Superior vena cava flow and color tissue Doppler imaging – two new methods for assessment of circulation and cardiac function in the newborn, preterm infant

PhD thesis

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Panta rhei

"Ever-newer waters flow on those who step into the same rivers."

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1 Preface

1.1 Acknowledgements

The present thesis is based on studies carried out while I was working in the Neonatal Intensive Care Unit at Oslo University Hospital Ullevål as part of my pediatric training.

This work has been supported by grants from the Women and Children's Division at Oslo University Hospital in 2006, from the Norwegian SIDS and Stillbirth Society in 2007, and from the Faculty of Medicine at the University of Oslo from October 2011 until today.

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Professor Rolf Lindemann, who passed away in 2012, was Medical Director of the NICU at Ullevål when I began working there in the summer of 2003. I will never forget how warmly he welcomed me on my first day, reminding me of our brief encounter at the annual meeting of pediatricians in Oslo three years earlier, where he had given a talk about brain injury in newborns. He had mentioned glutamate, and made a funny comment about this being the same kind of glutamate found in Mr. Lee's Chinese cup noodles. After his lecture, I introduced myself to him, merely wanting to correct him about the fact that Mr. Lee is Korean, not Chinese. Three years later, in his humble way, Rolf again apologized for his mistake. We had a good laugh, and many more in the following years. Rolf was just how a doctor should be; always present, empathic, well informed, curious and open-minded. Thank you, Rolf, for always being around.

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I thank my colleague Eirik Nestaas for introducing me to tissue Doppler imaging and for teaching me all I know about this. Thank you, Eirik, for insisting that I should aim for recording tissue Doppler images of the preterm infants. Your knowledge, persistence, thoroughness, sincere interest and technical support have been crucial throughout this entire process.

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I want to thank my research group NeoCHIBS (neonatal circulation, heart, infection and brain studies) at OUS Ullevål. Your critical input and positive feedback has been of great value in the preparation of abstracts and presentations. Special thanks to my friends and colleagues Beate Eriksen in Ålesund and Sissel Moltu in Oslo – you are the ones who really know what this journey has been like, and it definitely would have been less exciting without you.

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I thank my former colleagues at the NICU of OUS Ullevål, for remembering to call me whenever a preterm baby was born in the middle of the night, and special thanks to the always so cool, calm and collected NICU nurses at Ullevål – probably without being aware of it, you have taught me all I know about how to handle human beings of less than a kilo's weight.

I am deeply thankful to all the parents who were willing to let their tiny, newborn babies participate in these studies. Though small, I hope this work may be a contribution to the never ending process of improving the health of preterm children like yours.

Unable to address my thanks to a name or a face, I am thankful to the library of the University of Oslo, for the superb service you offer online. Within a few days of entering my wish on the

screen, I have been provided with the most obscure articles from all over the world – original works from last century which not only are impressive by their content, but also a reminder of keeping our own work in a certain perspective.

Thanks to my loving and inspiring parents for always believing in my abilities, my father Chul Ho, for showing me that everything is possible and that failure is not an option, and my mother Anneliese, who passed away much too early, but left me with a framework for many aspects of life. Thank you, Hae Jong for being there.

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My deepest gratitude goes to my husband Christian, for your never ending encouragement and interest, fruitful resistance and caring support through all the phases of this PhD work, and way beyond.

1.2 List of Papers

I. Lee A, Liestol K, Nestaas E, Brunvand L, Lindemann R, Fugelseth D. Superior vena cava flow: feasibility and reliability of the off-line analyses. Arch Dis Child Fetal Neonatal Ed 2010 Mar;95(2):F121-F125.

II. Lee A, Nestaas E, Liestøl K, Brunvand L, Lindemann R, Fugelseth D. Tissue Doppler imaging in very preterm infants during the first 24 h of life: an observational study. Arch Dis Child Fetal Neonatal Ed 2014 Jan;99(1):F64-F69.

III. Lee A, Nestaas E, Liestøl K, Brunvand L, Fugelseth D. Tissue Doppler imaging and superior vena cava flow for early prediction of haemodynamically significant ductus arteriosus in very preterm infants. J of Perinatology (in review)

1.3 Abbreviations

BP	blood pressure
BW	birth weight
CBF	cerebral blood flow
CO_2	carbon dioxide
CPAP	continuous positive airway pressure
CPU	clinician performed ultrasound
cTDI S´	peak systolic tissue Doppler velocity
cTDI D´	peak diastolic tissue Doppler velocity
DIS	displacement
GA	gestational age
HFO	high frequency oscillation
hsPDA	hemodynamic significant PDA
IVH	intraventricular hemorrhage
LV	left ventricle
LVO	left ventricular output
MABP	mean arterial blood pressure
nsPDA	non-significant PDA
PDA	persistent ductus arteriosus
PFO	persistent foramen ovale
RDS	respiratory distress syndrome
RV	right ventricle
RVO	right ventricular output
SVC	superior vena cava flow
TDI	tissue Doppler imaging
VSD	ventricular septum defect

2 General Introduction

2.1 The first day of life often begins in the middle of the night

During my pediatric neonatology trainee period, taking care of very preterm infants during their first hours of life, which often happened to be in the middle of the night, was always a time filled with suspense, skills, sweat and sincerity. Helping the baby breath without stressing her too much, getting the umbilical catheters right, keeping her blood sugar and carbon dioxide stable – all this, while at the same time giving her parents the right amount of information at the appropriate time, talk about the present situation, while carefully preparing them for what may come. Stay close to her cot all night, watch over her blood pressure (BP) and her pulse, oxygen saturation and pCO_2. What a relief when my colleagues finally arrived in the morning, and I could pass the baton and go home to sleep. During the day, she would have her first cerebral ultrasound. And even though her breathing had been stable, the blood gases within the acceptable range and the night altogether uneventful (from a neonatologist point of view) she could have suffered an intraventricular hemorrhage (IVH). Receiving this message from the attending radiologist was always a shock to me, not to think of how the parents must have felt.

2.2 The search for a better way of monitoring newborn circulation

Two neonatologists in Sydney, Australia,[1] first wrote about a novel method for assessment of systemic circulation in preterm infants. A neonatologist in Tromsø,[2] Norway, first introduced me to this method at the northernmost perinatal cardiology conference in 2004. I was eager to test this method, superior vena cava (SVC) flow, because it gave hope about providing us with a tool for prevention of IVH.

At the same time, a new method had emerged in the field of adult cardiology. With tissue Doppler imaging (TDI) it was possible to measure movement within the heart muscle, not merely the movement of the blood flow passing through the heart. The method had hardly been tested in infants. When a fellow in the NICU at Ullevål was planning to study TDI in healthy and sick newborns,[3] my supervisors found a way to combine our interests for these two new methods for monitoring newborn circulation.

2.3 A very short history of modern, western neonatology, including a summary of Norwegian ultrasound development

In order to understand the enthusiasm (part of) the neonatal community felt about SVC flow, we have to look back and realize how newborn circulation had been monitored since the beginning of modern neonatology in the 1960s. In many ways, this era began with the birth of Patrick Bouvier Kennedy, the youngest son of Jacqueline and John F. Kennedy. He was born on August 7, 1963 with birth weight (BW) 1860 grams and gestational age (GA) 34 weeks. He died two days later of hyaline membrane disease, later known as respiratory distress syndrome (RDS). His obituary in The New York Times stated that all that could be done for a victim of hyaline membrane disease "is to monitor the infant's blood chemistry and to try to keep it near normal levels."[4] His death led to an increased public awareness about the challenges of preterm birth, as well as increased research activity, primarily in the field of neonatal respiratory medicine. At the time, it was already known that RDS was caused by surfactant deficiency, and the first successful studies in animals were reported in the beginning of the 70s.[5] The first article about bovine surfactant treatment given to preterm babies was published in the Lancet in 1980.[6] With surfactant, an increasing number of preterm babies made it through the first critical stage of prematurity, and research focus shifted towards other complications of preterm birth, especially the high risk of brain damage which was thought to be caused by cerebral hemorrhage. In 1977, the first study of cerebral blood flow was published by a research group in Copenhagen, and a significant correlation between low BP and low cerebral blood flow (CBF; using the 133Xe clearance technique) was presented.[7] In 1980, this research group began using Doppler ultrasound for the studies of cerebral circulation in neonates.[8]

In parallel with this development, ultrasound entered the field of cardiology and in the 70s the combined use of M-mode and pulsed Doppler technique led to new insights in cardiac and circulatory physiology. In Norway, the first enthusiasts (Leik Woie and Per Lunde in Stavanger 72-73) met significant resistance, but fellow Lunde was invited to Rikshospitalet (by Professor Ole Storstein) in 1974 to give a lecture about this new method. Three years later Rikshospitalet got an ultrasound machine. However, the technical university in Trondheim (NTNU) came to be a major center for the development of ultrasound within medicine. Based on knowledge from cybernetics and computer technology the PEDOF, a pulsed echo Doppler Flow velocity meter which enabled the measurement of blood flow velocity (in the aorta) was

developed. Through cooperation between Rune Aaslid from NTNU and Jarle Holen at Rikshospitalet, a radiologist and engineer who was familiar with Bernoulli's equation from working in the field of aerodynamics, the technique was then further developed and made it possible to calculate pressure gradients. In 1976 the first report about the high degree of correlation between invasive and non-invasive measurements of mitral stenosis was published.[9] However, industry was not interested in development of these devices until SINTEF produced 10 pieces that were sold to technical laboratories in Norway and Europe. The department of cardiology at NTNU got one in 1976. Vingmed AS, a company established in Norway in 1968, had been working with the Doppler technology since 1972, and began cooperating with research groups in Trondheim and Oslo. Liv Hatle at NTNU played an important role in linking the clinical use with further research and development of the Doppler technique.[10] In 1979, echo and Doppler technique was combined, which made simultaneous imaging and velocity measurements possible. Color was added to the Doppler technique in 1984. Hatle kept working in the front line of cardiovascular research, and before her retirement in 2001 she contributed to the development of tissue Doppler imaging (TDI) working in Leuven, Belgium, which has become one of the major TDI centers in Europe.[11] Ever since the 90s, Asbjørn Støylen in Trondheim has been an important contributor to the development of TDI and strain rate imaging in particular.[12;13] By co-supervising the PhD work of Eirik Nestaas,[14] Støylen has also contributed to the introduction of TDI in neonatal, functional echocardiography.

