



Cerebral and peripheral tissue oxygenation in stable neonates: Absent influence of cardiac function

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Abstract

Aim: Cardiac function is a major factor for tissue perfusion and therefore may affect the tissue oxygen saturation. Aim was to analyse possible associations between cardiac function parameters and cerebral and peripheral tissue oxygenation in neonates on the first day after birth.

Methods: For the present study, we analysed secondary outcome parameters of a previously performed prospective single centre observational study. The prospective study was conducted at the Medical University of Graz, Austria between September 2011 and June 2013. We included preterm and term neonates who were admitted to the neonatal intensive care unit and in whom simultaneous near-infrared spectroscopy measurements and echocardiography were obtained on the first day after birth. Cardiac function parameters were correlated to cerebral and peripheral tissue oxygen saturation and cerebral and peripheral fractional tissue oxygen extraction at the time of echocardiography.

Results: A total of 60 neonates of whom 47 were preterm and 13 were term (median gestational age: 34; IQR 33-35 weeks, mean birth weight: 2276 ± 774 grams) were included. There were no statistically significant correlations between cardiac function parameters and regional tissue oxygenation parameters.

Conclusion: In the present study, we found no correlation between regional tissue oxygenation and parameters of cardiac function in cardio-circulatory stable neonates on the first day after birth.

KEYWORDS

cardiac function, echocardiography, near-infrared spectroscopy, neonate, tissue oxygenation

Abbreviations: FTOE, fractional tissue oxygen extraction; LV, left ventricular; LVEF, left ventricular ejection fraction; NIRS, near-infrared spectroscopy; SO₂, oxygen saturation; SpO₂, arterial oxygen saturation; SVC, superior vena cava; TAPSE, tricuspid annular plane systolic excursion.

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1 | INTRODUCTION

Tissue oxygenation depends on oxygen delivery and oxygen consumption. The balance of oxygen delivery and consumption is especially essential in critically ill neonates to ensure survival and prevent severe tissue injury.¹ Oxygen delivery is affected by the haemoglobin content of the blood by oxygen saturation of the arterial haemoglobin and tissue perfusion, which depends on vascular resistance and cardiac function. Echocardiography is a useful diagnostic tool to non-invasively investigate cardiac function and haemodynamic status in neonates, even during the first week after birth.² Widely used parameters of cardiac function in neonates are left ventricular ejection fraction (LVEF),³ tricuspid annular plane systolic excursion (TAPSE)⁴ and superior vena cava (SVC) flow.⁵

Near-infrared spectroscopy (NIRS) is a non-invasive method to continuously measure tissue oxygenation and perfusion in regions of interest, such as brain and peripheral muscle tissue. Regional tissue oxygen saturation and fractional tissue oxygen extraction (FTOE) give information about dynamic changes of oxygen delivery and oxygen consumption, supporting healthcare professionals to respond directly to changing clinical conditions.⁶ Increasing FTOE, for example, might be due to a decrease of oxygen delivery or an increase of tissue oxygen consumption.⁷ Especially in the condition of shock, where centralisation takes place, peripheral tissue oxygenation might be impaired due to impaired peripheral perfusion. Therefore, peripheral NIRS measurement might be used for the recognition of early states of centralisation.⁸ An impaired cardiac function may cause impaired peripheral perfusion and tissue oxygenation whereas cerebral tissue oxygenation remains stable due to centralisation and autoregulation.

NIRS is performed by a skin-related sensor that emits near-infrared light (700-1000 nm) through the tissue, getting absorbed by oxygenated and deoxygenated haemoglobin in the smaller blood vessels.⁹ Due to the spatially resolved NIRS technology, vessels with a diameter below 0.1 mm contribute to signal.¹⁰ Absorption changes of the near-infrared light indicate changes in oxygenated and deoxygenated haemoglobin concentrations.^{11,12}

The available literature about the relationship of LVEF, TAPSE and SVC flow and tissue oxygen saturation in neonates is inconsistent. Ishii et al¹³ and Kissack et al¹⁴ found a significant correlation between NIRS data and cardiac function both in term and preterm neonates. In contrast, Moran et al¹⁵ and Victor et al¹⁶ could not show a relationship between cerebral and peripheral NIRS data and echocardiographic parameters in preterm infants.

