www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2019;8(1):e080104
doi: 10.7363/080104
Received: 2018 May 27; revised: 2018 Jul 26; accepted: 2018 Jul 30; published online: 2019 Jan 24

Original article

Perfusion index in preterm newborns: predictive value for morbimortality and association with Apgar score at five minutes and CRIB-II score

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Abstract

Introduction: Perfusion index (PI) is a noninvasive indirect method of microcirculation measurement that might have a potential to predict morbimortality in preterm newborns. This study aims: 1) to define a critical value for post-ductal PI related to the morbimortality in preterm newborns under 32 weeks; 2) to define a prognostic value for post-ductal PI to predict that risk of morbimortality; and 3) to associate post-ductal PI values with the Apgar score at five minutes and the Clinical Risk Index for Babies II (CRIB-II) score.

Material and methods: This is an observational study, with a prospective character, performed in a Neonatal Intensive Care Unit that enrolled 34 preterm newborns with less than 32 weeks admitted between 1st February 2016 and 1st February 2017. Post-ductal PI values were evaluated in the newborns' feet at 24 hours of life. The Apgar score was registered at birth and CRIB-II score was calculated. The other clinical variables, including the presence of an adverse outcome and/or death, was assessed in clinical records.

Measurements and main results: We found significant correlations between post-ductal PI values, Apgar score at five minutes and CRIB-II score. The area under ROC curve was higher for CRIB-II score and lower for Apgar score at five minutes. The best cut-off points were: 1) post-ductal PI value ≤ 0.72; 2) Apgar score at five minutes < 6; and 3) CRIB-II score > 9. Preterms within these cohorts have higher rates of morbimortality.

Post-ductal PI values ≤ 0.72 were an independent predictor of mortality in preterm newborns (p-value = 0.047).

Conclusions: This study suggests that post-ductal PI value ≤ 0.72 at 24 hours of life might be a potential predictor of morbimortality in preterm newborns. However, it is important to clarify that this study has a small representative population which can reduce the accuracy of the results. The very high morbimortality rate in this cohort is another strong limitation for the quality of the results.

Keywords

Perfusion index, pulse oximeter, post-ductal, preterm, mortality, morbidity.

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How to cite

Costa Monteiro S, Correia-Costa L, Proença E. Perfusion index in preterm newborns: predictive value for morbimortality and association with Apgar score at five minutes and CRIB-II score. J Pediatr Neonat Individual Med. 2019;8(1):e080104. doi: 10.7363/080104.

Introduction

Preterm newborns are known to be at risk of developing severe adverse outcomes especially during the first week of life. The immaturity of the cardiovascular and autonomous nervous system may lead to hypoperfusion states that, when prolonged, can result in acute organ failure [1-4].

Apgar score is a validated score that has been widely used to assess the risk of infants at birth [5]. One limitation of the Apgar score is its use in preterm newborns. In this group, the score may be lower due to their immaturity, with a consequent heterogeneity in preterm classification, even when there are healthy [6-10].

The Clinical Risk Index for Babies II (CRIB-II) score is a validated tool to predict the initial risk of mortality amongst low birth weight babies admitted at Neonatal Intensive Care Unit (NICU) with less than 32 weeks. It is calculated through the birthweight, the gestational age, the body temperature, the base excess and the sex [11]. A better prognosis is linked to lower values in such classification [12].

Hemodynamic instability results in a reduction of peripheral perfusion with a consequent re-distribution of cardiac output to vital organs such as the brain, heart, kidneys and adrenal glands [13, 14]. In that context, monitoring peripheral perfusion in the skin could be an early marker of tissue hypoperfusion and recognition at its earliest phase is essential to begin immediate treatment before permanent damage occurs [14].

