Neonatal screening with pulse oximetry

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CHAPTER 2

Aspects of pulse oximetry screening for critical congenital heart defects: when, how and why?

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ABSTRACT

Pulse oximetry (PO) screening for critical congenital heart defects (CCHD) has been studied extensively and is being increasingly implemented worldwide. This review provides an overview of all aspects of PO screening that need to be considered when introducing this methodology. PO screening for CCHD is effective, simple, quick, reliable, cost-effective, and does not lead to extra burden for parents and caregivers. Test accuracy can be influenced by targets definition, gestational age, timing of screening, and antenatal detection of CCHD. Early screening can lead to more false positive screenings, but has the potential to detect significant pathology earlier. There is no apparent difference in accuracy between screening with post-ductal measurements only, compared with screening using pre- and post-ductal measurements. However, adding pre-ductal measurements identifies cases of CCHD which would have been missed by post-ductal screening. Screening at higher altitudes leads to more false positives. Important non-cardiac pathology is found in 35-74% of false positives in large studies. Screening is feasible in Neonatal Intensive Care Units and out-of-hospital births. Training caregivers, simplifying the algorithm, and using computer-based interpretation tools, can improve quality of the screening. Caregivers need to consider all aspects of screening to enable them to choose an optimal protocol for implementation of CCHD screening in their specific setting.

INTRODUCTION

Introduction

Critical congenital heart defects (CCHD) occur in 2-3 per 1,000 live births, usually require invasive medical intervention within the first month of life, and can lead to death or significant morbidity if not diagnosed in a timely manner.[1] Early detection is important for reducing the mortality and improving the postoperative outcome.[2-6]

Routine fetal ultrasound screening has led to increased antenatal detection of around 50-70% of all CCHD.[7] Postnatally, 20-30% of CCHD are still missed by physical examination, as symptoms often occur later, when the ductus arteriosus closes.[8, 9] Murmurs are not always present with CCHD, and may occur in up to 60% of healthy newborns.[10] Also, it has been shown that assessment of cyanosis is unreliable for detecting hypoxemia.[4, 11] Pulse oximetry (PO) is a widely available, accurate method to objectively quantify oxygen saturations (SpO_2), and thereby identify the clinically undetectable hypoxemia that occurs in the majority of neonates with CCHD.[11, 12]

Early studies assessing neonatal PO screening for CCHD demonstrated proof of concept,[13-15] followed by large accuracy studies.[16-20] This led to a recommendation in 2011 by the US Secretary of Health and Human Services to add CCHD screening to the recommended uniform screening panel, which was also endorsed by the American Academy of Pediatrics.[21] A meta-analysis of 13 screening studies, including almost 230,000 infants, reported a sensitivity of 76.5%, specificity of 99.9%, and false positive rate of 0.16%.[22] The authors concluded that PO screening met the universal screening criteria. Since then further studies focusing on feasibility, implementation, and logistical aspects of CCHD screening have been performed.[23-38]

This review provides an overview of all aspects that need to be considered when performing PO screening. We also provide an update of the current status of PO screening worldwide. Caregivers can use this information to implement an optimal screening protocol in their local care system.

Aspects influencing the accuracy of pulse oximetry screening

Sensitivity ranged from 60-100%, whereas specificity was ³94%, and in most studies >99% (Table 1). This high specificity is accompanied with a false positive rate varying between 0% and 1.8% (Table 1). So far, no difference has been shown in accuracy when pre- and post-ductal PO measurements are performed versus only post-ductal measurements.[18, 20, 22] Screening performed >24 hours after birth decreases the false positive rate, but increases the risk of late detection of infants with CCHD who may decompensate prior to screening.[18-20] Furthermore, non-critical cardiac defects and other significant pathology may be found in up to 80% of the false positive cases (Table 2).[18, 20, 25, 28]

Table 1. Overview of accuracy studies.