The aim of the present study was to investigate possible associations between parameters of cardiac function and cerebral and peripheral regional tissue oxygen saturation in preterm and term neonates on the first day after birth.

As tissue perfusion depends on vascular resistance and cardiac output, we hypothesised that there is a relationship between LVEF, TAPSE and SVC flow and regional cerebral and peripheral tissue oxygenation in term and preterm neonates on the first day after birth.

Key notes

- We analysed possible associations between parameters of cardiac function and cerebral and peripheral regional tissue oxygenation.
- Term and preterm neonates (n = 60) in whom simultaneous near-infrared spectroscopy measurements and echocardiography was performed on the first day after birth were included.
- We found no correlation between parameters of cardiac function and cerebral and peripheral regional tissue oxygenation in cardio-circulatory stable neonates on the first day after birth.

2 | METHODS

2.1 | Design

For the present study, we analysed secondary outcome parameters of a previously conducted prospective single-centre observational study.¹⁷ The prospective study investigated the association between haemodynamic parameters and cerebral oxygenation of neonates with and without arterial hypotension.¹⁷ The study was approved by the Ethics Committee of the Medical University of Graz, Austria, and written parental consent was obtained prior to inclusion (ethics committee number: 23-402 ex 10/11).

2.2 | Participants

We included preterm and term neonates who were admitted to the neonatal intensive care unit during the study period between September 2011 and June 2013 and in whom we obtained simultaneous NIRS measurements and echocardiography on the first day after birth. The single exclusion criterion was haemodynamically significant congenital cardiovascular malformations.

2.3 | Routine monitoring

Pre-ductal arterial oxygen saturation (SpO₂) and heart rate were monitored continuously on the right wrist using pulse oximetry. Blood pressure was routinely measured invasively using an arterial line or non-invasively every 30 minutes at the right lower leg during NIRS measurements. Routine monitoring was performed using the IntelliVue MP50 (Koninklijke Philips).

2.4 | Near-infrared spectroscopy

In the prospective observational study,¹⁷ the continuous NIRS measurements were started within the first 6 hours after birth

and continued for 24 hours using the InVivo 5100 Cerebral/Somatic Oximeter monitor (Covidien). The neonatal sensors were placed on the right fronto-parietal head for cerebral regional SO₂ measurements and on the right forearm for peripheral regional SO₂ measurements. The sample time for NIRS measurements was 8 seconds.

For the analyses of the present study, the mean NIRS values of 1 hour, at the time of performed echocardiography, were used. The cerebral and peripheral fractional oxygen extractions were calculated as follows: cerebral FTOE = [(SpO₂ - cerebral regional SO₂)/SpO₂]; peripheral FTOE = [(SpO₂ - peripheral regional SO₂)/SpO₂].

2.5 | Echocardiography

To reduce performance bias, echocardiography was performed by a single investigator (CBH) using Vivid 7 Pro (GE Medical Systems) with a 10 MHz probe. For the analysis of the present study, the echocardiography, which had to be performed within the first 18 hours after birth, was used.

The LVEF as a marker of left ventricular (LV) systolic function was calculated as follows: $LVEF = [(end-diastolic\ volume - end-systolic\ volume)/end-diastolic\ volume] \times 100$.¹⁸ TAPSE, as a marker of longitudinal systolic right ventricular function, was measured by two-dimensional M-mode recordings from the apical four-chamber view with the cursor placed at the free wall of the tricuspid annulus. The maximum excursion of the tricuspid annulus during ventricular systole was determined.⁴ For assessment of the SVC flow, the integral of the Doppler velocity tracings was used to compute the mean velocity of blood flow. The average of the mean velocity of blood flow was calculated using five consecutive cardiac cycles. The average of the vessel diameter measurements was calculated using three cardiac cycles. SVC flow was calculated as follows: $SVC\ flow = (velocity\ time\ integral \times (\pi \times (mean\ SVC\ diameter^2/4) \times heart\ rate))/body\ weight$.⁵ The parasternal long axis view was used, and we angled to the right of the ascending aorta such as described in literature.⁵