2.4 Cerebral injury in preterm infants

Meanwhile, back in Copenhagen, as well as in many other places, the research field of cerebral circulation kept growing along with an increasing awareness of the complexity and multifactorial genesis of cerebral injury in preterm infants.[15;16] Following the first report about hypotension and low CBF in 1977[7] the concept of autoregulation became central in a number of studies of the relationship between BP and CBF.[17-21] Animal and human studies led to increased awareness of the impact of CO_2 on CBF perhaps being stronger than that of BP[19;22-24] and so far, the mystery of cerebral autoregulation has not been solved.[8;25]

Intracranial hemorrhage occurs in 20 to 25% of infants with GA <30 weeks or BW <1500 g[26;27] and the incidence of severe IVH has been around 15% for the past 20 years.[28;29] Grade 1-2 IVH is associated with generally good clinical prognosis while IVH grade 3-4 is

associated with severe neurodevelopmental outcome.[30] Approximately 80% of IVHs occur by 72 h after birth. Earlier studies have found an association between BP changes and risk of IVH,[31] while recent studies have shown that infants who develop IVH during this period had lower systemic perfusion and cerebral blood flow prior to the occurrence of IVH than infants who did not develop cerebral injury.[32;33] A recent Danish study found that neonates with a large persistent ductus arteriosus (PDA) on day three of life had an increased risk of IVH compared with infants without PDA.[34]

2.5 Blood pressure

Measurement of BP is probably the most commonly applied technical method in modern medicine, even if it has been around for centuries. The discovery of BP can be attributed to Stephen Hales who in 1733, using arterial catheters, measured the BP of a horse and demonstrated reduction in BP following hemorrhage.[35] In 1855 Professor Hermann Vierordt of Tübingen developed the sphygmograph, the first non-invasive pulse monitor. The first investigations into hemodynamic pathology were performed with Samuel Siegfried Karl Ritter von Basch's sphyghmograph (1881), a water filled rubber bag which was connected to a mercury filled manometer bulb. Many clinicians found this instrument to be a useful tool, but the British Medical Journal stated that by using it, "we pauperize our senses and weaken clinical acuity".[35] The development of even more practical tools for BP measurement continued, and in 1896, Scipione Riva-Rocci came up with the method upon which present-day technique is based. The important advantage of his method was that the brachial artery was equally compressed from all sides. Later, an oscillatory method was added for a more precise detection of both systolic and diastolic pressure. It was Korotkoff, a Russian surgeon, who in 1905 discovered the auscultatory technique which is still in use today.[35]

Since the 19th century, the clinical examination has been at the core of any medical assessment. The general condition, skin color, muscle tone, capillary refill time, heart rate and urine output – these parameters give the clinician valuable information about the state of the patient. However, modern neonatology also relies heavily upon monitoring devices such as pulse oximetry and BP measurements. In neonatology, the rule of thumb has been that the mean arterial BP (MABP) in mmHg at least should equal GA in weeks or ≥30 mmHg.[36] Numerous papers have reported on the adverse effects of hypotension in the preterm, newborn infant.[37-39] However, during the past decades, there has been an increasing understanding

about BP not being the sole determinant of (cerebral) blood flow.[40-45] Some studies have demonstrated an adverse effect of antihypotensive treatment.[46-48] Recently, a large multicenter study in the US showed that factors other than BP contributed to the decision to use antihypotensive therapy, and infant outcomes were not improved with antihypotensive therapy for any of the 15 definitions of low BP investigated.[49] In a study of permissive hypotension, i.e. non-treated BP less than GA in weeks if clinical evidence of good perfusion, there was no difference in short term outcome (including IVH grade 3-4) compared to normotensive preterm infants.[48]

2.6 Superior vena cava flow

Since the late 90s, there has been growing awareness among clinicians that BP does not equal blood flow. Although physiologically and mathematically different, these have traditionally been used as equivalent entities in the setting of clinical circulatory monitoring. However, studies have demonstrated that measuring BP is not sufficient to detect low blood flow.[50-52] Left ventricular output (LVO) is an established non-invasive measure of systemic circulation. By means of the Doppler ultrasound technique, this is an easy and reliable bedside method which is applied in intensive care units worldwide.[53-56] However, in newborn babies the fetal shunts, the foramen ovale (PFO) and the PDA do not close immediately after birth. Because of the persistence of fetal shunts, LVO cannot be used as a measure of systemic output in the newborn infant. It has been shown that shunting across the PDA may overestimate LVO by 100%.[57-59]

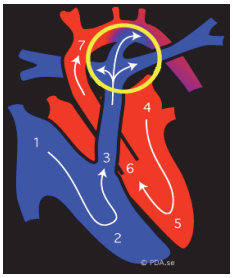
In 2000, Kluckow and Evans described a new method for assessment of upper body and systemic blood flow which was not influenced by the physiological shunts of the newborn infant.[1] They demonstrated a good correlation between SVC flow and LVO in infants with a closed duct. The following paper reported from a study which included 126 infants with GA <30 weeks, and showed a strong association between low flow states and development of IVH.[32] The findings were confirmed in a similar study from another hospital in Australia[60] and a follow-up study showed impaired neurodevelopment at three years of age in infants who had had low SVC flow during the first day of life.[61]

During the last decade, the method of assessing SVC flow has been applied in many different settings,[62-68] for prognostic purposes[69;70] and also for evaluation of treatment effect.[71-76] At the meeting of the European Society for Pediatric Research in Porto 2013,

one of the abstracts presented for the young investigator award was a pilot randomized, placebo-controlled trial of dobutamine for low SVC flow in low birth weight infants.[77]

2.7 Persistent ductus arteriosus and foramen ovale

In fetal life, the oxygenated blood from the placenta passes through the umbilical vein to the sinus porta in the fetal liver. Part of this blood then passes through the liver circulation, while about 1/3 of it passes through the ductus venosus to the right atrium and directly through the foramen ovale (PFO) to the left side of the heart, thus supporting the upper part of the body with well oxygenated blood.[78] The ductus arteriosus is an artery connecting the pulmonary artery with the aorta, enabling the non-oxygenated blood from the right side of the heart to pass directly to the descending aorta and to bypass the fetal pulmonary circulation (figure 1).



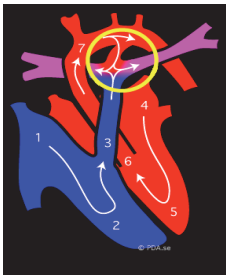


Figure 1 and 2 (Courtesy of Stefan Johansson, Karolinska Universitetssjukhuset, Stockholm)

In term infants, the duct usually is closed within the first 3-4 days,[78;79] while the PFO closes by 3 months in approximately 90% of term infants.[80;81] In the preterm infant, these processes may be delayed. In 60% of very preterm infants, the duct does not close within the first days, and the PFO remains open for several months.[58] Due to the fall in pulmonary vascular resistance and the increase in systemic arterial resistance after birth, a PDA will allow for left to right shunting, i.e. blood escaping the systemic circulation and returning to the pulmonary artery (figure 2). The incidence of PDA is inversely correlated with GA and BW.[82] In a study of infants with BW <1500 g who were discharged from the NICU with a PDA, spontaneous closure was seen in 18 of 21 infants by the end of the first year.[83] Another study of infants with GA <27 weeks and PDA despite indomethacin treatment found that 8 of 12 closed spontaneously by 6 months of age.[84]

The PDA, also known as Ductus Botalli (Leonardo Botallo, 1530-87) remains one of the major controversial issues within neonatology. Innumerable studies have demonstrated an association between PDA and increased morbidity and mortality in preterm infants.[34;85-87] However, in these studies the definition of "hemodynamically significant" (hs)PDA varies from purely clinical findings to various combinations of echocardiographic criteria.[88] There is continuous debate about if, when and how the PDA should be treated. During the past decade(s), refinement of echocardiographic equipment and techniques has allowed for better understanding of the duct, but still, no consensus has been reached about the significance of PDA or how to deal with it.

2.8 Functional echocardiography

Assessment of cardiac function in neonates without cardiac malformations, also known as "functional echocardiography",[89;90] "targeted neonatal echocardiography"[91] or "clinician performed ultrasound" (CPU)[92] is now recommended in a growing number of neonatal intensive care units (NICU) worldwide.[91;93] CPU is increasingly common within other fields of medicine,[94-99] and was lifesaving during the Boston Marathon bombing.[100]

The primary aim of CPU in the setting of the NICU is to use echocardiography as a tool for assessment of cardiac function and the hemodynamic situation of sick and/or preterm infants as an extension of clinical care. NICU patients differ from adult intensive care patients in many ways, but two aspects make them unique: they are in the process of transition from fetal to postnatal circulation, and they have an increased risk for having congenital heart disease.[101] Different scenarios may demonstrate how various loading conditions influence upon conventional measures of contractility. Hypovolemia reduces preload and thus contractility. However, the contractile elements of the heart may be completely healthy. Another example is persistent pulmonary hypertension in the newborn, which leads to reduced RV function. The reduced pulmonary blood flow will also cause low LV preload and hence apparently poor LV contractility. The opposite is seen in the presence of a large PDA which increases the preload to the left heart and reduces the afterload due to run-off into the pulmonary circulation, resulting in excellent measures of contractility. Yet, the hemodynamic situation of the baby may be compromised.

