Physiol. Res. 71: 607-614, 2022 *https://doi.org/10.33549/physiolres.934888*

Evaluation of Tissue Perfusion Status in Moderate to Late Preterm

Yuan ZHAO[1], Guang YANG[2], Suwen NIU[1], Min ZHANG[1], Fengyan GAO[1], Kezhan LIU[1]

[1]Department of Neonatology, Children's Hospital of Shanxi and Women Health Center of Shanxi, Affiliate of Shanxi Medical University, Taiyuan, China, [2]Department of Pediatric Medicine, Shanxi Medical University, Taiyuan, China

Received February 13, 2022
Accepted August 5, 2022
Epub Ahead of Print August 31, 2022

Summary

The aim of this study was to investigate the tissue perfusion status and circadian rhythm in moderately premature infants. As a prospective study, from July 2019 to October 2019, the haemodynamic stability of moderate to late preterm, including such indicators as perfusion index (PI), blood pressure (systolic/diastolic) (BP), heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2) and body temperature were monitored in the morning and at night within eight days after birth. There was no difference of statistical significance between PI values in the morning and at night (P>0.05). The HR from days six to eight after birth was higher than days one to three (P<0.05). The HR increased significantly on days seven and eight compared with days four and five (P<0.05). The BP from days three to eight was significantly higher than on day one (P<0.05), and the BP from days four to eight was higher than on day two. There was a weak positive correlation between the PI values and gestational age (GA) (r=0.097), HR (r=0.067) and time (r=0.284), and a negative correlation with SpO_2 (r=-0.113). The PI and HR of moderate to late preterm increased within eight days after birth. BP was relatively lower after birth and gradually increased to a stable level on days three to four. The PI and BP circadian rhythms associated with tissue perfusion were not established on day eight after birth.

Key words

Infant • Premature infant • Perfusion index • Pulse rate • Blood pressure

Corresponding author

Y. Zhao, Department of Neonatology, Children's Hospital of Shanxi and Women Health Center of Shanxi, Affiliate of Shanxi Medical University, No. 13, Xinmin North Street, Taiyuan City, Shanxi Province, China. E-mail: yz321yz@21cn.com

Introduction

Premature infants refer to infants born at less than 37 weeks of gestation [1]. Premature infants are deficient in body function due to inadequate maternal incubation time. At the same time, the change of living environment (from inside to outside the uterus) changes the hemodynamic state of premature infants. Hemodynamic instability may lead to perfusion changes, leading to various perinatal complications and even death [2-5]. Therefore, monitoring the hemodynamic status of preterm infants can master the perfusion level of preterm infants and provide a theoretical basis for clinical treatment.

In recent years, the wide application of pulse oximeter and noninvasive sphygmomanometer in neonatal intensive care unit has promoted the preliminary evaluation of neonatal blood circulation stability to a certain extent [6]. Blood pressure may not be a good indicator of peripheral perfusion due to the influence of receptor fluid and sympathetic nervous system [7]. Perfusion index (PI) is the ratio of pulsatile blood flow to non pulsatile blood flow in the monitored tissue. It has been proved to be a simple and noninvasive method to reflect the changes of peripheral perfusion [8,9]. Studies have shown that perfusion index plays an important role in the evaluation of disease severity, the screening of congenital heart disease, the early identification of neonatal shock, and so on [10]. In addition, circadian rhythm is the basic feature of life phenomena, and its changes can lead to pathological changes in human tissues [11]. Some studies suggested that the introduction of a robust light dark cycle in the neonatal intensive care

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unit can be used to guide the circadian rhythm system of preterm infants, which may be conducive to the growth and development of preterm infants [12]. However, there is no research on the correlation between PI and circadian rhythm in preterm infants.

Therefore, in this paper, correlations between the PI value and blood pressure (BP) (systolic/diastolic), heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2) and circadian rhythm were evaluated by continuously monitoring the data of preterm infants under stable conditions within eight days after birth.

Methods

The prospective study was conducted consecutively at the Neonatology Department of Children's Hospital of Shanxi from July 2019 to October 2019. The criteria for the subjects included: (1) moderate to late preterm at 32 to 36 weeks gestational age (GA) [13]; (2) admitted within six hours after birth; (3) an Apgar score of eight at 1 min and 10 at 5 min; (4) haemodynamically stable preterm newborns, characterized by smooth breathing, normal color and cry, normal position and activity, normal muscle strength and muscle tone; (5) no need for oxygen or respiratory support. Exclusion criteria included: newborns with infections, congenital heart diseases (CHD), NEC, continuous apnea episodes, hyperpyrexia (≥37.5 °C) and pneumothorax during hospitalization. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Children's Hospital of Shanxi.

