Early detection of critical congenital heart defects in Sweden

- with a focus on coarctation of the aorta

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To my family with love

Abstract

Introduction

Despite the implementation of prenatal and neonatal screening, newborn infants with critical congenital heart defects (CCHD) remain at risk of being discharged undiagnosed, particularly newborns with coarcation of the aorta (CoA). Recent studies have suggested that perfusion index (PI) may potentially identify additional cases of CoA.

Aim

To investigate the relative contributions of prenatal screening, pulse oximetry screening (POS) and newborn physical examination (NPE) to the early detection of CCHD with special attention to CoA. A second aim was to investigate the use of PI to improve the early detection of CoA.

Methods

Retrospective population-based cohorts of isolated CoA (Paper I) and CCHD (Paper III) were studied with respect to the contribution of pre- and postnatal screening methods to early diagnosis. PI was measured prospectively in healthy newborns to determine the false positive rate (Paper II). The sensitivity of PI to detect aortic arch obstructions (AAO), such as CoA, was studied retrospectively in newborns with AAO who were routinely screened with PI (Paper IV).

Results

In Paper I, three of 90 with CoA were diagnosed prenatally. Among 87 diagnosed postnatally, 4/19 (21%) born in units using POS screened positive. Forty-six (53%) were discharged undiagnosed. At readmission, 22 were in circulatory failure and one died at home. In Paper III, 264/630 (42%) with CCHD were diagnosed prenatally, 142 (23%) by POS and 86

(14%) as a result of NPE. Although prenatal detection increased significantly during the study period, 4 newborns died undiagnosed before discharge and 64 (10%) were discharged undiagnosed. Upon readmission 24 were in circulatory failure with one preoperative death. Of 184 with CoA, 55 (30%) were discharged undiagnosed. In Paper II, the false-positive rate of PI in 463 newborns was reduced to 0% by using repeated PI measurements and a threshold of <0.7% for a positive screen. In Paper IV, the sensitivity of PI to detect AAO in 38 cases could be increased from 45 to 76% by combining PI in right hand with POS and NPE.

Conclusions

POS and NPE remain important for the early detection of CCHD, complementing the increasing prenatal detection. While the overall pre-discharge detection of CCHD was high, and improvements were made in the prenatal detection of CoA, this defect was still frequently not diagnosed before discharge. Adding PI to CCHD screening has the potential to further improve early detection of CoA but requires additional evaluation.

Sammanfattning på svenska

Bakgrund

Nyfödda med kritiska hjärtfel behöver snar kirurgisk åtgärd, vanligtvis inom 1-2 veckors ålder. Att ställa diagnos tidigt är avgörande för att undvika allvarliga komplikationer och död. Trots att vården av nyfödda med kritiska hjärtfel har gjort betydande framsteg, är sen upptäckt fortfarande ett problem i vissa fall. Nuvarande screeningmetoder inkluderar ultraljudsundersökning under fostertiden, mätning av syrehalten i blodet på nyfödda (POX-screening) och barnläkarundersökning innan hemgång från BB. Risken att förbise hjärtfelet under BB-vårdtiden är särskilt hög hos nyfödda med coarctation (CoA), dvs en förträngning av kroppspulsådern. Om tillståndet inte upptäcks i tid kan CoA leda till cirkulationssvikt och död. Tidigare forskning har visat att ett tillägg av mätning av perfusionsindex (PI) till den rutinmässiga screeningen av nyfödda kan upptäcka en del fall av nyfödda med CoA som annars hade skickats hem från BB utan diagnos.

Mål

Att studera resultatet av nuvarande screeningmetoder för tidig upptäckt av kritiska hjärtfel i Sverige, med ett särskilt fokus på CoA. Att undersöka om ett tillägg av PI till nuvarande screeningmetoder kan öka upptäckandegraden av CoA.

Metod och resultat

Studie I redovisar resultatet av en uppföljning av 89 nyfödda barn med CoA, födda mellan 2003 – 2012, och opererade i Göteborg före två månaders ålder. Över hälften (53%) av de nyfödda med CoA skickades hem från

BB utan diagnos. Vid återinläggning hade närmare hälften utvecklat svår hjärtsvikt som krävde intensivvård. Ett barn dog i hemmet vid 11 dagars ålder.

I Studie II gjordes mätning av PI i hand och fot på 463 nyfödda på BB. Vi undersökte andelen PI-mätningar som uppmättes ligga under ett tidigare föreslaget tröskelvärde på 0.7% för ett positivt screeningutfall. Genom att utföra en upprepad mätning av PI, om första värdet var under tröskelvärdet, kunde de falskt positiva utfallen minskas till 0%.

Studie III redovisar nationella data av barn födda med kritiskt hjärtfel i Sverige mellan åren 2014 - 2019. Totalt ingick 630 fall i studien varav 42% var diagnostiserade innan födseln. POX-screeningen diagnostiserade 23% och 14% av barnen fick sin diagnos efter barnläkarundersökningen på BB. Fyra fall avled på sjukhus innan diagnos. Av 630 barn, skrevs 10% hem odiagnostiserade, en stor andel av dessa hade CoA.

I Studie IV bestod studiepopulationen av 38 nyfödda (36 med CoA och två med avbruten aortabåge) som mellan åren 2014 - 2019 föddes på sjukhus där man rutinmässigt mätte PI i samband med POX-screeningen. Inget fall identifierades endast genom mätning av PI. Genom att använda ett kombinerat screeningförfarande; ett PI tröskelvärde >3% i höger hand och/eller POX-screening och/eller resultatet av barnläkarundersökning kunde fler fall identifieras i jämförelse med resultatet av enbart POX-screening och barnläkarundersökning.

Slutsatser

De screeningmetoder som idag används i Sverige för att tidigt upptäcka kritiska hjärtfel kompletterar varandra och har en generellt hög upptäckandegrad. Trots förbättringar under studietiden, är tidig detektion (innan utskrivning från BB) av nyfödda med CoA fortfarande otillräcklig. Screeningmetodernas effektivitet och precision framför allt vad gäller CoA behöver förbättras, såväl prenatalt som postnatalt. Ett tillägg av PI till screeningen har potential att förbättra upptäckandegraden av nyfödda med CoA men behöver utvärderas ytterligare.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals (I-IV)

I. Lannering Katarina, Bartos Marie, Mellander Mats.
Late Diagnosis of Coarctation Despite Prenatal Ultrasound and Postnatal Pulse Oximetry
Pediatrics 2015 Aug Vol 136 (2) e406-e412.

II. Lannering Katarina, Elfvin Anders, Mellander Mats.
Low false-positive rate of perfusion index as a screening tool for neonatal aortic coarctation
Acta Paediatrica. 2020 Nov Vol 110 (6) p.1788-1794

III. Lannering Katarina, Kazamia Kalliopi, Bergman Gunnar, Liuba Petru, Östman-Smith Ingegerd, Alenius Dahlqvist Jenny, Elfvin Anders, Mellander Mats.
Screening for critical congenital heart defects in Sweden. A retrospective national cohort study 2014-2019
Under revision

IV. Lannering Katarina, Östman-Smith Ingegerd, Mellander Mats.
Enhancing neonatal screening for aortic arch obstructive lesions: the added value of using perfusion index
Manuscript

Abbreviations

AAO	aortic arch obstruction
AS	aortic stenosis
AUC	area under the curve
AVSD	atrioventricular septal defect
CCHD	critical congenital heart defect
CHD	congenital heart defect
CoA	coarctation of the aorta
HLHS	hypoplastic left heart syndrome
IAA	interrupted aortic arch
LHOD	left heart obstructive defect
NPE	neonatal physical examination
PA/IVS	pulmonary atresia with intact ventricular septum
PA/VSD	pulmonary atresia with ventricular septal defect
PDA	patent ductus arteriosus
PGE1	prostaglandin E1
PI	perfusion index
POS	pulse oximetry screening
PS	pulmonary stenosis
SpO2	peripheral oxygen saturation
TA	tricuspid atresia
TAPVR	total anomalous pulmonary venous return
TGA	transposition of the great arteries
VSD	ventricular septal defect

CONTENT

1

Introduction

Over the last several decades, the care of newborns with congenital heart defects (CHD) has undergone tremendous changes due to significant advancements in imaging techniques, surgery and catheter interventions as well as improved pediatric intensive care. Furthermore, the centralization of surgery of congenital heart defects in Sweden has contributed to reduced mortality. A recent report, based on national Swedish registers, estimated that over 97% of pediatric patients with CHD will reach adulthood, highlighting the progress made in this field.[1]

However, some newborns with life-threatening CHD do not exhibit symptoms of heart disease during the postnatal stay at maternity units, putting them at risk of being discharged without a diagnosis. This risk is particularly high for neonates born with coarctation of the aorta (CoA). A timely diagnosis of CoA is crucial to prevent morbidity and mortality resulting from a missed diagnosis.

This thesis originated from a newborn with CoA who had been discharged from a referral hospital after passing all screening levels. The newborn experienced a sudden deterioration at home at 5 days of age, requiring intensive care and surgery. As a pediatric resident, I became interested in exploring to what extent this case was representative of neonates born with CoA. The resulting retrospective study, reported in *Paper I*, analysed a complete population-based cohort of isolated CoA.

While conducting the study on isolated CoA, it motivated me to explore the broader research field of screening for critical congenital heart disease (CCHD). Specifically, I was interested in evaluating current screening methods and identifying opportunities for improvement, especially for newborns with CoA. Previous research, from our institution and others had already had a significant impact on this field of research, contributing to the widespread adoption of pulse oximetry screening (POS).[2-4] In a

national collaboration we were able to retrospectively collect data on a large cohort of newborns with CCHD and to explore the current contribution of various methods for CCHD screening to an early diagnosis, *Paper III*.

In *Papers II* and *IV*, the aims were to build on the work from our institution, studying the value of using perfusion index (PI) in newborns for early detection of CCHD.[5] We conducted one study on apparently healthy newborns with a focus on the false positive rate in using PI. In addition, we performed a study examining whether the sensitivity for aortic arch obstruction (AAO) can be increased by adding PI to POS.

The findings of this thesis provide insight into current CCHD screening in Sweden and highlight the remaining issues that require future research.

2

Background

Congenital heart defects - CHD

CHD is the most common malformation at birth including a wide spectrum of lesions, varying in complexity.[6] Some defects are minor and will spontaneously resolve, others are significant and require several surgical procedures.

The etiology of CHD is still largely unknown, only about 20% can be attributed to known factors such as genetic syndromes, teratogens or maternal diabetes.[7] Chromosomal aneuploidy is a significant contributor. CHD is prevalent in 40-50% of cases with trisomy 21, 20-50% of cases with Turners syndrome and in almost all cases of both trisomy 13 and 18.[8] Many cases are believed to be multifactorial as environmental and genetic factors interplay.

PREVALENCE

CHD affects approximately 7-9 out of every 1000 live births, representing around one-third of all major congenital anomalies. [8-12] The prevalence of CHD varies widely depending on the population studied, study designs, method of detection, and type of CHD included. The inclusion of trivial lesions such as small muscular ventricular septal defects (VSD) will influence prevalence rates.[9,11-13] Since a prenatal diagnosis of CHD sometimes results in a parental decision to terminate the pregnancy, it is important to distinguish between fetal and live birth prevalence of CHD when reporting the results of screening.

Figure 1 indicates different cardiac malformations usually detected in infancy, estimated prevalence per million live births.

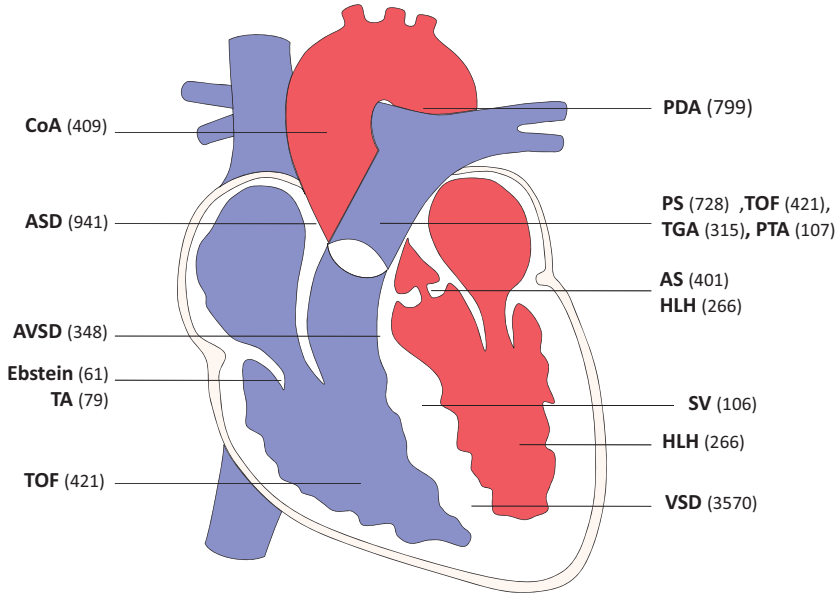


Figure 1: Locations of heart malformations that are usually identified in infancy, and estimated prevalence based on the CONCOR14 database. Numbers indicate the birth prevalence per million live births. AS: aortic stenosis; ASD: atrial septal defect, AVSD: atrioventricular septal defect, CoA: coarctation of the aorta, Ebstein: Ebstein anomaly, HLH: hypoplastic left heart, MA: mitral atresia, PDA: patent ductus arteriosus, PS: pulmonary stenosis, PTA: persistent truncus arteriosus, TA: tricuspid atresia, TGA: transposition of the great arteries, SV: single ventricle, TOF: tetralogy of Fallot, VSD: ventricular septal defect.