First Author, year	N	Prenatal detection of CCHD	GA	Sensor probe location
Hoke, 2002[29]	2,876	17%	≥34 wk	Pre and post
Richmond, 2002[13]	5,626	10%¥	All, not neonatal unit	Post
Koppel, 2003[14]	11,281	45%	All, well infant nursery	Post
Reich, 2003[36]	2,114	33%	All, not NICU	Pre and post
Rosati, 2005[31]	5,292	Not mentioned	Healthy term	Post
Bakr, 2005[32]	5,211	0%	All healthy	Pre and post
Arlettaz, 2006[33]	3,262	28%¥	≥35wk	Post
Ruangritnamchai, 2007[34]	1,847	Not mentioned	All healthy	Pre and post
Meberg, 2008[16]	50,008	7%	Healthy at nursery	Post
Sendelbach, 2008[17]	15,233	80%	≥35wk	Post
De-Wahl Granelli, 2009[18]	39,821	3.3%		Pre and post
Riede, 2010[19]	41,445	63%	Healthy term	Post
Tautz, 2010[35]	3,364	10%	≥35wk	Post
Ewer, 2011[20]	20,055	50%	>34 wk	Pre and post
Turska-Kmiec, 2012[23]	51,698	38%	All at neonatal unit	Post
Kochilas, 2013[24]	7,549	Not mentioned	Healthy newborns	Pre and post
Singh, 2014[25]	25,859	76%	Postnatal ward	Pre and post
Zuppa, 2014[26]	5,750	82%	Healthy at nursery	Post
Bhola, 2014[27]	18,801	11%	>36 wk	Post
Zhao, 2014[28]	120,707	8%†	all	Pre and post

FP= false positive; GA=gestational age; PE=physical examination; pre=pre-ductal; post=post-ductal; ¥for all CHD; ^group too small to assess sensitivity; †for major CHD; &for CCHD; *mean

Cut-off values	Time screening, h (median)	Sensitivity	Specificity	FP rate
<92%; Pre-post>7%	24 or discharge	69%[¥]	99.0%	1.8%
2x <95% or 1x<95% and abnormal PE	>2, <discharge (11.7*)	25%[¥]	99.0%[¥]	1.0%
≤95%	>24	60.0%	99.95%	0.009%
3x <95% or Δ>3%	<discharge	---^	99.8%	0.04%
≤95%	>24 (72)	66.7%	100%	0.019%
1x <90%, 3x 90-94%	<discharge (31.7*)	77%	99.7%	0.02%
1x <90%, 2x 90-94%	6-12 (8)	100%	99.6%	0.4%
1x <95%	24-48	98.5%	96.0%	0.05%
2x <95% or 1x <95% and symptoms	First day (6)	77.1%	99.4%	0.6%
<96%	4	75%	94%	5.6%
	<discharge (38)	82.7%	97.9%	0.17%
2x <96%	24-72 (-)	77.8%	99.9%	0.1%
<90%, 2x <90-94%	6-36 (12)	82.0%	99.9%	0.3%
1x <95% or Δ>2% + symptoms OR 2x <95% or Δ2%	<24 (12.4)	75.0%[&]	99.1%[&]	0.9%[&]
2x <95%	2-24(7)	78.9%	99.9%	0.026%
1x <90 3x 90-94% or Δ>3%	≥24 (30*)	100%	99.9%	0.07%
<95% or Δ>2%	<24 (7.5)	60%	99.2%	0.8%
2x <95%	48-72 (64)	--	99.9%	0.05%
1x <90% or 3x 90-95%	24-72 (-)	80%	99.8%	0.13%
1x <90% or 2x 90-95% or Δ>3%	6-72 (43)	83.6%	99.7%	0.3%

Table 2. detection of pathology other than CCHD.

Author, year	N	TP	FP (%)	PPHN	Other lung pathology	Infection/ sepsis	Non-critical CHD	Other	Healthy (%)
Hoke, 2002[29]	2,876	4	53 (1.8)	1	-	-	-	-	39 (74)[#]
Richmond, 2002[13]	5,626	4	47 (0.8)	1	2	-	-	4	40 (90)
Koppel, 2003[14]	11,281	2	1 (0.009)	1					0 (0)
Reich, 2003[36]	2,114	2	2 (0.1)	-	-	-	-	-	2* (100)
Rosati, 2005[31]	5,292	2	2	-	-	-	-	1	1 (50)
Bakr, 2005[32]	5,211	3	2 (0.04)	-	-	-	1	1	0 (0)
Arlettaz, 2005[33]	3,262	14	10 (0.3)	5			4		1 (10)
Ruangritnamchai, 2007[34]	1,847	2	1	-	-	-		-	Not mentioned
Meberg, 2008[16]	50,008	27	297 (0.6)	6	68	55	17	4	147 (49)
Sendelbach, 2008[17]	15,233	3	856 (5.6)	-	-	-	2	12	841 (98)
De-Wahl Granelli, 2009[18]	39,821		69 (0.2)	6	7	10	14	8	24 (35)
Riede, 2010[19]	41,445	14	40 (0.1)	15	-	13	-	-	12 (30)
Tautz, 2010[35]	3,364	8	10 (0.3)	2	-	7	1	-	- (0)
Ewer, 2010[20]	20,055	18	177 (0.9)	40			14		123 (69)
Turska, 2012[23]	51,698	15	14 (0.026)	-	-	5	1	-	8 (57)
Kochilas, 2013[§24]	7,549	1	5 (0.07)	3	-	-	-		1 (20)
Singh, 2014[25]	25,859	9	199 (0.8)	12	-	85	8	44	43 (22)
Zuppa, 2014[26]	5,750	0	3 (0.05)	3					
Bhola, 2014[27]	18,801	4	11 (0.13)	3	2	1	-		5 (45)
Zhao, 2014[28]	120,707	122	394 (0.3)	41	23	10	106		214 (54)

