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New born pulse oximetry screening: A global perspective

Asad Abbas [a,*], Andrew K. Ewer [a,b]

[a] Department of Neonatology, Birmingham Women's Hospital NHS Trust, Birmingham, United Kingdom
[b] Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom

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ABSTRACT

The possibility of pulse oximetry screening (POS) for congenital heart defects was first described over 20 years ago. Since then, an accumulation of research evidence and clinical practice experience has established POS as an important test to detect critical congenital heart defects (CCHDs). POS meets the criteria for universal screening and professional bodies around the globe have recommended universal POS. Many countries have already adopted POS while several others are working towards its implementation. In low and low-middle-income countries (LLMIC), POS has the additional potential for reducing morbidity and mortality from neonatal sepsis. This review summarises the evidence for POS and looks at current global uptake and different approaches to the implementation of POS.

1. Introduction and overview

Congenital hearts defects (CHDs) are the most common group of congenital malformations and a leading cause of infant death in developed countries [1]. In 2017, CHDs were responsible for 261,247 deaths globally, with more than half of these deaths occurring in infants less than 1 year of age [2].

Critical congenital heart defects (CCHDs) are defined as those defects that lead to death or require invasive intervention within the first 28 days of life [3] and have an incidence of 2 to 3 per 1000 live births [1,4,5]. CCHDs include left or right- sided obstructive lesions such as interrupted aortic arch, critical coarctation of the aorta, critical aortic or pulmonary stenosis, pulmonary atresia with intact septum, tricuspid atresia, hypoplastic left heart syndrome or lesions that cause abnormal drainage and inadequate mixing such as total anomalous pulmonary venous return and transposition of the great arteries [6]. The obstructive lesions rely on the presence of a patent ductus arteriosus to maintain pulmonary or systemic circulation. Lesions with inadequate mixing sometimes require a balloon atrial septostomy or valvuloplasty soon after birth [7]. Failure to detect these lesions before closure of the ductus arteriosus can result in postnatal collapse, shock, acidosis, end organ damage and sometimes death [3,8,9]. Detection of CCHDs before decompensation occurs allows prostaglandin infusion to be commenced to maintain ductal patency and transfer to a cardiac centre for surgical intervention. However, neonates who undergo operation after cardiovascular collapse has already occurred have worse outcomes in terms of mortality, length of hospital stay and duration of mechanical ventilation [3,8,10]. In addition, a further important consequence of haemodynamic compromise following collapse from undiagnosed CCHDs is neurological injury. Several studies have reported worse neurological outcomes in infants when intervention is performed following cardiovascular collapse [11–15]. Timely detection is therefore vital to improve mortality and long-term outcome for babies with CCHDs.

Routine screening for CCHDs is usually by antenatal ultrasound and postnatal physical examination. Antenatal detection is the preferred option as this allows optimisation of care in a timely manner, but despite steady improvement in detection rates, less than half of CCHDs are diagnosed before birth with wide variation in reported detection rates depending on population screened, type of defect and examiner expertise [16]. In most developed countries, the antenatal detection rate varies from 30 to 60% [17,18]. In 2012, The Society of Thoracic Surgeons Congenital Heart Surgery Database in United States noted an average antenatal detection rate of 42% with a variation of 11.8%–53.4% between different states [16]. Some single centres have reported higher detection rates following implementation of quality improvement measures and using newer scanning techniques such as outflow tract imaging and imaging of blood vessels in the upper mediastinum, however, when applied to larger populations the overall detection rates remain low [19]. Conditions such as total anomalous pulmonary venous drainage (TAPVD) and coarctation of aorta remain a challenge to detect even in the hands of most experienced operators [20]. In the United Kingdom, mean antenatal detection rate for CHDs has improved from

* Corresponding author.
E-mail address: asad.abbas1@nhs.net (A. Abbas).