In recent decades, studies have reported an increase in global and national birth prevalence rates of CHD.[10,15,16] Most likely, rather than a true increase, this is due to improved diagnostics detecting minor defects.[9,13] Diverging trends have been reported in different lesions; atrial septal defects and persistent ductus arteriosus (PDA) increasing while left heart obstructive defects (LHOD) declining significantly[15]. The decline in the LHOD group is likely a consequence of a higher rate of termination of pregnancy following prenatal diagnosis of severe LHOD such as hypoplastic left heart syndrome (HLHS).[17,18]

CRITICAL CONGENITAL HEART DEFECTS - CCHD

About 15% of all CHD are immediately life-threatening for the newborn.[6] The term *critical* usually refers to a defect in a newborn that requires early medical and surgical care to prevent serious complications or death. These lesions typically present within the first days or weeks of life, often as a result of the closure of the ductus arteriosus and changes in pulmonary vascular resistance. However, in some cases, the ductus arteriosus may remain patent, making an early in-hospital diagnosis challenging.

The term CCHD was first applied in 1968 in the New England Regional Infant Cardiac Program to refer to cases that would require surgery and catheter intervention within the first year of life[19]. However, this definition was not useful for public health surveillance programs such as CCHD screening, due to the time lag between screening and outcome[20].

Reports on CCHD screening often use different definitions of CCHD. Some define CCHD as defects requiring intervention or resulting in death before 28 days of age.[6,21,22] Others use a defined list of diagnoses or include only lesions with duct-dependent circulation.[2,23]

FETAL AND NEONATAL TRANSITIONAL CIRCULATION

The fetus undergoes a major circulatory transition from fetal to neonatal life, as normal fetal and neonatal circulations are fundamentally different. (Figure 2) Some of the changes occur immediately after birth, others may evolve over a longer period. During fetal life, most defects are well tolerated because of the unique fetal circulation with its shunts, foramen ovale at the atrial level, and ductus arteriosus between the two great arteries. The fetal shunts allow for redistribution of blood flow when there is a cardiac defect compromising right or left ventricular output.[24] Because of the parallel organization of the fetal circulation the pressures in the right and left heart are equal.[24,25] Since the lungs are unexpanded and filled with fluid the pulmonary vascular resistance is high in comparison to the low systemic resistance caused by the low resistance cerebral and placental circulations.[26] Therefore, most of the right ventricular output is shunted through the ductus arteriosus, into the thoracic aorta, mixing with flow from the left heart.[26]

Oxygenated blood from the placenta and the umbilical vein enters the right atrium via the third fetal shunt; ductus venosus. The flow of oxygenated blood is preferentially directed across the foramen ovale to the left atrium, ventricle and aorta. It supplies the brain, heart and upper part of the body with relatively highly oxygenated blood at around 65%. [24,27] A small portion, about 10%, crosses the aortic isthmus.

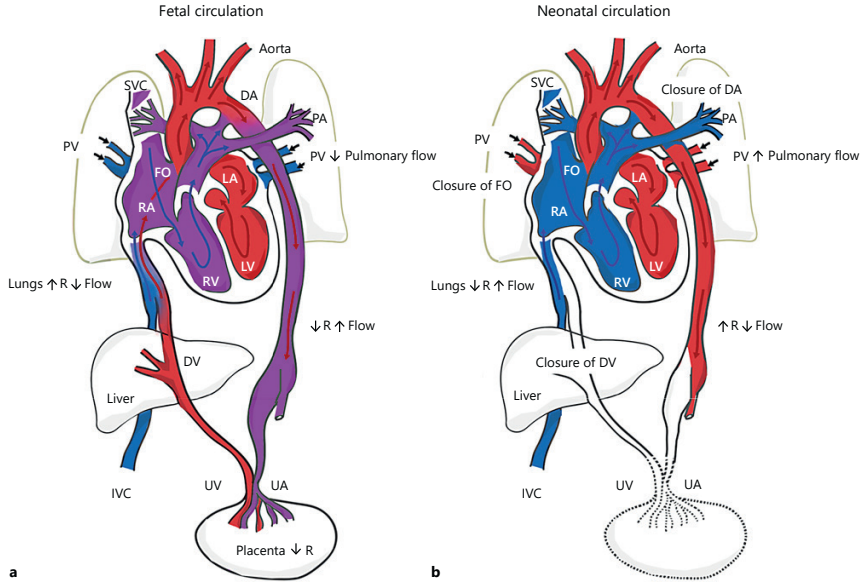


Figure 2: Illustration of the fetal (a) and neonatal (b) circulatory system. DV: ductus venosus, UV: umbilical vein, UA: umbilical artery, IVC: inferior vena cava, RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle, FO: foramen ovale, SVC: superior vena cava, PA: pulmonary artery, DA: ductus arteriosus, PV: pulmonary veins, R: resistance

After birth, the first breaths inflate the lungs, leading to a drop in pulmonary vascular resistance and increased pulmonary blood flow.[27] The closure of the umbilical-placental circulation blocks the low-resistance placental flow and stops the blood flow through the ductus venosus. Pulmonary

venous return increases, leading to higher left atrial pressures and the functional closure of the foramen ovale. The ductus arteriosus gradually closes, usually within 2-3 days of birth, under the influence of oxygen and the metabolism of prostaglandins and the shunt reverses.[26] These changes ultimately result in a complete separation of the systemic and pulmonary circulations that previously occurred in parallel.

In cases with LHOD such as CoA or aortic stenosis (AS), the response of the fetal left ventricle depends on the severity of the obstruction and how quickly it progresses.[24,25] LHOD are usually well tolerated by the fetal heart as long as there is no mitral or aortic valve insufficiency present. The combined fetal cardiac output is maintained by a compensatory increase of the right ventricular output.[25] In LHOD, fetal flow patterns can predict postnatal hemodynamics. For example, retrograde isthmus flow in systole indicates a ductal-dependent postnatal circulation where the left ventricle would not be able to manage the circulation.[28]

LATE DETECTION

Timely diagnosis of CCHD in neonates is crucial since a missed or delayed diagnosis can result in death or prevent successful surgical repair or palliation. Late diagnosis of CCHD has been reported in up to 30%, although study designs and definitions of CCHD differed between reports.[6,29-33] For example, in California between 1989-2004, it was estimated that up to 30 neonates with CCHD died every year from a missed diagnosis, HLHS and CoA being the dominant diagnoses among missed cases.[34] In another study, two-thirds of infants with a missed diagnosis had CoA and HLHS.[34] In a report from our institution 1993-2001, 45% of newborns with CoA were discharged from maternity units undiagnosed. A few of these children died at home, but most of them came back to the hospital in time, but often in a more or less critical condition[29]. The trend towards early discharge from maternity wards and other changes in postnatal care may have contributed to the increasing incidence of missed cases.[29] In another study between 2004-2007, an unexpectedly large proportion of newborns with simple and complex transposition of the great arteries (TGA) (11/25, 44%) were undiagnosed upon hospital discharge.[2]

MORTALITY

Despite the progress in medical care, CHD is a leading cause of death in infants and young children.[35-37] According to national mortality data from England and Wales in 2012, CHD accounted for 3% of all infant deaths and 46% of deaths caused by congenital malformations, with most deaths occurring within the first year of life[38,39]. In a nationwide study conducted in Norway, it was found that the 2-year mortality rate among liveborn infants diagnosed with severe CHD was 10%, with 58% of these deaths occurring before surgery.[40] Co-morbidities and univentricular hearts were common among these cases.

Various factors play a role in infant mortality resulting from CHD. These factors include the complexity of the defect, the presence of co-morbidities and the availability of specialized pediatric cardiology, pediatric cardiac surgery and intensive care.[39,41]

Coarctation of the aorta – CoA

CoA accounts for approximately 5-7 % of all congenital heart defects, which translates to approximately 4 out of 10 000 live births with a male predominance.[9,42] CoA is a localized narrowing of the aortic lumen typically in the proximal descending aorta, distal to the left subclavian artery sometimes in combination with a hypoplastic arch (Figure 3). It is often localized opposite to the insertion of the ductus arteriosus (juxta ductal area).[43]

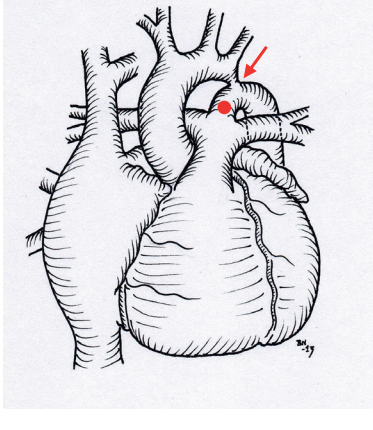


Figure 3: Coarctation of the aorta. The red arrow points at the coarctation. The red dot points out the patent ductus arteriosus.

Picture by pediatric cardiac surgeon Boris Nilsson, printed with kind permission

CoA can occur as an isolated defect or in combination with other cardiac defects. CoA may also be viewed upon as a systemic vasculopathy, considering the association of bicuspid aortic valve, observed in 50-75% of individuals with CoA.[44]

DEVELOPMENTAL THEORIES

Although the underlying pathophysiology of CoA is not fully understood, three main theories explaining the formation of CoA have been proposed. One theory suggests that aberrant smooth muscle tissue of the ductus arteriosus, sometimes encircling the aorta, plays a role.[45] Ductal tissue is found in the shelf-like infolding of the posterolaterally aortic medial wall layer, which is one of the echocardiographic markers of CoA. As the ductus arteriosus constricts after birth, the ectopic ductal tissue pulls the shelf towards the ductus region, leading to a constriction of the aortic lumen.[25]

According to the abnormal fetal flow theory,[46] reduced blood flow through the aortic arch during intrauterine development could explain tubular hypoplasia, including an aortic arch interruption (IAA) in extreme cases. In fetal life, the blood flow through the aortic isthmus normally receives 10-20% of the systemic cardiac output, resulting in a physiologically narrow diameter.[25,47,48] This area normally grows in size after birth as the blood flow increases. CoA is commonly associated with lesions that include an obstruction to the left ventricular outflow with a reduced intrauterine blood flow across the isthmus, promoting the coarctation. [25]

One other theory relates to a disturbance in the complex embryological development of the aortic arch, taking place already during the third week of gestation. Various segments of the aortic arch develop from different embryologic origins. Six sets of pharyngeal arches develop the aortic arch and its branches. Any disturbances in this developmental process can lead to aortic anomalies including CoA. [25]

Additionally, research on inheritance patterns have suggested that several genes are significant in CoA etiology, including the NOTCH1 gene, which plays an important role in cardiac development and vasculogenesis[43]. Nevertheless, the identified genes and variants associated with CoA and other LHOD so far only explain the etiology in a small fraction of the CoA population.[49]

CLINICAL PRESENTATION

The symptoms of CoA typically develop within days or weeks after birth, following closure of the ductus arteriosus[50] (Figure 4). Initial symptoms are tachypnea, signs of poor peripheral perfusion and feeding difficulties. It is a lesion that often can go unnoticed before discharge from the maternity ward. The symptoms may however develop very rapidly, and immediate treatment is needed.

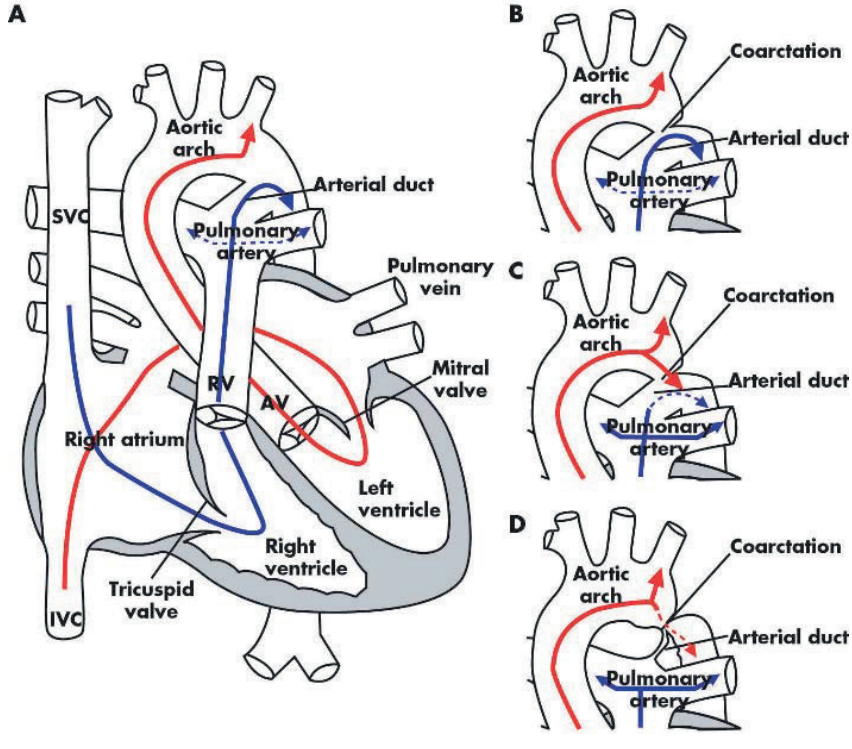


Figure 4: A) The normal fetal circulation B) Coarctation of the aorta in utero does not affect the fetal blood flow pattern C) After birth there is an increased pulmonary blood flow and forward flow from the aortic arch to the descending aorta D) As the ductus arteriosus constricts, the narrowing of the coarctation is accentuated and the increased obstruction leads to a gradient.