FP= false positive; TP= true positive. [#]unknown in 13 infants; * these two infants had a large patent ductus arteriosus; [§]test of 1 infant was misinterpreted.

Targets

To interpret the observed accuracy in PO screening studies, the specified target should be taken into account as they vary between studies (all CHD,[13, 29, 32] significant CHD,[30, 33] major CHD,[20, 28] all duct dependent CHD,[18, 20] and CCHD[17, 26, 28, 31, 34]).

Targeting all CHD instead of only CCHD could decrease the sensitivity, as not all CHD lead to hypoxemia in the first days of life. In contrast, when considering only CCHD as a target for PO screening, the false positive rate will be higher. However, the false positive screens will include other, non-critical CHD, which are also important to detect. Non-critical CHD could therefore be classified as secondary target for the screening.

Gestational age

While most PO screening studies included only asymptomatic infants, not admitted to a Neonatal Intensive Care Unit (NICU),[13, 16, 19, 24-26, 31, 32, 34, 36] a few studies also included late preterm infants (≥34 weeks of gestational age).[20,29] Although the extra value of PO screening in monitored preterm infants is uncertain, concomitant pre- and post-ductal PO measurements may detect CHD earlier when these infants are also included in the screening (Table 3).

Timing

The meta-analysis demonstrated a significantly lower false positive rate when the screening was performed ≥24 hours after birth.[22] In several countries, there is a tendency for early discharge, <24 hours of life.[37] Moreover, up to half of all infants with CCHD presented with symptoms prior to the screening, with circulatory collapse in up to 9% of these infants when screening > 24 hours was performed.[18,38]

Ewer *et al.* showed the highest sensitivity if screening took place 6-12 hours after birth, but specificity was the highest at 0-6 hours after birth.[20] In a large Chinese study, the false positive rate was higher when screening was performed at 6-24 hours after birth (0.55%) as compared to 25-48 (0.29%) and 9-72 (0.26%) hours after birth. but sensitivity was 10% higher at 6-24 hours.[28]

Performing PO screening in the first hours of life is likely to lead to more false positive screenings, but this must be weighed against the potential benefit to detect significant pathology, including non-critical CHDs, infections and pulmonary disorders, at an early stage of the disease, preventing deterioration (Table 3).

When determining the timing of screening, the logistics of perinatal care should be taken into account as the duration of hospitalization after birth and the rate of home births vary between hospitals and countries. An international group of experts on CCHD screening recommended pilot studies in individual European countries to test feasibility, accuracy and cost-effectiveness in the local care systems.[37]

Post-ductal or pre-and post-ductal measurement

All studies performed post-ductal measurements, as there is a possibility of missing CCHD associated with predominant right to left shunting at the ductus arteriosus and stenosis of the aortic isthmus when only pre-ductal measurements are obtained (Table 1). However, in half of the studies, pre- and post-ductal measurements were obtained (Table 1). The meta-analysis showed no difference in accuracy between only post-ductal versus combined measurements, but certain left outflow tract obstructions might be missed with post-ductal measurements alone.[20, 22] However, Ewer *et al.* and Granelli *et al.* observed that adding a pre-ductal measurement also increased the false positive rate.[18, 20]

Cut-off values

The definition of threshold values will determine the sensitivity and specificity of the screening tool. When choosing the cut-off value, the false positive rate must be balanced against the risk of missing CCHD. Ewer *et al.* defined SpO_2 <95% in either limb or a difference of >2% between the limbs as abnormal.[20] In their study, the false positive rate would have been reduced from 0.8 to 0.5% if they had used a difference of >3% in both limbs; however, 13 respiratory disorders and 3 CHDs would have been missed.[18, 20] Cost-effectiveness and accuracy analyses should be performed for different thresholds and probe placement approaches to determine the optimal threshold values.