All enrolled preterm infants were assessed by physical examinations and laboratory tests to clarify their physical conditions (smooth breathing, normal color and cry, normal position and activity, normal muscle strength and muscle tone) after admission, and every morning their conditions were checked. The pulse oximeter was placed on the foot of preterm newborns in a calm state for half an hour after feeding between 8:00-10:00 in the morning and 22:00-0:00 at night. The following data were then recorded: PI, HR, SpO_2, BP, RR and body temperature (T). The PI and HR were detected by a Masimo Radical-7 (USA) monitor, and SpO_2 was read three consecutive times in six seconds to obtain the average value.

Statistical analyses

The Kolmogorov-Smirnov test was used to quantify the normal distribution data, which were expressed as mean ± standard deviation (m ± SD). Two groups of parametric variables were compared by a *t*-test, and variance analysis was adopted for multi-group comparison. $P<0.05$ was considered statistically significant. The Pearson correlation coefficient was used to analyse the correlation of variables. Multiple linear regression analysis was applied to establish multiple linear regression equations. All statistical calculations were processed by *SPSS* 22.0 in Windows (IBM *SPSS* Statistic).

Results

A total of 95 preterm infants (32 to 36 weeks GA) were admitted to the Neonatology Department of Children's Hospital of Shanxi. One patient suffered from NEC on day eight after birth, one patient was suspected of sepsis due to persistent fever during hospitalization, and six patients were excluded due to incomplete information. Eighty-seven preterm infants, all infants were inborn, were involved in the study. There were 2 cases of placenta previa, 2 cases of mild anemia during pregnancy, 2 cases of mild pregnancy induced hypertension, 1 case of breech position, 2 cases of premature rupture of membranes >6 h, and 3 cases of test tube infants. Intrauterine growth restriction occurred in 3 cases. There were 16 cases of natural delivery and the rest were caesarean section. The average umbilical cord ligation time was (1.4±0.3) min. There were 48 M and 43F, with a mean GA of 34.4±1.1 weeks (W), BW (birth weight) of 2,142.6±384.8 g and a mean Apgar score of 9.8±0.4 at 1 min and 9.9±0.3 at 5 min after admission.

The mean PI, HR, BP, SpO_2 and T values of preterm infants eight days after birth are shown in Table 1. The PI values of the preterm infants were in a growing trend after birth, which increased significantly from days five to eight compared to days one and two ($P<0.05$), and the PI values on days seven and eight were much higher than those from days one to four ($P<0.05$). However, there were no significant differences among the PI values on the other days ($P>0.05$). The HR increased gradually after birth, with the values from days six to eight after birth much higher than those from days one to three ($P<0.05$). The HR increased significantly on days seven and eight compared with those on days four and five ($P<0.05$), and the HR increased significantly on day eight compared with day six ($P<0.05$). There were no significant differences between the HR values from days one to five ($P>0.05$). BP from days three to eight was significantly higher than on day one ($P<0.05$), days four to eight were higher than on day two, while the value stayed stable on the other days (*P*>0.05) (Fig. 1). The T values on days two and three after birth were higher than on day one. On day six, the value was lower than on day two (*P*<0.05), and for the remaining days, the values were similar (*P*>0.05). There was no significant difference between the RR and SpO_2 during the period.

BP (systolic/diastolic) in the morning and night were similar (t=1.691, P=0.194; t=0.370, P=0.543) from day one to day eight. The PI in the morning and night from days one to eight were similar (*P*>0.05) (Table 2). There was a difference of statistical significance for PI values among different GAs (F=6.233, P<0.001), and the PI value increased along with GA (Table 3).

The results of the Pearson correlation analysis showed a weak positive correlation between the PI value with GA (r=0.097), HR (r=0.067) and time (r=0.284) and a negative correlation with SpO_2 (r=-0.113, P<0.01) (Table 4). Multiple linear regression analysis was adopted with the PI as the dependent variable, while GA, HR, time and SpO_2 were independent variables. The calculation of the PI value under the non-standardised regression model was based on the following equation: PI = 2.253 + 0.057 × GA (w) + 0.062 × time (day) – 0.03 × SpO_2 (%) (Table 5).

