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Pulse Oximetry

Evaluation of a potential tool for early detection of critical congenital heart disease

by

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Cover picture of newborn baby undergoing pulse oximetry screening in right hand and one foot: Anne de-Wahl Granelli

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"Anyone who has never made a mistake has never tried anything new."

Albert Einstein

To my beloved family

Pulse oximetry: evaluation of a potential

tool for early detection of critical congenital heart disease

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Abstract

Background: About one third of newborns with life-threatening congenital heart disease leave newborn nurseries without the problem being recognized, and risk death or serious damage from circulatory collapse. The main aim of this thesis has been to evaluate if routine newborn screening with pulse oximetry could improve early in-hospital detection of newborns with duct-dependent circulation (DDC). Papers I, II and IV are methodological studies describing optimal screening cut-offs for pulse oximetry (*Paper I)*, normal range for perfusion index; PPI *(Paper II)*, and deviation of pulse oximetry values from true arterial saturation in cyanosed children (*Paper IV). Paper III* includes a multicentre screening-study that tests the method prospectively in all newborn nurseries in West Götaland Region (WGR) on 39821 newborns, with blind comparison with neonatal physical examination (NPE), as well as a complete cohort comparison of all newborns with DDC in WGR with all other referring regions (ORR) not screening newborns, and a cost-benefit analysis of screening.
Results: Best sensitivity for DDC was achieved with both pre- and postductal saturation cut-off <95% or a hand/foot difference of >$\pm$3% with a New-generation oximeter(NGoxi) on 3 repeated measurements. 29 babies with DDC remained undetected until the discharge examination. NGoxi-screening detected 18/29 (62%) but combining with NPE increased sensitivity to 24/29 (83%). A positive pulse oximetry screening gives a relative risk of 719.8 (95% confidence interval 350.3 to 1479; p <0.0001) of having duct-dependent heart disease. False-positive rate for NGoxi-screening was 0.17% (compared with 1.90% for NPE), and yielded other significant pathology in 45%. Total cohort-size of DDC in WGR was 60/46963 total live births, and in ORR 100/108604 live births. The risk of leaving hospital with undetected DDC was 5/60 (8%) in WGR compared with 28/100 (28%) in ORR; p=0.0025. In ORR an alarming 11/25 (44%) babies with transposition of the great arteries left hospital undiagnosed, versus 0/18 in WGR (p=0.0010). No baby died undiagnosed in WGR during the screening-study but 5 babies (5%) died undiagnosed in ORR, including two with duct-dependent cyanotic lesions. A PPI-value <0.7 gives an odds ratio for systemic duct-dependent circulation of 23.8 (95%CI 6.4 to 88.7), but its use in screening needs to be prospectively evaluated. *Paper IV* Both NGoxi and Conventional-technology oximeters(CToxi) show an increasing positive bias with falling arterial saturations, leading to significant overestimation of true arterial blood gas particularly in the below 80% saturation range. Overestimates by >7% of the arterial blood gas saturation occurred in 66.7% (10/15) of CToxi-readings and in 40.0% (6/16) of NGoxi-readings in the below 80% saturation range.
Conclusion: Adding NGoxi-screening to neonatal physical examination significantly improved detection of DDC, detected 100% of duct-dependent pulmonary circulation (present in 2 of 5 undiagnosed deaths in ORR), yielded only 0.17% false-positives, and came out cost-neutral.
Key words*: pulse oximetry, duct-dependent, newborn screening, congenital heart disease, perfusion index*

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List of Papers

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. de-Wahl Granelli A, Mellander M, Sandberg K, Sunnegardh J, Östman-Smith I. Screening for duct-dependent congenital heart disease with pulse oximetry: A critical evaluation of strategies to maximise sensitivity. Acta Paediatrica 2005; 94:1590-1596.

II. de-Wahl Granelli A, Östman-Smith I. Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction. Acta Paediatrica 2007; 96:1455-9.

III. de-Wahl Granelli A, Wennergren M, Sandberg K, Mellander M, Bejlum C, Inganäs L, Eriksson M, Segerdahl N, Ågren A, Ekman-Joelsson B-M, Sunnegårdh J, Verdicchio M, Östman-Smith I. Impact of pulse-oximetry screening on the detection of duct-dependent congenital heart disease: a Swedish prospective screening study in 39 821 newborns. BMJ 2009;338:a3037.

IV. de-Wahl Granelli A,* Bratt E-L,* Östman-Smith I. Important inaccuracies in pulse-oximetry readings in cyanosed children. (*Equal contributors) *Submitted*

Table of Contents

General Abbreviations

CCHD	Critical Congenital Heart Disease
CHD	Congenital Heart Disease
CToxi	Conventional Technology Oximeter
COHb	Carboxy Haemoglobin
DDC	Duct-Dependent Circulation
DDS	Duct-Dependent Systemic Circulation
DDP	Duct-Dependent Pulmonary or Mixing Circulation
Hb	Haemoglobin
RHb	Reduced Haemoglobin or Deoxyhaemoglobin
IR	Infra Red
LED	Light Emission Diode
LHOD	Left Heart Obstructive Disease
MetHb	Ferrihaemoglobin or Methaemoglobin
NGoxi	New Generation Oximeter
NPE	Neonatal Physical Examination
O_2Hb	Oxyhaemoglobin
ORR	Other Referring Regions
POX	Pulse Oximeter
PPI	Peripheral Perfusion Index
R	Red
SET	Signal Extraction Technology
WGR	West Götaland Region

Abbreviations for Congenital Heart Disease

AS	Aortic Stenosis
ASD	Atrial Septal Defect
AVSD	Atrio-Ventricular Septal Defect
A-Pw	Aorto-Pulmonary window
CoA	Coarctation of the Aorta
DILV	Double Inlet Left Ventricle
DORV	Double Outlet Right Ventricle
HLHS	Hypoplastic Left Heart Syndrome
IAA	Interrupted Aortic Arch
LPA	Left Pulmonary Artery
PA	Pulmonary Atresia
PDA	Patent Ductus Arteriousus
PFO	Patent Foramen Ovale
PS	Pulmonary Stenosis
RPA	Right Pulmonary Artery
TA	Tricuspid Atresia
TAPVR	Total Anomalous Pulmonary Venous Return
TGA	Transposition of the Great Arteries
ToF	Tetralogy of Fallot
VSD	Ventricular Septal Defect

Introduction

The incidence of congenital heart disease (CHD) is 5-8 per 1000 live births[1-7] and for immediately life-threatening CHD 1-2 per 1000.[5, 7-10] Over the last 20 years a disappointing finding has been consistent. The neonatal physical examination is not sensitive enough to detect these newborns. About one third of children with life-threatening congenital heart disease leave the newborn nurseries without a diagnosis.[10-12] Most of them return to hospital in a circulatory collapse,[12] but around five percent of the babies die in the community without a diagnosis.[10, 13] Apart from the fact that circulatory collapse can cause long term morbidity,[14] the critical care costs for stabilizing the babies before any surgery can be offered are high. Sometimes severe brain damage caused by the collapse means that surgical correction is denied.[11] Ideas for how to improve the poor results were proposed. The need for an additional tool to improve early detection of critical congenital heart defects was obvious.

"Principles and Practice of Screening for disease" was published in 1968 from World Health Organization (WHO) in Geneva (Public Health Paper No. 34) by J.M.G Wilson and G. Jungner. In chapter 2 (p. 26-39), they stated and discussed 10 criteria to be met for implementing screening. The knowledge about life-threatening CHD, its natural cause and good surgical outcome in Sweden already meets 6 of the 10 criteria. The remaining four are that a proper screening test exists that is accepted by the population, that screening is cost-balanced (comparison of the screening costs versus the medical care costs for not screened and ideally a prospective comparison of reduced morbidity and improved working life in the screened population compared with a cohort of non-screened) and lastly that case-finding should be a continuing process and not a "once and for all" project. Since a screening test should be quick and easy, pulse oximetry was proposed as a candidate technique for newborn screening. In 2002 and 2003 four studies were published about screening newborns with pulse oximetry, in order to find congenital heart disease, but each was too small to properly assess sensitivity.[8-9, 15-16]

The Discovery of Pulse Oximetry

"A skilled physician can treat only a limited number of patients. But an excellent medical instrument can treat countless of patients in the world". Words from the founder of Nihon Koden Corporation, (Tokyo, Japan), Dr Yoshio Ogino. They inspired a young Takuo Aoyagi so much, that he less than two years later, in Februari 1971, transferred to that company. The first order the 35 year old electrical engineer Takuo Aoyagi got from his new division manager was "Develop something unique"…

In 1972, Takuo Aoyagi at Nihon Kohden Corporation developed pulse oximetery.[17, 18] In 1973 Susuuma Nakaiima, a surgeon in Sapporo placed an order with Nihon Koden. Aoyagi built the prototype oximeter between September 1973 and March 1974, so that Nakaiima could test it on his patients at Sapporo Minami National Sanatorium. Aoyagis abstract "Improvement of the Ear-Piece Oximeter" was submitted in October 1973 with a description of his invention.

On March 29, 1974 an application titled "Apparatus for Photometric Blood Analysis" was submitted to the Japanese Patent Office by the Second Division of Technology at Nihon Kohden Corporation, naming Takuo Aoyagi and Michio Kishi as inventors. That was 28 days before Aoyagi was going to present his discovery to the Japanese Society of Medical Electronics and Biologic Engineering in Osaka.

Two days before the meeting, another patent application was submitted, naming Konishi and Yamanishi at Minoruta Camera Company as inventors of pulse oximetry.

In the autumn 1973, Akio Yamanishis supervisor, Masaichiro Konishi, gave him a copy of the oximeter chapter from a book (Medical physics, Vol 2, 1950:664-80). In January 1974, Yamanishi presented an idea of pulse oximetry to the person in charge of patent at his company.[18] The Japanese Patent Office later rejected the second application from Minoruta Camera (known as Minolta Camera in Europe and USA) and listed Takuo Aoyagi as the inventor of pulse oximetry. The patent was granted on April 20, 1979.

The first commercial instrument from Aoyagis group was an ear-oximeter OLV-5100 in 1975. However, Nihon Kohden Corporation never applied for a patent abroad, and Minoruta got their United States patent application approved. In 1977 Minoruta (Minolta) marketed their devise, OXIMET M-1471 with a fingertip probe. The first oximeters were primarily research devises. The first available pulse oximeter, manufactured for clinical use, was the Nellcor N-100, marketed in 1982.[17-19]

As many other inventions, pulse oximetry was a result of a failed research experiment. Aoyagi was actually working on a non-invasive dye densitometer for cardiac output measurement.[17]

When Takuo Aoyagi discovered that changes in oxygen saturation voided his pulse cancellation and caused his research test to fail, he worked his way around the problem by inventing a method to eliminate the noise. That led to the discovery of pulse oximetry.[17, 20] Aoyagi never anticipated that his failed research experiment would turn into success and later to be quoted as "the greatest advance in patient monitoring since electrocardiography" by Hanning and Alexander-Williams in a pulse oximetry review in 1995.[21]

Haemoglobin

The red blood cells are biconcave, around 7-8µm in diameter,[23, 24] and lives about 4 months.[22] A neonate have 6 million erythrocytes per µl, a child 4-5.5 million and adults 4.1-6 million per micro litre.[23, 24] The adult bloodstream contains $24x10^{12}$ erythrocytes and that is around 1/3 of the total number of cells in the body.[22] They are red because they contain an iron rich protein called Haemoglobin. Haemoglobin is a protein that transports oxygen from the lungs to the muscles and tissues in the body and carry back the carbon monoxide (waste) to the lungs where it leaves the body. There are about $3x10^{8}$ haemoglobin molecules in every red blood cell. The normal haemoglobin content in newborns is 170-200 g/ml,[25, 26] in neonates 100-150 g/100ml, in children 80-100 g/100ml and 90-120 g/100ml in adults.[23] The name *haemoglobin* gives a clue to its contents: *haeme* for heme-group and *globin* for globular protein. The protein consists of four sub-units, 2α (alpha) and 2β (beta) polypeptide chains.[22, 24] To every sub-unit an iron containing haeme-group is attached. Every haeme-group contains one iron ion that can carry one oxygen molecule, which means that one Haemoglobin molecule can carry four oxygen molecules,[27] see Figure 1.

When the haemoglobin molecule carries oxygen it is called *oxyhaemoglobin (O_2Hb)* and when no oxygen is attached it is called reduced haemoglobin or *deoxyhaemoglobin (RHb)*. The iron ion can be in Fe^{2+} or Fe^{3+} states. It can only bind oxygen when it is in Fe^{2+} state though. The Fe^{3+} state of the molecule (ferrihaemoglobin) is also called *methaemoglobin (metHb)*. Another form of haemoglobin is found in fetuses and is called HbF and contains 2α and 2γ sub-units.[22, 24] The difference is that HbF binds to oxygen more strongly than Hb to ensure that the fetus receives enough oxygen supply from the mothers blood. At about one year of age less than 1% of HbF remains and the γ sub-units has been replaced by β chains.[22]

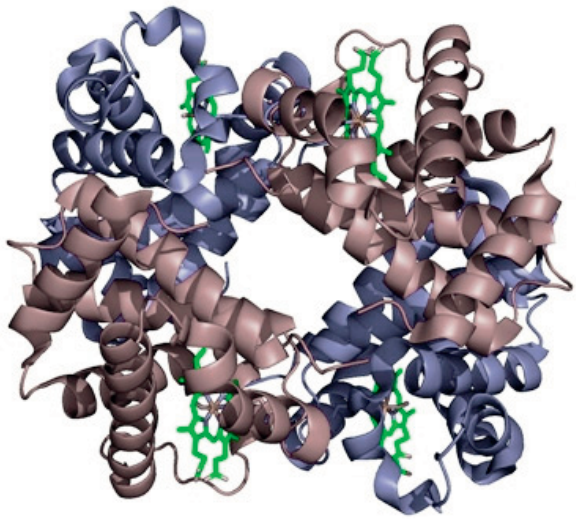


Figure 1. Schematic structure of Haemoglobin with the 2α and 2β polypeptide chains in purple and pink, and the iron-containing heme-groups in green (Wikipedia, printed with permission and modified layout by Soffi Petersson).

Air consists of 21% O_2 and 79% N_2.[27] The total gas pressure in air at sea level is 100 kPa. This pressure is generated of both O_2 and N_2.[27] In the blood (liquid), the amount of a gas that is soluble depends on the partial pressure, volume and temperature of the gas. The amount of oxygen available for us is determined of the alveolar ventilation and partial oxygen pressure (pO_2) in the air we breathe. In room air the pO_2 is around 21 kPa.[27]

The ability for haemoglobin to bind to oxygen depends on the physical conditions (pressure, temperature and pH). In the lungs when the pO_2 (oxygen pressure) is high, around 13 kPa, and the CO_2 (carbondioxide) level is low, the affinity is high and the Hb molecule binds to oxygen. In the pulmonary capillaries the haemoglobin is fully saturated. One gram of haemoglobin can carry about1.34ml O_2.[22] When pO_2 drops to around 5.3 kPa in the veins the haemoglobin is about 75% saturated.[27] In the capillaries in the tissues, the pressure is very low, CO_2 high and the oxygen is released.

The oxyhaemoglobin dissociation curve (Figure 2) can be shifted due to response to physiological conditions.[22, 24] A leftward shift, promoting oxygen uptake occurs if pH is raised, temperature is lowered, if Hb is replaced by HbF or a fall in 2,3-diphosphoglycerate, (important substance in the red blood cell with main regulatory

function to facilitate unloading of oxygen). A rightward shift of the dissociation curve occurs if pH is lowered, temperature is raised (exercise), or a rise in 2,3-diphosphoglycerate (anemia, high altitude).[22, 24, 27] The ability for haemoglobin to bind to oxygen also depends on the presence of carbon monoxide (CO). If CO is present, it competes successfully with O_2 at the haeme binding sites and is 200 times more likely to bond to Hb.[27] An air concentration of CO of 0.02% causes headache and nausea. If the CO concentration reaches 0.1% it leads to unconsciousness and death. Heavy smokers expose themselves to CO and may have up to 20% of their haemoglobin oxygen sites occupied by carbon monoxide whereas non-smokers have a COHb of less than 2%.[20] An infant whose mother smoked heavily shortly before delivery, could have a relative high concentration during the immediate postnatal period.[28]

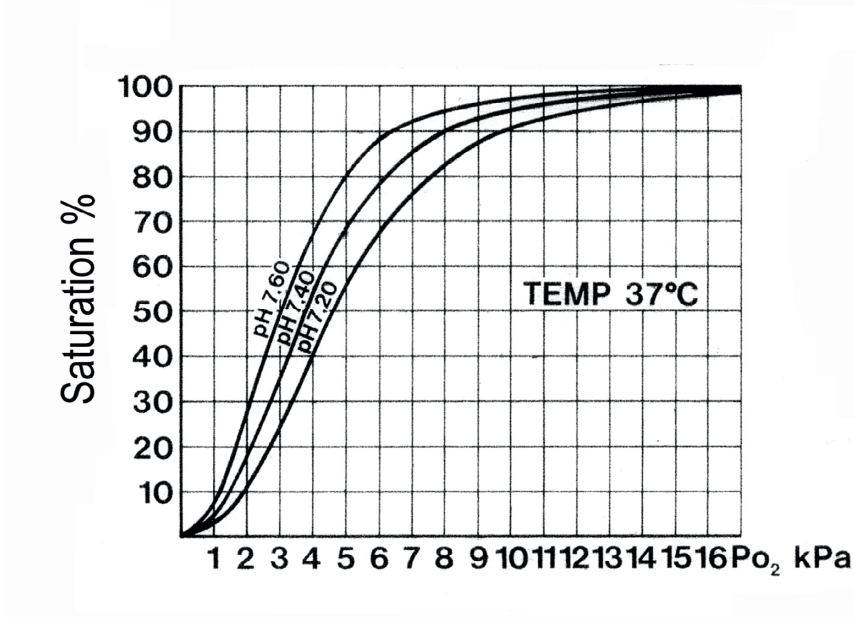


Figure 2. The Oxyhaemoglobin Dissociation curve (Datex Ohmeda, modified Layout by Soffi Petersson).