SVC: superior vena cava, IVC: inferior vena cava, PV: pulmonary valve, AV: aortic valve

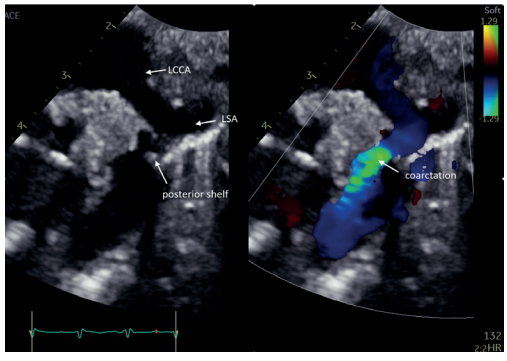
An infusion of prostaglandin E1 (PGE1) will relax the ductus arteriosus and reduce the obstruction, restoring the blood flow to the lower body. If not treated with PGE1 in time, the pressure load created by the coarctation causes left ventricular failure, pulmonary hypertension, right ventricular failure and cardiovascular collapse. [25,50,52] Pulmonary edema is a common finding although it may be less frequent in the presence of a patent foramen ovale, permitting a left-to-right shunt to lower atrial pressure. Low blood perfusion to the lower body leads to ischemia of abdominal organs and secondary organ failure.[50]

In infants with milder CoA, when the narrowing occurs slowly, the clinical presentation appears later.[53] Also, with time, collateral circulation around the coarctation may develop, decreasing left ventricular afterload and securing some blood flow to the lower body.[52] The development of collateral circulation has been shown to occur already during fetal life or within the first few weeks of postnatal life.[54] An animal model had collateral development already within 48 hours after birth.[55]

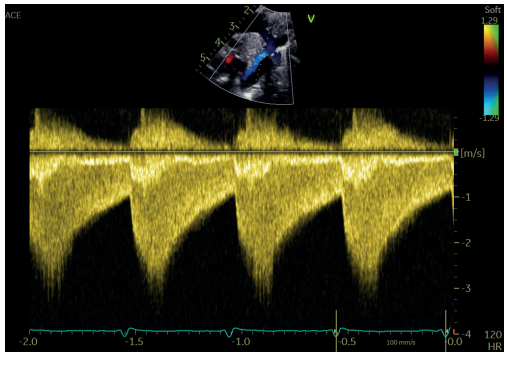
ECHOCARDIOGRAPHY

For most CHD, including CoA, transthoracic echocardiography is the first-in-line diagnostic method.[56,57] In using two-dimensional echocardiography, colour Doppler and continuous wave Doppler, the hallmark findings on echocardiography include a posterior "shelf" with a constriction of the aortic isthmus at the insertion of the ductus arteriosus. The narrowing causes a turbulent flow on Doppler with flow acceleration during systole and a continuous antegrade flow in diastole[57,58] (Figure 5). Other findings consists of a blunted pulsatility of the abdominal aorta using pulse wave Doppler. Indications for intervention include a narrow obstruction, a high Doppler flow velocity with diastolic extension and depressed left ventricular function.[59]

Echocardiography has its limitations, however, and it can sometimes be hard to obtain a good acoustic window for adequate visualization of the CoA area, giving a non-consistent result.[60] When the ductus arteriosus is still widely patent, the diagnosis of CoA can be especially difficult due to the lack of flow acceleration in the isthmus area, and repeated echocardiograms may be required until the PDA closes.[61,62]



A)



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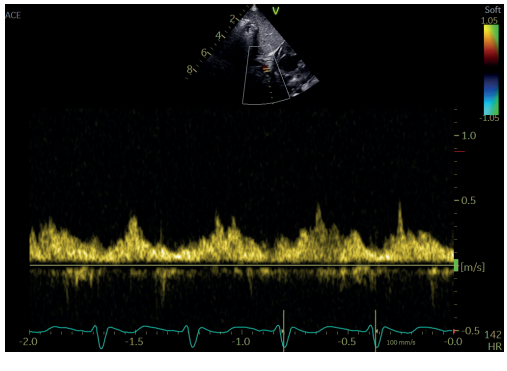

C)

Figure 5: Echocardiographic hallmarks in a newborn with CoA and with a closed ductus arteriosus. A) Sagittal view of the aortic arch with and without colour flow Doppler. There is a short coarctation in the aortic isthmus with a posterior shelf. B) Continuous wave Doppler in descending aorta. There is an increased flow velocity in systole and a diastolic extension. C) Pulsed wave Doppler of the abdominal aorta showing blunted pulsatility and diastolic extension. LCCA: left common carotid artery, LSA: left subclavian artery

SURGERY

Newborns and infants with CoA who are symptomatic should undergo surgery as soon as possible after stabilization. Cases with a borderline aortic arch are usually monitored without the initiation of prostaglandins for the coarctation to "declare itself". In neonates, the treatment of choice is surgical resection of the CoA segment. An extended CoA-resection with an end-to-end anastomosis through a left thoracotomy (without cardiopulmonary bypass) is the preferred treatment[63] (Figure 6). In neonates with associated defects that need repair concurrently and in cases with a hypoplastic arch, the procedure is performed via a median sternotomy. Several large series have demonstrated excellent surgical outcomes with a rate of re-coarctations of < 10%.[64 63]

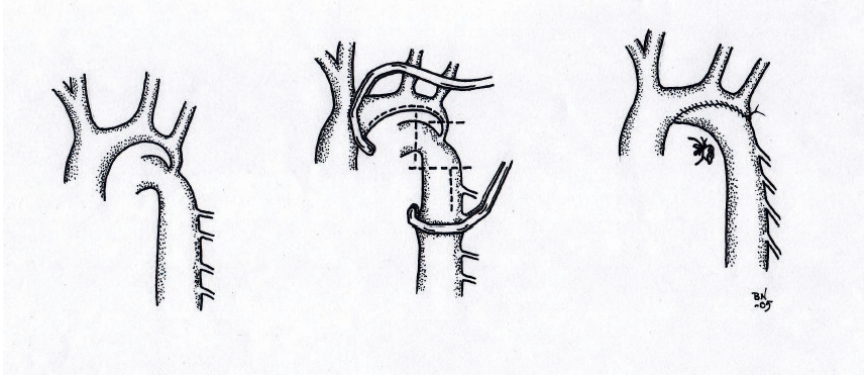

Figure 6: Extended end-to-end resection.

Picture by pediatric cardiac surgeon Boris Nilsson, printed with kind permission

Screening for CCHD

PRENATAL ULTRASOUND SCREENING

Prenatal diagnosis of CCHD allows for planning of the delivery and postnatal care, including centralization of deliveries in selected cases. Prenatal diagnosis has also been shown to lower the risk of serious neonatal events including death.[65-70] Also, it allows for the choice of terminating the pregnancy, with the potential to affect the live birth prevalence of

CCHD in a population.[71] A recent population-based study from Denmark reported a prenatal detection rate for major CHD of 71% and termination of pregnancy was performed in 59%.[17] The reported antenatal detection rate varies widely between and within countries. Usually, detection rates of around 50% are reported in low-risk populations.[72,73]

In Sweden, 97% of pregnant women undergo routine prenatal ultrasound examination at 18-20 weeks of pregnancy. [74] Current national screening protocols are performed by trained midwives and obstetricians. In 2016, in Sweden, outflow views and the three-vessel and the tracheal view became mandatory in addition to the four-chamber view following international guidelines.[75] Since 2022, the guidelines have been made more strict, and colour Doppler is also recommended.[76]

Currently in Sweden, a prenatal diagnosis of serious CHD (defined as requiring surgery or catheter intervention within 1 year of age) is now more common than a postnatal diagnosis, if terminations and fetal deaths are included.[76] Figure 7 shows the improvement in prenatal detection rate in Sweden from 2010 to 2021 in selected diagnostic groups.

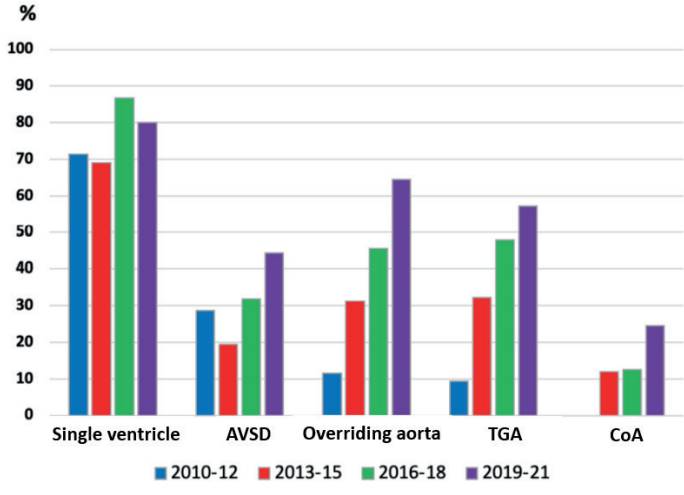

Figure 7: The proportion of liveborns with a prenatal diagnosis (%) subdivided by diagnostic groups and by year of birth; Single ventricle (all forms), AVSD: atrioventricular septal defect, overriding aorta (the most common variants), TGA: transposition of the great arteries, CoA: coarctation of the aorta.

Data from the Swedish registry of congenital heart disease (SWEDCON)76 with kind permission.

Prenatal diagnosis of CoA

A recent study showed that prenatal diagnosis improves survival in severe coarctation.[77] These findings confirms earlier published data, indicating the benefits of a prenatal diagnosis.[78] Accurately predicting postnatal CoA during fetal life is one of the most challenging tasks in fetal medicine. Prenatal detection rates vary but most studies report rates between 22-35%.[72,73] There is no single reliable criterion established but diagnosis typically relies on secondary and indirect signs such as disproportions in ventricular and great arterial sizes with smaller left heart structures. However, these findings can be subtle early in fetal life and may have low diagnostic accuracy late in gestation.[79-81] Prenatal diagnosis of CoA also carries a high false positive rate.[80,81] Prenatal suspicion of CoA usually needs repeated assessments during gestation to improve diagnostic accuracy and to evaluate potentially evolving arch hypoplasia.[48,81]

POSTNATAL SCREENING

Neonatal physical examination - NPE

Soon after birth, before discharge, neonates typically undergo a physical examination including auscultation of the heart, palpation of femoral pulses alongside with observation for cyanosis, peripheral perfusion and tachypnea. However, several studies have shown that neonatal physical examination fails to detect over half of babies with CCHD, particularly those with duct-dependent systemic circulation.[34,82-84] Challenges in unrevealing the cardiac defects is due to the transitional changes that occur from fetal to postnatal circulation. Those changes may create flow murmurs that can be mistaken for a CHD, while murmurs of significant defects may not be apparent until after discharge following the decline in pulmonary vascular resistance.[85]

Changes in routine newborn care

Over the last 50 years in Sweden, the mean stay at the maternity ward after vaginal delivery has decreased from 6.1 days to 1.6 days in 2020. [86] This trend is also evident in other countries and is likely to continue.[21,87,88] In several countries, the responsibility of performing the predischarge examinations of newborns has shifted from doctors to trained nurses.[21,89-91]

PRINCIPLES OF PULSE OXIMETRY AND PERFUSION INDEX

Pulse oximetry enables continuous, non-invasive monitoring of the peripheral oxygen saturation (SpO_2) which serves as an estimate of arterial oxygen saturation (SaO_2) levels.[92]

Pulse oximetry works on the principle of photoelectric plethysmography and the Beer-Lambert law.[92,93] The device includes a sensor, a light-emitter and a light detector, placed on for example a finger or an earlobe. The sensor emits one red and one near-infrared (IR) beam. The measurement is based on the amount of light absorption at the two different wavelengths (red and IR) by the oxygen-loaded form of hemoglobin (oxyhemoglobin) and reduced hemoglobin (deoxyhemoglobin).[92] The amount of light transmitted and absorbed varies with the pulsatile arterial blood flow as the arterial blood volume increases during systole and decreases during diastole. In contrast, the blood volume in the veins and capillaries, as well as in skin, fat, bone and other tissues, remains fairly stable.[92] When light passes through these tissues without being absorbed, it reaches the photodetector of the probe, generating signals that have a steady, non-pulsatile "direct current" (DC) component, as well as a pulsatile "alternating current" (AC) component (Figure 8). The pulse oximeter´s microprocessor calculates the ratio of absorbance between AC and DC components of blood flow, which is used to display the SpO_2 level.

Perfusion index (PI) has been incorporated into the latest generation of pulse oximeters. It is non-invasive, automatically obtained and is displayed on the monitor alongside with the saturation value. It gives a real-time assessment of the peripheral tissue perfusion using photoplethysmography (Figure 9).

