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UNIVERSIDADE DO PORTO

Clinical Investigation

Mestrado Integrado em Medicina

PERFUSION INDEX IN PRETERM NEWBORNS DURING THE FIRST WEEK OF LIFE AND ASSOCIATION WITH NEONATAL MORBIMORTALITY

SÉRGIO COSTA MONTEIRO

Orientador(a):

Elisa Eugénia Barros Proença

Co-orientador(a):

José Augusto Pombeiro Veloso

Porto 2017

Cover Letter

Perfusion index in preterm newborns during the first week of life and association with neonatal morbimortality: a prospective observational study.

Sérgio Costa Monteiro, BA[a]; Liane Correia-Costa, MD[b]; Elisa Proença, MD[c]

[a]*Centro Hospitalar do Porto (CHP), Instituto de Ciências Biomédicas Abel Salazar (ICBAS), University of Porto, Porto, Portugal.*

[b]*Pediatric Nephrology Department, Centro Materno-Infantil do Norte (CMIN) - Centro Hospitalar do Porto (CHP), Porto, Portugal; EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal.*

[c]*Neonatal Intensive Care Unit - Pediatric and Neonatal Intensive Care Service, Centro Materno-Infantil do Norte (CMIN) – Centro Hospitalar do Porto (CHP), Portugal.*

Keywords: Perfusion Index; Pulse Oximeter; Preterm; Mortality; Morbidity.

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.

The authors have nothing to disclose. No specific funding was obtained for the present study. The material contained in the manuscript was not previously published and is not being concurrently submitted to other publishers. The authors have disclosed that they do not have any potential conflicts of interest.

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[a]*Centro Hospitalar do Porto (CHP), Instituto de Ciências Biomédicas Abel Salazar (ICBAS), University of Porto, Porto, Portugal.*

[b]*Pediatric Nephrology Department, Centro Materno-Infantil do Norte (CMIN) - Centro Hospitalar do Porto (CHP), Porto, Portugal; EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal.*

[c]*Neonatal Intensive Care Unit - Pediatric and Neonatal Intensive Care Service, Centro Materno-Infantil do Norte (CMIN) – Centro Hospitalar do Porto (CHP), Portugal.*

Corresponding author:

Sérgio Costa Monteiro

E-mail: sergio.costamonteiro@gmail.com

Address: *Neonatal Intensive Care Unit*, Largo da Maternidade de Júlio Dinis, 4050-651 Porto, Portugal.

Phone number: +351 222 077 500.

Keywords: Perfusion Index; Pulse Oximeter; Preterm; Mortality; Morbidity.

ABSTRACT

Objective: Perfusion index (PI) is a noninvasive method of peripheral perfusion measurement. Previous publications suggest that PI might be an useful and accurate predictor of morbidity and mortality risk in preterm newborns. This study aims 1) to assess the perfusion index values of preterm newborns (<37 weeks) in the first seven days of life according to gestational age and 2) to assess differences in PI values between healthy preterm newborns and those who developed adverse outcomes during the neonatal period.

Design: Prospective observational study.

Setting: Neonatal Intensive Care Unit.

Patients: Sixty preterm newborns with less than 37 weeks admitted to the Neonatal Intensive Care Unit were enrolled in this study.

Interventions: Post-ductal PI was evaluated in the newborns' feet in the first hour and at 24 hours, 48 hours, 72 hours and 168 hours of life. The presence of an adverse outcome and/or death in the neonatal period was assessed in clinical records, along with several other clinical variables.

