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Low false-positive rate of perfusion index as a screening tool for neonatal aortic coarctation

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Abstract

Aim: Adding perfusion index (PI) to pulse oximetry screening (POS) may increase neonatal detection of CoA (aortic coarctation). A cut-off <0.7% has been suggested but is associated with a high rate of false positives. We aimed to evaluate the specificity of PI when using repeated instead of single measurements.

Methods: A pilot study was conducted in 50 neonates. PI was recorded in right hand and a foot by pulse oximeter. If PI was <0.7%, the measurement was immediately repeated up to 3 times. If all three measurements were <0.7% in hand and/or foot the screen was positive and echocardiography was performed. There were 3/50 false-positive screens. The protocol was therefore modified requiring 30 min intervals between measurements.

Results: An additional 463 neonates were included using the modified protocol at a median age of 18 h. There were no false positives. The only neonate with CoA had a negative screen (PI hand 1.2% and foot 0.8%). The measurement required on average an extra 3 min and 30 s compared with POS only.

Conclusion: The false-positive rate of PI was reduced by using repeated PI measurements. The sensitivity for CoA using this protocol should be evaluated in large-scale prospective studies.

KEYWORDS

aortic coarctation, perfusion index, screening

1 | INTRODUCTION

Pulse oximetry screening (POS) for critical congenital heart defects (CCHD) has contributed to preventing serious morbidity and death.[1] Nevertheless, delayed diagnosis of critical aortic coarctation (CoA), which has a prevalence of approximately 4 per 10 000 live births,[2] continues to be a problem along with other left heart obstructive disease (LHOD).[3–6] We, and others, have shown that the sensitivity of POS for CoA is low and that neonates with CoA are being discharged without suspicion of heart disease risking circulatory collapse and death.[6–8]

In recent years using perfusion index (PI) to assess the neonate in different clinical situations has been investigated.[9–11] PI is an assessment of the pulsatile strength given as a ratio between the pulsatile signal of arterial blood to the non-pulsatile signal (for example connective tissue, venous blood and bone) and is obtained from the

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photoelectric plethysmographic signal of the pulse oximeter. It can provide real-time information reflecting peripheral perfusion.[12,13] PI as a screening tool has raised some hope in increasing neonatal detection of CoA and other LHOD,[14-19] with reported sensitivities for CoA varying between 33% and 100% depending on the cut-offs used.[15,16,18] However, existing data do not yet support inclusion of PI to neonatal CCHD-screening, the high false-positive rate is one concern.[20,21]

We hypothesised that the false-positive rate of PI can be reduced by repeating the measurement if below cut-off. Thus, our primary aim was to prospectively determine the false-positive rate of PI in the newborn in a screening setting, using previously proposed cut-offs and three consecutive measurements if below cut-off. Secondary aims were to study the feasibility of using PI as a routine screening method; to investigate potential reading inaccuracies by comparing automated trend recordings of PI to manually obtained recordings and to measure the amount of time required to perform the recording.

2 | METHODS

2.1 | Design

A prospective cohort study.

2.2 | Study population and setting

Between May and June 2018 and during September 2018 and May 2019, data from 513 newborns were collected at the time for POS. Three maternity units for normal delivery took part in the study, all at Sahlgrenska University hospital in Gothenburg, a public hospital with approximately 10 000 deliveries a year. Eligible newborns were born at gestational age (GA) 37 + 0–42 + 0 and were considered healthy at the time of screening.

2.3 | Data collection

Masimo Radical 7 pulse oximeters were used (Masimo Corporation). The pulse oximeter monitors displayed both SpO_2 (peripheral oxygen saturation) and PI simultaneously. A sensor was placed on the newborns right hand (pre-ductal) and either foot (post-ductal) with a strap and when the signal was artefact free, the values were registered.

2.4 | Study protocol

Initially, a pilot study of 50 healthy newborns was conducted. According to the protocol, nursing staff was instructed to record PI-values in the right hand and a foot at the time for POS. Additional data were registered separately (personal identity number, GA, birthweight, time of birth). In case of a PI-recording below 0.7%, the

Key notes

- The false-positive rate of perfusion index (PI) can be reduced by using repeated measurements.
- Measuring PI is practically feasible with a manageable extra time required
- Although promising with regard to the false-positive rate, the sensitivity of PI, when using repeated measurements, needs to be determined in large-scale prospective studies before it can be recommended as a routine screening tool

pilot study protocol called for immediate repeated recording. If three consecutive recordings of PI were <0.7% in either (1) right hand, (2) one foot or (3) both, the test was considered positive. A full echocardiographic study was then performed within 24 h.