As previously described, pulse oximetry distinguishes the pulsatile or "alternating current" (AC) and the non-pulsatile or "direct current" (DC) signals, where the former represents arterial blood.[94] The PI is calculated as a fraction of AC/DC multiplied by 100, reflecting the amplitude of the pulse oximeter waveform.[95] The non-pulsatile components, such as bone, venous blood and connective tissue remains relatively constant during the cardiac cycle whereas the pulsatile components (arterial blood) are dynamic. The changes in these components causes changes in the PI value. Both signals are derived from the amount of infrared light reaching the detector of the pulse

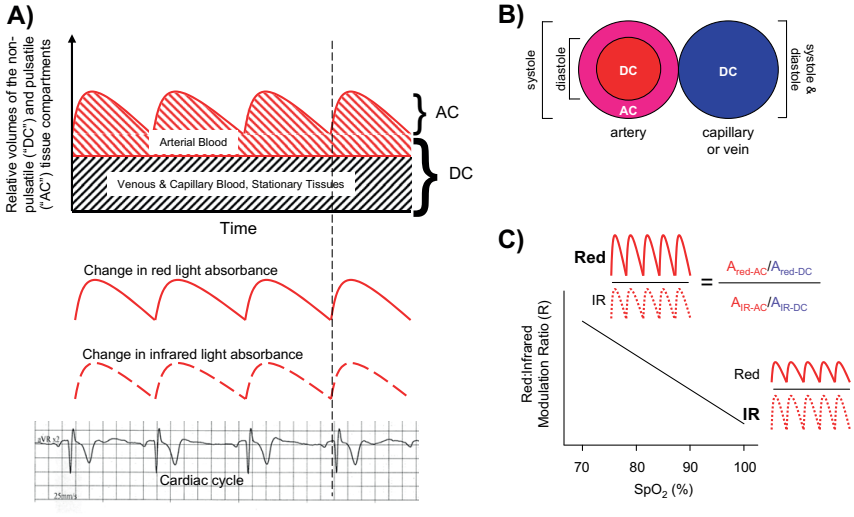

Figure 8: This figure depicts how a pulse oximeter absorbs light to measure oxygen saturation levels. A) Systole is marked by an elevation in arterial blood volume, and an increase in the absorption of both red and infrared light in the pulsatile (AC) component. In diastole, the amount of absorbed light in the AC component decreases. In contrast, the non-pulsatile (DC) compartment maintains a consistent blood volume throughout the cardiac cycle. B) The cross-sectional view of an artery and a vein and the AC and DC compartments where only the artery has a pulsatile component. C) Curve illustrates the correlation between the Red:Infrared Ratio and SpO2.

SpO2: oxygen saturation

Figure 9: The perfusion index (PI) value is displayed at the very right, over the plethysmographic curve, and is in this example 3.7%. The oxygen saturation (SpO2) is 98% and the heart rate is 80 beats per minute.

oximeter when the vascular bed is illuminated, which reflects the amplitude of the signal.[92] This value can be used to estimate the relative strength of the pulse, i.e. the amount of blood at the monitoring site (for example hand or foot).

Variations in PI values depends upon both the blood flow in the peripheral circulation and vascular tone.[96] Thus, it reflects the cardiac output and the balance between the sympathetic and parasympathetic nervous systems.[97]

THE INTRODUCTION OF PULSE OXIMETRY SCREENING (POS)

As several studies highlighted the unsatisfactory result of neonatal screening in detecting newborns with CCHD, POS was evaluated as a possible additional screening tool. The method seemed simple, quick and non-invasive. Early large, population-based studies from Scandinavia and Germany had a great impact.[2-4] The Swedish study included 39 821 screened newborns.[2] Combining physical examination with pulse oximetry had a sensitivity of 82.8% for lesions with duct dependent circulation. The false positive rate of pulse oximetry was low (0.17%).

In 2012, a large meta-analysis including 230 000 newborns and a large multi-cenre study from China confirmed the additional value of adding POS to CCHD-screening.[98,99] A Cochrane analysis conducted in 2018 including 437 000 screened babies, showed that POS had a moderate sensitivity (76.5%) and a high specificity (99.9%), with a false positive rate of 0.14%, which supported its introduction.[100] It was concluded that out of 10,000 apparently healthy late term infants, five with CCHD would be detected by POS and one would be missed (false negative). Comparable results were reported by a subsequent systematic review.[98]

Over the last decade, POS has been adopted in an increasing number of countries. For example, all US states had implemented the screening by 2018.[101] In 2017, Abouk *et al* reported a 33% reduction in infant deaths of CCHD in US states with mandatory POS compared to states without mandatory POS.[102] However, POS has not yet been generally recommended in the UK due to reasons such as unnecessary investigation of neonates with false positive results, prolonging hospital stays and parental anxiety[103] Other countries have argued against the introduction of POS due to high prenatal detection rates and that the added value of POS would be limited.[91]

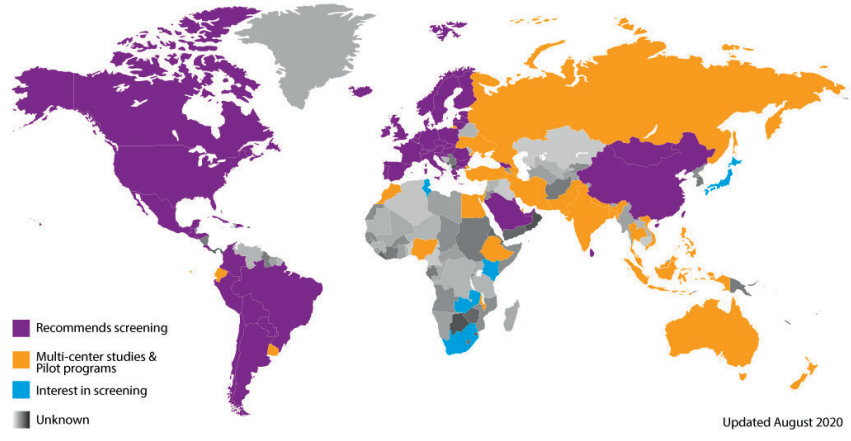

Figure 10: Critical congenital heart disease screening global implementation map.

Reprinted with permission Newborn Critical Congenital Heart Disease Screening Using Pulse Oximetry: Value and Unique Challenges in Developing Regions, Hom L, Gerard, M, International journal of neonatal screening, 2020, Vol.6 (3), p.74-74104, CC BY 4.0.

PULSE OXIMETRY SCREENING IN SWEDEN

In Sweden, with 110 000 - 120 000 live births annually, POS had reached full coverage in all delivery units by 2013.[86,91] Currently, without national guidelines, all units in Sweden routinely use a protocol measuring in the right hand (pre-ductally) and in one foot (post-ductally).[105,106] The protocol calls for POS before discharge or before 24 hours of age if discharge occurs later.

This algorithm (Figure 11) or modifications of it, is endorsed by most countries using POS, but there are significant variations.[101]

In addition to POS, 12 out of 46 delivery units routinely collects PI values as part of the general CCHD screening program corresponding to approximately 20 000 newborns undergoing this screening yearly. However, delivery units use different cut-offs for a positive PI screen, varying between <0.5% - <1.0%. Most units use the cut-off <0.7% corresponding to the 5th percentile in the study by Granelli *et al*[5].

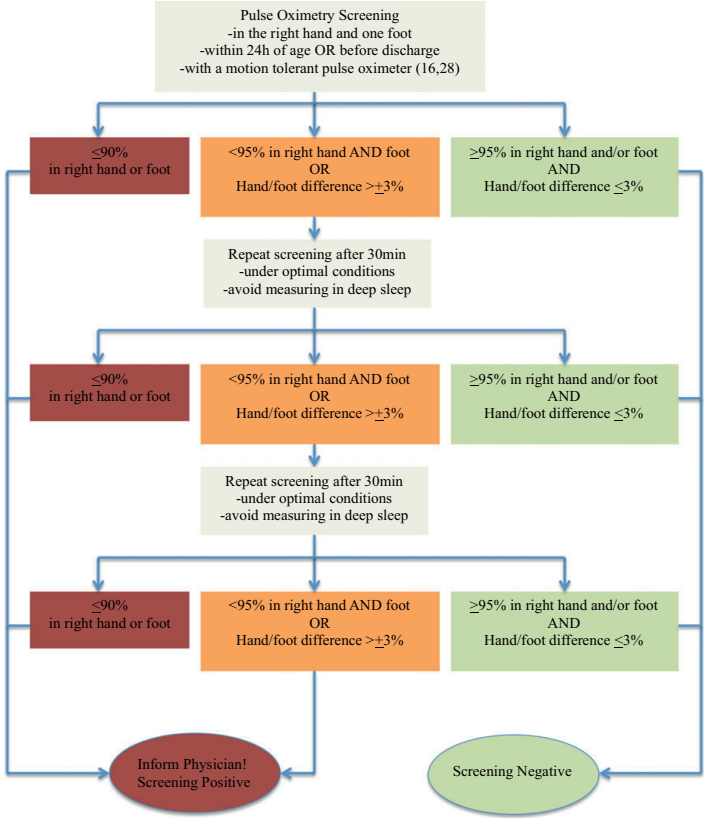

Figure 11: Screening algorithm used by delivery units in Sweden.

Reprinted with permission, Nordic pulse oximetry screening – implementation status and proposal for uniform guidelines, Granelli et al.91, CC BY 4.0

FALSE NEGATIVE RESULT OF POS

Detecting false negatives is challenging as it requires comprehensive follow-up of all discharged newborns.[107] False negative screenings occur particularly in cases of duct-dependent systemic circulation, such as CoA, AS, IAA and HLHS. [4,108] In the Swedish POS study, the false negative rate was 50% (10 of 20) in LHOD, whereas all cases with duct-dependent pulmonary circulation were detected.[106] In a large cohort of 122 000 asymptomatic newborns, 13 of 22 cases with LHOD had a false negative result on POS.[99]

A study compared pulse oximetry with umbilical artery blood gas oxyhemoglobin in patients with CCHD using paired observations[109]. It was found that pulse oximetry overestimated arterial oxyhemoglobin by an average of 5%. Likewise, in another observational study, arterial blood-gas measurements were simultaneously compared to pulse oximeter saturations. Pulse-oximeters tended to over-estimate the arterial saturation in cyanosed children, especially when arterial saturations were below 80%.[110] Overestimation of SaO_2 below 80% has also been shown in other studies, potentially impacting clinical treatment decisions.[121-123]

THE USE OF PI IN NEWBORNS

Pediatric researchers have shown interest in exploring the use of PI in various clinical situations to assess neonates. In 2005, a study proposed that PI could be used to detect subclinical chorioamnionitis in newborns after delivery.[111,112] This was followed by studies that found a strong correlation between PI and left ventricular output in healthy infants, suggesting that PI could help identify pathologies that restrict systemic blood flow.[113] This led to further studies on the potential role of PI in detecting CCHD in newborns, CoA and other LHOD in particular.[5,114-116]

In 2007, Granelli *et al* conducted a study on a large cohort of newborns to measure PI between 1-120 hours after birth (median 42 hours). The study reported a median PI value of 1.7% in hand and foot, with the 5th and 95th percentiles ranging from 0.7-4.5%.[5] Using the 5th percentile at 0.7% as a cut-off, five out of nine newborns with LHOD had a pre-or postductal PI-value < 0.7%. A small-scale study confirmed the PI-values in healthy newborns at 24 hours of age.[117]

PI IN CCHD SCREENING

Several studies from 2017 onwards investigated the potential benefits of adding PI to CCHD-screening[114,116-118] (Table 1). A prospective study conducted in 2017 screened 42 169 healthy newborns at 48-72 hours of age.[114] The study used a slightly higher threshold at PI 0.9% (not reporting 5th and 95th percentiles), and one out of four diagnosed with CoA/IAA screened positive. Another study from 2019, screened 3 175 newborns at

24-48 hours of age.[116] The 5th percentile was 1.1% pre-ductally and 1.2% post-ductally. When retrospectively applying this cut-off on a group of newborns screened by POS and in addition 33 cases of prenatally detected cases of CCHD, this resulted in a sensitivity in detecting CCHD at 64% pre-ductally and 61% post-ductally. When a more commonly accepted cut-off of 0.7 % was applied, the sensitivities were 33% and 36% respectively. In a 2020 study, analyzing the post-ductal PI-values in healthy newborns at 24 hours of age, the post-ductal 5th percentile was 0.5%.[115] When applying this threshold to cases of CCHD (including prenatally suspected cases), three out of four newborns with CoA/IAA were picked up, all of whom had been missed by POS.[115]

Table 1: Studies on PI in newborns.

First Author	Year	Design	Cohort (N)	Screening (h)	Cut off PI (%)	Results
Granelli[5]	2007	Prospective, adding PI to POS after NPE	10 000	1-120	< 0.7	5/9 with LHOD had PI below cut-off.
Jegatheesan[117]	2017	Retrospective, stored PI-data collected	2 768	>24		Median PI 1.8 in healthy newborns (IQR 1.2-2.7), 5th percentile 0.7
Schena[114]	2017	Prospective, adding PI to POS after NPE	42 169	48-72	< 0.9	1/4 with CoA/IAA had PI below cut-off, False positive rate: 0.27%, two consecutive screenings (one unit had 6%)
Uygur[116]	2019	Prospective, adding PI to POS	3 175	24-48	< 1.1 (pre-ductal) < 1.2 (post-ductal)	61% and 64% with CCHD had PI below cut-off (LHOD not reported separately), false positive rate: 2.7%
Ramesh[118]	2018	Prospective, adding PI to POS	1 011	24-72	< 0.7	1/1 with LHOD had PI below cut-off False positive rate (0.1%), three consecutive screenings
Siefkes[115]	2020	Prospective, adding PI to POS	144	>24	< 0.5	3/4 with CoA/IAA had PI below cut-off. False positive rate: 2.4%

PI: perfusion index, POS: pulse oximetry screening, NPE: neonatal physical examination, LHOD: left heart obstructive defect, CoA: coarctation of the aorta, IAA: interrupted aortic arch, CCHD: critical congenital heart defect

In conclusion, the above-mentioned studies provide evidence that PI can detect some cases of LHOD missed by POS and NPE. However, most studies were underpowered. When combining PI, POS and NPE the Swedish study reported a sensitivity of 100% in newborns with LHOD.[5] Combining PI and POS also increased the false positive rate. Most studies reported false positive rates of PI ranging from 0.27% to 6%.[114 116] While a high false positive rate is anticipated when using the 5th percentile cut-off, there has been limited research on reducing the false positive rate such as repeating abnormal measurements. However, in one study, repeated measurements were taken during screening at an average age of 34 hours, successfully reducing the false positive rate.[118] A systematic review from 2019 concluded that current evidence does not support the routine use of PI in newborn screening.[119] More data is needed on the test-accuracy of PI in newborns with LHOD.