Altitude

At moderate or high altitudes, a delay in the decrease in pulmonary vascular resistance will lead to lower SpO_2 after birth when compared to infants born at sea level.[39-41] At mild elevation Han *et al.* concluded that the screening is feasible with a low false positive rate.[42] Wright *et al.* observed more positive screenings (1.1%) in infants at moderate altitude with the recommended screening protocol.[43] Infants with SpO_2 ≥95% and ≤3% difference in SpO_2 passed the screening, while infants with SpO_2 <85% at any screening were assigned fail screen status. More studies need to be performed to define optimal cut-off levels for PO screening at moderate and high altitudes and the sensitivity must be balanced against the high false positive rate

The influence of the antenatal detection rate

The sensitivity and cost-effectiveness of the screening will also be influenced by the antenatal detection rate of CCHD (Table 1), which is strongly influenced by the training, experience and equipment of the sonographer, and by the quality and organization of the antenatal health services.[7, 44] Fetal echocardiography was not routinely available in two large PO screening studies.[18, 32] In case of low antenatal CCHD detection, the value by PO will be higher compared to settings with high fetal detection rates. Furthermore, infants with prenatally detected CHD were excluded for PO screening in the majority of studies.[13, 20, 29, 33, 35]

Devices

It is recommended to use pulse oximeters that are cleared for use in newborns, are usable in low perfusion states, report functional oxygen saturation, and are motion tolerant.[45, 46] Dawson *et al.* demonstrated a good agreement between measurements obtained with Masimo and Nellcor PO when SpO_2≥70%, but a low agreement when SpO_2 <70%.[47] This is unlikely to affect screening sensitivity.

Table 3 provides an overview of the described aspects of the screening and their advantages and disadvantages.

Table 3. advantages and disadavantages of aspects in protocol for pulse oximetry screening.

Aspect in protocol	Advantage	Disadvantage
Targeting all CHD instead of only CCHD	Increased specificity Decreased false positive rate	Decreased sensitivity
Including preterm infants	Earlier detection of CCHD and other pathologies	Possible increase in false positive rate
Early screening (<24 h)	Detect significant pathology in an early stage Possible higher specificity Fits in setting with early discharge	Possible increase in false positive rate
Adding pre-ductal measurement to post-ductal PO measurement	Possible improved detection of left outflow tract obstructions	More time consuming
Screening at moderate-high altitude	Early detection of significant pathology	Possible increase in false positive rate
Including infants with antenatal CHD detection	Increase in sensitivity and specificity	No clinical consequences for CHD
Reusable sensors	Decrease costs	Must be disinfected between uses to minimize risk of infection

CCHD: critical congenital heart defect; CHD: congenital heart defect; PO: pulse oximetry

Detection of other pathologies

PO can also detect other causes of hypoxemia, including infections and pulmonary/respiratory disorders. In Table 2 we calculated the detection of important pathology other than CCHD. Although detection of these conditions is currently considered as false positives, it is important to detect them early, so treatment can be started before deterioration occurs with increased risk of death, morbidity and longer hospitalization. There is large variation in detection of other pathology in the reported studies (0-90%; Table 2). Since different screening targets were used in the studies, the false positive rates are difficult to compare. According to the power analysis of Ewer *et al.* 20,000 neonates were required to accurately assess accuracy of

PO screening. There are 7 studies with inclusion of >20,000 neonates, in which the detection of other important pathology amongst the false positive screening was 27-74%.[16, 18-20, 23, 25, 28]

Setting

In most countries where it has been implemented, the screening takes place in hospitals. Screening has been performed in major centers and regional hospitals.[24, 48]

PO screening in the NICU has been less well investigated. However, a recent study showed similar discharge SpO_2 values in late preterm and term infants at a NICU with a 100% screening rate and, therefore, the current screening protocol is feasible for these groups upon discharge from a NICU.[49] Although screening in the NICU is feasible, underlying illnesses and timing of the screening increased the false positive rate.[50]

Studies have also investigated PO screening out-of-hospital and after early discharge from hospital.[19, 25, 27, 51] In Australia, the screening was performed 24-72 hours after birth or, in case of early discharge, prior to discharge with a repeated measurement at home within the first 3-5 days after birth.[27] All four detected cases of CHD were found prior to discharge from the maternity service. Also, in Wisconsin, with a home birth rate of 1.67%, screening could be obtained in only 1/3 of all home births.[51] In the Netherlands 33% of births are supervised by community midwives, in birthing facilities or at home, and an adjusted screening protocol has been developed to fit in the working scheme of the midwives.[52, 53]