Pulse Oximeter Principle

Pulse oximetry is a non-invasive way of measuring the oxygen saturation in arterial blood SpO_2. A pulse oximeter is based on spectral analysis and combines two technologies, spectrophotometry and optical plethysmography.[20, 29]

Spectrophotometry: A spectrophotometer measures light intensity as a function of the colour, or more specifically, the wavelength of light. There are two a classes of spectrophotometers; single beam and double beam. Single beam spectrophotometer measures the absolute light intensity, whereas double beam spectrophotometer measures the ratio of the light intensity from two different light paths. The pulse oximeters use double beam for measuring the hemoglobin oxygen saturation.

Optical Plethysmography: A plethysmograph is a pulse-volume recorder, a way of measure the pulsatile changes from the arterial blood at the sensor site.

The principle of pulse oximetry is based on the different absorption characteristics of oxyhaemoglobin (O_2Hb) and reduced haemoglobin (RHb) for red and infrared light.[20, 28, 30]

Red light (R) is in the 600-750 nm wavelength light band. Pulse oximeters often use a wave length of 660 nm in their light emission diode (LED).[20, 28, 29, 31] Takuo Aoyagi used 630 nm in the first pulse oximeter.[17]

Infrared light (IR) is in the 850-1000 nm wavelength light band. Pulse oximeters often use a wave length of 940 nm in their LED.[20, 28, 31] Aoyagi used a wavelength of 900 nm in the first pulse oximeter.[17]

Beer Lambert law: $A = D \times C \times \varepsilon$

Where A= absorbtion
D= the distance light is transmitted through the liquid
C= concentration
ε= extinction coefficient of the solute (a constant for a given solute at a specific wavelength).

Transmittance (T): how much intensity of the incident light (Io) that is transmitted (I). Transmittance plotted against concentration is not linear, but the negative log 10 of the transmittance is. Therefore absorption is measured as:

Absorption: $A = -\log 10 (I/Io)$ or $A = -\log 10 (T)$

The principle of Beer Lambert law is used to measure the relative concentrations of RHb and O_2Hb in pulse oximeters. The ratio of light absorbed at the red light to that of infrared light A660nm (RHb)/A940nm (O_2Hb) correlates with oxygen saturation, since the concentration of a given solute in a solvent is measured by the amount of light that is absorbed by the solute at a specific wavelength.[20] Since a cutaneous vascular bed (for example a finger) also contains soft tissue, bone, skin and venous blood apart from the arterial blood, correction factors needs to be built into the pulse oximeters to overcome absorbance by tissues other than Haemoglobin.[20] In order to select the arterial blood, the pulse oximeter differ the pulsatile component (AC) from the non-pulsatile (DC) components (soft tissue, bone, skin, venous- and capillary blood). A microprocessor then calculates the ratio (R) of the absorbance:

$$R = \frac{\text{AC 660nm/DC 660nm}}{\text{AC 940nm/DC 940nm}}$$

In order to display the SpO_2, the oximeter compares R with stored values in a memory.[28, 31] Those values in the memory were obtained by human adult volunteers[32] breathing hypoxic mixtures until their saturations dropped to 80%. That is the probable reason for the limitation of declining accuracy in saturation values for conventional technology pulse oximeters under 80%.[20, 33]

O_2Hb absorbs more infrared light and the red light passes through to the photodetector. RHb absorbs more red light and the infrared light passes through to the photodetector.[28] Conventional pulse oximeters are based on the assumption that the blood contains 1.6% of COHb and 0.4% MetHb (the Fe^{3+} state that cannot bind oxygen) and no other pigments.[34] Any alteration from that assumption leads to errors in SpO_2 readings.[20, 35, 36] A pulse oximeter can be calibrated in two ways, either displaying *functional* saturation or *fractional* saturation.[31, 37] Functional saturation is the quantity of HbO_2 expressed as a percent of haemoglobin that can transport oxygen (since MetHb and COHb cannot transport oxygen they are not included).[8, 20, 28, 37, 38] The functional SpO_2 value is obtained by multiplying the fractional saturation by 1.02. Fractional saturation is the HbO_2 expressed as a percent of all the haemoglobin measured, including carboxyhaemoglobin and methaemoglobin.[20, 28] That means that a pulse oximeter calibrated for *fractional* saturation displays about 2% lower values than an oximeter calirated for *functional* saturation.[37, 38] The calibrations are performed by the manufacturer and thus cannot be changed by the user.

Functional $SpO_2 = \left(\frac{O_2Hb}{O_2Hb + RHb}\right) \times 100$

Fractional $SpO_2 = \left(\frac{O_2Hb}{O_2Hb + RHb + MetHb + COHb}\right) \times 100$

Conventional Technology Pulse Oximetry at a glance

- Two light emission diodes (LED) with different wavelenghts (R and IR light)
- Emits through a cutaneous vascular bed, for example, a finger
- RHb absorbs more light at 660 nm
- O_2Hb absorbs more light at 940 nm
- A detector (on the opposite site of the LED) measures the intensity of transmitted light at each wavelength
- The photodetector then converts the light into an electronic signal for processing
- The oxygen saturation is derived from the ratio between the red light (660 nm) and IR (940 nm) light that reached the detector
- However other soft tissue, bone, skin and venous blood absorbs light
- Thus the pulse oximeter must separate the non-pulsatile components (DC) from the arterial boood, the pulsatile component (AC)
- By using the double beam wavelength system, the DC component is then discriminated

- The pulsatile AC component is then calculated in the microprocessor and the ratio R is compared with stored values in the calibration curve memory
- The SpO_2 value is then displayed
- The SpO_2 values displayed are not instantaneous. They are averages taken over 3 to 10 seconds to help reduce the effect of pressure wave variations due to motion of the subject[39]

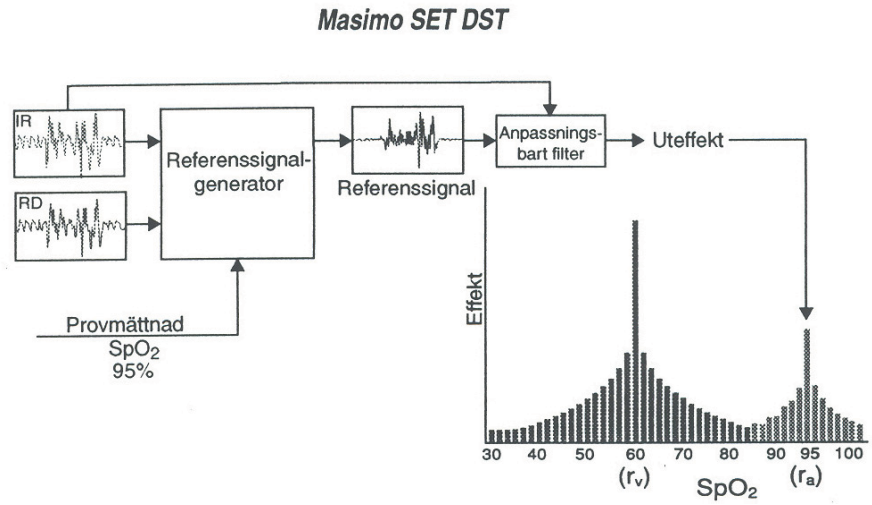
Limitations with Conventional Technology Pulse Oximetry

- Motion artefact (when the patient is moving, the venous blood is also moving and the pulse oximeter adds the moving venous blood to the AC component, thus the displayed SpO_2 is underestimated)[20, 28, 30, 31, 40-49]
- Ambient light (phototherapy and bright light can affect SpO_2 accuracy)[20, 28, 31, 43, 45, 48, 49]
- Skin pigmentation (overestimations of SpO_2 in dark pigmented skin, increasing with lower saturations) [20, 28, 31, 49, 50]
- Low peripheral perfusion states[20, 31, 43, 47-49]
- Dyshaemoglobinemia[20, 28, 35]
- Low oxygen saturation[20, 45, 51]
- Nail polish[20, 52, 53]
- Irregular heart rythm[20, 47]
- Temperature (low peripheral temperature and vasoconstriction contributes to inaccuracy)[28]

New Generation Pulse Oximetry Technology

Monitoring oxygen saturation continuously via pulse oximetry has become a standard of care in most emergency units in hospitals since ASA Standards for Basic Monitoring during anaesthesia adopted pulse oximetry as of January 1st, 1990.[20] Spreading from operating rooms via postanesthesia units into different intensive care units and neonatal units[54] pulse oximetry is regarded as one of the most important advances in clinical monitoring and even quoted as "the fifth vital sign".[28] Retailers and software versions increased quickly, by 1989 there were 29 manufacturers producing 45 different models of pulse oximeters.[55] Limitations of the conventional technology oximeters (CToxi) are well known and the technique has improved over the years. In recent years the limitations of pulse oximetry like motion artefact and low perfusion, are claimed to have been overcome with the introduction of the new-generation oximeters (NGoxi).[44, 49]
In 1989, Diab and Kiani invented a "motion-resistant" technology claimed be accurate during conditions of patient motion and low perfusion. The technology was the first to get FDA clearance for accuracy during motion and low perfusion.[28] It was available commercially in 1998 as SET; Signal Extraction Technology.[56] Two other major motion-resistant technology oximeters are Oxismart (Nellcor, Pleasanton, California), first marketed in 1994 and FAST SpO2; Fourier artifact suppression technology SpO2, (Philips Medical Systems, Andover, Mass), first marketed in 1999.[44] These second-generation pulse oximeters are often referred to as new-generation oximeters (NGoxi). In this thesis only one lone of NGoxi technology has been used in paper I-VI, the Masimo SET (signal extraction technology). Nellcor uses adaptive filtering in their Oxismart technology, Agilent Virida (Agilent, Böblingen, Germany) uses frequency and time domain analysis and Masimo uses a combination of both adaptive filtering and frequency and time domain analysis in their SET technology.[57, 58] Therefore any in depth explanation of the other major motion resistant technologies is beyond the scope of the thesis.

Signal Extraction Technology (SET)[49] with Discrete Saturation Transform Algorithm (DST)[29] at a glance



- A *Reference Signal Generator (Referenssignal generator)* builds a noise reference for the incoming red (RD) and infrared (IR) signal for every % SpO_2 between 1-100%
- It passes through an *Adaptive filter (Anpassningsbart filter)* that eliminates the correlating frequencies between the Reference signal and the incoming IR-signal
- When the frequencies are different, a small part of the signal is removed and a "high-energy-output" occurs
- "Energy output" from the *Adaptive filter* is measured and plotted for all saturations between 1-100% with 0.5% intervals every 0.4 second

➢ No motion => 1 "energy output peak"

➢ Motion => several "energy output peaks"

- Since the arterial blood have the highest saturation (r_a), compared with moving venous blood (r_v), the *Peak Picker* algorithm picks the highest saturation peak, r_a, as the % SpO_2 with which the Masimo SET model is met

The signal averaging time for Masimo Radical SET can be set to 2, 4, 8, 10, 12 or 16 seconds.[29] The shorter averaging time the quicker response to rapid changes but also false alarms.[44] The longer averaging time the less false alarms but at the risk of missing rapid changes. One should therefore choose the appropriate averaging time for the intended purpose. Lack of reporting averaging time when comparing different oximeters makes comparisons hard to make.

Sensors

There are different pulse oximeter sensors depending on measuring site (ear, finger-probe, forehead and multisite) and size of the "patient" (newborn, infant, paediatric, or adult). There are also disposable sensors (band-wrap or adhesive) or reusable (band-wrap or clip-on). *Bell et al.* studied the effect on probe design on accuracy and reliability of pulse oximetry in pediatric patients.[59] They compared disposable band-wrap with reusable clip on sensors from three conventional technology pulse oximeters; Nellcor N200, Novametrix 520A and Ohmeda 3700, in 18 children under 12 years old in a clinical setting in an operating room. The saturation values were compared with simultaneous arterial blood gas (hemioximetry). They found that bias was less than 2% for any of the probe-machine combinations and concluded that type of sensor had little effect on accuracy. However they pointed out that the children were sedated and in a real paediatric setting an adhesive sensor might be more practical. *Feiner et al.* compared clip-on and adhesive/disposable finger sensors from three New-generation oximeters in 36 adults with various skin pigmentation.[50] The subjects breathed an air-nitrogen-CO_2 mixture to achieve stable low plateau saturation values. All values were compared with blood gas. The mean bias (SpO_2 – SaO_2) for Masimo Radical (clip-on sensor) for the 70-80% saturation range was 2.61% and -1.58% for the disposable. For Nellcor N-595 clip on 2.59% and 3.6% for the disposable and for Nonin 9700 clip-on -0.60% and for the disposable 2.43%. Dark skin increased bias at low saturations. They also concluded that greater bias was seen with adhesive/disposable sensors than with clip-on sensors.[50]
With the introduction of New-Generation pulse oximeters, improvements of the sensors followed. Masimo SET introduced LNOP-sensors (Low Noice Optical

Probe).[49] The difference from a conventional sensor is that the photo detector is recessed in a cavity to minimize optical path length changes during motion. This cavity is covered by a conformable adhesive that allows the fleshy part of the digit to move in and out of the cavity during motion. In a conventional sensor, the photo detector is directly in contact with the tissue. Two other advantages are that the recessed detector together with the overall shield makes it protected from electromagnetic noise and ambient light.[49] It is also claimed to minimize the effect of venous blood movement at the site caused by motion (www.Masimo.com). Another new type of sensor is the LNOP Blue Sensor, designed specifically for cyanotic children. It is claimed to be the only adhesive sensor proven to be accurate on paediatric patients with congenital heart disease with saturations as low as 60%.[60, 61] The sensors used in Paper I-IV are shown in Figure 3.

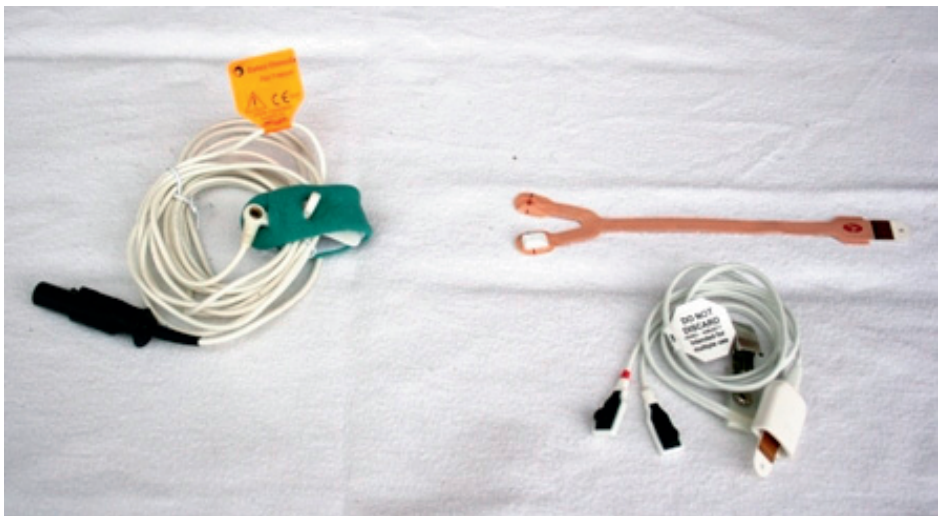


Figure 3. Reusable Flex II sensor (TuffSat, used in Paper I) to the left. On the top to the right the disposable LNOP-Neo sensor (Radical SET, used in Paper I) and bottom right the reusable multisite LNOP-YI sensor (Radical SET, used in Paper II-IV). We used posey wrap to attach all sensors in all studies (seen on the Flex II sensor) and to shield the sensors from ambient light.