The protocol was thereafter revised due to a high rate of false positives (6%); in case of a PI-value below 0.7%, the test was now repeated after a delay of 30 min. The test was considered positive if there were three consecutive measurements <0.7%. This modified protocol was used in 463 neonates. All recordings were performed by research nurses.

In order to identify all cases of CCHD in the studied population, also those who were not detected before neonatal discharge, included infants were searched for in the electronic medical record using their unique personal identification number.

In a subgroup of 100 neonates, at the same time as for the PI-reading, trend data was simultaneously stored in 2 s intervals in the pulse oximeter using MICT software (Masimo Instrument Configuration Tool, Masimo Corporation). The trend PI-data were downloaded to an excel file for comparison with the manually read PI-values for every neonate in the subgroup. Also, the time required to obtain stable SpO2 and PI-values was registered.

2.5 | Statistics

Results were given as mean and their 95% confidence intervals (CI) for normally distributed data and medians with interquartile range (IQR) for non-normal distributions. For comparison between two groups, *t* test and the Wilcoxon signed-rank test were used. Statistical significance was set to a *p*-value of <0.05. Analysis of distribution was carried out by IBM SPSS Statistic, version 25.

2.6 | Ethics

This study was approved by The Regional Ethical Review Board in Gothenburg on the 30 of March 2017 (Dnr 045-17). Written informed consent was obtained from the caregiver before screening.

3 | RESULTS

Out of 466 eligible newborns, 463 caregivers accepted participation in the study. Included newborns ($n = 463$) were screened at a median age of 18 h (range 6–33 h). The mean GA was 39 weeks (range 37 + 0–42 + 0) and mean birth weight 3512 g (range 2290–4945). The median pre-ductal SpO2 was 97% (90%–100%), and the median post-ductal SpO2 was 98% (93%–100%).

The median PI in the right hand was 1.9% with an IQR of 1.4–2.5 and the median PI foot was 1.7% with an IQR of 1.2–2.5. The median PI-ratio right hand/foot was 1.1 with an IQR of 0.8–1.5. The percentile distribution of PI in right hand, foot, right hand and foot, and ratio right hand/foot is shown in (Table 1). The PI values were not normally distributed (Kolmogorov–Smirnov test; $p < 0.01$) (Figure 1). PI in the right hand was not significantly different from the PI in the foot. There were no significant age-related differences in PI-values in the right hand and foot (Figure 2). The distribution of the differences between PI in the hand and foot is normal with a mean difference of −0.004% with SD 1.3 (95% CI −0.11–0.12) (Figure 3).

During the pilot study, three neonates had three, consecutive measurements with PI-values below cut-off 0.7% (false-positive rate 6%) and therefore underwent a full echocardiographic study. None had CCHD.

After revising the protocol, we found zero (0%) false positives among 463 consecutively included neonates, specificity 100% (exact 95% CI 99.2–100). In five cases the initial value was <0.7% (0.5, 0.5, 0.6, 0.6, 0.6) and therefore a second recording was made after 30 min, then giving normal values in all five. A third recording was never needed.

There were no deaths before 2 months of age but in one case a CoA was diagnosed. This newborn was discharged at 2 days of age, POS was normal. PI-values were 1.2% in the right hand and 0.8% in the foot, the ratio hand/foot was 1.5. The infant developed tachypnea and was diagnosed with CoA at 12 days of age.

In a subgroup of 100 neonates, PI trend data were stored in the pulse oximeter simultaneously as the manual reading. Manually read PI-values were compared with automatically stored trend data for the same individual. The downloaded median PI value was not significantly different from the manually collected PI value (Wilcoxon signed-rank test $p = 0.704$). Figure 4 shows the Bland–Altman plot, which indicated a good agreement between the manually collected and download PI.