2.9 Doppler, Bernoulli, Ohm, Darcy, Poiseuille & Starling

Studies of hemodynamics and cardiac function are based upon physical laws discovered centuries ago. A brief description of some of the principles which have direct relevance for the papers of this thesis will follow.

The Doppler effect describes the change in frequency of a returning sound wave experienced by a receiver when there is a relative movement between the receiver and the object transmitting the wave (figure 3).

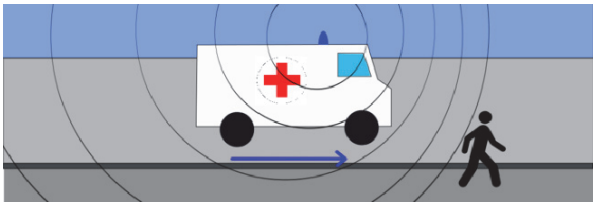


Figure 3 (Courtesy of François Duhesme, Detektor-Magazin.de)

This phenomenon was first described by Christian Johann Doppler (1803-53) in "Über das farbige Licht der Doppelsterne und einiger anderer Gestirne des Himmels" (1842) while he was a professor of mathematics at the Technical Institute of Prague. In ultrasound, the Doppler principle is used to detect and measure blood flow, using the red blood cells as the reflecting, moving object. The velocity of the object is calculated using the Doppler shift (Df), insonating frequency (f), speed of sound (c), and the angle of insonation (cos q) in the Doppler equation: V = (Df x c)/(2 x f x cos q). An increasing angle of insonation leads to increasing underestimation of flow velocity. An angle of 18° will underestimate flow by 5%.[102] In clinical practice, an angle <20° is within the acceptable range.

Steady blood flow in large, central vessels is characterized as laminar, with a flow profile that is parabolic. This implies that when flow velocity is measured using pulsed Doppler, the velocity represents the average velocity of the cross-section of the vessel. Blood flow (Q) in mL/kg/min is calculated as follows: $Q = (VTI \times \text{heart rate} \times (\pi \times d^2/4))/\text{body weight}$, where $\pi \times d^2/4$ is the cross-sectional vessel area, assuming that the vessel is round, and VTI is the velocity time integral, the area under the velocity envelope, when plotting the average velocity against time.

With the modified Bernoulli equation (Daniel Bernoulli, 1700-82), assuming that there is a steady flow, that hydrostatic pressure changes due to differences in elevation and the viscosity and compressibility of the liquid are negligible, Doppler technique can be used to estimate pressure: ΔP (the pressure difference) = 4 x V^2, where v is the velocity of blood (m/s).[103]

With laminar flow, there is a linear relationship between perfusion pressure and flow. With turbulence, more pressure is needed for a given flow. Potential measurement errors may come from inaccurate measurement of vessel diameter or inaccurate measures of VTI due to high angle of insonation or placement of the Doppler gate out of the laminar stream.

Georg Ohm (1789-1854), a German physicist and mathematician, found that there is a direct proportionality between the voltage applied across a conductor and the resultant electric current. This relationship, known as Ohm's law, has its analogue in hemodynamics, stating that flow (Q) is determined by pressure difference ΔP and vascular resistance (R): $Q=\Delta P/R$, also known as Darcy's law (Henry Philibert Gaspard Darcy, 1803-58).

Poiseuille's law (Jean Léonard Marie Poiseuille, 1797-1869) describes the pressure drop in a fluid flowing through a long cylindrical pipe, and demonstrates that the resistance is in proportion to the 4^{th} power of the radius, making the vessel diameter the main contributing factor to blood flow.

The Frank-Starling law of the heart (Ernest Starling, 1915) states that the stroke volume of the heart increases in response to an increase in preload (the end-diastolic pressure; figure 4). The stroke volume may also increase as a result of greater contractility, independent of the end-diastolic volume.

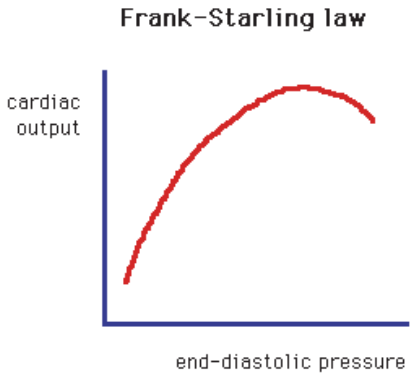


Figure 4

2.10 Tissue Doppler imaging

Doppler methods can be used both for blood flow and tissue velocities. However, while blood velocities usually are around 1 m/s, tissue velocities usually are less than 20 cm/s. Using a low pass filtering technique, tissue Doppler imaging is used for acquisition of myocardial tissue velocities.[104] The method was first applied by Yoshida et al. in 1961.[105]

Ventricular function has been a major focus in cardiology ever since ultrasound technology made real-time measurements of the movement (M-mode) of the heart walls possible.[106] Assessment of heart function by ultrasound was traditionally based on measurements of left ventricular wall thickness and the changing left ventricular cavity diameters during systole and diastole. Fractional shortening, defined as the percentage fall in left ventricular cavity dimension in systole with respect to that in diastole, still is in routine use and the most established measure of ventricular function. However, in the beginning of the 90s, the development of a technique which enabled direct velocity imaging of the myocardium marked the beginning of a new era of cardiac function studies, [107;108] and the first reports on normal values for myocardial velocities during childhood were published in 2000 when Harada et al.[109] studied children age 7 days - 18 yrs. and Kapusta et al.[110] included children 4 - 18 yrs. During the past decade, different TDI modes have been applied in fetal,[111-113] neonatal[114-118] and pediatric[119-124] studies. Only a few studies have used TDI in preterm newborns.[125-129] Longitudinal annular motion is a measure of global ventricular function[13;110;130] and can be assessed by measuring longitudinal annular velocities and displacement.[129;131;132]

3 Aims of the Thesis

A general aim for this thesis was to investigate two new methods for assessment of circulation and cardiac function in preterm infants: SVC flow and cTDI. The specific aims of the three papers were:

Paper I

This was a methodological study where we investigated the off-line analysis of SVC flow. The aim was to describe the variability of the different measurements that make up SVC flow, i.e. the diameter of the vessel and the VTI of the blood flow.

Paper II

This was a prospective, observational longitudinal cohort study aiming at gaining new knowledge about myocardial function in very preterm infants assessed by cTDI during the first day of life. We also wanted to explore the impact of gestational age, birth weight, ductal shunting, and respiratory support on myocardial function. Finally, the prognostic value of myocardial function during the first day of life regarding later development of IVH was evaluated.

Paper III

This prospective longitudinal cohort study was based on the same study population as the previous study. The aim was to investigate the usefulness of SVC flow and cTDI for prediction of hemodynamic significant (hs) PDA.

4 Methodological considerations

All studies were performed in accordance with the Helsinki declaration of 1964 including later amendments (www.wma.net). Written informed consent was acquired from the parents of all included infants. All studies were accepted by the Regional Committee for Medical Research Ethics and by the Scientific Committee at Oslo University Hospital Ullevål.

4.1 Recruitment and selection of study populations

4.1.1 Healthy term infants, paper I

For this study, healthy newborn term infants were recruited from the Maternity Ward at Oslo University Hospital Ullevål between March and May 2005. Inclusion criteria were Apgar score ≥8 at 5 min, GA ≥37 weeks and availability of one of the investigators. A total of 49 neonates were included, but one infant was later excluded because of an asymptomatic left side pneumothorax. Parental informed consent was obtained for the collection of data for two separate studies: TDI images were used for several papers[3;115;133;134] and the PhD theses of Eirik Nestaas. SVC images were used for paper I of this thesis. The data were collected by Eirik Nestaas and Drude Fugelseth.

4.1.2 Very preterm infants, paper II and III

At the time of data collection, the NICU at Oslo University Hospital Ullevål was the largest in Norway, and it served both the local community and as a third level unit for the south-eastern region of Norway. The unit was, and still is located directly next to the Maternity ward, which at the time of the study had approximately 6000 births per year. From April 2005 to October 2007, infants born at GA <32 weeks and/or with BW <1500 g were eligible for inclusion. Eligibility depended on the availability of the investigator (AL) to perform echocardiography. Exclusion criteria were age >8 h at first exam, missing images of PDA, TDI or SVC, congenital heart defects and other specific conditions that influenced upon hemodynamics. The reason for the slightly different number of infants included in the final analysis of paper II and III is that the infants in paper II were selected because the cTDI data sets were the most complete, although several measurements are missing at 12 and 24 h. For paper III, infants were selected due to the completeness of the data sets pertaining to SVC flow.

4.2 Echocardiography

4.2.1 Equipment for echocardiographic studies

All echocardiographic examinations for paper I, II and III were performed with equipment from GE Vingmed Horten, Norway. We used a Vivid 7 ultrasound scanner. For paper I the images were recorded using a 5S probe and for paper II and III we used a 10S probe. All echocardiographic recordings were performed with simultaneous ECG monitoring. The images were stored in an integrated digital archiving system and analyzed off-line using the manufacturer's software (EchoPac version 10-12; GE).