Peripheral Perfusion Index (PPI)

Advances in NGoxi technology now enable measurements of the peripheral perfusion index (PPI). Using the ratio between pulsatile (AC) and non-pulsatile (DC) components of the light reaching the pulse-oximeter detector PPI is calculated.[62-64] Since the AC/DC ratio components of the infrared signal correspond to the pulsatile (arterial) and non-pulsatile amounts of blood, alterations in peripheral perfusion will change the ratio and reflect real time changes in PPI.[62] The relationship between the pulsatile and non-pulsatile amount of blood at any measuring site corresponds to the PPI at that specific site. It is displayed on the oximeter monitor (as PI seen in Figure 4) and is influenced primarily by the amount of blood at the monitoring site – not by the level of oxygen saturation of the arterial blood. PPI varies as physiologic conditions vary and would therefore be expected to be affected by a reduction in stroke volume in the arterial circulation. The lower and upper PPI limits reported by the manufacturer (Masimo Corp) are 0.02-20.00%. Other brands may have different limits for PPI.[65]

De Felice et al. found that PPI was a predictor for high illness severity in neonates[63] and were able to pick up early postnatal changes in PPI in newborns with subclinical chorioamnionitis.[64] When our study started there were only two small studies giving reference values on PPI that had been published.[64, 65] One was based on 108 healthy adults in a sitting position. Median PPI (finger) was 1.4 with an inter-quartile range of 0.7-3.0.[65] The system used by *Lima et al.* was Philips Medical Systems Virida/56S monitor with lower and upper limits of normal perfusion index in adults reported by the manufacturer to be 0.3-10.0.[65] *De Felice et al*. published the only reference values on newborns. They studied 115 newborns during the first 5 minutes after birth, which does not represent a stable cardiovascular situation.[64] PPI (foot) was measured immediately after birth every 4th second for at least 5 minutes with Radical SET (they did not state which version they used). The 115 newborns were a matched control group to 51 newborns with intrauterine subclinical chorioamninitis on histology in order to to define a PPI cut-off value (phase 1). In a subsequent prospective study (phase 2), the only two false positive newborns not having subclinical chorioamninitis had congenital heart disease! One had coarctation of the aorta and the other Ebstein's anomaly. *De Felice et al*. used a PPI cut-off of $\leq$1.74 at one minute and $\leq$2.18 at 5 minutes after birth. Their paper inspired us to explore the normal values pre- and post ductally in our prospective multicentre study in WGR. Since *De Felices* only false positives were babies with congenital heart disease, almost the same target condition as we had, we wanted to find out if a single screening measure of PPI possibly could be used as a tool for early detection of critical left heart obstructive heart conditions.

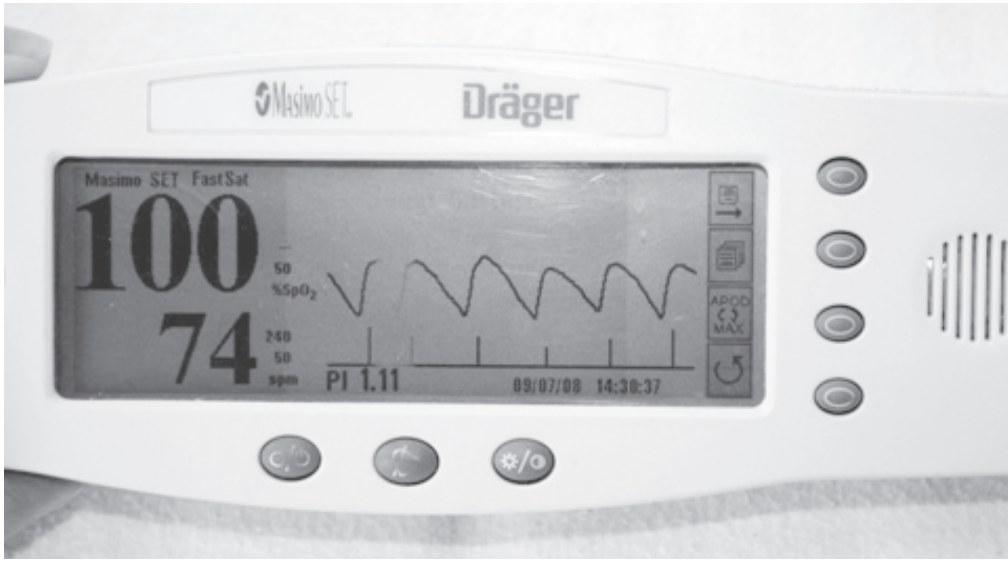


Figure 4. The PI (PPI) value is displayed under the plethysmographic curve and is in this example 1.11. The saturation is 100% and the heart rate is 74 beats per minute.

Causes of Congenital Heart Defects

Congenital heart defects (CHD) is one of the most common birth defects in the general population, with an incidence of 5-8 per 1000 live births.[1-7] The aetiology is multifactorial including genetic factors (chromosomal disorders, single-gene disorders and polygenic disorders) and environmental risk factors (smoking, paints, varnishing, auto body repair, pesticides, solvents and hair dye).[2, 66, 67]Examples of cardiovascular teratogens are:
Drug exposure to alcohol (septal defects), Diazepam, Corticosteroids, Hydantoin (pulmonary- and aortic stenosis), Lithium, Trimethadione (transposition of the great arteries, tetralogy of Fallot, hypoplastic left heart syndrome), Folate antagonists, Thalidomide (conotruncal abnormalities) Retinoic acid (conotruncal and aortic arch abnormalities), Ecstacy, Phenothiazine and paternal exposure to Cocaine).[67]
Maternal diseases increasing the risk are Epilepsy (pulmonary stenosis), poorly controlled Diabetes (tetralogy of Fallot, truncus arteriosus, double outlet right ventricle), poorly controlled Phenylketonuria (Tetralogy of Fallot), Systemic Lupus Erytematosus (AV-block grade III).[67]

Infections such as Rubella infection during the first trimester (Patent Ductus Arteriosus and peripheral pulmonary artery stenosis) and other viral infections (Coxsackie and HIV).[1-3, 67] Folate intake in the periconception period reduces the risk for neural tube defects, and conotruncal heart malformations.[3]

Cardiac Development and Fetal circulation

By 6 weeks postconception (note that the gestational age is 2+6=8weeks), the fetal heart is morphologically developed.[3, 66] From two primitive parallel endocardial heart tubes (day 17-22), changes in blood flow allows smaller vessels to connect in-between the two parallel vessels, forming a wider "heart-tube" that fuses together. When fusion is completed the heart beats (during the 4th week after fertilization).[68] By the end of the fourth week, the contractions are coordinated and the blood flow unidirectional.[69] Between day 23-28 the tube is making a loop to the right, moving the atrial portion cranially, the ventricular part caudally and the outflow tract remains positioned cranially.[2, 70] When something goes wrong at this stage, the results can be a physiologically corrected transposition of the great arteries, or an incorrect relation between the left atrium and aorta, causing an AV-plane displacement, resulting in a double inlet left ventricle or a double outlet right ventricle.[70] The "normal" asymmetry caused by the rightward rotation determines the situs of the fetus and normal situs is called situs solitus. If the normal asymmetry does not occur, the result can be situs inversus (mirror image of the normal atrial relationship), situs ambiguous or left- or right atrial isomerism (bilateral left sided or bilateral right sided atria) or a so called "criss-cross-heart". [69]
The chamber differentiation then occurs between day 27-37 and can be divided into four parts beginning with the development of aortic arches. There are originally 6 paired branchial arches developed. They form at different times and regress in a complex way. The first ones develops further to become vessels in the face and carotid arteries. Only the 6th remains complete as *the* aortic arch. Interruptions here can result in a vascular ring compressing the trachea, like double aortic arch, right aortic arch with left ligamentum arteriosum or pulmonary artery sling (aberrant left pulmonary artery arising from the superior surface of the right pulmonary artery and coursing between the trachea and esophagus).[69]
The second stage is the development of the muscular part of the inter-ventricular septum that grows from the bottom (apex) to the top where the last part is constituted of the perimembranous septum. Naturally defects here results in muscular VSD's or perimembranous VSD's.

The third stage is the development of the intra-atrial septum that grows from both sides (septum primum) leaving a patent foramen ovale (PFO) open in the middle. A second septum, septum secundum is then growing down to the right of the septum primum. The secundum part does not cover the foramen ovale during fetal life, because it is important that the PFO remains open until after birth.[66, 68]
Lastly the septation of the outflow vessel is completed between day 35-42.[66, 68] The outflow septation from one into two, is formed as a spiral and if something goes wrong here, the result can be a common arterial trunk (truncus arteriousus), aorto-pulmonary window (A-Pw), transposition of the great arteries (the outflow wall is growing straight in stead of spiral formed, causing parallel outflows), tetralogy of Fallot (the wall is shifted rightwards) or hypoplastic left heart syndrome (HLHS), where the wall is shifted leftwards. Note that for HLHS the etiology is not clear, the primary problem could be a mitral stenosis/atresia supporting the "no flow, no grow" theory or a restrictive PFO.[1] The septation is completed between day 49-53. Incomplete septation can also result in atrio-ventricular septal defect (AVSD) with or without outflow defects.
The conducting system develops from day 35 to birth and the coronary circulation between day 48-51. Innervation of the heart takes place from day 49 to birth. Formation of the AV-valves occurs by excavation and cushions in the ventricles and semilunar valves of excavations and growth in the pulmonary artery and aorta. Incomplete formation of the valves can result in Ebstein anomaly, stenosis or atretic valves.
The cells forming the heart origins from different structures. The primary heart field is the original "tube" and the secondary heart field, a little bit further away and "behind", contributing to the right ventricle outflow tract, atria, pulmonary veins, sinus venousus, conducting system and sinus node.[70] Neural tube cells from the brain is migrating downwards, contributing to the development of the aortic arches (face, aorta, carotid vessels, pulmonary artery) and cells from the liver results in the epicardium and coronary arteries.[3, 70]
This overview is brief and is not meant to cover all possible defects, but rather give an understanding about different heart lesions.

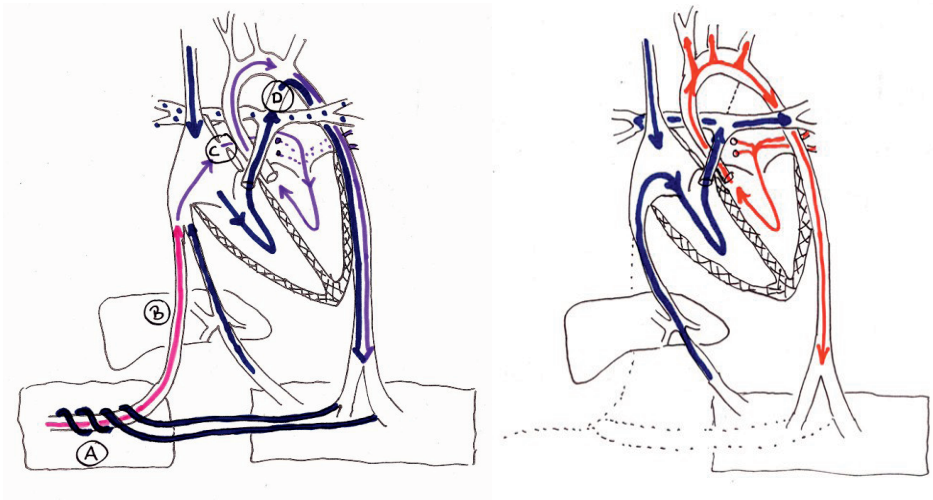


Figure 5. Schematic pictures showing the normal fetal circulation to the left and the normal postnatal circulation, with closed fetal connections, to the right.

Fetal circulation is different from the circulation after birth, figure 5. There are four shunts enabling the circulation during fetal life: the placenta (A), Ductus Venosus (B), the Patent Foramen Ovale (C) and the Patent Ductus Arteriousus (D). To make it simple, the fetus is not using the lungs for oxygenating the blood, so only a small part (about 10%) of the blood during fetal life reaches the lungs,[2] instead the placenta is oxygenating the fetal blood. Since the fetus is not "using" the lungs, they need to be partially bypassed and that is done by the fetal connections: the ductus arteriousus (PDA) and the patent foramen ovale (PFO). When the intra-atrial septum develops, the wall grows from the two opposite sites. During fetal life however it is important that the intra-atrial wall maintains open. When fetal blood enters the right atrium, the Eustachian valve directs the blood through the PFO and enables the blood to take a shortcut and bypass the lungs to go directly to the left atrium, through the left ventricle and aorta, supplying the upper part of the body with the best oxygenated blood. A large part of the blood returning from the superior vena cava that does not pass through the PFO, continues through the right ventricle and main pulmonary artery. Instead of continuing to the lungs via left and right pulmonary artery, the open PDA allows the blood to bypass the lungs and instead distributes blood directly to the descending aorta, sending the blood with the lower saturations to the lower part of the body. The fetal blood gets oxygenated in the placenta. The placenta collects deoxygenated blood from the fetus and is delivering oxygenated blood via the vein in the umbilical cord. The Ductus Venosus is the last shunt completing the fetal circulation, routing blood from the umbilical vein past the liver. The umbilical cord normally contains three vessels, two arteries and one vein. After birth when the baby starts breathing with

its lungs, the process of closing the fetal connections begin. The middle parts of the intra-atrial wall start coming together due to the increased pressure in the left atrium and the PDA starts to close. Clamping the umbilical cord puts en end to the blood flow through the ductus venosus. A picture of normal post-natal circulation with closed fetal connections is shown in figure 5 to the right. Echocardiographic studies have shown that the PDA is closed in <10% of full-term newborns at 12 hours of age, in about 50% at 24 hours and in 81% of newborns at 48 hours of age.[71-73] Our own echocardiographic study (paper I) confirms these results, showing that almost all of the 200 normal newborn babies had a PFO and 58% had an open PDA at a median age of 24 hours (range 12 to 48 hours).[74]

Duct-dependent Congenital Heart Disease

Being born with a life-threatening condition such as a duct-dependent heart lesion is a challenge from the beginning. During fetal life most of them grow adequately and maintain their circulation to all parts of the body due to their ductus arteriousus (PDA) and patent foramen ovale (PFO) bypassing the obstruction. Depending on what type of duct-dependent lesion the fetus has, the circulation looks different. The common denominator is that all these babies need to maintain their PDA open even after birth to survive. It is paramount that these babies are diagnosed as early as possible and before the fetal connections have closed too much. When diagnosed, prostaglandin E1is given to them to maintain the PDA open until surgery. For example, a fetus with a left heart obstructive disease (LHOD) such as hypoplastic left heart syndrome (HLHS; including aortic atresia, hypoplastic left ventricle, mitral hypoplasia or atresia and hypoplastic ascending aorta) maintains adequate circulation in utero because the PDA delivers sufficient blood so that one part of the blood goes “backwards” up in the transverse aortic arch to ensure blood circulation to the upper part of the body and down the ascending aorta retrograde all the way to the coronary arteries, see Figure 6A. Since there is no way through the left ventricle, the shunting direction through the PFO is left-to-right. Other examples of *duct-dependent systemic* circulation are critical aortic stenosis (AS), interrupted aortic arch (IAA) and severe coarctation of the aorta (CoA), all classified as LHOD in paper I.

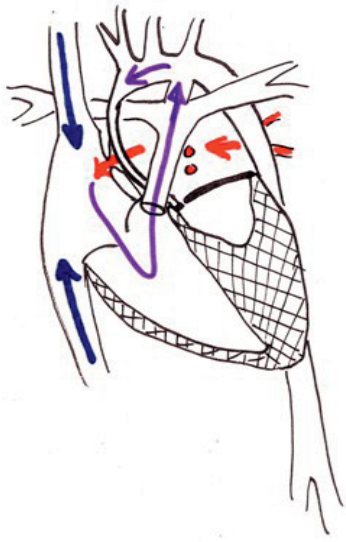


Figure 6A

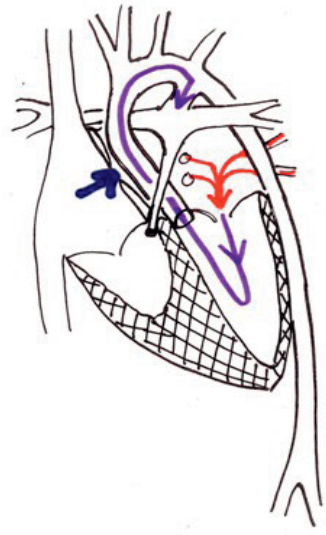


Figure 6B

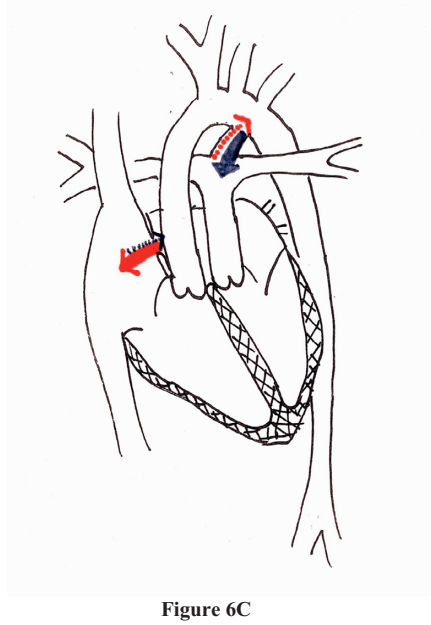


Figure 6C

Figure 6A. Duct-dependent systemic circulation. The blood through the PDA is shunting right-to-left and through the PFO left-to-right. A schematic picture of a HLHS with mitral atresia/severe hypoplasia, aortic atresia/severe stenosis, hypoplastic left ventricle, hypoplastic ascending aorta.
Figure 6B. Duct-dependent pulmonary circulation A schematic picture of a Pulmonary Atresia (PA). The blood through the PDA is shunting left-to-right, and through the PFO right-to-left.
Figure 6C. Duct-dependent mixing circulation.The blood through the PDA is bi-directional with large left-to-right shunt and a small right-to-left shunt. The blood througt the PDA is also bi-directional, with a large left-to-right shunt and a small right-to-left shunt. A schematic picture of a TGA with parallel great arteries with aorta from the right ventricle and main pulmonary artery from the left ventricle.

