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Abstract

Echocardiography was combined with pulse oximetry plethysmography to investigate postnatal cardiovascular adaptation in late preterm and term infants. Median(IQR) pleth variability decreased over three days and similar, day2 15%(12-18%) preterm versus 16%(15-18%) term infants. Median(IQR) pulse transit time heart rate normalised was lower in term babies, day2 0.55(0.51-0.63) versus 0.64(0.62-0.68).

Keywords: pulse oximeter, plethysmogram, echocardiography, late prematurity, cardiovascular adaptation

1. Introduction

Previous research in cardiovascular adaptation to birth has been mainly in extremely preterm or term infants. There is emerging evidence that infants who are of late prematurity (33^{+0} to 36^{+6} weeks gestational age) are at increased risk of morbidity and of neurodevelopmental delay when compared to term infants [1]. However, changes in cardiovascular adaptive physiology in late preterm infants are not well understood even though this cohort makes up 70% of preterm births [2].

There is evidence that the identification of cardiovascular compromise, its treatment and outcomes are all improved when bedside echocardiography is utilised alongside clinical examination [3]. Superior vena cava flow (SVCF) and right ventricular output (RVO) are two well studied surrogates for systemic blood flow in neonates. Both have also been associated with important neonatal morbidities and even mortality. [4,5] .

The Pleth Variability Index (PVI) can be derived from the pulse oximetry plethysmographic trace and expresses the variability in the ratio of pulsatile and non-pulsatile components associated with respiration[6]. Reference values for PVI exist and it has been investigated as a potential non-invasive measure of hypovolaemia and of ductal shunt patterns in neonates[6,7]. Pulse transit time (PTT) is defined as the time it takes for an arterial pulse wave to travel between two sites in the body [8]. In the clinical domain, it can be measured from the period of time between the R wave on an electrocardiogram (ECG) and a particular point on a concurrently recorded plethysmographic trace derived from a pulse oximeter. [8]. PTT is inversely proportional to pulse wave velocity and it is shortened by vasoconstriction which causes the pulse wave to propel more rapidly [8]. A very small study using paired PTT measurement in 3 neonates found that PTT shortened in clinical states such as hypovolaemia associated with peripheral vasoconstriction [9].

The aim of this study was to investigate cardiovascular adaptation to birth in healthy late preterm (gestational age 33^{+0} to 33^{+6} weeks) and term infants ($\geq 37^{+0}$ weeks gestational age) using both established echocardiographic measures and non-invasive pleth derived measurements.

Material & Methods

2.1 Subjects & Study Design

The study recruited infants within 72 hours of birth who were born later than 33^{+0} weeks GA and receiving either routine care on the post-natal ward or special care on the Trevor Mann Baby Unit at the Royal Sussex County Hospital, Brighton. Infants were excluded if they were considered to be non-viable or chromosomal abnormalities were suspected, if they had congenital hydrops, cardiovascular malformations, or required surgical treatment. Ethical approval was gained from the City and East London National Research Ethics Committee and written informed consent was obtained from parents. Basic demographic and clinical data were obtained from inpatient notes. Assessments were performed once each day during the first three days of life starting from the time of recruitment. As not every baby was recruited immediately after birth, there were up to three sets of research measurements for each infant.

The following measurements were made at each assessment: heart rate, oxygen saturation, capillary refill time (CRT), blood pressure, echocardiography and plethysmography from pulse oximetry. Where measurements where not recorded or missed the most recent measurement completed for clinical purposes was used if available.

Plethysmographic (pleth) traces, were collected using a Nonin pulse oximeter module and SOMNOscreen™ Plus recording system (SOMNOmedics GmbH, Germany) to calculate the modified PVI (mPVI) and PTT as defined below. The oximeter probe was placed preferentially on the left hand, or if not possible, on one of the other limbs. Three electrodes were sited on the chest wall to record the ECG during plethysmographic measurement. The pleth traces were recorded on a compact flash memory card and subsequently downloaded to a computer.