Measurements and Main results: We found a non-significant trend towards decreasing PI values in the first two days of life, with an increase at 48 hours and stable values at 72 hours after birth. PI values had an inverse relationship with gestational age (p for linear trend: 24 hours p=0.029, 48 hours p=0.001, 72 hours p=0.037, 168 hours p=0.001). The most prevalent adverse outcomes were shock (n=8, 13.2%), anemia (n=10, 16.7%) and intraventricular hemorrhage grade >2 (n=10, 16,7%). Median PI values were found to be significantly lower in newborns with an adverse outcome (0.90 vs. 0.70 at hour 24; 0.87 vs. 0.72 at hour 48; 0.91 vs. 0.79 at hour 72; and 0.90 vs. 0.80 at hour 168) and/or death in neonatal period (0.87 vs. 0.55 at 1 hour; 0.80 vs. 0.70 at 24 hours; 0.81 vs. 0.55 at 48 hours; 0.88 vs. 0.74 at 72 hours; and 0.89 vs. 0.49 at 168 hours).

Conclusions: PI values differed according to gestational age and to the presence of comorbidities, confirming that it might represent a valuable tool in the early identification of adverse outcomes in the neonatal period.

INTRODUCTION

Preterm newborns, mainly those admitted to neonatal intensive care units (NICU), are known to be at risk of developing several adverse outcomes, which ultimately can lead to an increase in morbimortality, especially during the first week of life. The development of hemodynamic instability that, when prolonged, may lead to an acute organ failure, is in part due to the immaturity of the cardiovascular and autonomous systems. The assessment and the maintenance of adequate tissue oxygen supply are generally considered primary objectives (1-4).

In clinical practice, tissue perfusion and oxygenation is usually assessed by noninvasive techniques essentially based on macrocirculatory parameters, such as systemic blood pressure (BP), heart rate (HR), oxygen saturation (SpO_2) and functional echocardiography (5, 6). However, it is suggested that these methods are poor representatives of microcirculatory functioning (6).

During circulatory failure, the classical mechanism of peripheral vasoconstriction diverts blood flow from less important tissues to essential organs, which calls attention for the fact that, particularly in preterm newborns, techniques monitoring microcirculation in less vital tissues could allow to early identify vital tissue hypoperfusion, before the installation of decompensated shock leading to organ failure (7, 8). It is important to note that indirect measures actually used for assessment of microcirculation, such as urine output, capillary refill time and serum lactate levels, are considered insensitive markers of tissue perfusion, especially in the first days of life, when extra-uterine life adaptation occurs. In face of this, new hemodynamic monitoring methods have been studied and the perfusion index (PI), translating the real time variations of the pulse oximetry signal in the peripheral circulation, has emerged as an easily applicable, noninvasive and continuous parameter that reflects changes in the cardiac output and vasomotor tone (9, 10). 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 (11, 12). Its application has been explored in several specific settings, such as in states of inflammatory systemic responses (13), detection of subclinical chrorioamnionitis (14), in the screening or early detection of hemodynamic instability associated with congenital heart diseases (15, 16), patent ductus arteriosus (17), low superior vena cava flow (18) and in response to volume restitution and blood transfusion (19). Moreover, previous studies have reported positive correlations between post-ductal PI and indirect measures obtained by near-infrared spectroscopy (NIRS), another noninvasive technique of microcirculation monitoring (20).

Despite all this, only a few studies have focused on the relevance of PI in preterm infants and more studies are needed to determine the prognostic value of PI, in order to strengthen and standardize the application of this tool as clinical marker of illness in this age group (9, 21, 22). The present study aimed to evaluate post-ductal PI values in a population of preterm newborns during the first week of life, according to their gestational ages and to evaluate the association between PI and the occurrence of adverse outcomes, such as disease and/or death during the neonatal period.

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 1th February 2016 and 1th February 2017. All preterm newborns with less than 37 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 sixty 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 was recorded at birth.

Newborns were classified in three groups, as stated by the World Health Organization gestational age classification: less than 28 weeks (extremely preterm); from 28 weeks to less than 32 weeks (very preterm) and from 32 weeks to less than 37 weeks (moderate to late preterm) (23).

PI measurements were assessed with Masimo Radical-7 Set(R) (*Masimo Corp*) and according to the equipment settings were recorded between the values of 0 and 20. Post-ductal PI values were obtained with the sensor placed in one of the feet at the first hour of life and at day 1 (24 hours), day 2 (48 hours), day 3 (72 hours) and, whenever the newborn was still on the NICU, at day 7 (168 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.

