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Position statement

The importance of screening for critical and severe congenital cardiac diseases by pulse oximetry in the early neonatal age – Position statement of the Hellenic Society of Perinatal Medicine (HSPM)

Andreas C. Petropoulos[1], George Daskalakis[2], Fani Anatolitou[3], Makarios Eleftheriadis[4], Panos Antsaklis[5], Athina Moutafi[6], Panagiotis Petropoulos[7], Anastasia Varvarigou[8], Antonia Charitou[9]

[1]Pediatric Cardiology Clinic and Pediatric Intensive Care Unit of IASO Children's Hospital, Athens, Greece; the "Aziz Aliyev" national postgraduate and CME medical training center, Baku, Azerbaijan; Member of the Hellenic and European Association for Congenital and Pediatric Cardiac Associations and the Hellenic Society of Perinatal Medicine (HSPM), Greece

[2]Vice President of the Executive Board HSPM; Prof. Obstetrics and Gynecology, National and Kapodistrian University of Athens (NKUA), Athens, Greece

[3]General Secretary of the Executive Board HSPM; Pediatrician-Neonatologist, Greece

[4]Treasurer of the Executive Board HSPM; Assoc. Prof. Obstetrics and Gynecology, NKUA, Athens, Greece

[5]Member of the Executive Board HSPM; Assist. Prof. Obstetrics and Gynecology, NKUA, Athens, Greece

[6]Member of the Executive Board HSPM; Pediatrician-Neonatologist, Consultant Aghia Sofia Children's Hospital, Athens, Greece

[7]Member of the Executive Board HSPM; Consultant Pediatric Surgery Aghia Sofia Children's Hospital, Athens, Greece

[8]Prof. Pediatrics and Neonatology, School of Medicine, University of Patras, Patras, Greece

[9]President of the Executive Board HSPM; Head of the Neonatal Intensive Care Unit, REA Maternity Hospital, Athens, Greece

Abstract

Background: From its first reported use in 2002, the efficiency of pulse oximetry (POX) screening in detecting critical and severe congenital heart disease (c/s-CHD) in term neonates in early days after delivery has been proved by numerous studies. It is low-cost, non-invasive, easy to use, repeatable, time-saving, applicable by even less-skilled nursing staff, proven to have excellent sensitivity and high specificity. When used in addition to the initial physician's examination before dismissing a newborn home, this postnatal test can increase the clinical accuracy of detecting c/s-CHD. In this sense, it must be used as an early detecting screening test. Its use is more

important during the period in which the patent ductus arteriosus (PDA) conceals the signs and symptoms of low cardiac output syndrome (LCOs) or severe cyanosis that will lead to notably hypoxia and acidosis. These free-of-symptoms babies that leave maternity units although critically ill, as well as those that are born at home and assessed by primary care, will benefit the most through a compulsory use of this test. Despite the benefits, it has failed to become a universal screening test for early detection of c/s-CHD, especially in Europe.

Aim: To discuss the existing evidence on safe, effective, and efficient screening, using POX in combination with initial pre-discharge physical examination at the end of its stay under maternity services, including births out of medical facilities, for every term baby as a compulsory health screening test in Greece.

Methods: The authors, members of the Hellenic Society of Perinatal Medicine (HSPM), reviewed the existing up-to-date literature and the trend of using this test worldwide and especially in European countries. They also consulted with pioneers and experts in the field.

Results: Based on published data, the authors clarify existing policies of using POX and initial clinical assessment, aiming to a standardized approach of screening and diagnostic follow-up, when needed. Key issues for future research and evaluation were identified and addressed.

Conclusions: The authors clarify existing policies in the use of POX, aiming to suggest the most appropriate way of using the test for compulsory screening term newborns during the early neonatal period in Greece. Special conditions of screening are being discussed. Public health organizations and private health agencies will have an important role in quality assurance and surveillance of this screening test aiming to significantly reduce morbidity and mortality from c/s-CHD in Greece.

Keywords

Critical/severe congenital heart diseases, neonatal pulse oximetry screening test, early detection screening test for CHD, perfusion index.