PTT was calculated by measuring the time between the R wave on an ECG and the peak (Kotidis et al. 2021) on the concurrent plethysmographic trace (Figure 1a), using SOMNOmedics™ Domino software (Version 2.6. SOMNOmedics GmbH, Germany, 2013); the pleth trace peak is easier to define precisely than the mid-point of the pleth waveform increase in view of the high heart rate seen in neonates and hence used to measure PTT .[10] Because of the expected variability in neonatal heart

rate, the PTT measurements were also normalised (nPTT) for the heart rate by dividing the resulting PTT by the time difference between two R waves on the ECG at the time the PTT calculation was made. For each recording, the mean value from nPTT measurements was calculated.

Modified PVI (mPVI) assessments were calculated from the same 'raw' plethysmographic recording that was used for PTT. The plethysmographic trace was low-pass filtered in order to extract the respiratory cycle data required to calculate mPVI [11].

We developed software in MATLAB (The MathWorks Inc., Natick, Massachusetts, USA) to derive mPVI. Over a respiratory cycle the maximum pulse amplitude (PAmax) and minimum pulse amplitude (PAmin) from the unfiltered plethysmographic trace was selected by the observer. The mean of three mPVI measurements was calculated where mPVI was defined using the following equation:

$$mPVI = \left(\frac{PAmax - PAmin}{PAmax}\right) \times 100\%$$

Figure 1b provides a graphical depiction of how mPVI was calculated.

SVCF and RVO measurements were acquired using either a HD11 XE (Phillips Healthcare, The Netherlands) or a Sonosite Edge ultrasound machine (Fujifilm Sonosite Inc., Japan). SVCF and RVO measurements were taken according to methods described elsewhere [12]. M-mode measurements were used preferentially to measure SVC diameter, but when not possible B-mode measurements in a true left sagittal mid-parasternal window were used. All measurements were either performed at the bedside using the in-built software on the ultrasound machines or later using Intellispace PACs Enterprise programme (Phillips Healthcare, The Netherlands).

Data Analysis

There were two groups, late preterm infants between 33^{+0} and 36^{+6} weeks GA, and term infants ≥37 weeks GA. Statistical calculations were performed using Prism version 6.05 for Windows (GraphPad Software, La Jolla California USA) and a p-value of <0.05 was considered statistically significant. The Shapiro-Wilk test was used to assess for data normality (significance level of <0.05 applied). As data were not generally normally distributed, they are summarised as median and interquartile ranges (IQR), and the Mann Whitney U test was used to compare pooled data from late preterm and term cohorts. Paired comparisons using the Wilcoxon rank test were used to assess change in mPVI between day 1 and day 3 after birth. For categorical data the Chi Squared test was used.

2. Results

52 infants were recruited, but two were excluded, one due to incidental echocardiographic finding of a cardiac malformation, another due to inability to record the research measures. Table 1a outlines the demographics of the late preterm and term cohorts. Statistically significant differences were seen in gestational age, birthweight and gender between the late preterm and term cohorts. Infants in the late preterm cohort were more likely to be a twin or triplet and to have received antenatal steroids.

Changes in measurements of cardiovascular adaptation to birth: late preterm vs. term cohort

Table 1b shows that the mean blood pressure was significantly higher in the term cohort than in preterm cohort over the first 72 postnatal hours, whereas the heart rate, SVCF and RVO were significantly higher in the preterm infants after the first 24 postnatal hours. Significant differences in PTT were noted between preterm and term infants on day 1 and 3 of life. When PTT was normalised for heart rate; nPTT was significantly greater in late preterm infants between 24 to 48 hours of life (Table 1b and Figure 1c).

When performing pairwise comparisons there was a significant decrease between day 1 and 3 for the preterm cohort (n=15, p <0.0001 Wilcoxon paired test). The same comparison for term babies was not significant (p=0.1) however, there were only four paired measurements in that group.

3. Discussion

As expected blood pressure was significantly higher in the term infants compared with the preterm cohorts. There was little difference in mPVI between the groups which may reflect that the babies were normotensive with appropriate tissue perfusion as indicated by similar capillary refill times between the groups and over the three days. nPTT was lower in the term group indicating flow arriving peripherally at an earlier part of the cardiac cycle which may suggest an earlier increase in vascular tone in the more mature group. Interestingly there was a significant difference in nPTT seen between late preterm and term infants on the first and second days of life with nPTT values found o be higher in the late preterm cohort. We speculate that this could represent a more gradual increase in systemic vascular resistance (SVR) through vasoconstriction and also supported by previous research in neonates finding that measures of pulse transit time shorten in conditions that stimulate vasoconstriction [9].