Acceptability

Two studies reported that parents widely accepted the test and the false positive results did not lead to more anxiety.[23, 54] Furthermore, the medical staff considered the test as highly important and easy to carry out.[20] Tautz *et al.* reported a feeling of security and confidence of the nursery staff by using the PO measurements.[35] Most of the physicians involved in newborn medicine endorsed it as an effective tool.[55]

Cost-effectiveness

Several studies on cost-effectiveness of pulse oximetry screening have been performed.[18, 24, 56-58] Roberts *et al.* calculated incremental costs of £24,900 per timely diagnosis, with a 90% chance of being cost-effective with a Willingness To Pay threshold of £100,000.[56] Peterson *et al.* also demonstrated that the screening was cost-effective. The PO screening costs $3.83 per newborn, or $4,693 for each life saved by screening. With an estimation of 248 cases of CCHD detected early by the screening and 110 deaths averted annually, they conclude that the screening is cost effective.[57] Kochilas *et al.* reported the costs of $5.10 per screening and, con-

sidering the numbers needed to screen, $46,300 per patient diagnosed with CCHD.[24] Griebsch *et al.* and De-Wahl Granelli *et al.* concluded that the screening is at least cost neutral, since in the Swedish study the costs per timely diagnosis made due to screening were £3,430 while the costs per infant with circulatory collapse due to CCHD were £3,453.[18, 58] All these studies imply that PO screening for CCHD is cost-effective.

Quality improvement

Experience has been gathered in ways to improve the use of the PO for CCHD screening.[15, 24, 59-62] Training could lead to more adequate use of PO and the algorithm.[15, 24, 59, 60] Also, the use of a computer-based tool for interpretation of the results could improve the accuracy, since human interpretation is susceptible to errors.[61, 62]

Barriers for implementation

Impact on echocardiography service

The concern of a possible increased workload for echocardiography services and paediatric cardiologists could not be confirmed. Bhola *et al.* reported only 5 extra echocardiograms during a 42 months screening period of 18,801 infants.[27] Also, studies showed that only a few infants had structurally normal hearts on performed echocardiograms.[24, 30]

Furthermore, the introduction of PO screening reduced the number of emergency and "unnecessary" echocardiograms.[14, 30, 35]

In addition, when PO screening is routinely implemented, it is reasonable to perform echocardiography only in infants with persistent abnormal SpO_2 without evidence for another, non-cardiac diagnosis.[25] All infants with positive screens should be carefully assessed by well-trained paediatric staff. Next to CHD the differential diagnosis includes respiratory pathology (inter alia pneumonia, aspiration, pneumothorax), infections and sepsis, and transitory problems, such as persistent pulmonary hypertension of the neonate (PPHN).

Staff/working time

All studies reported a maximum of 5.5 minutes per screening, with a mean of even 1.6 minutes in Zhao's study.[18, 24, 27, 28, 33, 48] No extra staff members were needed to perform the screening.[26, 47]

Current Implementation

There is an increased interest in CCHD screening all over the world. It was estimated that ≥90% of infants born in the United States were screened for CCHD screening by the end of 2014.[63] Finland has the highest screening rate after implementation (97%), followed by Sweden (91%) and Norway (90%).[64] In 2009 Switzerland screened 85% of infants.[65] PO screening has been

recommended in Abu Dhabi, Ireland, Sri Lanka, and Poland.[66] Furthermore, pilot studies are or have been performed in many countries, including UK, Germany, Spain, Italy, Australia, China, and the Netherlands.[23, 27, 28, 38, 53] A group of international CCHD screening experts encourage European societies to formulate statements regarding CCHD screening to enhance implementation of the screening across Europe.[37]

Limitations

It is important to emphasize that PO screening does reduce the diagnostic gap but will not lead to 100% detection of CCHD. Defects with aortic obstruction are most commonly missed with PO, and these are also more difficult to diagnose with prenatal ultrasound.[14, 28, 67, 68]

Although CCHD screening has been thoroughly investigated and implemented in settings with delivery in hospitals, more studies are needed testing the accuracy and (cost)effectiveness of the screening in special settings, such as home births, very early discharge, moderate-high altitude, and NICUs.

CONCLUSION

PO is an effective method to detect CCHD, as an adjunct to prenatal ultrasound and physical examination. The tool is simple and reliable, has low costs, is not time consuming, and there is no extra burden for the parents and infants. Furthermore, it is widely available and detects other potential life-threatening pathology such as infections, and persistent pulmonary hypertension of the newborn. Early detection of CCHD reduces the mortality and morbidity. Studies on protocols at NICUs, out-of-hospital births, and early discharge are still subject to investigation.