LVEF is expressed as percentage, TAPSE is given in millimetres (mm) and SVC flow is expressed as mL/kg/min. A patent ductus arteriosus was considered as haemodynamically significant with a diameter >1.4 mm/kg.¹⁹

2.6 | Statistics

Mean values of heart rate, SpO₂, cerebral regional SO₂, cerebral FTOE, peripheral regional SO₂ and peripheral FTOE, which were assessed during the prospective observational study,¹⁷ were calculated for each hour after birth. The mean 1-hour values of cerebral regional SO₂, cerebral FTOE, peripheral regional SO₂, peripheral FTOE, heart rate and SpO₂ when echocardiography was performed

were used for the present analysis. Values are given as mean \pm SD or median (IQR) depending on data distribution. Cerebral regional SO₂, cerebral FTOE, peripheral regional SO₂ and peripheral FTOE were correlated with LVEF, TAPSE, SVC flow, respectively, using Spearman rank correlation coefficient. Since the included neonates differed widely in gestational age from 29 to 40 weeks and time of measurement was from the second hour after birth to the 18th hour after birth, analyses were also performed with correction for these parameters using partial correlation.

To determine which neonate was small for gestational age, we used the 10th centile of the 'Fenton 2013 Growth Calculator for Preterm Infants'.²⁰ A P value < .05 was considered as statistically significant. The analyses were performed using SPSS statistics versions 24 (IBM Corp).

3 | RESULTS

The original prospective single-centre observational study included 61 preterm and term neonates. During the study period, 544 neonates were admitted to the neonatal intensive care unit and thus eligible. For the study, however, 483 neonates were excluded since no research team was available, parents were not approached for informed consent or no informed consent was obtained. For the secondary outcome parameters analysis, one infant was excluded due to missing echocardiographic data on the first day after birth. A total of 60 neonates in whom simultaneous NIRS measurements and echocardiography were performed on the first day after birth were included to the present study. Of the included neonates, 47 (78%) were born preterm (median gestational age: 33, IQR 29-36 weeks, median birth weight: 1.963, IQR 990-3070 g) and 13 (22%) were born term (median gestational age: 39 (37-40) weeks, median birth weight: 3408, IQR 2430-4300 g). Of the included neonates, 10 (17%) were delivered vaginally and 50 (83%) were delivered by Caesarean section, thereof 10 mothers (20%) received general anaesthesia. Of the 60 included neonates, 30 (50%) were female and eight (13%) were multiples, nine (15%) were small for gestational age.

Regarding to the diagnoses, 21 (35%) were premature, 20 (33%) had transient respiratory distress of the newborn, nine (15%) had infant respiratory distress syndrome, seven (12%) had an infection and three (5%) had other diagnoses.

None of the included neonates suffered from myocardial or cardio-circulatory failure or had arterial hypotension during echocardiography. Of the included neonates, 24 (40%) needed respiratory support, 16 (27%) received nasal continuous positive airway pressure and eight (13%) were mechanically ventilated. None of the neonates received catecholamines for arterial hypotension. Sedation with midazolam was necessary in eight neonates (13%) during the performance of echocardiography.

Echocardiography was performed at 4, IQR 4-6 hours after birth. A patent ductus arteriosus was identified in 55 neonates and in one, it was considered to be haemodynamically relevant. Routine

TABLE 1 Demographic data, routine monitoring parameters, echocardiography data and cerebral and peripheral oxygenation data of the whole cohort (n = 60)

Demographic data	Mean ± SD or median; IQR
Gestational age (wk)	34; 33-35
Birth weight (g)	2276 ± 774
Age at measurement (h)	4; 4-6
Haemoglobin (g/dL)	17; 15-18
Routine monitoring	
Heart rate (bpm)	142 ± 13
SpO ₂ (%)	95 ± 3
Blood pressure mean (mm Hg)	42 ± 8
Echocardiographic data	
LVEF (%)	63 ± 7
TAPSE (mm)	7 ± 2
SVC flow (mL/kg/min)	77; 62-93
Regional tissue oxygenation	
Cerebral regional SO ₂ (%)	76 ± 11
Cerebral FTOE	0.20 ± 0.11
Peripheral regional SO ₂ (%)	87; 80- 92
Peripheral FTOE	0.08; 0.04-0.15

Note: Mean ± SD for normally distributed values and median: IQR for not normally distributed values.

monitoring parameters, echocardiography data and cerebral and peripheral regional tissue oxygenation data are presented in Table 1.