By analysing recorded trend data, we were able to compare the time required to receive a stable value of SpO2 and PI. The PI readings were collected during a mean of 2 min and 27 s in the right hand (range 22 s–9 min 28 s) and during 2 min 8 s in one foot (range 42 s–7 min 9 s). In comparison, the time required for POS was; 34 s in right hand (range 4 s–5 min 20 s) and 32 s in foot, respectively (range 4 s–3 min 24 s). An additional 3 min and 30 s (mean) were required to record PI in addition to POS.
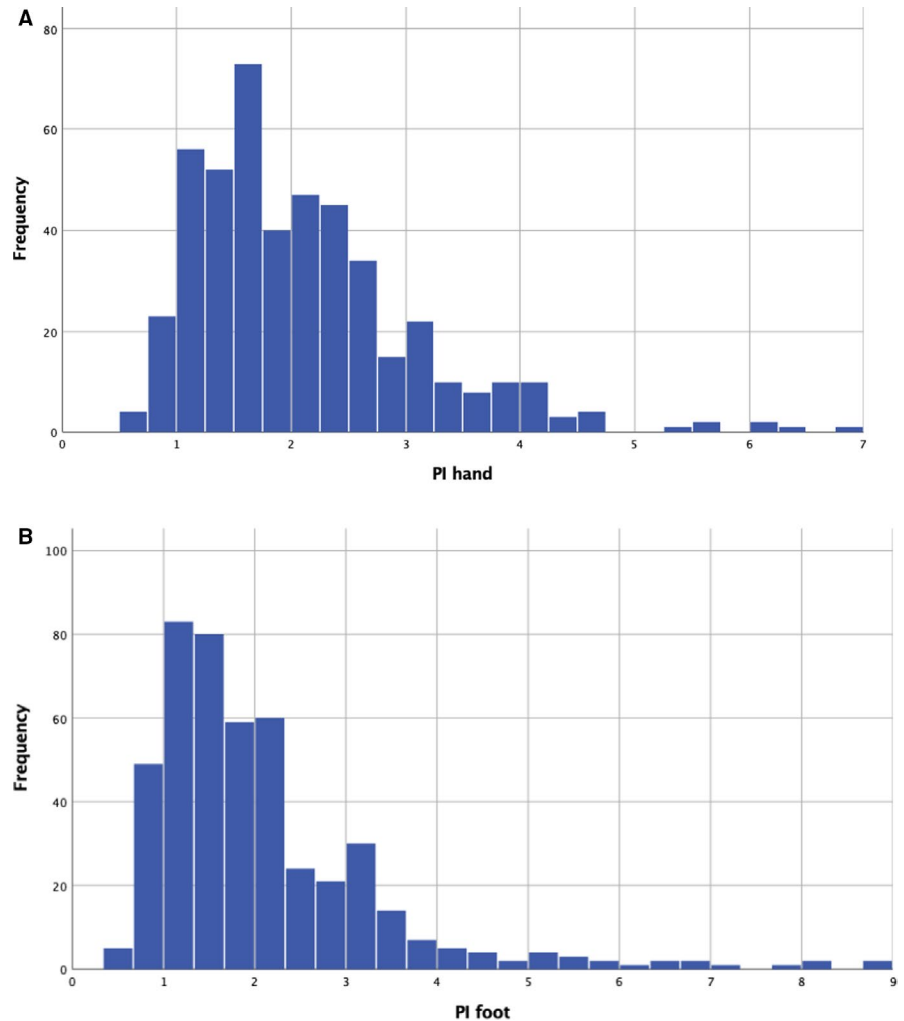
4 | DISCUSSION

The present study aimed to determine the false-positive rate of perfusion index (PI) when using repeated measurements and to investigate the feasibility of using PI in addition to pulse oximetry screening (POS) at the time of critical congenital heart defect (CCHD)-screening. We found a zero false-positive rate already when using two measurements with a 30-min interval and a cut-off of 0.7%. We also found that the readings of PI-values done by research nurses matched the automated recorded trend data of PI by the pulse oximeter. The pulse oximeter monitor displays the values of SpO2 and PI simultaneously giving PI-values at no extra cost and, according to our results, with an acceptable time consumption. Our results suggest that measurement of PI is feasible in a newborn screening setting. However, one neonate that was diagnosed with CoA 12 days after screening had a PI value (0.8% at 20 h of age) above the cut-off used in this study (0.7%).

So far, there is no national recommendation for PI in addition to POS in Sweden. A few units are, however, routinely recording PI as part of the general screening program for CCHD using a cut-off of 0.7%.