4.2.2 Standard pediatric echocardiography, PFO and PDA grading

In order to confirm structural normality of the heart, all the infants included in the studies of this thesis had a standard pediatric echocardiogram[102;135] performed as part of the initial exam, including assessment of the physiological shunts of the newborn. The PFO was assessed as open or closed. A PFO with diameter ≤3 mm and left-to-right shunt was considered physiological.[58] If the PFO diameter was >3 mm, it was classified as an atrial septum defect and the infant excluded from the study. Likewise, the PDA was defined as open or closed. Using color Doppler mapping technique, the flow pattern was defined as left-to-right, bidirectional or right-to-left shunt. Ductal shunting was classified into three grades, according to the method described by Hirsimäki et al.[136] Grade I: Left-to-right flow was minimal red-orange near the pulmonary origin of the PDA. Grade II: A narrow jet passed through the PDA and the flow did not reach the pulmonary valve. Grade III: A broad flow in the main pulmonary artery reached the leaflets of the pulmonary valve. A grade I PDA was defined as non-significant (ns)PDA, while grade II or III was defined as hsPDA. None of the infants received medical treatment for PDA closure during the study period.

4.2.3 SVC flow (paper I and III)

For analysis of SVC diameter and SVC flow, five to ten consecutive waveforms were recorded according to the method described by Kluckow et al.[1] SVC flow was calculated using the formula: SVC flow = [VTI x (π x [mean SVC diameter^2/4]) x heart rate]/body weight, where VTI is the velocity time integral in cm, π is 3.14, and the flow is expressed as mL/kg/min. The VTI was calculated from the Doppler velocity tracings and averaged from 5-10 consecutive cardiac cycles (figure 5).

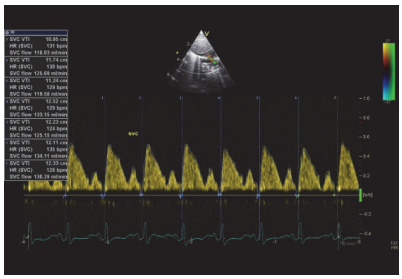


Figure 5

Forward flow was positively integrated. In paper I, retrograde flow was ignored due to its small volume and inconsistent appearance (figure 6), while in paper III, retrograde flow was subtracted.

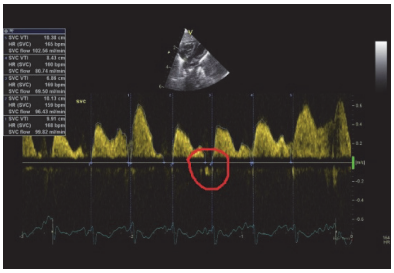


Figure 6

As described by Kluckow and Evans[1], the maximum and minimum internal diameters were measured from frozen images at the point where the SVC starts to open up into the right atrium (figure 7). Due to the variation in vessel diameter through the cardiac cycle, a mean of the maximum and minimum diameter was used for the flow calculation.

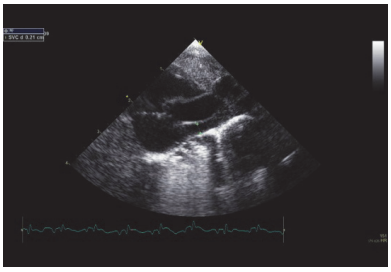


Figure 7

Diameters measurements were averaged from 5 to 10 cardiac cycles and varied by a mean of 18% (SD 9%). The heart rate was derived from the intervals between cardiac cycles.

4.2.4 Tissue Doppler imaging (paper II and III)

TDI is a relatively new method for quantitative evaluation of myocardial motion, using the low Doppler shift frequencies of high energy generated by the ventricular wall motion that are filtered out in standard Doppler blood flow studies. Ventricular wall motion is defined by three variables: velocity, acceleration, and displacement. With M-mode, myocardial function is mainly measured as circumferential contraction, while tissue Doppler measures velocity, acceleration and longitudinal contraction. From studies in older subjects it is known that abnormalities of wall motion may initially appear in the longitudinal axis, and several studies in adults, children and newborn infants have demonstrated that TDI is more sensitive than conventional myocardial function measures for detection of reduced left ventricular function.[134;137-140]

Three different TDI modes can be used for analysis of myocardial velocities: pulse-wave (pw), M-mode color, and two-dimensional cTDI. Compared with pwTDI, which requires separate images from each position, only one single cTDI cine loop from the apical four-chamber view is required for visualization of multiple segments of the heart (figure 8).

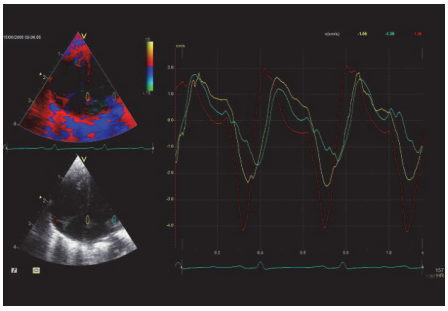


Figure 8

Due to the vulnerability of the infants (paper II and III) the exams had to be performed as quickly and carefully as possible. A time limit of each examination was set to 10 minutes. We therefore chose to use cTDI. Two-dimensional cTDI images were recorded with the left and right lateral walls as parallel to the ultrasound beams as possible, using tissue velocity range ±16 cm/s and default settings for frame rate (170 - 220/s). The images were stored in an integrated digital archiving system. Postprocessing was done in the Q-analysis mode of the EchoPac software (EchoPac PC SW, GE Vingmed Ultrasound). The region of interest (ROI) was set to 3 x 1 mm and all measurements were made with the ROI set stationary in the ultrasound sector and placed just apical of the atrioventricular valve insertion. If artefacts

occurred the ROI was slightly repositioned. All measurements are averages of three consecutive heartbeats. Peak systolic velocity (cTDI S´) was measured at the maximum height of the systolic velocity curve. Due to frequent fusion of the early (E´) and atrial (A´) diastolic waves, the tallest point of the diastolic waveform was chosen as the peak diastolic velocity (D´). After defining the point of aortic valve closure (AVC), which defines end-systole, peak systolic and diastolic displacement was measured at the points described above (figure 9).

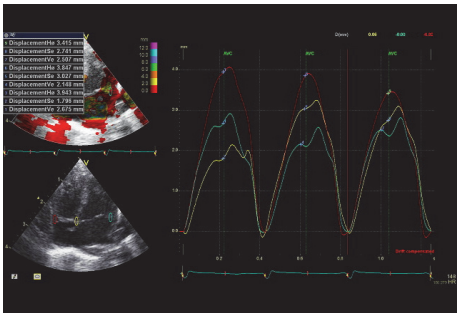


Figure 9

4.3 Blood pressure measurements (paper II and III)

In most infants, BP was measured through indwelling arterial lines (mostly umbilical artery catheters). In the remaining, BP was measured with a manual manometer (HP MI008B, Hewlett-Packard Co., Palo Alto, CA, USA), with cuff adjusted to upper arm circumference and in heart level position.

4.4 Statistical methods

Demographic data and data with skewed distributions are reported as median and quartiles, otherwise means ± standard deviation (SD) are used. Testing of approximately normally distributed variables were carried out by Students t-tests (two groups) or analysis of variance (ANOVA, three or more groups). Skewed distributions were log-transformed to satisfy the assumption of approximate normal distribution, and results were confirmed by non-parametric methods (Mann Whitney U tests or Kruskall-Wallis tests). Correlations between variables were assessed by Pearson's coefficient of correlation. Two-sided p-values ≤ 0.05 were considered significant.

Intra- and inter-observer variability was assessed by Bland-Altman like procedures. In paper I we used both standard Bland-Altman plots[141] and plots modified to allow the comparison of three observers. As numerical indicators of variability, we used repeatability coefficients

(two times the SD of the difference between the measurements) and the average variability (the difference between two measurements expressed as a percentage of the mean of the two measurements). The statistical analyses were performed with JMP (SAS Institute V.9.1.) and IBM SPSS v. 20.

Paper I: Bland–Altman plots were used to illustrate intra- and interobserver variability. Variability between measurements was computed as the difference between two measurements expressed as a percentage of the mean of the two measurements. For the inter-observer variability, we used the mean of all values obtained from the pairwise comparisons of the observers. Systematic differences between observation periods for SVC diameter, VTI and flow were assessed using paired t-tests and ANOVA.

Paper II: Demographic data and BP are reported as median and range. All other variables are reported as mean and SD. To compare cTDI variables at 5, 12 and 24 h, we used t-tests based on ANOVA with patients as random factors. Two-sided p values ≤ 0.05 were considered significant. Correlations between variables were assessed by Pearson's coefficient of correlation. Recordings from 15 infants were analyzed by two observers (AL and EN) separately for interobserver variability and re-analyzed after 6 months by one observer (AL) for intraobserver variability. Reproducibility was assessed by calculating the repeatability, the mean variability between measurements and by Bland-Altman analysis.

Paper III: Demographic data, BP and hemoglobin (Hb) are reported as median and range, otherwise means with 95% confidence intervals are given. Differences between variables at different time points were analyzed using ANOVA, while groups were compared using two-sample t-tests. Correlations between variables were assessed by Pearson's coefficient of correlation. For variables with skewed distributions also non-parametric tests were used; however, results were very similar and only results from the parametric tests are presented.