A cyanotic fetus with for example transposition of the great arteries (TGA), has the pulmonary artery going from the *left* ventricle and the aorta going from the *right* ventricle, in other words two parallel circulations instead of one serial circulation. As long as the fetal connections are patent, they provide the only possibility to connect the two circuits and maintain oxygenation. When born, the baby gets desaturated, as the aorta with the aortic arch providing the blood to both upper and lower part of the body goes from the right side of the heart and thus receives systemic venous blood. The left ventricle on the other hand, is connected to the main pulmonary artery, branching into the left and right pulmonary arteries, going to the lungs. The lungs oxygenate the blood and through the four pulmonary veins the blood enters the left atrium and then into the left ventricle. Thus the oxygenated blood only travels between the left side of the heart and the lungs unless mixing occurs across the PDA and the PFO. At the same time the deoxygenated blood travels between the right side of the heart and the rest of the body without getting oxygenated at all, see Figure 6C. TGA is an example of *duct-dependent pulmonary/mixing* circulation whereas pulmonary atresia has a duct-dependent pulmonary circulation, as shown in Figure 6B. Both however, result in profound arterial desaturation. Since some babies are born with combinations of cardiac malformations, a TGA combined with pulmonary atresia (PA) is classified as having a *duct-dependent pulmonary* circulation but a TGA combined with a CoA and VSD is classified as having a *duct-dependent systemic+mixing* circulation. A baby with TGA and a large VSD is on the other hand not duct-dependent, as mixing occurs across the VSD.

Critical Congenital Heart Disease

All babies with duct-dependent circulation are included in this group. But a baby can have a life-threatening heart defect and not being defined as duct-dependent. The definition of a critical congenital heart disease/defect (CCHD) is not straightforward and usage of the term is not uniform. *Liske et al.* uses the words "paediatric cardiologists commonly defines" CCHD as a condition that either is duct-dependent or requires surgery or intervention during the *first* month of life to survive,[75] as did *Rosati et al.*[76] and *Koppel et al.*[9]
Mellander and Sunnegårdh uses the definition of critical as "a heart defect that most likely would have caused circulatory collapse or death if surgery or catheter intervention had not been performed before 2 months of age".[11] *Wren et al*. used a time period before death/surgery/intervention of 28 days[10] for "pragmatic reasons", but clearly stated in their previous reports that two babies with critical aortic

stenosis died at 2 month of age.[13] *Sendelbach et al*.[4] defined CCHD by listing diagnoses, not severity or time before death or intervention and included tetralogy of Fallot, pulmonary atresia, truncus arteriosus, transposition of the great arteries, total anomalous pulmonary venous return and tricuspid atresia in the cyanotic group and coarctation of the aorta, critical aortic stenosis, interrupted aortic arch and hypoplastic left heart syndrome in the LHOD-group. In paper I, since *Mellander and Sunnegårdh* used the same referral regions to gather infants as in our CCHD-group, we adopted their definition. In paper III however, we wanted to use a clear-cut definition (since other screening papers have lacked clear statements of their definition of "critical" or the time period)[9, 15] of the congenital heart defects, and to avoid any qualitative judgements. Examples of other critical, but not duct-dependent defects are infracardiac total anomalous pulmonary venous return, severe tetralogy of Fallot (ToF), truncus arteriousus and some cases of double inlet left ventricle (DILV) and double outlet right ventricle (DORV). The judgement as to whether a patient with ToF is severe enough to need surgery before two months of age is however a qualitative one, and we wanted to avoid subjective assessments in our classification for the screening paper (III).

Background of saturation screening in Congenital Heart Disease

A new potential application for pulse oximetry was proposed in 2002-2003. Four studies about screening newborns with pulse oximetry, in order to detect congenital heart disease were published.[8, 9, 15, 16] The reason was concern about reports of newborn babies with critical congenital heart disease (CCHD) leaving hospital without a diagnosis.[11, 12, 77] The neonatal physical examination alone is not sensitive enough to detect these lethal conditions. Of babies that died from congenital heart disease, studies have shown that 10-30% died before diagnosis.[13, 78] Failure to diagnose duct-dependent congenital heart defects leads at worst to death or circulatory collapse with so severe brain injuries that the surgeons have to turn down surgery as an option. At best the collapse leads to expensive neonatal intensive care costs to stabilize the baby before the life saving surgery can be offered. Then additional costs are expected in some due to the possible long term neurological morbidity. The idea of introducing pulse oximetry screening in the newborn nurseries to improve the early detection of critical CHD occurred independently to many researchers.

Hoke et al. used a Nellcor N-50 (Conventional Technology oximeter) calibrated for functional saturation. Cut-off was 7% lower in foot (post-ductal site) than right hand (pre-ductal site) or <92% in foot. In the screening part (at 6 hours, 24 hours and discharge) 2908 babies were included and 4 had CCHD. In the case-part 32 babies referred with CCHD was included, 5 was not detectible by saturation screening (2 with pulmonary stenosis (PS), one with double inlet left ventricle (DILV), one with valvular aortic stenosis (AS) and one interrupted aortic arch (IAA) and choanal atresia).[15] No estimates of missed cases dying in the community.

Richmond et al. used a Radiometer Oxi machine (Conventional Technology oximeter) calibrated for fractional saturation (gives about 2% lower values than functional saturation). Cut-off was <95% (two repeated readings). 5626 babies were screened and 6 were screening positive. Three of six coarctations (CoA) were not detected by the screening.[8]

Reich et al. used a Nellcor N-395 (New Generation oximeter) calibrated for functional saturation. Cut-off was <95% (three repeated times or one <90% or >4% difference between pre- and postductal sites). 2114 babies were screened, 2 CCHD-babies were detected and one with Total Anomalous Pulmonary Venous Return (TAPVR) missed.[16] No estimates of undiagnosed cases dying in the community.

Koppel et al. did not even state what oximeter they used. Cut off was <96% at 24 hours of life. 11 281 babies were screened, 3 detected and 2 missed (one CoA and one with hypoplastic left pulmonary artery (LPA) and aorto-pulmonary collaterals.[9] Knowing that the incidence of life-threatening congenital heart disease is 1-2 per 1000 live-borns,[5, 8-10] these four studies all lacked the proper size to estimate the sensitivity of a screening programme, and none included any unscreened control populations.

This research project (paper I-IV) was undertaken in order to establish the "true sensitivity" of a screening programme in the newborn nurseries. The thesis includes a study assessing how to optimise screening performance (I), establishing normal values of peripheral perfusion index in 10 000 newborns with a comparison with babies with critical left heart obstructive disease (II), conducting a prospective multicentre screening-study in all newborn nurseries and special nurseries in the region of West Götaland including 39 821 newborns over a 2.5 year period and comparing the outcome with all referring regions not using pulse oximetry screening (III) and lastly a study to highlight clinically important differences between pulse-oximetry readings and arterial blood-gas saturations in cyanosed children (IV).
During the work with this thesis, the literature in this field has expanded. Several other screening studies were conducted, using conventional pulse oximeters (*Arlettaz,* 2006),[79] fractional saturation (*Bakr* 2005),[80] or not stated what pulse oximeter used (*Rosati,* 2005).[76] No single screening study large enough to estimate

sensitivity and false positive rate was published. Only two of these studies ascertained missed cases dying in the community.[8, 9]

Lacking a large enough screening study, *Thangaratinam et al.* (2007)[81] rewieved 8 studies[8, 9, 15, 16, 74, 76, 79, 80] (excluding 6 for insufficient methodological quality) that included 35 960 screened newborns and conducted a summary calculation giving estimated sensitivity of 63% for diagnosing congenital heart disease using <95% as cut-off. However, this calculation ignores that 6 of 8 screened for critical CHD, the other two for all CHD in asymptomatic newborns, so they should not be amalgamated. *Valmari* rewieved 10 studies[8, 9, 15, 16, 76, 79, 80, 82, 83] (7 studies, 2 abstracts and one unpublished Finnish study: "Lapland Central Hospital" with 4354 children) and gathered 44 969 newborns and stated an overall sensitivity of screening in serious CHD of 72% compared to the sensitivity of 58% after the clinical examination.[38] In his rewiew 5 papers used oximeters calibrated for fractional saturation[8, 9, 82] (plus the Lapland Central Hospital unpublished study), 4 calibrated for functional saturation[15, 16, 79, 83] and one had not stated type of pulse oximeter.[76] The variety of oximeters used (conventional vs new-generation / functional vs fractional), and variety of cut-off limits and probe sites (pre- or postductal) make comparisons hard to make, and adding these studies together for meta-analysis is highly questionable. A member of the Tennessee state legislature proposed a bill that would mandate all newborns to a screening programme to detect CHD before discharge. The Tennessee Task Force on Screening Newborns for Critical Congenital Heart Disease was formed in 2005. The group gathered data from the literature and the Tennessee Department of Health and debated pro and cons for a state-wide screening programme. Four studies were rewieved.[8, 9, 15, 16] A meaningful cost/benefit analysis could not be performed so *Liske et al.* concluded to recommend against mandatory screening at that time, but urged the need for a very large prospective study to define the sensitivity and false-positive rate.[75] The need for a large enough prospective screening studies has also been proposed from others.[7, 11, 38, 81, 84-87] After we submitted paper III one further large screening study was published. A Norwegian multi-centre study by *Meberg et al*. screened 50 008 babies with the same NGoxi and sensors as we used (Version 5 though). They only screened post-ductally with a cut-off <95% repeated twice the first day of life. They reported a sensitivity of 77.1% for CCHD and combined with physical examination it reached 83.6%. They "were not aware" of any undiagnosed deaths in the community in their study, however their study did not contain an unscreened control population. *Wren et al.* who carefully ascertained undiagnosed deaths reported 4.4 undiagnosed deaths per 100 000 live born in unscreened populations.[10]
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Aims

The aims of the studies were:

Paper I

To define a saturation screening cut-off by comparing normal newborns with newborns with critical congenital heart disease. All babies in the newborn nurseries had an echocardiographic examination to verify normal intracardiac anatomy. Two different handheld pulse oximeters calibrated for functional saturation were used in order to compare performance; a conventional technology oximeter (CToxi) and a new generation oximeter (NGoxi).
Inter- and intra-observer variability was calculated in a broad saturation span.

Paper II

To define normal peripheral perfusion index (PPI) values pre- and post-ductally in newborns between one and 120 hours of age, and compare with PPI-values from newborns with critical left heart obstructive disease.

Paper III

To implement a mandatory prospective screening study in all newborn nurseries and special nurseries in the West Götaland Region (WGR) and test the defined screening cut-offs from (I) in a large enough cohort. Our aims were
(1) To identify the diagnostic accuracy of pulse oximetry screening for duct-dependent circulation with a new-generation pulse oximeter and comparing the detection-rate of duct-dependent circulation in a blind neonatal physical examination with that of pulse oximetry plus neonatal physical examination.
(2) To estimate the excess number of neonatal cardiac ultrasound investigations generated by a screening programme compared with neonatal physical examination as currently performed.
(3) Comparing the overall cohort detection (well-baby nurseries plus neonatal special care units) of babies with duct-dependent circulation in WGR versus all other referring regions (ORR) not screening newborns, that refer children to the Queen Silvia Children's Hospital, Gothenburg.
(4) Comparing undiagnosed sudden deaths due to duct-dependent circulation in the community in West Götaland Region versus those in other referring regions during the study period.
(5) Our last aim in this study was to make a cost-benefit analysis of this screening programme.

Paper IV
To compare the saturation readings (SpO_2) from our equipment in the paediatric cardiac ward at Queen Silvia Children's Hospital (CToxi) and Signal Extraction Technology (NGoxi) with simultaneous blood gas analysis (SaO_2) in spontaneously breathing children with cyanotic congenital heart disease.

Material and Methods

Paper I

Subjects
Reference-group 200 full-term babies in the "well-baby" nurseries (wards 310 and 311) at The Sahlgrenska University Hospital/Östra, Gothenburg, were recruited between January 2002 and April 2003. Male/female ratio was 103/97 (0.52). Median age was 24 hours (range 12 to 48 hours). Eighty-seven per cent of the babies were Caucasian.

Critical Congenital Heart Disease (CCHD) group 66 infants with cyanotic or duct-dependent heart disease admitted to the Queen Silvia Children's Hospital, prospectively included between January 2002 and April 2004. Male/female ratio was 44/22 (0.67). Median age was 3 days (range 10 hours to 45 days).

Pilot study
In order to find optimal age for screening we first conducted a pilot study on 20 newborns (with echocardiographically normal heart, but patent foramen ovale). They were followed and studied between 2 and 48 hours of age with repeated saturation measurements every 4th hour between 8 am and 10 pm. An initial saturation reading <95% were seen in 9/20, but seven of the nine infants were above 95% on the first repeated measurement (about 4 hours later). All of them were above 95% after ≤ 12 hours of age, therefore the reference-group was measured from 12 hours of age.

Equipment
CToxi: Datex-Ohmeda TuffSat (Datex-Ohmeda Division Instrumentation Corporation, Helsinki, Finland) with a Flex II sensor. Average time ≤12 seconds from start (and ≤10 seconds when already on),[34] see Figure 7.

NGoxi: Radical SET version 3 (Masimo Corporation, Irvine, CA, USA) with LNOP-Neo sensors. Average time set on 8 seconds, see Figure 7.

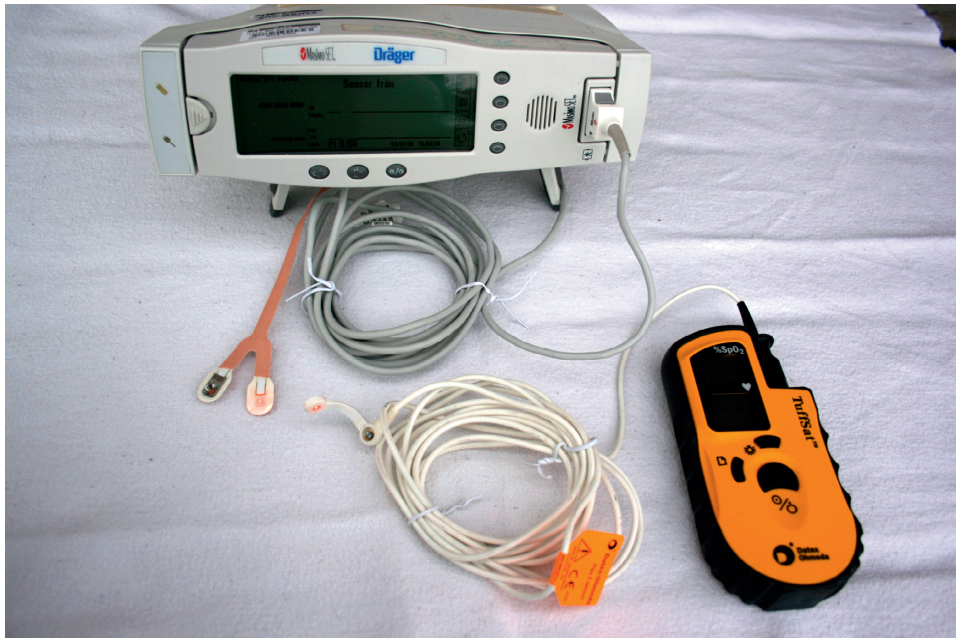

Figure 7. On top the Radical SET with LNOP-Neo sensor and bottom right the TuffSat with Flex II-sensor. The LED are red in the picture. The posey wraps used to attach the sensors and shield them from ambient light are not displayed on this picture.

Method

The measurements were carried out both pre-ductally (palm of right hand) and post-ductally (either foot) with both NGoxi and CToxi and before the neonatal physical examination. Both oximeters were attached at the same time, one pre-ductally and the other post-ductally in random orders. As soon as the saturations were achieved the position of the oximeter were swopped, thus all readings were obtained simultaneously.

In order to assess peripheral circulation, the capillary refill time (CRT) were documented by measuring the time for the color to return to normal after compressing (and emptying the capillary bed) of a finger and toe.[62] CRT < 2 seconds, 2-3 seconds or > 3 seconds were stated as well as activity state of the newborn at measurement (asleep, calm, fussy, feeding or upset).

When saturation measurements were done, a complete echocardiographic evaluation (2D and colour-Doppler) of the heart was performed to ensure that the reference-group was constituted of anatomically normal hearts. As expected the

patent foramen ovale was open in almost all babies and 116/200 had a small patent ductus arteriousus. All measurements (saturations and echoes) were obtained by one single observer (AWG).

Since the *CCHD-group* included babies that were already diagnosed, 52/66 received prostaglandin infusion. Five patients had complex heart disease but were not defined as duct-dependent. The diagnoses are listed in Table 1, page 46. All saturation measurements were performed prior to surgery as described above for the reference group. In the 19 babies with an arterial line in the right radial artery, the measurement was obtained from the right ear instead. Using the NGoxi we obtained recordings in all CCHD patients, but with the CToxi satisfactory recordings were obtained in only 50 of the 66 babies.