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, patent ductus arteriosus (PDA)

with hemodynamic significance and intraventricular hemorrhage (grade higher than two). 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 (25^{th} percentile (P25) - 75^{th} percentile (P75)) if skewed. Differences between groups in independent continuous variables were assessed by Student's T-test or by Mann-Whitney or Kruskall-Wallis. Trends for PI values according gestational ages were assessed with linear regression. Differences between groups in paired continuous variables were assessed by Wilcoxon test. Chi-square tests were used for categorical variables. Linear trend in PI values was tested using linear regression models with classes of gestational age included as independent continuous variables. 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 60 newborns (60% male) were recruited for this study. The median gestational age was 31.4 (24.1-35.3) weeks. Thirteen (21.7%) infants were extremely preterm, 22 (36.7%) were very preterm and 25 (41.7%) infants were moderate to late preterm. The general characteristics of the study population, according to gestational age groups, are presented in Table 1.

Sex distribution and maternal age were similar between gestational age groups. The anthropometric characteristics, birthweight, length and head circumference were significantly higher among the preterm with higher gestational age.

The extreme preterm group presented lower Apgar score values at the 1^{st} (5 (3-5) vs. 8 (6-9) vs. 8 (7-9), $p<0.001$), at the 5^{th} (6 (5-7) vs. 9 (8-10) vs. 9 (9-10), $p<0.001$) and at the 10^{th} minutes (7 (5-7) vs. 10 (9-10) vs. 10 (9-10), $p<0.001$) than the very preterm and the moderate to late preterm groups, respectively. The extreme preterm group presented more frequently adverse outcomes (100% vs. 45% vs. 40%, $p=0.006$, in extreme, very and moderate to late preterm groups, respectively) and death during the neonatal period (62% vs. 4,5% vs. 0%%, $p<0.001$, in extreme, very and moderate to late preterm groups, respectively).

The PI measurements in the first seven days of life, according to gestational age groups, are presented in Table 2. In all gestational age groups, PI values were lower in the first 48h after birth and higher at 72 and 168 hours. No differences were found in the PI values between gestational age groups at the first hour, but at all other measurements the PI values increased with gestational age (p for linear trend: 24 hours $p=0.029$, 48 hours $p=0.001$, 72 hours $p=0.037$, 168 hours $p=0.001$).

When considering the occurrence of adverse outcomes, newborns that developed disease presented lower PI values at all times, with the exception of the first hour (Table 3). Newborns who died during the neonatal period also presented lower PI values at all times recorded (Table 3).

DISCUSSION

In the present study, we found that PI values differed according to gestational age, being lower in extremely preterm newborns and higher in moderate to late preterm. Moreover, we showed that PI values suffered higher variations during the first hours of life, to later stabilize at around 72 hours of life. Importantly, we were able to describe that PI values are lower in preterm newborns with pathological adverse outcomes and in those that died during the neonatal period.

The post-ductal PI trends observed along the first three days of life may reflect the physiological variability of the peripheral microvascular blood flow that characterizes the transitional period, in which a hypoperfusion-reperfusion cycle occurs (24, 25). The preterm heart is structurally and functionally immature and is not capable of adapting to relatively small changes in preload and afterload, in order to effectively deliver oxygen and nutrients to the tissues. Briefly, the sudden increase in systemic vascular resistance due to cord clamping cannot be immediately compensated by the immature myocardium, with insufficient contractile reserve, which may determine a peripheral hypoperfusion state. A reflex increase in cardiac output tends to occur over the first 48 to 72 hours of life of neonate and depends on gestational age (25).