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28.8% in 2008 to 53.5% in 2017. There are still significant variations between different regions in England, with lowest reported antenatal detection rate of 30.2% to highest of 82.5%. [18]

Newborn physical examination relies on the detection of signs of a heart defect such as murmur, cyanosis and absence of peripheral pulses. In the immediate neonatal period, presence of patent ductus arteriosus often masks clinical signs such as cyanosis and weak pulses [21,22]. In neonates, cyanosis only becomes apparent when the oxygen saturation falls below 80%, however, those with CCHD often have only a mild hypoxemia [23]. Heart murmurs are neither sensitive nor specific for the presence of CHDs [24]. Transitional circulation with high pulmonary vascular resistance can also lead to a heart murmur. Similarly, small muscular ventricular septal defects (VSD), which are of no clinical significance, often cause a heart murmur [8]. Conversely, a murmur may be absent in TAPVD or only appear after the pulmonary vascular resistance falls in conditions such as tricuspid atresia with VSD and double outlet right ventricle [8,24]. No corelation exists between presence of heart murmur and severity of cardiac condition [25]. Physical examination is also subject to wide variations, depending on the expertise of the examiner. Newborn physical examination is often performed by junior clinicians and studies have noted that physical examination skills have declined in trainee clinicians. [26–28]. Overall, physical examination alone fails to identify up to 30% of neonates with a CCHD [3].

2. Pulse oximetry screening (POS) for CCHDs

Pulse oximetry is a simple, non-invasive measure of oxygen saturation. Early proof-of-concept studies showed that infants with CCHD often have lower oxygen saturation, which doesn't always result in clinical cyanosis [29,30]. In addition, mild cyanosis is often difficult to identify clinically, especially in dark-skinned neonates [31]. The use of POS to identify such babies was further investigated in several large test accuracy studies [32–37]. A systematic review and meta-analysis published in 2012, including over 250,000 screened babies, showed an overall sensitivity of pulse oximetry for detection of CCHD of 76.5% and specificity of 99·9% with a false-positive rate of 0·14% and concluded that POS was a highly specific and moderately sensitive test fulfilling the criteria for screening test [38]. A further large study from China, including over 120, 000 screened babies, showed that the addition of pulse oximetry to clinical assessment increased the sensitivity for detection of CCCDs to 93·2% [39]. In the subsequent years, further pilot studies were conducted in Spain, the United Kingdom and Netherlands [40–43]. In 2018, a Cochrane systematic review analysed data from over 457,202 screened babies from 21 studies replicated the findings of the previous review reporting a sensitivity of 76.3% a specificity of 99.9% and a false positive rate of 0.14% [44]. Further investigation of 'false positive' results (i.e., CCHD not present) showed that a significant proportion of these have clinically important non-cardiac conditions, such as pulmonary disorders and infections. Meberg et al. screened 50,008 neonates with pulse oximetry, 134 (41%) of those that tested positive had conditions such as pneumonia, sepsis, transient tachypnoea of newborn (TTN), persistent pulmonary hypertension (PPHN), pneumothorax and meconium aspiration syndrome (MAS) [33]. In a study from Germany, Riede et al. reported 28 of the 40 (70%) false-positive results had either PPHN or sepsis [35]. In United Kingdom, Singh et al. screened 25, 859 neonates with POS. Out of 208 positive results, CCHD was diagnosed in 9 patients, 103 (49.5%) had a respiratory illness such as congenital pneumonia, meconium aspiration syndrome, TTN requiring oxygen. 2 babies had culture positive sepsis and 28 babies had evidence of culture-negative sepsis. 8 neonates had serious congenital heart disease which did not meet the criteria for CCHD [45]. These findings may be considered an additional benefit of POS, as many of these conditions can cause serious illness, including cardiovascular collapse and therefore would benefit from early identification and intervention.

