angular concordance rate	
	SV	CO	SV	CO	SV	CO
GA	0.319	0.333	0.191	0.202	0.512	0.742
Birth weight	0.319	0.330	0.191	0.202	0.512	0.742
PNA	0.352	0.245	0.636	0.097	0.012	0.013
PDA	0.012	0.550	0.051	0.654	0.013	0.182
Respiratory support mode	0.379	0.864	0.649	0.415	0.963	0.252
CO level	0.207	0.367	0.332	0.592	**<0.001**	**<0.001**

Bonferroni correction applied $p < 0.005$ significant (0.05/36 groups). ANOVA, analysis of variance; CO, cardiac output; PDA, patent ductus arteriosus; PNA, postnatal age; SV, stroke volume; GA, gestational age. * ANOVA *p* value; calculated on non-weight indexed CO, with no exclusion zone.

differences depending on the choice of exclusion zone. The choice of the size of the applied exclusion zone remains unclear.

In this study, nearly 50% of all measurements fell within the 5% exclusion zone. These small changes could be concordant or discordant. Although these small changes in CO or SV (ΔCO or ΔSV) are considered noise in adults, this may not hold true in neonates, especially in ELBW infants with small SV and low CO. It is therefore unclear whether an exclusion zone should be applied, as ranges of clinically important haemodynamic data may be excluded.

Haemodynamic monitors are measurement systems and are only able to improve clinical outcomes if they are able to assist during protocol-driven treatment strategies [35]. It is unclear how the small values within the 5–10% exclusion zone would impact clinical decision-making in this scenario.

No difference in trending data existed for WI as compared to NWI hemodynamic variables. It may be possible to use these interchangeably, based on this dataset.

An obstacle, in method comparison studies, is the requirement for an accurate and reliable reference measurement method [2]. For CO measurement, this is traditionally via thermodilution by means of a pulmonary artery catheter, which is not practical in neonates. TTE has become routine in most NICU's but requires training and clinical experience and only provides intermittent measurements of systemic blood flow. However, TTE indices variability may be as high as 28%, as compared to other standard methods [36], making the choice of single comparative values difficult. Echocardiography's trending ability, as compared to the gold reference standard of thermodilution, has been reported to vary, with polar angle reported between 1.0 and 53.6° in a variety of stable and unstable adult patients [37, 38]. It is therefore unclear if TTE can be judged a reliable reference method for TEBT trending studies. This may affect trending statistical analysis.

The aim of a TEBT continuous monitor would be to timely detect hemodynamic abnormalities, initiate, and monitor the appropriate therapy. In neonatology, BR is increasingly used to monitor CO [39], ductal persistency [24], thoracic fluid content [40], haemodynamic changes during blood transfusion [41], septic shock [42], hypoplastic heart [43] and adverse neonatal outcomes [44]. It is therefore of utmost importance that an TEBT monitor is accurate in its trending ability. Currently, this study's data does not support the use of BR to trend CO (or SV) in neonates. This underlines the need for more studies exploring the trending ability of BR as well as the bioimpedance technologies (Aesculon® and ICON®, Osypkamed, Berlin, Germany) in neonates.

This study has several limitations. Despite a large initial cohort, significant data loss occurred due to electrical issues during the study period, leading to corrupted data and monitor failures. The NICOM Reliant averages haemodynamic variables over 1 min. TTE was performed as rapidly as possible but took longer than documenting a single BR measurement. This "time delay," although unavoidable, may also have influenced the accuracy of trending data, as they are not strictly simultaneous. Despite the clinical stability of this cohort's patients, CO was relatively low. This may be due to CO calculation incorporating aortic cross-sectional area at the level of the aortic valve, rather than the sino-tubular level, which may lead to underestimation of the CO [45]. This research also lacks a correlation with clinical outcome data. This should be explored in future research.

The study was performed with the NICOM Reliant which has since been upgraded to the NICOM Starling, which may have another algorithm and improved trending ability. This should be explored in future research.

The study was performed in a relatively stable cohort of neonates which limits the generalizability of the conclusions reached. The study was performed during the transitional phase (first 72 h of life) and the dramatic changes in cardiovascular physiology may also have impacted on the study results.

Conclusion

Trend monitoring by BR is very poor in comparison with TTE in neonates. The ability of BR to accurately track changes in CO should be further elucidated, preferably in a validation study against a true golden reference technology and using the updated version of BR. Until this has been investigated, BR as a trend monitor for changes in CO or SV to determine clinical decisions around interventions in neonatology should be used with caution.

Statement of Ethics

Research was conducted in accordance with the World Medical Association Declaration of Helsinki. All parents provided informed written consent. Research was approved by the Human Research Ethics Committee of the Stellenbosch University, Cape Town, South Africa (N13/04/053).

Conflict of Interest Statement

L. Van Wyk declares that Amayezu Medical, South Africa, provided BR monitors and sensors, but no monetary incentives were provided. W.-P. de Boode declares research support by Cheetah Medical. Neither Amayezu Medical nor Cheetah Medical had any input into research design, statistical analysis, or manuscript editing.

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Author Contributions

Lizelle Van Wyk and Johan Smith contributed to conceptualization; Lizelle Van Wyk and Willem-Pieter de Boode contributed to methodology; Lizelle Van Wyk and Carl Lombard contributed to formal analysis and investigation; Lizelle Van Wyk, Johan Smith, John Lawrenson, and Willem-Pieter de Boode contributed to writing – original draft preparation; Lizelle Van Wyk, Johan Smith, John Lawrenson, Willem-Pieter de Boode, and Carl Lombard contributed to writing – review and editing; Johan Smith, John Lawrenson, and Willem-Pieter de Boode contributed to supervision.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online suppl. files. Further enquiries may be directed to the corresponding author.

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Supplemental Data: Bioreactance cardiac output trending ability in preterm infants: a single center, longitudinal study

Supplemental table S1: Comparison of trending data for weight indexed vs non-weight indexed hemodynamic variables according to different exclusion zones

Grey shaded data represent non-weight indexed data

	n	Mean ± SD	Concordance rate (%)	p-value	Angular bias (°)	p-value	Radial LOA (°)	Angular concordance rate (%)	p-value
No exclusion zone									
ΔCO-TTE (ml/kg/min)	690	-1.47±30.07	57.2	1.000	16.7±60.0	1.000	134.3; -100.9	14.3	0.957
ΔCO-BR (ml/kg/min)	690	0.89±29.85							
ΔCO-TTE (ml/min)	690	-2.38±46.44	57.2		16.7±60.0		134.3; -100.9	14.4	
ΔCO-BR (ml/min)	690	1.33±47.70							
ΔSV-TTE (ml/kg)	690	-0.11±0.19	57.8	0.940	16.2±61.1	0.951	132.2; -99.8	15.0	1.000
ΔSV-BR (ml/kg)	690	0.00±0.21							
ΔSV-TTE (ml)	690	-0.01±0.31	58.0		16.4±61.2		136.3; -103.5	15.0	
ΔSV-BR (ml)	690	0.00±0.35							
10% exclusion zone*									
ΔCO-TTE (ml/kg/min) (25ml/kg/min excl zone)	182	-1.43±47.21	92.3	0.756	43.8±45.4	0.417	132.7; -45.1	19.7	0.868
ΔCO-BR (ml/kg/min) (25ml/kg/min excl zone)	182	-2.40±45.85							
ΔCO-TTE (ml/min) (38ml/min excl zone)	176	-2.06±72.48	91.4		39.8±47.9		133.6; -45.9	20.4	
ΔCO-BR (ml/min) (38ml/min excl zone)	176	-3.53±74.50							
ΔSV-TTE (ml/kg) (0.16ml/kg excl zone)	184	-0.14±0.29	91.2	0.679	43.3±45.9	0.685	133.2; -46.6	21.7	0.342
ΔSV-BR (ml/kg) (0.16ml/kg excl zone)	184	-0.00±0.335							
ΔSV-TTE (ml) (0.28ml excl zone)	159	-0.02±0.49	89.8		41.2±50.1		139.3; -56.9	17.6	
ΔSV-BR (ml) (0.28ml excl zone)	159	-0.02±0.58							
5% exclusion zone#									
ΔCO-TTE (ml/kg/min) (12.5ml/kg/min excl zone)	374	-0.59±37.5	78.3	0.766	29.8±55.7	0.769	138.9; -53.4	17.3	0.971
ΔCO-BR (ml/kg/min) (12.5ml/kg/min excl zone)	374	0.10±37.1							
ΔCO-TTE (ml/min) (19ml/min excl zone)	377	-1.70±57.41	77.2		28.6±56.6		139.5; -82.3	17.4	
ΔCO-BR (ml/min) (19ml/min excl zone)	377	1.38±59.12							
ΔSV-TTE (ml/kg) (0.08ml/kg excl zone)	377	-0.00±0.236	78.2	0.896	24.4±57.7	0.167	137.4; -88.6	19.1	0.651
ΔSV-BR (ml/kg) (0.08ml/kg excl zone)	377	-0.00±0.272							
ΔSV-TTE (ml) (0.14ml excl zone)	353	-0.00±0.38	77.8		30.3±57.7		143.3; -82.7	17.8	
ΔSV-BR (ml) (0.14ml excl zone)	353	-0.00±0.45							

* 10% excluion zone: ΔCO 25ml/kg/min & 38ml/min based on average cardiac output in neonates (150-350ml/kg/min)[12] and 229-534ml/min([13,14]) and ΔSV 0.16ml/kg and 0.28ml for stroke volume (based on an average stroke 1.63ml/kg and 2.97ml [15]
# 5% exclusion zone: ΔCO 12.5ml/kg/min & 19ml/min based on average cardiac output in neonates (150-350ml/kg/min)[12] and 229-534ml/min([13,14]) and ΔSV 0.08ml/kg and 0.14ml for stroke volume (based on an average stroke 1.63ml/kg and 2.97ml [15]
BR – bioreactance; CCC – concordance correlation coefficient; CO – cardiac output; LOA – limits of agreement; TTE – transthoracic echocardiography; SD – standard deviation

Supplemental data Table S2: Comparison of trending data for different exclusion zones

		No exclusion zone		5% exclusion zone		10% exclusion zone		Difference (no-5%)*	p-value	Difference (5 – 10%)**	p-value
Cardiac Output											
Concordance rate (%)	ml/kg/min	690	57.2	374	78.3	182	92.3	21.1	**<0.001**	14	**<0.001**
	ml/min	690	57.2	377	77.2	176	91.4	20.0	**<0.001**	14.2	**<0.001**
Angular bias (°)	ml/kg/min	690	16.7 ±60.0	374	29.8 ±55.7	182	43.8 ±45.4	13.1	**<0.001**	14	**0.003**
	ml/min	690	16.7 ±60.0	377	28.6 ±56.6	176	39.8 ±47.9	11.9	**0.001**	11.2	**0.023**
Angular concordance rate (%)	ml/kg/min	690	15.0	374	17.3	182	19.7	4.7	0.326	2.4	0.490
	ml/min	690	15.0	377	17.4	176	20.4	2.4	0.305	3	0.396
Stroke volume											
Concordance rate (%)	ml/kg	690	57.8	377	78.2	184	91.2	20.4	**<0.001**	13	**<0.001**
	ml	690	58.0	353	77.8	159	89.8	19.8	**<0.001**	12	**0.001**
Angular bias (°)	ml/kg	690	16.2 ±61.1	377	29.4 ±57.7	184	43.3 ±45.9	13.2	**<0.001**	13.9	**0.004**
	ml	690	16.4 ±61.2	353	30.3 ±57.7	159	41.2 ±50.1	13.9	**<0.001**	10.9	**0.040**
Angular concordance rate %)	ml/kg	690	15.0	377	19.1	184	21.7	4.1	0.084	2.6	0.469
	ml	690	15.0	353	17.8	159	17.6	2.8	0.242	-0.2	0.956

* Difference between no exclusion and 5% exclusion zone data (5% exclusion zone minus no exclusion zone)
** Difference between 5% and 10% exclusion zone data (10% exclusion zone minus 5% exclusion zone)

Supplemental data Table S3: Influence of clinical parameters on trending data

	n*	Concordance rate (%)	p-value	Angular bias (°)	p-value #	Angular concordance rate° (%)	p-value#
Cardiac Output							
PDA closed	391	56.5	0.712	17.8±59.3	0.583	85.1	0.816
PDA Open	299	57.9		15.2±60.7		85.7	
CO level ≥ 150ml/kg	169	62.7	0.098	19.1±62.3	0.548	91.1	0.017
CO level <150ml/kg	521	55.4		15.9±59.2		83.7	
No CPAP	372	55.1	0.219	17.1±60.3	0.851	84.4	0.383
CPAP	318	59.7		16.3±59.7		86.7	
Stroke Volume							
PDA closed	391	65.1	0.341	20.1±59.8	0.097	83.7	0.229
PDA open	299	56.1		12.2±62.7		87.0	
CO level ≥ 150ml/kg	169	56.8	0.694	13.0±64.6	0.400	93.4	**<0.001**
CO level <150ml/kg	521	58.5		17.5±60.0		82.1	
No CPAP	372	54.0	0.020	14.1±62.6	0.286	85.6	0.572
CPAP	318	62.8		19.1±59.4		84.1	

* n is number of measurements
# Bonferonni correction applied p<0.005 significant (0.05/36 groups)
CPAP – continuous positive airway pressure; PDA – patent ductus arteriosus; CO level – left ventricular output level (as measured by TTE)

CHAPTER 5

Systematic review of electrical biosensing technology in neonates

Accuracy and Trending Ability of Electrical Biosensing Technology for Non-invasive Cardiac Output Monitoring in Neonates: A Systematic Qualitative Review

Lizelle Van Wyk[1], Samir Gupta[2,3], John Lawrenson[4], Willem de Boode[5]
(submission ready)

Abstract

Background: Electrical biosensing technology (EBT) is an umbrella term for non-invasive technology utilising the body's resistance to electrical current flow to estimate cardiac output. Monitoring cardiac output in neonates may allow for timeous recognition of hemodynamic compromise and allow for prompt therapy, thereby mitigating adverse outcomes. For a new technology to be safely used in the clinical environment and to allow therapeutic decisions to be based upon it, it must be proven to be accurate, precise and to accurately track temporal changes. The aim of this systematic review was to identify and analyze studies that describe the accuracy, precision, and trending ability of EBT to non-invasively monitor cardiac output and/or stroke volume in neonates. **Methods**: A qualitative systematic review was performed. Studies were identified from PubMed NCBI, SCOPUS and EBSCOHost up to December 2020, where EBT technologies in comparison to a reference technology, were used in neonates. Outcome measures were bias, limits of agreement, percentage error for agreement studies and data from 4-quadrant and polar plots for trending studies. Effect direction plots were used to present results. **Results:** Thirteen neonatal studies were identified. Only thoracic electrical biosensing technology, with transthoracic echocardiography (TTE) as the comparator, studies were available for analyses**.** High heterogeneity existed between studies. All studies showed small bias, wide limits of agreement, with most studies having a percentage error >30%. Sub-analyses for prematurity vs term gestational age, respiratory support mode, cardiac anomalies and type of technology showed similar results. No neonatal trending study was available for inclusion. **Discussion:** Overall, TEBT shows

reasonable accuracy, poor precision and non-interchangeability with TTE. However, high heterogeneity made analysis difficult. TEBT should be used with caution in the neonatal population for monitoring and determining therapeutic interventions. The use of TEBT trend monitoring has not been studied and requires evaluation in future trials.

Introduction

Adequate systemic perfusion is dependent on cardiac output (CO), as determined by heart rate (HR) and stroke volume (SV) and influenced by systemic vascular resistance (SVR). A complex interaction exists between HR, blood flow, SVR and BP to ensure that cellular metabolic oxygen demand is met [1]. The circulatory system of neonates is significantly different from that of adults or children, as the neonatal population is a heterogeneous mix of gestational and postconceptional ages, with different degrees of cardiovascular maturation[2]. Indirect measures of CO, such as HR and blood pressure (BP), are inadequate for the assessment of neonatal hemodynamic status[3].

CO is considered a fundamental physiological parameter for diagnosis and guidance of therapy in various neonatal conditions[4]. Maintaining optimal perfusion and oxygenation is of prime concern in neonatal intensive care units (NICU). Comprehensive monitoring of various physiological variables is required as low CO has been associated with increased morbidity, adverse neurodevelopmental outcome, and increased mortality[5].

CO measurement, via invasive techniques (e.g., intermittent pulmonary artery thermodilution and Fick's method) are considered the gold standards for accurately determining CO [6]. However, in neonates these methods are inappropriate[7] as catheters are often too big and the invasiveness of these methods have been questioned in adult medicine[8]. Minimally invasive cardiac output monitoring technologies encompass devices not requiring the insertion of a pulmonary artery catheter, (e.g. pulse contour, pulse power analysis, partial gas re-breathing and transpulmonary ultrasound dilution[9]). Some of these technologies require the placement of an arterial line (e.g., pulse contour and pulse power analysis) and may need placement of a central venous line for calibration purposes [7]. These technologies have been poorly studied in the neonatal population whilst others are still under development (transpulmonary ultrasound dilution [10]). Most other CO measurement methodologies in neonates offer only intermittent measurement values as they are labor, skill or technology intensive

(transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (cMRI))[7].

Non-invasive cardiac output monitoring technologies were therefore developed, offering fully non-invasive methods of monitoring stroke volume (SV) and CO. These include intermittent measurements via Doppler ultrasound (Ultrasound Cardiac Output Monitor (USCOM) and transthoracic echocardiography (TTE))) and continuous measurements via the various electrical biosensing technologies (EBT) (bioimpedance and bioreactance).

For a new technology to be safely used in the clinical environment and to allow therapeutic decisions to be based upon it, it must be proven to be accurate and precise. A good agreement between a new technology and a gold standard reference technology is defined by a small bias (indicating a high accuracy), narrow limits of agreement (indicating a high precision) and a percentage error ≤ 30% (indicating technology interchangeability)[11,12]. Trending ability (change over time) should also be assessed to ensure that the new technology's direction and magnitude of change is in line with that of the reference technology[13].

Technology Background

The first type of non-invasive cardiac monitoring, rheocardiography, was developed in 1949 by Kedrov[14] but only found popularity in 1966 when Kubicek re-designed it for use in the aerospace industry [15]. Since then, numerous iterations of this technology have become available in the healthcare industry, with methodologies measuring changes in whole body, segmental or thoracic impedance from which SV and hence CO is derived. Numerous nomenclatures are used – whole body electrical bioimpedance (WBEB), thoracic electrical bioimpedance (TEB), electrical velocimetry, electrical cardiometry, impedance cardiometry, impedance cardiography, thoracocardiography, bioreactance and rheocardiography. These have subtle differences, often with proprietary algorithms

and models to estimate SV and CO. The umbrella term of electrical biosensing technology (EBT) encompasses all these technologies.