Corresponding author

Ass. Prof./Dr. Andreas C Petropoulos, Pediatric Cardiology and Pediatric Intensive Care Unit, IASO Pediatric Hospital, Athens, Greece; email: andrepetropoulos@gmail.com.

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Introduction

Congenital heart diseases (CHD) are among the most common malformations. The average prevalence reported as 1/100 live births of the general population [1, 2] has increased, reaching 1.2/100 live births or even higher [3, 4]. This prevalence increases up to 2/100 live births when considering also bicuspid aortic valve among CHD. CHD present in any age group with a variety of symptoms and signs [2]. They carry a high mortality and morbidity rate [2]. Their treatment combines medicine, interventional and surgical procedures [2]. In complex and severe forms, treatment must start in the neonatal period. It can be extremely complicated, chronic, expensive, and not applicable in many low-middle income countries [2-6]. A specific type of them, known in the literature as "critical CHD" (c-CHD), are defined as cardiac lesions that require surgery or cardiac catheterization within the first month of life to prevent death or severe end-organ damage [1, 5-6]. Next to them, another subcategory, called "severe CHD" (s-CHD), are non-cyanotic, mostly severe forms of left-sided heart obstruction (LSHO's) diseases that will soon present with low cardiac output syndrome (LCOs) (**Tab. 1**). These seriously ill babies that in many cases can be seen clinically as "well term babies" are raffle estimated as 25-30% of all CHD [3-7]. Although infant mortality has decreased over the past three decades in all forms of CHD, many are still diagnosed too late to avoid significant morbidity and death [5-7]. Delayed diagnosis of c/s-CHD is unfortunately too common. Up to 25% of infants suffering from CHD are missed diagnosed as newborns when the identification of CHD is based on clinical assessment even in clinics where prenatal echocardiography (echo-2D) is offered as a routine [8-11].

Since its first application in the early 1980s [7, 12], fetal echo-2D screening has been used as a universal detecting test. It has failed to diagnose all CHD prenatally. This screening method is still limited worldwide due to its cost and the need for specifically trained physicians to deliver it [2-3, 5].

Table 1. Critical congenital heart diseases (c-CHD's) as proposed by defects indicated as core targets by the Newborn Screening for Critical Congenital Heart Disease Expert Panel (CDC-AAP) and * defects added by the Neonatal Cardiology Study Group of the Italian Society of Neonatology and known as serious CHD's [5, 7].

Defects	Cyanotic	Non-cyanotic	Low PI
Pulmonary valve atresia with intact ventricular septum (PAvatr/IVS)	Yes		
Pulmonary valve atresia with ventricular septal defect (PAvatr + VSD)	Yes		
Tetralogy of Fallot with moderate and/or severe right ventricular outflow tract stenosis (ToF)	Yes		
Double outlet right ventricle (DORV)	Yes		
Persistent truncus arteriosus (TA)	Yes		+/- Low
Total anomalous pulmonary vein drainage (TAPVD)	Yes		
Tricuspid valve atresia (Tvatr)	Yes		
Hypoplastic left heart syndrome (HLHS)	Yes		
Types of single ventricle physiology (SV)	Yes		
Transposition of the great arteries (d-TGA)	Yes		+/- Low
Ebstein Anomaly with moderate and/or severe tricuspid valve regurgitation (Ebst.An)	+/- Yes		
Moderate and/or severe coarctation of the aorta (CoA)		Yes	Low
Interrupted aortic arch (IAA)		Yes	Low
Other complex CHD with low systemic perfusion		Yes	Low
Moderate/severe aortic valve stenosis (AovS)*		Yes	Low
Moderate/severe pulmonary valve stenosis (PAvS)*	Yes		
Complete atrio-ventricular septal defect (c-AVSD)*	+/- Yes		Low

CHD: congenital heart disease; PI: perfusion index.

A recent study shows that, despite the technological advances and continuous training of sonographers and physicians in the last 40 years, the rate of prenatal detection of c/s-CHD increased from 44% in 2007 to 69% in 2013 [6, 12]. All these facts point to the need for preventive measures or screening tests to detect early onset of CHD, mostly the c/s-CHD, as this would minimize mortality and morbidity [6, 13-14].