The sensitivity and specificity of POS is also affected by the targets chosen for screening, the timing of screen and the cut-off values of oxygen saturation used [46]. POS is highly sensitive for the detection of CCHDs that lead to hypoxemia, whereas sensitivity is decreased when all CHDs are taken as a target, as not all CHDs lead to low oxygen saturations. Sensitivity of POS appears highest when screening is done between 6 and 12 h of birth at the expense of a slightly higher false positive rate [3]. Delaying screening beyond 24 h reduces the false positive rate, however, this may miss infants presenting within the first 24 h. Moreover, there is a tendency towards early discharge of otherwise healthy newborn infants in many countries. For these reasons, an individual approach based on the perinatal care practices of each country is advised [47]. As previously stated, when pulse oximetry is added to existing screening, overall detection of CCHDs increases to 92% [36]. Assuming a prenatal detection rate of 50% for CCHDs, the addition of POS is likely to result in the detection of additional 35 neonates with CCHDs per 100,000 live births [36]. When applied to larger populations, this is likely to result in the detection of a significant number of babies with CCHD that would otherwise have been missed. The additional benefit of POS is likely to be greater in areas where antenatal detection rates are lower.

POS is readily acceptable to parents and widely endorsed by the staff looking after newborn babies. False-positive results do not appear to lead to greater parental anxiety, which is consistent with parental experience from other screening programs such as hearing screening [37,43,48,49].

3. Global uptake of POS

Switzerland was the first country to have a national recommendation for POS. The recommendation was put forward by Swiss Societies of Neonatology and Paediatric Cardiology in 2005 [50].

In the United States (US), POS for CCHDs was added to the recommended uniform screening panel for newborns in 2011 and by July 2018, it was adopted by all US states. A retrospective review of 27 million live births in United States conducted in 2017 showed that state adoption of POS was associated with a 33% reduction in mortality rates from CCHDs compared to states where pulse POS had not yet started [51]. Further studies in US showed that POS is cost effective and is acceptable to parents [52] and there is no evidence that it resulted in an increased burden on clinical services [53].

In 2011, The German Society for Paediatric Cardiology supported the use of POS and formulated guidelines for its implementation in 2013. The German Society for Neonatology and Paediatric intensive care also recommended the use of universal POS in 2012 [54] and in 2017, POS was implemented in routine neonatal care in Germany [54]. In 2014, a working group of Austrian Society for Pediatrics and Adolescent Medicine recommended POS [55].

The Nordic countries were amongst the first adopters of POS with over 90% of the births being screened in Sweden, Norway and Finland by 2014 [56]. The Spanish national neonatal society recommended universal POS in 2017 [40].

In 2017, a European Pulse Oximetry Screening Workgroup published their recommendations for the use of POS in neonates for detection of CCHDs [57]. In the same year, Canadian Cardiovascular Society and Canadian Pediatric Cardiology Association issued a position statement endorsing the routine use of POS for detection of CCHDs [58]. Subsequent study from the province of Ontario showed that the intervention is likely to be cost effective [59].

In South America, national recommendations for universal POS are in place in Brazil and Argentina [60]. In 2017, The Ibero-American Society of Neonatology issued a consensus statement for adoption of universal pulse POS in Latin America [61].

In the United Kingdom, the National Screening Committee has considered POS but recently decided not to introduce universal POS [62,63]. Despite this, a 2020 survey of the 189 neonatal units in the UK reported that 96 (51%) were performing routine POS and a further 26 were considering introduction in the near future [64].