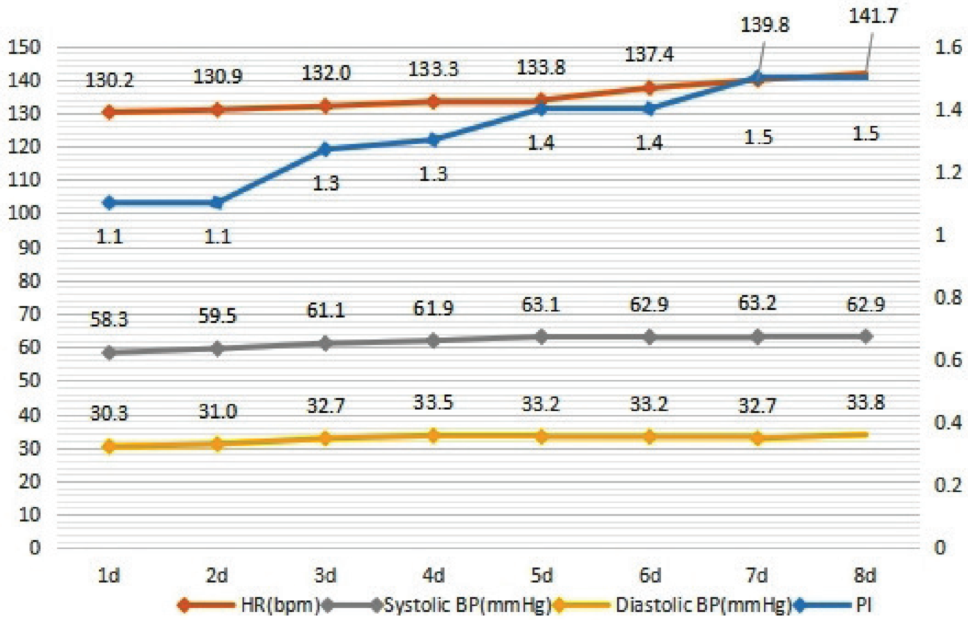

Fig. 1. Mean of PI, HR, BP values of preterm infants during 8 days after birth.

Table 1. Mean PI, HR, BP, SpO_2, T values of preterm infants during 8 days after birth.

Time (day)	PI	HR (bpm)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	SpO_2 (%)	RR (bpm)	T (°C)
1	1.1±0.5	130.2±10.7	58.3±7.9	30.3±6.1	97.6±2.1	44.8±8.2	36.8±0.4
2	1.1±0.5	130.9±10.1	59.5±6.2	31.0±5.5	97.3±2.4	43.4±7.0	37.0±0.2
3	1.3±0.5	132.0±12.1	61.1±7.2	32.7±5.9	97.5±2.2	42.9±7.3	37.0±0.3
4	1.3±0.5	133.4±14.6	61.9±8.6	33.5±6.6	97.1±2.2	43.2±6.7	36.9±0.3
5	1.4±0.6	133.8±15.2	63.1±7.6	33.2±4.7	97.5±2.1	44.6±7.2	37.0±0.3
6	1.4±0.5	137.4±12.3	62.9±6.0	33.2±5.6	97.2±2.7	44.0±6.6	36.9±0.8
7	1.5±0.6	139.8±12.4	63.2±6.0	32.7±4.5	97.7±1.9	44.5±7.3	37.0±0.3
8	1.5±0.5	141.7±12.2	62.9±7.1	33.8±6.7	97.5±2.3	43.5±7.4	36.9±0.3
F	12.872	18.589	10.411	7.185	1.262	1.609	3.442
P	<0.001	<0.001	<0.001	<0.001	0.266	0.129	0.001

Note: Tukey test for post-test.

Table 2. PI values in the morning and night.

Time (day)	**Morning**	**Night**	***t***	***P***
1	1.1±0.5	1.1±0.4	0.417	0.678
2	1.2±0.5	1.1±0.4	0.553	0.582
3	1.3±0.6	1.3±0.5	-0.188	0.851
4	1.3±0.6	1.3±0.5	-0.522	0.603
5	1.4±0.6	1.5±0.5	-0.82	0.415
6	1.4±0.5	1.4±0.4	-0.329	0.743
7	1.4±0.6	1.5±0.6	-1.397	0.166
8	1.5±0.6	1.5±0.5	-0.484	0.630

Table 3. PI values at different gestational ages.