During the past years, several pioneering studies around the world have provided compelling evidence for the addition of pulse oximetry (POX) to routine clinical assessment as a complementary method for detection of c/s-CHD [2-6, 13-16]. In 2011, POX screening for c-CHD was added to the Recommended Uniform Screening Panel by the Health and Human Services Secretary in the USA, and since 2014 it has been suggested as a mandatory screening test for c/s-CHD in China [3, 17]. In Europe, large prospective, population-based multicenter studies from Norway, Sweden, Germany, the United Kingdom, and Poland have confirmed POX accuracy as a screening test [18]. In 2012, a large meta-analysis of 13 high-quality studies comprising nearly 230,000 infants came to the same conclusion [19]. Adding the 139,065 Chinese infants of the prospect study by Zhao et al. raises the tested population to at least 369,069 neonates in which POX has proven to be a reliable screening test [3, 17-19].

As stated in **Tab. 1**, 85% of the c-CHD will present with cyanosis. In term babies with no additional health issues, this amount is based on the anatomy of the defect, the hemoglobin (Hb) of the neonate, the resistance of the pulmonary vascular bed, the altitude at which the baby is born, and the time elapsed since its birth [20]. In 1953 Dr. Virginia Apgar firstly published the use of five clinical signs (skin color, heart rate, respiratory effort, muscular tone, and reflex irritability) to evaluate a newborn's condition at birth. She linked skin color with hypoxia in the neonate [21]. This was worldwide adopted in 1966 as a comprehensive screening test to evaluate the need for resuscitation after birth. It has also been used as an index of possible neurological sequelae that can present because of a long resuscitation procedure [21]. To determine whether a neonate is pink or blue involves examining the face and mucous membranes to detect the presence of central cyanosis. However, several factors other than oxygen saturation ($SatO_2$) can influence the neonate's color. Patient factors as skin thickness and color, perfusion, and hemoglobin concentration can influence the color. Also, environmental factors such as ambient light conditions can influence color perception. Therefore, a major limitation of the newborn physical examination is the inability of the human eye to detect important degrees of cyanosis. The

gap between normal oxygen saturation and visible cyanosis has been described as the "cyanotic blind spot" [22]. So, even the best trained clinical skilled person can misjudge a $SatO_2$ from its normal value of 95% and above, to 83% or even less, reaching 78% in a neonate with a Hb level of 13.5 g/dL [22]. The benefit of the use of POX in the early diagnosis of c-CHD's is linked to early detection of subclinical cyanosis. Its use surpasses the so-called "blind spot" and delivers an accurate detection of cyanosis, even when no additional symptom as tachypnoea or tachycardia is present [22]. The reported sensitivity and specificity of POX vary according to the evaluation timing, adopted cut-off value of $SatO_2$, use of a single or paired measurement site (post-DA [ductus arteriosus] only or pre-DA and post-DA), and lesion type [3, 5-7]. However, all previous studies described a low sensitivity for LSHO's, including coarctation of the aorta (CoA), interrupted aortic arch (IAA), critical aortic valve stenosis (AovS), and hypoplastic left heart syndrome (HLHS), as the main limitation of POX [3, 4-8, 15-19]. These defects, which are known as s-CHD, sum up approximately 15% of all types of CHD, and are the most frequently missed by POX and routine physical examinations [3, 5-8]. This can explain an increase of unexpected neonatal deaths, in which POX was thought to be "normal". To deal with this, a further evaluation by echo-2D will be needed to improve our diagnostic rates [3, 5-7].

In 2007 de Granelli et al. suggested that peripheral perfusion index (PI) can possibly be an additional screening tool for LSHO's. In neonates, PI correlates with other measures of peripheral and systemic perfusion obtained via functional echocardiography or near-infrared spectroscopy [7, 23-25]. Although promising, the effectiveness of the use of PI added on a screening protocol based on POX has not yet been studied prospectively in depth [7]. The Italian national study suggests that, although the use of PI requires further evaluation in populations with higher rates of LSHO's, its use can help to identify cases of CoA, missed by POX and clinical evaluation [6, 7].

