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Distribution and reference values of peripheral perfusion index in neonates from population-wide screening

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ABSTRACT

Background Peripheral perfusion index (PPI) is useful in a variety of neonatal settings. Currently, available reference values are from small numbers and highly variable.

Methods We sought to generate reference values of PPI by analysing previously collected data from newborns who underwent mandated universal pulse oximetry and PPI screening from 2018 to 2021 using uniform protocol and equipment. Q-Q plots and boxplots were used to visualise distributions. Kernel density estimation for heaped and rounded data was used to estimate percentiles of the distributions.

Results Data from 388 205 newborns who underwent universal pulse oximetry screening in the first week of life were used for this analysis. Pre and postductal values showed a non-normal distribution and skewed to the left, the former had a thicker tail with more extreme values. Minor, but statistically significant differences were seen in the PPI values from day 1 to 7. Median preductal PPI (2.77, IQR:1.83–3.93) was significantly higher than postductal (2.38 IQR: 1.41–3.55) (p<0.01). PPI values increased with weight and boys had higher PPI. Kernel estimates of the percentiles in the overall sample and subgroups for gender and weight have been provided for preductal and postductal values.

Conclusion This study, based on the largest available dataset, provides reference values for PPI in newborns. A significant influence of gender and birth weight on PPI values in newborns has been identified. Future research on understanding the influence of age, sex, birth weight, gestational age, ambient temperature and genetic factors on PPI is recommended.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Peripheral perfusion index has been recommended as a bedside tool for assessment of a variety of neonatal illnesses and for newborn screening for congenital heart disease.

WHAT THIS STUDY ADDS

⇒ Perfusion index varies significantly with gender and birth weight. The study provides reference values of peripheral perfusion index, stratified by gender and birth weight, from the largest published dataset.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The reference values can be used in clinical setting as well as for neonatal screening purposes.

INTRODUCTION

Peripheral perfusion index (PPI) is measured alongside oxygen saturation (SpO2) by modern pulse oximeters. It represents the ratio of pulsatile (AC) to non-pulsatile (DC) components of the infrared signal, indicating the pulsatile to non-pulsatile blood flow relationship at the measurement site. The numerical value is displayed on the monitor, reflecting real-time changes in peripheral blood flow and tissue oxygen supply adequacy.[1] During hypoperfusion, early redistribution of cardiac output towards vital organs like the brain, heart and adrenal glands can be detected by PPI. It is influenced by physiological conditions and varies among patients and measurement sites.[2]

The value of PPI in newborn care settings includes, early sepsis detection after chorioamnionitis exposure,[3] prediction of illness severity in conditions such as sepsis, pneumonia, intraventricular haemorrhage, periventricular leukomalacia and necrotising enterocolitis.[4] Additionally, it has been suggested for screening critical congenital heart diseases (CCHD) with left heart obstruction.[2] Reference values, currently available from limited European and US newborn samples, show significant variability.[2 5 6]

In Kerala, Southern India, routine newborn screening for congenital heart disease (CHD) using pulse oximeters has been implemented[7]; PPI masurement for all screened neonates is mandated using standardised protocols and equipment. We sought to use the opportunity presented by the extensive dataset to establish PPI reference ranges for newborns.

METHODS

Design

This is a retrospective analysis of a large dataset of PPI obtained as a part of mandatory neonatal screening.

Setting

Government of Kerala (GOK) introduced mandatory universal pulse oximetry screening (UPOS) in 2017 in all public sector hospitals in Kerala. The PPI is being recorded as part of the UPOS program of the GOK since 2018.

Screening protocol

The mandatory state UPOS protocol is identical to the current American Academy of Pediatrics (AAP)-recommended protocol,[8] (online supplemental material 1).

Study population and data retrieval

Study population included all newborn babies who underwent UPOS between 2018 and 2021. Dataset included SpO2 values, PPI values, age at screening, birth weight and gender. Data were retrieved from the web-based storage system electronically.

Patient and public involvement

Patients or public were not involved in the design, conduct, reporting or dissemination plans of this research.

Statistical methods

All statistical analyses were done in R V.4.3.1. The distributions of preductal and postductal PPI measurements were visualised by Q-Q plots. Kernel density estimation for heaped and rounded data was used to estimate the percentiles of the distributions including subgroups for gender and weight.[9] Differences between subgroups were compared using Mann-Whitney U tests. Agreement between preductal and postductal measurements was investigated using Bland-Altman plot.[10] Boxplots were used to visualise changes in the distribution of PPI based on age. Smoothed conditional means with 95% confidence bands from generalised additive models were used to visualise the dependency of PPI on weight and gender, using the mcgv package.[11] Median regression models were used to quantify the dependency of PPI on weight and gender, using the package quantreg.[12] Logistic regression was used to assess the risk for having PPI less than 0.7 depending on age and sex. The strength of association between SPO2 and PPI was assessed using Spearman's rank correlation. Furthermore, the proportion of variance in PPI values explained by SPO2 was estimated by the R^2 statistics from linear regression model. To investigate if newborns with abnormal PPI values (<0.7) can be predicted from SPO2, weight, sex and day of measurements, random forest machine learning technique was evaluated with a 80%–20% training—testing spilt. All p values are for two-sided alternatives and in tests, a level of 5% was considered significant.