3

Aims

The primary objective of this thesis was to examine the efficiency of screening for CCHD in Sweden, with a particular emphasis on the detection of CoA. A secondary aim was to assess whether utilizing PI could improve early detection of aortic arch obstructions.

The specific aims of the included studies were:

Paper I

To determine the extent to which prenatal ultrasound screening and POS contributed to the early detection of isolated neonatal CoA in a population-based cohort. In addition, the study aimed to investigate the symptoms and signs that led to the diagnosis and the potential consequences of a missed diagnosis.

Paper II

To study the false positive rate of PI in apparently healthy newborns. A previously suggested cut-off <0.7% for a positive screen in combination with repeated measurements, as opposed to a single measurement, was studied. Additionally, the study sought to assess the feasibility of using PI in the well baby nursery and examine potential reading inaccuracies.

Paper III

To assess the relative impact of prenatal ultrasound screening, POS and NPE to early detection of CCHD in the context of increasing prenatal detection rates.

Paper IV

To investigate whether adding PI to POS improves the timely diagnosis of AAO in a cohort of infants born in units routinely using POS as well as PI in the screening for CCHD. The study also aimed to establish optimal PI screening cut-offs for AAO detection by comparing newborns with and without AAO.

4

Patients and methods

Overview of patients and methods

Paper	I	II	III	IV
Study design	Population based retrospective cohort study.	Prospective cohort study.	Nationwide population based retrospective cohort study.	Population based retrospective cohort study.
Inclusion criteria	Newborns with isolated CoA operated before 2 months of age or who died without receiving surgery.	Apparently healthy fullterm newborns.	Liveborn, fullterm newborns with a CHD requiring surgery or catheter intervention within 28 days of birth or who died without receiving surgery.	Liveborn, fullterm newborns with CoA or IAA from Paper III, born in units using PI routinely in addition to POS. Controls: subjects from Paper II.
Study period	2003-2012	May-June 2018 and during September 2018-May 2019	2014-2019	2014-2019
Main research question	To investigate the contribution of pre- and postnatal screening to the early detection of this condition.	To determine the false-positive rate of PI with repeated measurements if below cut-off.	To evaluate the relative contributions of prenatal ultrasound, POS and NPE to the timely detection of CCHD.	To investigate if addition of PI to CCHD screening increases early detection of AAO.

Patients and study designs

Paper I: This retrospective population based study was conducted on a single-centre cohort of infants with a diagnosis of isolated CoA who either underwent surgery within 2 months of age, or died without treatment within the same period. The study included patients born between 2003 and 2012 in the referral area of The Pediatric Heart Centre at Queen Silvia Children´s Hospital in Gothenburg. The hospital covers approximately half of the pediatric population in Sweden. Isolated CoA was defined as a defect without associated significant cardiac lesions that required surgery.

Paper II: This prospective study enrolled fullterm infants who were born at Sahlgrenska University Hospital between May - June 2018 and September 2018 - May 2019. The hospital has an annual delivery rate of approximately 10 000. Only infants who were considered well at the time for data collection were included.

Paper III: This nationwide, retrospective population-based cohort study included all fullterm newborns with CCHD in Sweden between 2014 and 2019, who required surgery or catheter intervention, or died without such treatment within 28 days of birth.

Paper IV: In this retrospective population-based study, all fullterm newborns with AAO included in *Paper III* and born in units routinely using PI in addition to POS, were included. The cohort in *Paper II* served as controls.

Data collection and methods

Paper I:

All cases of isolated CoA were identified from the local cardiac surgery registry at the pediatric cardiac centre in Gothenburg, using the ICD-10 code Q25.1. Also, deaths from undetected CCHD were identified from the Causes of Death Registry maintained by the Swedish National Board of Health and Welfare. Local fetal registries were also searched. Data from hospital charts was collected including CCHD screening results, age at first symptoms and time of diagnosis relative to hospital discharge.

Paper II:

PI was measured using Masimo Radical 7 pulse oximeters. A sensor was placed on the right hand and one foot. Initially, a pilot study was conducted with up to two repeat recordings in case of PI <0.7%. The protocol was then adjusted to require a delay of 30 minutes before repeating the test. In case of a positive screen echocardiography was performed within 24 hours. The recordings in the pilot study were undertaken by the nursery staff and the author. All subsequent recordings were obtained by two research nurses.

In a subgroup, automatically sampled trend data of PI and $SpO_{2,}$ was downloaded from the pulse oximeter using a software tool (MICT – Masimo Instrument Configuration Tool, Masimo Corporation, USA). The time required for the recording was registered. The trend PI-data was compared to the manually read PI-values for each neonate.

To ensure no cases of CCHD were included in the cohort, all included cases were searched for in the electronic medical records using their unique personal identification number.

Paper III:

Cases were identified using the ICD-10 codes Q20-Q28 from local surgery registries at the two pediatric cardiac surgery centres in Sweden (Lund and Gothenburg) and in cardiac catheter registries in Lund, Gothenburg and Stockholm. Deaths from undetected CCHD were identified by the Causes of Death Registry maintained by the Swedish National Board of Health and Welfare. To collect clinical data including CCHD screening results, time of diagnosis relative to hospital discharge and mortality, case note review was conducted using a unique 12-digit personal identification number in each case. The total number of births in the background population was retrieved from Statistics Sweden (www.scb.se) and The National Board of Health and Welfare (www.socialstyrelsen.se).

We choose a definition of CCHD consistent with the definition used by Wren and Ewer.[6,23] However, by including all CHD intervened upon before 28 days of age, we also included defects usually not considered to be critical, such as VSD and vascular rings. We therefore excluded a number of diagnoses.

Paper IV:

All cases of CoA and IAA from *Paper III*, born in units using PI routinely, were identified. Deaths from undetected CCHD were identified by the Causes of Death Registry maintained by the Swedish National Board of Health and Welfare. Data from hospital charts was reviewed including CCHD screening results, age at screening and time of diagnosis relative to hospital discharge. For the controls, medical case notes were reviewed to ensure no case with late presentation of CCHD was included.

STATISTICAL METHODS

Demographic data was presented as mean with 95% confidence interval (CI), standard deviation (SD) or range for normally distributed continuous variables and median with interquartile range (IQR) for non-normal distributions. Absolute numbers and percentages were used for categorical variables. For group comparisons, Fisher's exact test was used for dichotomous variables and the Chi-Square test for non-ordered categorical variables. Mann-Whitney U test was used for comparisons between two groups and Wilcoxon signed rank test for within-patient comparisons. For all tests, a p-value < 0.05 was considered statistically significant. Other statistical methods used in the papers are presented below.

Paper I: Incidence was given as the number of liveborns with isolated CoA divided by the total number of liveborns within the population.

Paper II: Kolmogorov–Smirnov test was used for distribution pattern of normality. Distributions were displayed using frequency distribution histograms. Specificity and false positive rate were studied. Bland-Altman´s plot was used for assessing agreement between two quantitative measurements.

Paper III: Prevalence was given as the number of fullterm liveborns with a cardiac lesion divided by the total number of liveborns within the population. Sensitivity was calculated.

Paper IV: Distributions were displayed using frequency distribution histograms. Potential cut-offs were assessed with frequency distribution analysis using Youden´s rule. Identified cut-off values were assessed using

receiver operating characteristic (ROC) curves measuring area under the curve (AUC) with confidence limits and significance of difference from 0.5. In addition, sensitivity and specificity was calculated.

For *Paper I, II, III* and *IV*, statistics were performed using SPSS Statistics (IBM Corp.), and in *Paper IV,* Graph Pad Prism was also used.

Ethical considerations

Epidemiological research involves studying the occurrence and distribution of health outcomes, such as diseases or deaths within a specific population over a period of time. The Helsinki declaration is a set of ethical principles that serves as the foundation for research involving human subjects.[120] The observational cohort studies in *Paper I, III* and *IV* are examples of epidemiological studies that include data such as medical history, clinical condition and mortality, collected from patients records. While obtaining individual consent is a fundamental ethical principle in human research, in some situations, such as small patient groups, minimizing patient loss is crucial for conclusive results. To facilitate observational studies, the general rule of informed consent has been modified,[121] as seen in *Papers I, III* and *IV* where consent was not obtained. However, ensuring patient privacy and confidentiality remained a primary ethical concern, and patient data was coded and stored safely to mitigate these risks. Precautions were taken to protect the participating subjects and ensure that it was not possible to identify subjects from any published information.

Paper I was approved by the Central Ethical Review Board in Gothenburg, approval number 542-L3 with supplementary permit 137-12.

Paper II was approved by the Central Ethical Review Board in Gothenburg, approval number 045-17. Written legal caregiver consent was obtained from all included cases. Caregivers were informed that they could leave the study at any time.

Paper III and *IV* were approved by the Central Ethical Review Board in Gothenburg and the Swedish Ethical Review Authority, approval number 119-16, 714-17 and 2020-02762.

5

Results

Paper I

Out of 89 liveborn infants, 14 were born preterm (< 37 weeks) or had a birthweight < 2500 grams. Male infants accounted for the majority of cases (58%). Six infants died preoperatively, and 83 had surgery at a median age of 8 days (2-52).

Three cases (3.3%) had a prenatal diagnosis including one termination of pregnancy. Among the 19 newborns with CoA, born after the implementation of POS, 4 (21%) were diagnosed as a result of a positive screen. In the remaining 83 cases, the first clinical signs were observed at a median age of 2.2 days (0 - 41.5 days) (Figure 12).

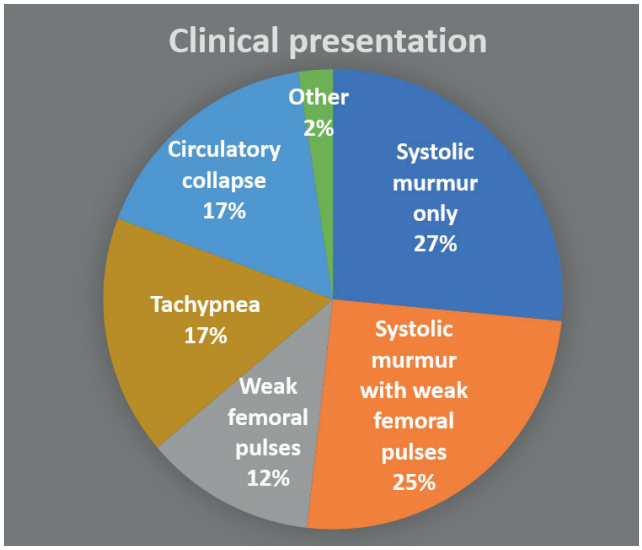

Figure 12. First presenting symptom at a median age of 2.2 days in 83 newborns with isolated CoA.

DIAGNOSIS AFTER DISCHARGE

Following a median hospital stay of 2.4 days, 46 of 87 (53%) cases with postnatal diagnosis were discharged from hospital. Among them, 28 had a normal NPE. However, the remaining 18 neonates had abnormal findings at the NPE but were discharged nevertheless, although 14 of them had a planned re-visit. Seven of the 18 newborns underwent echocardiography with either normal or inconclusive findings. Of 46 discharged, 22 were in a circulatory failure (needing intensive care for stabilisation) at readmission or shortly thereafter. One additional infant died at home and was diagnosed at autopsy (Figure 13).

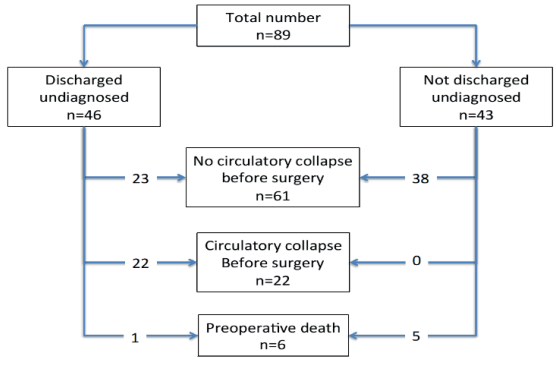

Figure 13: Outcome in 89 infants with isolated CoA.

INCONCLUSIVE EARLY ECHOCARDIOGRAPHY

The first echocardiographic examination failed to diagnose the CoA in 16 patients, including 7 who were examined before discharge. Furthermore, three neonates with CoA who died prior to surgery at referral hospitals had also undergone a nondiagnostic echocardiographic examination before death.

PREOPERATIVE MORTALITY

Among six infants who died prior to surgery, one was premature with a very low birthweight (1090 grams) (Table 2). The diagnosis of CoA was

made 1 day after birth, and PGE1 was started. However, the newborn developed necrotizing enterocolitis and died at 9 days of age. Three neonates died within 24 hours; one had sepsis (early echocardiography was considered normal), one had diaphragmatic hernia and the third had signs of pulmonary hypertension on echocardiography. The study did not include images of the aortic isthmus and the ductus arteriosus. Although the infant received PGE1, death occurred at 19 hours of age, and autopsy confirmed a diagnosis of CoA. Another case, a fullterm infant, who was small for gestational age, had a murmur at 7 days of age. An echo study at 8 days could not visualize the ductal area but the study was consistent with pulmonary hypertension. The child suddenly died at 9 days of age. The last case was discharged undiagnosed at 3.3 days of age and was considered well at two NPEs. However, this infant died at home at 11 days of age, and the caregivers reported tachypnea before death.