So far few studies have explored the use of PI in newborns but, globally, the PI values and trends observed in our study are similar to others previously published. We found that PI values stabilized at 72 hours, independently of gestational age, at a median value of 0.89 (0.62-0.97). *Hakan et al.* reported that PI values reached a steady state on the fifth day of life and *Hawkes et al.* also described a high variability of PI values in the transitional period (22, 26). Both authors concluded that this initial period is marked by high PI variability, which is concordant with our findings (22, 26). *Vidal et al., Kinoshita et al.* and *Hakan et al.* reported median PI values similar to those described in our study but *Cresi et al.* reported somehow higher values (17, 21, 26, 27). These differences might be explained by the inclusion of a sample of newborns with a different distribution of gestational ages, possibly with different clinical and hemodynamical states.

Naturally, if extreme and very preterm babies are over or sub represented in the samples considered, especially if the samples are small, the conclusions obtained might substantially differ.

In our study, we described lower PI values among preterm newborns with pathological adverse outcomes. In previous studies, *Granelli et al.*, *De Felice et al.* and *Laere et al.* also described significant lower PI values in infants with high severity diseases (15, 18, 28). *Tuten et al.* reported that, at 24 hours of life, PI values lower than 0.5 could be used as an early predictor of prematurity retinopathy and of broncopulmonar dysplasia (29).

In the context of vascular compromise, peripheral vasoconstriction is an early event that reflects the deviation of blood from less important structures to vital organs. This concept suggests that monitoring microcirculation can result in early detection of hypoperfusion conditions avoiding the development of acute organ dysfunction and failure. For assessment of peripheral perfusion in newborns, a number of methods are currently available, such as laser Doppler, orthogonal polarization spectral, side-stream dark field, visible light technology, amplitude integrated electroencephalogram, NIRS and perfusion index. While, none of these methods is currently validated to monitor microcirculation in preterm newborns in clinical practice, pulse oximetry technology is widely diffused in NICU and PI is a value that can be readily and easily acquired. In our study, we reinforced that PI values might be considered a parameter of microcirculation monitoring and that they might be used as an additional tool for prediction of morbidity and mortality risk in preterm newborns.

The major strength of the present study was that it included a relatively large sample of newborns, encompassing a wide range of gestational ages. Nonetheless, the need for a detailed analysis and the comparison between gestational age groups, implicates that some comparisons are made between smaller subgroups, which might limitate our ability to find significant differences. This situation also didn't allow the comparison of PI values between preterm newborns with adverse outcome and/or neonatal death, according gestational ages groups.

Another important limitation is due to the fact that PI records were not always performed by the same medical staff member. Although it has been recently implemented a standardized protocol for PI measurement in our NICU, inter-variability between observers might have occurred affecting the results. Moreover, although trying to ensure perfect conditions at the time of PI values recording, some potential artifacts, 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 and newborn position (prone vs. supine) (26, 30), 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.

CONCLUSION

In conclusion, we described PI values variation according to gestational age and during the first seven days of life and we were able to associate PI values with the presence of neonatal adverse outcomes.

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

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Table 1. Characteristics of the study population.

Variables	Total (n=60)	Extremely preterm	Very preterm	Moderate to late preterm	p*
Maternal age, years	31.5 ± 3.9	32.8 ± 4.3	30.9 ± 4.4	31.5 ± 3.1	NS
Gestational age, weeks	31.4 (24.1 - 35.3)	26.3 (24.1 - 27.5)	28.1 (31.6 - 30.4)	32.4 (32.2 - 35.3)	NS
Male sex	36 (60.0%)	7 (53.8%)	15 (68.2%)	14 (56.0%)	NS
Birthweight, g	1444 ± 548	763 ± 198	1367 ± 347	1865 ± 416	<0.001
Length, cm	8.3 ± 4.7	32.2 ± 3.5	38.7 ± 2.6	41.2 ± 3.6	<0.001
Head circumference, cm	28.2 ± 3.6	23.8 ± 1.8	27.8 ± 2.1	30.9 ± 2.7	<0.001
Apgar score at one minute	8 (5 - 9)	5 (3 - 5)	8 (6 - 9)	8 (7 - 9)	<0.001
Apgar score at five minutes	9 (7 - 10)	6 (5 - 7)	9 (8 - 10)	9 (9 - 10)	<0.001
Apgar score at ten minutes	9 (8 - 10)	7 (5 - 7)	10 (9 - 10)	10 (9 - 10)	<0.001
Adverse outcome	32 (53.3%)	13 (100%)	10 (45.2%)	10 (40.0%)	0.006
Shock	8 (13.3%)	6 (46.2%)	1 (4.5%)	1 (4.0%)	
Intraventricular hemorrhage grade >2	10 (16.7%)	8 (61.5%)	1 (4.5%)	1 (4.0%)	
Anemia	10 (16.7%)	5 (38.5%)	2 (9.0%)	3 (12.0%)	
Asphyxia	1 (1.7%)	1 (7.7%)	-	-	
Necrotizing enterocolitis	4 (6.7%)	1 (7.7%)	1 (4.5%)	2 (8.0%)	
PDA with hemodynamic significance	4 (6.7%)	2 (15.4%)	1 (4.5%)	1 (4.0%)	
Neonatal death	9 (15%)	8 (61.5%)	1 (4.5%)	-	<0.001