PO screening is introduced increasingly in countries all over the world and in different settings, with different timing of the screening. Before implementing the screening in a specific setting, it is important to know the experience and evidence for CCHD screening in that setting. In this review we have given an overview of the different aspects of the screening, which can be used for developing an optimal screening protocol for a specific local setting.

REFERENCES

1. Hoffman JI, Kaplan S. The incidence of congenital heart disease. JACC 2002;39:1890-1900.
2. Fixler DE, Xu P, Nembhard WN, et al. Age at referral and mortality from critical congenital heart disease. Pediatrics 2014;134:e98-105.
3. Brown KL, Ridout DA, Hoskote A, et al. Delayed diagnosis of congenital heart disease worsens preoperative condition and outcome of surgery in neonates. Heart 2006;92:1298-1302.
4. Hoffman JI. It is time for routine neonatal screening by pulse oximetry. Neonatology 2011;99:1-9.
5. Limperopoulos C, Majnemer A, Shevell MI, et al. Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. J Pediatr 2002;141:51-58.
6. van Velzen CL, Haak MC, Reijnders G, et al. Prenatal detection of transposition of the great arteries reduces mortality and morbidity. Ultrasound Obstet Gynecol 2015;45:320-325.
7. Liu H, Zhou J, Feng QL, et al. Fetal echocardiography for congenital heart disease diagnosis: a meta-analysis, power analysis and missing data analysis. Eur J Prev Cardiol 2015;22(12):1531-47.
8. Gorska-Kot A, Blaz W, Pszeniczna E, et al. Trends in diagnosis and prevalence of critical congenital heart defects in the Podkarpacie province in 2002-2004, based on data from the Polish Registry of Congenital Malformations. J Appl Genet 2006;47:191-194.
9. Meberg A, Andreassen A, Brunvand L, et al. Pulse oximetry screening as a complementary strategy to detect critical congenital heart defects. Acta Paediatr 2009;98:682-686.
10. Valmari P. Should pulse oximetry be used to screen for congenital heart disease? Arch Dis Child Fetal Neonatal Ed 2007;92:F219-224.
11. O'Donnell CP, Kamlin CO, Davis PG, et al. Clinical assessment of infant colour at delivery. Arch Dis Child Fetal Neonatal Ed;92:F465-467.
12. Dawson JA, Davis PG, O'Donnell CP, et al. Pulse oximetry for monitoring infants in the delivery room: a review. Arch Dis Child Fetal Neonatal Ed 2007;92:F4-7.
13. Richmond S, Reay G, Abu Harb M. Routine pulse oximetry in the asymptomatic newborn. Arch Dis Child Fetal Neonatal Ed 2002;87:F83-88.
14. Koppel RI, Druschel CM, Carter T, et al. Effectiveness of pulse oximetry screening for congenital heart disease in asymptomatic newborns. Pediatrics 2003;111:451-455.
15. Mahle WT, Newburger JW, Matherne GP, et al. Role of pulse oximetry in examining newborns for congenital heart disease: a scientific statement from the AHA and AAP. Pediatrics 2009;124:823-836.
16. Meberg A, Brugmann-Pieper S, Due R, Jr., et al. First day of life pulse oximetry screening to detect congenital heart defects. J Pediatr 2008;152:761-765.
17. Sendelbach DM, Jackson GL, Lai SS, et al. Pulse oximetry screening at 4 hours of age to detect critical congenital heart defects. Pediatrics 2008;122: e815-820.
18. de-Wahl Granelli A, Wennergren M, Sandberg K, et al. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. BMJ 2009;338:a3037.
19. Riede FT, Dahnert I, Schneider P, et al. Pulse oximetry screening at 4 hours of age to detect critical congenital heart defects. Pediatrics 2009;123:e542; author reply e-3.
20. Ewer AK, Furmston AT, Middleton LJ, et al. Pulse oximetry as a screening test for congenital heart defects in newborn infants: a test accuracy study with evaluation of acceptability and cost-effectiveness. HTA 2012;16:v-xiii, 1-184.
21. Mahle WT, Martin GR, Beekman RH, 3rd, et al. Endorsement of Health and Human Services recommendation for pulse oximetry screening for critical congenital heart disease. Pediatrics 2012;129:190-192.
22. Thangaratinam S, Brown K, Zamora J, et al. Pulse oximetry screening for critical congenital heart defects in asymptomatic newborn babies: a systematic review and meta-analysis. Lancet 2012;379:2459-2464.
23. Turska Kmiec A, Borszewska Kornacka MK, et al. Early screening for critical congenital heart defects in asymptomatic newborns in Mazovia province: experience of the POLKARD pulse oximetry programme 2006-2008 in Poland. Kardiologia Polska 2012;70:370-376.
24. Kochilas LK, Lohr JL, Bruhn E, et al. Implementation of critical congenital heart disease screening in Minnesota. Pediatrics 2013;132:e587-594.
25. Singh A, Rasiah SV, Ewer AK. The impact of routine predischarge pulse oximetry screening in a regional neonatal