5 Summary of Results

5.1 Paper I

This study established the range of SVC flow in healthy term infants during the first three days of life. We found a decrease in mean SVC flow from 99 mL/kg/min at day one to 77 mL/kg/min at day three. Further, we found that reliable diameter images were obtained in 85% and velocity recordings in 81%. The mean variability of SVC flow was 17% in the intraobserver analysis and 29% in the interobserver analysis. These findings demonstrate that the main challenge of the method is the measurement of SVC diameter. The same observer should ideally perform sequential analyses. Special caution should be taken when making clinical implications from non-optimal pictures.

5.2 Paper II

This was the first published serial study applying cTDI in very preterm infants during the first day of life. We found that there was a significant reduction of systolic and diastolic velocities and displacement of both ventricles from 5 to 12 h age. From 12 to 24 h there was a non-significant increase of myocardial velocities and displacement. At 5 h, babies with hsPDA had significantly higher systolic and diastolic velocities in both ventricles than those with nsPDA. These findings could, if confirmed by further studies, have potential value in the management of cardiovascular support in very preterm infants.

5.3 Paper III

In paper III we combined the methods from the previous two papers, and used data from the same, preterm population as in paper II. We found that infants with hsPDA had higher myocardial velocities (cTDI) at 5 h than babies with nsPDA. However, infants with an hsPDA throughout the first day of life tended to have lower cTDI velocities at all exams than infants in whom an initial hsPDA became nsPDA by 24 h. SVC flow was significantly lower in infants with hsPDA than nsPDAs at 24 h. An additional finding of this study was the correlation between cTDI indices of the LV at 5 h and SVC flow at 24 h, and between various cTDI indices at 24 h and SVC flow at 24 h. We concluded that cTDI and SVC flow may be useful for early assessment and prediction of hsPDA in addition to conventional echocardiography in very preterm infants.

6 General Discussion

In the present thesis we have examined two new methods for assessment of circulation and cardiac function in newborn, preterm infants. In paper I we defined the range of SVC flow in healthy, newborn term infants, and demonstrated that the major contributor to the variability of the method was the diameter measurement. In paper II we found that the myocardial function, assessed by cTDI, decreased significantly from 5 to 12 h postnatal age in a population of preterm infants. In paper III, using the same preterm population, we showed how cTDI and SVC flow could be applied for prediction of hsPDA.

The newborn infant is a complex model for the study of the physiological changes taking place during early postnatal transition. Clinical studies are associated with many different challenges and limitations, but carry the potential of giving directly relevant insight. Better understanding of the ever changing hemodynamic situation during transition may contribute to clinical decision making, and in some situations, such as persistent pulmonary hypertension of the newborn, it is of critical importance. Studies have shown that clinical assessment has low sensitivity for detection of impaired systemic circulation in newborn, preterm infants,[50;142;143] revealing a need for better ways of monitoring newborn circulation.

6.1 Discussion of the methods

6.1.1 SVC flow

The use of non-invasive techniques such as 2D echocardiography to estimate blood flow carries some degree of uncertainty. Regarding SVC flow, earlier echocardiographic studies have found a good correlation between LVO and SVC flow in infants without PDA,[1] but a validation study of SVC flow with magnetic resonance imaging (MRI) as the reference measure showed a poor correlation between echocardiographic and MRI results.[144] Paper I demonstrated a marked variability both in intra- and interobserver measurements, mainly due to substantial variability in diameter measurements. This is in accordance with previous studies of SVC.[1;66] However, when excluding two specific recordings (outliers), the mean variability of the intraobserver diameter measurements was reduced from 5% to 2%. This demonstrates the importance of quality assessment of the recordings and that low quality recordings should be used with great caution in flow estimation. The inter-observer differences were also mainly caused by differences in diameter measurements.

In addition to random variation, we found marked differences between the observers (figure 10). These differences persisted even after repeated discussions among the investigators on measurement procedures.

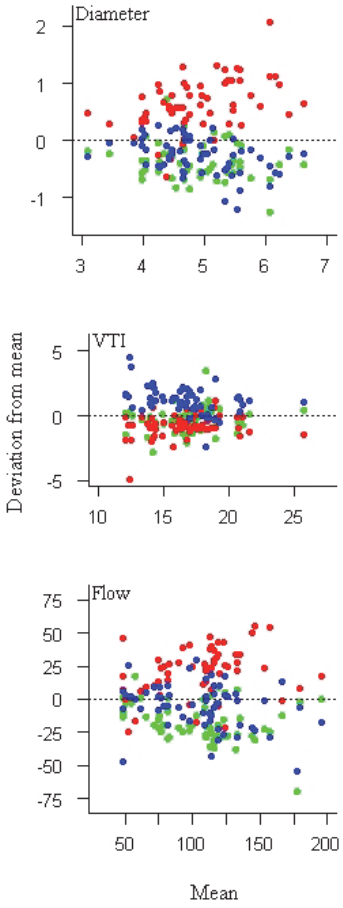


Figure 10: Bland-Altman-like plots of inter-observer repeatability of SVC diameter, VTI and SVC flow. Red dots LB, green dots DF, blue dots AL.

Variability of the SVC diameter measurement is caused by the physiologic variation of the SVC during the cardiac cycle, but also by the subjective decision about where exactly to place the calipers for measurement. This remains a challenge whether one chooses to measure from a frozen 2D picture or by M mode. Averaging from repeated measurements strengthen the final mean value.[145]

Kluckow and Evans,[1] measured VTI from the abdominal approach. One study has compared this approach with a suprasternal or high parasternal approach, and found that the SVC VTI from the abdominal approach yielded slightly higher values by approximately 5%, but the individual results were within the 95% confidence interval for intraobserver variability of the suprasternal approach in 36 of 40 neonates.[146] All VTI recordings in our study were performed from the abdominal approach.

Measurement of SVC flow is based on extrapolation from diameters, an area measurement assuming constant geometry. The squaring of the data amplifies measurement errors. A monodimensional length measure, such as VTI, will have a better repeatability than area measurements. Thus we speculated if just measuring SVC VTI could be a better way of defining systemic or upper body perfusion. However, VTI only provides information about how far the blood moves within a certain amount of time, while in the clinical context, we want to know the amount of blood (i.e. the flow) that is actually passing through the SVC. For this reason, VTI must be related to the diameter of the vessel. Further, it is useful to standardize the flow by relating it to the weight of the infant.

As SVC is a vein in close connection with other structures, one must assume that other organs also may influence upon SVC flow. The effect of respiration is obvious and easy to detect while performing the ultrasound exam. In our study, we did not specifically investigate the magnitude of this effect. However, we tried to minimize the effect of respiration by using average diameter and Doppler velocity tracings from 6 to 10 consecutive cardiac cycles. Physiological factors, such as preload, afterload, heart rate and the intrinsic properties of the ventricles also influence upon SVC flow. These factors were not investigated in this study.

6.1.2 Color tissue Doppler imaging

TDI has emerged as a new tool for assessment of myocardial function, and several TDI modalities are available. We chose cTDI because one single cine loop from the apical four-chamber view is sufficient for visualization of multiple heart segments. This makes the image acquisition less time consuming than for pwTDI, which requires separate images of each heart segment/wall. Another difference between these methods is that cTDI velocities are mean values (usually from 3 consecutive loops) while pwTDI velocities are peak values which to some degree depend on the gain setting of the ultrasound machine. An advantage of cTDI compared to pwTDI is that cTDI provides data from the entire sector simultaneously, which is

important for comparison of parameters. However, there are some issues with cTDI that need to be discussed: 1) feasibility 2) frame rate 3) fusion of diastolic wave signals 4) intra- and interobsever variability 5) time consuming post processing.

1) Feasibility is the percentage of successful exams. In study II images of good quality were obtained in 68, 42 and 46%, and in study III good quality images were obtained in 81, 66, and 61% of infants at 5, 12 and 24 h, respectively. The main reason for our poor feasibility was the challenging circumstance of image acquisition. The investigator stood bed-side holding the probe inside the incubator. The infants were usually lying on their back, sometimes slightly turned to their left side, because this could counterbalance the effect of the mechanical ventilator support and reduce the grey areas produced by lung shadow. Yet, correct image acquisition of the left ventricle often was very difficult, also due to the right ventricular dominance in preterm infants. Thus, it was not always possible to obtain good quality images within the 10 minutes time limit. We cannot really explain why the degree of feasibility differed between study I and II, considering that the study population was recruited from the same group of infants. However, in both studies, the best feasibility was obtained in the first exams. General experience from performing echocardiography in preterm infants with respiratory support (ventilator) has taught us that the echocardiographic "window" often becomes smaller as lung inflation leads to "foggy" ultrasound images. This may be part of the reason why feasibility was better at 5 h than at the following exams.

2) The frame rate defines the temporal resolution, i.e. how many pictures can be recorded for each heart cycle. TDI loops are like very small pieces of a movie. If for example the heart beat is 120/min, a frame rate of 220/sec will result in 110 pictures taken for each heart cycle. These 110 pictures make up the movement of each heart beat in the TDI loop. Insufficient frame rate implies the risk of not detecting signals of higher frequency than the frame rate (aliasing, undersampling; figure 11).

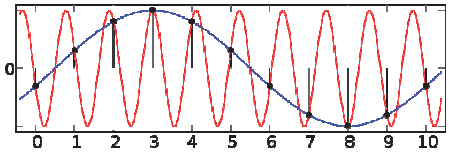


Figure 11 (From Wikimedia Commons)

Frame rates will be reduced if the image sector is widened or the image depth increased. We used a frame rate of 170-220/sec as the infants had heart rates 140-180/min (i.e. 76 tissue Doppler images for each heart beat if heart rate is 180/min). The width and the depth of the apical four-chamber image required for cTDI analyses were quite similar for all the infants.