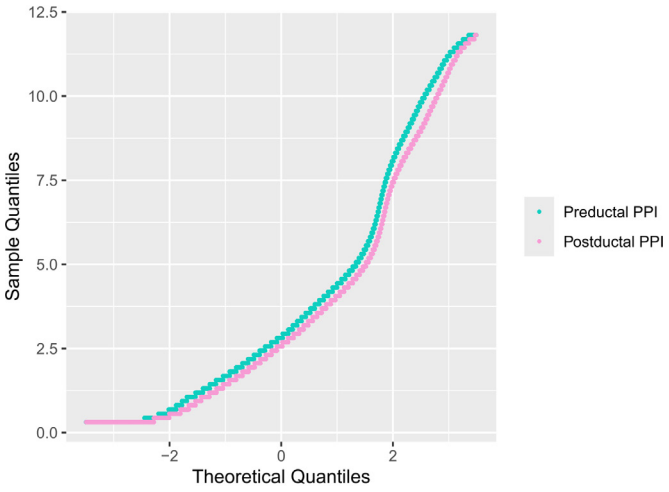

Figure 1 Quantile-Qunatile plot of preductal and postductal PPI values. The plot compares the quantiles of the study sample against theoretical quantiles of normal distribution. PPI, peripheral perfusion index.

RESULTS

Study population

A total of 402 678 newborns underwent UPOS from 2018 to 2021. 388 205 newborns underwent UPOS in the first week of life and form the study population. 14 473 neonates who were screened after day 7 of life were excluded. Nearly 75% of babies were screened by day 2 of life, 90% by day 3 and 95% by day 4. Among the babies screened, 51% were boys and 49% girls. The majority (82.7%) of newborn babies had a birth weight above 2.5 kg. Fourteen per cent of the babies failed screening.

Distribution of preductal and postductal PPI of the entire cohort

Figure 1 shows Q-Q plots of preductal and postductal PPI values. Comparison of the quantiles shows a slightly lower postductal values. Neither pre nor postductal PPI values are normally distributed. Percentiles of the PPI distribution are shown in online supplemental table 1.

Normal ranges for PPI

The median value of preductal PPI was 2.77 (IQR 1.83–3.93) and postductal 2.38 (IQR1.41–3.55). Online supplemental table 1 shows the kernel estimate of the percentiles in the overall sample and in subgroups for gender and weight. These values provide normal ranges. The table shows results both for preductal and postductal values.

Comparison of paired preductal and postductal PPI values

Pairs of preductal and postductal PPI values were available for 182 859 (%) babies. Median preductal value was 2.77 and postductal 2.38; difference between medians is highly significant (p<0.01 in a Mann-Whitney U test). Analysing the patterns of difference in the Bland-Altman plot in figure 2, it can be seen that for values up to PPI 2.5, there is good agreement between preductal and postductal values. In contrast, for values greater than

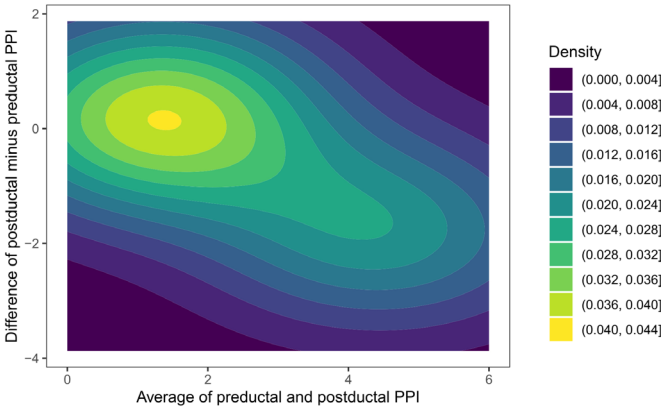

Figure 2 Bland-Altman plot of the density of the average and the difference of the preductal and postductal PPI values. Lighter yellow colours indicate higher densities, whereas darker blue colours indicate lower densities. PPI, peripheral perfusion index.

2.5, preductal measurements are larger on average than postductal measurements. This difference between pre and postductal measurements keeps increasing with increasing values of the PPI.