In EBT a high frequency, low amplitude electrical current is applied across the thorax (TEBT) or whole body (WBEBT). The resistance (impedance, Z0) to this electrical current varies between different tissues in the body, with the primary distribution being to the blood and extracellular fluid. This change in electrical current (ΔZ0) over time (dZ0/dt) corresponds to SV, from which CO can be computed.

EBT is divided into 2 broad categories: (1) bioimpedance which encompasses thoracic electrical velocimetry/ electrical cardiometry, impedance cardiography as well as WBEBT and (2) bioreactance.

Electrical velocimetry and electrical cardiometry. Electrical cardiometry (EC) is the method of thoracic non-invasive cardiac output technology that utilizes the model of thoracic electrical velocimetry (EV) to determine SV and CO[16]. These are used by Aesculon™ and ICON™, manufactured by Osypka Medical GmbH, Germany

In EV, the change in impedance (ΔZ0) is due to the degree of erythrocyte alignment in the aorta throughout the cardiac cycle. During diastole, as the aortic blood flow ceases, erythrocytes are randomly orientated and interfere with electrical conduction. During systole as the left ventricle contracts, the erythrocytes are forced to align parallel to aortic flow and the electrical current in the aorta passes with less impedance, hence an increased conductivity. This pulsatile changes in volume and thus in impedance, in relation to the cardiac cycle(ΔZ0(t)), is used to calculate SV. EV estimates SV by means of the following equation

$$SV_{TEB} = CP.v_{ft}.FT \qquad \text{[Eq. 1]}$$

where SV_{TEB} is SV estimated by thoracic electrical bioimpedance, CP is the patient constant (in ml), v_{ft} is the mean blood velocity index (in s^{-1}) during flow time (FT) and FT

is flow time (measured in s). The EV model estimates SV based on the input of the patient's body mass, an empiric mean velocity index derived from a peak amplitude measurement assumed to be the peak aortic blood flow acceleration and a measurement of flow time.

Impedance cardiography (ICG) and electrical cardiometry (EC) are similar as both rely on periodical volumetric changes in the aorta to determine SV and CO. However, ICG and EC differ in the model applied to determine impedance measurements, specifically as to how the change in impedance is calculated. In ICG the change in impedance (conductivity) ($\Delta Z(t)$) is solely attributed to the volumetric expansion of the ascending aorta due to the increase of volume within the aorta or due to its wall motion. The index of peak velocity of the volumetric change is used in ICG as compared to the index of peak acceleration in EV. EV includes direction of flow whereas ICG does not. In EV, volume changes also incorporate the alignment of erythrocytes.

Bioreactance (BR). In BR, it is assumed that blood flow changes are not only related to changes in impedance but also changes in capacitance (biological tissue's ability to store an electrical current) and inductance (biological tissue's ability to store energy in a non-electrical form). BR measures phase shift (φ) of an oscillating current as it traversed the thorax. BR uses the following formula to estimate stroke volume (SV)

$$SV = C \times VET \times d\varphi / dt_{max} \quad \text{[Eq. 2]}$$

where C is a constant of proportionality, VET is ventricular ejection time, and $d\varphi / dt_{max}$ is the peak rate of change of the phase shift (φ). BR is used by the Reliant® and its newer version, Starling®, manufactured by Cheetah Medical, USA.

Four pairs of sensors, one electrode acting as a high frequency generator and the other as a receiver, are placed on either side of the thorax. Cardiac output measurements are determined separately from each side of the body and the final CO is the average of the measurements.

Significant differences exist between BI and BR (table 1).

Table 1: Comparison of technological differences between bioimpedance and bioreactance

	Bioreactance	Bioimpedance
Assumptions regarding blood flow	Related to change in body's resistance, capacitance, and inductance	Related to the change in body's resistance only
Anatomical assumptions regarding thorax	Thorax is an electrical circuit with resistor and capacitor	Fluid-filled cylinder or truncated cone
Electrical signal from which SV is calculated	Calculated from phase shift, determined from resistance and capacitance (amplitude (magnitude of impedance) and phase (direction of impedance (Z0)	Calculated from estimated changes in resistance/ impedance (Z0) – electrical current flow over time due to aortic blood flow changes
SV calculation	Peak rate of change of the phase shift ($d\varphi/dt_{max}$) is proportional to the peak aortic flow from which SV is calculated (eq 2)	Instantaneous rate of change in Z0 is related to aortic blood flow and SV is proportional to the maximal rate of change of Z0 ($dZ0/dt_{max}$) and the ventricular ejection time (VET)
Electrode placement	Applied at the base of the neck (thoracic inlet) and costal margins (thoracic outlet). Measurements are sensitive the electrode placement	2 pairs of dual-electrode sensors are placed on each side of the thorax. Measurements stated not to be sensitive to placement
VET determination	VET is determined by BR (first and second zero crossing of the $d\varphi/dt$ signal) and electrocardiographic signals (peak of the QRS complex)	VET is determined by the distance between QRS complexes

Modified from [17]
SV – stroke volume; VET – ventricular ejection time, Z0 - impedance

The aim of this systematic review was to identify and analyze studies that describe the accuracy, precision, and trending ability TEBT to non-invasively monitor cardiac output and/or stroke volume in neonates.

Methods

A systematic search was performed on PubMed NCBI, SCOPUS and EBSCOHost to identify English language studies published up until December 2020. Search terms included: non-invasive cardiac output, thoracic impedance, bioreactance, whole body bioimpedance, electrical velocimetry, electrical cardiometry, impedance cardiometry, impedance cardiography, cardiac output, stroke volume, neonate, newborn, infant.
Studies on human neonates of any gestational and postconceptional age, were eligible for inclusion. The search strategy did not explicitly exclude animal studies to ensure that studies reporting animal and human research would be identified. However, studies

reporting pure animal data were excluded upon screening of the title and abstract. Studies describing accuracy, precision, agreement, or trending data for non-invasive cardiac output monitors, as compared to a standard reference technique were eligible for inclusion. Thoracic and whole body electrical biosensing technology, encompassing bioimpedance and bioreactance technologies, were eligible for inclusion. Any standard comparative technology (transthoracic echocardiography (TTE), thermodilution techniques (TD), including Fick principle, or cardiac MRI (cMRI)) was eligible for inclusion. Studies investigating cardiac output (CO), and/ or stroke volume (SV) were eligible. Studies that did not compare an investigational technology to a reference technology were excluded.

Any study reporting outcome measures allowing validation of EBT technologies were included. All published and pre-print manuscripts pending publication were eligible for inclusion.

Studies were selected for inclusion by screening titles and abstracts against selection criteria by 2 independent reviewers (LVW and WPdB) and conflicts were resolved through discussion, arbitrated by a third reviewer (SG), as required. Full text articles of the included studies were reviewed by the same reviewers to confirm eligibility and perform data extraction.

Extracted data included study details (first author, year of publication and study population details), investigational technology device name, comparator technology type and outcome data. If outcome data were not specifically reported, but were calculatable from provided data, the missing outcome measures were calculated. Where median and interquartile range (IQR) were reported, the mean and SD were calculated[18].Where SEM was reported, SD was calculated as $SD=SEM \times \sqrt{n}$. Where studies presented both CO and SV data, only data on which PE was calculated were used.

Outcome measures were defined as follows:

For agreement (accuracy and precision)[13]

1. Bias CO/ SV, mean difference (investigative technology – comparator))
2. Mean CO/ SV (investigative technology + comparator/2)
3. Percentage error (1.96 SD of bias /mean x100%)
4. Limits of agreement (bias ± 1.96SD)
5. True precision of comparator correcting for the true precision of TTE's precision of ±30%: $TP=\sqrt{(PE)^2-(0.3)^2}$

For trending ability[19]:

6. Concordance rate: number of sequential changes in CO (ΔCO) or SV (ΔSV): (data points in concordant quadrants/ all data points) x 100%.
7. Mean angular bias: average angle between all polar data points and polar axis
8. Radial limits of agreement (LOA): defined as the radial sector containing 95% of data points (mean angular bias ± 1.96SD)
9. Angular concordance rate: calculated as the percentage of data points in the ±30˚ radial zone

Strategy for data synthesis

Data synthesis strategy was defined by the extracted data. Although included studies were quantitative in nature and data were descriptively summarized, data gathered in this review were considered to be too heterogenous to allow statistical pooling for meta-analysis. There was variable reporting of measured hemodynamic parameters (CO or SV), hemodynamic parameter measurement unit (weight index and non weight indexed) as well as data reported in a wide variety of clinical situations. Studies were thus grouped primarily according to hemodynamic parameter, measurement unit, and according to clinical variables and interventions.

Heterogeneity was visually assessed by tabulation of the primary author, year of publication, hemodynamic variable, measurement unit, investigational technology, study

population (gestational age, postnatal age, birth weight) and interventions. Data were analysed in line with these factors.

Effect direction plots were utilized to visually synthesize the diverse outcome measures, providing a link between the data and the narrative [20]. Size and direction of arrows were used to indicate sample size, bias direction, and percentage error (above or below 30% benchmark). Results were presented for overall results as well as for sub-analyses.

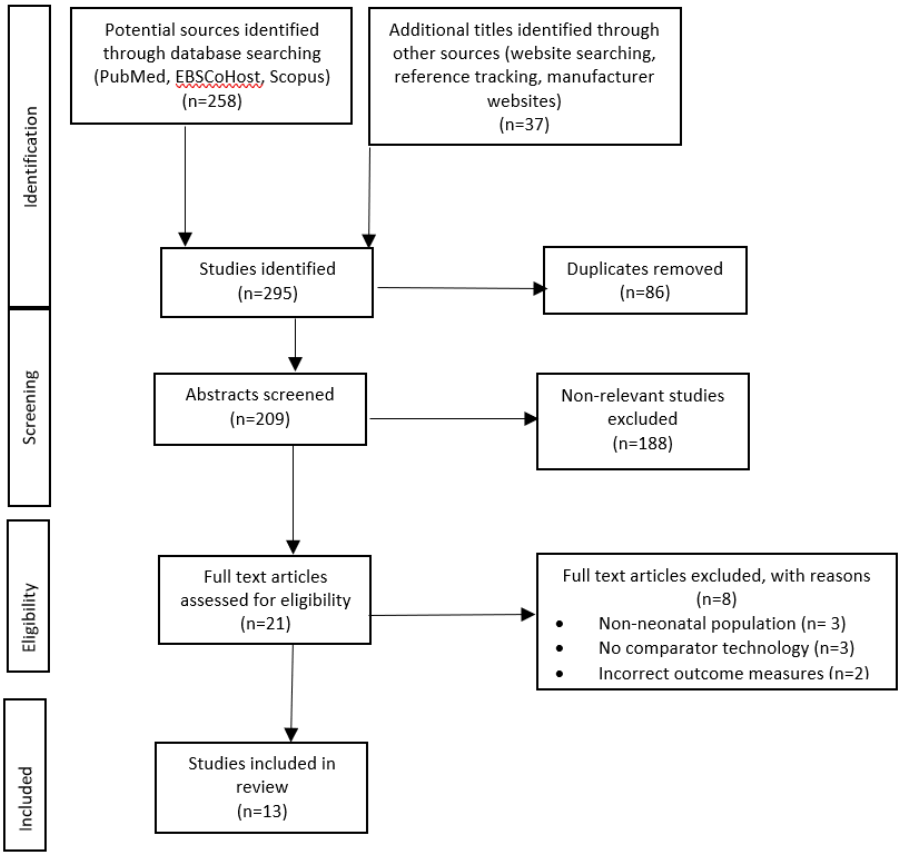
This review was performed according to the Synthesis without meta-analysis (SWiM) guideline[21].

Results

From an initial search, 295 studies were identified, which were assessed for eligibility. After full-text review, 13 studies were included [22–34] comparing electrical biosensing (EBT) to a reference technology. All studies were observational prospective method comparison studies. No study utilised whole body electrical biosensing technology (WBEBT), therefor only thoracic electrical biosensing technologies (TEBT) were included. The only reference method utilised in the included studies was transthoracic echocardiography (TTE). Investigational technologies comprised bioreactance (BR) (3 studies) and bioimpedance (BI) (10 studies) (table 1). BI included: NCCOM3® (1 study), Aesculon®/ ICON® (6 studies) and technology not specified in 3 studies. BR included NICOM® Reliant (3 studies) (table 2).

Most studies (n=7) reported CO measurements only, 2 studies reported CO and SV, 2 studies reported SV only and 1 study reported TTE-VTI (velocity time integral) as well as TTE-MM (M-mode). Most studies (n=7) reported weight-indexed measurements only, 6 studies reported non-weight indexed measurements, and 1 study reported both (table 2).

Figure 1: Flow chart of literature search strategy



Only studies reporting accuracy and precision outcome measures could be identified with no neonatal study reporting trending data. Descriptive tables were ordered by hemodynamic parameter, weight/ non-weight-indexed measurement and sample size.

The 13 eligible studies involved a total number of 504 patients, encompassing 2668 paired measurements. Study sample sizes were generally small (average patient per study 38.7 (range 10-99)) with only 3 studies recruiting more than 50 patients. The average number of measurements per patient was 5.4 (range 1.5-11.9) with only 5 studies performing more than 5 measurements per patient (table 2).

Studies varied widely in gestational ages, birth weight and chronological ages of enrolled neonates. Disease states, ventilation requirements and surgical intervention also varied widely between studies (table 2), illustrating the high heterogeneity between studies.

Overall accuracy and agreement

To determine the overall accuracy and precision of TEBT vs TTE, all studies were included in the analysis. Most studies (8 out of 12) were large (>100) in sample size (number of measurements). In 6 out of 12 studies the mean bias was positive, indicating TEBT overestimated TTE measurements. In 6 out of 12 studies, the mean bias was negative, indicating that TEBT underestimated TTE.

Non-weight indexed SV mean bias was reported in 4 studies and varied between 0.6 to 1.1ml. Limits of agreement (LOA) varied between ± 0.75 and ± 2.35ml. Percentage error (PE), reported in only 3 studies, varied between 29% and 58% (table 3, supplementary data table S1).

CO mean bias measurement was reported in 8 studies and ranged between 8.9 to -18.5 ml/kg/min for weight indexed and 6 to -153 ml/min for non-weight-indexed CO. LOA varied between ±13.5-132.7 ml/kg/min and ± 66.5-233 ml/min. PE ranged between 5.3% to 71.6% (table 3, supplementary data table S1).

One study used VTI as hemodynamic reference parameter. The bias percentage was 39% and PE was 46%.

Although the mean bias in most studies was small, LOA were wide, suggesting reasonable accuracy but poor precision, in comparison to TTE. Only 5 of the 12 included studies reported a PE within the generally accepted 30% benchmark, suggesting TEBT cannot be considered interchangeable with the reference method (TTE).

Table 2: Study characteristics of included neonatal studies comparing TEBT and a reference technology

Authors	Year of publication	Patient characteristics	Gestational age (weeks) (mean ± SD)	Birth weight (kg) (mean ± SD)	Postnatal age (days) (Median (range))	Investigative method (model used)	Reference method	Sample size (patients/ measurements)	Variable measured (unit)
Tibballs [34]	1989	Ventilated neonates post cardiac surgery and RDS 100% IV Inotropes - NS	Prem & term	0.75-4.95	17 (0-121)	BI (NCCOM3)	TTE	26 (81)	CO (ml/kg/min)
Grollmuss[24]	2012	TGA switch procedure 100% IV Inotropes: NS	NS	3.3±0.5	10 (3-29)	BI (Aesculon™)	TTE	24 (240)	SV (ml)
Noori [29]	2012	40% PDA	39.2±1.1	3.09±0.33	4 (1-13)	BI (Aesculon™)	TTE	20 (115)	CO (ml/min)
Weisz [23]	2012	10% IV 20% NIV	37±6.6	2.72±1.23	NS	BR (Reliant)	TTE	10 (ns)	CO (ml/min) SV (ml)
Blohm [28]	2014	4.9% IV 38.3% NIV 5% PDA	25-34	1.66 (0.84-2.40)	NS	BI (Aesculon™)	TTE	26 (40)	
Grollmuss [35]	2014	67% IV	31.7±3.1	3.1±1.61	15 (1-48)	BI (ICON™)	TTE	28 (228)	SV (ml/kg)
Song [33]	2014	50.4% IV 49.4% NIV 64% PDA 42.5% inotropes	27±2.96	1.07±0.78	0-1.5	BI (NS)	TTE	40 (109)	CO (ml/kg/min)
Weisz [22]	2014	PDA ligation 88% IV 100% IV 52% inotropes	30.6±2.51	0.7±0.11	NS	BR (Reliant®)	TTE	25 (ns)	CO (ml/kg/min)
Torigoe [30]	2015	29.6% IV 45.6% NIV 100% PDA	32±2.9	1.63±0.53	NS	BI (NS)	TTE	28 (ns)	CO (ml/min)
Blohm [27]	2016	4% PDA 42% PFO 21% PDA & PFO	Preterm & term	3.3±2.51	1.9 (0.16-240)	BI (Aesculon™)	TTE	99 (291)	CO (ml/min)
Boet [26]	2016	31.6% IV 41.8% NIV 4% PDA	31±3.2	1.11±0.53	0-7	BI (NS)	TTE	79 (451)	CO (ml/min) SV (ml)
Hsu [31]	2017	67% IV 35% NIV 100% PDA	27.2±6.6	1.01±1.00	6(2-22)	BI (Aesculon™)	TTE	36 (105)	CO (ml/kg/min)
Van Wyk [32]	2020	70% NIV	31.3±2.7	1.56±0.41	0-3	BR (Reliant®)	TTE	63 (754)	CO (ml/kg/min) SV (ml/kg)

BI – bioimpedance; BR – bioreactance; CO – cardiac output; ICON – index of contractility monitor; IV – invasive ventilation; NCCOM3 – noninvasive computerized cardiac output monitor; NIV – non-invasive ventilation; NS – not specified; PDA – patent ductus arteriosus; PFO – patent foramen ovale; SD – standard deviation; TTE – transthoracic echocardiography

Accuracy and precision in preterm and term infant studies

To determine whether there were differences in accuracy and precision when studies were performed in different gestational ages, studies including only preterm or only term infants were analysed. Six studies recruited preterm infants only and 2 studies only term infants. Most studies (6 out of 8) showed TEBT underestimated hemodynamic parameters.

In studies enrolling premature infants only, weight-indexed CO mean bias ranged between -18.5 and 10.4ml/kg/min with LOA varying between ± 58.7-132.7ml/kg/min. PE ranged between 23.5% and 71.6% (table 4, supplementary data table S2).

