Review of pulse oximetry screening for critical congenital heart defects in newborn infants

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Purpose of review
The concept of using pulse oximetry as a screening method to detect undiagnosed critical congenital heart defects (CCHD) in asymptomatic newborns was first explored over 10 years ago. A number of studies were subsequently reported, which initially involved relatively small numbers of patients, low prevalence of CCHD and heterogeneous methodology. As a consequence, the majority of clinicians felt the case for routine pulse oximetry screening had not been proven.

Recent findings
In the last 3 years, four European studies reporting the test accuracy of routine pulse oximetry screening, and involving over 150 000 babies, have strengthened the argument. A systematic review and meta-analysis of almost 230 000 screened babies has also recently been published which reported high specificity, moderate sensitivity and a low false-positive rate. In addition, acceptability to parents and staff, cost-effectiveness and feasibility of implementing screening outside the research context have also been reported.

Summary
Pulse oximetry screening is a highly specific, moderately sensitive test, which is acceptable to parents and staff, likely to be cost-effective and fulfils the criteria for universal screening. Routine screening for CCHD using pulse oximetry is being increasingly supported and was added to the recommended uniform screening panel in the USA in 2011.

Keywords
critical congenital heart defects, detection, newborn infant, pulse oximetry, screening

INTRODUCTION

The estimated incidence of ductal-dependent critical congenital heart defects (CCHDs) (defects leading to death or requiring invasive intervention within 28 days of life) is between two and three per 1000 livebirths [1,2]. Early detection of CCHDs reduces the risk of acute cardiovascular collapse, acidosis and death and improves outcome [2,3▪▪,4].

Screening for CCHDs has previously relied on antenatal ultrasound and postnatal examination but both have a relatively low detection rate [2,3▪▪,4]. It is estimated that up to a third of babies may be discharged with undiagnosed critical defects [3▪▪,4].

Pulse oximetry is a well-established, accurate, non-invasive test for objective quantification of hypoxaemia. On the basis of the rationale that clinically undetectable hypoxaemia is present, to some degree, in most CCHDs, the use of this technique as a screening method for early detection was first reported over 10 years ago [5,6] with a number of additional studies subsequently reported. In 2007, a systematic review drew attention to the difficulties in precise assessment of the true accuracy of pulse oximetry screening because of small numbers of patients recruited, the low prevalence of CCHDs and methodological variations reported in the studies [7]. In 2009, a statement on behalf of the American Heart Association and The American Academy of Paediatrics [2], which included two further screening studies [8,9], also concluded that 'further studies in large populations and across a broad range of newborn delivery systems were needed to determine if (pulse oximetry screening) should become a standard of care' [2].

More recently, additional large studies have added significant weight to the argument for

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KEY POINTS

- Screening newborn infants for critical congenital heart defects using pulse oximetry is feasible and adds value to existing screening techniques.
- The addition of pulse oximetry screening to antenatal ultrasound and physical examination may increase detection rates for CCHD to over 90%.
- Pulse oximetry screening has been endorsed by an increasing number of professional bodies and universal screening is being considered by health-care systems across the world.

universal screening [10,11,12▪,13] and have provided essential data on important issues regarding screening strategies [10,11,12▪], acceptability to parents and clinical staff [3▪▪,14▪] and cost-effectiveness [3▪▪,15▪].

This article will focus on the latest evidence and give an update on the progress of the implementation of universal pulse oximetry screening.

RECENT TEST ACCURACY STUDIES

In 2009, de-Wahl Granelli *et al.* [10] from Sweden published the results of a test accuracy study involving over 39 000 babies. Screening included an assessment of both preductal and postductal saturation (as opposed to postductal testing alone, which had been the strategy in the majority of previous studies) and reported a sensitivity of 62% and specificity of 99.8%. Screening was performed at a median postnatal age of 38 h with a low false positive rate of 0.17%. Pulse oximetry demonstrated additional benefit as an adjunct to physical examination and the detection rate of 92% of CCHD when both methods were used was much improved when compared with hospitals in other regions of Sweden where pulse oximetry screening was not performed.

In 2010, a German study by Riede *et al.* [11] screened over 40 000 babies using only postductal saturations and reported a sensitivity of 78%, specificity of 99.9% and a false positive rate of 0.1%. Screening was performed between 24 and 72 h, but the average screening time is not reported.