Influence of age on PPI

Figure 3 shows the boxplots of preductal and postductal PPI values depending on the age of the babies. The distributions are similar from day 1 to day 7.

Influence of weight and gender on PPI

Figure 4 shows that PPI values increase with weight, and boys tend to have higher PPI values. This difference is consistently observed in both preductal and postductal values, except for postductal measurement in baby girls with weights above 3.5 kg. The dependency of the median of PPI on weight is almost linear. For preductal PPI, the difference between boys and girls is constant over the whole weight range. On the other hand, for postductal PPI, the difference is observed only for babies weighing less than 3 kg. The dependencies on weight and sex is highly significant, as shown in table 1. The table also quantifies the strength of the dependency in terms of median differences. Furthermore, logistic regression finds that the OR for girls having PPI less than 0.7 is 1.14 (95% CI 1.07 to 1.23, p<0.01) and the OR for measurements on

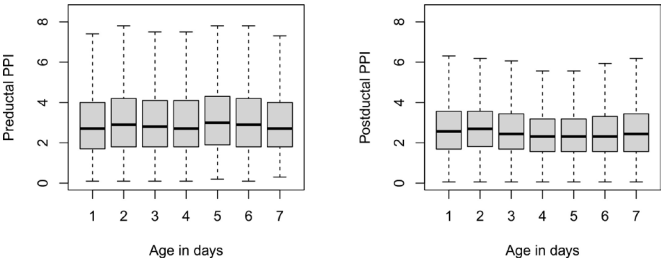

Figure 3 Boxplots of preductal and postductal PPI values stratified by age of the newborn babies in days. PPI, peripheral perfusion index.

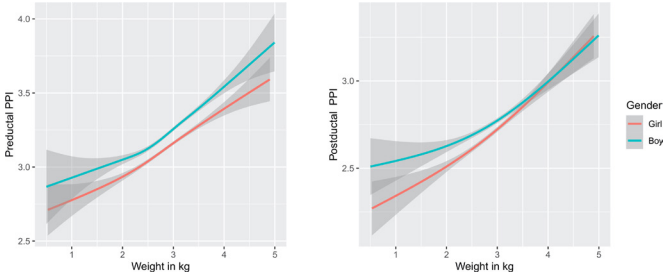

Figure 4 Smoothed conditional means with 95% confidence bands from generalised additive models of preductal and post-ductal PPI values depending on weight and gender. PPI, peripheral perfusion index.

days 3–7 compared with days 1–2 is 1.27 (95% CI 1.18 to 1.37, p<0.01).

Association with SPO_2

PPI values were almost uncorrelated with SPO2. The Spearman rank correlation coefficient between preductal PPI and preductal SPO2 is 0.03 and 0.02 for postductal values. The proportion of variance in preductal PPI that can be explained by preductal SPO2 is less than 0.01. The same is true for postductal values. Furthermore, PPI <0.7 could not be predicted well from SPO2, weight, sex and day of measurement using a random forest machine learning model: on the testing set, ROC-AUC was 56.6%, indicating a low predictive value.

DISCUSSION

This is the largest study on reference ranges for newborn PPI values. Since all babies born in public sector hospitals were included in the screening, the study is representative of the population and the risk of bias is low. The fact that the same protocol was followed by all screening units and that the same type of device was used is a major strength of the study. This allows for the extrapolation of these reference values in other settings by calibrating other machines to the reference machine.

The median values of preductal as well as postductal PPI from this study are higher than those reported previously. There is a high degree of heterogeneity in PPI values reported thus far. The corresponding values from 3952 neonates, between 24 and 48 hours of age from China were 2.10 (IQR 1.60–3.30) and 2.30 (IQR 1.70–3.40), respectively.[13] Lower values were reported from 241 newborns in Turkey on day 1, preductal 1.35 (IQR 1.02–1.91) and postductal 0.88 (IQR 0.62–1.22)[5] ; preductal 1.68 (IQR 1.18–2.46) and postductal 1.71 (IQR 1.20–2.50) from Sweden at age 0–120 hours.[2] When day-wise stratified median values from the current study were reviewed, values on each day through days 1–7 were consistently higher than previously reported values mentioned above. This heterogeneity merits further investigation.