Table 3: Effect direction plot of accuracy and precision of all included studies

Study	Measurements	Unit of measurement	Bias*	Precision	PE	Effect Direction		
						Sample size	Mean Bias	PE
Stroke Volume								
Grollmuss 2012 [24]	240	ml	0,28	±2,3	29	▲	▲	▼
Weisz 2014 [22]	78	ml	-0,6	±0,75	58	▲	▼	▲
Blohm 2016 [27]	291	ml	0,7	±2,35	44,9	▲	▲	▲
Boet 2016 [26]	451	ml	1,1	±1,85	NS	▲	▲	
Cardiac Output								
Tibbals 1989 [34]	78	ml/kg/min	0,23	±13,5	5,3	▲	▲	▼
Grollmuss 2014 [35]	228	ml/kg/min	8,9	±62,7	24	▲	▲	▼
Song 2014 [33]	109	ml/kg/min	-18,8	±132,7	60,2	▲	▼	▲
Hsu 2017 [31]	105	ml/kg/min	-5,3	±72,9	28,2	▲	▼	▼
Van Wyk 2020 [32]	754	ml/kg/min	-18,5	±87,6	71,6	▲	▼	▲
Noori 2012 [29]	115	ml/min	-4	±233	43,6	▲	▼	▲
Weisz 2012 [23]	97	ml/min	-153	±152,5	48,3	▲	▼	▲
Torigoe 2015 [30]	81	ml/min	6	±66,5	21	▲	▲	▼
VTI								
Blohm 2014 [28]	41	m	39%	NS	46,2	▲	▲	▲

* Bias = TEBT – TTE
NS – not specified; PE – percentage error; VTI – velocity time integral.
Legend: Sample size (based on number of measurements: large arrow – large sample size >100, medium arrow 50-100, small arrow <50. Bias effect: Downward green arrow – TEBT underestimates reference method, upward red arrow – TEBT overestimates reference method; size of arrow indicates degree. Percentage error: downward green arrow PE <30%, upward red medium arrow 30-50%, upward large red arrow > 50%

Two studies reported outcome measures in term neonates – 1 study non-weight-indexed CO and 1 study non-weight-indexed SV. Both studies showed high PE (43.6 – 50.7%) (table 4, supplementary data table S2).

In the studies performed in preterm neonates, only 3 out of 7 studies reported a PE within the 30% benchmark whereas both the studies which included term neonates reported PE above the 30% benchmark.

All studies, both for studies in premature and term neonates, were performed at different postnatal ages (table 1). Three studies were performed solely within the first week of life, with the rest at varying chronological ages (up to 240 days) and three studies did not specify the chronological age. Van Wyk et al [32] observed an association between CO and SV bias and chronological age (p=0.018 and p=0.050, respectively). Hsu et al[31] showed no proportional CO bias associated with gestational age or weight.

Table 4: Effect direction plot of accuracy for studies reporting outcome measures for preterm or term neonates only

Study	Measurements	Unit of measurement	Bias*	Precision	PE	Effect Direction		
						Sample size	Mean bias	PE
Preterm infants								
Boet 2016 [26]	451	ml	1,1	± 0,59	57	▲	▲	▲
Grollmuss 2014 [35]	94 (VLBW)	ml/kg/min	5,3	± 58,7	17,3	▲	▲	▼
Grollmuss 2014 [35]	134 (LBW)	ml/kg/min	10,4	± 60,5	78,5	▲	▲	▲
Song 2014 [33]	109	ml/kg/min	-18,8	± 132,7	69,7	▲	▼	▲
Hsu 2017 [31]	105	ml/kg/min	-5,3	± 73	27,4	▲	▼	▼
Van Wyk 2020 [32]	754	ml/kg/min	-18,5	± 87,6	85,5	▲	▼	▲
Blohm 2014 [28]	40	l/min	NS	NS	37,8	▲		▲
Term Infants								
Torigoe 2016 [30]	32	ml	-0,4	± 2,2	50,7	▲	▼	▲
Noori 2012 [29]	115	ml/min	-1,5	± 77,5	43,6	▲	▼	▲

* Bias = TEBT – TTE
NS – not specified; PE – percentage error.
Legend: Sample size (based on number of measurements: large arrow – large sample size >100, medium arrow 50-100, small arrow <50. Bias effect: Downward green arrow – TEBT underestimates reference method, upward red arrow – TEBT overestimates reference method; size of arrow indicates degree. Percentage error: downward green arrow PE <30%, upward red medium arrow 30-50%, upward large red arrow > 50%

Grollmuss et al 2012[24] showed a doubling of the bias between VLBW and LBW premature infants, although both mean biases were small (5.3 and 10.3ml/kg/min, respectively), with similar LOA (±58.7 and ±60.5 ml/kg/min, respectively) and similar PE (23.5% and 23.9% respectively). Van Wyk et al[32] reported increasing bias with decreasing body weight and variable bias with various gestational age categories (supplementary data table S2).

Accuracy and precision related to different respiratory support modes

To determine whether there were differences in accuracy and precision when studies were performed with different ventilation modes, studies reporting outcome measures for various respiratory support methods were analysed. Four studies reported outcome measures for non-invasively ventilated infants and 3 studies for invasively ventilated infants (table 5).

For studies reporting outcome measures for non-invasive ventilation (NIV), most sample sizes (number of measurements) were small (8-54) with one large study [32]. TEBT underestimated TTE in 3 out of 4 studies. Weight-indexed CO mean bias varied between -2.8 and -23.0ml/kg/min with wide LOA (±40.7-124.9 ml/kg/min) and PE ranged between 17.3 to 78.5%. The single non-weight-indexed study showed a CO mean bias of 3.6 ml/min with a PE of 25%. Only 2 out of 4 NIV studies had a PE <30% (table 5, supplementary data table S3).

For invasive ventilation, outcome measures were reported in 3 studies utilising intermittent mandatory ventilation modes (IMV and SIMV), 3 studies utilised high frequency ventilation (HFV) and 1 study utilising high frequency jet ventilation (HFJV). In all studies, sample sizes (number of measurements) were small (<50). TEBT underestimated TTE in most studies (6 out of 7). For IMV, the weight-indexed CO mean bias (2 studies) was -1.4 to -30.2 ml/kg/min with wide LOA (±70.1 – 94.6ml/kg/min) and non-weight-indexed (1 study) CO mean bias of -29.6 ml/min. For IMV studies, PE ranged between 27.4- 69.7%, with only 1/3 of studies reporting a PE ≤30% (table 5, supplementary data table S3). For high frequency ventilation (HFV) studies, the weight-

indexed CO mean bias ranged between -16.2 to 38.2ml/kg/min and wide LOA (± 79.0-179.1 ml/kg/min) (2 studies) and non-weight-indexed CO mean bias was -12ml/min (1 study). For HFV studies, PE ranged between 33.2 and 85.5% with no studies reporting a PE ≤ 30% (table 5, supplementary data table S3). The single HFJV study reported a CO mean bias of -10.9ml/kg/min and PE of 76.4%.

Numerous other studies included neonates on CPAP but did not specifically report outcome measures for that subset of patients [23,24,26,28].

For NIV, Van Wyk et al[32] showed a significant difference in weight-indexed CO bias between CPAP and no respiratory support (78.0% vs 74.4%, p=0.026) but not for weight-indexed SV bias (p=0.113). Blohm et al[28] showed a variable effect of CPAP on the bias between EBT-SV and method of TTE-derived SV measurement (VTI vs M-mode, p=0.022 and p=0.732, respectively).

Song et al[33] showed no significant difference in PE between CPAP and SIMV (57% vs 69.7%, p=0.160) nor SIMV and HFV (69.7% and 85.5%, p=0.729). Hsu et al[31] showed minimal change in bias between CPAP and IMV but a large increase in bias between IMV and HFV, with incremental increases in PE from CPAP to IMV to HFV . Song et al[33] reported a worsening of weight-indexed CO bias between neonates on CPAP and SIMV. Increased complexity of respiratory support intervention seemed to cause an increase in PE in most studies (supplementary data table S4).

Other studies reported no effect of respiratory support mode on CO bias. Torigoe et al [30] showed no effect of mechanical ventilation on bias (estimated mean bias of 60ml/min for no respiratory support and SIMV and approximately 25 ml/min for nCPAP and HFV, p=0.14). Grollmuss [25] reported that method interchangeability was not affected by respiratory support mode although no data was provided.

Table 5: Effect direction plot of studies reporting outcome measures for respiratory support modes

Study	n Measurements	Unit of Measurement	Type ventilation	Mean Bias*	Precision	PE	Effect Direction		
							Sample size	Mean bias	PE
Non-invasive ventilation									
Song 2014 [33]	54	ml/kg/min	CPAP	-18,2	±124,9	57	▲	▼	▲
Hsu 2017 [31]	37	ml/kg/min	CPAP	-2,8	±40,7	17,3	▲	▼	▼
Van Wyk 2020 [32]	335	ml/kg/min	CPAP	-23	±84,8	78,0	▲	▼	▲
Torigoe 2015 [30]	37	ml/min	CPAP	3,6	±73,1	25	▲	▼	▼
Invasive ventilation									
Song 2014 [33]	39	ml/kg/min	SIMV	-30,2	±94,6	69,7	▲	▼	▲
Hsu 2017 [31]	44	ml/kg/min	IMV	-1,4	±179,1	27,4	▲	▼	▼
Song 2014 [33]	8	ml/kg/min	HFV	38,2	±160,1	85,5	▲	▲	▲
Hsu 2017 [31]	24	ml/kg/min	HFV	-16,2	±70,1	37,8	▲	▼	▲
Song 2014 [33]	8	ml/kg/min	HFJV	-10,9	±79	76,4	▲	▼	▲
Torigoe 2015 [30]	10	ml/min	SIMV	-29,6	±97,8	31,7	▲	▼	▲
Torigoe 2015 [30]	14	ml/min	HFV	-12	±105,9	33,2	▲	▼	▲

* Bias = TEBT – TTE
CPAP – continuous positive airway pressure; HFV – high frequency ventilation; HFJV – high frequency jet ventilation; IMV – intermittent mandatory ventilation; SIMV – synchronized intermittent mandatory ventilation; PE – percentage error.
Legend: Sample size (based on number of measurements: large arrow – large sample size >100, medium arrow 50-100, small arrow <50. Bias effect: Downward green arrow – TEBT underestimates reference method, upward red arrow – TEBT overestimates reference method; size of arrow indicates degree. Percentage error: downward green arrow PE <30%, upward red medium arrow 30-50%, upward large red arrow > 50%
* Bias = TEBT – TTE

Accuracy and precision related to cardiac anomalies

To determine whether there were differences in accuracy and precision when cardiac lesions were present, studies reporting outcome measures for different congenital cardiac lesions (pathological and physiological) were analysed. Five studies were included. Most studies reported small sample sizes (number of measurements) with only 3 studies consisting of more than 100 measurements (table 6). Most studies (6 out of 8) showed that TEBT underestimated TTE (table 6, supplemental data table S5).

Two studies reported outcome measures in cardiac surgical interventions. The TGA switch study [24] showed a non-weight-indexed SV mean bias of 0.27 ml and a PE of

29%. The study also showed varying bias and PE dependent on timing of measurements after surgery (24%, 35% and 28% within 0-36, 36-72 and after 72hrs of surgery, respectively). The PDA ligation study [22] reported a non-weight-indexed SV mean bias of -0.6ml and a PE of 58%. The study also showed an increase in bias over time 7.9% (6-8 hours post-ligation) and 9.7% (16-18 hours post-ligation) as compared to scans 1-hour post-ligation.

In studies reporting outcome measures for PDA, SV and CO mean bias were reported for both weight- and non-weight indexed measurements. PE in the 4 studies varied between 21% to 74.4%. Only in 1 study was the size of the PDA defined (table 6, supplemental data table S5)

In studies reporting outcome measures for a PFO, only 1 study reported data for PFO only and one for PDA combined with PFO. Both studies showed high PE (40.2 and 56.3%, respectively) (table 6, supplemental data table S5).

Numerous other studies included neonates with a PDA but did not specifically report outcome measures for that subset of patients [26,33]. Blohm et al[28] showed that PDA showed a trend towards significance, dependent on method of TTE measurement (VTI compared ($p=0.077$) to m-mode).

Various studies reported data between open and closed PDA. Noori 2012[29] reported no statistically significant difference in bias (12 vs 2 ml/min, $p=0.800$) or precision (±296 vs ±218ml/min) between neonates with a hemodynamically significant left-to-right shunt PDA (ductal diameter >2mm) as compared to those without. Van Wyk et al[32] reported a higher mean bias for infants with an open PDA compared to a closed PDA (diameter not defined) (-28.7ml/kg/min vs -12.5ml/kg/min, $p<0.001$).

Table 6: Effect direction plot of accuracy for studies reporting outcome measures for cardiac anomalies

Study	n Measurements	Unit of measurement	Cardiac anomaly	Mean Bias*	Precision	PE	Effect direction		
							Sample size	Mean bias	PE
Cardiac surgical intervention									
Grollmuss 2012 [24]	240	ml	TGA switch surgery			29	▲	▼	▼
Weisz 2014 [22]	78	ml	PDA ligation	-0,6	±0,75	58	▲	▼	▲
Physiological shunts									
Blohm 2016 [27]	12	ml	PDA only	-0,8	±0,98	72.1	▲	▼	▲
Blohm 2016 [27]	63	ml	PDA + PFO	-1,1	±1,09	56.3	▲	▼	▲
Blohm 2016 [27]	125	ml/kg/min	PFO only	-0,6	±0,59	40.2	▲	▼	▲
Van Wyk 2020 [32]	304	ml/kg/min	Open PDA	-28,7	±78,1	74,4	▲	▼	▲
Torigoe 2015 [30]	23	ml/min	PDA <1.5mm	6	±66,2	21	▲	▲	▼
Torigoe 2015 [30]	58	ml/min	PDA ≥1.5mm	-36,1	±119,5	38,6	▲	▼	▲

* Bias = TEBT – TTE
PDA – patent ductus arteriosus; PE – percentage error; PFO – patent foramen ovale; TGA – transposition of the great arteries.
Legend: Sample size (based on number of measurements: large arrow – large sample size >100, medium arrow 50-100, small arrow <50. Bias effect: Downward green arrow – TEBT underestimates reference method, upward red arrow – TEBT overestimates reference method; size of arrow indicates degree. Percentage error: downward green arrow PE <30%, upward red medium arrow 30-50%, upward large red arrow > 50%

Accuracy and precision according to type of TEBT technology

To determine if accuracy and precision were related to the type of TEBT technology utilized, studies were analysed according to whether bioimpedance or bioreactance was used. Three studies used bioreactance and 10 studies used bioimpedance technology.

In studies utilizing bioimpedance, 5 out of the 10 studies showed overestimation and 5 out of 10 showed underestimation of TTE hemodynamic parameters. SV mean bias varied between 0.28 and 1.1ml with LOA between ±1.85 and 2.35ml. CO mean bias varied between -18.8 and 0.23 ml/kg/min and -4 to 6ml/min with LOA between 13.5 to 132.7ml/kg/min and 66.5 to 233ml/min. PE varied between 5.3 and 46.2%, with 5 out of 10 studies meeting the PE<±30% benchmark (table 7, supplementary data table S6).

In studies utilizing bioreactance, all studies showed that bioreactance underestimated TTE hemodynamic parameters (table 7, supplementary data table S6). PE ranged between 48.3-71.6% with all studies exceeding the PE<±30% benchmark.

Table 7: Effect direction plot of accuracy for studies utilizing different types of TEBT

Study	Measurements	Units of measurement	Monitor	Mean Bias*	Precision	PE	Effect direction		
							Sample size	Mean bias	PE
Bioimpedance									
Grollmuss 2012 [24]	240	ml	Aesculon	0,28	±2,3	29	▲	▲	▼
Blohm 2016 [27]	291	ml	Aesculon	0,7	±2,35	44,9	▲	▲	▲
Blohm 2014 [28]	41	VTI	Aesculon			46,2	▲		▲
Hsu 2017 [31]	105	ml/kg/min	Aesculon	-5,3	±72,9	28,2	▲	▼	▼
Noori 2012 [29]	115	ml/kg/min	Aesculon	-4	±233	43,6	▲	▼	▲
Tibbals 1989[34]	78	ml/kg/min	NCCOM3	0,23	±13,5	5,3	▲	▲	▼
Grollmuss 2014 [35]	228	ml/kg/min	ICON	8,9	±62,7	24	▲	▲	▼
Boet 2016 [26]	451	ml	NS	1,1	±1,85		▲	▲	
Song 2014 [33]	109	ml/kg/min	NS	-18,8	±132,7	60,2	▲	▼	▲
Torigoe 2015 [30]	81	ml/min	NS	6	±66,5	21	▲	▼	▼
Bioreactance									
Weisz 2014 [22]	78	ml	Reliant	-0,6	±0,75	58	▲	▼	▲
Van Wyk 2020 [32]	754	ml/kg/min	Reliant	-18,5	±87,6	71,6	▲	▼	▲
Weisz 2012 [23]	97	ml/min	Reliant	-153	±152,5	48,3	▲	▼	▲

* Bias = TEBT – TTE
NS – not specified; PE – percentage error; VTI – velocity time integral.
Legend: Sample size (based on number of measurements: large arrow – large sample size >100, medium arrow 50-100, small arrow <50. Bias effect: Downward green arrow – TEBT underestimates reference method, upward red arrow – TEBT overestimates reference method; size of arrow indicates degree. Percentage error: downward green arrow PE <30%, upward red medium arrow 30-50%, upward large red arrow > 50%

Inaccuracies of data analysis and technology

Heteroscedasticity implies proportionality of bias, or variability of changes with magnitude of measurement, which is a problem with healthcare method comparison studies [36].In TEBT method comparison studies, this implies increasing bias (difference between EBT and reference method) with increasing CO or SV. Three studies reported heteroscedasticity in CO and/ or SV bias. Boet et al[26] showed that TEBT overestimated

TTE when SV >2ml and CO >0.4l/min. Van Wyk et al [32] showed an increasing CO and SV bias when CO ≥150ml/kg/min as compared to <150ml/kg/min (p<0.001). Hsu et al[31] showed a statistically significant increase in CO and SV bias (p=0.001) but no statistically significant difference in PE when comparing a CO ≥ 280ml/kg/min as compared to a CO <280ml/kg/min.

Tibballs et al[34] showed that the NCCOM3 was inaccurate if the heart rate exceeded 180bpm or if arrhythmias were present due to the technology's inability to detect the R-wave on the electrocardiogram. In addition, impedance-derived measurements could not be performed in a neonate with edema.

Discussion

In this review of EBT technology in neonates, 13 studies were found comparing TEBT technology (bioimpedance (n=10) and bioreactance (n=3)) to transthoracic echocardiography. A total number of 504 neonates were enrolled in these studies, comprising 2668 paired measurements.