Further, the larger cohort study by Zhao et al., as well as the most recent study by the Neonatal Cardiology Study Group of the Italian Society of Neonatology, stressed the need for a combined POX test with a clinical assessment to improve the diagnostic value of c/s-CHD [3, 6-7]. All published studies on the use of POX, up to date, have documented the ability of the test to detect additional pathology. These non-c/s-CHD conditions include a non-critical CHD, early-onset neonatal sepsis, other infections, persistent pulmonary hypertension of the neonates, parenchymal or anatomical pulmonary disease, transient tachypnea of the newborn, hypothermia, and hemoglobinopathies [3, 5-8, 14-19, 26-33]. This additional pathology detected by POX is a secondary diagnostic gain in neonatal care. Although not the primary targets of c/s-CHD screening, these secondary conditions can be detrimental to the neonate if not diagnosed and treated in a timely manner [6, 7].

Finally, POX with or without the addition of physician's examination and with or without the addition of PI is universally used in the USA, China, and many countries worldwide, many also represented in the Association for European Paediatric and Congenital Cardiology (AEPC). A complete approach based on guidelines setting the mandatory use of POX as a screening test towards early detection of the c/s-CHD's has not yet been achieved. In addition, for countries or centers that can add a PI measure and a physician's examination, this will increase their diagnostic ability significantly [3, 7]. The aim of this paper is to clarify the optimal use of POX in term neonates.

Position statement of the Hellenic Society of Perinatal Medicine (HSPM) on the use of POX

Taking into consideration the existing scientific published data, the authors, after consulting with pioneers and experts in the field, concluded to suggest for Greece to adopt the combination of POX + physicians' evaluation. This combined test can serve as an early detection/screening test for c/s-CHD and additional pathology that can secondarily surface and can be life-threatening for a neonate.

Important elements of our position are:

A. As normal values for term neonates, we adopt:
   1. pre- and post-DA $SatO_2$ measurements equal to or over 95%, when measured after the first day of life;
   2. pre- and post-DA $SatO_2$ measurements equal to or over 95% with a difference less than 3% in an assessment after the first day of birth and as later as possible after birth, based on discharge from maternal services. The accurate time would be after the fourth day of life [3-4, 6, 17]. In home births or early discharges from maternity service, the test must be applicable as above mentioned and delivered by a primary healthcare visitor, training to deliver it [6].

B. A suggested double repeated assessment in 30 minutes intervals with optimal conditions that include no crying, warm limbs and a quite but not deeply sleeping baby, to the initial intermediate measurements. As those, we are describing all cases where the initial measurements are between 91-94%, but with a pre-/post-DA difference less 3%, as well as those whose initial measurements are equal to or over 95%, but with a pre-/post-DA difference more than 3% [5-6, 18].
C. As a high number of CHD or cyanotic c-CHD diseases are mostly presenting early after birth, we initiate the measurement of POX at the end of the first day, aiming to diagnose a mixed sick population of neonates, suffering from severe forms of cyanotic c-CHD or s-CHD and non-cardiac conditions mentioned above. All these neonates will benefit from early detection and treatment [3, 5-7].
D. As many studies [3, 5, 7, 16-18, 28, 29] have shown that the detection rate for non-cyanotic c-CHD and s-CHD increases with applying the test as late as possible during the first few days after birth, an additional screening test is offered to all neonates with intermediate measurements. This test is delivered at the latest time before discharging the neonate and preferably after the third day of life [3, 6, 7]. If this cannot be achieved as an inpatient, the infant must be followed up by primary care. These neonates are those that have previously scored pre- and post-DA $SatO_2$ measurements equal to or over 95% with a pre- to post-DA difference more than 3%. If the new scores are with $SatO_2$ measurements equal to or over 95% and a pre- to post-DA difference less than 3%, they are pronounced to have a negative test and are discharged. In any other result with a pre- to post-DA difference persisting more than 3%, they are pronounced positive for the test and referred immediately to further investigation and potential treatment [6].
E. In cases of young infants with persisting intermediate measurements, we suggest that these neonates undergo further investigation with echo-2D. These cases will also serve as a "study population" to specify the appropriate cut-off of PI in the setting of s-CHD that presents with LCOs.
F. All neonates that test positive are immediately referred to higher-level care (Neonatal Intensive Care Unit) and an urgent cardiology assessment is offered. This will initially combine a clinical examination and an echo-2D. It can escalate to a cardiac CT or cardiac MRI and even a diagnostic cardiac catheterization if this is requested. Based on the obtained diagnosis, further treatment and follow-up will be offered.