There are a few studies aiming to establish reference values for PI in newborns and late preterm infants,[15,22-24] as well as for preterm infants during the first 72 h of life.[25] The effect on PI of a hemodynamically significant patent ductus arteriosus (PDA) in preterm infants has been studied but results are inconclusive.[11,26] In a large cohort, Granelli and Östman-Smith performed a single measurement of PI between 1 and 120 h after birth, giving constant values after 6 h of age. Median PI was reported to be 1.7% and the 5th and the 95th percentiles were 0.7%–4.5%, suggesting values below 0.7% would be useful to indicate hypoperfusion and illness.[15] In another study, PI was studied in neonates at 24 h of age, giving a median PI of 1.8% and a near-identical population distribution as in the study by Granelli and Östman-Smith, with 5th percentile at 0.7%.[24] Our median value was similar to previously reported values of PI in newborns but we had a slightly narrower population distribution with a higher 5th percentile (0.9%).

The correlation between PI and left ventricular output in healthy infants has been studied, supporting the potential role of PI in

TABLE 1 The percentile distribution of PI in right hand, foot, right hand plus foot and ratio right hand/foot ($n = 463$)

Percentile	PI right hand (%)	PI foot (%)	PI right hand plus foot (%)	PI-ratio right hand/foot
1st	0.7	0.7	0.7	0.3
5th	1.0	0.9	0.9	0.4
25th	1.4	1.3	1.3	0.8
50th	1.9	1.7	1.8	1.1
75th	2.5	2.5	2.5	1.5
95th	4.0	4.6	4.1	2.6
99th	5.8	7.8	6.6	3.6

Abbreviation: PI, Perfusion index.

FIGURE 1 The distribution of PI in the right hand (A) and one foot (B)

screening for newborns with LHOD.[27] A number of studies have investigated the clinical use of PI in screening for CCHD [15–19,24] using different cut-offs, corresponding to the 5th percentile (0.5%–1.2%).[15,16,18,19,24] In the study by Granelli and Östman-Smith,[15] in a pre-selected group of newborns with LHOD, 5 out of 9 newborns had either pre- or post-ductal PI values <0.7%, when screened at between 19 and 120 h after birth. Schena et al and Uygur et al[18,19] screened a healthy population of newborns with POS and PI at 48–72 and 24–48 h of age, respectively. Schena et al used a PI cut-off <0.9%. Of 4 screened with LHOD, one with CoA was detected solely by PI (value 0.3%) but 3 cases were not (2 CoA and 1 with interrupted arch). The false-positive rate of PI alone was 0.27% (two measurements).[18] Uygur et al used a higher PI cut-off (1.2% pre-ductal and 1.1% post-ductal). The sensitivity of PI alone in detecting CCHD pre-ductally was 64% and post-ductally 61%, respectively, not giving the exact numbers for the LHOD-group. The false-positive rate was high, 2.7% (pre-ductal) and 3.6% (post-ductal) (one measurement). If they would have chosen the cut-off 0.7%, the sensitivity for CCHD would have been 33% pre-ductally and 36% post-ductally.[19] Siefkes et al used a cut-off <0.5% in a group of newborns with LHOD (with and without prenatal diagnosis) at 24 h of age.[16] 3 out of 5 newborns had post-ductal PI values below cut-off with a high false-positive

rate of 2.4%. If using a cut-off of 0.7%, 4 out of 5 would fail the PI screen.

If we would have chosen our 5th percentile with a PI cut-off of 0.9% we might have detected the one neonate born with CoA in our cohort with the downside of more false positives requiring investigation, parent anxiety, and possibly delayed discharge.

Two other studies, with the primary aim to evaluate the impact of the combination of POS and PI on CCHD-screening, could also show that it is possible to decrease the false-positive rate when using repeated measurements.[17,18] Ramesh and Kumutha had zero false positives when repeating the test twice if SpO2 and/or PI was abnormal (with 1 h between each of the three measurements). The screening was performed at a mean age of 34 h.[17] In the study by Schena et al, screening with SpO2 and PI at 48–72 h, the false-positive rate of PI was 0.27% when using one repeated measurement after 30 min if below cut-off.[18]