Correlation coefficients and *P* values of LVEF, TAPSE SVCflow and cerebral and peripheral regional SO₂ are demonstrated in Table 2 and Figures 1-4.

Even after correcting for gestational age and time of measurement, partial correlation analyses found no significant correlations between echocardiographic parameters and NIRS data.

4 | DISCUSSION

In the present study, we investigated potential associations between regional tissue oxygenation and echocardiographic parameters of

cardiac function in neonates on the first day after birth. This is the first study including cardio-circulatory stable term and preterm neonates with simultaneous echocardiographic LVEF, TAPSE and SVC flow and NIRS-derived cerebral and peripheral regional tissue oxygenation measurements. We found no significant correlations between parameters of cardiac function and cerebral and peripheral regional tissue oxygenation in our study cohort.

Sirc et al²¹ investigated 22 preterm neonates with a birth weight below 1250 g and found a significant negative correlation between cerebral tissue oxygenation index and SVC flow 6 hours after birth. Conversely, Moran et al¹⁵ described in 29 preterm neonates with a birth weight below 1500g a weak positive correlation between cerebral tissue oxygenation index and SVC flow on the first day after birth. Kissack et al¹⁴ observed in 36 neonates born before 32 weeks of gestation a significant negative correlation between cerebral FTOE and LV output.

The results of these studies are inconsistent with both positive and negative correlations between cerebral regional oxygenation and parameters of cardiac function. Further studies described no correlation of cerebral regional oxygenation and cardiac function parameters. In 27 very low birth weight neonates, there was no significant correlation between cerebral tissue oxygenation index and LV output or right ventricular output.¹⁵ Suresh et al¹⁶ also found no significant correlation between cerebral FTOE and LV output or right ventricular output in 17 very low birth weight neonates below 30 weeks of gestation. Janaillac et al²² investigated the correlation between cerebral regional SO₂ and LV output and right ventricular output in extremely preterm infants and found no correlation at several time points within the first 72 hours after birth. These studies with positive, negative and no correlations from rather small sample sizes suggest that the influence of cardiac function on cerebral oxygenation is weak especially in cardio-circulatory stable neonates. This assumption is emphasised by the present study. We included a larger cohort of cardio-circulatory stable term and preterm neonates compared with other studies, and we found no correlation between cerebral regional tissue oxygen saturation and echocardiographic parameters of cardiac function.

An independent factor affecting cardiac function and regional tissue oxygenation might be birth weight. Ishii et al¹³ investigated neonates born appropriate and small for gestational age by using cerebral NIRS and echocardiography during the first 3 days after birth. In neonates born appropriate for gestational age, there

TABLE 2 Correlation coefficients of cardiac output parameters and NIRS parameters

	LVEF (%)	<i>P</i> value	TAPSE (mm)	<i>P</i> value	SVC flow (mL/kg/min)	<i>P</i> value
Cerebral regional SO ₂ (%)	ρ = 0.173	.223	ρ = -0.032	.822	ρ = -0.083	.657
Cerebral FTOE	ρ = -0.099	.509	ρ = 0.039	.792	ρ = 0.106	.572
Peripheral regional SO ₂ (%)	ρ = 0.251	.089	ρ = 0.040	.787	ρ = -0.318	.087
Peripheral FTOE	ρ = -0.056	.729	ρ = -0.140	.378	ρ = 0.243	.213