Recently, particular emphasis has been given to the perfusion index (PI) as a noninvasive method for hemodynamic monitoring. The PI is a real-time parameter resulting from the signal of pulse oximetry and reflects the modifications in peripheral circulation that occurs at a specific monitoring site [15-20]. This is a numeric value that reflects the ratio between pulsatile signal and non-pulsatile signal [20-22]. Hypoperfusion induces a reflex peripheral vasoconstriction that lowers the regional pulsatile signal detected by the sensor and, because non-pulsatile signal maintains equal, PI value decreases [21, 22].

It is important to refer that pre-ductal PI tends to have higher values when compared with post-ductal PI values. This is explained by the shunt through the ductus arteriosus, an event which is more prominent in preterm newborns. So, post-ductal PI value is a more reliable measure of microcirculation and systemic response to hypoperfusion and allows a more precise comparison between newborns [23, 24].

In recent studies with newborns, PI has been reported to be associated with gestational age, pulse pressure, peripheral temperature, capillary refill time, mean arterial pressure and oxygen saturation [18, 25, 26]. Its application has been explored in several specific settings, such as in states of inflammatory systemic responses [27], in detection of subclinical chorioamnionitis [28] in the screening or early detection of hemodynamic instability associated with congenital heart diseases [29, 30], patent ductus arteriosus (PDA) [31], low superior vena cava flow [32], and in response to volume restitution and blood transfusion [33]. However, only a few studies have focused on the relevance of post-ductal PI in preterm infants and more studies are needed to determine its prognostic value and its potential to be a clinical marker in these specific population [31, 34].

The present study aimed to define a critical value for post-ductal PI related to the morbidity and mortality in a population of preterm newborns

under 32 weeks, to define a prognostic value for post-ductal PI to predict the risk of morbimortality during the neonatal period, and to associate post-ductal PI values with Apgar score at five minutes and with CRIB-II score.

Material and methods

Study design and sample

We conducted a prospective observational study that aimed to enroll preterm infants admitted to the NICU of Centro Materno-Infantil do Norte, Porto, Portugal, a tertiary center, between 1st February 2016 and 1st February 2017. All preterm newborns with less than 32 weeks were eligible for the study protocol. Newborns with major congenital malformations and/or cases in whom technical limitations occurred in PI data collection were excluded. We finally enrolled 34 preterm newborns in the study.

Data collection and variable definition

Data on demographic and general maternal characteristics were abstracted from clinical records. Newborns' sex, gestational age, anthropometric data and Apgar score were recorded at birth.

PI measurements were assessed with Masimo Radical-7® SET™ (Masimo Corp) and, according to the equipment settings, they were recorded between the values of 0 and 20. Post-ductal PI values were obtained with the sensor placed in one of the feet of the newborn at 24 hours of life. The PI values were recorded after a stable pulse wave obtained for a minimum period of 10 seconds, to minimize artifacts in the record.

CRIB-II score was used as a validated tool to assess neonatal risk and calculated with the online tool available at http://www.sfar.org/scores2/crib22.php, based on gender, gestational age (in weeks), birth weight (in grams), axillary temperature (obtained with a digital thermometer at admission in the NICU), and base excess (obtained in the first hour of life).

The presence of at least one of the following clinical situations was considered as an adverse outcome: asphyxia, shock (cardiogenic, hypovolemic and/or distributive), respiratory distress syndrome, anemia, sepsis, pneumonia, necrotizing enterocolitis, PDA with hemodynamic significance, intraventricular hemorrhage (grade higher than two), periventricular leukomalacia, retinopathy of prematurity, and bronchopulmonary dysplasia. The occurrence of death during the neonatal period was also considered. In the absence of the former conditions, the newborns were classified as healthy preterm.