Discussion

Any prevention method used in clinical practice ought to deliver specific qualities. It must be reliable in detecting a common and/or even lethal disease with a high level of sensitivity and specificity. It needs to be minimally invasive, easy to apply and inexpensive worldwide [32]. The diagnostic accuracy attenuates when the number of independent preventive testing methods increases [6, 32]. Therefore, a combination of the best of them is needed [32].

The c/s-CHD's address the need for an early detective test. When using the general term "c-CHD" we need to take into consideration that this term addresses two major entities of CHD. The first is the so-called "cyanotic" entity that includes different severity of hypoxia, for example Ebstein Anomaly with a small intra-atrial communication shunting right to left to the extreme form of d-TGA with both restrictive foramen ovale (FO) and DA in which hypoxia and consequent acidosis is severe and will present an early life-threatening condition. The second entity is the severe LSHO's; for example, either isolated critical – near-atretic aortic valve (Aov) disease or a combination of the valve disease with at least moderate CoA – or even multiple stenoses as seen in Shon's complex [20]. In these conditions, if additional shunts do not exist mixing the two circulations, cyanosis is absent. The major clinical presentation would be LCOs that will lead to low tissue perfusion and through that therefore to acidosis and finally to an amount of peripheral hypoxia and a low PI. This creates a difference in POX between the so-called pre-DA and post-DA measurements. This secondary event has permitted the detection of this second entity of the c-CHD, called LSHO's or s-CHD, by POX mostly if the test is executed as late as possible, far beyond the second day of life of these newborns, when the physiological closure of the DA mostly happens [3, 5-8, 30-33]. As POX has substituted nowadays the so-called "color" index of the Apgar score, it is easier to establish the full test [33]. The combination of POX and PI and a physician's assessment, as late as possible, before discharging the neonate from the maternity facilities, seem to be the best preventive/

early detective method worldwide nowadays [3, 5-7, 13-17, 19, 20, 27-33]. A very recent study regarding the use of POX as an early detective test for c-CHD reported the use of the test in 160 centers in 35 European countries – members of AEPC. More than half of the providers in these centers use POX screening for c-CHD (68.1%); however, there is no consensus regarding oxygen saturation cut-off level and the timing of the measurement. Most responders (91.3%) are interested in the implementation of European guidelines [34].

We propose a normal value cut-off of $SatO_2 \geq 95\%$ achieved by a dual simultaneous measurement [3, 6-8, 18, 19, 23, 27-29]. The optimal time to apply the test would be after the first day of life, and to be more beneficial it must be repeated as late as possible before discharge from maternal facilities for the neonates with intermediate measurements persisting after the third day of life. Additionally, a physician's assessment will complete the screening.

These proposed guidelines can be adjusted to the specific Health Care Systems of different European nations, taking into consideration that by applying the test after the first day of life the accuracy of detecting non-cardiac early neonatal nosology and cyanotic c-CHD increases significantly [3, 5-8, 27-31, 33]. A further application of the combined POX + PI as late as possible and preferably after the 72 hours from birth [3, 7] increases the detection rate of non-cyanotic CHD and other s-CHD [7].

Two issues that need to be addressed are the increasing numbers of deliveries out of maternity facilities and deliveries that take place in locations with high altitudes. Today screening protocols for c-CHD have been published in the Netherlands and the USA, addressing these issues [5, 35]. Recent studies conclude that POX screening for c/s-CHD is feasible after home births and incredibly early discharge from the hospital. Important neonatal pathology can be detected at an early stage, potentially increasing the safety of home births and early discharge policy [5, 35]. Due to the lower partial pressure of oxygen, neonates at a higher altitude typically have a lower $SatO_2$ according to POX than those at sea level [5, 33, 36]. This difference has important implications for c-CHD screening, particularly in settings with altitudes over 2,250 m [37].