Assessing agreement

Since the whole study was conducted by one single person we also needed to assess if the method was operator-dependent. In the context of screening, a method needs to be easy to perform by all users. Since the results with the CToxi were poor, we decided to only assess variability with NGoxi. Inter- and intra-observer variability was studied according to Bland and Altman[88] by comparing AWG with 44 different observers (they had never previously used the equipment), either parents (n=30) or staff at the paediatric cardiology ward at the Queen Silvia Children's hospital (n=14). They were only given brief instructions beforehand. Intra-observer variability was assessed by two recordings on the same patient (n=48). To make sure that the assessment would represent the saturation-ranges in the CCHD-group, 45/92 readings were obtained from children with cyanotic heart disease with a median saturation of 88% (range 74% to 94%).

Paper II

Subjects

Reference group 10 000 newborns were consecutively recruited from our ongoing prospective multicentre screening study (for details, see paper III) in the West Götaland Region (WGR), see Figure 8 (the purple region). All newborn nurseries and special nurseries in WGR participated; Göteborg, Mölndal, Borås, Skövde and Trollhättan accounting for 25%, 26%, 8%, 15%, and 26% of the total participating newborns respectively. Median age was 42 hours (range 1 to 310 hours).

Left Heart Obstructive Disease comparison group (LHOD group) Nine newborns with duct-dependent systemic circulation (19 to 120 hours of age) were defined as the LHOD-group. Four with coarctation of the aorta (CoA), two with interrupted aortic arch (IAA), two with hypoplastic left heart syndrome (HLHS) and one with critical aortic stenosis (AS).

Equipment
The NGoxi used were Radical SET, version 4 (Masimo Corporation, Irvine, CA, USA) with multisite LNOP YI-sensors. The average time set on 8 seconds. All oximeters were locked by a key-code to ensure unchanged settings through the study period.

Method
A single PPI value was recorded at the same time as the saturation value (as soon as the signal was free from artefact), both pre- and postductally. Thus each PPI value had a simultaneous corresponding SpO_2 value and vice versa.

Paper III

Pre-study logistics and considerations
To ensure uniform operating conditions all pulse oximeters were set up identically and the settings were locked by one person (AWG). Information about the study was given to all prenatal care centres (Mödravårdscentraler; MVC) in West Götaland Region (WGR). It included a poster at each MVC and handout of parental information (in Swedish or English) to every parent to be, at the last scheduled check-up at MVC before delivery. The same information was also posted and available at every newborn nursery and special nursery ward (n=11) in WGR including Östra, Mölndal, Borås, Skövde and Trollhättan. Information to personnel was presented before the study started, halfway through the study period and after the study ended (including preliminary and final results) both orally and written with an opportunity to directly contact AWG or IÖS for further information. The participating personnel included: all midwifes, nurses and nursery nurses carrying out the saturation measurements, all neonatologists/physicians performing the discharge physical examinations in WGR, all clinical physiologists/paediatric cardiologists performing the echocardiograms on screening positives, all personnel in the delivery units (in case of early discharge before admittance to newborn nurseries) and medical engineers handling the pulse oximeters at each participating hospital. Education about the screening performance and blind neonatal protocol procedure were given by the same instructor (AWG) to all participants for one week (day-time) before the study started up at each unit to reach staff on rotating schedules. All protocols were blue (to avoid being mixed with other papers) and named with the birth hospital name. The protocols were distributed by AWG personally or by the WGR internal postal service. All protocols were returned weekly to AWG by the internal postal service and to avoid writing the wrong address all envelopes were posted with a pre-written self adhering return address to AWG.

In a meeting with all co-authors before the study started, we discussed the different routines at the five participating nurseries in WGR. We realised that the screening test might be carried out more than ten hours before the discharge examination and decided that withholding information about saturation values below 90% would not be ethical. Therefore we decided to exclude optimal quality measurements ≤90% from the blind procedure and immediately inform the physician. Instead of repeating the measurement, all babies with a saturation ≤90% were classified as test positive directly and referred for an echocardiogram the same day.

Subjects

Study population 39 899 babies were eligible for the screening study in WGR. 13 455 from SU/Östra Hospital (200 babies between July 1st and September 5th 2004 from the pilot period and 13 255 between September 6th 2004 and March 31st 2007), 8 953 from SU/Mölndal Hospital (between September 20th 2004 and March 31st 2007), 5 382 from Borås Hospital (between September 27th 2004 and March 31st 2007), 5 090 from Skövde Hospital (between October 25th 2004 and March 31st 2007) and 7 019 from Trollhättan Hospital (between November 8th 2004 and March 31st 2007).

Exclusion criteria from saturation screening were children already admitted to neonatal special care units. 39 821 babies (99.8%) had complete data from saturation screening filled in and 38 429 (96.3%) had complete data from both saturation screening and neonatal physical examination filled in. Most of the empty neonatal part of the protocol was from the early start-up period, probably due to the new routine.

29 of the screened babies had duct-dependent circulation (DDC). Median age at screening was 38 hours, inter-quartile range 5.5 to 95.5 (range 1 to 406 hours). Earliest discharge was 6 hours in WGR and 3.3% of the babies were screened that early. 90% of the babies were screened ≤72 hours of age. 13.4% of the babies were delivered with caesarean section in WGR during the study period.

Cohort population In West Götaland Region 46 963 babies were born between July 1st 2004 and March 31st 2007. 62 babies were born with duct-dependent circulation during that period, but two were excluded due to prenatal diagnosis, so the WGR cohort included 60 babies with DDC. The comparison cohort from all other referring regions not screening newborns was defined as all babies born between January 1st 2004 and December 31st 2007. The reason for different time interval was that we were not able to obtain correct birth numbers per month through official statistics, therefore we were forced to use full 12 month periods. During the study period the referring regions changed. “Norrland” (the northern part of Sweden) was included as a referring region to the Queen Silvia Children’s Hospital

as of January 1st 2006 and accordingly included during 2006 and 2007 (see Figure 8, the dark green area). In ORR there were 108 604 live births during the period and 109 had DDC. Nine were excluded due to prenatal diagnosis, so the ORR cohort included 100 babies with DDC.

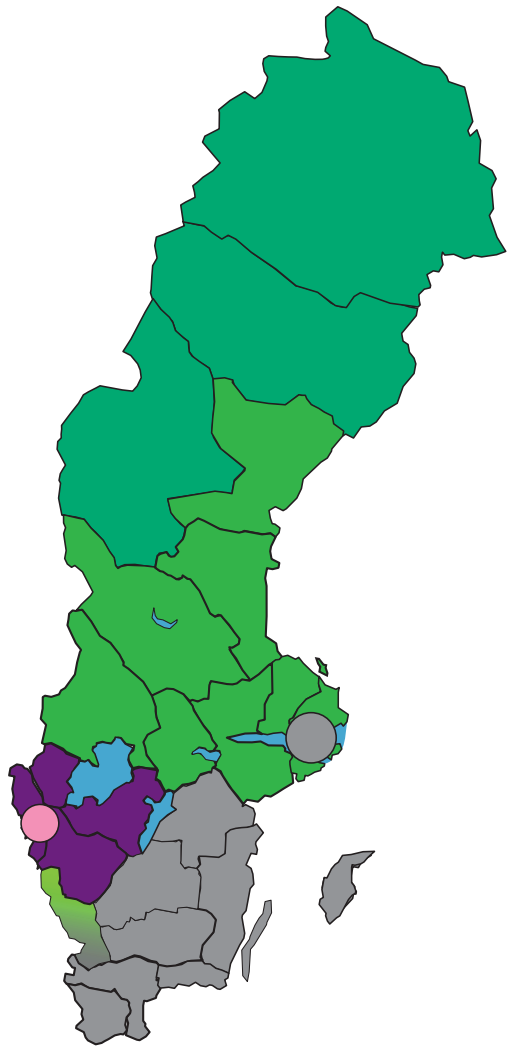

Figure 8. Map of Sweden. West Götaland Region (WGR) in purple, with Göteborg marked with a light circle. The Other Referring Regions (ORR) in green. Light green indicates referring regions 2004-2007 and dark green area indicates "Norrland" added as a referring region 2006-2007. Areas in grey (with Stockholm marked with a grey circle) are referring children to Lund for paediatric cardiac sugery.

Equipment

The new generation oximeters used were Radical SET, version 4 (Masimo Corporation, Irvine, CA, USA) with multisite LNOP-YI sensors. The average time was set on 8 seconds.

Prospective Screening Study

All delivery hospitals in WGR participated (Östra, Mölndal, Borås, Skövde and Trollhättan). Prospective pre- and postductal screening (palm of right hand and sole of either foot) were carried out with identical set and locked pulse oximeters before the routine neonatal physical examination. Age, sex, delivery mode (caesarean section/vaginal), technical quality of measurement (optimal/not optimal) were recorded.

The cut-off values from paper I were used but we introduced repeated measurements (to lower the false positive rate) as described by both *Richmond* [8] and *Reich*[16]. When both pre- and postductal saturation were <95% or the pre-to-postductal difference was more than $\pm$3% (= >2 standard deviations of the inter-observer measurement variability we had documented in paper I) a repeat measurement was done. Three repeated positive measurements or a single saturation of 90% or below (and of optimal measurement quality) was defined as screening positive. All screening positives were referred for an echocardiogram the same day.

Since we needed a blind comparison between the methods to know the "normal" referring frequency to cardiac clinic after routine neonatal physical examination (to compare false positive rates), all saturation measurements were performed before the NPE. The saturation protocols were then sealed until after the routine neonatal physical examination. Before un-sealing the saturation results, the paediatrician had to fill in a protocol stating 1= no suspicion of congenital heart defect, 2= weak suspicion of congenital heart disease or 3= strong evidence of congenital heart defect and then state Yes/No as to whether a referral of the baby for neonatal cardiac ultrasound was indicated based on the physical findings.

Cohort comparison study

This part constituted of a comparison of detected duct-dependent circulation in the cohort population in West Götaland Region versus detected duct-dependent circulation in the cohort from other referring regions. Data were retrospectively retrieved from logbook over children turned down for surgery, the surgical and catheter-procedure records and deaths in the community (data from Rattsbase, the National data base of the National Board of Forensic Medicine, reviewing all undiagnosed deaths of cardiovascular malformations in children under 1 year of age in Sweden). The cases we found all occurred within 30 days from birth. We

also contacted all referring hospitals and asked them specifically to detail children that had died in hospital before being referred or been declined referral.
Medical records of all babies with duct-dependent circulation in the two cohort populations were examined to compare pre-operative acidosis, 30 day mortality after surgery and undiagnosed sudden deaths in the community.

Cost benefit analysis
We based our cost analysis on the model in the study "Comparing the clinical and economical effects of clinical examination, pulse oximetry, and echocardiography in newborn screening for congenital heart defects: A probabilistic cost-effectiveness model and value of information analysis" published 2007 in the International Journal of Technology Assessment in Health by *Griebsch et al.* [85] This paper had worked out detailed cost-estimates based on British Health Service costs.

Paper IV

Study design: Clinical observational study.

Subjects
56 consecutively recruited children with congenital heart defects and an arterial line present, scheduled for blood-gas analysis and admitted to the Queen Silvia Children's Hospital. Median age was 15 days (range 1 day to 10 years).

Equipment
Hemioximeter (Arterial blood-gas analysis): ABL 725 (Radiometer, Copenhagen, Denmark).
New-generation oximeter (NGoxi): Radical SET, version 4, average time set on 8 seconds with multisite LNOP YI-sensors (Masimo Corp. Irvine, CA, USA).
Conventional technology oximeters (CToxi): HP M1205A Virida, average time set on 10 seconds, with M1193A sensors, n=41 (Hewlett-Packard, Andover, MA, USA). Datex-Ohmeda S/5, average time 10 seconds, with OxyTip+ wrap MultiSite sensors, n=13 (Datex-Ohmeda, Finland/GE Healthcare) other CToxi n=2 (Datascope Accutorr Plus and Datex-Ohmeda Biox 3740).

Method
Measurements with NGoxi, CToxi and arterial blood-gas saturation were obtained simultaneously under optimal measuring conditions to compare saturation readings with the hemioximeter golden standard for both NGoxi and CToxi. A pulse-

oximetry reading (SpO_2) ≤7% from the ABL saturation (SaO_2) was defined as clinically acceptable according to *Barker's* definition.[40, 89] The NGoxi sensor was placed on the same side of the ductus arteriousus (PDA) as the CToxi. When the readings were of optimal quality and stable, the arterial blood-gas sample was drawn. Two persons were in eye-contact with one monitor each during the time the syringe was filled. All blood samples were analyzed within 2-10 minutes.

Statistical Methods

Paper I: *Screening for duct-dependent congenital heart disease with pulse oximetry: A critical evaluation of strategies to maximise sensitivity*

Mann-Whitney U-test for comparing the groups.
Fisher's exact two-tailed test for comparing the groups.
Kolmogorov-Smirnov test for assessing distribution fitting.
ROC-curves for assessing optimal cut-off for screening.
Bland and Altman's method for assessing agreement[88] (inter- and intra-observer variability).
Box- and Whisker plots were used to display the saturation results.
Odds ratios for comparing proportions of test-positives and test-negatives.

Paper II: *Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction*

Kolmogorov-Smirnov test for assessing distribution fitting.
Two-tailed Fisher´s exact test for comparing proportions.
Box- and Whisker plots were used to display the PPI results.
Odds ratios for comparing proportions of test-positives and test-negatives.

Paper III: *Impact of pulse-oximetry screening on the detection of duct-dependent congenital heart disease: a Swedish prospective screening study in 39 821 newborns*

Two-tailed Fisher´s exact test for comparing proportions (small numbers).
Chi-square test for comparing proportions (larger numbers).
Relative risk for comparing proportions (except when no patient in the group had an adverse outcome, see below).
Odds ratios for comparing proportions (when relative risk could not be employed, see above).
Motulsky's[90] method of calculating confidence limits for population mortality as the confidence intervals of proportions.

Paper IV: *Important inaccuracies in pulse-oximetry readings in cyanosed children.*

Altman and Bland's method[91] for assessing agreement as plotting versus the line of unity (when comparing with a calibration method).
Fisher´s exact test for comparing proportions of readings outside clinically acceptable range.
The non-linear regression curve fit for saturation versus arterial pO_2 was carried out with a polynomial fourth order equation (because the Hb molecule has four binding sites for O_2-molecules).

Ethics

Ethical approval was obtained for Paper I – III. The last study, paper IV, was a clinical observational study, therefore ethical approval was not required. The results from paper IV showed a poor agreement between the saturation equipment present at the paediatric cardiac ward (CToxi) and arterial blood-gas. As a consequence of our findings, all conventional technology oximeters (CToxi) at the cardiac ward have now been replaced with New-generation pulse oximeters.

Results

Paper I: *Screening for duct-dependent congenital heart disease with pulse oximetry: A critical evaluation of strategies to maximise sensitivity*

Table 1. Diagnoses in the CCHD group n=66

Predominant Cardiac lesion	n	Prostaglandin infusion	False negative < 95% foot	False negative < 95% hand+foot or diff >±3%
TGA (+complex)	18	14		
TA (+complex)	4	2	1*	
PA (+complex)	8	6		
DILV complex	3*	3		
DORV complex	2	1		
TAPVR	1	0		
ToF	1	1		
Truncus Arteriosus	1	0		
HLHS	10	10		
IAA (+complex)	6	5	1	
Crit AS (+complex)	2	2		
Simple CoA (+VSD)	6	4	4	1
CoA complex	4	4	1	

Table 1. TGA indicates transposition of the great arteries; TA, tricuspid atresia; PA, pulmonary atresia; VSD, ventricular septal defect; DILV, double inlet left ventricle; DORV, double outlet right ventricle; TAPVR, total anomalous pulmonary venous return; ToF, Tetralogy of Fallot; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; Crit AS, critical aortic stenosis; CoA, coarctation of the aorta; Complex, additional cardiac malformations; *, CoA included in the diagnosis.
(Printed with permission from Wiley-Blackwell: de-Wahl Granelli A, Mellander M, Sandberg K, Sunnegardh J, Östman-Smith I. Screening for duct-dependent congenital heart disease with pulse oximetry: A critical evaluation of strategies to maximise sensitivity. Acta Paediatrica 2005;94:1590.)

76% of the normal newborns and 73% in the CCHD-group were asleep or calm during the measurement. Capillary refill time was over 3 seconds in 65% of normal newborns and 61% of infants with CCHD. The diagnoses (predominant cardiac lesion) in the CCHD group are listed in Table 1.

Comparison between pulse-oximeters

CToxi showed significantly greater proportion of normal newborns below 95% compared with NGoxi both pre-ductally ($p<0.0001$) and post-ductally ($p<0.0001$). In 2.5% of the normal newborns the CToxi was unable to even get a signal. The poor initial results with the CToxi excluded it from being used for screening. Therefore no further analyses were made with the conventional technology pulse oximeter.