One infant was born prematurely and had discrete signs from the intestines pre-operatively, but still received surgery at 7 days of age. The infant died shortly after surgery in necrotizing enterocolitis.

Table 2: The combined preoperative and 30-day postoperative mortality

Gestational age (w)	Echocardiography performed	Echocardiography result	Co-morbidity	Discharged undiagnosed	Surgery	Age at death
38	No	-	CDH	No	No	<24 h
39	Yes	"Normal"	GBS sepsis	No	No	<24 h
42*	Yes	"Normal"**	None	No	No	<24 h
31	Yes	CoA	Prematurity, NEC	No	Yes (+7 d)	7 d
26	Yes	CoA	Prematurity, NEC	No	No	9 d
38*	Yes	PHT	SGA	No	No	9 d
40*	No	-	None	Yes	No	11 d

CDH: congenital diaphragmatic hernia, GBS: group B Streptococcus, PHT: pulmonary hypertension, NEC: necrotizing enterocolitis, SGA: small for gestational age

*Death potentially preventable by prenatal or early postnatal diagnosis

**The aortic arch could not be visualized

Paper II

A total of 463 newborns were included in the cohort and were considered well at the time for obtaining the measurements, at a median age of 18 hours. The mean gestational age was 39 weeks (range 37+0 - 42+0) and mean birth weight 3512 g (range 2290 - 4945).

PI-VALUES

The median PI values in the right hand (pre-ductally) and foot (post-ductally) were 1.9% (IQR 1.4-2.5) and 1.7% (IQR 1.2-2.5) respectively. There were no significant differences in PI values between the right hand compared to the foot and no age-related PI differences. The PI-values were not normally distributed (Kolmogorov–Smirnov test; $p < 0.01$). The 5th percentile in the foot corresponded to 0.9% (Table 3).

Percentile	PI right hand (%)	PI foot (%)
1 st	0.7	0.7
5 th	1.0	0.9
25 th	1.4	1.2
50 th	1.9	1.7
75 th	2.5	2.5
95 th	4.0	4.6
99 th	5.8	7.8

Table 3: The percentile distribution of PI in right hand and foot in 463 newborns.

FALSE POSITIVE RATE

In the pilot study, a high false positive rate of 6% was observed. After revising the protocol to include a 30-minute delay in obtaining additional PI-values after a value below cut-off, there were no false positives in the subsequent 463 newborns. In five cases the first measurement was < 0.7% and therefore repeated. All five had values ≥ 0.7% at the second measurement. In no case was a third measurement indicated.

For comparison, in a subgroup of 100 newborns, the manually obtained PI-values were compared to automatically stored trend data in the same individual. The results did not show any significant differences in the PI values comparing the mean stored PI data to the manually collected values (p= 0.704)

TIME CONSUMPTION IN COLLECTION OF PI

The median recording time per screen in the right hand was 2 minutes and 27 seconds (range 22 seconds - 9 minutes 28 seconds) and 2 min and 8 sec in the foot (range 42 seconds – 7 minutes and 9 seconds). Collecting PI values took an additional mean of 3 minutes and 30 seconds in addition to POS. In terms of duration, collecting PI-values was more time-consuming than POS, as POS only required 34 seconds (range 4 seconds – 5 minutes and 20 seconds) in the hand and 32 seconds in the foot respectively (range 4 seconds – 3 minutes and 24 seconds).

Paper III

The cohort included 630 fullterm infants with CCHD. As defined in this study, CCHD had a prevalence of 0.91 per 1 000 term infants. Table 4 provides the prevalence of the specific diagnostic groups included (cases per 100 000 fullterm liveborns).

Out of 630 newborns with CCHD, 66% were males with a median gestational age of 39 weeks and a median birth weight of 3.4 kg. Delivery was at one of the two surgical centres for pediatric cardiac surgery in 240 (39%) cases and 83% of those with a prenatal diagnosis were delivered there. PGE1 was given to 82% and the median age at first intervention was five days. Cardiac surgery was the first procedure in 481 (79%) cases and catheter intervention in 128 cases (21%), including balloon atrial septostomy.

Cardiac diagnosis	All N	Prevalence per 10 000
HLHS	59	0.9
IAA	12	0.2
CoA isolated	128	1.8
CoA complex	57	0.8
AS	18	0.3
Unbalanced AVSD	7	0.1
DILV	12	0.2
SV	7	0.1
TA	10	0.1
Ebstein	2	0.0
PA/IVS	27	0.4
PA/VSD	16	0.2
ToF	15	0.2
DORV	24	0.3
PS	39	0.6
Truncus arteriosus	25	0.4
TGA simple	106	1.5
TGA complex	44	0.6
TAPVR, unobstructed	11	0.2
TAPVR, obstructed	13	0.2
Total	**632**	**9.1**

Table 4: Prevalence of CCHD subdivided diagnostic groups (2 additional cases with missing POS data were included in the prevalence calculations, N=632) HLHS: hypoplastic left heart syndrome, IAA: interrupted aortic arch, CoA: coarctation of the aorta, AS: aortic stenosis, AVSD: atrioventricular septal defect, DILV: double inlet left ventricle, SV: single ventricle, TA: tricuspid atresia, PA/IVS: pulmonary atresia with intact ventricular septum, PA/VSD: pulmonary atresia with ventricular septal defect, ToF: Tetralogy of Fallot, DORV: double outlet right ventricle, PS: pulmonary stenosis, TGA: transposition of the great arteries, TAPVR: total anomalous pulmonary venous return

EARLY DETECTION

The early detection rate was 90% (566/630) which included 70 cases having early symptoms before the postnatal screening took place. When excluding those cases, the combined detection rate resulting from screening (prenatal + POS + NPE) was 78% (492/630).

CONTRIBUTION OF PRENATAL SCREENING

During the study period, the overall proportion of newborns with a prenatal diagnosis was significantly higher during the last three years compared to the first three years (151/326, 46% vs 113/304, 37%, p=0.018) (Figure 14).

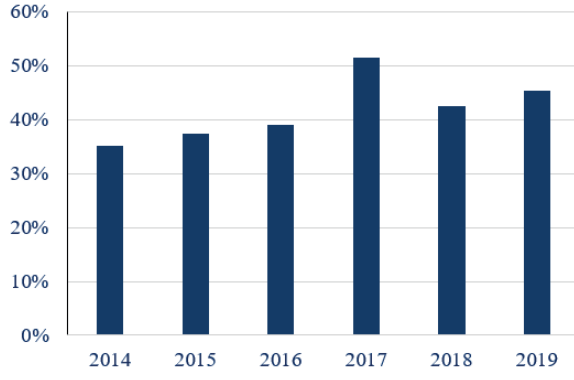

Figure 14: Proportion with prenatal diagnosis subdivided by study years.

In total, 42% (264/630) had a prenatal diagnosis. In neonates with HLHS, simple TGA and those with isolated CoA, 78% (46/59), 42% (44/106) and 23% (30/128) respectively were prenatally diagnosed.

CONTRIBUTION OF PULSE OXIMETRY SCREENING

Among newborns who were not detected prenatally or through early symptoms or died early, 292 underwent POS, with 144/292 (49%) having a positive result. However, the overall contribution of POS to early diagnosis was 23% (142/630) due to two neonates with CoA who had positive POS results

but were discharged after a non-diagnostic echocardiogram. Table 5 shows the contribution of POS to early diagnosis subdivided by CCHD category.

Table 5: Result of POS and the contribution of POS to early diagnosis subdivided by lesion.

Cardiac diagnosis	All	Result of POS		Diagnosis as a result of POS	
	N	Pos	Neg	N	%
HLHS	59	6	6	6	10
IAA	12	4	1	4	33
CoA isolated	128	17	77	16	13
CoA complex	56	7	30	6	11
AS	18	4	12	4	22
Unbalanced AVSD	7	0	0	0	0
DILV	12	1	1	1	8
SV	7	1	1	1	14
TA	10	1	0	1	10
Ebstein	2	0	0	0	0
PA/IVS	27	8	0	8	30
PA/VSD	16	3	0	3	19
ToF	15	5	0	5	33
DORV	24	5	1	5	21
PS	39	20	11	20	51
Truncus arteriosus	25	6	4	6	24
TGA simple	106	34	1	34	32
TGA complex	44	15	0	15	34
TAPVR, unobstructed	10	4	2	4	40
TAPVR, obstructed	13	3	1	3	23
Total	**630**	**144**	**148**	**142**	**23**

POS: pulse oximetry screening, HLHS: hypoplastic left heart syndrome, IAA: interrupted aortic arch, CoA: coarctation of the aorta, AS: aortic stenosis, uAVSD: unbalanced atrioventricular septal defect, DILV: double inlet left ventricle, SV: single ventricle, TA: tricuspid atresia, PA/IVS: pulmonary atresia with intact ventricular septum, PA/VSD: pulmonary atresia with ventricular septal defect, ToF: Tetralogy of Fallot, DORV: double outlet right ventricle, PS: pulmonary stenosis, TGA: transposition of the great arteries, TAPVR: total anomalous pulmonary venous return

Among lesions with a negative POS screening, left-sided obstructive lesions such as CoA, accounted for 85% (126/148) of the cases. On the other hand, lesions usually considered to be the primary targets for POS[20] (TGA, TAPVR (total anomalous pulmonary venous return), truncus arteriosus, Tetralogy of Fallot, PA/IVS (pulmonary atresia with intact ventricular septum), PA/VSD (pulmonary atresia with ventricular septal defect), tricuspid atresia (TA) and HLHS), had positive results in 85/99 (86%) cases. All except one newborn with TGA were detected by POS (49/50, 98%) (Table 5).

CONTRIBUTION OF NPE

Out of 148 cases that passed POS, 96 (65%) exhibited signs or symptoms at the subsequent NPE. The symptoms led to a pre-discharge diagnosis in 86 cases, resulting in an overall contribution of NPE to early diagnosis before discharge in 86/630 (14%). In cases with CoA, 53 of 86 (62%) were diagnosed as a result of findings at the NPE including 33/53 (62%) newborns that had weak or absent femoral pulses.

DEATHS IN UNRECOGNIZED CASES

During the study period, there were four deaths from unrecognized CCHD, diagnosed only at autopsy (0.6% of all with CCHD). None of these had undergone an echocardiogram before death. Two infants with simple TGA exhibited early symptoms with severe desaturation and died within 10 hours of birth, prior to both POS and neonatal examination. The autopsy findings revealed intact atrial septum in both cases. One newborn with isolated CoA experienced extreme asphyxia with bradycardia and needed intensive care immediately after birth but died within a few hours. This infant was never given prostaglandin PGE1. The fourth infant had CoA and VSD and passed all screening levels but died at two days of age, despite receiving prostaglandin E1 infusion while at the maternity ward.

DISCHARGED WITHOUT IN-HOSPITAL DIAGNOSIS

Ten percent (64/639) were discharged without in-hospital diagnosis, CoA being the most prevalent diagnosis among those discharged (56/64, 88%). Of these, 39% (25/64) were readmitted in circulatory failure, with one death

(HLHS) before surgery. Of the CoA cases 39% (22/56) were readmitted in circulatory failure and needed intensive care before surgery. One case died later (just before one year of age) due to neurological complications.

INCONCLUSIVE FIRST ECHOCARDIOGRAPHY IN COA

In 184 with CoA, 38 (21%) cases had an inconclusive result on their first echocardiography. Among them, six were examined before their discharge from maternity ward; one had early symptoms before postnatal CCHD-screening, two had a positive POS and three had a positive NPE. Eight newborns with CoA were discharged without previous echocardiography and were later examined during a planned follow-up or at readmission due to symptoms. The remaining 24 cases had an in-hospital diagnosis after repeated examinations.

MORTALITY

When excluding comfort care cases, the preoperative mortality was 1.9% (12/630). Among 609 neonates who underwent surgery or catheter intervention, 1.6% (10/609) died within 30 days of the procedure. In this group, HLHS was the most common diagnosis (3 out of 10). However, when excluding comfort care cases, the combined preoperative and 30-day postoperative mortality was 9/257 (3.5%) for those with a prenatal diagnosis and 13/364 (3.6%) for those with a postnatal diagnosis (p=0.99). Table 6 shows the combined preoperative and 30-day postoperative mortality (including comfort care cases). The combined preoperative and 30-day postoperative mortality subdivided by prenatal and postnatal diagnoses in HLHS, simple TGA and isolated CoA is shown in Table 7.

Table 6: The combined preoperative and 30-day postoperative mortality (including comfort care cases).