unit. Arch Dis Child Fetal Neonatal Ed 2014;99:F297-302.
26. Zuppa AA, Riccardi R, Catenazzi P, et al. Clinical examination and pulse oximetry as screening for congenital heart disease in low-risk newborn. J Matern Fetal Neonatal Med. 2015;28:7-11.
27. Bhola K, Kluckow M, Evans N. Post-implementation review of pulse oximetry screening of well newborns in an Australian tertiary maternity hospital. J Paediatr Child Health 2014;50:920-925.
28. Zhao QM, Ma XJ, Ge XL, et al. Pulse oximetry with clinical assessment to screen for congenital heart disease in neonates in China: a prospective study. Lancet 2014;384:747-754.
29. Hoke TR, Donohue PK, Bawa PK, et al. Oxygen saturation as a screening test for critical congenital heart disease: a preliminary study. Pediatr Cardiol 2002;23:403-409.
30. Reich JD, Connolly B, Bradley G, et al. The reliability of a single pulse oximetry reading as a screening test for congenital heart disease in otherwise asymptomatic newborn infants. Pediat Cardiol 2008;29:885-889.
31. Rosati E, Chitano G, Dipaola L, et al.Indications and limitations for a neonatal pulse oximetry screening of critical congenital heart disease. J Perinat Med 2005;33:455-457.
32. Bakr AF, Habib HS. Combining pulse oximetry and clinical examination in screening for congenital heart disease. Pediatr Cardiol ;26:832-835.
33. Arlettaz R, Bauschatz AS, Monkhoff M, et al. The contribution of pulse oximetry to the early detection of congenital heart disease in newborns. Eur J Pediatr 2006;165:94-98.
34. Ruangritnamchai C, Bunjapamai W, Pongpanich B. Pulse oximetry screening for clinically unrecognised critical congenital heart disease in the newborns. Paediatr Cardiol 2007;9:10-15.
35. Tautz J, Merkel C, Loersch F, et al. Implication of pulse oxymetry screening for detection of congenital heart defects. Klin Padiatr 2010;222:291-295.
36. Reich JD, Miller S, Brogdon B, et al. The use of pulse oximetry to detect congenital heart disease. J Pediatr 2003;142:268-272.
37. Ewer AK, Granelli AD, Manzoni P, et al. Pulse oximetry screening for congenital heart defects. Lancet 2013;382:856-857.
38. Riede FT, Worner C, Dahnert I, et al. Effectiveness of neonatal pulse oximetry screening for detection of critical congenital heart disease in daily clinical routine--results from a prospective multicenter study. Eur J Pediatr 2010;169:975-981.
39. Niermeyer S. Cardiopulmonary transition in the high altitude infant. Alt Med Biol 2003;4:225-239.
40. Salas AA. Pulse oximetry values in healthy term newborns at high altitude. Ann Trop Paediatr 2008;28:275-278.
41. Said Habib M. Oxygen saturation trends in the first hour of life in healthy full-term neonates born at moderate altitude. Pak J Med Sci 2013;29:4.
42. Han, LM, Klewer SE, Blank KM, et al. Feasibility of pulse oximetry screening for critical congenital heart disease at 2643-foot elevation. Pediatr Cardiol 2013;34:1803-1807
43. Wright J, Kohn M, Niermeyer S, et al. Feasibility of critical congenital heart disease newborn screening at moderate altitude. Pediatrics 2014;133:e561-569.
44. Clur SA, Bilardo CM. Early detection of fetal cardiac abnormalities: how effective is it and how should we manage these patients? Prenat Diagn 2014;34:1235-1245.
45. Kemper AR, Mahle WT, Martin GR, et al. Strategies for implementing screening for critical congenital heart disease. Pediatrics 2011;128:e1259-1267.
46. US Food and Drug Administration. Pulse Oximeters- Premarket Notification Submissions (510(k)s): Guidance for Industry and Food and Drug Administration Staff. March 4, 2013.
47. Dawson JA, Saraswat A, Simionato L, et al. Comparison of heart rate and oxygen saturation measurements from Masimo and Nellcor pulse oximeters in newly born term infants. Acta Paediatr 2013;102:955-960.
48. Bradshaw EA, Cuzzi S, Kiernan SC, et al. Feasibility of implementing pulse oximetry screening for congenital heart disease in a community hospital. J Perinatol 2012;32:710-715.
49. Iyengar H, Kumar P, Kumar P. Pulse-oximetry screening to detect critical congenital heart disease in the neonatal intensive care unit. Pediatr Cardiol 2014;35:406-410.
50. Manja V, Mathew B, Carrion V, et al. Critical congenital heart disease screening by pulse oximetry in a neonatal intensive care unit. J Perinatol 2015;35:67-71.
51. Lhost JJ, Goetz EM, Belling JD, et al. Pulse oximetry screening for critical congenital heart disease in planned out-of-hospital births. J Pediatr 2014;165:485-489.
52. Stichting Perinatale Registratie Nederland. Perinatal care in the Netherlands 2008.
53. Narayen IC, Blom NA, Verhart MS, et al. Adapted protocol for pulse oximetry screening for congenital heart