Statistical analysis

The statistical analysis was performed using the software Statistical Package of Social Science® (SPSS Inc., Chicago, IL, USA), version 24. Continuous variables were expressed as mean ± standard deviation (SD) or as median (25th percentile [P25]-75th percentiles [P75]) if skewed. Differences between groups in independent continuous variables were assessed by Mann-Whitney. Categorical data were present in absolute frequencies and percentage. Chi-square tests were used for categorical variables. Associations between continuous data were assessed with Spearman rank correlation. Discrimination of values was performed using receiver operating characteristic analysis (ROC curve). The area under the curve (AUC) was conducted to explore the discrimination ability of post-ductal PI, CRIB-II score and Apgar score at five minutes in predicting morbidity and mortality. The critical values for post-ductal PI, CRIB-II score and Apgar score at five minutes derived from the best cut-off point at ROC curve. The best cut-off values of post-ductal PI, Apgar score and CRIB-II were defined as those who showed the best sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The CRIB-II score, the Apgar score at five minutes and the post-ductal PI values were integrated into a multivariate regression model in order to establish which had an independent predictive role for the risk of morbidity and mortality.

A two-tailed p-value of < 0.05 was considered as statistically significant.

Legal considerations

The study was approved by the Ethics Committee of Centro Hospital do Porto (CHP), the Research Coordinating Office of the Department of Education, Training and Research of CHP and the Clinical Direction. Informed consent was obtained for legal representatives of all infants.

Results

A total of 34 newborns (53.8% male) were recruited for this study. The median gestational age

was 30.4 (29.2-31.5) weeks and the median post-ductal PI values recorded were 0.73 (0.52-0.97). The general characteristics of the study population are presented in **Tab. 1**.

The occurrence of disease was significantly linked with Apgar score at five minutes (p = 0.048). Post-ductal PI values (p = 0.335) and CRIB-II score (p = 0.103) were not significantly different between newborns with an adverse outcome and healthy newborns. However, mortality was related to all variables in the study, namely post-ductal PI values at 24 hours of life (p = 0.004), Apgar score at five minutes (p = 0.048) and CRIB-II score (p = 0.003).

The post-ductal PI values was significantly correlated with Apgar score at five minutes (ϱ = 0.388, p = 0.021) and CRIB-II score (ϱ = -0.588, p = 0.023). A negative correlation was found between Apgar score at five minutes and CRIB-II score (ϱ = -0.613, p < 0.0001). When considered post-ductal PI values ≤ 0.72 the relationships seem to be strengthened with Apgar score at five minutes (ϱ = 0.588, p = 0.821) and CRIB-II score (ϱ = -0.678, p = 0.713). Considering post-ductal PI values > 0.72, the relationships with Apgar score at five minutes (ϱ = 0.110, p = 0.665) and CRIB-II score (ϱ = -0.209, p = 0.405) was lacked. However, none of these results was significant.

Tab. 2 shows the AUC values for Apgar score at five minutes, CRIB-II score and post-ductal PI values, as well as the best cut-offs points and their respective sensitivity and specificity values for the occurrence of disease and/or death in the neonatal period. ROC curve analysis shows that the best cut-off points to predict morbidity and mortality were Apgar score at five minutes < 6, PI value ≤ 0.72 and CRIB-II score > 9. PPV and NPV values are showed in **Tab. 3**.

Looking to the occurrence of disease, and using the critical values defined, the following findings were observed: 1) the CRIB-II score showed the highest sensitivity (81.8%), specificity (54.5%) and PPV (80.0%); 2) the post-ductal PI showed a higher NPV (44.0%) when compared with CRIB-II score (42.0%) and Apgar score at five minutes (20.0%); and 3) the post-ductal PI showed higher specificity (27.3%) and PPV (75.0%) than Apgar score at five minutes.

Considering the occurrence of death, the following findings were observed: 1) CRIB-II score showed the highest sensitivity (87.5%), specificity (70.8%) and PPV (50.0%); 2) the post-ductal PI showed higher NPV (88.8%) when compared with CRIB-II score (82.0%) and Apgar score at five minutes (87.0%); and 3) the post-ductal PI showed a higher specificity (32.3%) than Apgar score at five minutes.