GA (W)	**PI**	***F***	***P***
32	1.2 ± 0.4		
33	1.3 ± 0.5		
34	1.4 ± 0.6	6.233	<0.001
35	1.5 ± 0.6		
36	1.4 ± 0.6		

Table 4. Results of correlation analysis.

Variables	**HR (bpm)**	**SpO_2 (%)**	**PI**	**Systolic BP (mm Hg)**	**Diastolic BP (mm Hg)**	**RR (bpm)**	**T (℃)**	**GA (W)**	**BW (g)**	**Time (day)**
HR (bpm)	1.000									
SpO_2 (%)	-0.014	1.000								
PI	0.067*	-0.113*	1.000							
Systolic BP (mm Hg)	0.102*	0.026	0.025	1.000						
Diastolic BP (mm Hg)	0.114*	0.017	-0.018	0.296*	1.000					
RR (bpm)	0.110*	-0.036	0.019	0.069*	-0.055	1.000				
T (℃)	0.107*	-0.085*	0.002	0.023	0.026	0.081*	1.000			
GA (W)	-0.116*	-0.014	0.097*	0.027	-0.004	0.058	0.073*	1.000		
BW (g)	-0.102*	-0.072*	-0.011	0.084*	0.028	0.124*	0.030	0.287*	1.000	
Time (day)	0.361*	0.028	0.284*	0.197*	0.147*	0.017	0.004	-0.058	-0.011	1.000

Pearson test, * *P*<0.01.

Table 5. PI value under Multiple Linear Regression Model.

	B	**Std. Error**	*Beta*	*t*	*P*	*VIF*
Constant	2.253	0.760		2.965	0.003	
GA (W)	0.057	0.013	0.108	4.501	0.000	1.014
HR (bpm)	0.001	0.001	-0.032	-1.235	0.217	1.165
SpO_2 (%)	-0.030	0.006	-0.120	-5.048	0.000	1.002
Time (day)	0.062	0.005	0.305	11.938	0.000	1.153

Discussion

As an optical plethysmography parameter related to systemic perfusion, PI can serve as a sensitive reflection of the perfusion level of peripheral tissues, with a correlation to ventricular output [8,14]. Sivaprasath *et al.* proposed that the PI value was positively correlated to pulse pressure and systolic and diastolic BPs to various degrees among children aged 1~12 years. The decline of the PI value may predict impending shock but was not reliable for detecting hypotension [15]. It was found that the PI and HR of moderate to late preterm in the first eight days after birth were growing slowly at the points of time in our study, similar to findings from previous researches at home and abroad [16-18]. A positive correlation between the PI and HR was also found, but there was no significant correlation between the PI and BP. A physiological theory holds that BP is decided by cardiac output (heart stroke volume and HR) and peripheral vascular resistance (arterial compliance, ratio of systemic blood flow to systemic vascular volume) while neonatal BP is affected by multiple factors, including GA, age in days, BW, postnatal age, antenatal hormones, patent ductus arteriosus and temperature. So far, there is no unified definition of hypotension, weakening its credibility as an indicator for evaluation. Therefore, blood flow may be a better indicator of perfusion than BP. Neonatal myocardial contractile elements were significantly fewer compared with older children and adults. The immature myocardial cells tended to exhibit a higher basal contractile state and were more sensitive to cardiac afterload [19], hence the mobilization of the cardiac reserve may first be characterized by an increase in HR rather than BP despite the instability of systemic blood perfusion. All infants, especially premature infants, experience a series of haemodynamic changes during the transitional period after birth, including intrauterine to extrauterine changes, decreased pulmonary arterial pressure, shunting of blood flow from the systemic circulation to the pulmonary circulation, closure of the ductus arteriosus and increased volume of the systemic circulation. A HR value between 120 and 160 bpm coupled with weak myocardial contraction means that the cardiac reserve could be achieved by increasing HR to maintain tissue perfusion. Even in the absence of adequate tissue perfusion during the compensatory period of shock, peripheral blood vessels are responsive to ischemic stimuli *vi*a the sympathetic nervous system and humoral regulation. This is also one of the reasons that many newborns have tachycardia with or without increased BP and no hypotension during the compensatory period of shock. However, the inflammatory reaction during shock can seriously affect the microcirculation of adjacent tissues and skin, as indicated by the significant decrease of the PI value of peripheral blood flow in the first 45 s after ischemic stimulus [20]. Our study showed that the BP of moderate to late preterm was lower after birth and tended to stabilize on days three to four after birth. The PI and HR were recorded until day 10 after delivery in the preliminary study, which was found to be increasing, while there was not much change in BP. However, part of the data was eliminated because the patients were discharged. Therefore, arterial BP is not an accurate indicator to evaluate neonatal peripheral tissue perfusion, while PI, which reflects the ratio of arterial blood flow against non-arterial blood flow, is considered more reliable in this regard. Theoretically, the cardiac reserve capacity would increase with age. As the HR of infants and young children is lower than newborn infants, the HR value of preterm infants should gradually decrease and stabilize at a particular stage. However, at least on day eight after birth, we have not seen a drop in RP. Whether there is a similar trend of HR for term infants will be the focus of future studies.