In the current review, the mean bias (difference between TEBT technology and the TTE reference) was small in many studies but limits of agreement were wide, indicating acceptable accuracy but a lack of precision. This was similar to 2 systematic reviews in adults, where bias was also determined to be small (-0.22 to 0.03l/min[37,38]) with wide LOA (-2.78; 2.84 l/min[37,38]). A pediatric systematic review showed similar small bias and wide LOA (-0.02l/min and -1.22; 1.18l/min, respectively)[38]

Most studies (8 out of 13) in this review did not meet the percentage error benchmark of equal/ less than 30%, thereby indicating that TEBT is not interchangeable with the reference technology, TTE. PE represents the LOA adjusted for the mean of both methods and therefore represents the random error between the two methods. It describes the intrinsic variations in the assessed hemodynamic parameter that are not linked to true changes of that parameter (CO or SV), but rather to the environment and

random precision error of the investigated or reference technology[38]. The commonly accepted 30% arises from the original cardiac output method comparison studies using thermodilution as the reference technology, which has an inherent precision of 20% or less. Thus, if a new technology has a similar precision to thermodilution (i.e., ±20%), the combination will lead to a total error of ±28.3% ($\sqrt{(0.2)^2-(0.2)^2}$), which is commonly rounded off to 30%. Therefore, if a new technology has a percentage error of <±30%, the technology has a similar percentage error to the reference technology and is therefore an acceptable alternative[11]. However, this PE only holds true when the reference technology has a same PE as thermodilution, i.e., 20%. The inherent percentage error for other technologies is often higher. For this reason, it has been suggested that the PE threshold should be increased to 45%, to compensate for the variability of the reference method [39]. If this argument were to be followed in this review, it would only increase the studies meeting the benchmark by 1 i.e., 6 out of13 studies having a PE<±45%.

The current review showed significant heterogeneity amongst studies regarding measured hemodynamic parameter, unit of measurement, gestational and postnatal age of included neonates as well as different management strategies (respiratory support modes, inotropic support) as well as presence of physiological shunts or congenital cardiac disease. This is similar to the adult and pediatric systematic reviews showing high heterogenic indices (79.2- 93%)[37,38]

Sub-analyses for studies regarding preterm vs term neonates, respiratory support mode, presence of physiological shunts or cardiac disease/ cardiac surgery as well as type of EBT technology, showed persistence of small bias, wide LOA, and high PE.

Most studies were performed in preterm infants, confirming the interest by clinicians to determine CO in this vulnerable population. All studies in term infants exceeded the ±30% PE benchmark, indicating non-interchangeability of the studied methods. In preterm infants, the majority of studies also indicated non-interchangeability. If the adjusted benchmark of 45% were used only 1 of the 2 term studies would indicate interchangeability and majority of preterm studies would still show non-interchangeability.

PE differed between studies depending on respiratory support mode. In general, mean bias and PE increased with complexity of respiratory support mode, with invasive ventilation having higher PE than non-invasive ventilation methods. Most studies reported PE exceeding the benchmark, suggesting that respiratory support modes made TEBT less interchangeable with TTE. In most studies, the level of respiratory support was not stated, i.e., mean airway pressure, which may affect bias, due to the amount of air between the sensors and aorta interfering with the sensors ability to measure cardiac outflow.

In studies reporting accuracy and precision for cardiac anomalies, accuracy was reasonable, but precision was poor. PE exceeded the benchmark in most studies. However, different definitions were used to define PDA and size of PFO was not defined. Two studies were performed in neonates undergoing cardiac surgical intervention. This inaccuracy may be due to changes in CO (causing increased bias) or possible signal confusion due to the proximity of the PDA to the aorta.

The mean bias depends on the systematic error between measurements i.e., the mean constant difference. Although bias and LOA are used to statistically define accuracy and precision, there is no consensus regarding acceptable clinical cut-off values for these factors. What, therefore, represents an acceptable bias in neonatal studies? Three studies showed heteroscedasticity of bias, where bias increased with increased level of CO and/ or SV. This may be relevant in larger babies with higher CO and SV and requires further research.

In method comparison studies, the aim is to determine whether a new technology's accuracy and precision is similar to that of a gold reference technology and can therefore be used interchangeably. However, even the most accurate technologies (thermodilution) are known to have a degree of error. Thus, the inherent inaccuracy of the reference technique is brought into consideration when calculating the percentage error of the new technique. However, the reference technology in all these studies was TTE, which in itself

is known to be a relatively inaccurate reference technology [11]. Therefore, it cannot be considered a standard reference method. However, the lack of other reference technologies attests to the difficulties of invasive testing for CO or SV in small, sick neonates or the difficulties in performing cMRI studies.

Various United States health insurers have stated that bioimpedance “continues to be reasonable and necessary” in various adult cardiac disease processes[40] despite an earlier finding by the National Institute for Health Research of inadequate evidence to support its use[41]. However, various concerns in adult and pediatric medicine regarding the accuracy of these non-invasive cardiac output monitors have been raised[37,38,42]. Despite this, these monitors have been used in neonatology in research and clinical environments for monitoring transition at birth[43,44], cardiac adaptation after birth[45], patent ductus arteriosus (PDA)diagnosis [46], PDA ligation[22], PDA medical therapy[47], monitoring congenital heart disease[48,49], managing neonatal hemodynamic shock[50] and to predict clinical outcomes[51].

Several technological and physiological aspects have to be met prior to routine use of non-invasive cardiac output monitors in the clinical environment: (1) validation against gold reference standards, (2) accuracy along the entire spectrum of gestational age and birth weight, (3) ability to provide continuous measurements in absolute numbers, (3) be reliable, practical and non-invasive, (4) easy to apply, (5) inexpensive for widespread use, (6)feasible, (7) useful in neonates with extra- and intra-cardiac shunts as well as congenital cardiac disease and (8) continuously recordable alongside other physiological monitors[1]. Although many of the technical usability aspects (continuous measurements, ease of use, non-invasive, easy to apply, recordable alongside other physiological monitors) have been proven in various studies, this review suggests more research is required regarding the accuracy in different gestational ages, cardiac shunts and congenital heart disease and the technology should be validated against a true reference method.

Conclusion

TEBT, irrespective of the type of technology, has a poor interchangeability with TTE in newborn infants. High heterogeneity of patients and interventions in the neonatal population made direct comparisons of studies difficult. TTE, as a comparator in this review, cannot be considered an ideal reference method and studies evaluating TEBT against an accurate reference method is required. TEBT should be used with caution in the neonatal population for monitoring and determining therapeutic interventions. The use of TEBT trend monitoring has not been studied but may hold promise and requires evaluation in future trials for clinical decision making.

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Supplemental Data: Accuracy and Trending Ability of Electrical Biosensing Technology for Non-invasive Cardiac Output Monitoring in Neonates: A Systematic Qualitative Review

Supplemental data Table S1: Overall data regarding accuracy and precision of TEBT and reference technology

Authors/ Year	Unit of measurement	Number Patients (measurements)	Mean *	Bias** Mean ± SD	LOA (precision)	Overall PE
Stroke Volume						
Grollmuss 2012 [24]	ml	24 (240)	3.7	**0.28±0.05**	**± 2.3**	29
Weisz 2014 [22]	ml	25 (78)	1.25	**-0.6±0.37** (39%)	± 0.75	**58.0**
Blohm 2016 [27]	ml	99 (291)	5.2	0.7	± 2.35	44.9
Boet 2016 [26]	ml	79 (451)	NS	1.1	± 1.85	NS
Cardiac Output						
Tibballs 1989 [34]	ml/kg/min	26 (78)	239	0.23±6.5	± 13.50	5.3
Grollmuss 2014 [35]	ml/kg/min	28 (228)	256.4	8.9±31.9	± 62.7	24
Song 2014 [33]	ml/kg/min	40 (109)	209.5	-18.8±67.7	± 132.7	60.2
Hsu 2017 [31]	ml/kg/min	36 (105)	258	-5.3±37.2	± 72.9	28.2
Van Wyk 2020 [32]	ml/kg/min	63 (754)	124.4	-18.5	± 87.6	71.6
Noori 2012 [29]	ml/min	20 (115)	536	-4	± 233	43.6
Weisz 2012 [23]	ml/min	10 (97)	417	-153±56	± 152.5	48.3
Torigoe 2015 [30]	ml/min	28 (81)	314	6±46.9	± 66.5	21
VTI						
Blohm 2014 [28]	m	26 (41)	NS	39%	NS	46.2

* Mean= (mean TEBT + mean TTE)/ 2; ** Bias = TEBT – TTE
LOA – limits of agreement; NS – not stated; PE – percentage error; SD – standard deviation; TEBT – thoracic electrical biosensing technology; TTE – transthoracic echocardiography; VTI – velocity time integral
Bold values have been calculated from available data or determined from provided from graphs

Supplemental data Table S2: Accuracy and precision in studies with preterm or term neonates only

Authors/ Year	Unit of measurement	n Patients (measurement)	Mean*	Bias ** Mean ± SD	LOA (precision)	PE
Preterm infants						
Boet 2016 [26]	ml	79(451)	NS	1.1±0.7	± 0.59	67.5
Grollmuss 2014 [35]	ml/kg/min	11 (94) (VLBW)	256.4	5.3±21.9	± 58.7	23.5
		17 (134) (LBW)		10.4±30.9	± 60.5	23.9
Song 2014 [33]	ml/kg/min	40 (109)	NS	-18.8±67.7	± 132.7	60.2
Hsu 2017 [31]	ml/kg/min	36 (105)	258	-5.3±37.2	± 73.0	28.6
Van Wyk 2020 [32]	ml/kg/min	63 (753)	124.4	-18.5	± 87.6	71.6
Blohm 2014 [28]	l/min	26 (40)		39%	NS	46.3
Term infants						
Noori 2012[29]	ml/min	20 (115)	535	-1.5	± 77.5	43.6
Torigoe 2016[30]	ml	(32)	4.8	-0.4	± 2.2	50.7

* Mean= (TEBT + TTE)/ 2; ** Bias = TEBT – TTE
LBW – low birth weight; LOA – limits of agreement; NS – not stated; PE – percentage error; SD – standard deviation; TEBT – thoracic electrical biosensing technology; TTE – transthoracic echocardiography; VLBW – very low birth weight

Supplemental data Table S3: Accuracy and precision in studies with different respiratory support modes

Authors	Unit of measurement	n Measurements	Type of respiratory support	Mean*	Bias** Mean ± SD	LOA (precision)	PE
Non-invasive ventilation							
Song 2014 [33]	ml/kg/min	54	CPAP	209.5	-18.2±63.7	±124.9	57
Hsu 2017 [31]	ml/kg/min	37	CPAP	258	-2.8±20.8	±40.7	17.3
Van Wyk 2020 [32]	ml/kg/min	335	CPAP	124.4	-23.0±45.8	±84.8	78.5
Torigoe 2015 [30]	ml/min	37	CPAP	314	3.6	±73.1	25.0
Invasive ventilation							
Song 2014 [33]	ml/kg/min	39	SIMV	209.5	-30.2±73.8	±94.6	69.7
Torigoe 2015 [30]	ml/min	10	SIMV	314	-29.6	±97.8	31.7
Hsu 2017 [31]	ml/kg/min	44	IMV	258	-1.4±36.0	±70.1	27.4
Song 2014 [33]	ml/kg/min	8	HFOV	209.5	38.2±91.4	±179.1	85.5
Torigoe 2015 [30]	ml/min	14	HFOV	314	-12.0	±105.9	33.2
Hsu 2017 [31]	ml/kg/min	24	HFOV	258	-16.2±40.4	±79	37.8
Song 2014 [33]	ml/kg/min	8	HFJV	209.5	-10.9±81.7	±160.1	76.4

Supplemental data table S4: Comparative outcome measures for type of ventilation for included studies

	CPAP				IMV/ SIMV				HFO/HFOV			
Authors	**n**	**Mean bias**	**Precision**	**PE**	**n**	**Mean bias**	**Precision**	**PE**	**n**	**Mean bias**	**Precision**	**PE**
Song 2014 [33]	54	-18,2	±124,9	57	39	-30,2	±94,6	69,7	8 (HFO)	38,2	±160,1	85,5
									8 (HFJ)	-10,9	±79	76,4
Hsu 2017 [31]	37	-2,8	±40,7	17,3	44	-1,4	±179,1	27,4	24 (HFO)	-16,2	±70,1	37,8
Torigoe 2015 [30]	37	3,6	±73,1	25	10	-29,6	±97,8	31,7	14 (HFO)	-12	±105,9	33,2
Van Wyk 2020 [32]	335	-23	±84,8	78,0								

* Mean= (TEBT + TTE)/ 2
** Bias = TEBT – TTE
CPAP – continuous positive airway pressure; SIMV – synchronized intermittent mandatory ventilation, HFOV – high frequency oscillatory ventilation, HFJV – high frequency jet ventilation; LOA – limits of agreement; PE – percentage error; TEBT – thoracic electrical biosensing technology; TTE – transthoracic echocardiography

Supplemental data Table S5: Accuracy and precision in studies with cardiac shunts

Authors/ Year	Unit of measurement	n measurements	Cardiac defect	Mean*	Bias ** Mean ± SD	LOA (precision)	PE
Cardiac surgical intervention							
Grollmuss 2012 [24]	ml	240	TGA switch surgery	3.7	**0.27**	**±1.06**	29.0
Weisz 2014 [22]	ml	78	PDA ligation	1.25	**-0.6** (39%)	**±0.75**	**58.0**
Physiological shunt							
Blohm 2016 [27]	ml	12	PDA only	4.1	-0.8±**1.73**	±0.98	72.1
		63	PDA + PFO		-1.1±**1.58**	±1.09	56.3
		125	PFO only		-0.6±**1.11**	±0.59	40.2
Van Wyk 2020 [32]	ml/kg/min	304	PDA	124.4	-28.7±43.7	±78.1	74.4
Torigoe 2015 [30]	ml/min	23	PDA ≥1.5mm	317	5.5	±66.2	21.0
	ml/min	58	PDA < 1.5mm		-36.1	±119.5	38.6

* Mean= (TEBT + TTE)/ 2
** Bias = TEBT – TTE
Bold data indicates calculated data or data estimated from provided graphs
LOA – limits of agreement; PDA – patent ductus arteriosus; PE – percentage error; PFO – patent foramen ovale SD – standard deviation; TGA – transposition of great arteries

Supplemental data Table S6: Outcome measure for studies using bioimpedance or bioreactance technology

Authors Year	Unit of measurement	n Patients (measurements)	Specific Technology	Mean*	Bias ** Mean ± SD	LOA (precision)	Overall PE
Bioimpedance							
Grollmuss 2012 [24]	ml	24 (240)	Aesculon	3.7	**0.28±0.05**	**±2.3**	29
Blohm 2016 [27]	ml	99 (291)	Aesculon	5.2	0.7	±2.35	44.9
Boet 2016 [26]	ml	79 (451)	NS	NS	1.1	**±1.85**	NS
Hsu 2017 [31]	ml/kg/min	36 (105)	Aesculon	258	-5.3±37.2	±72.9	28.2
Tibballs 1989 [23]	ml/kg/min	26 (78)	NCCOM3	239	0.23±6.5	±13.50	5.3
Grollmuss 2014 [35]	ml/kg/min	28 (228)	ICON	256.4	8.9±31.9	±62.7	24
Song 2014 [33]	ml/kg/min	40 (109)	NS	209.5	-18.8±67.7	±132.7	60.2
Noori 2012 [29]	ml/min	20 (115)	Aesculon	536	-4	±233	43.6
Torigoe 2015 [30]	ml/min	28 (81)	NS	314	6±46.9	±66.5	21
Blohm 2014 [28]	m[#]	26 (41)	Aesculon	NS	39%	NS	46.2
Bioreactance							
Weisz 2014 [22]	ml	25 (78)	Reliant	1.25	**-0.6±0.37** (39%)	± 0.75	**58.0**
Van Wyk 2020 [32]	ml/kg/min	63 (754)	Reliant	124.4	-18.5	±87.6	71.6
Weisz 2012 [23]	ml/min	10 (97)	Reliant	417	-153±56	±152.5	48.3

[#] TTE VTI was hemodynamic parameter measured by TTE
* Mean= (TEBT + TTE)/ 2
** Bias = TEBT – TTE
Bold data indicates calculated data or data estimated from provided graphs
LOA – limits of agreement; NS – not specified; PDA – patent ductus arteriosus; PE – percentage error; PFO – patent foramen ovale SD – standard deviation; TGA – transposition of great arteries

CHAPTER 6

Bioreactance-derived thoracic fluid content in preterm infants

Bioreactance-derived Thoracic fluid content during transition and respiratory distress in preterm infants

Lizelle Van Wyk, Johan Smith, John Lawrenson, Carl J Lombard, Willem-Pieter de Boode. (Submission ready)

Abstract

Introduction: Thoracic fluid content (TFC) is a non-invasive electrical biosensing parameter derived from thoracic impedance changes. TFC may be able to assess lung fluid in neonates. **Methods:** Secondary analysis of a bioreactance study of stable preterm (<37 weeks) neonates was performed, comparing neonates who received non-invasive respiratory support (nCPAP) and surfactant (SRT) administration to a group who received nCPAP only and a group requiring no respiratory support. TFC parameters were monitored for the first 72 hours of life via bioreactance: absolute TFC, TFC change (TFCd) and TFC change from baseline (TFCd0). Data were analysed longitudinally over the first 72 hours of life as well as set time points pre- and post- respiratory intervention. **Results:** 63 preterm infants with a mean gestational age of 31 weeks and mean birth weight of 1563g were included. Twenty-two percent required no respiratory intervention, 57% required nCPAP only and 21% required surfactant replacement while on nCPAP. Only TFC and TFCd0 showed association with clinical variables (postnatal age, gestational age, birth weight, respiratory support mode and PDA) during statistical analysis. In longitudinal analysis, multivariate analysis showed only postnatal age remained associated with TFC and TFCd0. During respiratory intervention analysis, TFC and TFCd0 were associated with pre and post intervention time periods for both CPAP and CPAP+SRT groups, with gestational age, birth weight and PDA also remaining significant. **Conclusion:** In neonates, TFC parameters may offer the ability to monitor lung fluid content and provide longitudinal follow-up during interventions and disease processes.

Introduction

For successful adaptation to extrauterine life, an infant is dependent on efficient lung fluid clearance for successful lung recruitment [1]. Therefore, intra-alveolar and interstitial fluid needs to be cleared. In preterm and term neonates, this requires reduced surface tension to allow alveolar expansion as well as numerous physical, biochemical and neurohumoral interactions to adequately clear interstitial pulmonary fluid[2,3].