3) Frequent fusion of the E´ and A´ wave (82% of exams at 5 h, paper II) made us define D´ as the "peak diastolic velocity" (figure 6). This makes interpretation of diastolic myocardial performance difficult. Fusion of E´ and A´ waves has been reported by other study groups.[119;147;148] A feline cTDI study of longitudinal left ventricular velocities[148] concluded that fusion of E´ and A´ waves in 64% of examinations was caused by increased heart rate (i.e. >224 bpm). In a study of moderately premature infants, Eriksen et al.[149] reported that fusion was observered mainly in infants with HR >155-160/min, and there was a significant correlation between degree of fusion and HR. However, in a study of diastolic dysfunction in mice with heart rate >500 bpm, there is no mention of any problems with fusion,[150] and a study of RV diastolic function in newborn term infants with pulmonary hypertension (due to congenital diaphragmatic hernia in most of them), reported absence of E´ wave in half of the patients, even in infants with lower heart rates.[151] The author concludes that "these changes may be considered to indicate inherent impairment of systolic and early diastolic function in the PHT group". Absence of E´ may also be caused by severe LV systolic dysfunction, leading to an elevated end-diastolic pressure and preventing early diastolic relaxation.

4) Regarding myocardial velocities, our intra- and interobserver variability was 19.9 - 29.3% and 11.4 - 25.9% respectively (paper II). The only comparable study of cTDI in preterm infants is the one by Joshi et al.[147] which reported intra- and interobserver variability of 10 - 15% for LV myocardial velocities as well as annular displacements in term and preterm infants. To explain this discrepancy, one needs to look very closely at the way each study was carried out. As opposed to us, Joshi et al. acquired cTDI images separately of the LV and RV, which may have resulted in a higher image quality, implying a lower variability of measurement. In our study, all parameters were measured in three beats and averaged. Joshi's study did the same, but exceptions were made if the signal from an individual beat was too noisy, in which case only 1-2 beats were analysed. As we did not make such exceptions, our averaged results are based on a wider range of measurements, implying a higher variability. Another interesting reproducibility study of TDI parameters found a variability range of 18-

56% for peak systolic velocities in patients with advanced LV dysfunction.[152] This leads us to speculate if our study population may have been sicker than that of Joshi et al., which included 25 preterm infants <34 weeks GA. Our population could perhaps be comparable to patients with varying degrees of systolic dysfunction.

Regarding displacement, our results also had a higher variability than the only previous published study. While we did all the measurements from one single recording, Joshi et al.[147] acquired separate images of the left and right ventricle, which is likely to give better image quality. As Joshi, we also used tissue tracking at the lateral mitral and lateral tricuspid annulus for measurement of displacement. However, there is a series of choices to be made in the tissue tracking process which are not described in Joshi's report. In the following, the actual measurement process will be described as detailed as possible, and hopefully it will become clear why a certain degree of variability is an invariable result of cTDI measurements. Annular displacement was measured with the EchoPac software version 112. First, one has to do the Q-analysis, which means that one has to choose the ROI size. Defining the ROI size is a trade-off. A large sample area will give an improved signal to noise ratio compared to a small sample area, but if the sample area involves parts of the myocardium between the AV-plane and the apex, or part of the epicardium, false low velocities could be measured, leading to a false low average for the area. Similarly, if the sample area involves parts of the atrial myocardium, false high velocities could be measured. One could speculate that the repeatability measurements would have shown a better reproducibility if a larger part of the ventricle myocardium were placed within the sample area, but then systematically lower velocities would have been measured.

After defining the ROI size one must place the ROI at the AV valve insertion. Replacing the ROI just 1 mm to the left or right will change the curve from which the tissue velocity is read. So far there is no general recommendation about ROI size or position for cTDI analysis in preterm infants. After the Q-analysis, and while keeping the ROI in the same position, one moves on to tissue tracking. Now the curve will display the length of the forward movement of the myocardial tissue. But before measuring the displacement length, one has to define the point of aortic valve closure (AVC). This is because one wants to measure the maximum systolic forward movement. Usually, this length is less than the maximum displacement of the tissue. Defining the AVC also contributes to some degree of variability between measurements. In addition to ROI size, sampling location and definition of the AVC, there are

further choices to be made within the post-processing program. The EchoPac software version 112 enables the user to make the following choices regarding smoothing: 3, 5, or 7 sample average or 30-50-70 ms average. We used the default settings for smoothing (70 ms average). In sum, all these technical steps and choices contribute to increasing the variability. When comparing cTDI studies by different investigators, one needs very detailed information about the measurement process.

5) The post processing is time consuming. The measurements are performed off-line after the exam is finished, so you do not get the results during image acquisition, and thus, no chance to improve the recorded image in order to obtain higher quality measurements. The post-processing is rather complicated (as described above) and the resulting variability high. Hence, one must be careful when drawing conclusions about individual patients.

6.1.3 Grading of the PDA (paper III)

A validated definition of "hemodynamic significant PDA"[88] does not exist. During the past decades, there has been a trend towards using diameter measurement for defining a significant degree of ductal shunting.[153-157] However, not unlike the challenges of measuring the SVC diameter, measuring the PDA diameter is also a matter of individual choice. This influences the placing of the calipers either when measuring from the 2D grey scale image or when measuring at the narrowest point of the color flow image. Some investigators have suggested to use a quantitative measure of the degree of shunting, such as flow pattern of the PDA[158], LA/Ao ratio,[159] flow pattern in the descending aorta,[160] celiac artery blood flow to left ventricular output ratio,[161] superior mesenteric artery blood flow,[162] and perfusion index[163] either instead of or in addition to the diameter measurement.

We chose to use the grading system described by Hirsimäki et al.[136] This method is based on a visual assessment of the color flow into the pulmonary artery, as described earlier (methods). Like other measures based on the color Doppler mapping technique, this is also influenced by technical matters, such as good image quality and gain setting. However, Hirsimäki et al.[136] found good correlation between this color Doppler technique and pulsed Doppler assessment of flow pattern in the main pulmonary artery, as well as with cardiac output.

6.2 Discussion of the results

6.2.1 SVC flow (paper I and III)

Paper I is an analysis of the post-processing variability of SVC flow measurements. The substantial variability found in SVC flow measurements is in concordance with other SVC studies[1;63;66] as well as with a study in which SVC flow was validated against phase-contrast magnetic resonance imaging.[144] Paper I demonstrates how the diameter measurement is the major cause of the variability. Basically, this is a consequence of anatomical matters combined with the equation of blood flow (Q) calculation: $Q = (VTI \times \text{heart rate} \times (\pi \times d^2/4))/\text{body weight}$, where $\pi \times d^2/4$ is the cross-sectional vessel area and VTI is the velocity time integral. The underlying assumption is that the vessel is a perfectly round structure. This same equation is used for the calculation of cardiac (LV) output. However, an important difference between measuring LV output and SVC flow is the stiffness of the vessel wall: while the caval vein is compliant and distensible the aortic wall is much stiffer and thus less influenced by the amount of blood flow passing through it. In addition, the pressure in the aorta is much higher than in the SVC, resulting in higher repeatability of the diameter measurements. The venous character of the SVC also becomes apparent during echocardiography when one gets a direct image of how respiratory movements influence upon the diameter. This anatomical (physiological) variability is part of both the intra- and interobserver variability described in paper I. The study also clearly demonstrates the personal variability of each of the investigators. Repeated measurements of recorded, echocardiographic images are performed manually. As described by Kluckow and Evans,[1] the maximum and minimum internal diameters were measured at the point where the SVC starts to open up into the right atrium (figure 5). This is a matter of personal judgement. Regarding the VTI curve, the tracing of the curve also is a subjective matter. However, we demonstrated that the variability of VTI measurements was smaller than that of diameter measurements. As the variability effect of the manual placement of the cursor should be equal for both SVC diameter and VTI measurements, the main reason for the difference in variability is probably the intrinsic (anatomical/physiological) variability of the SVC. Paper I demonstrates that serial measurements, for the above mentioned reasons, preferentially should be performed by the same investigator.

In paper III, SVC flow was measured serially by the same investigator, and we found that the mean (SD) SVC flow was 90 (44), 81 (43) and 81 (46) mL/kg/min at 5, 12 and 24 h

respectively. This variability is comparable to the results in paper I, where SVC flow was 99 (34) mL/kg/min at 24 h (same investigator). The slight decrease of SVC flow during the first 24 h (paper III) and the first three days (paper I) of life is in accordance with studies showing a fall in LVO over the first days of life in healthy term infants.[164-168] In a study of preterm infants, Murase et al.[169] found that LVO dropped transiently at 12 h of life and then increased again after 24 h before reaching a steady level after 48 h of age. However, some studies have found a steady increase of SVC flow, LVO and RVO during the first 24 to 48 h of life.[170-172] The reason for this discrepancy is not known.