Finally, studies that have estimated the cost for POX are based both on equipment use and time required. In the USA, the cost estimation ranges from approximately $5 to $14 per infant screened, with an estimated cost of $40,385 per life-year potentially gained through screening. This estimate does not include potential life-years gained through the diagnosis of secondary conditions; the estimated cost per life-year gained will be lower if these cases were included. Time and motion studies have revealed that point-of-care screening incurs approximately 3.5 to 9 minutes per infant [5]. Opportunities to reduce costs include using reusable pulse oximetry sensors instead of disposable, single-use sensors. More comprehensive cost-effectiveness analyses will become feasible as more detailed data collection is implemented by each individual country, including analyses of costs or savings for a neonate suffering from c-CHD by screening and comparing the total costs of human life and subsequent offered treatment for cardiac and non-cardiac morbidity [5].

Limitations still exist regarding the optimal PI [7], applying the combined POX + PI test and the basic training that is needed by a physician to detect at a higher possible rate c/s-CHD and other above-mentioned early neonatal morbidities. As future data from public health agencies will be known and used in clinical practice, we will be able to improve the use of this screening test. Until then, these proposed strategies wish to contribute as an easy-to-apply screening/early detecting test, in both in- and out-of-hospital facilities in minimizing the burden of CHD worldwide.

Conclusions

Since the "Holy Grail" of CHD prevention/early detection has not yet been found and patient numbers in the less privileged countries suffering from CHD are vastly increasing [2-4], a prevention/early detection strategy is needed. Additional to avoiding the teratogenic elements or conditions leading to CHD's, promoting a healthy pregnancy, and offering under indications fetal cardiac consultations [6], POX combined with clinical assessment (with an accurate PI in the future) is a feasible and reliable postnatal early detection screening test [3, 5-8, 17-19, 33]. This simple, low-cost, non-invasive and accurate method must be used as a worldwide screening test for c/s-CHD and additional specific early neonatal morbidity.

Although it has been adopted in many healthcare facilities around the world, we still lack a consensus on its use in Greece and Europe. To achieve this, specific guidelines are needed to unify its use. The essence of this paper is to contribute to this noble goal.

Abbreviations

AEPC: Association for European Paediatric and Congenital Cardiology
Aov: aortic valve
AovS: aortic valve stenosis
c-CHD: critical CHD
c/s-CHD: critical and severe CHD
CHD: congenital heart diseases
CoA: coarctation of the aorta
d-TGA: d-transposition of the great arteries
DA: ductus arteriosus
DORV: double outlet right ventricle
echo-2D: echocardiography
FO: foramen ovale
Hb: hemoglobin
HLHS: hypoplastic left heart syndrome
HSPM: Hellenic Society of Perinatal Medicine
IAA: interrupted aortic arch
LCOs: low cardiac output syndrome
LSHO's: left-sided heart obstructions
PAvatr + IVS: pulmonary valve atresia with intact interventricular septum
PDA: patent ductus arteriosus
PI: perfusion index
POX: pulse oximetry
Prevention: prevention of cardiovascular diseases
s-CHD: severe congenital cardiac disease
$SatO_2$: saturation of oxygen
TA: common truncus arteriosus
TAPVD: total anomalous pulmonary venous drainage
ToF: tetralogy of Fallot
Tvatr: tricuspid valve atresia
VSD's: ventricular septal defects

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Declaration of interest

None of the authors have any conflicts of interest.