In 2011, the PulseOx study from the United Kingdom reported the test accuracy, acceptability to parents and clinical staff and cost-effectiveness of pulse oximetry screening in over 20 000 babies [3▪▪,12▪]. Once again, both preductal and postductal saturation measurements were performed and an earlier time of screening (mean postnatal age at screening – 12 h) was adopted. Sensitivity for detecting CCHD was 75%, specificity 99.1% and the false positive rate was relatively high at 0.8%.

Data from these recent large studies were added to those from existing studies and in 2012 a further systematic review and meta-analysis was performed [16▪▪]. This review included 13 good quality studies examining test accuracy of pulse oximetry which involved almost 230 000 babies – an addition of over 100 000 since the previous reviews. With such a large cohort, and the subsequent improvement in the prevalence of CCHD, the overall test accuracy could be reported with more precision. The systematic review reported that pulse oximetry was a highly specific test for CCHD (99.9%) with moderate sensitivity (76.5%) and a low false positive rate (0.14%). This was particularly low if the test was performed after 24 h of age (0.05%). The authors concluded that pulse oximetry met the criteria for universal screening. They also concluded that, in view of the number of babies who had now been studied, it was unlikely that any further research would demonstrate substantially different findings. Since the publication of the systematic review, a further study of over 50 000 babies in Poland has been reported [13]. Testing postductal saturations within the first 24 h (mean age at testing 7 h), a sensitivity and specificity of 78.9 and 99.9% respectively and a very low false positive rate of 0.026% were reported, which is broadly consistent with the findings of the systematic review.

The rigour of follow-up to identify false negatives was variable between studies and only two studies [10,12▪] included mortality databases to identify those dying from unidentified CCHD, but this is unlikely to affect the conclusions significantly.

Importantly, the authors of all four studies emphasized that pulse oximetry should not replace the existing screening strategies but should be employed as an adjunct investigation. Riede *et al.* [11] describes a 'diagnostic gap' for CCHD, that is, babies who are missed by routine screening alone. When pulse oximetry is included in addition to antenatal ultrasound and physical examination the percentage of babies with CCHD who are identified prior to discharge is increased to over 90% (range 92–96%) [10,11,12▪,13].

In addition, the detection of non-critical CHDs and significant non-cardiac conditions such as respiratory problems or early-onset sepsis is reported as an additional benefit. It is noteworthy that these clinically important conditions contributed between 37 and 70% of the false positive groups (average 50%) [10,11,12▪,13].

SCREENING STRATEGIES

There is a degree of heterogeneity between the screening protocols used in the reported studies.

The main differences are as follows: timing of screening; postductal or preductal and postductal saturation measurement; saturation threshold for a positive test.

Timing of screening

There is no doubt that later screening (>24 h) has a lower rate of false positive results than early screening (<24 h); this has been a consistent finding in published reviews [2,7,16▪▪]. Interestingly, the recent Polish study (which has not been included in a systematic review) screened at an average age of 7 h and reported one of the lowest false positive rates [13].

A high false positive rate could potentially have significant impact on clinical services and is, therefore, an important consideration. However, a number of countries (including the United Kingdom) have an increasing trend towards earlier discharge, and discharge before 24 h is often the norm for uncomplicated deliveries. In this situation waiting until after 24 h to administer a screening test will place an unmanageable pressure on resources and will, therefore, be untenable. In the later screening studies up to half of the babies with CCHDs who were eligible for screening presented with symptoms prior to the onset of screening, and in de-Wahl Granelli's study five babies are reported as collapsing in hospital prior to diagnosis [10]. In Riede 's study 18/36 babies presented with symptoms prior to screening, although details of the severity of symptoms are not described [11]. In the PulseOx study which screened at an average time of 12 h no babies are reported as presenting prior to screening taking place and the only case of cardiovascular collapse was in a baby who was discharged home after passing all screening tests [12▪]. In contrast, the Polish study, which screened at an average of 7 h, reported that 68% of babies with undiagnosed CCHD presented with symptoms prior to screening, which suggests an exceptionally high degree of close observation of babies in the postnatal nursery, although the number of babies presenting with collapse prior to diagnosis is not reported [13].

It is also worth considering that babies with important non-cardiac conditions such as congenital infection and pulmonary hypertension are more likely to present in the first 24 h and the early identification of these problems may also reduce morbidity and mortality.