Late preterm infants exhibited significantly higher measures of SVCF and RVO after the first 24 hours of life compared to term infants in this study. Heart rate was also significantly higher in the late preterm cohort; increasing heart rate is likely to be part of the mechanism for achieving the higher measure of systemic blood flow and is in keeping with prior research [13].

The changes in daily values for mPVI were similar between the two groups; this change was significant between day 1 and 3 in the late preterm cohort. Pleth variability index is influenced by both vascular filling and swings in pleural pressure related to work of breathing. Lung compliance is very low at birth, falls rapidly with the first breaths, and then improves more gradually over the first few days of life.[14] The changes we noted in mPVI in the late preterm group could be related to the respiratory rather than cardiovascular aspects of neonatal adaptation to birth, and are consistent with delayed improvement in lung compliance.

In sixteen traces PTT and mPVI analysis was not possible due to artefact on the ECG or plethysmographic traces. Both plethysmographic and echocardiographic measures are operator-dependent in terms of their interpretation and calculation. We have previously reported repeatability

of echocardiographic measures of systemic blood flow [12]. Another possible limitation is that vascular stiffness could be affected by gestational age; as vascular stiffness increases, pulse wave velocity increases thus shortening PTT [15]. Furthermore late preterm infants were more likely to receive antenatal steroids and it is known that these will have effects on the cardiovascular adaptation to birth, such as increasing blood pressure.

Further research is needed to establish reference values for nPTT and mPVI, including changes in the values of over the few days of life in a larger population including more premature infants. Developing automated measurement of nPTT and mPVI in order to explore this would help as performing the calculations manually is time-consuming. The plethysmographic traces used in this study are derived from standard technology widely used in many NICUs.

4. Conclusions

Our study shows that serial plethysmographic and echocardiographic measures are feasible in newborn infants and indicate that the cardiovascular adaption to birth in well late preterm infants can show differences from that of term infants. We observed that mPVI reduces over the first three days after birth as well as differences in nPTT between preterm and term babies. We speculate that these indices may provide novel insights into the cardiovascular and respiratory adaption of newborn infants.

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Conflict of interest statement: None declared

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Table 1a: Demographic data of Late Preterm and Term Cohorts

	Late Preterm Cohort (n=30)	**Term Cohort (n=20)**
Gestational age (weeks)	34*	40*
	(33-35)	(39-41)
Gender n (%)		
Male	9 (30)*	12 (54)*
Female	21 (70)*	8 (46)*
Birth weight (grams)	2150*	3455*
	(1823-2372)	(3190-3581)
Multiplicity n (%)		
Singleton	14 (46)*	20 (100)*
Twin	13 (44)*	0 (0)*
Triplet	3 (10)*	0 (0*
5 min Apgar	9 (8-10) [#]	9 (8-10)
Type of delivery n (%)		
Vaginal	22 (74)	13 (74)
C-section	8 (26)	7 (26)
Antenatal steroids n (%)		
None	8 (26)*	19 (95)*
Incomplete	2 (4)*	0 (0)*
Full	20 (70)*	1 (5)

Median (IQR), *$p \leq 0.05$, [#]n=29

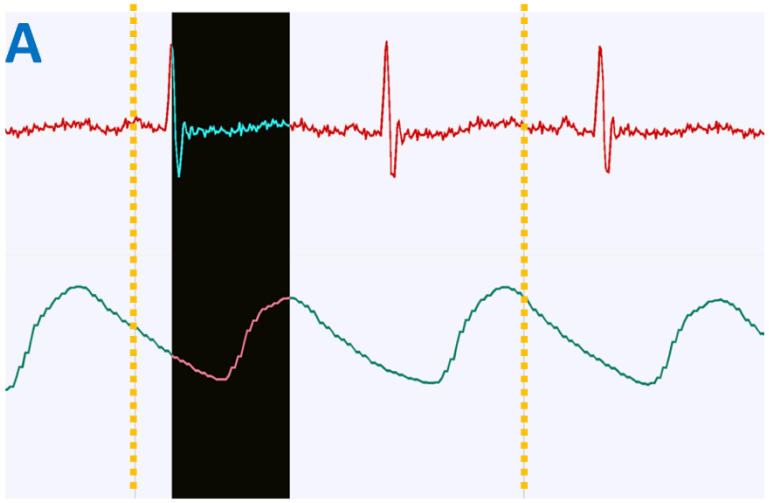
Table 1b: Daily comparisons of research measurements (median, IQR) between late preterm and term neonates