Thoracic fluid content (TFC) is a non-invasive electrical biosensing parameter estimated by various non-invasive cardiac output monitors (NICOM). TFC is derived from thoracic impedance and is measured as Z0. It represents the resistance to electrical current flow by all thoracic tissue (skeletal muscle, cardiac muscle, lung, chest wall, subcutaneous fat, bone and fluid (intra- and extracellular). As body fluids are the most variable of these components, changes in Z0 primarily occur due to changes in thoracic fluid[4]. Z0 has an inverse relationship with fluid volume and therefore the reciprocal of Z0 is used to measure TFC i.e., 1/Z0, enabling 1/Z0 to parallel fluid level changes. As Z0 is a very small number, both numerator and denominator are multiplied by 1000. Thus, TFC is measured in kohms^{-1} (kΩ^{-1})[4].Bioreactance measures the phase shift of an oscillating current as it traverses the thorax, which may be more accurate in determining Z0, as compared to traditional [5]

TFC assessment has been described in a late preterm and term population, showing TFC independently correlated with respiratory distress at birth and at 24 hours of age[6]. Most of this population were diagnosed with transient tachypnoea of the newborn.

The most common respiratory pathology in preterm neonates is respiratory distress of the newborn for which the mainstay of treatment is nasal continuous positive airway pressure (nCPAP) and surfactant replacement therapy (SRT), as required[7].

No studies utilizing TFC have been performed to study the change of TFC in preterm neonates with application of different respiratory support modes and with administration of surfactant.

The objectives of this study were to describe the average values of TFC parameters (TFC, TFCd, TFCd0) over the first 72 hours of life as well as to determine whether TFC parameters were influenced by the application of different respiratory support interventions.

Methodology

Study design and setting

A prospective observational, longitudinal study cardiac output method comparison study was performed in the neonatal service of Tygerberg Children's Hospital, Cape Town, South Africa, between December 2016 and July 2017[8]. This was a post hoc analysis of neonates in this cohort who had received respiratory support (nCPAP) and surfactant administration as compared to nCPAP support alone or neonates not requiring any respiratory support.

Study population

All preterm infants (<37 weeks gestational age) admitted to the neonatal service were eligible for enrolment. Infants were enrolled within 3 hours after delivery.

The study was performed in a group of stable preterm infants. All infants received respiratory care as per standard hospital protocol: flow driver nasal continuous positive airway pressure (nCPAP) at 5-6cmH_20 PEEP (peak end expiratory pressure) and surfactant replacement therapy (SRT) via less invasive surfactant administration (LISA), as required, with peripheral saturation monitoring. Surfactant is administered, per institutional protocol, as rescue therapy when oxygen requirements reach 35%. No sedation is administered prior to LISA procedure but atropine is administered prior to laryngoscopy. LISA is performed with a nasogastric tube whilst nCPAP is maintained.

The choice of surfactant is at the discretion of attending medical personnel and dependent upon availability but is per hospital protocol poractant alpha (200mg/kg) for neonates ≤1250g and beractant (100mg/kg) for neonates > 1250g. Follow-up doses of surfactant may be administered if FiO2 exceeded 0.35. nCPAP was weaned at the discretion of the attending medical personnel.

The University of Stellenbosch granted ethical approval (N13/04/053). All parents provided written consent.

Bioreactance monitoring

All infants underwent continuous bioreactance (BR) monitoring (NICOM® Reliant, Cheetah Medical, Massachusetts) until 72 hours of life. Sensors were placed as per manufacturer's specifications. Sensor size was decreased by cutting the edges of the sensors down to the size of the gel electrode only.

BR-derived thoracic fluid content (TFC) is presented as 3 parameters:

1. TFC – an absolute value at a specific time point ($k\Omega^{-1}$)
2. TFCd (dynamic TFC) – change in TFC from the previous measurement (as compared to the measurement 15 minutes prior) (i.e., 15-minute to 15-minute TFC changes) ($k\Omega^{-1}$)
3. TFCd0 – cumulative TFC change from baseline measurement (i.e., change in TFC from first measurement at patient enrolment to the specific time point) (%)

Statistical analysis

Various data were categorised. Gestational age was dichotomised to ≤32 weeks and 33-36 weeks. Birth weight was categorized as extremely low birth weight (<1000g)(ELBW), very low birth weight (1001-1500g) (VLBW) and low birth weight (1501-2500g) (LBW). Patent ductus arteriosus (PDA) was categorized as open or closed.

Data are presented as mean ± standard deviation for normally distributed data, otherwise as median (interquartile range) and number (proportion).

Statistical analysis was performed for longitudinal data over the first 72 hours of life as well for categorised respiratory support interventions on a pre-post intervention basis.

Longitudinal data

TFC parameters were assessed over the first 72 hours of life. Time series graphs were constructed for all TFC variables over the first 72 hours of life, using the mean value of each variable at each time point. Linear mixed model, incorporating repeated measurements, was performed to determine the association between the different BR-derived hemodynamic parameters and relevant clinical variables (postnatal age (PNA), gender, gestational age (GA) and birth weight (BW)), separately. If significance was determined ($p<0.05$), post-hoc pairwise comparison of means analysis, with Bonferonni correction, was performed to determine between-group differences. A linear mixed effects regression was performed to determine the fixed effects of PNA and clinical variables on all TFC parameters with the participant as the random effect to account for the repeated measure. A linear time effect model was specified for the random effect with an unstructured covariance matrix.

Pre- and post-intervention data

Pre- and post- intervention TFC parameters were determined for neonates in 3 groups: those who received SRT combined with nCPAP (CPAP+SRT group), nCPAP only (CPAP group) and neonates requiring no respiratory support (NONE group). Time intervals for 10, 30 and 60 minutes prior to SRT were determined as well as 10,30,60, 120, 180-, 360, 720- and 1440-minutes post SRT. The median age at which SRT was administered was calculated and this was assumed to be “time 0” for neonates not receiving SRT (CPAP and NONE groups) and from this time point the pre- and post-intervention time points were calculated with their respective TFC parameters. . For aggregate time points the

PRE time points T-60 to T0 were combined and for the aggregate POST time points T+10 to T+1440 were combined.

Data were analysed using STATA IC15 (StataCorp, 2017, College Station, TX, USA) and MedCalc v18.10 (MedCalc Software bvba, 2016, Ostend, Belgium). Statistical significance was defined as a p-value <0.05, apart from Bonferonni corrections (p<0.006).

Results are reported according to STROBE guidelines[9].

Results

Seventy-nine infants were enrolled in the study in the larger parent study[8] Power disruptions at the hospital led to machine failures and corrupted data, thereby leading to incomplete data sets in 16 patients. After excluding these 16 patients, 63 were included in the study. Patient demographics are shown in Table 1.

Table 1: Study patient demographics

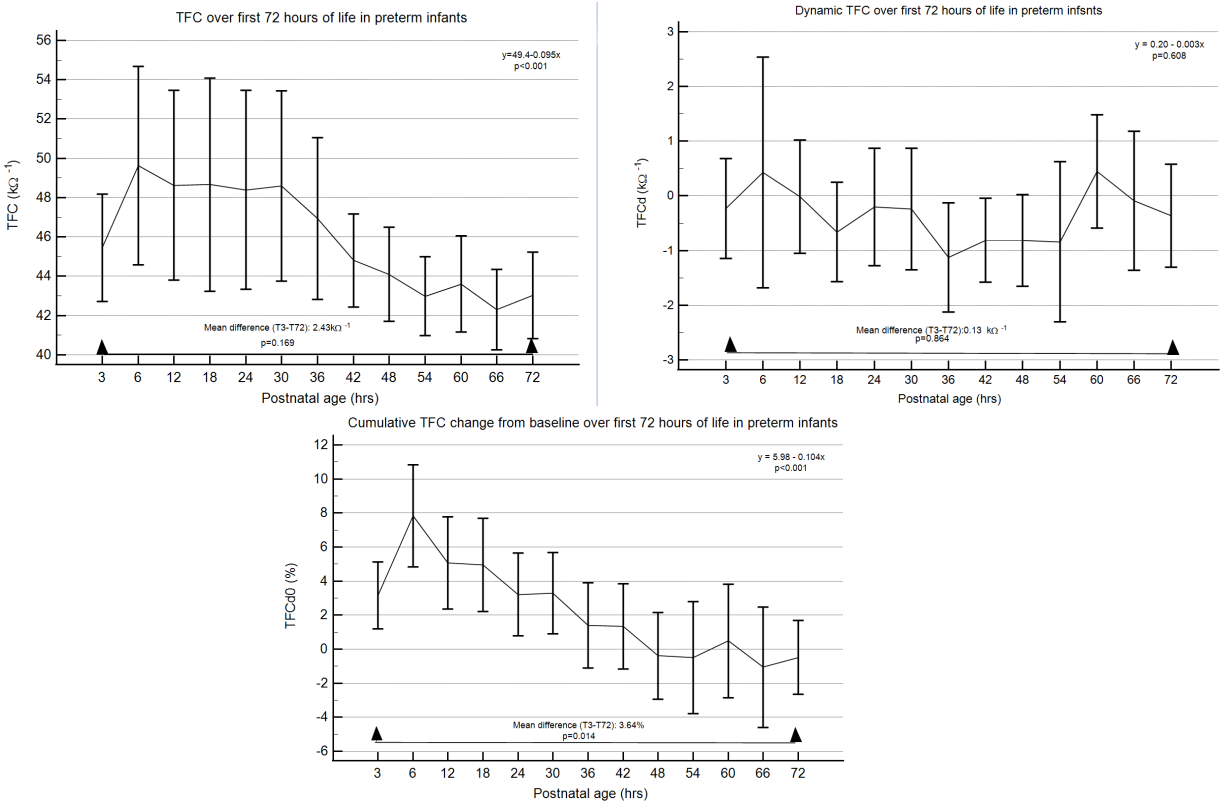
Parameter		**n=63**
Male, n (%)		33 (52)
African race, n (%)		34 (54)
Gestational age (weeks), mean ± SD		31.3±2.7
Gestational age category	≤32 weeks, n(%)	40 (63)
	33-36 weeks, n(%)	23 (37)
Birthweight (grams), mean ±SD		1563±411
Birth weight category	ELBW (≤1000g), n(%)	5 (8)
	VLBW (1001-1500g), n(%)	24 (38)
	LBW (1501-2500g), n(%)	34 (54)
Complete course antenatal steroids, n (%)		21 (33)
Cesarean section, n (%)		51 (81)
Respiratory support mode	None, n(%)	14 (22)
	nCPAP only, n(%)	36 (57)
	nCPAP plus surfactant administration, n(%)	13 (21)
Age of SRT (hours), median (IQR)		6.2 (3.6-13.4)
CXR diagnoses	RDS (mild)*	14 (22)
	RDS (moderate)*	4 (6)
	RDS (severe)*	2 (3)
	TTN	14 (22)
	Congenital pneumonia	2 (3)
	Normal	18 (29)
	Not performed	9 (14)
PDA spontaneous closure before 72hrs postnatal age, n(%)		56 (89)
SNAPPE-II score, mean ± SD		11.4 ± 13.2
Number BR measurements		754

* Degree of RDS defined according to Jin et al[10] (Mild is designated as stage 1, moderate as stage 2 and severe as stage 3&4)
BR – bioreactance; CPAP – nasal continuous positive airway pressure; CXR – chest x-ray; ELBW – extremely low birth weight; HFNC – high flow nasal cannula (3-6l flow); LBW – low birth weight; NPO_2 – nasal prong oxygen (≤2l flow); PDA – patent ductus arteriosus; RDS – respiratory distress syndrome; SNAPPE-II – SNAPPE-II – Score for neonatal acute physiology with perinatal extension-II; SRT – surfactant replacement therapy; TTN – transient tachypnea of the newborn; VLBW – very low birth weight

TFC parameters over the first 72 hours of life

Time series graphs were drawn for all TFC parameters (fig 1). Postnatal age (PNA) was significantly associated with TFC ($p<0.001$) and TFCd0 ($p<0.001$) but not TFCd ($p=0.606$). Both TFC and TFCd0 showed downward trends over the first 72 hours of life whilst TFCd showed a plateau pattern during the same period (figure 1).

Figure 1: Time series plots over first 72 hours of life for (a) TFC, (b) dynamic TFC (TFCd) and (c) cumulative TFC change from baseline (TFCd0)



Overall, gestational age category was associated with TFCd0 but not with TFC or TFCd (table 2). Few between-group differences were apparent and only at different postnatal age periods for different TFC parameters (supplemental data figure 1).

Overall, birth weight category showed borderline significance with TFCd0 but not with not TFC or TFCd (table 2)However, for all PNA time points, significant between-group

differences (p<0.05) were apparent for ELBW vs VLBW and ELBW vs LBW for TFC and between LBW vs ELBW TFCd0 (figure 3). TFCd showed no between group differences (supplemental data figure 2).

PDA closed vs open status was only associated with TFCd0 but not TFC) nor TFCd with no between-group differences for the studied 72 hours (supplemental data figure 3).

Overall, Respiratory support mode (CPAP vs none) was significantly associated with TFC and TFCd0 but not TFCd nor with very few between-group differences at any time point in the studied 72 hours (supplemental data figure 4).

After multivariate analysis, only postnatal age remained significantly associated with TFC and TFCd0 (table 2).

Table 2: Univariate and multivariate for association between TFC parameters and clinical variables

	TFC	TFCd	TFCd0
Univariate p-values*			
Postnatal age	**<0.001**	0.608	**<0.001**
Gestational age	0.940	0.138	0.015
Birth weight	0.426	0.225	0.071
Respiratory support mode	**<0.001**	0.171	**<0.001**
PDA	0.953	0.853	**<0.001**
Multivariate p-values#*			
Postnatal age	**0.007**	n/a	**<0.001**
Gestational age	n/a	n/a	0.062
Birth weight	n/a	n/a	0.454
Respiratory support mode	0.755	n/a	0.405
PDA	n/a	n/a	0.035

n/a – not applicable
All univariate variables with p<0.1 included in multivariate analysis
* Bold indicates significance after application of Bonferroni correction: p=0.05/10 groups, p<0.005 regarded as significant.

Respiratory management and TFC parameters

SRT was administered in 54% (7/13) of neonates with mild RDS, 60% (3/5) with moderate RDS and in 75% (3/4) with severe RDS. No neonate with an alternative diagnosis received SRT.

TFC parameters were determined in neonates undergoing the different respiratory support interventions (no respiratory support (NONE), CPAP only (CPAP) and surfactant administered with CPAP (CPAP+SRT)). Average TFC parameters differed significantly between the different respiratory support interventions: TFC ($p=0.044$), TFCd ($p=0.050$) and TFCd0 ($p<0.001$) (supplemental data table S1).

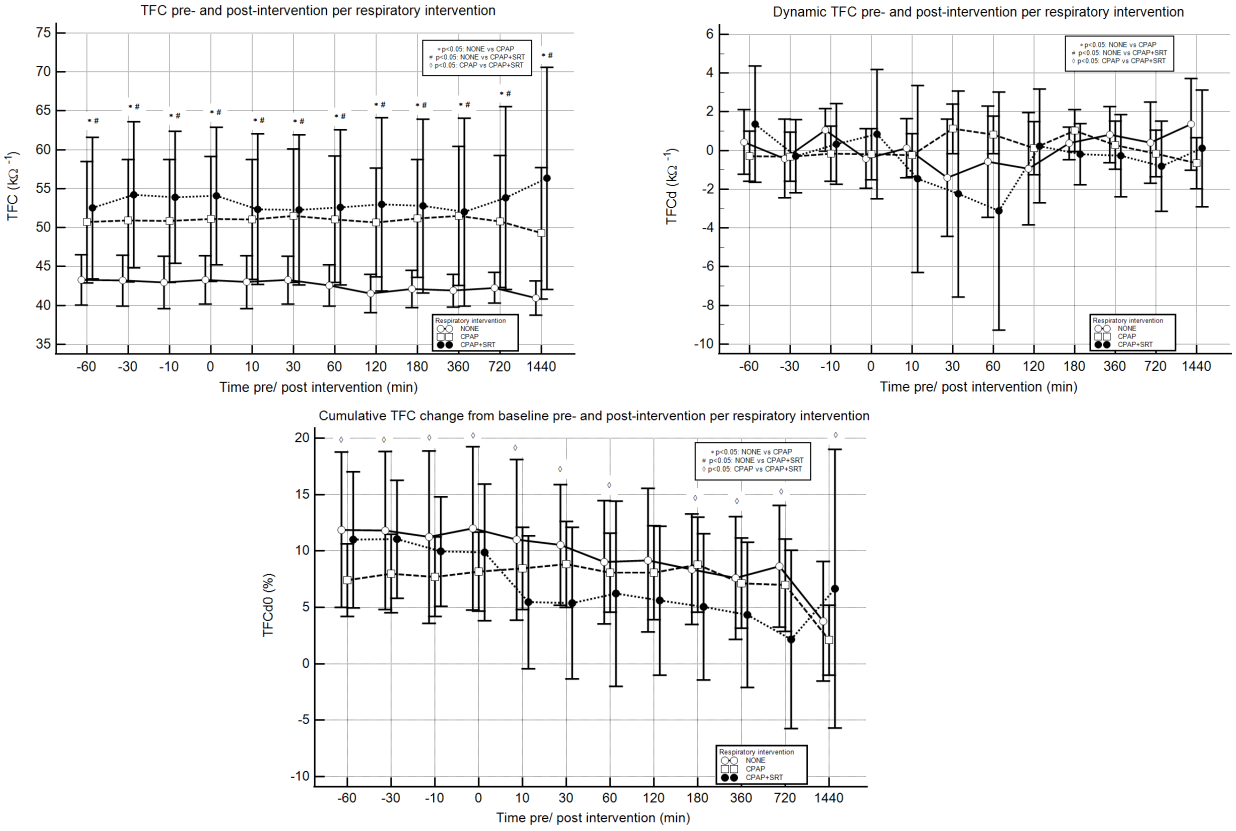
Pre intervention (10 to 60 minutes prior to intervention) was compared to post intervention (0 to 1440 minutes after intervention) TFC parameters values. Average values at each time point showed no differences for TFC ($p=0.186$) nor TFCd ($p=0.979$) but were significantly different for TFCd0 ($p<0.001$) (supplemental data table S2).

Time series graphs for all TFC parameters were drawn to compare the different respiratory interventions (fig 2). TFC differed over all time points between NONE and both respiratory support interventions (CPAP and CPAP+SRT) but with no differences between CPAP and CPAP+SRT. TFCd0 only showed differences between CPAP and CPAP+SRT at all time points. TFCd showed no differences between any respiratory intervention (figure 2).

To determine the interaction of the respiratory support intervention and time, the pre- and post-intervention time points were combined: PRE as T-60 to T0 and POST as T+10 to T+1440. In neonates receiving no respiratory support and CPAP only, there were no differences in TFC, TFCd nor TFCd0. In neonates receiving CPAP+SRT, TFCd0 differed significantly pre- and post-intervention ($p=0.007$) (supplemental data table S3).

Overall, pre & post intervention, TFC showed no differences. However, when analysed per intervention, CPAP showed no differences (p=0.353), whilst CPAP+SRT showed significant differences (p<0.001) as compared to NONE.