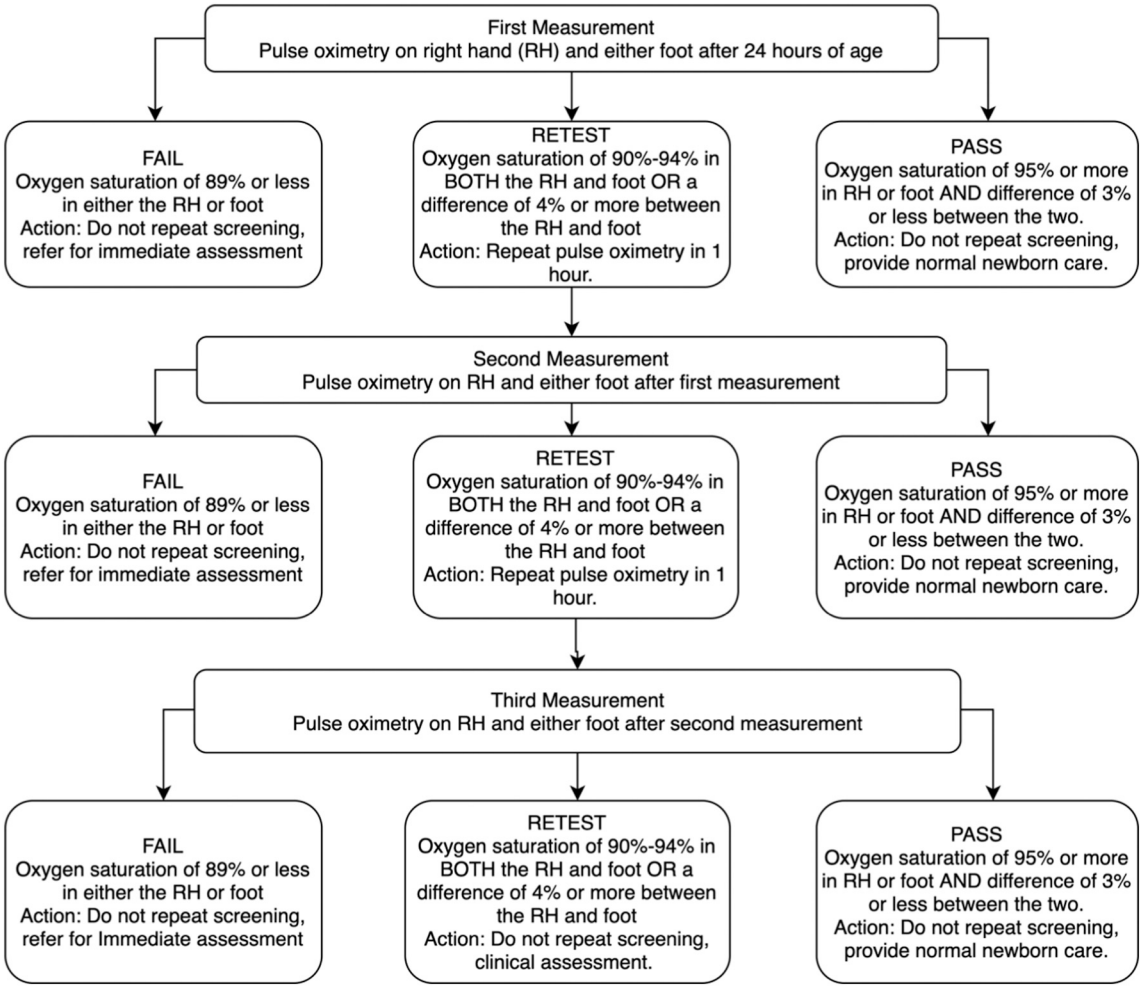

Fig. 1. US algorithm for POS.

In Australia and New Zealand, the implementation of POS has been on a hospital to hospital and region by region basis [65,66]. A survey of Neonatal Intensive care units in Australia and New Zealand revealed that 77% of the neonatal units have implemented POS [65]. A study funded by Health Research Council of New Zealand has also advocated nationwide adoption of POS in the country [66].

National recommendation for POS also exists for Ireland, Poland, Saudi Arabia, Abu Dhabi, Kuwait, Israel, China and Sri Lanka [60].