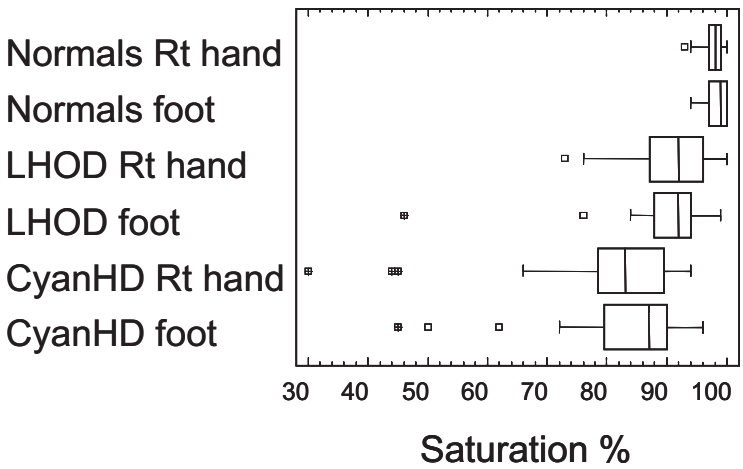

Figure 9. Saturation results with the new generation oximeter (NGoxi). Abbreviations: Rt = right; LHOD = left heart obstructive disease in the CCHD group; CyanHD = cyanotic heart disease in the CCHD group. The box-and-whisker plots indicates the median value as a line, with the box enclosing the middle two quartiles, and the whiskers indicating upper and lower quartiles. Outlier values are indicated as square dots.
(Printed with permission from Wiley-Blackwell: de-Wahl Granelli A, Mellander M, Sandberg K, Sunnegardh J, Östman-Smith I. Screening for duct-dependent congenital heart disease with pulse oximetry: A critical evaluation of strategies to maximise sensitivity. Acta Paediatrica 2005;94:1590.)

Screening Cut-Off with New-generation pulse oximeter

Saturation results with the NGoxi are shown in Figure 9. A cut-off <95% would provide optimal separation between the *reference group* and the *CCHD-group.* With only this cut-off we were however left with seven false negative CCHD patients with duct-dependent arch obstruction. In order to improve the detection of

arch-obstruction, we also studied the difference between the pre- and postductal saturation in patients with CoA (n=17) and compared them with the *reference group*. Adding hand-foot difference > ±3% as a criterion, the combined cut-off reached a sensitivity of 98.5%, a specificity of 96.0%, positive predictive value (PPV) of 89.0% and negative predictive value (NPV) of 99.5%.

Comparison with neonatal physical examination

Eleven of the babies in the CCHD-group (16.7%) had been missed on the routine neonatal physical examination and discharged home without a diagnosis. All eleven were positive on our saturation screening.

Inter- and Intra-Observer Variability with NGoxi

Measurement variability with Radical SET showed an inter-observer variability with a mean difference of 0% (SD 1.5%) and intra-observer variability with a mean difference of 0% (SD 1.3%).

Paper II: *Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction*

The measuremens were performed under optimal conditions in 96% of the babies. The difference in medians of PPI values measured under optimal versus non-optimal conditions were 0.03-0.06 and not statistically significant. Median age was 42 hours (range 1 to 310 hours).

Normal PPI-values in newborns between 1 and 120 hours of age

The Peripheral Perfusion Index (PPI) had a non-normal distribution, in concordance with *Lima et al.*[65] Median PPI (right hand) was 1.68 with inter-quartile range 1.18-2.46 (range 0.06 to 20.0). Median PPI (foot) was 1.71 with inter quartile range 1.20-2.50 (range 0.02 to 16.20). There were no significant age-related differences in PPI values between one hour and five days of age. The PPI 5th centile and 95th centile values were 0.70 and 4.50 for both right hand and for foot. PPI values of the 1st and 99th centile were 0.50 and 7.00 respectively. Normal newborn values of PPI are shown in Figure 10.

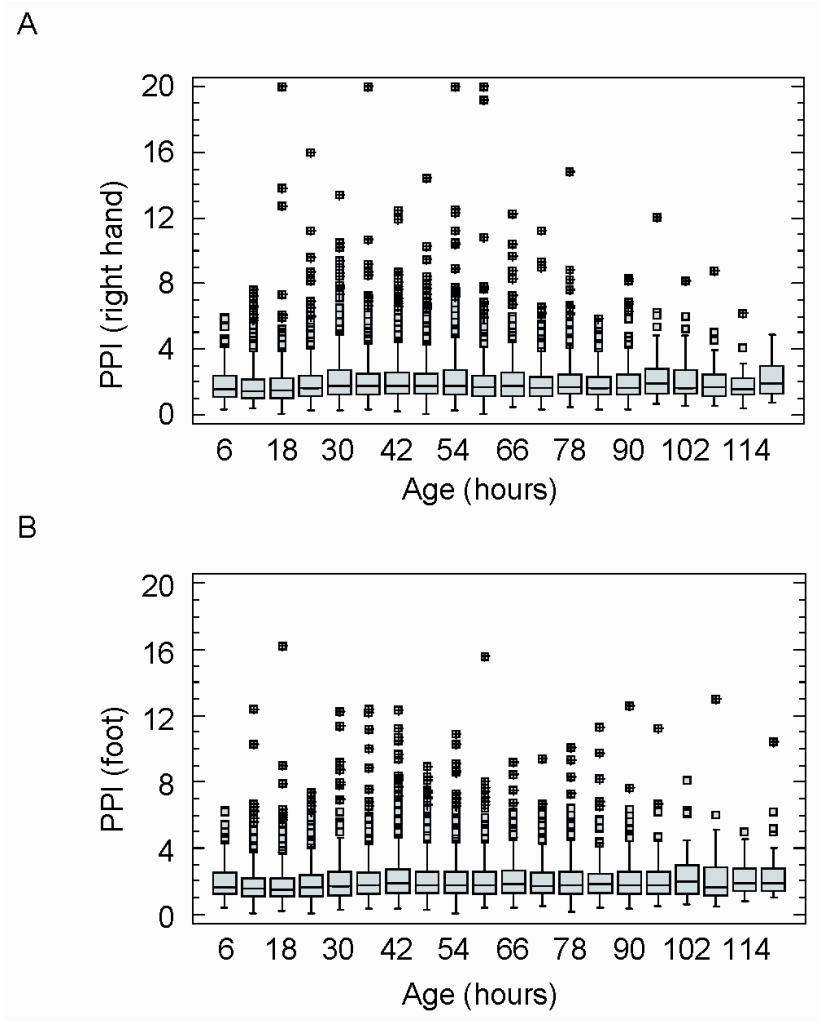

Figure 10. PPI right hand (A) and foot (B) values at the first measurement. PPI values are stratified according to age at recording, spanning from 1 to 120 h. Each box- and whisker plot represents a 6-hour age interval, the first 1-6 hours of age and so on.
(Printed with permission from Wiley-Blackwell: de-Wahl Granelli A, Östman-Smith I, Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction. Acta Paediatrica 2007;96:1455.)

PPI-values in the Left Heart Obstructive Disease (LHOD) group

In the comparison group nine newborns with LHOD contributed with 11 PPI-recordings shown in Table 2. In four of the babies with LHOD we also have information regarding whether or not neonatal physical examination (NPE) and saturation screening (POX) managed to detect the lethal heart condition. Three out

of four had been missed on neonatal clinical examination. POX detected an interrupted aortic arch with AP-window missed on NPE and NPE detected one coarctation missed on POX. Thus, combining NPE and ordinary POX-screening still failed to diagnose two out of four infants with LHOD.

Table 2. PPI values recorded in the LHOD-group.

Diagnosis	Age (hours)	PPI Right hand	PPI Foot	Test failed to diagnose lesion
IAA, AP-window	20	0.36	1.27	NPE
IAA,DILV,TGA, hypopl RV	86	0.90	0.92	
	86	0.83	0.92	NA
	87	0.77	0.43	
Critical AS, hypopl LV, hypopl aortic arch	23	0.82	1.38	NA
CoA	19	1.00	1.48	POX
CoA	44	2.28	0.17	NPE + POX
CoA*	120	1.10	0.25	NA
CoA*	96	0.37	1.23	NA
HLHS	23	0.65	2.15	NPE + POX
HLHS*	66	0.82	1.38	NA

NPE= neonatal physical examination; POX= saturation screening; NA=not applicable; [a]Prostaglandin infusion; PPI= peripheral perfusion index; IAA= interrupted aortic arch; AP-window=aorto-pulmonary window; DILV=double inlet left ventricle; TGA= transposition of the great arteries; hypopl= hypoplastic; AS=aortic stenosis; CoA=coarctation of the aorta; HLHS=hypoplastic left heart syndrome.
*Prostaglandin infusion.
(Printed with permission from Wiley-Blackwell: de-Wahl Granelli A, Östman-Smith I, Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction. Acta Paediatrica 2007;96:1455.)

Comparison between normal newborns and the LHOD-group

All infants in the LHOD-group had either pre- or postductal PPI below the interquartile range (less than 1.18). Defining the PPI cut-off value as <0.70 (values below the 5th centile), five of the babies in the LHOD-group were test-positive ($p<0.0001$, Fisher's exact test). Having a PPI value <0.70 in at least one limb, gave an odds ratio for LHOD of 23.8 (95% CI 6.4 to 88.7).

PPI hand-foot difference

The distribution of PPI hand-foot difference showed a normal distribution. Taking PPI hand minus PPI foot, the mean difference of the 10 000 values was -0.02 with a standard deviation of 1.64.

Paper III: *Impact of pulse-oximetry screening on the detection of duct-dependent congenital heart disease: a Swedish prospective screening study in 39 821 newborns*

Screening study population

The study achieved a very high compliance rate during the 2.5 year study period. Of the 39 899 eligible newborns there were only 19 refusals, 2 not screened because of staff shortages, and 18 due to pulse oximeter failure. We chose to exclude another 39 with no saturations filled in, and 1392 with NPE-findings not filled in by the neonatologist (although they did have saturation values). In total we obtained completely filled in pulse oximetry protocols in 99.8% and completely filled in protocols including both saturation screening data and neonatal protocols in 96% of the eligible babies. Due to rolling start and admissions to special care units (roughly 10% of newborns) 7064 babies were not eligible for the screening study. The birth prevalence of duct-dependent circulation in West Götaland Region (DDC) was 62/46 963 (1.32 per 1000).

Prospective Screening Study

Median pre-ductal saturation was 99% (inter-quartile range 98 to 100) in babies without critical congenital heart defect or lung pathology. Median post-ductal saturation was also 99% with the same inter-quartile range.

29 babies with DDC had remained undetected up to the time for the discharge examination and were included in the study. Their screening results and physical findings are presented in Table 3.

Results fom blind physical examination, POX-screening and the combined results are presented in Table 4. The sensitivity of NGoxi screening for DDP was 9/9 (100%) but for essentially acyanotic left heart obstruction only 10/20 (50%). NGoxi screening alone gave an abnormal result in 19/29 DDC. Due to a protocol violation one baby with IAA with two repeated positive screening results was discharged. Without this protocol violation, sensitivity would have been 65.5%.

Table 3 Details of the 29 babies in the screening study in West Götaland (1 July 2004 to 31 March 2007) who were found to have duct dependent circulation, including the results from pulse oximetry screening and physical examination

Final diagnosis	Pulse oximetry screening		Physical examination		
	Preductal/postductal oxygen saturation (%)	Test result	Murmur present (day of life)	Femoral pulses	Referral for echocardiography
Referred for urgent echocardiography according to protocol*					
TGA	47/22	+ve	No	Normal	N/A
TGA	59/59	+ve	No	Normal	N/A
TGA, PA, DILV	65/72	+ve	Yes	Normal	N/A
PA, VSD	75/84	+ve	Yes	Normal	N/A
PA, VSD	78/83	+ve	Yes	Normal	N/A
Critical AS, CoA	86/46	+ve	Yes	Very weak	N/A
TGA, DILV	85/89	+ve	Yes	Normal	N/A
Critical AS	93/80	+ve	Yes	Weak	N/A
CoA, VSD	99/86	+ve	No	Weak	N/A
TGA, CoA, VSD	87/93	+ve	Faint	Normal	N/A
Critical PS	70/60	+ve	Faint	Weak	N/A
HLHS	90/91	+ve	Yes	Weak	N/A
TGA, DILV, CoA	91/93; 94/91	+ve	Faint	Very weak	N/A
Blind neonatal examination					
Critical SAS	98/89; 98/94	+ve	Yes (day 2)	Normal	Yes
HLHS	90/93; 92/92; 91/94	+ve	Faint (day 2)	Normal	Yes
CoA	97/postductal value (foot) unrecordable	Pathological result	No (day 1)	Weak	Yes, arrythmia
IAA, TGA, DILV	97/92; 97/93; 95/90	+ve	Yes (day 4)	Weak	Yes
HLHS	96/82; 95/81	+ve	Yes (day 2)	Difficult (crying)	Yes
IAA, TA	95/96	–ve	Yes (day 1)	Increased	Yes
Aortic atresia, AVSD, CoA	96/96; 90/92	–ve	No (day 1) Yes (day 2)	Normal	No Yes (no urine)
CoA, ASD	100/99; 99/100	–ve	Yes (day 1) Yes (day 2)	Impalpable Impalpable	No Yes
CoA	98/99	–ve	Yes (days 1-4) Faint (day 5)	Normal Impalpable	Yes
CoA	99/100	–ve	Yes (day 3) No (day 4)	Palpable Impalpable	Yes
CoA, VSD, ASD	97/98	–ve	Yes (day 1)	Impalpable	Yes
Discharged home without diagnosis and echocardiography					
IAA, AP window	98/92; 99/95	+ve	No (day 1) Circulatory collapse day 8	Normal	No (protocol violation) —
CoA	99/93; 95/95	–ve	No (day 2) Circulatory collapse day 7	Normal	No —
CoA, VSD	98/100	–ve	No (day 2) Circulatory collapse day 4	Normal	No —
IAA, ASD	97/99	–ve	No (day 1) Circulatory collapse day 4	Normal	No —
CoA	99/97	–ve	No (day 1) Circulatory collapse day 4	Normal	No —

TGA=transposition of the great arteries, PA=pulmonary atresia, DILV=double inlet left ventricle, VSD=ventricular septal defect, AS=aortic stenosis, CoA=coarctation of the aorta, PS=pulmonary stenosis, HLHS=hypoplastic left heart syndrome, SAS=subvalvar aortic stenosis, IAA=interrupted aortic arch, TA=truncus arteriosus, AVSD=atrioventricular septal defect, ASD=atrial septal defect, AP=aorto-pulmonary.
*Physical examination performed with knowledge of oxygen saturation results.

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Table 4 The performance of screening methods in the detection of duct dependent circulation in newborn infants in West Götaland (1 July 2004 to 31 March 2007)

Performance	Physical examination alone (n=38 374)	Pulse oximetry (n=38 429)	Physical examination plus pulse oximetry (n=38 429)
Sensitivity (95% CI) (%)	62.50 (35.43 to 84.80)*	62.07 (42.3 to 79.31)	82.76 (64.23 to 94.15)
Specificity (95% CI) (%)	98.07 (97.93 to 98.21)	99.82 (99.77 to 99.86)	97.88 (97.73 to 98.03)
Positive predictive value (95% CI) (%)	1.35 (0.65 to 2.47)	20.69 (12.75 to 30.71)	2.92 (1.88 to 4.31)
Negative predictive value (95% CI) (%)	99.98 (99.96 to 99.99)	99.97 (99.95 to 99.99)	99.99 (99.97 to 100.00)
Likelihood ratio	32.37	344.8	39.08
False-positive rate (%)	1.90	0.17†	2.09
No of true positives	10*	18‡	24‡
No of false negatives	6*	11§	5§
No of false positives	729	69	798
No of true negatives	37 022	38 259	36 881
Relative risk (95% CI) (%)	83.6 (30.5 to 229.5)	719.8 (350.3 to 1479)	215.4 (82.4 to 563.0)

*Blind physical examination alone cannot be compared directly with the other two methods as the number of babies with duct dependent circulation was 16 in this group.
†False positive rate calculated on total numbers of patients completing pulse oximetry (n=39 821).
‡Patient who was diagnosed after repeated failures of obtaining a pulse oximetry signal in the feet is counted as true positive.
§Patient who fulfilled screening criteria but was discharged due to protocol violation is counted as false negative.
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Excess number of echocardiograms generated

69 "false" positives were generated by the screening programme (0.17%). Almost half of them had other pathology, shown in Table 5. Only 2.3 echocardiograms with normal findings were required per true positive baby with DDC detected by NGoxi screening. The neonatal physical examination in comparison generated 729 false positives (1.90%), so the screening study generated less than one tenth of the ultrasound examinations normally performed after referrals from routine neonatal physical examination.

Table 5 Pathology found in 69 babies with false positive results from pulse oximetry screening for duct dependent circulation in West Götaland (1 July 2004 to 31 March 2007)

		Subsequent management			
		Stay in neonatal intensive care			
Pathology found	No (%) of babies	≥5 days after screening	<5 after screening	Follow-up only	Surgery
Other critical congenital heart disease*	4 (6)	4/4	0/4	0/4	4/4
Other milder congenital heart disease	10 (14)	4/10	1/10	5/10	4/10
Persistent pulmonary hypertension	6 (9)	3/6	0/6	3/6	N/A
Transitional circulation†	8 (12)	0/8	3/8	2/8	N/A
Infections	10 (14)	6/10	4/10	N/A	N/A
Pulmonary pathology	7 (10)	5/7	1/7	1/7	N/A
Normal (verified from hospital charts)	24 (35)	N/A	N/A	N/A	N/A

*Pulmonary atresia with multiple aorto-pulmonary collaterals (n=2), tricuspid atresia with pulmonary stenosis and ventricular septal defect (n=1), total anomalous pulmonary venous return (n=1).
†Right to left shunting across foramen ovale without pulmonary hypertension.
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Cohort comparison study

There was a significant difference in detection of DDC between WGR and the ORR not performing POX-screening. Table 6 shows that the difference in detection of DDS does not reach statistic significance, although the difference is 16%. The alarming finding however was the low clinical detection of only 77% of the markedly desaturated babies with duct-dependent lung and mixing circulation (DDP) in the other referring regions. This large proportion of failures in detection of duct-dependent pulmonary circulation has not been reported before.