Where to suggest the cut-off in a screening situation depends on the trade-off between a timely detection of CCHD (sensitivity) and the false-positive rate (specificity). We have shown that it is possible to reduce the false-positive rate substantially by using repeated measurements at the time for CCHD-screening. Our study was not designed to determine the sensitivity of PI with
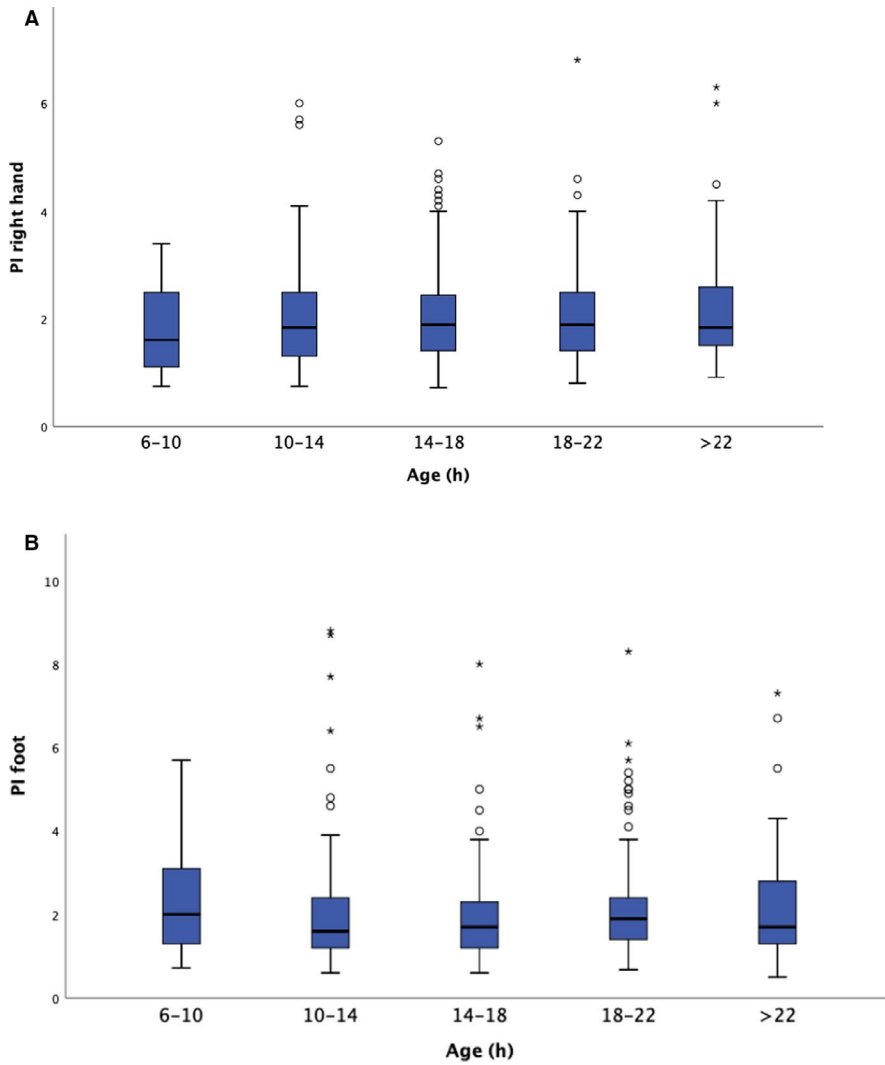
A

FIGURE 2 PI in the right hand (A) and foot (B). Each box-and whisker plot at 4 h age intervals

B

repeated measurements to detect CoA. For this, much larger prospective studies would be required. Using a protocol similar to ours, with repeated measurements if below cut-off, would minimise the false-positive rate. Nevertheless, it could possibly result in a lower sensitivity compared to single PI measurements since