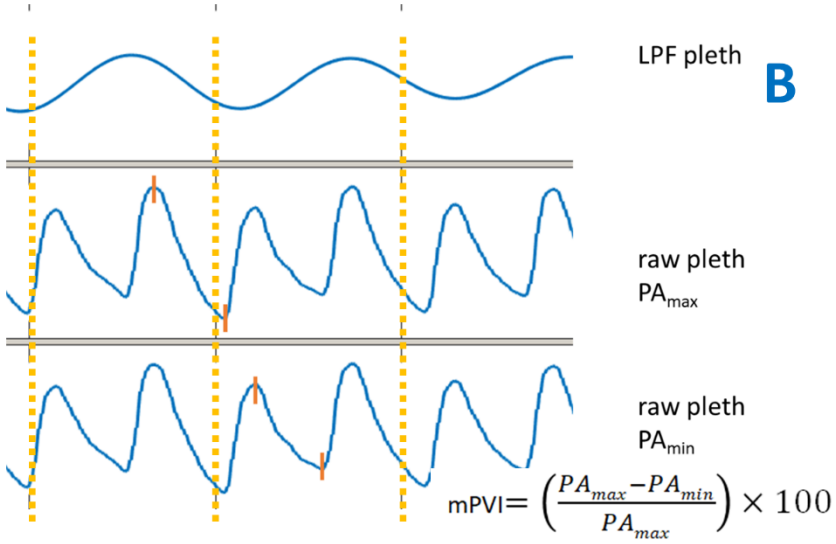
Bedside Measure	Cohort	Day 1	Day 2	Day 3	Between Cohort Comparisons (p-value)		
					Day 1	Day 2	Day 3
Age taken (hours)	Late preterm	21 (13-23)[¥]	40 (34-45)*	63 (54-68.5)[□]	0.12	0.02	0.1
	Term	14 (12-20)[+]	33 (28-36)[#]	56 (52.5-60)[#]			
Mean BP (mmHg)	Late preterm	37 (35-40)[¥]	42 (40-45)*	45 (42-58)[ł]	**<0.0001**	**<0.0001**	**0.002**
	Term	51 (43-57)[†]	51 (47-57)[Σ]	56 (51-65)[#]			
HR (Beat per minute)	Late preterm	132 (121-137)[¥]	132 (124-145)*	142 (125-150)[□]	0.66	**0.006**	**0.007**
	Term	127 (118-137)[+]	119 (105-127))[#]	123 (105-133)[#]			
CRT (Seconds)	Late preterm	2 (1.9-2.3)[¥]	2 (2.0-2.3)*	2 (1.8-2.2)[□]	0.99	0.86	0.02
	Term	2 (1.9-2.3)[+]	2 (2.0-2.3)[#]	2.4 (2.0-2.5)[#]			
Echocardiographic Measures							
SVCF (mls/kg/min)	Late preterm	149 (128-178)[¥]	133 (105-167)*	128 (97-150)[□]	0.06	**0.04**	**0.001**
	Term	118 (90-151)[+]	116 (72-126)[#]	84 (69-98)[#]			
RVO (mls/kg/min)	Late preterm	263 (241-329)[¥]	297 (250-368)*	283 (216-357)	0.09	**0.004**	**0.0003**
	Term	222 (195-319)[+]	213 (169-290)[#]	165 (143-236)[#]			
Plethysmographic Measures							
mPVI (%)	Late preterm	20 (16-24)[¥]	15 (12-18) [¥]	8 (5-12)*	0.96	0.56	0.28
	Term	20 (15-29)[Δ]	16 (15-18) [∞]	11 (8-15)[∞]			
PTT	Late preterm	0.29 (0.27-0.30)[¥]	0.28 (0.26-0.29)[¥]	0.27 (0.26-0.29)*	**0.05**	0.56	**0.036**

