Perfusion index as a screening test for neonatal aortic coarctation

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DOI:
10.1111/apa.15768

Editorial

Perfusion index as a screening test for neonatal aortic coarctation: should we be using it routinely?

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Abbreviations: CCHD – critical congenital heart defect, POS – pulse oximetry screening, left heart obstructive defects (LHOD), CoA – coarctation of the aorta, IAA - interrupted aortic arch, PI – perfusion index

Word count - 1446

Refs - 13

Conflict of interest: Prof Ewer has received travel and accommodation expenses from Medtronic and Masimo to present at scientific meetings only and has received no personal payments or honoraria from any oximeter manufacturers. He has no financial interests in any oximeter manufacturers.

Routine, pre-discharge, newborn pulse oximetry screening (POS) has consistently been shown to identify babies with critical congenital heart defects (CCHD) that would otherwise be missed by antenatal ultrasound and newborn physical examination.[1] The addition of POS to these existing screening tests increases the proportion of CCHD identified from 50-70% to over 90%.[2,3] As a result, POS is now recommended in many countries[4] and a recent study of over 27 million babies in the USA clearly demonstrated that the introduction of POS reduces neonatal mortality from CCHD by 33%.[5]

However, POS does not identify all babies with CCHD and some, particularly those with left heart obstructive defects (LHOD) such as coarctation of the aorta (CoA) and interrupted aortic arch (IAA), are often missed by POS and other routine screening tests.[2,3] Reported sensitivity of POS for identifying these conditions varies, but is usually less than 50%.[2,3]

LHOD are likely to reduce systemic circulation; and the fact that modern pulse oximeters can now record perfusion index (PI; an assessment of the strength of the peripheral pulse) at the same time as measuring oxygen saturations has led researchers to investigate the potential role of PI as an additional screening tool for these specific defects.[6-11]

These studies have attempted to investigate two important parameters - i) the normal range of PI in healthy newborn babies and ii) the threshold below which PI becomes an accurate and useful screening test for CCHD particularly LHOD. Both have proven to be quite inconsistent.

Granelli *et al* reported the first evidence to suggest the use of PI as a possible screen for LHOD in 2007.[6] They measured pre- and post-ductal PI in 10 000 healthy newborns between 1 and 120 hours of life and reported a median PI of 1.7 and a 5th centile of 0.7. Applying the 5th centile as a cut-off for 'normal' perfusion to a cohort of 9 babies with previously diagnosed LHOD (including two with hypoplastic left heart) they showed that 5/9 (56%) had PI <0.7 (either pre or post ductal) including 2 out of 3 that were missed by POS. Between 2017 and 2020 five additional studies investigated this further. Jagatheesen *et al* reported a similar normal range of pre- and post-ductal PI values in 2768

healthy newborns at around 24 hours of age and also established a 5th centile of 0.7.[7] However, Schena *et al* investigating a much larger cohort of over 42 000 asymptomatic babies screened after 48 hours reported a higher threshold value of 0.9. Yet using this cut-off they identified only 1/4 babies (25%) with CoA/IAA; although all 4 defects were missed by POS.[8] In a much smaller study of 1011 babies, Ramesh *et al* used PI identified a cut-off of 0.7 at 24-72 hours of age and used this to successfully pick-up one baby with LHOD that had also been identified by antenatal ultrasound and POS.[9] In a cohort of 3175 babies, Uyger *et al* reported the PI 5th centile at 24-48 hours of life to be 1.1 (pre-ductal) and 1.2 (post-ductal).[10] After retrospectively applying these cut-offs to both the original cohort and to another cohort of 33 babies with an antenatal diagnosis of CCHD they demonstrated a sensitivity for detection of CCHD of 64% (pre-ductal) and 61% (post-ductal) - LHOD were not reported separately. If the threshold of 0.7 was applied then sensitivities fell to 33% and 36%.

In 2020, Siefkes *et al* measured PI after 24 hours of life and at the same time as POS in 123 healthy newborns and established the post-ductal 5th centile to be 0.5.[11] When they applied this threshold value to 13 babies with CCHD (including four with CoA/IAA) they showed that PI would pick up 3 out of 4 (75%) of the CoA/IAA defects, all of which had been missed by POS.