The incidence of death was higher in infants with a post-ductal PI value ≤ 0.72, an Apgar score at five minutes < 6 and a CRIB-II score > 9. With respect to the occurrence of disease, the incidence

Table 1. Characteristics of the study population.

	Total (n = 34)
Maternal age, years	31.57 ± 4.36
Gestational age, weeks	30.4 (29.2-31.5)
Male sex	21 (53.8%)
Birthweight, g	1,121.8 ± 73.09
Length, cm	36.29 ± 4.3
Head circumference, cm	26.23 ± 0.49
Post-ductal PI	0.73 (0.52-0.97)
Apgar score at 1 minute	6 (5-9)
Apgar score at 5 minutes	8 (5-10)
Apgar score at 10 minutes	9 (7-10)
CRIB-II score	7 (3-10)
Adverse outcome	22 (56.4%)
Neonatal death	9 (23.1%)

The results are present as mean ± standard deviation, as median (P25-P75) or as absolute frequencies (percentage).
PI: perfusion index.

Table 2. ROC curve analysis for Apgar score at 5 minutes, CRIB-II score and post-ductal PI at 24 hours of life: AUC, the respective 95% confidence interval and the best cut-off point (with respective sensitivities and specificities).

Variables	Occurrence of disease						Occurrence of death					
	AUC	p	Cut-off	Sn	Sp	CI 95%	AUC	p	Cut-off	Sn	Sp	CI 95%
Apgar score at 5 minutes	0.260	0.022	< 6	45.5%	18.2%	0.084-0.436	0.263	0.048	< 6	37.5%	16.7%	0.049-0.461
CRIB-II score	0.721	0.041	> 9	81.8%	54.5%	0.548-0.895	0.813	0.009	> 9	87.5%	70.8%	0.640-1.000
Post-ductal PI at 24 hours	0.324	0.045	≤ 0.72	45.5%	27.3%	0.142-0.507	0.290	0.010	≤ 0.72	25.0%	32.3%	0.050-0.428

AUC: area under the curve; CI: confident interval (for AUC); CRIB-II: Clinical Risk Index for Babies II; PI: perfusion index; Sn: sensitivity; Sp: specificity.

Table 3. Positive and negative predictive values for Apgar score at 5 minutes < 6, CRIB-II score > 9 and post-ductal PI ≤ 0.72 and correlations with occurrence of disease or death.

Variables	Occurrence of disease			Occurrence of death		
	PPV	NPV	p [a]	PPV	NPV	p [a]
Apgar score at 5 minutes < 6	50.0%	20.0%	NS	46.6%	87.0%	0.018
CRIB-II score > 9	80.0%	42.0%	NS	50.0%	82.0%	0.023
Post-ductal PI ≤ 0.72	75.0%	44.0%	NS	40.0%	88.8%	0.034

CRIB-II: Clinical Risk Index for Babies II; NPV: negative predictive value; PI: perfusion index; PPV: positive predictive value.
[a] Chi-square correlation coefficient for associations between cohorts defined by critical values and occurrence of disease or death.

of events was slightly higher for newborns with a post-ductal PI value ≤ 0.72, an Apgar score at five minutes < 6 and a CRIB-II score > 9. However, no significant differences were found in the occurrence of disease.

When considering different cohorts (CRIB-II score ≤ 9 and > 9 and Apgar score at five minutes < 6 and ≥ 6), post-ductal PI presented lower values in newborns classified with Apgar score < 6 (0.69 [0.50-0.70] vs. 0.80 [0.61-0.80]) and with CRIB-II score > 9 (0.70 [0.41-0.94] vs. 0.80 [0.62-0.99]). However, none of these differences had statistical significance (**Tab. 4**).

Multivariable logistic regression demonstrated that post-ductal PI was an independent predictor of neonatal mortality (relative risk 5.33, 95% CI 0.89-32.2, p = 0.047) but not an independent predictor of neonatal morbidity. No significant results were obtained for the CRIB-II score and for the Apgar score at five minutes.