In paper III, we showed that SVC flow was lower in infants with hsPDA and nsPDA. This is in accordance with earlier findings[32] and may indicate that our method for PDA grading is hemodynamically relevant, as left-to-right shunting across an hsPDA increases the LVO/SVC ratio.[68;173]

6.2.2 cTDI (paper II and III)

Myocardial function

Paper II was an observational study of myocardial velocities and displacement of the LV and RV in very preterm infants during the first 24 h of life, and demonstrated a significant decrease of cTDI indices from 5 to 12 h postnatal age. As discussed earlier, myocardial function can be defined in a number of ways. Neither conventional echocardiography nor newer modalities such as TDI allow direct measurements of contractility. Higher myocardial velocities do not equal higher contractility, as contraction of the heart is influenced not only by the intrinsic properties of the myocytes (the contractility, the ability of the myocytes to contract at a given preload), but also by loading conditions and heart rate. However, studies have shown that strain rate, which measures deformation per time unit and can be quantified with TDI, is a robust measure of contractility.[174;175] When performing repeated cTDI measurements in the preterm heart within the first day of life, the longitudinal movement (displacement) may be comparable to the strain of a segment which equals the length of the entire left (or right) ventricular wall. Assuming that this segment length (the heart size) remains unchanged within the first day of life, the velocity of this movement (the cTDI velocity) then equals strain rate. In this sense, we interpret the cTDI velocities in this study as an expression of myocardial contractility.

As shown in table 1, the actual values of cTDI velocities and displacement at 5, 12 and 24 h after birth are lower than reported in other studies of cTDI in infants.[129;147] However, both the study by Eriksen et al.[129] and that of Joshi et al.[147] were of more mature infants than ours, and the exams were performed somewhat later in terms of postnatal circulatory transition.

Age at exam	**5 hours**	**12 hours**	**24 hours**	**p value***
cTDI S´ LV (cm/s)	1.8 (0.7)* n=32	1.3 (0.4)* n=18	1.5 (0.6) n=22	0.002
cTDI S´ RV (cm/s)	2.8 (0.9)* n=33	2.2 (0.9)* n=20	2.5 (0.9) n= 21	0.01
cTDI D´ LV (cm/s)	2.3 (1.1)* n=32	1.8 (0.8)* n=18	2.1 (0.9) n=22	0.035
cTDI D´ RV (cm/s)	4.1 (1.6)* n=33	2.8 (0.9)* n=20	3.3 (1.5) n=21	<0.001
Dis LV (mm)	1.9 (0.9)* n=30	1.4 (0.7)* n=18	1.8 (0.8) n=22	0.024
Dis RV (mm)	3.3 (1.2)* n=31	2.2 (1.2)* n=20	2.9 (1.3) n=21	0.002

*Table 1: * p value pertains to the difference between 5 and 12 h exams*

When comparing our results to the findings of Nii et al.,[176] who studied myocardial diastolic velocities with cTDI in normal fetuses, we find that our preterm infants had even lower right and left ventricular diastolic velocities than fetuses at GA 20 – 29 weeks. We speculate that this reflects the increased work load during postnatal transition.

Influence of different loading conditions

The decrease of myocardial contractility from 5 to12 h, followed by a non-significant increase from 12 to 24 h, could be related to the profound changes taking place at birth, when the low-resistance placental circulation is removed, leaving the LV with a major increase in afterload. The high-resistance pulmonary circulation of intrauterine life is replaced by a sub-systemic level of resistance, and the rapid reduction in pulmonary artery pressure leads to an increase in pulmonary blood flow and subsequent increase in preload to the LV. Hence, both preload and afterload increase dramatically at birth.[177]

Previous studies have shown that elevation in preload increases cardiac output and aortic flow similarly in term and preterm heart.[167;178;179] LVO increases two- to threefold at birth.[167;180] This rapid adaption at birth, thought to be triggered by a sudden release of circulating catecholamines,[181;182] is also found in preterms.[183] However, it has been demonstrated that the immature myocardium of the newborn is more sensitive to changes in afterload than the more mature heart.[179;184] We therefore speculate that the significant reduction of LV contractility from 5 to 12 h may represent a transitional response to the postnatal increase in afterload.

The PDA may play a role in this timespan. Our findings in paper II and III indicate that infants with hsPDA at 5 h age had a higher contractility than infants with nsPDA. This is in accordance with the Frank Starling mechanism, as the increase in preload and reduction of afterload due to run-off into the pulmonary circulation enables the myocardium to increase the stroke volume. However, there has been some debate as to whether the Frank Starling mechanism can be applied in newborn and preterm infants. In 1985, Baylen et al.[178] found unchanged contractility in preterm lambs with hsPDA, and therefore concluded that the compensatory increase of cardiac output was accomplished primarily by increasing LV end-diastolic volume and stroke volume, i.e. by the Frank Starling mechanism. In this study, contractility was defined by the peak dP/dt, a volume sensitive isovolumic index of contractility, and ejection fraction was measured by cineangiocardiography. Similarly, Lindner et al.[185] demonstrated that preterm infants with symptomatic PDA increased their LVO by increasing stroke volume, not heart rate. Some years later, in 1992, Takahashi et al.[184] found that premature infants had less reserve capacity in the LV than mature babies and that the low left ventricular stroke volume was compensated with an increased heart rate. Thus the author concluded that the Frank Starling mechanism seemed to be limited in preterm infants. It is known that the myocardium of the newborn is immature[186-189] and that the preterm, immature myocardium operates at a higher contractile state and therefore, has less cardiac reserve than the heart of an older person.[190;191] This could explain our findings at 24 h, when the myocardial contractility was consistently lower in infants with hsPDA than with nsPDA. We may speculate if this was caused by fatigue of the immature myocardium or if it was merely a physiological response to the demands of the circulatory system.

The right ventricle

The overall higher cTDI velocities and displacement in the RV than in the LV are in accordance with other studies in preterm infants[192] and may reflect the functional preference of the right heart typical of the fetal circulation.[193] However, also in healthy children myocardial velocities are consistently found to be higher in the RV than in the LV. Thus, the difference may also point to an intrinsic property of the RV, such as the pattern of contraction.[194] Despite the physiological decrease of pulmonary vascular resistance, the myocardial velocities and displacement of the RV also decreased from 5 to 12 h after birth. We may speculate if this was caused by right-left heart interactions[195] and/or transient diastolic dysfunction.[116]

Myocardial contractility and SVC flow

As shown in paper III, we found a correlation between contractility at 5 h age and SVC flow at 24 h (figure 12), and between various cTDI indices at 24 h and SVC flow at 24 h. This is in accordance with a study by Osborn et al.[196] in a population comparable to ours, and probably reflects the relationship between cardiac function and systemic flow. Parikh et al.[128] studied myocardial function in preterm infants on day 3 and found that infants with hsPDA had worse myocardial systolic and diastolic function than infants with no or nsPDA. This may indicate that the impaired myocardial function we found at 24 h persists at day 3 in the presence of an hsPDA. Thus, not only could an early echocardiographic exam identify infants with an hsPDA, but also those who are at risk of low systemic blood flow and in need of cardiovascular support.

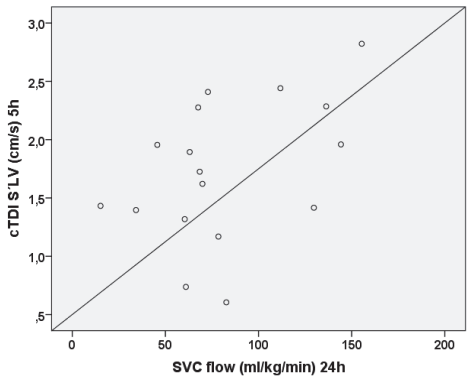


Figure 12

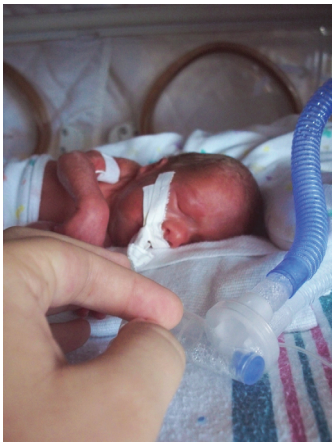
6.2.3 Blood pressure (paper III)

MABP did not differ between infants with hsPDA or nsPDA at any time. This is in accordance with a previous study showing no difference in BP related to the hemodynamic significance of ductal shunting in infants with BW 1000-1500 g.[197] Our finding contrasts the result of a prospective study showing significant blood pressure response to indomethacin treatment of PDA in 24 preterm infants,[198] however, the mean BW of the study population was <1000 g, thus not exactly comparable to the previously mentioned study. Our findings also contrast the results of a retrospective study demonstrating an independent association of PDA with hypotension,[199] but at the time of examination the infants were older (2-7 days) than in our study, and one may assume that the pulmonary vascular resistance was lower, thus allowing for a higher degree of left to right shunting across the PDA. In our study, only 1-2% of infants received vasopressor treatment during the first 24 h of life, thus, this may not explain the lack of significant BP difference between infants with nsPDA and hsPDA.

There was a strong correlation between MABP and SVC flow at 12h ($r=0.5$; $p=0.007$) and a similar but non-significant trend at 5h ($r=0.1$; $p=0.4$) and 24h ($r=0.2$; $p=0.2$). This is in accordance with earlier findings,[50] but contrasts the findings of Groves et al.[40] who reported an inverse relationship between blood pressure and SVC flow at 5 and 12 h.

7 Limitations

Both methods examined and applied in this thesis have contributed to new knowledge about cardiac function and circulation in the preterm infant. However, both methods also have their limitations. Further, the study of these methods has been limited by the study population itself. Due to the vulnerability of the newborn, and especially the preterm infant, the exams had to be carried out very carefully and with first priority given to the wellbeing of the infant. Sometimes this meant finishing with an incomplete exam, or not performing the exam at all.