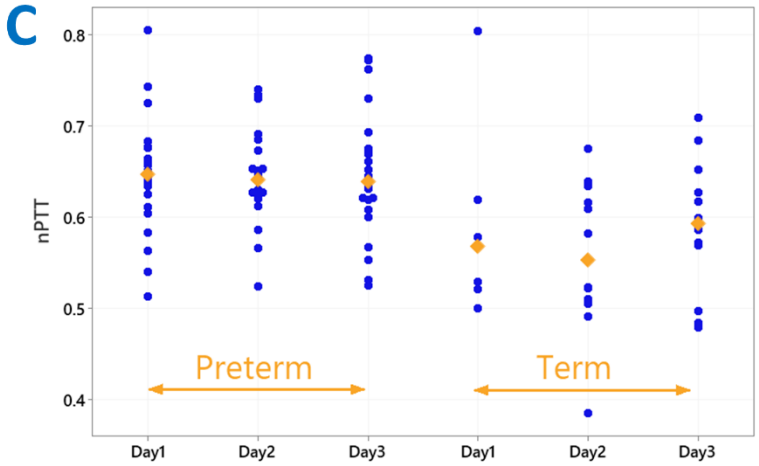
	Term	0.27 (0.22-0.29)$^{\Delta}$	0.30 (0.24-0.31)$^{\Sigma}$	0.28 (0.27-0.29)$^{\Sigma}$			
nPTT	Late preterm	0.65 (0.61-0.68)$^{¥}$	0.64 (0.62-0.68)$^{¥}$	0.64 (0.61-0.68)*	**0.04**	**0.002**	0.054
	Term	0.57 (0.52-0.62)$^{\Delta}$	0.55 (0.51-0.63) $^{\Sigma}$	0.59 (0.51-0.65) $^{\Sigma}$			

Median (IQR), $^{□}$n=24, ^{ł}n=23, *n=22, $^{¥}$n=21, $^{\#}$n=13, $^{\Sigma}$n=12, $^{\infty}$n=11, $^{+}$n=9, $^{\Delta}$n=7, †n=6.

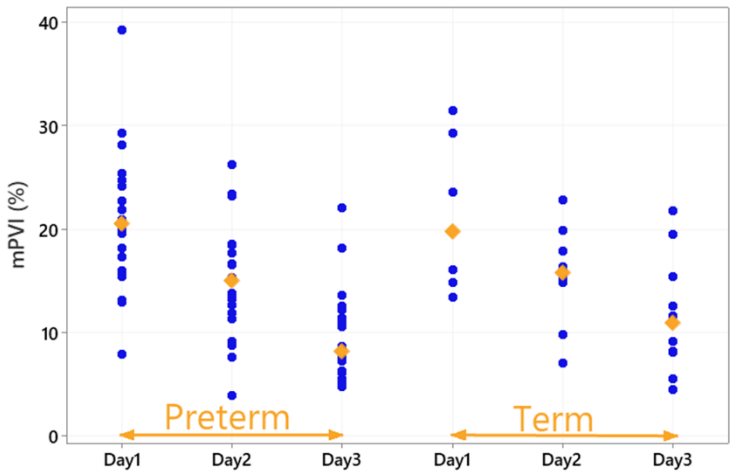
Table legend: 1a) Demographic data of Late Preterm and Term Cohorts 1b) Daily comparisons of median (Interquartile range IQR) measurements between late preterm and term neonates. Mean Blood Pressure (BP), Heart rate (HR), capillary refill time (CRT), Superior vena cava flow (SVCF), right ventricular output (RVO), modified Pleth Variability Index (mPVI), normalised Pulse Transit Time (nPTT).







nPTT over first 3 days after birth in preterm and term groups



mPVI over first 3 days after birth in preterm and term groups

Figure 1. a) PTT calculated as the time difference between the ECG r wave and the following maximum of the oximetry pleth trace. b) top trace low-pass filtered (LPF) oximetry trace, middle and lower traces show 'raw' pleth trace with middle trace showing points in red the difference of which gives PA_{max} and lower trace showing points in red the difference of which gives PA_{min}. Orange dashed vertical lines at 1 second intervals. c) Individual value plot of nPTT over the first three days after birth in preterm and term infants, median for each day shown as orange diamond symbol. d) Individual value plot of mPVI over the first three days after birth in preterm and term infants, median for each day shown as orange diamond symbol. The graphs for 1c and 1d were prepared with Minitab v19 (Minitab, LLC., USA).