Table 4. Differences between post-ductal PI values according to cohorts defined by critical values of CRIB-II score and Apgar score at 5 minutes.

CRIB-II score	Post-ductal PI	p [a]	Apgar score at 5 minutes	Post-ductal PI	p [a]
≤ 9, n = 24	0.80 (0.62-0.99)	NS	**< 6, n = 14**	0.69 (0.50-0.70)	NS
> 9, n = 10	0.70 (0.41-0.94)		**≥ 6, n = 20**	0.80 (0.61-0.80)	

The results are presented as median (P25-P75).
CRIB-II: Clinical Risk Index for Babies II; NS: no significance; PI: perfusion index.
[a] Mann-Whitney U to assess differences between PI values and cohorts defined by critical values for CRIB-II and Apgar score at 5 minutes.

Discussion

In the present study, we found that PI is a noninvasive index, easy to get and with potential to be applied in clinical practice. So far, few studies have explored the use of PI in newborns but, globally, the post-ductal PI values observed in our study are similar to others previously published [24, 32-36].

The post-ductal PI in our cohort showed a lower value of AUC both for the occurrence of disease and for the occurrence of death, compared with CRIB-II score. We concluded that PI had a lower discriminative power when compared with CRIB-II score. Although, we also have shown that PI had higher discriminating power than Apgar score at five minutes to assess the risk of morbidity and mortality of infants in our cohort. This confirms that the Apgar score is not optimal for use in preterm newborns for several reasons, namely immaturity of preterm development, its potential lack of reliability and the likelihood that each of the five components carries different clinical significance, despite having the same weight in scoring [5-10].

The CRIB-II score shows the best values of AUC for both disease and mortality, differing significantly from post-ductal PI and from Apgar score at five minutes. So, an analysis of the predictive accuracy of post-ductal PI, Apgar score at five minutes and CRIB-II score in relation to the risk of morbidity and mortality determined that the CRIB-II > 9 showed the best power as a diagnostic test when compared to post-ductal PI ≤ 0.72 and to Apgar score at five minutes < 6. We also showed that post-ductal PI had a low specificity to detect the risk of neonatal death and to diagnose preterm disease. We think that these results are not surprising, as the PI is an isolated index of peripheral perfusion, the Apgar score has limitations outlined above, and CRIB-II score involves clinical and analytic parameters, which make that score a more complete source of evaluation. We also found that morbidity and mortality rates were higher when the PI value was ≤ 0.72, the Apgar score at five minutes was < 6 and the CRIB-II score was > 9. These differences were only significant for mortality.

Our study revealed that post-ductal PI values were significantly negatively correlated with CRIB-II score and positively associated with Apgar score at five minutes. When considered post-ductal PI values ≤ 0.72 these relationships seemed to be strengthened and when used a cohort of post-ductal PI values > 0.72 these relations were lacked. However, none of these differences were significant, maybe due to the small size of these cohorts and consequent higher levels of cohort homogeneity. We also found lower values for post-ductal PI in infants with Apgar score at five minutes < 6 and with CRIB-II score > 9, which help to confirm these conclusions. However, none of these differences were significant. We believe that these results support the role of post-ductal PI values as an additional tool to monitor peripheral microcirculation.

Multivariate analysis showed that only post-ductal PI had a role as an independent predictor for mortality in preterm infants. These findings propose that post-ductal PI ≤ 0.72 will be a potential independent predictor of preterm death. We can also suggest that post-ductal PI might be an early predictor of disease, although without confirmation in this cohort.