	CCHD	Detected	Age at death (days)	Surgery/catheter intervention	Age at surgery/catheter intervention (days)	Co-morbidity	Comfort care	
1	**TGA**	autopsy	<1	No				cardiac arrest
2	**CoA**	autopsy	<1	No				cardiac arrest
3	**HLHS**	prenatal	<1	No				coronary artery fistula
4	**PA/IVS**	prenatal	<1	No		Trisomy 21		unable to ventilate
5	**TGA**	autopsy	<1	No				cardiac arrest
6	**TAPVR, unobstructed**	early symptoms	<1	No				cardiac arrest
7	**TAPVR/obstructed**	early symptoms	<1	No		Anal atresia		ECMO
8	**TAPVR, obstructed/ MA**	prenatal	<1	No			Yes	unsuitable for surgey
9	**DORV**	prenatal	<1	No		Trisomy 13	Yes	
10	**HLHS**	prenatal	<1	No		Cystic kidney		unsuitable for surgey
11	**CoA**	early symptoms	2	No		Duplication X		cardiac arrest

Table 6: Continued

12	**CoA complex**	autopsy	2	No				cardiac arrest
13	**PA/IVS**	POS	2	No				cardiac arrest
14	**HLHS**	prenatal	4	No			Yes	right-sided heart failure
15	**HLHS**	prenatal	5	No			Yes	lung-vein stenosis
16	**CoA**	early symptoms	5	No		Trisomy 13	Yes	
17	**DORV**	early symptoms	5	No		Trisomy 18	Yes	
18	**HLHS**	readmission	6	No				collapse at readmission
19	**TGA**	early symptoms	7	Yes	<1			collapse before septostomy, on ECMO before surgery
20	**TA**	early symptoms	7	No		VACTERL		unsuitable for surgey
21	**ToF**	prenatal	8	No		Trisomy 13	Yes	
22	**HLHS**	prenatal	8	Yes	7			perioperative complication

Table 6: Continued

23	**HLHS**	prenatal	9	Yes	8	Yes	coronary artery fistulas, heart failure after surgery, ECMO
24	**uAVSD**	prenatal	10	Yes	6		cardiac arrest
25	**HLHS**	prenatal	11	No		Yes	coronary artery fistula, obstructed lung veins
26	**Truncus arteriosus**	neonatal examination	13	Yes	4		coronary artery fistulas, ECMO
27	**DORV**	prenatal	17	Yes	10		coronary artery fistulas, ECMO
28	**CoA complex**	prenatal	18	Yes	9		severe tricuspid regurgitation, ECMO
29	**TA**	neonatal examination	25	Yes	7		BT-shunt occlusion
30	**PA/VSD**	prenatal	27	Yes	4		BT-shunt occlusion
31	**HLHS**	prenatal	30	Yes	4		heart failure after surgery

HLHS: hypoplastic left heart syndrome, CoA: coarctation of the aorta, uAVSD: unbalanced atrioventricular septal defect, TA: tricuspid atresia, PA/IVS: pulmonary atresia with intact ventricular septum, PA/VSD: pulmonary atresia with ventricular septal defect, ToF: Tetralogy of Fallot, DORV: double outlet right ventricle, TGA: transposition of the great arteries, TAPVR: total anomalous pulmonary venous return, MA: mitral atresia, VACTERL association: acronym for affected organs and systems (vertebrae, anus, cardiac anomalies, trachea, esophagus, renal, limb), ECMO: extracorporeal membrane oxygenation

Table 7: The combined preoperative and 30-day postoperative mortality subdivided by prenatal and postnatal diagnoses in HLHS, simple TGA and isolated CoA.

	Mortality	
	Prenatal diagnosis	**Postnatal diagnosis**
HLHS	8*/46	1/13
TGA simple	0/44	3/62
CoA isolated	0/30	2/98

*Including four comfort care cases. HLHS: hypoplastic left heart syndrome, TGA: transposition of the great arteries, CoA: coarctation of the aorta

Paper IV

This study included a cohort of 38 neonates with AAO who were born in one of 12 units in Sweden that routinely conducted CCHD screening using both PI and POS. The study also included 512 controls.

PERFORMANCE OF CCHD SCREENING INCLUDING PI

Median age at screening was 10 hours (3-36) in the AAO-group and 18 hours (6-33) in controls. None of the AAO cases were diagnosed solely due to a positive PI-screen based on local screening protocols. Three out of 38 newborns with AAO had a first PI <0.7%. One of them had low PI-values at 24 hours of age (PI 0.5%) but according to the local protocol a positive screen was set at <0.5%. Four had positive POS (11%) and 14 had a positive NPE (37%). In total, 21 of 38 in the AAO-group were discharged undiagnosed and 12 of them were readmitted with circulatory compromise. In the controls, none had a positive POS and 12 had PI <0.7%. Three newborns in the control group had an echocardiogram due to three consecutive PI-readings <0.7%.

In the AAO-group, PI in the right hand was significantly higher (3.0%) compared to the foot (1.8%), $p< 0.001$. In the control group, the median

PI-value collected in the right hand was significantly lower (1.9%) than in the AAO-group, $p< 0.001$.

The 5th and 95th percentiles were -2.6% and 2% respectively for the PI hand-foot difference in the control group. Youden´s rule was used to determine the optimal cut-off criterion for discriminating between the AAO and control groups. A PI-hand-foot difference >2% or >-2% was most effective and yielded a sensitivity of 37% and a specificity 90% with an AUC (area under the curve) of 0.63 (p=0.003) (Table 8).

Youden´s rule suggested a right hand cut-off criterion at >3% to discriminate between the AAO-group and controls. This resulted in a sensitivity and specificity of 58% and 86% respectively with an AUC 0.72 (p=<0.001) (Table 8).

A combination of criteria that included PI >3% in the right hand, as well as a positive POS, and/or a positive NPE resulted in a higher sensitivity (76%) for discriminating between the AAO and controls compared to only using POS and/or NPE (p=<0.009). The specificity was 85%. The AUC for this combined cut-off criterion was 0.81 (95% CI 0.72-0.89, p=<0.0001) (Table 8).

Table 8. Comparing different cut-off criteria to discriminate between the AAO-group and the control group. Results given as AUC (95% Confidence Interval), sensitivity and specificity (Unpublished data)

	AUC (95% CI)	P-value	Sensitivity	Specificity
POS + NPE	0.72 (0.61-0.82)	<0.0001	17/38 (45%)	505/512 (99%)
PI >3% right hand	0.72 (0.62-0.82)	<0.0001	22/38 (58%)	441/512 (86%)
PI hand and foot diff >2% or >-2%	0.63 (0.53-0.74)	0.006	14/38 (37%)	460/512 (90%)
PI <0.7 %	0.53 (0.43-0.63)	0.57	3/38 (8%)	500/512 (98%)
POS + NPE + PI >3% + PI hand and foot diff >2% or >-2%	0.79 (0.72-0.87)	<0.0001	30/38 (79%)	399/512 (78%)
POS + NPE + PI >3% right hand	0.81 (0.73-0.89)	<0.0001	29/38 (76%)	435/512 (85%)

AUC: area under the curve, POS: pulse oximetry screening, NPE: neonatal physical examination, PI: perfusion index

6

Discussion

AIM OF THESIS

The primary aim of this thesis was to examine the efficiency of screening for CCHD in Sweden, with a particular emphasis on the detection of CoA. An additional aim was to explore the potential benefit of incorporating PI as an additional screening tool alongside POS and NPE to improve early detection rates of AAO.

Early diagnosis plays a crucial role in enabling timely medical intervention to improve outcomes for affected infants with CCHD. Research on large populations with high case ascertainment is needed to study the extent to which newborns with CCHD are leaving hospital undiagnosed after failed pre-and postnatal screening. Continuous evaluation of results of prevailing CCHD screening policies is important as an indicator of quality of care. Areas for improvements can be identified, with the overall aim of optimizing outcomes for newborns with CCHD.

SCREENING STRATEGIES IN SWEDEN

NPE before discharge has been a routine in Sweden since the 1950´s and prenatal ultrasound screening developed steadily beginning in the late 1980´s. POS was gradually introduced and reached full coverage by 2013.[91]

THE SIGNIFICANCE OF PRENATAL DETECTION

Prenatal diagnosis allows for immediate and appropriate care of the newborn with CCHD. In selected cases delivery can be relocated to a tertiary centre with complete pediatric cardiology and pediatric cardiac surgery services. This is especially essential for cases with TGA, as newborns with this condition cannot always be stabilized with a PGE1 infusion only. They may require an emergency balloon atrial septostomy immediately

after birth, which can only be performed in a few centres in Sweden. Not surprisingly then, prenatal diagnosis has been shown to reduce mortality rates in TGA. [68] Improved survival after a prenatal diagnosis has also been shown in HLHS and CoA. [78,121] Nevertheless, when considering the whole group of newborns with CCHD, there is conflicting evidence regarding the impact of prenatal diagnosis on morbidity and mortality.[122-125] In fact, some outcome studies have even reported higher mortality rates in CCHD after prenatal diagnoses.[126,127] This finding is explained however by the fact that more complex cardiac defects, some of whom may have associated extracardiac anomalies and/or chromosomal aberrations, are more likely to be identified prenatally with generally poorer outcome.[72,126] Additionally, there may be a heterogeneity of phenotypes even within specific diagnostic groups and comparing prenatal diagnosis to defects diagnosed postnatally is associated with selection bias unless you restrict the comparison to clearly defined diagnoses.[124] As survival rates have improved, focus has increased on long-term outcomes and morbidity-related end-points such as neurodevelopmental outcomes.[66,70,128,129]

PRENATAL ULTRASOUND SCREENING

Efforts to improve prenatal detection rates is ongoing, such as continuous training of midwifes performing the routine scans and the implementation of comprehensive heart scans.

While prenatal screening can detect significant proportion of CCHD, the cohort described in *Paper III* had a moderate prenatal diagnosis of 42%. However, it should be noted that this rate does not include terminated pregnancies or cases with spontaneous fetal death after a prenatal diagnosis. In a population-based study conducted in our region 2013-2017, 36 out of 108 (33%) pregnancies complicated by fetal CCHD were terminated and there were three spontaneous fetal deaths after a prenatal diagnosis.[121] Extrapolating these results to our cohort, the true rate of prenatal diagnosis could be estimated at 63% (981 fetuses with CCHD, 27 spontaneous fetal deaths, 324 terminations, 264/630 liveborn with prenatal diagnosis). Additionally, it is important to note that the results from 2014-2019 may not fully represent current rates of prenatal detection, as detection rates are continuously improving.

Some prenatal programs have reached near 100% detection of some cardiac lesions such as PA/VSD, Ebstein, double outlet right ventricle and univentricular hearts.[17,21,73,123,130] The prenatal detection of univentricular hearts (HLHS, unbalanced atrioventricular septal defect, double inlet left ventricle, TA, single ventricle) was 79% in *Paper III*. Improvements owes to advances in obstetric ultrasonographic equipment, training of midwifes/sonographers as well as the implementation of additional imaging-planes including the addition of colour Doppler.[73]

In contrast, defects, such as TGA, TAPVR and CoA are more difficult to detect prenatally resulting in lower detection rates.[72,130] Nevertheless, in most programmes, a gradual increase in prenatal detection was observed also for these defects.[21,131,132] We found in *Paper III* that 43% of TGA and only 9% of TAPVR were detected prenatally.

CoA has been considered one of the most difficult lesions to detect prenatally, as shown in *Paper I* and *III*. Even in the hands of a fetal cardiologist it is not always possible to be categorical and there is a high false positive rate leading to sometimes unnecessary postnatal surveillance until the ductus arteriosus closes. *Paper III* reported an improved prenatal detection of CoA compared to *Paper 1*. This improvement is in line with other studies.[80,81] Improving prenatal detection rates is essential in this condition since the defect is often missed also by postnatal screening. The newborn risks being discharged undiagnosed and may develop circulatory failure or die as shown in *Paper I* and *III*.[69] Nonetheless, detection rates of CoA are improving.[21,133] A study from Sweden reported a surprisingly high prenatal detection rate (92%) after implementing an extended screening model.[134] However, this came with the cost of a high false positive rate (79%) in suspected CoA, as has been described by others.[80,81,135] Since our data was restricted to liveborn infants, false positive rates of prenatal diagnosis could not be calculated. Data from the Swedish national fetal cardiology registry (2021) showed that 29 of 38 (76%) cases with a prenatal suspicion of CoA based on ventricular disproportion did not have CoA postnatally.[76] Twelve of these cases retrospectively satisfied applied diagnostic criteria for CoA (isthmus/ductus diameter ratio or the product of isthmus/ductus diameter ratio and mitral tricuspid annulus diameter ratio or carotid-subclavian artery index).[81,136,137] Nine of these 12 had CoA postnatally.

Others have also proposed echocardiographic predictors to potentially improve the fetal detection rates of CoA.[79,136,138]. The results have shown that combining different cardiac measurement can improve prenatal detection rates. However, in CoA, reaching very high prenatal detection rates with acceptable false positive results is probably not possible since CoA may develop after birth when the ductus arteriosus constricts.

POSTNATAL CCHD SCREENING

Postnatal screening routines in Sweden are continuously undergoing changes. The trend towards shorter postnatal stays after delivery is ongoing as in many other countries. Early discharge after delivery could potentially negatively influence timely detection of CCHD, thereby necessitating effective pre- and postnatal screening routines.

PULSE OXIMETRY SCREENING

Initially, concerns about false positives and the potential burden on the health care system contributed to the delay in adopting POS. However, subsequent evidence has shown that false positive rates are low.[100] POS has been shown to be accurate, cost effective and acceptable to both parents and clinical staff. In using POS, newborn mortality from CCHD has been reduced.[100,106,139,140]

In *Paper III,* it was shown that POS had a low contribution in cases with LHOD, but a high contribution in newborns with cyanotic defects, such as TGA, PA/IVS and PA/VSD. Among newborns with TGA, the second largest diagnostic group, almost all had a positive POS. Although it is believed that TGA could not be missed by POS, several studies have described occasional such cases.[4,108,139] Our results confirm the benefit of POS in detecting cyanotic lesions before discharge.