So, these studies show that using PI as an additional screening test will identify some babies with CoA/IAA that would have been missed by POS and this is interesting and important. However, taking a number of additional factors into consideration makes the case for PI screening less clear cut. The identified 'normal' values vary quite significantly between studies as do the screening thresholds used, this may be related in part to the timing of screening following birth but this does not explain the differences completely. In addition, all screening studies report a single PI measurement and none reported longitudinal measurements within an individual which might demonstrate both the stability of PI over time and how representative is one measurement as a reflection of actual perfusion. Although Granelli's[6] and Siefke's[11] studies showed moderate sensitivity (56% and 75%

respectively), this was in a cohort of babies who had already been diagnosed with LHOD, and many were receiving prostaglandin to maintain ductal patency (i.e. representing a pre-selected group rather than an apparently healthy population that might undergo screening). This is likely to create bias where unblinded PI measurements take place at a later time after birth and where the original circulatory status quo has been modified. Schena *et al* reported a much lower sensitivity of only 25% for PI identifying LHOD in a larger, apparently healthy, cohort as described above, but with a low prevalence of CCHD.[8]. These factors cast some uncertainty on the true sensitivity of PI to detect LHOD.

In addition, most studies reported false positive (FP) rates which would be unacceptably high for a screening test. Although Schena *et al* reported a FP rate of 0.27% they screened babies much later (at 48-72 hours)[8] and studies screening earlier (within the first 24-48 hours) had higher FP rates between 2.4 and 3.6%.[10,11]

In their study, published in this edition of *Acta Paediatrica,* Lannering *et al* have investigated the effect of introducing repeated measurements of abnormal results (similar to the repeated measurements recommended for pulse oximetry screening) to reduce the false positive rate in PI screening[12]

They recorded pre- and post-ductal PI in a total of 513 apparently healthy term newborns at the same time as oxygen saturations were measured as part of POS (median age 18 hours). This included an initial pilot of 50 babies with up to 3 immediate repeats if PI was below the pre-determined cut-off of 0.7. If PI remained <0.7 for 3 consecutive measurements then an echocardiogram was performed. This resulted in a false positive rate of 6% and so the protocol was modified in the remaining 463 babies to perform the repeat tests after 30 minutes. No baby tested positive using this algorithm including one baby who had CoA. They estimate that it took an additional 3 minutes and 30 seconds to perform PI measurement

These data are interesting since they suggest a possible mechanism to successfully reduce the false positive rate, however the study was not designed to investigate the sensitivity of PI as a screening test which remains a problematic issue. Any successful screening test should have both acceptable specificity and sensitivity and although a specificity of 100% is reported, the sensitivity for detecting the condition of interest, i.e. LHOD, was 0%. Of course, the numbers of babies screened were very low and as the authors rightly conclude more studies in larger populations are required, however these data and those of previous studies do suggest a potential inherent problem with PI as a screening test for LHOD. The reported sensitivity for a single PI measurement is highly variable, inconsistent thresholds have been employed and many of the LHOD identified by PI have already been diagnosed by other screening tests. It is possible that the introduction of repeat testing may reduce the sensitivity further but due to the low number of babies with LHOD in this study, this is not yet proven.

Despite this, it is clear that PI alone will identify *some* babies with LHOD that would otherwise be missed by all other screening methods (including POS) and as LHOD are the most commonly missed CCHD perhaps PI screening should not be dismissed out of hand. Many of the early POS studies showed inconsistent and inconclusive test accuracy[13] which subsequent larger studies were able to clarify.[1]

As more countries include POS in recommended routine newborn screening, much larger potential datasets are available that may be used to more precisely define the test accuracy of PI for LHOD. If PI data were recorded at the same time as the POS and then linked with outcome data this may provide the necessary data required to more accurately model a possible algorithm to incorporate PI into CCHD screening with POS.

Lannering *et al* offer another piece of the jigsaw but until we have more conclusive evidence regarding test accuracy in much larger populations, adding PI to a newborn POS programme cannot be recommended.

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