The results are presented as mean ± standard deviation, as median (P25-P75) or as absolute frequencies (percentage).

**Kruskal-Wallis* for comparison between the three groups of newborns.

Abbreviations: NS – No significance; PDA – patent ductus arteriosus.

Table 2. Distribution of PI values in newborns, at first seven days of life, according gestational age.

Hours of life	Total (n=60)	Extremely preterm (n=13)	Very preterm (n=22)	Moderate to late preterm (n=25)	p*
1 hour	0.81 (0.64 - 1.08)	0.74 (0.37 - 1.35)	0.83 (0.66 - 1.03)	0.80 (0.66 - 1.09)	NS
24 hours	0.80 (0.63 - 0.98)	0.56 (0.40 - 0.86)	0.85 (0.64 - 1.00)	0.80 (0.68 - 0.99)	0.029
48 hours	0.80 (0.59 - 0.90)	0.53 (0.33 - 0.72)	0.75 (0.56 - 0.99)	0.85 (0.78 - 0.90)	0.001
72 hours	0.89 (0.62 - 0.97)	0.60 (0.52 - 0.85)	0.90 (0.69 - 1.09)	0.91 (0.78 - 0.98)	0.037
168 hours	0.85 (0.70 - 1.00)	0.60 (0.48 - 0.73)	0.83 (0.71 - 1.00)	0.90 (0.82 - 1.20)	0.001

The results are presented as median (P25-P75)

* P values for linear trend across groups of gestational age were calculated by linear regression.

Abbreviations: NS – No significance.

Table 3. Characterization of PI values according to the occurrence of adverse outcomes and neonatal death.

	Adverse outcome			Neonatal death		
Hours of life	**Yes (n=32)**	**No (n=28)**	**p***	**Yes (n=9)**	**No (n=51)**	**p***
1 hour	0.73 (0.60 - 0.87)	0.90 (0.69 - 1.35)	NS	0.55 (0.35 - 0.86)	0.87 (0.67 - 1.10)	0.043
24 hours	0.70 (0.62 - 0.94)	0.90 (0.71 - 1.00)	0.009	0.70 (0.41 - 0.95)	0.80 (0.66 - 0.98)	0.005
48 hours	0.72 (0.57 - 0.89)	0.87 (0.75 - 0.99)	0.008	0.58 (0.52 - 0.67)	0.81 (0.67 - 0.90)	0.001
72 hours	0.79 (0.60 - 0.90)	0.91 (0.78 - 1.20)	0.005	0.74 (0.54 - 0.93)	0.88 (0.69 - 0.96)	0.043
168 hours	0.80 (0.69 - 0.93)	0.90 (0.80 - 1.00)	0.033	0.49 (0.34 - 0.75)	0.89 (0.71 - 1.00)	0.042

The results are presented as median (P25-P75).

**Mann-Whitney* U to access differences between newborns with and without adverse outcome and between newborns with and without neonatal death.

Abbreviations: NS – No significance.