The majority of the deaths from CHDs occur in LLMICs and the proportion is also rising in these countries following improvement in the care of common infectious diseases and malnutrition. While the infant mortality from CHDs has declined by over 50% in middle, high middle- and high-income countries, the decline is only 6% in low-income countries [2]. The World Health Organisation has prioritised reduction in premature deaths from non-communicable diseases, including CHDs. It has been argued that significant resources are needed for treatment of CHD while they still make up a relatively low proportion of disease burden in low-income countries, however, it has been shown that development of services for treatment of CHD raises standards of care across the specialities and improvement in intensive care services through a 'towing effect' [67]. POS is a simple and effective tool for detection of congenital heart disease and could play an important role in low-income countries with the potential for a reduction of mortality. The benefits of POS for detection of CCHDs are greater when the antenatal detection rates are low, which is the case with most LLMIC. Furthermore, the burden of neonatal sepsis is much higher in developing countries, with neonatal sepsis rates being 1.8 times in middle-income countries and 3.5 times in low-income countries compared to high-income countries [68]. Small feasibility studies in LLMIC for detection of early-onset neonatal sepsis have shown promising results [69,70]. As POS detects a significant number of neonatal infections, and treatment of infectious diseases requires relatively fewer resources, POS has the potential to be an important tool to reduce neonatal morbidity and mortality in LLMIC.

4. Differences in approach to POS

POS can be undertaken by measuring the post-ductal saturation alone or by measuring both pre- and post-ductal saturations. The latter approach takes into account the difference in pre and post ductal saturations, even when both saturations are within the normal limits. Analysis of raw data from studies has shown that some infants with CCHDs will be missed when post-ductal saturations alone are used [47]. In coarctation of aorta, there is often a difference between pre and post ductal saturations, even with otherwise normal saturations. In transposition of great arteries (particularly with associated aortic obstruction), the post-ductal saturation may be normal while pre-ductal saturations are low [71]. However, post-ductal only screening is relatively simpler and concerns about increasing workload for screeners and the possibility of misinterpreting the result have led to some countries recommending post-ductal only screening [54,66].

As previously discussed, the timing of the test also varies with some algorithms recommending earlier (<24 h) or later (>24 h) screening. Many newborn infants with transitional circulation in the first few hours