Figure 2: TFC parameters pre- and post-intervention per respiratory intervention (a) TFC, (b) TFCd and (c) TFCd0



Overall TFCd showed no differences pre & post interventions. However, there were significant differences pre & post for CPAP+SRT (p=0.06) but not for CPAP (p=0.139) as compared to NONE

Overall TFCd did show significant differences pre & post interventions. However there no were significant differences pre & post for CPAP+SRT (p<0.001) but not for CPAP (p=0.240) as compared to NONE.

Multivariate regression of TFC parameters, accounting for clinical parameters (GA, BW, time, PDA) and the interaction of respiratory support intervention and pre/post intervention time aggregate, was performed. No clinical or intervention variable was associated with TFCd. TFC was significantly associated with gestational age as well as pre and post CPAP and CPAP+SRT. TFCd0 was significantly influenced by gestational age, birthweight as well as pre and post CPAP+SRT (table 3).

Table 3: Multivariate regression of influence of clinical and respiratory intervention variables' effect on TFC parameters

	TFC	**TFCd**	**TFCd0**
	p-values		
Gestational age	**0.029**	0.528	**0.009**
Birth weight	**0.010**	0.493	**0.006**
None	Ref	ref	ref
PDA	**0.013**	0.230	0.447
CPAP	0.055	0.606	0.202
CPAP+SRT	**0.019**	0.684	**0.008**
Pre/Post	0.150	0.329	0.079
NONE#PRE/ POST *	Ref	Ref	Ref
CPAP#PRE/POST*	0.085	0.097	**0.035**
CPAP+SRT #PRE/POST*	**0.047**	0.146	**0.028**

# Indicates interaction between variables
* PRE is the aggregate time point of time points T-60 to T0.
** POST is the aggregate time point of time points T+10 to T+1440.

Discussion

This is the first study to describe bioreactance-derived parameters related to thoracic fluid content in clinically stable preterm (<37 weeks) infants over the first 72 hours of life. The study also describes BR-derived TFC parameters for various respiratory interventions.

In adult patients, 80% of the lung is made up of water, with areas of gas exchange protected by various barriers[11]. This extravascular lung water (EVLW) component differs in neonates during the first days of life as they transition from an intra-uterine to an extra-uterine environment.

EVLW measurement is complex and is usually measured by various imaging (chest XR, chest computer tomography, nuclear magnetic resonance, positron emission tomography, magnetic resonance imaging, electrical impedance tomography) and indicator dilution methods[12]. Most of these methods are expensive, expose patients to radiation, differ in accuracy[12] or are difficult to perform in neonates and cannot be performed longitudinally. Recently, minimally invasive methods have become available (transpulmonary ultrasound dilution), and although still mostly experimental[13], it is feasible in neonates and can provide longitudinal assessment of EVLW. Thoracic electrical biosensing technologies (TEBT) (bioimpedance and bioreactance) are non-invasive and can provide continuous non-invasive monitoring of multiple hemodynamic variables, including thoracic fluid content (TFC). TFC represents the sum of intrathoracic extravascular, intravascular and intrapleural fluid. In neonates during the transitional phase, in the absence of a hydrops or other significant edema, it can be assumed that intrapleural fluid is absent. Pulmonary blood flow increases dramatically from intra- to extra-uterine life stabilizing after a few minutes when functional residual capacity has been established [14]. Therefore, with the intrapleural component being negligible and the intravascular component stabilizing within the first minutes of life (assuming adequate lung recruitment), TFC changes could be assumed to equate to EVLW changes in the neonate.

Changes in partial oxygen pressure, interactions of various hormones (glucocorticoids, catecholamines, thyroid hormones) as well as developmental regulation of membrane transport proteins enable the switch of lung epithelium from a secretory to an absorptive function during the transition from fetus to newborn [15]. Alveolar fluid is cleared to the interstitium and then further transported over the next hours through the lymphatic system and pulmonary vessels. Fluid clearance increases over the first 6 hours of life but continues for 48 hours[15]. This time association was confirmed in this study, with both absolute TFC and TFC change from baseline showing decreasing trends over the first 72 hours of life.

Both TFC (absolute TFC) and TFCd0 (cumulative TFC change from baseline) showed significant decreases over the first 72 hours of life. The relatively low magnitude of these decreases may be due to the late onset of monitoring in this study (within first 3 hours of life), as most lung fluid may already have cleared [15]. Antenatal steroid administration, in a third of the study population, may also have contributed to increased clearance. A sheep model showed that preterm lambs had 30% more lung fluid than late preterm lambs and that antenatal steroids decreased lung fluid by 55% [16]. This decrease in lung fluid, in addition to air ventilation, led to a 5 fold increase in FRC creation and static lung compliance at 30 minutes of life[16]. TFC decrease from baseline is a cumulative parameter with changes determined from the first measurement. The plausibility of this parameter showing the greatest change is therefore clear. TFCd0 may be the better TFC parameter to use in the clinical environment when monitoring lung fluid.

Preterm infants have approximately 25% more lung water than their full term counterparts and lung fluid clearance may be prolonged in preterm infants [2,15]. The association with gestational age was confirmed in this study, as well as an association of birth weight with TFC value and TFCd0. In adults, age was only able to explain 41.2% of intra-individual TFC variability which increased to 48.4% when sex was added [17]. The additive effects of these effects were not able to be determined in the current study.

In this study, TFC and TFCd0 were related to respiratory support mode but no differences were demonstrable between neonates on CPAP and neonates receiving no respiratory support. Air inflation has been shown to increase alveolar size as well shift fluid from the alveolar lumen towards the pulmonary interstitium. Total lung fluid is inversely related to lung compliance and directly related to lung resistance [16]. Neonates requiring no respiratory support can be assumed to already have cleared sufficient lung fluid whilst CPAP also facilitated lung fluid shift. the shift of lung fluid.

A hemodynamically significant PDA can cause an increase in the pulmonary blood flow, leading to increased interstitial fluid [18]. However, this is usually due to prolonged exposure to a PDA and dependant on transductal shunt volume. A PDA may therefore

be assumed to increase TFC. In this study, PDA was not shown to affect any TFC parameter. This is probably due to the short exposure time and the high closure rate within the first 72 hours of life in a reasonably mature set of stable preterm infants in this study. PDA was only assessed as open or closed. This is inaccurate as even PDA diameter is known to not be the only parameter dictating PDA significance[19]

Animal [20] as well as neonatal MRI studies [21] have shown the effect of body position on lung fluid distribution, with increased fluid in dependant lung parts, leading to non-uniform ventilation. TFC is a global parameter and cannot differentiate between areas of increased or decreased EVLW. All neonates in this study were consistently studied in the prone position.

Despite various physiological and intervention variables, only postnatal age (PNA) continued to influence TFC parameters during the first 72 hours of life. The only TFC parameters of clinical importance were absolute TFC (TFC) and TFC change from baseline (TFCd0) as dynamic TFC (TFCd) showed few associations with clinical variables.

Respiratory management and TFC parameters

Delayed or impaired lung fluid clearance may lead to transient tachypnea of the newborn in late preterm and term neonates due to a transient decrease in sodium transport by epithelial channels and noradrenaline levels. Preterm infants also have increased levels of lung fluid due to low expression of lung epithelial and nasal sodium channels, thereby increasing the predisposition to respiratory distress syndrome[15]. Monitoring TFC parameters may therefore be beneficial in neonates with increased lung fluid to monitor disease progress or resolution as well as monitor the effect of therapeutic interventions.

Neonates requiring no respiratory intervention showed no differences in any TFC parameter at any individual or aggregate pre-or post-intervention time point. This may be an indication of stable TFC values over the 1500minutes (25 hours) of the study period,

suggesting that most lung fluid had already been absorbed in these neonates prior to the TFC assessment.

TFCd showed no association with any clinical variable, similar to results found in the longitudinal data. There was also no association between TFCd and any respiratory intervention. Dynamic TFC (TFCd) is a change in TFC based on a 15-minute interval and this period may be too short to provide any clinically relevant lung fluid changes in neonates. In general, TFCd is not a useful parameter to monitor lung fluid in neonates. TFCd time period can be set up to 10 hours, which may be of use in neonates. This should be explored in future neonatal studies.

TFC is a minute-by-minute absolute measurement. In this study, TFC showed no temporal associations with individual or aggregate pre- and post-intervention time points. However, significant associations were apparent when pre- and post-intervention time periods were combined with respiratory intervention. Significant differences were apparent between neonates receiving any type of respiratory intervention as compared to those with receiving no respiratory support. This would suggest that respiratory support (CPAP with/ without surfactant administration) influences TFC values. However, as birth weight and gestational age also influenced TFC, these associations may be an indication of illness severity as well.

TFCd0 is the cumulative change of TFC from baseline. TFCd0 showed significant individual time point associations in neonates requiring no respiratory support and CPAP only support but these were insignificant on aggregate pre/ post time evaluation. However, aggregate time showed a significant association with TFCd0 in neonates who received CPAP and surfactant. There were also significant differences in TFCd0 values pre and post intervention. This confirms that lung fluid decreases after surfactant administration, in the presence of CPAP administration. This association persisted even when gestational age and birthweight were considered, as would be expected.

CPAP and surfactant are important components of the management of respiratory distress syndrome[22]. CPAP distends the alveoli, increasing the intrapulmonary pressure, thereby forcing fluid from the alveoli and interstitial space back into the lung lymphatics and pulmonary circulation[2], leading to improved ventilation-perfusion ratios and improved gas exchange. Surfactant is able to displace alveolar fluid due to its biophysical properties, with the compression and re-spreading of phospholipid during respiration allowing for fluid resorption. [23]. Surfactant also counteracts the pulmonary edema due to lung injury in preterm lung injury that often leads to higher oxygen requirements and repeated SRT doses[24]. The association between respiratory intervention and pre and post time periods for TFC and TFCd0 support the presumed mechanism of the reduction in lung fluid with the application of CPAP and surfactant administration in preterm neonates.

TFC has been stated to be higher in infants with respiratory distress at birth (76.8 vs 61.6 $k\Omega^{-1}$, $p<0.001$) and independent of GA and mode of delivery[6]. The TFC values in this study [6] as well as those in the study by Hsu et al [25], are much higher than in the current study. Both these studies utilized bioimpedance-derived TFC. The differences may be due to inherent technological differences between bioimpedance and bioreactance, emphasizing the need for technology-specific reference values. Further studies are required to elucidate BR-derived TFC parameter reference values.

TFC has been used to predict numerous clinical outcomes in adults: pulmonary edema in cardiac failure (TFC >35$k\Omega^{-1}$) [26] and pre-eclampsia (TFC >40 $k\Omega^{-1}$) [27], extubation failure in patients with a poor ejection fraction (TFC >50 $k\Omega^{-1}$) [28] as well as differentiate between patients with cardiac failure vs non-cardiac failure related dyspnoea (TFC>78.8$k\Omega^{-1}$) [29]. Individual measurements of TFC may not be discriminative for pathology or physiology but may alert to possible abnormality. Initial and peak TFC have been used to predict outcomes in children requiring ICU admission[30]. The direction and magnitude of temporal change from baseline(TFCd0) may be a better clinical indication and may offer a monitoring capability[4].

TEBT can continuously and non-invasively monitor lung fluid clearance, which may support lung mechanics. In neonates, TFC parameters may therefore offer the opportunity to monitor lung fluid and provide longitudinal follow-up of interventions and disease processes. The determination of TFC cut-off values may be able to alert to pulmonary fluid overload states in neonates with hemodynamically significant PDA and chronic lung disease. Further research is required in this field.

Limitations

Various limitations of this study need to be acknowledged. This was a post-hoc analysis of a larger study and the study design was not primarily aimed at studying the effect of respiratory interventions on thoracic fluid content. Although all study participants underwent comprehensive monitoring, the number of patients in each respiratory intervention category is small. Further research is required to confirm the current findings. The timing of surfactant administration varied widely and may have influenced data as average time had to be used. A prospective study with this as primary objective is required.

In a pediatric congenital cardiac surgery study, TFCd correlated well with body weight gain and intra-operative fluid balance[31]. It is well known that neonates lose weight in the first 7-14 days of life, and it is unknown how this may influence TFC measurements. However, it may be assumed as neonatal weight loss is due to trans-epidermal water loss[32], that this waterloss would also decrease TFC. This effect should be included in future research.

PDA was dichotomized in this research to open and closed. However, despite the lack of accuracy of PDA size in determining PDA significance, TFC may be associated to diameter as well as other PDA indices. This should be incorporated in future TFC studies.

Conclusion

In neonates, TFC parameters may offer the ability to monitor lung fluid and provide longitudinal follow-up of therapeutic interventions and disease processes. The change from baseline measurement of TFC (TFCd0) may be the best choice of parameter to use in neonates.

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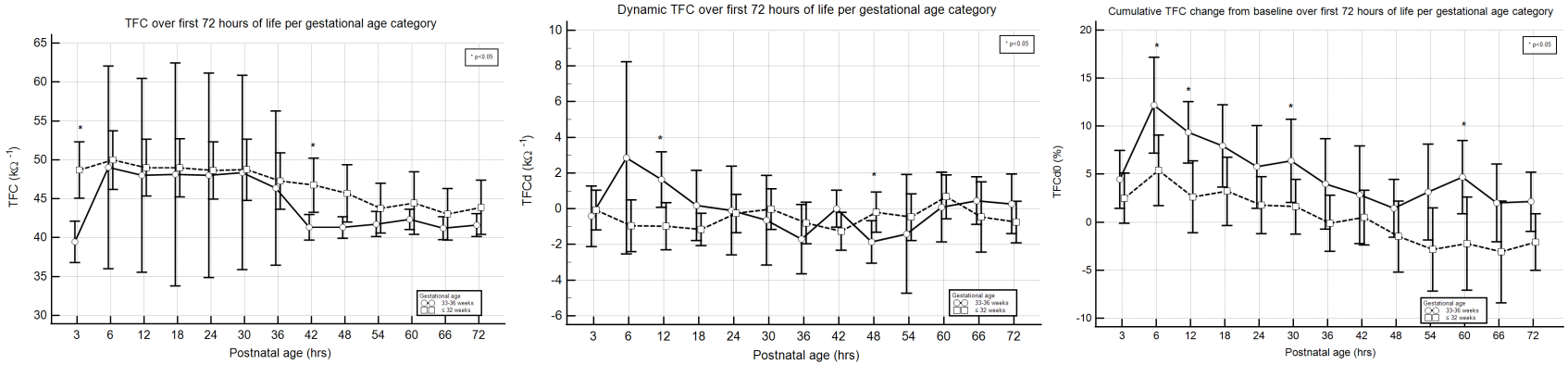
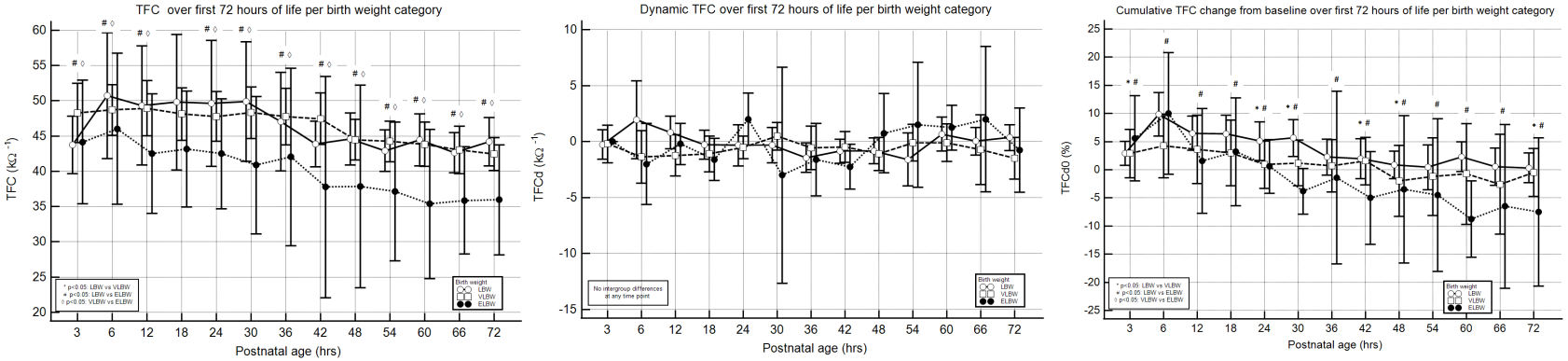
Supplemental data: Bioreactance-derived Thoracic fluid content and respiratory distress in preterm infants

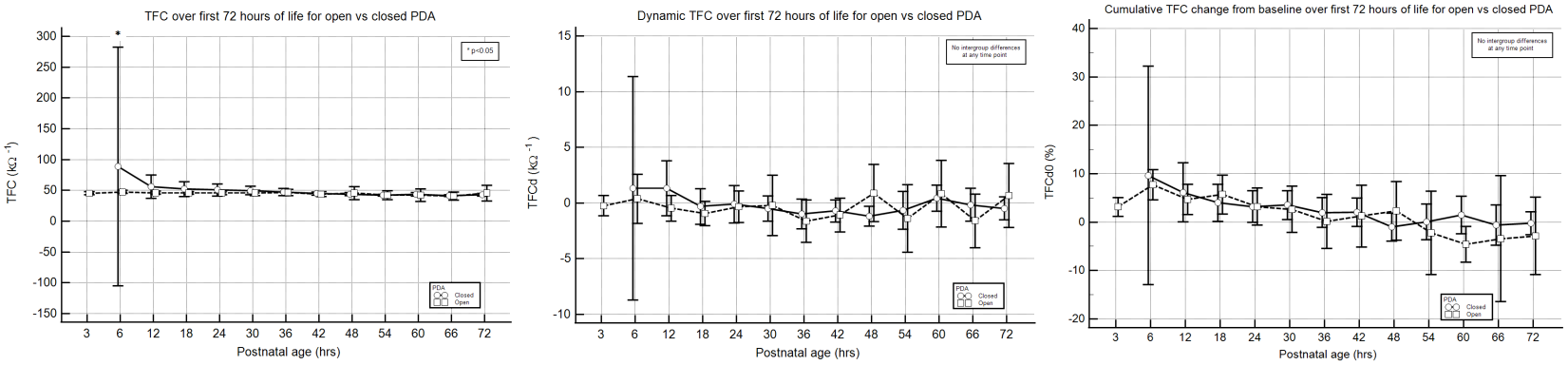
Supplemental data Figure S1: Time series plots over first 72 hours of life per gestational age category for (a) TFC, (b) dynamic TFC (TFCd) and (c) TFC change from baseline (TFCd0)



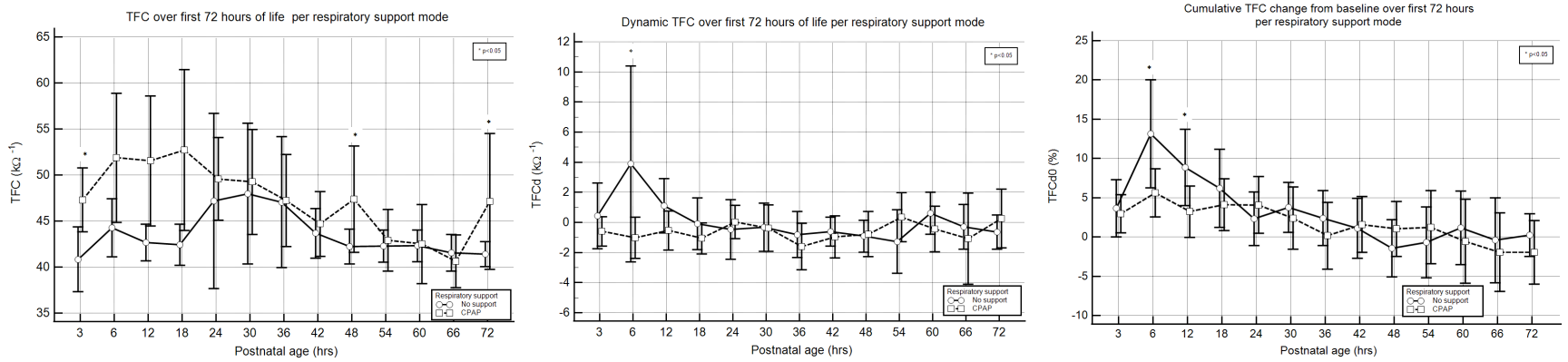
Supplemental data Figure S2: Time series plots over first 72 hours of life per birth weight category for (a) TFC, (b) dynamic TFC (TFCd) and (c) TFC change from baseline (TFCd0)



Supplemental data Figure S3: Time series plots over first 72 hours of life per open or closed PDA for (a) TFC, (b) dynamic TFC (TFCd) and (c) TFC change from baseline (TFCd0)



Supplemental data FigureS4: Time series plots over first 72 hours of life per respiratory support mode for (a) TFC, (b) dynamic TFC (TFCd) and (c) TFC change from baseline (TFCd0)



Supplemental data Table S1: Comparison of TFC parameters according to respiratory support intervention

	TFC ($k\Omega^{-1}$)	TFCd ($k\Omega^{-1}$)	TFCd0 (%)
None	42.53±5.36	0.06±3.97	9.59±11.96
CPAP	50.88±21.92	0.11±3.44	7.47±10.22
CPAP + SRT	53.25±16.34	-0.50±5.76	6.9±11.04
p-value*	**0.044**	**0.050**	**<0.001**

* Repeated measurement ANOVA

Supplemental data Table S2: Average TFC parameters per respiratory intervention per pre- and post-intervention time point for 63 preterm infants.