Table 6 Failure to diagnose duct dependent circulation in neonates (1 July 2004 to 31 March 2007) inWest Götaland with pulse oximetry screening and in other referring regions not using pulse oximetry. Values are numbers (percentages) of cases of duct dependent circulation unless stated otherwise

Type of duct dependent circulation	West Götaland	Other referring regions	Comparison
Systemic circulation	5/30 (17)	16/48 (33)	P=0.12
Lung and mixing circulation	0/30 (0)	12/52 (23)	P=0.0030
Total	5/60 (8)	28/100 (28)	P=0.0025; relative risk 3.36 (95% CI 1.37 to 8.24)

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Looking at the diagnoses missed in ORR, a very large proportion of all babies with Transposition of the Great Arteries (TGA), the lesion with the most profound cyanosis, left hospital undiagnosed, 11/25 (44%). In contrast, no baby with duct-dependent pulmonary- or mixing circulation was missed in WGR. Missing the diagnosis of duct-dependent circulation had severe consequences for many of the infants that left hospital undetected in ORR, as shown in Table 7.

Table 7 Details of the 28 cases of undetected duct dependent circulation in neonates (1 Jan 2004 to 31 Dec 2007) in Swedish referring regions not using pulse oximetry screening

	Sequelae	
Diagnoses	**Severe acidosis**	**Death within 30 days**
Pulmonary and mixing duct dependent circulation		
TGA	No	No
TGA	No	No
TGA	Yes	No
TGA	Yes (+ preoperative seizures)	No
TGA	Yes (ECMO, preoperative cerebral haemorrhage)	No
TGA, VSD	No	No
TGA, VSD	No	No
Complex TGA	N/A	Yes, undiagnosed
Pulmonary flow duct dependent circulation		
TGA, PA, VSD	No	No
TGA, PA	No	No
PA	N/A	Yes, undiagnosed
Systemic and mixing duct dependent circulation		
TGA, CoA, VSD	Yes, brain infarction, cerebral haemorrhage, preoperative seizures	No
Systemic flow duct dependent circulation		
HLHS	N/A	Yes, undiagnosed
Critical AS	No	No
IAA, truncus arteriosus	Yes (pH 6.80)	No
IAA, VSD	No	No
CoA, VSD	Yes (pH 6.90)	No
CoA, VSD	N/A	Yes, undiagnosed
CoA, VSD	No	No
CoA, VSD	N/A	Yes, undiagnosed
CoA, AVSD	No	No
CoA	Yes	No
CoA	Yes	No
CoA	Yes	No
CoA	No	No
CoA	No	No
CoA	Yes (pH 7.14)	No
CoA	No	No

ECMO=extracorporeal membrane oxygenation, N/A=information not available as infant died at home, severe acidosis would have preceded death, TGA=transposition of the great arteries, PA=pulmonary atresia, VSD=ventricular septal defect, AS=aortic stenosis, CoA=coarctation of the aorta, HLHS=hypoplastic left heart syndrome, IAA=interrupted aortic arch, AVSD=atrioventricular septal defect.

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We introduced the concept of a "timely diagnosis" in our analysis as defined by *Griebsch et al,*[85] namely occurring in hospital and in time to prevent severe acidosis. With this analysis 49/60 (82%) of the DDC in WGR had a "timely diagnosis" versus 55/100 (55%) in ORR, p=0.0006 and relative "timely" detection rate of 2.46 (95% CI 1.38 to 4.37).

Comparisons of undetected sudden deaths in WGR and ORR

Five children with undiagnosed DDC died in the other referring regions versus none in WGR, p=0.16. Two of them had duct-dependent pulmonary circulation (detectable to 100% in our screening study), one had hypoplastic left heart syndrome (HLHS) and would probably have been detected. The remaining two had coarctation of the aorta (CoA).

Cost-benefit analysis

Using the calculated predicted costs for different kinds of screening by *Griebsch et al,*[85] based on 2001 UK health service costs, their simulated decision model estimated a cost of £4894 per timely diagnosis made by POX-screening. However, they had estimated a much higher false-positive rate and lower sensitivity than the actual results in our POX-screening study. Using their basic costs on our actual NGoxi-screening result (positive predictive value=20.69% and false positive rate 0.17%), our cost for 18 timely diagnosis made by NGoxi-screening (would have been 19 except for the protocol violation) is observed to be £3430 per timely diagnosis made. The cost for an infant leaving hospital with DDC and returning with circulatory collapse was calculated by *Griebsch et al.* to be £3453.[85] Under Swedish conditions, with much longer transport distances to regional centres, and sometimes need for ambulance helicopter transport, these costs could easily be much higher. Thus introduction of NGoxi-screening is at minimum cost-neutral, as each additional DDC diagnosed saves at least as much as each missed case costs. In Sweden, it could well be cost-saving.

This cost analysis does not include other than acute costs. The results from the other referring regions not using screening (see Table 6) also shows that there is serious long-term neurological morbidity to be expected in missed cases. That would of course increase the costs of not making a timely diagnosis. Of the surviving patients with undiagnosed DDC, 5/23 (22%) had either pre-operative cerebral haemorrhage (n=2), pre-operative seizures (n=1) a known predictor for poor neurological outcome,[14] or extreme acidosis (n=2) causing serious concern for the neurological outcome.

Paper IV: *Important inaccuracies in pulse-oximetry readings in cyanosed children*

Of the 56 samples, all but one had pH and pCO_2 within normal range. The 56th was a borderline with a pH of 7.26 and pCO_2 of 7.01, but was not an outlier having SpO_2 values within 2-3% of SaO_2. Fetal haemoglobin (HbF) was detected in 38 samples and bilirubin in 16.

Below saturations of 95% both oximeters tend to overestimate saturations compared with the hemioximeter, with a slope significantly different from the line of unity (slope=1). NGoxi versus SaO_2 had a slope of 0.796 (95% CI 0.675 0.918) and CToxi versus SaO_2 a slope of 0.574 (95% CI 0.399 to 0.750). Thus the lower the saturation the greater the difference between SpO_2 and SaO_2. The regression line of the difference (SpO_2 minus SaO_2) has a slope significantly different from zero for both oximeters. NGoxi has a slope of -0.205 (-0.329 to -0.081), p=0.0014 and CToxi a slope of -0.424 (-0.601 to -248), p<0.0001, thus the slope of CToxi is outside the 95% CI of the NGoxi slope, in other words the deviation was significantly worse for CToxi.

The size of the difference from SaO_2 did not correlate with presence of HbF (p=0.99) or bilirubin (p=0.80), and thus the error was not caused by presence of fetal haemoglobin or bilirubin presence. Nor did it correlate within this physiological range with pCO_2 (p=0.80) or pH (p=0.65); all p-values calculated for NGoxi.

As expected the readings were satisfactory in the 90-100% saturation span. Work at a paediatric cardiac ward with cyanotic babies however, demands accuracy in much lower saturation ranges. Significant positive bias occurred already in the 80-89% range and very important bias was found in the 70-79% range for both oximeters.

Clinically acceptable readings

Significantly more readings were >7% from the arterial blood-gas saturation with CToxi than with NGoxi (19/56 versus 8/56), p=0.026 and odds ratio 3.1 (95% CI 11.2 to 7.8) over the whole saturation span. Serious underestimates of SaO_2 did not occur with NGoxi (0/56), whereas 3/56 of CToxi measurements had a SpO_2 >7% less than SaO_2. On the other hand, serious overestimates of arterial saturations (>7%) occurred in 6/15 (40%) of SaO_2 readings <80% with NGoxi versus 0/15 in SaO_2 readings >90%, p=0.017 odds ratio 20.0 (95%CI 1.1 to 417).
For CToxi corresponding results were 10/15 (67%) versus 2/15 (13%), p=0.0078, odds ratio 13.0 (95% CI 2.1 to 81.5). There were no significant difference between the two CToxi monitors used, HP Virida (4/15) versus Datex-Ohmeda (17/41), p=0.311.

Defining a difference within 7% as clinically acceptable can be disputed. We have previously shown that the intra-observer error (=repeatability) of our NGoxi had a standard deviation of 1.3% and inter-observer error had a standard deviation of 1.5% (paper I). One might therefore argue that all deviations >3% constitute an error, and that >5% deviations, the error margin suggested by *Durbin et al.*[92] constitute a significant error. Using the ≤5% difference criterion as clinically acceptable, 19/56 readings with NGoxi and 32/56 readings with CToxi fails this criterion over the whole saturation span. In the clinically important below 80% saturation range 11/15 (73%) of NGoxi and 14/15 (93%) of CToxi fails. Large differences of >10% from SaO_2 were found in 3/15 (20%) NGoxi readings and half of the CToxi readings.

Comparison between NGoxi and CToxi

In 7/15 (47%) a difference >5% were found. The largest difference between NGoxi and CToxi under optimal conditions was as large as 29%.

Discussion

Knowledge about pulse oximetry

Working with critically ill patients one must not forget to update oneself on the day-to-day basic equipment. Pulse oximeters are very common in the hospital wards and pulse oximetry is cited as "the fifth vital sign" by *Mower et al*.[93] It needs to be generally recognized that for population screening only NGoxi should be used in order to reduce numbers of false positives.[74]

The knowledge about this everyday tool is not as good as one might expect. *Guiliano and Liu* conducted a pulse oximetry knowledge survey with 551 experienced critical care nurses with a mean critical care experience of 15 years and found that 30% did not even know if their unit used NGoxi or CToxi.[47] Only 63% knew that the SpO_2 is likely to be less accurate during patient motion and 30% did not know that SpO_2 was not a replacement for arterial blood gas analysis in the care of critically ill patients. These results nevertheless represented an increased knowledge about SpO_2 technology compared to that reported in previous studies. *Howell* found that accurate knowledge of what a pulse oximeter measured ranged from 50-60% among 30 trained and 15 untrained nursing staff.[94] *Davies et al.* reported that only 65% of physicians and 45% of the nursing staff were able to identify shivering as a factor interfering with pulse oximetry reading.[95] Only 7.4% of physicians and nurses were able to correctly state that arrythmias affected the accuracy of pulse oximetry readings, reported by *Kruger and Longden.*[96] According

to *Sola et al.*[28] only 40-45% of bedside caregivers knew how a pulse oximeter works.

Optimal screening cut-off

Paper I was the first to assess optimal cut-off limits using a large spectrum of babies with critical congenital heart disease (n=66). Previous studies have not compared frequency distributions between normal newborns and newborns with critical congenital heart disease for assessing screening performance. Nor have they verified normal intra-cardiac anatomy in babies assumed to be normal. An important contribution of this study was the introduction of the >3% difference between right hand and foot criterion (in addition to the below <95% saturation cut-off), as a strategy to increase the detection of coarctation of the aorta. This is clinically important since CoA was reported to be the most common lesion missed and over-represented in cases dying undetected in the community,[78] especially since the prognosis after surgery is very good.[97]

It might seem simple and attractive to use only post-ductal saturation for screening purposes, but that disregards the fact that in babies with a combination of aortic arch obstruction and transposed vessels, the post-ductal saturation may be over 95%, as we found in paper I in 3% of the babies.[74] Since babies with systemic duct-dependent circulation (DDS) are most likely to develop early circulatory collapse with neurological and other morbidity, we feel that a presence of a saturation difference >3% which substantially increases the likelihood of a DDS being present is a useful diagnostic tool, as it does not increase false-positive rate but does detect a few more cases with pathology and alerts the physician to the possibility of aortic arch pathology. Using *Meberg et al*'s cut-off on our data in paper III, the sensitivity would have been 60.7%, i.e their criteria missed one positive on our screening criteria and did not add any true-positives. [98, 99]

Age at screening

In West Götaland Region the earliest discharge from maternity wards is six hours. In paper I the age difference of two days between the *reference group* and *CCHD group* is of relevance. Our reference group had a median age 24 hours, in order to be relevant for infants that are candidate for early discharge. However half of the children with CCHD develop symptoms only after the second day of life,[78] and thus the median age of 3 days in our *CCHD group* is typical. We had no physiological reason to believe that the age difference would make NGoxi screening less sensitive, on the contrary, most of the infants in the CCHD group would have had lower saturations before prostaglandin infusions were started, as reported by *Hoke et al,*[15] and also observed by us. Our subsequent results from the multi-centre study with a median screening age of 38 hours, showed this assumption to hold true for duct-dependent pulmonary/mixing circulation, but probably not for coarctation of

the aorta (CoA), where the detection rate on prospective pulse-oximetry screening was not as high as in the infants studied after resuscitation and with prostaglandin infusion. *Meberg et al*. screened 50 008 babies the first day of life with a median age of babies with critical CHD failing the test of 6 hours and a reported sensitivity of 77%, however, the false positive rate was 3.5 times higher than ours (0.6 versus 0.17).[98] Their apparent higher sensitivity figure may relate to the early screening, detecting some infants that in our study were detected clinically before the discharge examination was due. It is as emphasized above not due to their screening criteria, as their criteria applied on our infants (tested at discharge) had lower sensitivity than ours. The five babies discharged undiagnosed in paper III returned with circulatory collapse on day 4 of life or later. Our recommendation of optimal age at screening based on this experience would be one test within the first 24 hours for a timely diagnosis of duct-dependent cyanotic lesions and another either when the test for phenylketonuria or hearing loss is performed, or at discharge, for detecting duct-dependent systemic lesions, whichever is latest. Doing the test after 12 hours of age would be likely to reduce number of false positives (paper I).

Type of pulse oximeter

Previous screening studies have used various types of oximeters and omitted information about averaging times and software revisions,[16, 79, 80] important information for making comparisons, especially because of the 2% difference in normal values between functional and fractional saturation readings. We were the first to actually compare performance of a NGoxi and CToxi in Paper I. Our result with CToxi only confirms conventional technology limitations and demonstrates that this type of oximeter can not be used for screening. Since two of three normal newborns had a capillary refill time >3 seconds (poor peripheral perfusion) and one in four were unsettled at the time of the measurement, it is not surprising that we were unable to even get a signal in some of the normal newborns. The reason for choosing the Radical SET as a NGoxi was because it has been rated the best oximeter for avoidance of motion artefact[89] and had a high sensitivity and specificity in relation to arterial blood gasses around the 95% saturation region.[57]

Impact of oximeter-type in a clinical setting

In Paper IV we assessed the performance of different oximeters against the golden standard with blood gas analysis in a clinical setting in cyanosed children. If one compares a method against a calibration method, *Altman and Bland* (1983)[91] advocates a plot versus line of unity, as used in the present study. Other studies have not used this method and thus based their conclusions on erroneous analysis. *Lynn et al.*[100] compared pulse oximetry with arterial blood gasses during cardiac catheterisation and rated the correlation as “exellent” based on a correlation

coefficient of 0.95. *Altman and Bland* (1983)[91] states that a good correlation can be obtained in presence of a systematic error when both increase with increasing true values. Other studies have based their results on the conventional Bland-Altman plot when comparing with gold standard. Both *Schmitt et al.*[101] and *Tachibana et al.*[102] have reported that CToxi overestimate arterial blood gas saturations at lower saturations. There are reasons for not using that plot when comparing with arterial blood gas analysis (gold standard). Since one of the measures is the gold standard for calibration, any systematic error would be halved, thus underestimated. False low values caused by motion artefact would also lower average bias and underestimate the problem.

Our results confirm previous studies comparing NGoxi with CToxi, showing that in normal children or in premature children receiving supplemental oxygen (ie saturations above 90%) NGoxi performes adequately.[30, 57, 103, 104] *Torres et al.* studied cyanotic children in the recovery room after surgery by comparing two types of NGoxi with arterial blood saturation. However, they also used the conventional Bland-Altman plots for analysis and found increasing bias and lack of precision for saturations <90% compared with ≥90% both for Nellcor N-395 (4.9 ± 4.7 versus 1.4 ±1.6) and Masimo SET (4.1 ±2.9 versus 1.3 ±1.6).[105]

We were the first to compare CToxi and NGoxi with arterial blood gas in spontaneously breathing children with cyanotic heart disease, at a pediatric cardiac ward, representing the situation when pulse oximetry is used for clinical monitoring. The extent of positive bias against the line of unity found in our study in the <80% saturation range is most concerning. Our CToxi equipment at the ward was clearly inadequate for clinical monitoring of cyanotic patients and not even NGoxi performed satisfactorily.

Peripheral Perfusion Index (PPI)

In paper II we established normal values on PPI in normal neonates during the time period where pulse-oximetry screening is applicable. Combining neonatal physical examination and NGoxi screening detected 7/9 in the LHOD-group but when PPI was added all 9 showed test abnormalities, suggesting that including PPI might improve detection of DDS. When the PDA is small in a baby with CoA, the pulse volume is reduced but arterial blood can still lack desaturation in the lower limb. The missed CoA had a postductal saturation of 100% but the simultaneously measured postductal PPI was 0.17 and the only abnormal sign. The addition of PPI to screening would both increase detection and false positive rate. The optimal cut-off must be balanced and assessed in a prospective study.