References

1. Mahle WT, Newburger JW, Matherne GP, Smith FC, Hoke TR, Koppel R, Gidding SS, Beekman RH 3rd, Grosse SD; American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Interdisciplinary Council on Quality of Care and Outcomes Research; American Academy of Pediatrics Section on Cardiology and Cardiac Surgery, and Committee on Fetus and Newborn. Role of pulse oximetry in examining newborns for congenital heart disease: a scientific statement from the American Heart Association and American Academy of Pediatrics. Circulation. 2009;120(5): 447-58.
2. Hoffman JIe. The global burden of congenital heart disease. Cardiovasc J Afr. 2013;24(4):141-5.
3. Zhao QM, Ma XJ, Ge XL, Liu F, Yan WL, Wu L, Ye M, Liang XC, Zhang J, Gao Y, Jia B, Huang GY; Neonatal Congenital Heart Disease screening group. Pulse oximetry with clinical assessment to screen for congenital heart disease in neonates in China: a prospective study. Lancet. 2014;384(9945):747-54.
4. Petropoulos A, Hudiyeva A, Behbudov V, Mustafayeva G, Guliyev N, Huseynov R, Seyidov N. The incidence of congenital heart disease in Baku-Azerbaijan. Prospective epidemiology study. Arch Dis Child. 2019;104(Suppl 3):A16-7.
5. Oster ME, Aucott SW, Glidewell J, Hackell J, Kochilas L, Martin GR, Phillippi J, Pinto NM, Saarinen A, Sontag M, Kemper AR. Lessons Learned From Newborn Screening for Critical Congenital Heart Defects. Pediatrics. 2016;137(5):e20154573.
6. Petropoulos AC. Prevention and Early Detection of Congenital Heart Defects. Where do we Stand. J Cardiol. 2018;2(1):000111.
7. Schena F, Picciolli I, Agosti M, Zuppa AA, Zuccotti G, Parola L, Pomero G, Stival G, Markart M, Graziani S, Gagliardi L, Bellan C, La Placa S, Limoli G, Calzetti G, Guala A, Bonello E, Mosca F; Neonatal Cardiology Study Group of the Italian Society of Neonatology. Perfusion Index and Pulse Oximetry Screening for Congenital Heart Defects. J Pediatr. 2017;183:74-9.e1.
8. de-Wahl Granelli A, Wennergren M, Sandberg K, Mellander M, Bejlum C, Inganäs L, Eriksson M, Segerdahl N, Agren A, Ekman-Joelsson BM, Sunnegårdh J, Verdicchio M, Ostman-Smith I. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. BMJ. 2009;338:a3037.
9. Ng B, Hokanson J. Missed congenital heart disease in neonates. Congenit Heart Dis. 2010;5(3):292-6.
10. Wren C, Reinhardt Z, Khawaja K. Twenty-year trends in diagnosis of life-threatening neonatal cardiovascular malformations. Arch Dis Child Fetal Neonatal Ed. 2008;93(1):F33-5.
11. Kleinman CS, Hobbins JC, Jaffe CC, Lynch DC, Talner NS. Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. Pediatrics. 1980;65(6):1059-67.
12. Hill GD, Block JR, Tanem JB, Frommelt MA. Disparities in the prenatal detection of critical congenital heart disease. Prenat Diagn. 2015;35(9):859-63.
13. Arlettaz R, Bauschatz AS, Mönkhoff M, Essers B, Bauersfeld U. The contribution of pulse oximetry to the early detection of congenital heart disease in newborns. Eur J Pediatr. 2006;165(2):94-8.
14. Meberg A, Brügmann-Pieper S, Due R Jr, Eskedal L, Fagerli I, Farstad T, Frøisland DH, Sannes CH, Johansen OJ, Keljalic J, Markestad T, Nygaard EA, Røsvik A, Silberg IE. First day of