Time (minutes) (pre/ post intervention)	TFC ($k\Omega^{-1}$)			TFCd ($k\Omega^{-1}$)			TFCd0 (%)		
	NONE	**CPAP**	**CPAP+ SRT**	**NONE**	**CPAP**	**CPAP+ SRT**	**NONE**	**CPAP**	**CPAP+ SRT**
n	14	36	13	14	36	13	14	36	13
T-60	43.2±6.3	50.7±21.6	52.5±13.5	0.4±3.1	-0.2±3.5	1.3±4.4	11.8±13.4	7.4±8.9	11.0±8.9
T-30	43.2±6.3	50.9±21.8	54.2±15.5	-0.4±3.9	-0.3±3.5	-0.3±2.9	1.8±13.6	8.0±9.6	11.0±8.2
T-10	42.9±6.5	50.8±21.8	53.9±14.7	1.0±2.1	-0.1±3.9	0.3±3.4	11.2±14.8	7.7±9.7	9.9±8.3
T0	43.2±6.0	51.0±22.2	54.0±15.3	-0.4±3.0	-0.1±3.9	0.8±5.5	12.0±14.0	8.1±9.6	9.8±10.4
T+10	42.9±6.5	51.0±21.3	52.3±16.7	0.1±2.9	-0.1±3.6	-1.4±7.5	11.0±13.8	8.4±10.1	5.4±10.2
T+30	43.2±5.9	51.5±23.7	52.2±16.6	-1.4±5.8	1.1±3.5	-2.2±8.8	10.5±10.3	8.8±10.6	5.3±11.6
T+60	42.5±5.1	51.0±22.5	52.6±17.2	-0.5±5.5	0.8±2.7	-3.1±10.6	9.0±10.2	8.0±9.6	6.2±14.1
T+120	41.5±4.6	50.6±19.4	53.0±19.2	-0.9±5.4	0.1±3.8	0.2±5.0	9.1±11.9	8.0±11.5	5.5±11.4
T+180	42.1±4.4	51.1±21.0	52.7±19.3	0.3±1.5	1.0±2.9	-0.1±2.7	8.3±9.1	8.7±11.6	5.0±11.2
T+360	41.9±4.1	51.5±23.9	52.0±17.9	0.8±2.8	0.2±3.3	-0.2±3.1	7.5±10.5	7.1±10.6	4.3±9.5
T+720	42.2±3.8	50.7±23.4	53.8±17.4	0.4±4.0	-0.1±3.3	-0.8±3.4	8.6±10.4	6.9±11.3	2.1±11.6
T+1440	40.9±4.2	49.2±23.4	56.3±18.5	1.3±4.6	-0.6±3.6	0.1±3.9	3.7±10.3	2.0±8.5	6.6±16.0
p-value*	0.121	0.711	0.625	0.115	0.272	0.878	**0.015**	**0.003**	0.208

* Repeated measurement ANOVA

Supplemental data Table S3: TFC parameters according to aggregate pre- and post-intervention time per respiratory support intervention

	No respiratory support			CPAP			CPAP+SRT		
	Pre*	**Post****	**p-value#**	**Pre***	**Post****	**p-value#**	**Pre***	**Post****	**p-value#**
TFC ($k\Omega^{-1}$)	43.17±6.18	42.41±5.13	0.384	50.88±21.64	51.16±21.75	0.912	53.74±14.42	52.52±17.34	0.673
TFCd ($k\Omega^{-1}$)	0.16±3.11	-0.27±4.34	0.481	-0.23±3.63	0.52±3.26	0.054	0.54±4.14	-1.18±6.92	0.116
TFCd0 (%)	11.7±13.6	9.29±10.92	0.202	7.82±9.40	8.23±10.61	0.723	10.41±8.83	5.37±11.18	**0.007**

* Aggregate of pre-intervention time points (T-60 Includes T0)
** Aggregate of post-intervention time points (T+10 to T+1440)
# Repeated measurement ANOVA

CHAPTER 7

Discussion

Worldwide, 11% of all births are preterm with prematurity being the cause of 50% of all neonatal deaths [1]. With the growing number of surviving premature neonates, at an ever-increasing younger gestational age[2], the need for accurate monitoring is essential. The incidence of hemodynamic compromise is unknown as an exact definition is lacking. Often, blood pressure is the only parameter used and the definition of a “normal” blood pressure and the definition of hypotension is fraught with uncertainty[3,4]. Isolated, episodic clinical examination, vital signs and laboratory values are insufficient[5] to assess a system that is in a continuous state of change, such as the neonate’s cardiovascular system[6]. For this reason, continuous, objective hemodynamic monitoring is essential.

Non-invasive cardiac output monitoring offers the ability to continuously monitor several hemodynamic variables that may provide insight into the changing dynamics of the preterm neonate’s cardiovascular system. By monitoring heart rate (HR), oscillometric blood pressure (BP) and peripheral saturation (SpO_2), non-invasive cardiac output monitors provide similar data to a conventional vital signs monitor. In addition, it is able to provide stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR) and thoracic fluid content (TFC), allowing estimation of global blood flow and cardio-pulmonary interaction. This may enable the determination of the underlying pathophysiology of hemodynamic compromise.

The American College of Critical Care Medicine emphasizes the need for the early recognition of symptoms and the initiation of goal-orientated, time sensitive interventions to improve patient outcomes in neonatal shock. The guidelines also support the use of hemodynamic parameters, such as cardiac index (CO corrected for body surface area) [7]. In this regard, non-invasive CO monitoring may assist in the recognition of hemodynamic instability and shock, allowing the timely initiation of therapy and allowing therapeutic monitoring.

Characteristics of a hemodynamic monitor

The use of hemodynamic monitoring in critically ill patients is reliant on the following principles: (1)no hemodynamic monitoring technique can improve outcome by itself; (2) monitoring requirements may vary over time and may depend on local availability and training; (3) there are no optimal hemodynamic values that are applicable to all patients; (4) variables should be combined and integrated; (5) CO is estimated not measured; (6) monitoring hemodynamic changes over short periods of time is important; (7) continuous measurements of all hemodynamic variables is preferable and (8) non-invasiveness is not the only issue[8].

Various theoretical, hardware and patient-related factors must be considered when choosing a hemodynamic monitor (table 1). Desirable characteristics of CO monitoring technologies are accuracy, precision, reproducibility, operator independence, rapid response time, continuous monitoring and ease of use and application and cost effectiveness[9]. Currently, no such device exists for any patient population. The choice of CO monitor then depends on machine availability, patient characteristics, clinical situation, and practitioner preference.

Table 1: Factors for consideration when choosing a hemodynamic monitor

Theoretical considerations	Hardware considerations	Patient-related considerations
Safety & side-effects	Accuracy/ reproducibility of parameters	Influenced by cardiac rhythm, function & valvular disease
Versatility, number, relevance & utility of parameters	Rapid response time to interventions & accurate trending ability	Influence by mechanical ventilation: tidal volume, frequency, PEEP
Able to be utilised by nurses & physicians (operator independence)	Expertise proven: personal, colleagues, and literature	Type, severity & stage of disease warranting hemodynamic monitoring (e.g., shock, acute lung injury)
Ease of use and application, user-friendliness, education, learning curve	Uniformity of applicability: different patients, clinical situations, hemodynamic states	Type of circulatory support & change contemplated therein: fluids, drugs, devices
Possibility of assessing fluid responsiveness, goal-directed therapy, and other resuscitation strategies of proven outcome benefit even if not decreased mortality	Continuous vs intermittent measurements	Vascular access & other anatomical factors (contra-indications)
Demonstrated treatment alterations	Invasive vs non-invasive	Patient tolerance
Acceptable cost-effectiveness	Availability	
	Level of integration with existing monitors	

Adapted from [9,10]

Bioreactance (BR) is one type of thoracic electrical biosensing technology (TEBT) that offers the ability to non-invasively monitor several hemodynamic parameters, providing data in absolute numbers, as well as their respective indices. The BR

monitor consists of 4 dual gel electrodes that are easy to apply and are not known to cause skin damage. The monitor requires minimal training to operate and is easy to interpret. A 2-hour training session has been shown to provide competence in its use, by all level of medical personnel [11]. Despite these positive characteristics, a monitor should not be used prior to robust validation studies providing evidence of its accuracy, precision, and trending ability.

Statistical analysis in method comparison studies

To determine accuracy, precision and trending ability, method comparison studies need to be performed. Many types of statistical analyses exist in method comparison studies: intraclass correlation, concordance correlation, linear regression, bias, and limits of agreement (Bland Altman), total deviation index, coverage probability and intersection union principle[34]. However, the best analytical methods are the Bland Altman plot for determining agreement and 4-quadrant and polar plots for trend analysis [12,13].

Assessment of agreement

Despite the relatively large study size, the repeated, longitudinal research design, this research observed no agreement, and thus no interchangeability, between bioreactance (BR) and transthoracic echocardiography (TTE). The underestimation of CO and SV was in line with other BR [14,15] and bioimpedance (BI) studies[16–19]. The small mean bias, indicating reasonable accuracy, with wide limits of agreement, indicating poor precision, was also in keeping with other neonatal thoracic electrical biosensing technology (TEBT) studies [14–25]. The unacceptably high error percentage indicated non-interchangeability of BR with TTE, similar to other BR and BI studies [15,17,19,21,23].

Bias decreased with increasing postnatal age but was affected by numerous physiological and interventional variables. This improving accuracy may be due to the physiological improvements: decreasing need for CPAP, closure of the PDA and improvement of CO due to the closure of the PDA. Other studies have shown similar influences of respiratory support interventions[18,19,25] and PDA[15,17,18] on TEBT

accuracy. Another possible explanation is the physiological changes, per se, of numerous hemodynamic parameters in the transitional period[26].

In method comparison studies, a reference technology is used to determine the new technology's accuracy, precision, and trending ability. The importance of the reference technology has been emphasized, as an inaccurate reference technology may nullify method comparison study results [27]. For cardiac output, this has traditionally been thermodilution [28], although it has a percentage error of ±20%[29]. Aortic flow probes have a low percentage error of <5% [30] but have only been used in animal studies. Cardiac MRI has recently become a reference technology for CO measurements [31] but is dependent on various physiological and physics principles [32]. In neonatology, thermodilution, flow probes and cMRI are not clinically feasible. TTE has become routine practice in NICU and is therefore the only clinically, bedside feasible comparator technology for neonatal CO comparison studies. However, TTE has a high percentage error (16-48%), as compared to thermodilution [33], making it a poor reference technology. This complicates the analysis of TEBT in neonatology.

Correlation and linear regression cannot be used to assess agreement. Correlation describes a linear relationship between data, in this instance the two technologies assessed. Correlation quantifies the degree of relation between variables, but the correlation coefficient (r) only quantifies the strength of the linear relationship not the degree of agreement[35,36]. It is calculated as the ratio of the covariance between the variables and the product of their standard deviations. The coefficient of determination (r2) only describes the proportion of variance that the two variables have in common. To overcome these difficulties with correlation and linear regression regarding relationship vs agreement, the use of Bland Altman is preferred[36].

In Bland Altman analysis, agreement is determined by bias and limits of agreement (LOA). Bias indicates accuracy, defined as the mean difference between 2 technologies and LOA defines precision, defined as the spread of the mean differences [27,37]. However, there are no acceptable values defined for these parameters. It is therefore difficult to define what is an acceptable agreement (bias, LOA) between technologies. It would be a logical conclusion, to not allow bias or LOA

to exceed a certain percentage of a neonate's CO. However, what this should be, should be determined and pre-defined in future neonatal method comparison studies.

Due to the difficulty in interpreting bias and LOA, percentage error (PE) is used to determine whether a new technology can be used interchangeably with the reference technology. The commonly accepted PE<±30% arises from the original CO method comparison studies using thermodilution as the reference technology. However, PE is calculated based on the assumption that the reference technology's PE is ±20% (equivalent to thermodilution), which is not true for TTE. Due to TTE's high PE, the PE benchmark of 30% cannot be assumed to be generally acceptable [27,37]. For this reason, it has been suggested that the PE threshold should be increased to 45%, to compensate for the variability of TTE as reference method [38]. However, despite this, the current agreement study still exceeded this adjusted PE. Despite this, TTE remains the only clinically available, repetitive reference technology available for neonatal CO comparison studies.

Sample size calculation in method comparison studies, relies on bias and LOA determination. As these are ill-defined, sample size calculation is problematic. However, for a neonatal study with a theoretical bias of 5ml/kg/min, SD 20ml/kg/min and LOA ±50ml/kg/min (which may represent clinically acceptable data), p=0.05 and power of 80%, the sample size would equate to 277 paired measurements. However, this also assumes a PE of the reference method of 30%[13]. As expected, with decreasing bias, sample size also increases. The current study had a sample size of 754, which could be assumed to be sufficient. However, the repeated measurement methodology complicates sample size calculation[39].

It must be remembered that a monitor is a clinical tool, and that bias and LOA should be clinically acceptable to allow diagnostic or management decisions. As such, agreement parameters should be defined *a priori* [40]. To compensate for these uncertainties, the concept of a tolerability interval, to define what would be a clinically acceptable precision level, has been suggested[40]. The tolerability interval represents the range of values that would be clinically acceptable and would not prompt any medical intervention. This interval could be normal values (a reference range), or a predefined value based on a clinical disease state (clinical decision limit).

A calculated agreement: tolerability index would express the precision of the monitoring device in relation to the pre-defined tolerability interval (i.e., defined clinically acceptable range)[41]. This has not been performed in neonates due to the wide range of normal cardiac output (150-350ml/kg/min)[42]. However, it may be possible to use this index with pre-defined agreement parameters to clinically define values for unacceptably low CO values (i.e., CO< 150ml/kg/min), which may be associated with adverse outcomes. This should be explored in future neonatal TEBT research.

Assessment of trending ability

In this research, the longitudinal method design enabled trend analysis of CO and SV. This was the first such neonatal study. Results showed a poor trending ability for both CO and SV, as compared to TTE, in preterm neonates in the transitional period. PDA, CPAP and CO level showed a tendency to worsen trending parameters. The interaction between neonatal transitional physiology and the requirement of respiratory support may play a role in these discrepancies. Respiratory support may increase the air interface between the sensors and heart, thereby decreasing BR signal accuracy[43]. A PDA, an integral part of transitional physiology, due to its proximity to the aorta, may decrease the aortic blood flow-only signal detection, contributing to BR signal inaccuracy [44].

The 4-quadrant plot plots differences in sequential measurements between the two evaluated technologies (BR and TTE). From this concordance rate can be calculated. However, the magnitude and direction of these sequential changes cannot be assessed by 4-quadrant plots. To assess this, polar plots are used, where magnitude and direction of change are represented by polar coordinates. From this angular bias, radial limits of agreement and angular concordance can be calculated [30].

The 4-quadrant plot is an intuitive plot that allows illustration of the trending ability of a new device as compared to a reference device. The data point's quadrant allows for identification of concordance with the x and y- position indicating magnitude and direction of change of both technologies. Although numerous studies have provided cut-off values for good, acceptable, and poor agreement, no definitive values are

available[45]. Although time intervals have been stated to influence trend analysis, no data are available to support this statement[45]. However, the underlying principle may be based on physiological changes over time associated with the measured parameter rather than due to actual statistical principles. Four quadrant plots are known to have various limitations due to the arbitrariness of the exclusion zones, the inability of the concordance rate to consider the clinical range of variation and the lack of recommendations for correct interpretation of the concordance rate[46].

In 4-quadrant and polar plots, the methodology assumes that each pair of measurements is independent[47], despite the calculations clearly being dependant due to the requirement of subtraction of sequential measurements. Only 1 paper has addressed the statistical concepts underpinning repeated measurements in 4-quadrant plots and its effect on concordance rate calculation[48]. The repeated measurement method for concordance rate calculation may provide improved concordance as compared to the current analyses. Only one study in the literature has performed polar plots with repeated measurements but this involves advanced statistics[49]. This involved the use of a random effects model to estimate the with-in patient variability after accounting for other variations. Each subject was then presented as a different bias, magnitude, and polar angle over the observation period[49]. Both of these repeated measurement statistical analyses will need to be evaluated in future neonatal TEBT trending studies, as they may significantly impact results.