An intubated premature infant born prematurely at GA 26 weeks and 6 days with BW 990 grams. Photo taken at approximately 24 h after birth. (From Wikimedia Commons)

7.1.1 SVC flow

As paper I was a methodological study, the limitations of SVC flow have been thoroughly discussed in the paper, which demonstrates that the variability of diameter measurements are the main source of the high repeatability index. We did not investigate the effect of respiration on SVC flow, but sought to minimize the impact of respiration by averaging diameter and Doppler velocity tracings from 5 - 10 consecutive cardiac cycles. In a study of cardiorespiratory effects of changes in end expiratory pressure in ventilated newborns (median GA 30 weeks), a short-term modest increase in end expiratory pressure did not lead to clinically important change in systemic blood flow, assessed by SVC flow.[200]

A different aspect of the effects of respiration was investigated in an MRI study of caval blood flow during respiratory maneuvers, which showed a significant increase of SVC flow during deep inspiration.[201] A similar effect of fetal breathing movements on SVC flow has been reported.[202] However, in our study, infants were asleep or in a quiet awake state during image acquisition, hence the influence of breathing was assumed to be stable throughout the echocardiographic exam.

Regarding SVC flow, another possible source of error could be a persistent left SVC draining into the right atrium via the coronary sinus, a normal variant that occurs in 0.3% of the population.[203] We did not specifically look for this possibility.

7.1.2 cTDI

We emphasize that the results presented in paper II and III can only be applied to the conditions under which the study was performed, using a Vivid 7 GE with a 10S probe, tissue velocity range ±16 cm/s, frame rate 170/220/s, Echopac software and ROI size 3x1 mm.

As described in paper II, the major limitation of cTDI measurements is the high degree of intra- and interobser variability. We were surprised to find intraobserver variability to be higher than interobserver variability in our study, and are unable to find any reasonable explanation for this discrepancy.

A major limitiation to our cTDI studies is the lack of methodological guidelines and reference values in the field of neonatal, functional echocardiography. As discussed above in methodological considerations, a detailed description of the many technical aspects of cTDI measurements is required to allow for comparison between studies.

A recent study in moderately preterm infants has demonstrated that it may be useful to normalize cTDI indices for heart size.[129] Unfortunately, this was not possible in our study due to insufficient image quality, especially of the apical region, as our main focus during image acquisition was on the atrioventricular area.

Finally, the results reported in paper II and III are limited by the relatively small size and the heterogeneous clinical condition of the study population.

What would be a clinically relevant difference in tissue Doppler velocities between infants with hsPDA and nsPDA? So far, literature is scarce regarding cTDI values in this population

in general, and there are no previous published reports about these values in preterm infants with hsPDA during the first day of life.

In a study of myocardial function assessed by strain and strain rate in obese adolescents there was 21.3% reduced global strain rate and 16.3% reduced global strain in obese adolescents compared with lean counterparts before intervention. Maximal oxygen uptake was 41.4% lower in the obese group. No group difference was observed after 13 weeks aerobic interval training.[204] Thus, in this study, a difference in global strain rate of 21.3% was clinically relevant, as measured by maximum oxygen uptake.

Table 2 shows the number of infants needed to detect a 20% difference in cTDI peak velocities between infants with hsPDA and nsPDA, when using the formula $n = 2x\left(\frac{SD}{\Delta}\right)^2 x\, k$, where SD is the standard difference of the observed values, Δ is the desired difference (in this case 20% of the mean) and *k* is a constant which depends on the choice of significance (in this case 0.05) and test power (in this case 80%).

	5 h	12 h	24 h
cTDI S´LV	61	50	63
cTDI S´RV	36	76	68
cTDI D´LV	85	76	87
cTDI D´RV	24	49	88

Table 2

This means that we would need a total of approximately 180 infants to detect a 20% difference with a power of 80% and a two-sided p-value of 0.05.

8 Conclusions

Paper I: SVC flow in healthy term infants decreased from mean (SD) 99 (34) mL/kg/min at day one to 77 (27) mL/kg/min at day three after birth. The mean variability of SVC flow was 17% in the intraobserver analysis and 29% in the interobserver analysis. The diameter measurement was the main contributor to the variability of SVC flow measurement.

Paper II: Myocardial velocities measured by cTDI decreased significantly from 5 to 12 h postnatal age in very preterm infants. Infants with hsPDA had higher myocardial velocities than infants with nsPDA at 5 h age.

Paper III: An hsPDA was associated with decreased myocardial velocities measured by cTDI at 24 h postnatal age in very preterm infants. SVC flow was lower in infants with an hsPDA than with a nsPDA at 24 h postnatal age. There was a correlation between low myocardial velocities at 5 h and low SVC flow at 24 h postnatal age.

9 Future perspectives

The method of SVC flow for measurement of systemic circulation in neonates has been around since 2000. Meanwhile, more than 50 articles with various applications of the method have been published. During this time span, the concept of functional echocardiography, or CPU, has become part of the international neonatologist vocabulary. Thus, TDI entered neonatology at a time of growing interest for cardiac functional studies in the NICU.

One randomized controlled trial (RCT) has been carried out to assess the effectiveness of early prophylactic milrinone versus placebo for prevention of low systemic blood flow in high-risk preterm infants.[205] However, for various reasons milrinone did not prevent low SVC flow during the first 24 h of life. Presently, a large European multicenter RCT is planned to assess dobutamine versus placebo for treatment of low SVC flow in very preterm infants.[77]

Regarding TDI, the methodology is still in an early phase and further research is needed before TDI can be applied routinely in the NICU. Guidelines and reference values need to be established. However, from our experience in neonatology, we know how crucial these first, postnatal hours are for the wellbeing of very preterm infants. With the methods studied in this thesis, we hope to contribute to a better understanding of the changes taking place in the central cardiovascular system during this vulnerable phase of transition.

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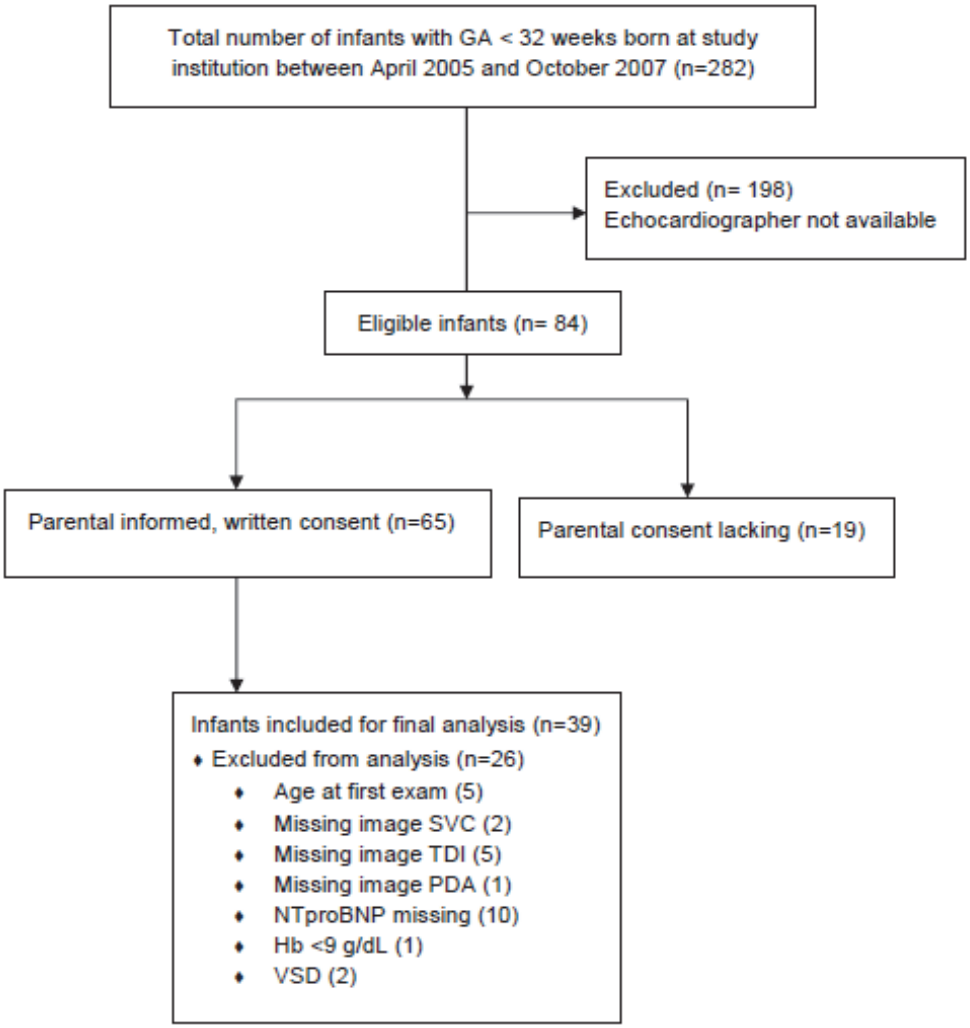
11 Errata

Page 22: in the methods section, the following flow chart should be added to show patient inclusion for study II and III:



Page 32: on feasibility: “We cannot really explain why the degree of feasibility differed between *study I and II*…” should be “*study II and III...* ”

Page 41: last paragraph: “There was a *strong* correlation between MABP and SVC flow …” should be “There was a *moderate* correlation…”

Page 42, picture text: “*From Wikimedia Commons*” should be “*Courtesy of Chris Sternal-Johnson*”

In paper II, we reported that cTDI images of adequate quality were obtained in *52, 32 and 35%* of infants at 5, 12 and 24 h, respectively. This is not correct, as these percentages were calculated on the basis of the eligible population (65 infants). However, as 15 infants were excluded for various reasons, the percentages should be *68, 42 and 46%* at 5, 12 and 24 h, respectively.

12 Papers

I

II

III