In the end, a balance needs to be struck between timely diagnosis of life-threatening conditions and an excess of false positives. It should be remembered that all false positives are babies with low oxygen saturations and in principle no baby should have persistent unexplained hypoxemia.

Preductal or postductal saturation measurement

The majority of pulse oximetry studies (60%) used postductal measurements only, and in meta-analysis there was no difference in sensitivity between postductal testing and preductal testing combined [16▪▪]. However, postductal testing included almost twice as many patients and the sensitivity estimates in the two sub-groups were too imprecise to make any inference [16▪▪]. Both of the recent studies using preductal and postductal testing reported that, if postductal testing alone had been used, babies with CCHD would have been missed; three babies in Ewer's study [12▪] and one in de-Wahl Granelli's [10].

Saturation threshold for a positive test

The lower limit for a positive test varies between 92 and 95% with the majority of studies using less than 95%. The numbers of patients in the different subgroups were too small to identify sensitivity differences.

The studies employing preductal and postductal saturations used two different thresholds – both less than 95% or a difference of more than 3% and either less than 95% or a difference of more than 2% [10,12▪]. The false positive rate was lower with the former threshold (although the patients were screened much later and there was an additional retest) and sensitivity of the latter was higher, but again numbers were too small to identify differences in sensitivity with precision [16▪▪].

ACCEPTABILITY

When new neonatal screening procedures are introduced it is important to consider their acceptability to both parents and clinical staff and also the psychological impact that screening may have on parents, particularly raising anxiety that the child has a serious health condition. Screening acceptability may have an effect on uptake, and the psychological effects of an inaccurate result may extend over a long period of time. Only two studies have addressed the issue of acceptability. In the recent Polish study all the parents of screened babies were asked two questions – one pertaining to the ease of deciding to participate and the second asking if the parent felt that screening should be adopted as a routine for all babies in Poland. In both instances 91% of respondents gave positive responses [13].

In the United Kingdom PulseOx study, a detailed psychological questionnaire was given to mothers of all babies with false positive and true positive results and to a sample of those with a true

negative result [3▪▪,14▪]. The questionnaire used rigorous methodology to assess satisfaction with the test, anxiety and depression, general feelings about the test and illness perception. The results showed that parents were predominantly satisfied with the test and those whose babies had a false positive result were no more anxious than those with true negative. Parents generally perceived it as an important and valued test to detect ill babies [14▪]. In addition, the views of clinical staff involved in testing were also sought, either at focus group meetings or by e-mail questionnaires. All staff groups (healthcare assistants, midwives, nurses and doctors) were predominantly positive about the testing procedure and perceived the test as important [3▪▪].

COST-EFFECTIVENESS

In 2005, an evaluation of newborn screening for CHD published by Knowles *et al.* [17] used decision analytic modelling to estimate the cost of screening. The model suggested an additional cost per timely diagnosis of £4500 for pulse oximetry compared with £4.5 million for routine screening echocardiography. de-Wahl Granelli *et al.* [10], using data from an older model, estimated cost at £3430 per timely diagnosis.

In the PulseOx study, a cost-effectiveness analysis was also performed employing the model used by Knowles *et al.* and using data from the test accuracy study [3▪▪,15▪]. The analysis compared clinical examination alone with clinical examination and pulse oximetry and found that the addition of pulse oximetry was twice as costly, but identified an additional 30 cases of CHD per 100 000 livebirths compared with examination alone. The incremental cost-effectiveness ratio for this strategy was £24 000 per timely diagnosis, and probabilistic sensitivity analysis suggested that, at a willingness-to-pay threshold of £100 000, the probability of pulse oximetry screening being cost-effective is more than 90%. The report concluded that, at current thresholds, the addition of pulse oximetry was likely to be cost-effective [15▪]. It is important to remember that this analysis was performed on data from a study with a relatively high false positive rate and an antenatal detection rate for CCHD of 50%. It was also assumed that a diagnostic echocardiogram would be performed in all test positive cases. In situations with a lower false positive rate and/or a lower antenatal detection, the cost-effectiveness is likely to improve. The diagnosis of a non-cardiac cause for hypoxemia would obviate the need for an echocardiogram, potentially reducing costs further.