defects in a country with homebirths. Eur J Pediatr 2015;174:129-132.
54. Powell R, Pattison HM, Bhoyar A, et al. Pulse oximetry screening for congenital heart defects in newborn infants: an evaluation of acceptability to mothers. Arch Dis Child Fetal Neonatal Ed 2013;98:F59-63.
55. Studer MA, Smith AE, Lustik MB, et al. Newborn pulse oximetry screening to detect critical congenital heart disease. J Pediatr 2014;164:505-9 e1-2.
56. Roberts TE, Barton PM, Auguste PE, et al. Pulse oximetry as a screening test for congenital heart defects in newborn infants: a cost-effectiveness analysis. Arch Dis Child 2012;97:221-226.
57. Peterson C, Grosse SD, Oster ME, et al. Cost-effectiveness of routine screening for critical congenital heart disease in US newborns. Pediatrics 2013;132:e595-603.
58. Griebsch I, Knowles RL, Brown J, et al. Comparing the clinical and economic effects of clinical examination, pulse oximetry, and echocardiography in newborn screening for congenital heart defects: a probabilistic cost-effectiveness model and value of information analysis. Int J Technol Assess Health Care 2007;23:192-204.
59. Reich JD, Connolly B, Bradley G, et al. Reliability of a single pulse oximetry reading as a screening test for congenital heart disease in otherwise asymptomatic newborn infants: the importance of human factors. Pediatr Cardiol 2008;29:371-376.
60. Ryan DJ, Mikula EB, Germana S, et al. Screening for critical congenital heart disease in newborns using pulse oximetry: evaluation of nurses' knowledge and adherence. Adv Neonatal Care 2014;14:119-128.
61. Oster ME, Kuo KW, Mahle WT. Quality improvement in screening for critical congenital heart disease. J Pediatr 2014;164:67-71 e2.
62. Pflugeisen BM, Amoroso PJ, Zook D, et al. Quality improvement measures in pulse-oximetry newborn heart screening: a time series analysis. Pediatrics 2015;135:e531-539.
63. Hom LA, Martin GR. U.S. international efforts on critical congenital heart disease screening: can we have a uniform recommendation for Europe? Early Hum Dev 2014;90 Suppl 2:S11-14.
64. de-Wahl Granelli A, Meberg A, et al. Nordic pulse oximetry screening- implementation status and proposal for uniform guidelines. Acta Paediatr 2014;103:1136-1142
65. Kuelling B, Arlettaz Mieth R, et al. Pulse oximetry screening for congenital heart defects in Switzerland: most but not all maternity units screen their neonates. Swiss Med Wkly 2009;139:699-704.
66. Al Mazrouei SK, Moore J, Ahmed F, et al. Regional implementation of newborn screening for critical congenital heart disease screening in Abu Dhabi. Pediatr Cardiol 2013;34:1299-1306.
67. Mouledoux JH, Walsh WF. Evaluating the diagnostic gap: statewide incidence of undiagnosed critical congenital heart disease before newborn screening with pulse oximetry. Pediatric Cardiol 2013;34:1680-1686.
68. Riede FT, Schneider P. Most wanted, least found: coarctation. Neonatology 2012;101:13; author reply