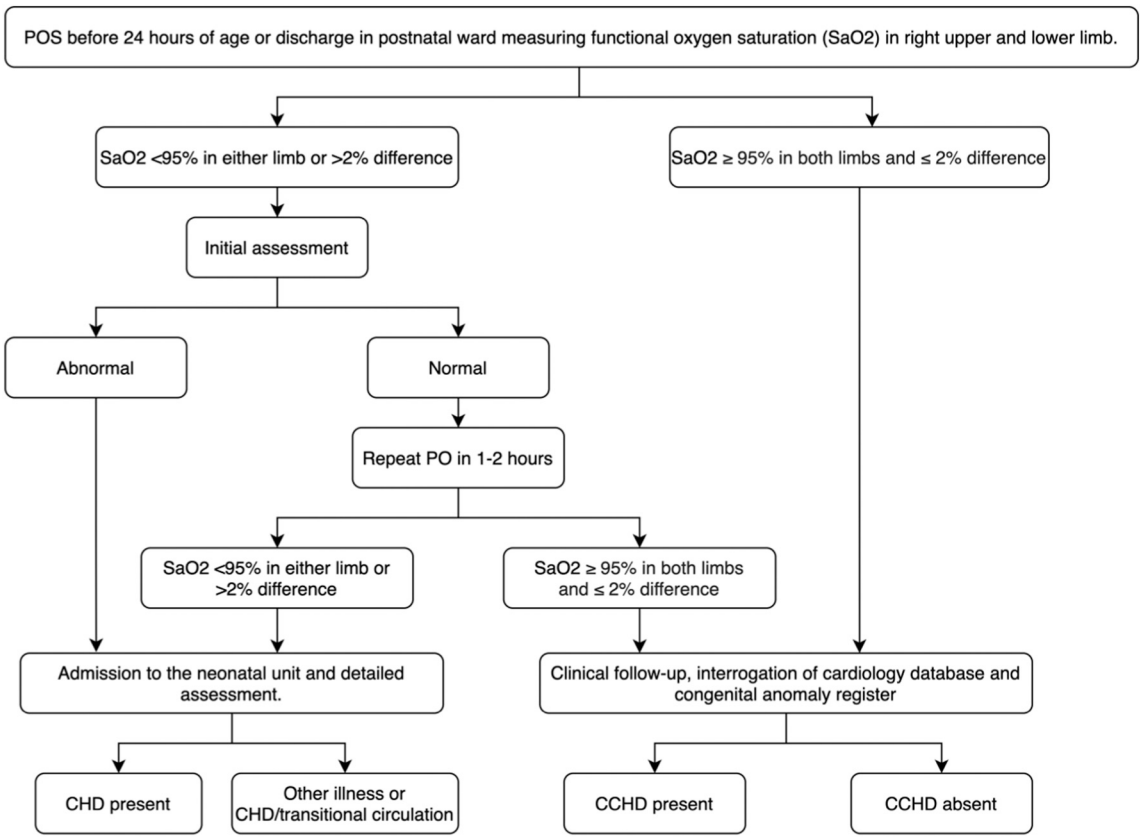

Fig. 2. UK algorithm for POS.

of life will have some degree of mild hypoxemia that will eventually resolve without treatment. Thus, earlier POS in the first 24 h of life will result in more false positive tests.

Based on these considerations, United States adopted a pulse oximetry algorithm (Fig. 1) where screening is performed after 24 h, using both pre- and post-ductal oxygen saturation [72]. A test is considered as 'pass' if both pre and post ductal saturations are above 95% and the difference between the two is less than 3%. A 'fail' test is pre or post ductal saturation of 89% or less. A retest is advised if the pre or post ductal saturations are between 90 and 95% or the difference between the two is 4% or more. The algorithm allows for two more retests at 1 h interval before referral for clinical assessment.

While earlier screening results in fewer false-positive results, there is evidence that up to half of the infant with CCHDs would present with symptoms within the first 24 h of life and over 10% will have a postnatal collapse [35,56]. Decompensation and acidosis in CCHDs significantly worsen outcomes and POS is used to identify infants at risk of this [10]. Additionally, early screening is also more likely to detect serious non-cardiac conditions that require early intervention. [35,47,56]. Perinatal care practices also differ between different countries. In many countries, most otherwise healthy infants would be discharged soon after birth and there is an increase in the number of home births. POS would not be feasible in these infants after 24 h without a home visit.

An alternative approach suggested in the UK utilises screening within 24 h with a slightly different definition of a positive test (Fig. 2) [36]. In this approach, a positive test is considered a pre or post ductal saturation of <95% or difference of more than 2% between the two. A positive test is followed by a clinical assessment. If clinical assessment is abnormal, admission to the neonatal unit and more detailed assessment is advised. With normal clinical assessment, a repeat screen is performed in 1–2 h. Using this approach, the false positive rate was 0.8%, however, 79% of these 'false positive' results had significant medical condition. Only 29% of infants who had a positive test underwent echocardiography, mainly because an alternative diagnosis was established after the initial assessment [45]. Recently, a US expert panel meeting in 2018 has recommended modifications to this algorithm; requiring both pre- and post-ductal oxygen saturation of at least 95% for a 'pass' result and including only one repeat screen in case of an indeterminate test result [60].

Globally, screening after 24 h is recommended in United States, Canada, Germany and Austria [54,55,58,72]. Early screening (before 24 h) is being performed or is recommended in United Kingdom, Nordic countries, Latin America, Saudi Arabia, Spain and Sri Lanka [36,40,56,61,73,74]. The European consensus statement also recommended screening between 6 and 24 h of life using both pre- and post-ductal measurements [57,75].

5. Summary

POS is simple, quick, acceptable and effective tool to detect neonatal hypoxemia. When POS is added to routine screening, the majority of the neonates with CCHDs will be detected, leading to early intervention and improved outcomes in these neonates. POS also helps identify several important non-cardiac neonatal conditions. Routine POS is endorsed by several neonatal societies and a number of countries have already adopted POS in their national screening programmes, while many others have national recommendations in place. There is still debate regarding the most appropriate screening algorithm and data from national screening programmes are likely to clarify this. However, the addition of POS improves detection of CCHD compared to standard screening regardless of the algorithm used.

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