a positive test result would require three consecutive measurements below cut-off. Whether or not this will be the case will depend on how stable PI is in neonates with CoA at the time of CCHD-screening. To our knowledge, there are no published studies addressing this. If neonates with CoA exhibit stable values
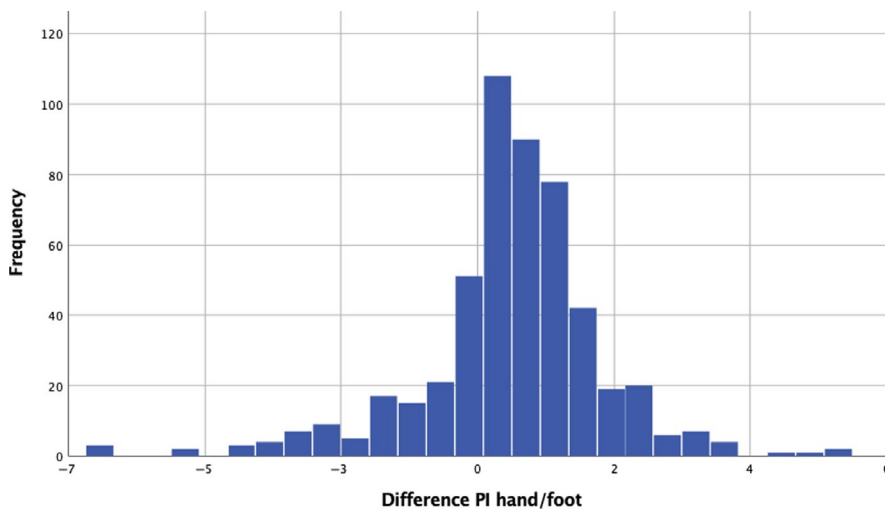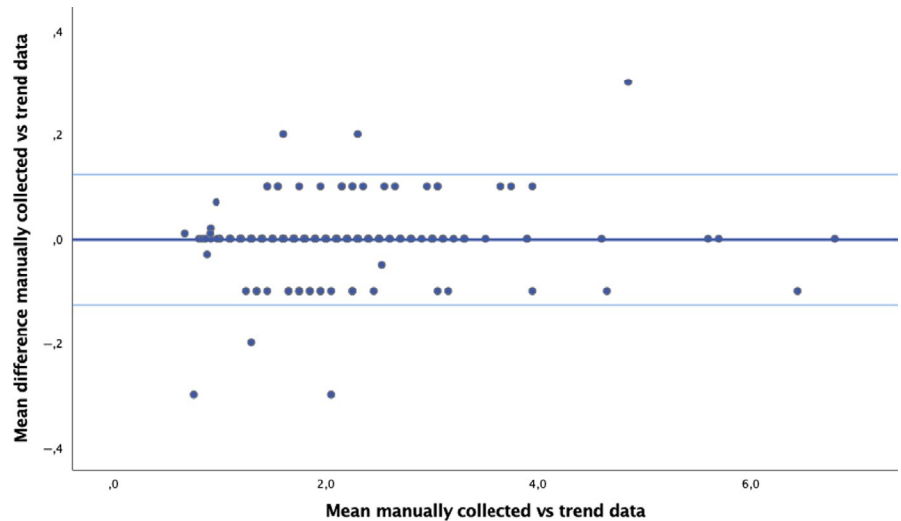

FIGURE 3 The distribution of the difference of PI between the right hand and one foot

FIGURE 4 Bland Altman Plot depicting the difference between manually collected vs trend data on PI. Dark blue line represents the mean and the light blue lines 95% CI (−0.13–0.12)

similar to healthy newborns,[15,23] sensitivity should not be negatively affected.

There have been some concerns about the feasibility of using PI in a screening setting. Measuring PI requires a motion-free situation, which is not always the case assessing the newborn. PI is also affected by the skin temperature at the monitoring site and the vasomotor tone (pain, anxiety).[13] During the pilot study, a few assistant nurses reported difficulty in getting an artefact-free signal. In addition, there were a couple of newborns in whom the measurement was very time-consuming. On average, adding PI-values to POS in hand and foot required an additional 3 min and 30 s. When we compared downloaded data in a subgroup of 100 neonates to the manually read data of PI, we could show that the differences in PI were small and insignificant and that the collected PI-values were representative of the perfusion status given by the pulse oximeter. The proportion of babies who required repeated measurements was only 1.1% (5/463), and three measurements were never required. However, adding PI to screening will increase the workload to some degree and can only be motivated if future studies show an acceptable degree of sensitivity using this protocol.

4.1 | Strengths and limitations

One strength of this study is its prospective design with follow-up of all cases until 2 months of age regarding diagnosis of CCHD. A limitation is that the measurement of PI was not repeated if the first value was above 0.7%. This study therefore is limited to investigate the specificity of PI with repeated measurements using a cut-off of 0.7%.

5 | CONCLUSION

No current screening method has the capacity of detecting all newborns with CCHD, but a combination of screening tools will help to improve detection rates. Previous studies have shown

that PI has the potential to improve detection of CoA and other LHOD but also that the false-positive rate may be unacceptably high. We have shown in this study that the false-positive rate can be reduced to a very low level by repeating the measurements if below cut-off. We could also show that this protocol is practically feasible for the nursing staff and could be introduced as an additional screening method with a manageable extra time required. Nevertheless, further large-scale studies are indicated to address the sensitivity of PI to detect CoA and other LHOD using repeated measurements.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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