Diagnosis missed after neonatal physical examination

Avoiding deaths due to undiagnosed duct-dependent pulmonary circulation was not an expected outcome from the cohort comparison in paper III, since most earlier reports have suggested that the majority of babies missed have duct-dependent systemic circulation,[10, 11, 84] and that DDS is the most common cause of undiagnosed death from CHD the community.[10, 13] Thus there appears to have been a significant increase in number of deeply cyanosed infants missed occurring during the last decade. *Mellander and Sunnegårdh* reported in a previous analysis covering the same Swedish regions between 1993-2001 that only 4.7% (5/106) of infants with DDP left hospital undiagnosed, compared to 23% (12/52) in our study, p=0.0016.[11] These reports contrast with the results from our cohort comparison study (paper III), that duct-dependent pulmonary circulation (detectable by our NGoxi-screening in 100% of cases), constitutes of 12/28 (43%) of babies being missed and that 44% of babies with transposition of the great arteries were discharged without heart disease being detected.

Decreased detection of DDP on neonatal physical examination

This change has occurred in parallel with a policy of shorter stay in the maternity units.[11] Average stay at the maternity ward has steadily fallen from, in 1993 3.3 days after vaginal delivery to 2.2 days in 2005 (www.socialstyrelsen.se/NR/rdonlyres/70A20A7A-F6A9-45DE-97FC-7BF15BFE299C/10789/BilagaGraviditeterforlossningarochnyfoddabarn.pdf). In WGR 63% of the mothers left the maternity unit ≤48 hours after delivery during 2005 (national average was 62%). Not all missed cases went home early, so another factor could be altered neonatal physical examination schedules (one instead of two as being the case in 4/5 participating units in WGR). Babies are now being kept separately with their mothers as opposed to in well lit rooms together with other babies with trained staff monitoring them. It is easier to spot a cyanosed newborn baby if it is lying next to a normally saturated infant in a brightly lit room, as used to be the case.

Detection of DDC on neonatal physical examination

There is no national recommendations to include the palpation of femoral pulses in the physical examination, so some maternity units have abandoned examinating femoral pulses (no unit in WGR though). Since 50% of babies detected at NPE had poor or absent femoral pulses as a major alerting sign (see Table 3), the omission of palpation of femoral pulses is likely to reduce detection rate of DDC on clinical examination.

Undetected sudden deaths

Five percent (5/100) of babies with DDC died without diagnosis in the other referring regions not performing NGoxi-screening. Two of them had duct-dependent pulmonary circulation and would have been detected on saturation screening. *Råsten-Almquist et al.* reported 7 infants dying suddenly from undiagnosed DDC in Stockholm region between 1982-2001, 1.6 deaths per 100 000 live born.[106] *Wren et al.* reported more similar figures to our current figure from ORR, in the Newcastle data,[10] with 4.4 deaths per 100 000 compared with our 4.6 deaths per 100 000 live borns. A possible reason for this is again the current shorter stay in maternity wards. In 1982, when the Stockholm study commenced, the average maternity in-patient stay in Sweden was 5.6 days (www.socialstyrelsen.se/NR/rdonlyres/70A20A7A-F6A9-45DE-97FC-7BF15BFE299C/10789/BilagaGraviditeterforlossningarochnyfoddabarn.pdf). *Meberg et al.*[98] presenting results from the largest screening study claim a sensitivity of 77% which appears optimistic as they have not provided details about how they searched for patients dying in the community with undiagnosed DDC. They also reported a surprisingly low incidence of critical CHD of 0.7 per 1000. The two other screening studies that actively ascertained cases dying in the community reported an incidence of critical CHD virtually identical to our 1.3 per 1000, *Richmond et al.*1.3 per 1000[8] and *Koppel et al.*1.2 per 1000.[9] However, after our paper was published, *Meberg* published a rapid response to our paper apologizing for reporting the wrong incidence in his abstract. He wrote that their incidence was infact 1.2 per 1000 (without giving the actual correct numbers). He also commented that they did not register any deaths based on information from coworkers and the Norwegian department of pathology. However, no baby died undiagnosed in our screening population either, so without a control population we still lack information about undiagnosed deaths in an unscreened population in Norway.

Cost-benefit analysis

The cost-benefit analysis we carried out based on *Griebsch et al*'s model[85] provided strong arguments for the introduction of mandatory pulse oximetry-screening using new-generation oximeters. Pulse oximetry-screening is at minimum cost-neutral in the short term as each additional case missed costs at least as much in resuscitation, emergency transport and extra intensive care days as the cost for each additional case found by pulse-oximetry screening. This comparison does not take account of long-term costs for neurological morbidity in missed cases. Furthermore we have shown that survival for standard-risk babies is better.

Newborn screening

Wilson and Jungner's proposed ten criteria for newborn screening which were published by WHO. Other studies have proposed POX-screening as meeting the criteria together with the neonatal physical examination,[38, 84, 87] but they concluded that larger studies were necessary. We believe that the results from the papers in this thesis fulfill the remaining screening requirements not addressed in previous saturation screening studies (that it is accepted by the population, cost-balanced and would reduce morbidity). The last criterion that "Case-finding should be a continuing process and not a "once and for all" project" is a rather self-evident proposal.

The few published studies against POX-screening must of course be addressed. *Sendelbach et al*. (2008)[4] based their negative opinion on 15 233 babies (the largest single-centre study, although too small) screened at 4 hours of age with Nellcor N-395 (NGoxi). Firstly, they selected a cut-off <96% with a NGoxi (functional saturation) based on two old studies,[37, 107] obtained with different oximeters (conventional technology oximeters), presenting normal newborn saturation values without actually having verified normal anatomy.

To assess a proper cut-off you need not only to measure normal newborns, but also the saturations of the CCHD-group, and clearly to use the same pulse-oximeter both for screening and reference values. Then they stated that "trained technicians" performed the measurement and "probes were held manually on either foot without the use of Velcro straps". This ignores the importance of shielding the sensor from ambient light, a known factor for erroneous readings. Holding the sensor by hand without using the proper equipment is highly questionable. They also state that when a reading was <96% they warmed the baby with blankets and re-measured. If the measurement then was higher "the higher value was recorded". Their definition of CCHD was by diagnosis, not severity or time before surgery. Although 3 of the 4 babies with CCHD was <96% on initial screening, they describe the result as "all developed signs and/or symptoms of a cardiac defect and received a diagnosis on the basis of the clinical findings, not screening results" and conclude that their "findings do not support a recommendation for routine pulse oximetry screening". Since they state that the saturation results were made available "on the day of discharge" you don't even know for sure if the saturation results were shown before the physical examination or after. Another contributing factor to their conclusion was probably that they already have a good routine (but not common, as stated by Keith Barrington in an editorial)[108] of monitoring all babies admitted to the newborn nurseries for four hours in a special area where most of the CCHD are picked up. Their false positive rate of 5.6% on a single reading is probably due to the 96% cut-off.

Reich et al. (2007)[7] conclude that POX-screening was "neither reliable nor an important diagnostic tool" based on 7 962 screened newborns (also too small). They used a NGoxi (functional saturation) with sensor placed on a toe and cut-off <95% at discharge. Interestingly, they screened asymptomatic babies *after* the

neonatal physical examination and then stated that “no child was identified initially by routine pulse oximetry”. They do address the importance of human factors and compare two phases in the study. Without stating if or what kind of education the staff was given before the study started, the oximeter readings were downloaded to a computer and compared with a logbook compiled by nurses, without the staff knowing (POX- reading reliable in 37%). In the second part the staff was given “additional training” and was aware of the surveillance and the reliability improved to 60%. Higher education and >360 seconds measuring time optimized the reliability to exceed 95%. However, they also recommended a larger study before one can recommend routine pulse oximetry screening.

Ideas, Research and Improvements

Working with critically ill children with congenital heart disease, we had a newborn with transposition of the great arteries (TGA) without an arterial line. The paediatric cardiologist on call was to decide if the baby needed a Rashkind septostomy late Friday evening or not. He looked at the saturation monitor at the paediatric cardiac ward displaying postductal oxygen saturation (optimal measurement quality) of 85%. By coincidence this baby was included in the research project with duct-dependent newborns, and had both pre- and postductal saturation measured with a new generation oximeter, Masimo SET at the same time (paper I). Postductal saturation with the new-generation oximeter was 67% (optimal measurement quality). Lacking an arterial line for blood gas analysis, the doctor on call made the decision to perform a Rashkind septostomy. Had he believed the 85% reading, a septostomy would not have been performed.
We were concerned about the huge differences in optimal quality readings from the different oximeters and lacking an arterial line we never found out the “true saturation” in this particular patient.
This observation lead to the idea of the fourth paper, the clinical observational study in our cardiac unit comparing our equipment with both blood gas (golden standard) and a new-generation oximeter. We really felt that we had to find out if this was a “one time” finding or not and that we had to make a “quality control” on our equipment monitoring or children with CHD. Today, a few years later I’m happy to see that the monitoring equipment at our paediatric cardiac ward have all been changed to the new-generation technology.
The medical technology improves all the time and working in a hospital, especially with sick children I believe one must keep oneself updated with the technology. It is important to utilize validated research results in a constructive way. Research and everyday hospital routines must be closely connected so that implementation of improvements can happen within a reasonable time frame.

On the horizon

Considering new equipment developed during the course of my thesis work, there is already on the market improved LNOP-sensors "blue sensor" designed for cyanotic babies. They are claimed be accurate on paediatric patients with congenital heart disease with saturations as low as 60% by the company.[60] However, independent researchers should of course test them.

To hypothesize about approaches for the future is of course exciting. A new experiment model of two-dimensional pulsation has been proposed to reduce discrepancies between theoretical calibration curves and human test results by *Yang et al*.[109] It has not been independently tested yet and is to our knowledge not available in commercial pulse-oximetry equipment.

Takuo Aoyagi et al, the inventors of pulse oximetry continued their work and recently presented a new "theory for the future" as being multi-wavelength pulse oximetry.[110] They considered three factors affecting pulse oximetry: optics, tissue and venous blood and derived a physical theoretical formula of pulse oximetry confirmed with a full SO_2 range experiment and based on the theory. A three-wavelength method eliminated the effect of tissue and improved the accuracy of SpO_2. A five-wavelength method eliminated the effect of venous blood and improved motion artefact elimination. They concluded that multi-wavelength is the key to solving almost all problems in pulse oximetry (motion artefact, accuracy, low-pulse amplitude, response delay and errors using reflection oximetry). *Barker et al.* tested a 8-wavelength pulse oximeter designed to measure both Carboxyhaemoglobin (COHb) and Methaemoglobin (MetHb) on volunteers breathing gas-mixtures. Three hemi-oximeters were used as reference, measuring arterial blood-gas. The Masimo Rad-57 measured COHb with an uncertainty of ±2% within the range of 0-15% and MetHb with an uncertainty of 0.5% within 0-12% and is the first on the market in this field.[111]

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Concluding remarks

The principal findings of these studies are summarized below:

Screening strategies to optimize sensitivity of pulse oximetry screening for duct-dependent congenital heart disease includes:

1. Using a New-generation technology pulse oximeter
2. Using a set of combined criteria with cut-off of <95% in both right hand and foot or a difference >±3% between the pre- and postductal site
3. Introducing three repeated positive measurements criterion to reduce false-positive rate (or one single optimal quality measurement ≤90%)
4. Adding peripheral perfusion index <0.70 gave an odds ratio for duct-dependent systemic circulation of 23.75 (but increased the false positive rate)

NGoxi screening (pre- and post-ductally) detected 100% of duct-dependent pulmonary circulation and combined with neonatal physical examination 92% of all babies with duct-dependent circulation before discharge and improved detection compared with physical examination alone.

Compared with earlier decades, an increasing proportion of babies with duct-dependent pulmonary circulation, including 44% of babies with transposition of the great arteries left hospital undetected in regions not using new-generation pulse oximetry screening.

No infants died without a diagnosis in West Götaland region during the study versus 5/100 in regions not screening newborns.

Introduction of new-generation pulse oximetry screening is cost-neutral short-term and most likely cost-effective long-term.

Pulse oximetry showed a systematic linear deviation from the true arterial blood-gas saturation that is greater the lower the saturation.

In the <80% saturation range clinical decision making should never be based solely on pulse oximetry monitoring.

Normal newborn peripheral perfusion index values (based on 10 000 normal newborns) pre- and postductally between 5th and 95th percentile were 0.70 to 4.50.

Populärvetenskaplig Sammanfattning

Bakgrund: En tredjedel av barn med livshotande hjärtfel lämnar BB utan att hjärtfelet upptäckts. De flesta inkommer akut till sjukhus med cirkulationskollaps, men 5% av barn med livshotande hjärtfel avlider innan rätt diagnos ställs.

Avhandlingens **huvudsyfte** har varit att utvärdera om en enkel mätning av syremättnaden i blodet med pulsoxymetri (röd lampa som mäter under ca 30 sekunder) skulle kunna vara en kompletterande metod att upptäcka fler av dessa barn innan de lämnar BB.

I ***Arbete I*** definieras gränsvärden och metod för att optimera upptäckten med hjälp av pulsoxymetri (POX).

I ***Arbete III*** utvärderas denna screening-metod prospektivt på 39 821 nyfödda i hela Västra Götalands Region (VGR). Andelen barn som lämnat BB utan diagnos med livshotande duktusberoende hjärtfel under studieperioden i VGR jämförs med övriga inremitterande regioner (ÖIR), liksom andel barn som avlidit utan diagnos. Kostnaden för införandet av screening uppskattas.

I ***Arbete II*** definieras normalvärden för perifert perfusions index (PPI) på nyfödda, för att utvärdera om metoden kan tänkas användas för att hitta kritiska hjärtfel där blodcirkulationen i kroppspulsådern är drabbad, och den omfattar tio tusen av de nyfödda som screenats i VGR.

I den kliniska observationsstudien ***Arbete IV,*** jämförs 56 arteriella blodgas-mätningar av syremättnaden i blodet (kalibreringsmetod) simultant med konventionell pulsoximeter (CToxi) och nya generationens pulsoximeter (NGoxi) på barn med cyanotiska hjärtfel.

Resultat: Bäst detektion av duktusberoende hjärtfel vid screening uppnås vid <95% syremättnad i både höger hand och ena foten eller en hand/fot skillnad på >3% med en ny generations pulsoximeter (NGoxi). Pulsoxymetri kombinerad med barnläkar-undersökning på BB upptäcker signifikant fler nyfödda med duktusberoende hjärtfel än enbart barnläkar-undersökning. Det var signifikant bättre detektionsprocent för duktusberoende cirkulation i VGR (92%) jämfört med ÖIR (72%) som inte screenade med POX. En signifikant högre andel barn var svårt sjuka och krävde intensivvård vid diagnos i övriga inremitterande regioner (som ej screenade) jämfört med VGR under POX-studien, där tidig diagnos gjorde att man kunde undvika cirkulationskollaps hos fler. 45% av barn som föll ut på POX-screeningen (utan att ha duktusberoende cirkulation) hade andra sjukdomar som

gynnades av tidig diagnos (sepsis, lungsjukdom, andra kritiska och mindre kritiska hjärtfel och pulmonell hypertension). Antalet extra ultraljud på friska barn var obetydlig; 5-6 per år och sjukhus. Det ska jämföras med 58 per år och sjukhus som gjordes på friska barn pga fynd från barnläkar-undersökningar (dvs mindre än 1/10 av arbetsbördan jämfört med de som remitteras rutinmässigt). Inga barn avled av oupptäckt hjärtfel i VGR under studien, jämfört med 5 barn från övriga inremitterande sjukhus som ej screenade med POX. Parallellt med kortare BB-vistelse har det skett en signifikant ökning av barn med duktusberoende lungcirkulation som lämnar BB utan diagnos (till 100% detekterbara med POX-screening). Screening med pulsoxymetri är kostnadsneutral, eftersom kostnaden för POX-screening uppvägs av minskade merkostnader för återupplivning och intensivvård av barn som kollapsat pga oupptäckta duktusberoende hjärtfel. Tillägg av simultant perifert perfusions index till NGoxi-screening skulle kunna ytterligare öka upptäckten av duktusberoende hjärtfel som orsakar obstruktion av flödet till stora kroppspulsådern, men formerna för detta bör utvärderas i en prospektiv studie. Den kliniska studien visade att pulsoxymetri på cyanotiska barn visar en systematisk linjär avvikelse från arteriell blodgas som ökar med minskad saturation, dvs vid låga syrgassaturationer så överskattade POX den faktiska syremättnaden. CToxi hade signifikant fler oacceptabla mätresultat än NGoxi. Vid syremättnader under 80% bör inga kliniska beslut enbart grunda sig på pulsoxymetri.

Slutsats: Tillägget av POX-screening till barnläkarundersökningen förbättrade upptäckten av duktusberoende hjärtfel signifikant, hittade alla med duktusberoende lungcirkulation (återfanns hos 2 av 5 som dog utan diagnos i övriga regioner), och var med en låg falskt-positiv frekvens av 0.17% kostnadsneutral.

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