life pulse oximetry screening to detect congenital heart defects. J Pediatr. 2008;152(6):761-5.
15. Riede FT, Wörner C, Dähnert I, Möckel A, Kostelka M, Schneider P. 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(8):975-81.
16. Ewer AK, Middleton LJ, Furmston AT, Bhoyar A, Daniels JP, Thangaratinam S, Deeks JJ, Khan KS; PulseOx Study Group. Pulse oximetry screening for congenital heart defects in newborn infants (PulseOx): a test accuracy study. Lancet. 2011;378(9793):785-94.
17. Kemper AR, Mahle WT, Martin GR, Cooley WC, Kumar P, Morrow WR, Kelm K, Pearson GD, Glidewell J, Grosse SD, Howell RR. Strategies for implementing screening for critical congenital heart disease. Pediatrics. 2011;128(5): e1259-67.
18. de-Wahl Granelli A, Meberg A, Ojala T, Steensberg J, Oskarsson G, Mellander M. Nordic pulse oximetry screening – implementation status and proposal for uniform guidelines. Acta Paediatr. 2014;103(11):1136-42.
19. Thangaratinam S, Brown K, Zamora J, Khan KS, Ewer AK. Pulse oximetry screening for critical congenital heart defects in asymptomatic newborn babies: a systematic review and meta-analysis. Lancet. 2012;379(9835):2459-64.
20. Rudolph A. Congenital Diseases of the Heart: Clinical-Physiological Considerations, 3rd Edition. Hoboken, NJ: Wiley-Blackwell, 2009.
21. Apgar V. A proposal for a new method of evaluation of the newborn infant. Curr Res Anesth Analg. 1953;32(4): 260-7.
22. Jopling J, Henry E, Wiedmeier SE, Christensen RD. Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period: data from a multihospital health care system. Pediatrics. 2009;123(2):e333-7.
23. de-Wahl Granelli A, Östman-Smith I. Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction. Acta Paediatr. 2007;96(10): 1455-9.
24. Hanning CD, Alexander-Williams JM. Pulse oximetry: a practical review. BMJ. 1995;311(7001):367-70.
25. Levesque BM, Pollack P, Griffin BE, Nielsen HC. Pulse oximetry: what's normal in the newborn nursery? Pediatr Pulmonol. 2000;30(5):406-12.
26. Piasek CZ, Van Bell F, Sola A. Perfusion index in newborn infants: a noninvasive tool for neonatal monitoring. Acta Paediatr. 2014;103(5):468-73.
27. de Wahl Granelli A, Mellander M, Sunnegårdh J, Sandberg K, Ostman-Smith I. Screening for duct-dependant congenital heart disease with pulse oximetry: a critical evaluation of strategies to maximize sensitivity. Acta Paediatr. 2005;94(11):1590-6.
28. Engel MS, Kochilas LK. Pulse oximetry screening: a review of diagnosing critical congenital heart disease in newborns. Med Devices (Auckl). 2016:9:199-203.
29. Kochilas LK, Menk JS, Saarinen A, Gaviglio A, Lohr JL. A comparison of retesting rates using alternative testing algorithms in the pilot implementation of critical congenital heart disease screening in Minnesota. Pediatr Cardiol. 2015;36(3):550-4.
30. Cresi F, Pelle E, Calabrese R, Costa L, Farinasso D, Silvestro L. Perfusion index variations in clinically and hemodynamically stable preterm newborns in the first week of life. Ital J Pediatr. 2010;36:6.
31. Singh A, Rasiah SV, Ewer AK. The impact of routine pre-discharge pulse oximetry screening in a regional neonatal unit. Arch Dis Child Fetal Neonatal Ed. 2014;99(4):F297-302.
32. Elmore J, Wild D, Katz D, Lucan S. Jekel's Epidemiology, Biostatistics, Preventive Medicine, and Public Health, 4th Edition. Philadelphia: Saunders, 2013.
33. Petropoulos AC. Right use of Pulse Oximetry must be used as a Screening Test for early detection of critical Congenital Heard Diseases. Open J Cardiol Heart Dis. 2018;1(2):OJCHD.000510.2018.
34. Jakab A, Dalla-Pozza R, Ehringer-Schetitska D, Fritsch P, Oberhoffer R, Petropoulos A. Assessment of Pulse Oximetry Screening Trends in AEPC. Cardiol Young. 2018;28(S1):S1-176.
35. Narayen IC, Blom NA, Bourgonje MS, Haak MC, Smit M, Posthumus F, van den Broek AJ, Havers HM, te Pas AB. Pulse Oximetry Screening for Critical Congenital Heart Disease after Home Birth and Early Discharge. J Pediatr. 2016;170:188-92.
36. Wright J, Kohn M, Niermeyer S, Rausch CM. Feasibility of critical congenital heart disease newborn screening at moderate altitude. Pediatrics. 2014;133(3):e561-9.
37. Han LM, Klewer SE, Blank KM, Seckeler MD, Barber BJ. Feasibility of pulse oximetry screening for critical congenital heart disease at 2643-foot elevation. Pediatr Cardiol. 2013;34(8):1803-18.