FEASIBILITY

It is important to assess the ability to perform routine pulse oximetry screening in all newborns outside a research study and in all clinical settings prior to recommending universal screening. In Switzerland, 76% of maternity units screen all newborns prior to discharge, although screening is performed significantly less in birthing centres than in hospitals [18]. In 2010, it was reported that 7% of UK maternity units undertook routine screening [19] and effective screening was established in a community hospital in the USA [20▪]. This is particularly relevant, as smaller hospitals may not always benefit from a robust antenatal screening programme. These reports demonstrate that screening can be achieved without additional staff and without overburdening clinical services, suggesting that implementation of universal pulse oximetry is feasible and achievable.

IMPLEMENTATION OF UNIVERSAL SCREENING

In 2005, the Swiss Society of Neonatology and the Swiss Society of Paediatric Cardiology recommended that all neonates in Switzerland should undergo first day pulse oximetry screening [18] and in 2010, this was also recommended by the Polish Ministry for Health [13]. In 2011, the US Secretary's Advisory Committee in Heritable Disorders in Newborns and Children convened a workgroup which reviewed the available evidence and recommended a standard protocol for routine screening. The subsequent statement by this group [21▪▪] was endorsed by a number of professional bodies, including the American Academy of Paediatrics, American Heart Association and the US Health and Human Services Secretary [22]. States across the USA are currently considering implementation of this recommendation and, to date, four states are currently screening all neonates, with the majority of the other states making progress towards this goal. In the United Kingdom, the National Screening Committee is currently undertaking a review of screening for paediatric congenital heart disease, which includes considering the value of the introduction of pulse oximetry screening.

LIMITATIONS

In high altitude settings, the normal threshold for saturations may not apply and may need to be adjusted. Evidence to define this adjustment more precisely is currently lacking.

Although the evidence strongly supports the conclusion that the addition of pulse oximetry will

significantly reduce the number of babies leaving hospital with undiagnosed CCHD, it is vital to remember that it will not detect all these babies. The sensitivity of around 75% means that approximately a quarter of babies with CCHD will not be detected by this method. Combining with other screening methods will reduce this diagnostic gap but some babies will still be missed. Most studies report that the commonest lesions missed are those causing obstruction to aortic outflow (e.g. coarctation and interrupted arch), which may not necessarily be associated with hypoxemia. The use of preductal and postductal saturation difference may improve this, but both recent studies employing this technique reported a failure to detect these conditions [10,12▪]. Interestingly, even lesions which one may assume will always be associated with cyanosis (such as transposition of the great arteries), may occasionally be missed [12▪,20▪]. It is essential that both clinical staff and parents are made aware of the limitations of this technique so that false expectations are not raised.

CONCLUSION

Recent studies, particularly when combined with data from previous studies, provide compelling evidence for the introduction of pulse oximetry screening into routine clinical practice. A recent Lancet editorial described the technique as 'a new milestone in the history of congenital heart disease' [23]. The test is well tolerated, simple and feasible; it is highly specific and sufficiently sensitive to qualify for screening. It is acceptable to parents and clinical staff and cost-effective in the current clinical setting and is endorsed by an increasing number of professional and national institutions.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 260).

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14. ▪ Powell R, Pattison HM, Bhoyar A, *et al.* Pulse oximetry as a screening test for congenital heart defects in newborn infants: an evaluation of acceptability to mothers. Arch Dis Child 2013; 98:F59–F63.

This is the first study to report the acceptability to mothers of pulse oximetry screening. The results of screening (including false positives) did not increase maternal anxiety.

15. ▪ Roberts TE, Barton P, Auguste P, *et al.* Pulse oximetry as a screening test for congenital heart disease in newborn infants: a cost effectiveness analysis. Arch Dis Child 2012; 97:221–226.

This study reports the cost-effectiveness of screening compared with physical examination alone using data from the PulseOx study. The conclusion is that pulse oximetry screening is cost-effective in the light of currently accepted thresholds.

16. ▪▪ Thangaratinam S, Brown K, Zamora J, *et al.* Pulse oximetry screening for critical congenital heart defects (CCHD) in asymptomatic newborns: a systematic review and meta analysis. Lancet 2012; 379:2459–2464.

This meta-analysis identified 13 studies investigating the use of pulse oximetry screening. The overall sensitivity for pulse oximetry screening was 76.5%, the specificity 99.9% and false positive rate 0.14%. The review concludes that pulse oximetry is highly specific for detection of critical congenital heart defects with moderate sensitivity and meets criteria for universal screening.

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