Overall we found that POS contributed to the early diagnosis of CCHD in 23% of all cases. The relative contribution of pulse oximetry to the early detection of CCHD is related to prenatal detection rates. In countries with high prenatal detection rates, the contribution by POS will be lower. However, despite high prenatal detection rates of CCHD, POS has still been found to be beneficial to detect other neonatal causes

of arterial desaturation. For instance, in a single hospital report, with a high level of prenatal detection (80%), POS had a limited ability to identify additional CCHD.[141] Of 77 000 screened infants over a study period of four years, only one case of CCHD was detected by POS. Yet, POS helped to identify other significant diseases such as infections, pulmonary hypertension and non-critical CHD, as shown also in other studies.[139,142 2,4,143]

As of now, there is no international consensus about the optimal screening algorithm for POS.[144] The most common variation in different algorithms is timing and site of measurements. Early testing (<24 hours) can result in a higher false positive rate [100], while later screening could miss CCHD cases before acute cardiovascular collapse. In one study, 28 out of 57 (49%) newborns with duct-dependent circulation already had symptoms before the screening took place at a median age of 38 hours.[2] As demonstrated in *Paper III*, 20% of the included CCHD cases developed symptoms before POS took place. Most units screened at 6-24 hours.

Screening between 6- 24 hours is probably a reasonable balance between false positives and a timely diagnosis, as recommended by Nordic countries.[91] In Sweden, later screening would not be practical due to an increasing number of early discharges.

NEONATAL PHYSICAL EXAMINATION UNDERGOING CHANGES

In our tertiary hospital (10 000 deliveries/year), the newborn pre-discharge examination by a pediatrician has recently been replaced with a checklist completed by midwives, already 6 hours after birth. Instead, the NPE by a pediatrician is performed at a follow-up visit at 48-72 h of age. These new local routines are in line with postnatal routines in other countries, for example Denmark[91] and New Zealand, two countries with high prenatal detection rates. Our local checklist includes heart and respiratory rate but not auscultation of the heart or palpation of femoral pulses. A shifted responsibility of performing the predischarge examinations of newborns from doctors to trained midwifes is most likely an ongoing trend. A study reported of significant cost savings when the examination was performed by a midwife rather than a senior house officer.[90] In addition, maternal satisfaction

increased when the NPE was undertaken by a care provider known to the woman or parents.

The importance of palpating femoral pulses is supported by several studies.[32,73,145] As demonstrated in our own research (*Paper III*) findings on NPE were able to provide a diagnosis in 53 of 107 infants with CoA, out of which 33 (62%) had weak femoral pulses. Similarly, in *Paper I*, we found that 52 of 83 (63%) newborns with isolated CoA had either a murmur and/or weak femoral pulses at a median of 2.2 days of age. Palpating femoral pulses is a critical component of the newborn pre-discharge examination and its exclusion in favor for a checklist may lead to missed diagnoses. On the other hand, replacing regular NPE with a checklist and a follow-up NPE at 48-72 hours can detect previously undetected cases of CoA with delayed presentation.

HOW TO FURTHER IMPROVE RESULTS OF POSTNATAL SCREENING

Perfusion index as a screening tool for CCHD

Low PI-values has been proposed as a proxy for inadequate peripheral perfusion. Due to the routine display of PI on modern pulse oximeters there has been increased interest in utilizing it for CCHD screening. Yet, a high false positive rate has been a concern. In response to this, in *Paper II* we could successfully reduce the false positive rate to 0% already at one repeated measurement if the first was < 0.7%. This approach to reduce false positives with repeated measurements is already recommended in the POS algorithm. In addition, our median PI value was similar to previously reported values of PI in newborns, although we had a slightly narrower population distribution with a higher 5th percentile (0.9%) in the foot. The result suggests that the use of PI as a screening tool for CCHD should be further explored.

The feasibility and the time consuming aspect of measuring PI in newborns is also important to assess. According to some nursing staff, measuring PI is time-consuming and obtaining an artifact-free signal is challenging. We showed that an additional 3 minutes and 30 seconds were required to record PI in addition to POS.

In our research presented in *Paper IV,* we have described for the first time and in a comparatively large number of AAO-cases, that newborns with AAO exhibit significantly higher PI-values in the right hand compared to the foot. In addition they had significantly higher PI-values in the hand compared to controls. None of the screened infants with AAO were detected solely by PI. One explanation could be that the screening was performed earlier (at 10 hours, range 3-36) than in previous studies and at this point in time, the constriction may not have significantly affected peripheral perfusion. The finding of higher PI-values in the right hand compared to the foot in newborns with AAO might be caused by the stiff and constricted segment in the aortic isthmus area, yielding a high and rapid arterial pulse curve waveform. However, we believe that using a PI value in right hand >3% as a cut-off could be a specific tool for AAO, whereas a threshold at <0.7% would be more sensitive in other LHOD, such as HLHS and critical AS. However, we found that using a PI value of >3% in the right hand, also when combined with POS and NPE to increase sensitivity, was associated with a high false positive rate. Each false positive screening result is associated with a burden of extra tests and potentially longer hospital stays. These are central considerations for any screening tool. Wether the false positive rate can be reduced by requiring up to two repeated measurements was not possible to analyze from the data in *Paper II* and should be further studied.

One of the limitations in using PI in clinical practice is the variation in peripheral perfusion in normal newborns, which can make it difficult to establish appropriate screening cut-offs. In studies, the 5th percentile in normal populations ranges from 0.5-1.2%. Possible reasons for this variability include differences in sample size among studies, timing of screening and variations in pulse oximeter models. Additionally, poor signal quality, particularly in cases with cold extremities and low temperature can generate unreliable photoplethysmographic signals. This may result in false positives or false negatives, leading to diagnostic errors.[97] The optimal cut-off for PI-values remains unclear highlighting the need for future research to evaluate the sensitivity and specificity when using different thresholds.

Follow up visit at 2-3 days of age

It is common for CoA to not exhibit coarctation physiology during neonatal CCHD screening. PI is likely to miss CoA-cases for the same reason. However, a potential solution to this diagnostic gap is an additional post-discharge examination including palpation of femoral pulses and a repeat POS and PI, preferably at 48-72 hours of age, at the time for phenylketonuria-screening. A re-visit at 48-72 hours of age is already a routine in our hospital using a pre-discharge checklist by midwifes.

NEGATIVE RESULT OF EARLY ECHOCARDIOGRAPHY IN COA

In both *Paper I* and *III,* the initial echocardiographic examination failed to detect CoA in 18% and 21% of cases, respectively. According to some of the echocardiography reports, the aortic isthmus area could not be visualised adequately. In a few cases, the isthmus area was not visualized at all. Imaging the aortic arch can be challenging due to surrounding lung limiting the echocardiographic windows. Additionally, in cases of a patent ductus arteriosus, Doppler evaluation of the aortic arch can be misleading. Sequential assessments are required until ductal closure. Nonetheless, despite excellent imaging of the aortic arch, it was clear in some cases that no coarctation had yet developed. Some of the same predictive measurements used during fetal life can be applied also in the neonatal period. Studies have demonstrated that the distance between the left carotid artery and the left subclavian artery was significantly longer in neonates with CoA compared to controls.[146] Isthmus-descending aorta index and carotid-distal transverse arch index have also been suggested to be useful. These indices were reported to be valid regardless of the presence of a PDA.146,147,148

DISCHARGE OF UNDIAGNOSED NEONATES WITH CCHD

Many studies of POS have shown high early detection rates of CCHD (>90%) when POS was added to prenatal ultrasound screening and postnatal NPE.[2,4,99] As shown in this work, pre-discharge detection rates in newborns with CCHD in Sweden have now reached near 90%. In addition, we found a low preoperative mortality at 1.9% among live-born fullterm infants (excluding comfort care cases). As reported in a nationwide study,

preoperative unexpected deaths in live-born infants with severe CHD, were rare (1.1%).[40] Lower preoperative mortality has been accomplished through advancements in prenatal and postnatal screening.

Before the era of prenatal diagnosis and postnatal pulse oximetry screening, up to 30% of infants with CCHD left hospital without a diagnosis.[6,29,33] Furthermore, 45% of infants with a postnatal diagnosis of CoA were discharged undiagnosed.[29] In the current work, as shown in Paper I and III, improvements have been made. In infants with isolated CoA, we found a significant increase in prenatal diagnosis as well as a significant decrease in the combined in-hospital death prior to diagnosis and cases discharged undiagnosed (Table 9). Despite this, the proportion of newborns with CoA leaving hospital undiagnosed remains high. Early detection of CoA continues to be the central remaining issue in CCHD screening.

Table 9. Proportion of infants with isolated CoA who either died undiagnosed before discharge or were discharged without a diagnosis. Results from two different study periods. The data from study period 2003-2012 was adjusted to include only liveborn, fullterm infants who died or had surgery within 28 days in order to make a comparison possible. It should be noted, however, that Paper 1 included cases from the referral area of Gothenburg, while Paper III was a national study and thus drew from different populations.

CoA, isolated	Prenatal diagnosis	Postnatal diagnosis before discharge or pre-discharge death	In-hospital death prior to diagnosis	Discharged without diagnosis)
2003-2012	2/68 (2.9%)	30/68 (44%)	4/68 (5.9%)	32/68 (47%)
2014-2019	30/128 (23%)	58/128 (45%)	1/128 (0.8%)	39/128 (30%)
p (2003-2012 vs 2014-2019)	< 0.001	0.87	0.03	0.02
			0.003	

CoA: coarctation of the aorta

PREVALENCE OF CCHD AT BIRTH

In *Paper III*, the selection criteria were designed to achieve a complete ascertainment of cases with CCHD. The liveborn prevalence was found to be 0.91 per 1000 term infants. This is in line with the study conducted by Wren *et al* on a population of similar size and using the same definition

of CCHD, reporting an incidence of 0.97 per 1000 live births (including preterm infants)[149]. As discussed previously, the fetal prevalence of CCHD in Sweden is higher at 1.41 per 1000 when adjusted for terminations and spontaneous fetal deaths.

There are large variations in the reported prevalence/incidence of CCHD.[73] The paper by Hoffman 2002 reported no significant differences in incidence of CHD across countries or over time.[9] Subsequent studies have however reported decreasing prevalence of severe defects, mainly univentricular hearts secondary to pregnancy terminations.[18,150] In a Danish cohort, the live-born incidence of major CHD decreased by almost 40% between 1996-2013 due to a high rate of termination of pregnancies.[17] In a Norwegian study, an increasing prevalence of severe CHD was noted from 1994 until 2005.[151] The increase was interpreted as an effect of improved reporting of birth defects. The increasing prevalence of minor CHD reported by many, can be explained as an effect of improved diagnostics.[15,16]

In summary, the reported incidences vary over time and it is still uncertain wether changes in prevalence are true or merely due to methodological differences.[73] However, some factors that could contribute to true changes in CHD prevalence include maternal risk factors (age, obesity, diabetes, exposure to environmental toxins). Intake of folic acid in fertile women has also been implicated as a potential factor, as improved survival rates and a growing population with CHD reaching adulthood having children at risk of having CHD.[152-154]

7

Conclusions

Paper 1: The study highlights the limited impact of prenatal and pulse oximetry screening in the detection of isolated coarctation of the aorta and emphasizes the need for an increased awareness and vigilance for timely diagnosis and management of this condition.

Paper II: The study demonstrated that repeating perfusion index measurements if below cut-off can significantly reduce the false positive rate to a very low level. Furthermore, using perfusion index at the maternity ward seemed feasible for the nursing staff with manageable additional time requirements.

Paper III: In Sweden, pulse oximetry screening and neonatal physical examination continue to play crucial roles in the early detection of critical congenital heart defects, complementing prenatal ultrasound screening. However, one in ten newborns with critical congenital heart defects leave hospital without a diagnosis, coarctation of the aorta being the predominant lesion.

Paper IV: This study suggests that the sensitivity of detecting aortic arch obstruction in newborns can be substantially increased by utilizing a combination of criteria, such as a perfusion index-value >3% in the right hand in combination with pulse oximetry screening and neonatal physical examination.

8

Future perspectives

To improve detection rates, future research on pre- and postnatal screening for CCHD should have a special focus on CoA.

Advancement in prenatal screening will most likely further improve prenatal detection rates in CCHD. Developments in fetal MRI [155,156] and neural network technology in fetal echocardiography to assist in the diagnosis might help to improve the diagnostic performance.[157]

National recommendations for CCHD-screening, based on available research, and aligned with best practice would be of benefit. Consistency in screening practices, early discharge and re-visit routines could contribute to improved accuracy and effectiveness of CCHD-screening, ultimately leading to better patient outcomes.

Further studies on the use of PI are needed with regard to the natural progression of PI in neonates with AAO. Prospectively collecting repeated PI-measurements in neonates with AAO could improve knowledge of the usefulness of PI as an indicator of peripheral perfusion. Additionally, studies analyzing morphology and amplitudes of the photoplethysmographic waveforms have shown promise in identifying infants with CoA.[158,159] Also, analyzing pulse-wave delay in between limbs for identifying infants with CoA need further evaluation.[159]

Newborn screening using dried blood samples on Guthrie cards has been established worldwide. For early identification of CHD in newborns, research on quantifying cardiovascular biomarkers in dried blood samples is ongoing.[160]

A retrospective review of all non-diagnostic echocardiography studies in cases with CoA from *Paper I* and *III*, could provide valuable insights into the postnatal course of echocardiographic hallmarks and development of the coarctation. In addition, utilizing previously proposed predictive measurements, and perhaps use an artificial intelligence (AI) model, could help identify patterns and relationships in neonates with CoA compared to normal newborns.

9

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