Previous studies focusing on the PI values at different ages claimed the median PI of preterm infants with a GA<32 W was 0.9 on the first day after birth, 1.8 at 24 h after birth [21,22], and 3.0 for children 1~3 years old [14]. Our research showed that the

PI values for preterm infants with a GA 34~36 W were significantly higher than those with a GA 32~33 W, which would increase with age, suggesting that PI was related to the maturity of preterm infants. Meanwhile, the correlation analysis in our study showed that PI is related to GA (W), time (day) and SpO_2 (%), which were incorporated into the equation for the calculation of PI. In this equation, SpO_2 is easy to be measured as both GA and time are objective indicators. The results of the equation were similar to those of previous studies, making it a useful tool to predict the normal value of PI in moderate to late preterm within eight days after birth. It may also be applied to term infants and earlier preterm infants. Previous studies reported that a low PI value below 0.7 indicated left heart obstructive disease [23]. In our study, it was found that the PI value of a preterm infant suffering from severe NEC on day eight eventually led to surgery, before which the PI value dropped from 1.5 to a much lower level of 0.76, suggesting that PI could be a signal of low systemic perfusion level. The significant decline of the PI value during neonatal shock should be taken as a reference based on the normal value of individuals for liquid recovery treatment. The PI equation obtained in this study was helpful to evaluate the node of fluid resuscitation. We tried to resuscitate a 2-day-old preterm infant with a GA of 34 W with a PI value of 0.28 from severe shock. When the PI value gradually increased to 1.9, saline dilatation was terminated. Unfortunately, the infant developed a pulmonary haemorrhage. Therefore, it is necessary to explore the node of PI value for different infants during fluid resuscitation to improve the prognosis of infants in shock.

PI is the pulse index of blood flow, which is influenced by multiple factors, such as muscle contraction, temperature, blood shunting, invasive procedures, neonatal posture, circadian rhythm, etc. The data was measured when the infants were in a calm state with minimum invasive procedures to ensure the accuracy of data. Due to the circadian rhythm of the sympathetic-parasympathetic nervous system and various activities, BP dipping of adults and older children within 24 h is usually higher than 10 % [24,25], a phenomenon gradually formed as a result of the development and maturity of children and the effect of various factors. This paper found no difference in BP and PI values between morning and night within eight days after birth, probably due to the instability of the sympathetic-parasympathetic nervous system in the early postnatal period of preterm infants, which prevented the establishment of the circadian rhythms associated with BP and PI at the end of day eight after birth. Yet in the primary stage of the study, namely on day 10 after delivery, no difference was found in BP values between morning and night while there were differences for PI. However, the data were eliminated, given that the absence of some data might lead to a deviation. Therefore, it remains unknown whether the circadian rhythm related to PI of moderate to late preterm could be established 10 days after birth.

The present study had several limitations. First, the sample size of this study was very small. Thus, our results should be confirmed in a further study with more infants. Second, this study was only monitored for 8 days, and only two monitoring periods of PI per day were set in this study. Finally, the hormone levels of infants were not measured in this study. So the relationship between PI changes and hormone levels was not detected.

Conclusions

This study established an equation for calculating PI value by recording and analyzing GA, PI, HR, BP, SpO_2 and day values of preterm infants within 8 days after birth. The equation can be used to preliminarily evaluate the peripheral perfusion of middle and late preterm infants within 8 days after birth.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

We thank Chengli Wang, Dongfan Zhao and Qianqian Song (Department of Neonatology, Children's Hospital of Shanxi and Women Health Center of Shanxi, Affiliate of Shanxi Medical University) for recording data. No compensation was received from a funding sponsor for these contributions.

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