The current study was done in Kerala, which has a tropical climate. South Asian population is known to be

Table 1 Multivariable median regression for PPI

	Preductal PPI			Postductal PPI		
	Coefficient	95% CI	P	Coefficient	95% CI	P
Weight (increase by 1 kg)	0.24	0.23 to 0.26	< 0.01	0.20	0.18 to 0.22	< 0.01
Gender (boys vs girls)	0.10	0.09 to 0.11	< 0.01	0.06	0.04 to 0.08	< 0.01

PPI, peripheral perfusion index.

genetically different from other populations with respect to various diseases including cardiovascular diseases.[14] In this context, whether the heterogeneity may be explained by factors like ambient temperature and genetic variability needs further exploration. In addition to factors that influence the differences in PPI value between populations, there is also a list of factors that are known to influence PPI values at an individual level. These include circadian rhythm, feeding, jaundice, sleep/awake state, prone/supine position, ongoing intravenous treatments, skin colour and site of measurement.[5 15 16] The distribution of preductal and postductal PPI is skewed to the left, from the extremely high values in a small subset of patients. As the focus from a newborn screening perspective is primarily on lower PPI, the higher values may not be of relevance.

The study also brings to light the challenges faced by population screening of such a large number of newborns. UPOS was recommended after 24 hours of life and before 48 hours. However, 39.8% were conducted on day 1 and 25.2% on day 3 of life or later. This resulted from the fact that the sheer numbers demanded workflow to be distributed between the initial few days of life. Considering the timing of ductal closure, this may not meet the goal of detecting CCHD before ductal closure in the later screens. This may also result in higher false-positive UPOS rates from day 1. Age at the measurement of PPI holds relevance from CCHD screening perspective.

On the other hand, when it comes to screening for other new born illnesses, day of measurement of PPI may not hold great relevance. However, this is yet to be systematically investigated. The current study has identified minor differences in PPI values from day 1–7 that have achieved statistical significance, the clinical relevance of which may also need further investigation. Previous studies have shown no significant difference in the PPI of term babies in the early days of life.[3] The minor variations in the early newborn period found in this study can be attributed to the transitional physiology. On the other hand, in preterm babies, a significant increase in PPI values from day 1 to day 3 has been noted in previous studies, attributed to maturation of the sympathetic system during the first few days of life.[13]

Another practical challenge was the lack of postductal measurements in a large number of newborns. This was because babies are uncomfortable when unwrapped for screening and may not allow the completion. Time and staffing constraints setting make repeat screens challenging. Based on this, the UPOS protocol of the state of Kerala was changed to record the postductal measurements first. From the Bland Altman plot (figure 2), agreement between preductal and postductal PPI measurements was better in the lower range. Since PPI screening is done primarily to identify lower values, screening either the foot or arm may have provided adequate information to identify CCHD.

The few studies that have examined the influence of gender on PPI in newborns have not found any association.[2 5 11] Therefore, a noteworthy finding from this large database is the effect of birth weight and gender on PPI, as represented in table 1. For the same weight, boys tend to have higher values for both preductal and postductal PPI. Since the median difference adjusted for weight is only 0.1, the effect is relatively small (table 1). This effect may have been missed by previous studies with smaller sample sizes. This difference in PPI values between genders may necessitate deriving gender-based threshold values to define abnormality. This would be important in designing research protocols for outcome studies. Further significance of these differences and reasons thereof is yet to be explored and understood.

The absence of association between PPI and SPO2 values suggests that they measure different aspects of the physiology. Moreover, low PPI values less than 0.7 could not be predicted well from SPO2. Therefore, PPI may have complementary value to SPO2 in population screening for CCHD.

Limitations

This retrospective study benefits from a large data collected using a predefined screening protocol. Despite the substantial database enabling meaningful analysis, numerous postductal PPI values were absent. Furthermore, measurements were spread over the first week of life, as opposed to the recommended time frame for UPOS. Other demographic and clinical variables like prenatal care, comorbidities, gestational age, maternal age were unavailable. The retrospective nature of the study precluded scheduled follow-up visits to assess outcomes. This paper does not investigate the predictive value and clinical utility of UPOS or PPI.

Future directions

PPI distributions from diverse populations are necessary to account for the impact of factors such as ambient temperature. Gender and birth weight's overlooked

influence on PPI should be studied across various demographics. Prospective studies, designed to encompass all live births, would add significant value. Outcome-based studies from large populations are imperative before PPI can be recommended for population screening for early detection of CCHD.

CONCLUSIONS

This study provides reference values of PPI from a large dataset. A significant influence of gender and birth weight on PPI values in newborns has been identified although not clearly understood. Accordingly, reference values stratified by age and birth weight have been provided.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval Necessary approval was obtained from institutional scientific and ethical review boards (ECR129/Ist/KL/2013/RR/−19; IEC-AIMS-2022-CARD-089, dated 26 April 2022). Patient confidentiality and data protection guidelines were adhered to throughout the retrieval and analysis. Consent was waived because there were no patient identifiers in datasets or manuscript and it was practically impossible to go back to all the families for consent.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request. Data will be stored by the responsible author for 5 years from publication. Sharing will be contingent upon existing stringent data safeguards.

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