In previous studies, De Felice et al. concluded that PI values ≤ 1.24 shows a best predictive value compared with peripheral capillary oxygen saturation and heart rate. However, the maximum PI value recorded in our cohort was 1.2 and only in 56.4% infants an adverse outcome was registered. The cut-off value of 1.24 was obtained in a population with higher gestational ages, so we considered that extrapolation of this value to our population of newborns is not adequate [26]. Granelli and Ostman-Smith reported that a post-ductal PI value < 0.70 might indicate illness and that this index might be a useful additional tool in the early detection of left heart obstruction [29]. Takahashi et al. also found that a post-ductal PI value < 0.44 had good sensitivity and specificity for detecting low superior vena cava flow, a predictor of intraventricular hemorrhage in the first days of life [32]. Also, Tuten et al. reported that, at 24 hours of life, post-ductal PI values lower than 0.5 could be used as an early predictor of retinopathy of prematurity and bronchopulmonary dysplasia [37].

Peripheral vasoconstriction is an early marker of hemodynamic instability and can be assessed by monitoring microcirculation [13, 14]. The PI is a variable that detects variations in microcirculation and has been considered a promising variable for monitoring peripheral circulation. In our study, we reinforced the observation that post-ductal PI values might be considered a parameter of microcirculation monitoring. Our results support that the post-ductal PI alone is probably not useful to predict morbidity and mortality in preterm infants. However, we believe that this index can be used as an additional tool to help in the diagnosis of conditions that compromise peripheral circulation, in monitoring therapeutic response, and in predicting an adverse outcome in newborns, including their risk of death.

The major strength of the present study is that it was the first, at the best of our knowledge, which explored the ROC curves for post-ductal PI in preterm infants and laid down a relationship between post-ductal PI values, CRIB-II index and Apgar score. From our point of view, it is an important step to define the role of post-ductal PI in clinical practice.

We believe that the preterm population under 32 weeks is very heterogeneous and, in our study, it was clearly characterized by a higher prevalence of events, which may confound the results. Nonetheless, the need for a detailed analysis and the comparisons between gestational age groups implicate that some comparisons are made between smaller subgroups, which might limitate our ability to find significant differences. It is important to clarify that the small sample (n = 34) was an obvious limitation of the present study, which makes it difficult to obtain valid conclusions [38].

Another important limitation is due to the fact that PI records were not always performed by the same medical staff member. Although a standardized protocol for PI measurement has been recently implemented in our NICU, inter-variability between observers might have occurred, affecting the results. Moreover, although we tried to ensure perfect conditions at the time of PI values recording, some variables, not controlled in our study protocol, such as light exposure, skin color, peripheral temperature, peripheral perfusion and other movement artifacts, might have influenced the records obtained. Moreover, previous studies reported that PI might also be influenced by circadian rhythms, feeding periods, intravenous treatments, body temperature, peripheral perfusion state and newborn position (prone vs. supine), factors that we also could not account for in the present analysis. In fact, the application of a standardized methodology for PI values recording

might represent the major limitation for clinical extrapolation of evidence about this index [39, 40].

Conclusion

We concluded that post-ductal PI values obtained at 24 hours of life might be considered as a predictor of morbidity and mortality in preterm. In our study, post-ductal PI values ≤ 0.72 were able to predict these conditions. However, since this is a first study done with a small cohort, new lines of research are necessary to consolidate this information and to understand the pertinence of PI in the context of a NICU. Still, it is important to clarify that this study has a small representative population, which can reduce the accuracy of the results. Also, the very high morbimortality rate in this cohort is another strong limitation for the quality of the results.

In the future, we believe that multicentric and randomized controlled clinical trials are needed in order to standardize protocols of PI use in clinical practice and to reinforce previous findings in this field. We also consider that the definition of reference values for PI is essential, in order to allow the establishment of PI as a prognostic value of morbimortality, integrated into clinical decision algorithms.

Declaration of interest

We used the pulse oximeter Masimo Radical-7® Set™ (Masimo Corp.). None of the Authors have relationship with Masimo. The Authors declare no other conflict of interest. No specific funding was obtained for the present study.

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