Other limitations of the polar plot are also the arbitrariness of the choice of the central exclusion zones, the limited evidence upon which the 30º polar limits are based, the subjectiveness of the polar concordance and that the exclusion zones may exclude the most discordant measurements[46].

Due to these factors various other statistical analyses have been devised. Clinical concordance with error grids (based on percentage of ΔCO changes) may bring concordance in line with therapeutic interventions [13]. However, these percentages were also arbitrarily chosen, have been deemed to be subjective and also do not take the reference technology's repeatability into account[46] . It has also brought into question how CO should be classified. This CO classification dilemma is similar to that

in neonates, where low systemic flow is defined as <150ml/kg/min[50] with no other stratifications.

Another alternative is the trend interchangeability method[41]. This analytical method incorporates the repeatability of both the reference and new technology. A pair of measurements are deemed to be interchangeable when the difference between the measurements is less than that of the expected range when the repeatability of both technologies was considered.

In trending method comparison studies, a *priori* exclusion zones should be established[47]. These have not been established in neonates. In adult medicine, exclusion zones are based on 10% (or 15%) of a normal CO of 5l/min. However, “normal” CO in neonatology is unknown and is simply described as a range of 150-350ml/kg/min[42]. As such, it is difficult to determine a single CO (or SV) cut-off value upon which to base an exclusion zone. In this study, exclusion zones were chosen based on animal studies [51,52] and extrapolated from adult percentage values (5-15%). Trending data results showed significant differences depending on the choice of exclusion zone. The choice of the size of the applied exclusion zone, thus, remains unclear. The exclusion zone should also be adapted considering the range of ΔCO (or ΔSV) observed in the study population and the time interval between the measurements[45]. This was not applied in this research. As this was the first research of its kind in neonates, the accepted norm of exclusion zones of adults (5-15%) based on normal CO values was used rather than adapting to study population values.

In this study, nearly 50% of all measurements fell within the 5% exclusion zone. These small changes may be concordant or discordant but are considered statistical noise[47]. However, this may not hold true in neonates, especially in ELBW infants with small SV and low CO. It is therefore unclear whether an exclusion zone should be applied as ranges of clinically important hemodynamic data may be excluded.

Despite this research’s finding of poor agreement and trending ability, physiological variables during the transitional period may influence the accuracy of the electrical signal. Statistical analyses are also fraught within consistencies that make a clear

decision regarding the clinical usefulness of bioreactance as a non-invasive cardiac output monitor in neonatology difficult.

Systematic review

In the narrative systematic review performed, the included studies showed that most studies indicated that TTE and TEBT were not interchangeable, despite many studies showing small bias and wide limits of agreement. In an effort to present all relevant quantitative data in a transparent way[53], effect direction plots were utilised [54]. Although the effect direction plots may enable clear visualization of complex data, the arrows may be interpreted as effect sizes, complicating interpretation[54]. The plots, however, do provide a way to link data and what may be a lengthy discourse in a narrative review. Arrows are also arbitrary and remain indicative of an outcome and not linked to a specific effect size.

No trend analysis studies were available at the time of review for inclusion. Only TEBT technology was utilised and only TTE was used as a comparator. WBEBT is still a new technology and should be investigated in neonates. The lack of alternative comparator technologies, attested to the difficulty of alternative bedside available CO measurement techniques in neonates.

Significant heterogeneity prevented the performance of a statistical meta-analysis. However, this allowed for sub-analyses for gestational age (preterm vs term neonates), respiratory support mode, presence of physiological shunts and cardiac disease/ cardiac surgery as well as type of EBT technology. These showed persistence of small bias, wide LOA, and high PE in most studies. Although these factors complicated the performance of the systematic review, it also attested to the clinical diversity in which CO monitoring is required.

Future neonatal TEBT method comparison studies should:

1. Compare TEBT to an accurate reference method (e.g., (transpulmonary ultrasound dilution, cMRI)

2. Expand agreement and trending studies should be performed in neonates with intra and extra-cardiac shunts, various respiratory and hemodynamic support interventions
3. Determine clinically appropriate bias and LOA.
4. Determine clinically appropriate exclusion zones.
5. Determine appropriate statistical methods to determine accuracy, precision and trending ability if repeated measurement studies are performed (which should ideally be performed)

Clinical uses for TEBT

Despite various concerns in adult and pediatric medicine regarding the accuracy and precision of TEBT monitors [28,55,56], United States health care funders have stated that TEBT “continues to be reasonable and necessary” in adult cardiac disease [57], despite an earlier finding by the National Institute for Health Research of inadequate evidence to support its use[58]. TEBT continues to be used in numerous adult clinical scenarios for diagnostic and therapeutic monitoring purposes – e.g., cardiac failure management, pulmonary edema diagnosis and response to therapy, fluid overload due to hemodialysis, pregnancy, hypertension[59].

In neonatology, TEBT has been used in both research and clinical environments for monitoring transition at birth[60,61], cardiac adaptation after birth[62], PDA diagnosis [63], monitoring PDA ligation[15] and medical therapy[64], monitoring congenital heart disease[65,66], managing neonatal hemodynamic shock[67] and to predict clinical outcomes[68]. A recent review explored the extensive use of this technology despite a lack of data supporting agreement, as compared to TTE or other reference technologies[69].

In numerous fields of medicine, the concept of a minimal clinically important difference in determining patient improvement exists. This is a threshold number at which a patient is stated to have improved or experienced an important level of improvement. According to research, this should be a context-specific value rather than a fixed number[70]. Although the accuracy for TEBT technology has been questioned, this inaccuracy does not necessarily translate into the inability to use such a monitor in the

clinical environment[28]. In this regard, an inaccurate monitor may be able to be used to monitor change from an individual's specific baseline [70].

Monitoring of the transitional period

This research showed that bioreactance could monitor numerous hemodynamic parameters during the transitional period. BP, HR, SV, CO and TPR followed trends as described in the literature [71–73] .Most parameters stabilised around 48 hours of postnatal age. This may be due to a stabilisation of physiology (absorption of lung fluid, PDA closure, decreasing pulmonary pressures, decreasing CPAP requirement) in the stable cohort of neonates. Average hemodynamic parameter values differed from those of other TEBT methodologies[74]. This may be related to the inherent differences in the technology underlying BI and BR[9]. This reinforces the need for technology-specific references values.

The transition from intra-uterine to extra-uterine life comprises significant hemodynamic changes. Failure to adapt may lead to hemodynamic compromise for the preterm neonate. Hemodynamic monitoring in this period may decrease the incidence of hemodynamic compromise as well as identify its pathophysiology. BR may, therefore, be able to track a neonate's hemodynamic status if reference values are known.

Reference values are defined as typical ranges of a variable seen in a healthy reference population whereas clinical decision limits are values above or below which a significant risk exists for an adverse outcome[75]. It may therefore be possible to define clinical decision limits, in sick neonates, for BR-derived hemodynamic values in order to use it for pathophysiology-based monitoring and management.

Monitoring thoracic fluid content

CO and thoracic fluid content (TFC) have been used to monitor a variety of decompensated cardiac abnormalities in adults. Cardiopulmonary interaction and interdependency are well known in neonatology[76]. TFC may therefore offer another hemodynamic parameter in the clinician's arsenal.

This was the first study to longitudinally describe BR-derived TFC in clinically stable cohort of preterm neonates during the transitional period. Absolute and cumulative changes in TFC parameters (TFC & TFCd0, respectively) were associated with postnatal age. TFC parameters decreased over the first 72 hours of life as would be expected with absorption of fetal lung fluid. TFC parameters were also able to monitor changes during respiratory interventions. Significant differences were apparent in TFC parameters pre- and post-intervention in neonates requiring CPAP and surfactant replacement, as compared to those requiring no respiratory support or CPAP only, suggesting that the combination therapy increased lung fluid shift. TFC parameters were not associated with a PDA in the transitional period. TFC may therefore be a viable parameter to monitor lung fluid during the transitional phase as well as respiratory interventions in preterm neonates.

TEBT can continuously and non-invasively monitor lung fluid clearance, which may support cardio-pulmonary mechanics. TFC cut-off values have been used to predict various outcomes in adults [77–80] and children [81,82]. Similar TFC cut-off values may be able to identify neonates requiring more intensive respiratory intervention, as well as possibly identify neonates at risk of PDA complications. This requires further research.

Although TFC, similar to the other non-invasive CO monitoring parameters, is an absolute number and easy to track, TFC's accuracy cannot be confirmed. It must be remembered that TFC is an electrical measurement (1/Z0) rather than an actual volume measurement. In adult cardiac failure studies, its diagnostic accuracy has been compared to chest XR, B-type natriuretic peptide[83], lung ultrasound[78] and chest tomograph but no other parameters are available to compare TFC with directly[84]. One such system may be transpulmonary ultrasound dilution (TPUD), but this requires further research[85].

TFC parameters may, therefore, offer another parameter with which to monitor the possible pathophysiology of respiratory and hemodynamic compromise.

Bioreactance as a non-invasive monitor in neonates

BR has been stated to be easy to apply, be operator independent, cost-effective, and able to provide continuous hemodynamic monitoring[9]. It would therefore seem to be an alternative to TTE, the current standard for non-invasive CO measurements in NICU. Significant differences exist between TTE and BR, when considering them as potential hemodynamic monitors (table 1). However, a new technology must be proven to be accurate, precise and be able to track temporal changes in CO to enable its use in clinical practice[86].

For clinical use, BR may be able to monitor hemodynamic variables at a patient level. However, the lack of accuracy and trending ability should be kept in mind. Rather than monitoring an absolute number, a patient's change from baseline may be an indication of deterioration or improvement.

Table 1: Characteristics of the ideal hemodynamic monitor: comparison of transthoracic echocardiography and bioreactance. Adapted from [9]

	Definition	**Transthoracic echocardiography**	**Bioreactance**
Accuracy	Measured parameter is equal to the true parameter as measured by the reference method. Quantified by bias	Varies widely, poorly described in pediatric population	Poorly described
Precision	Repeated measurements are similar under stable conditions. Quantified by limits of agreement.	Varies widely, poorly described in pediatric population	Poorly described
Response time	Continuously updates hemodynamic parameters to reflect current clinical status	Cannot be performed	Able to perform
Risk	Non-invasive application provides no risk to patient	Very low risk	Very low risk
Ease of use	Quick and easy to set up & use. Minimal components. Minimal training required. Ongoing data acquisition and processing. Fully automated display	Relatively easy to set up Set-up dependant on probes Extensive training required Only single time point study	Very easy set up Minimal training required Continuous data Fully automated
Transportability	Suitable for inter and intra-hospital use and transfer. Small footprint. Compatible with other monitoring and imaging technology	Dependant on type of device Stand-alone devices	Easily transportable Not currently integratable with current monitors
Cost	Inexpensive acquisition, maintenance & disposables	Expensive acquisition No disposables	Inexpensive acquisition Disposables required
Familiarity	Similarity to established monitoring devices and parameters	Well established in clinical practice	Not established in practice Well known parameters
Generalisability	Able to be used in a broad spectrum of specialities, clinical conditions, and hemodynamic states	Well used in wide variety of clinical circumstances	Literature attests to wide use
Efficacy	Proven benefits in clinical trials with patient-centred outcomes	Goal-directed echocardiographic in adult and pediatric shock. Few neonatal studies	Some adult studies. No pediatric or neonatal studies

The ideal hemodynamic monitor should be able to accurately determine the degree of hemodynamic compromise as well as its underlying pathophysiology, to allow the appropriate choice of therapy and allow therapeutic monitoring[87]. In neonates, a significant hindrance still remains the presence of intra- and extra-cardiac shunts, which may be physiological or pathophysiological, that seem to influence the accuracy of BR. This research showed significant effects of PDA on accuracy, precision and trending ability, similar to other studies [14,15].

Data from a hemodynamic monitoring device can only improve patient outcomes if the data is relevant to the patient's disease process, sufficiently accurate to influence therapeutic decisions, and if the initiated therapeutic changes, based on the sampled data, are indeed able to change patient outcomes. This entails patient-tailored hemodynamic monitoring[10], and this, together with appropriate management, may improve patient outcome. TEBT has not been used in any neonatal goal-directed trials. The current research performed no pre-planned interventions with which to determine the ability of BR to monitor therapeutic intervention on an individual level. This would require further research.

In this research, the NICOM Reliant® was used. This monitor has since been discontinued and been replaced by the NICOM Starling®. The Starling® monitor also has an updated algorithm and it is unknown how this would influence the accuracy, precision and trending ability of CO and SV monitoring in neonates.

For future clinical neonatal TEBT studies, the following should be considered:

1. TEBT monitoring of interventions
2. Medium and long-term outcomes of neonates monitored with TEBT technology
3. Evaluation of the NICOM Starling in neonatology

Conclusion

Despite bioreactance seeming attractive and meeting many of the technological requirements for an ideal cardiac output monitor (non-invasive, practical, easy to apply and use, feasible in neonates, continuous measurements in absolute numbers,

recordable alongside other physiological monitors, inexpensive for widespread use[88]), some characteristics have not been met according to the current research (accuracy, precision, accurate trending ability).

The lack of a true reference method is detrimental in determining the agreement and trending ability of bioreactance. Further research is required in many areas to enhance the current knowledge base and improve the safety of the use of this technology in the clinical environment.

Reference values should be determined as bioreactance underreads true CO values. No monitor can be used without clinical outcome data, and this should also be explored in future neonatal bioreactance research.

Until such time, TEBT should be used with caution in the neonatal population for hemodynamic monitoring and determining therapeutic interventions.

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APPENDICES

Other publications on cardiac-output related topics (2018-2021)

1. Neonatal hypotension survey: a South African perspective. **Van Wyk L**, Smith J, Hall M. SAJCH 2019; 13(2):73-77
2. Introduction to neonatologist performed echocardiography. Groves AM, Singh Y, Dempsey, Molbar Z, Austin T, El-Khuffash A, de Boode WP, European Special Interest Group 'Neonatologist performed Echocardiography' (NPE). Pediatr Res 2018;84(Suppl 1):1-12 (**Van Wyk L** as part of the European Special Interest NPE group)
3. The role of Neonatologist perfumed Echocardiography in the assessment and management of neonatal shock. Pediatr Res 2018;84(Suppl 1):57-67. De Boode WP, van der Lee R, Horsberg Eriksen B, Nestaas E, Dempsey E, Sing Y, Austin T et al, European Special Interest Group 'Neonatologist performed Echocardiography' (NPE) (**Van Wyk L** as part of the European Special Interest NPE group)
4. Application of NPE in the assessment of a patent ductus arteriosus. Van Laere D, van Overmeire B, Gupta S, El-Khuffash A, Savoia M, McNamara PJ, Schwarz et L, European Special Interest Group 'Neonatologist performed Echocardiography' (NPE). Pediatr Res 2018;84(Suppl 1):46-56. (**Van Wyk L** as part of the European Special Interest NPE group)
5. Application of Neonatologist Performed echocardiography in the assessment and management of neonatal heart failure unrelated to congenital heart disease. Levy PT, Tissot C, Horsberg Eriksen B, Nestaas E, Rogerson S, McNamara PJ et al. European Special Interest Group 'Neonatologist performed Echocardiography' (NPE). Pediatr Res 2018;84(Suppl 1):78-88 (**Van Wyk L** as part of the European Special Interest NPE group)
6. Application of Neonatologist Performed Echocardiography in the assessment and management of persistent pulmonary hypertension of the newborn. De Boode WP, Singh Y, Molnar Z, Schubert U, Savoia M, Sehgal A et al. European Special Interest Group 'Neonatologist performed Echocardiography' (NPE). Pediatr Res 2018;84(Suppl 1):68-77 (**Van Wyk L** as part of the European Special Interest NPE group)

Presentations related to PhD research (2018-2021)

1. Non-invasive cardiac output monitoring in premature infants: influence of gestational age and time. Joint European Neonatal Society Conference, Venice, September 2017 (oral presentation)
2. Bioreactance-derived thoracic fluid content in preterm neonates: Here be Lungs, Stellenbosch, March 2019
3. Hemodynamic effects of PDA closure: a longitudinal study using echocardiography and bioreactance: Joint European Neonatal Society Conference, Maastricht, September 2019 (oral presentation)

Student supervision on cardiac output/ non-invasive monitoring-related topics (2018-2021)

Graduated:

Sebastiaan Gerricke, MMed (Paed), 2018: Changes in cerebral blood flow and cardiac output in premature neonates in the first 72 hours of life

Current:

Mardie Conradie, BSc (Industr Engineering): Investigating the use of machine learning for predicting neonatal outcomes using HeRO data.
Idris Munir, PHD (Industr Engineering): A Novel Algorithm to Monitor and Predict the Risk of Intra Ventricular Hemorrhage (IVH) Incidence in Preterm Neonates Using Non-Invasive Continuous Monitor Parameters

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LIST OF ABBREVIATIONS

ANS	Antenatal steroids
BI	Bioimpedance
BP	Blood pressure
BR	Bioreactance
BW	Birth weight
cMRI	Cardiac magnetic resonance imaging
CO	Cardiac output
DBP	Diastolic blood pressure
EBT	Electrical biosensing technology
ELBW	Extremely low birth weight
EV	Electrical velocimetry
EVLW	Extravascular lung water
GA	Gestational age
HFJV	High frequency jet ventilation
HFNC	High flow nasal cannula
HFOV	High frequency oscillatory ventilation
HR	Heart rate
ICG	Impedance cardiography
IMV	intermittent mandatory ventilation
LBW	Low birth weight
LISA	Less invasive surfactant therapy
LOA	Limits of agreement
MBP	Mean blood pressure
ME	Mean error
nCPAP	Nasal continuous positive airway pressure
NIBP	Non-invasive blood pressure
NICOM	Non-invasive cardiac output monitor
NICU	Neonatal Intensive Care
NPO_2	Nasal prong oxygen
PDA	Patent ductus arteriosus
PE	Percentage error
PEEP	Positive end expiratory pressure

PFO	Patent foramen ovale
PNA	Postnatal age
SD	Standard deviation
SBP	Systolic blood pressure
TD	Thermodilution
TEBT	Thoracic electrical biosensing technology
TFC	Thoracic fluid content
TFCd	Dynamic thoracic fluid content
TFCd0	Cumulative thoracic fluid content from baseline
TP	True precision
TPR	Total peripheral resistance
TPRI	Total peripheral resistance index
TTE	Transthoracic echocardiography
SIMV	Synchronised intermittent mandatory ventilation
SNAPPE-II	Score for neonatal acute physiology with perinatal extension – II
SRT	Surfactant replacement therapy
SV	Stroke volume
SVR	Systemic vascular resistance
VLBW	Very low birth weight
VTI	Velocity time integral
Z0	Impedance