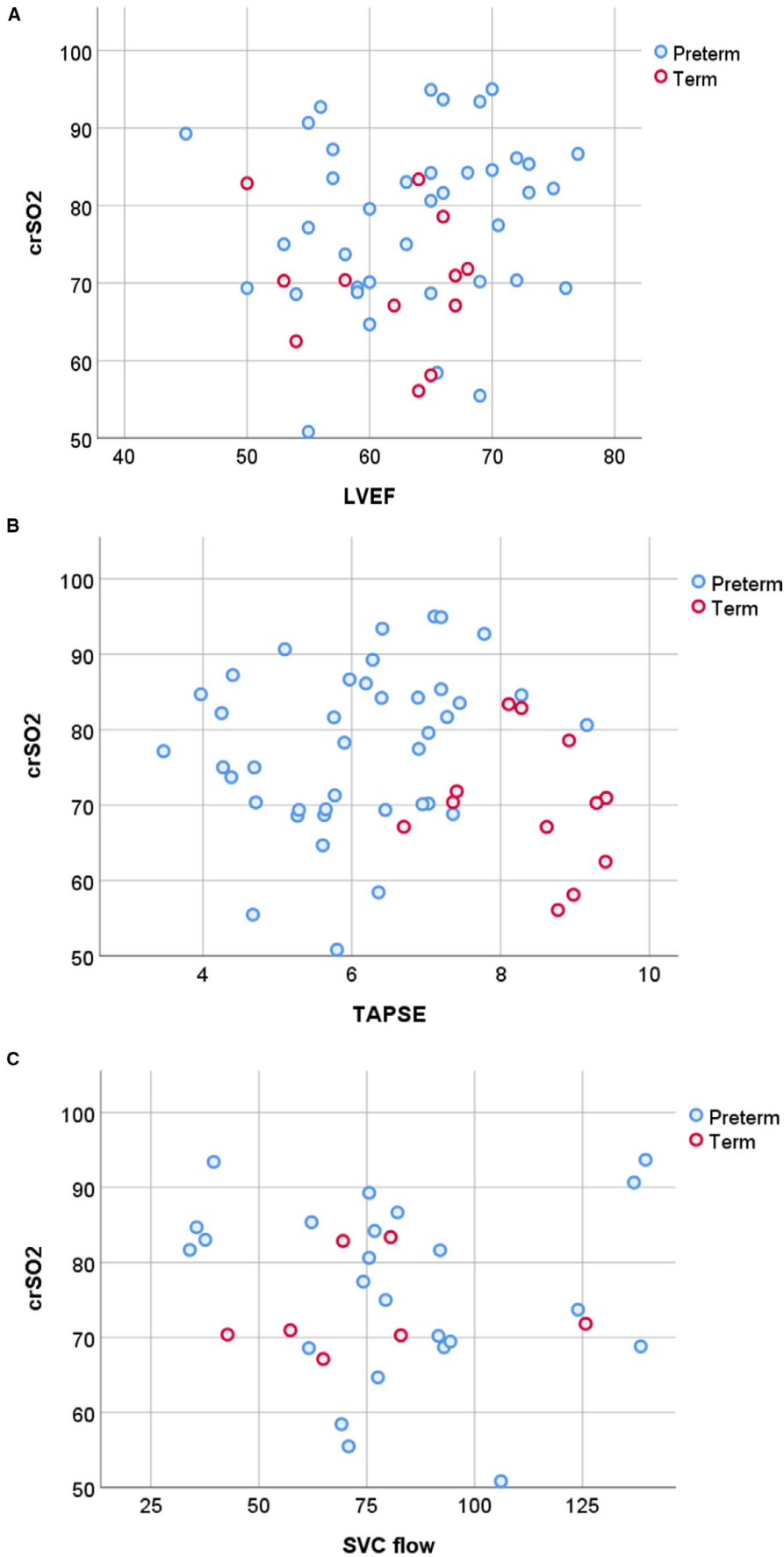
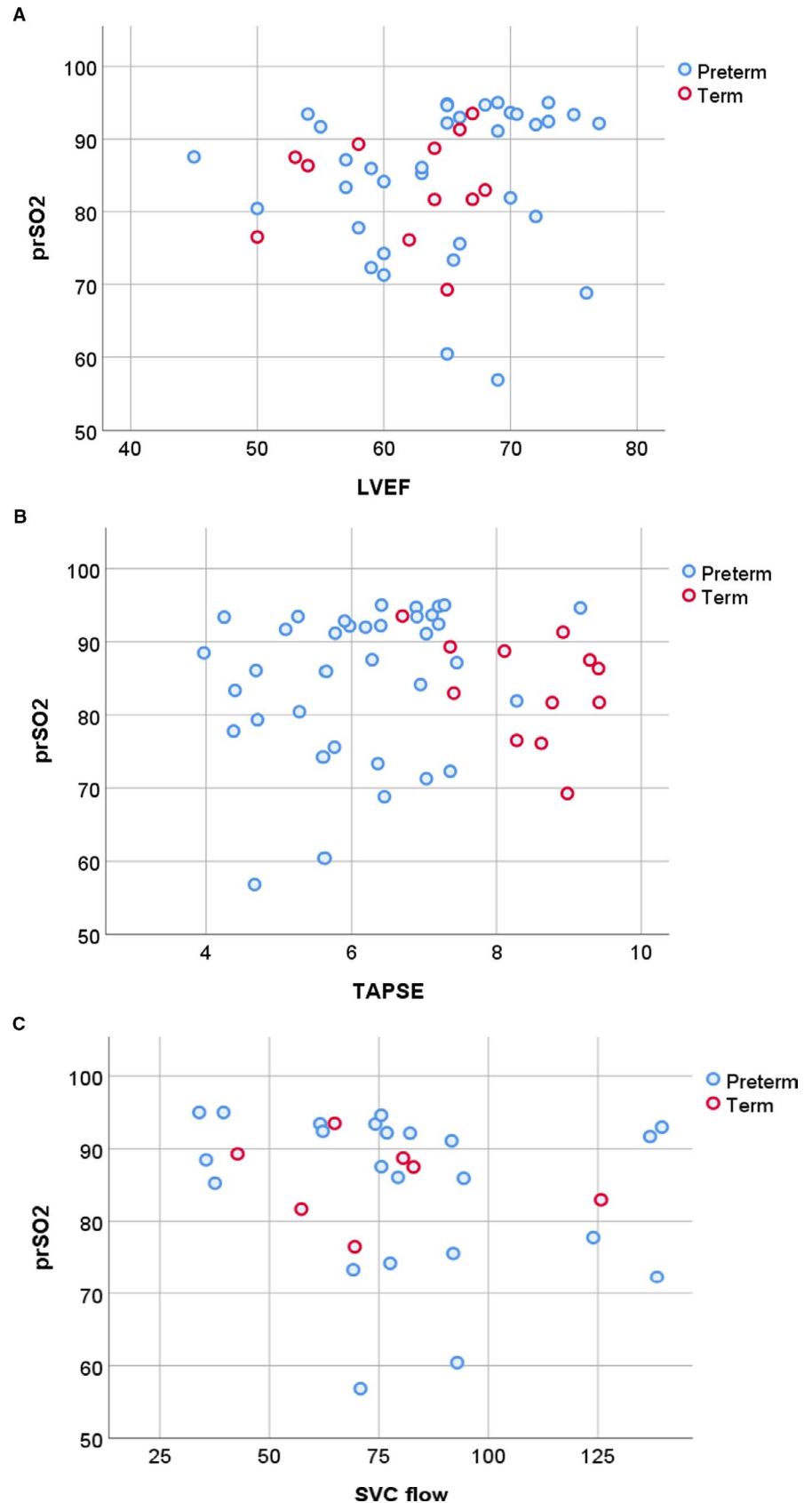


FIGURE 1 Scatter plot of cerebral regional SO2 and echocardiographic data: 1A) cerebral regional SO2 (%) and LVEF (%), 1B) cerebral regional SO2 (%) and TAPSE (mm), 1C) cerebral regional SO2 (%) and SVC flow (mL/kg/min)

FIGURE 2 Scatter plot of peripheral regional SO₂ and echocardiographic data: 2A) peripheral regional SO₂ (%) and LVEF (%), 2B) peripheral regional SO₂ (%) and TAPSE (mm), 2C) peripheral regional SO₂ (%) and SVC flow (mL/kg/min)



were significant positive correlations between cerebral regional SO₂ and LVEF at 12 hours and between cerebral regional SO₂ and LV output at 48 hours after birth. In neonates born small for

gestational age, no significant correlations between cerebral NIRS and echocardiographic parameters were observed.¹³ In the present study with mainly appropriate for gestational age neonates,

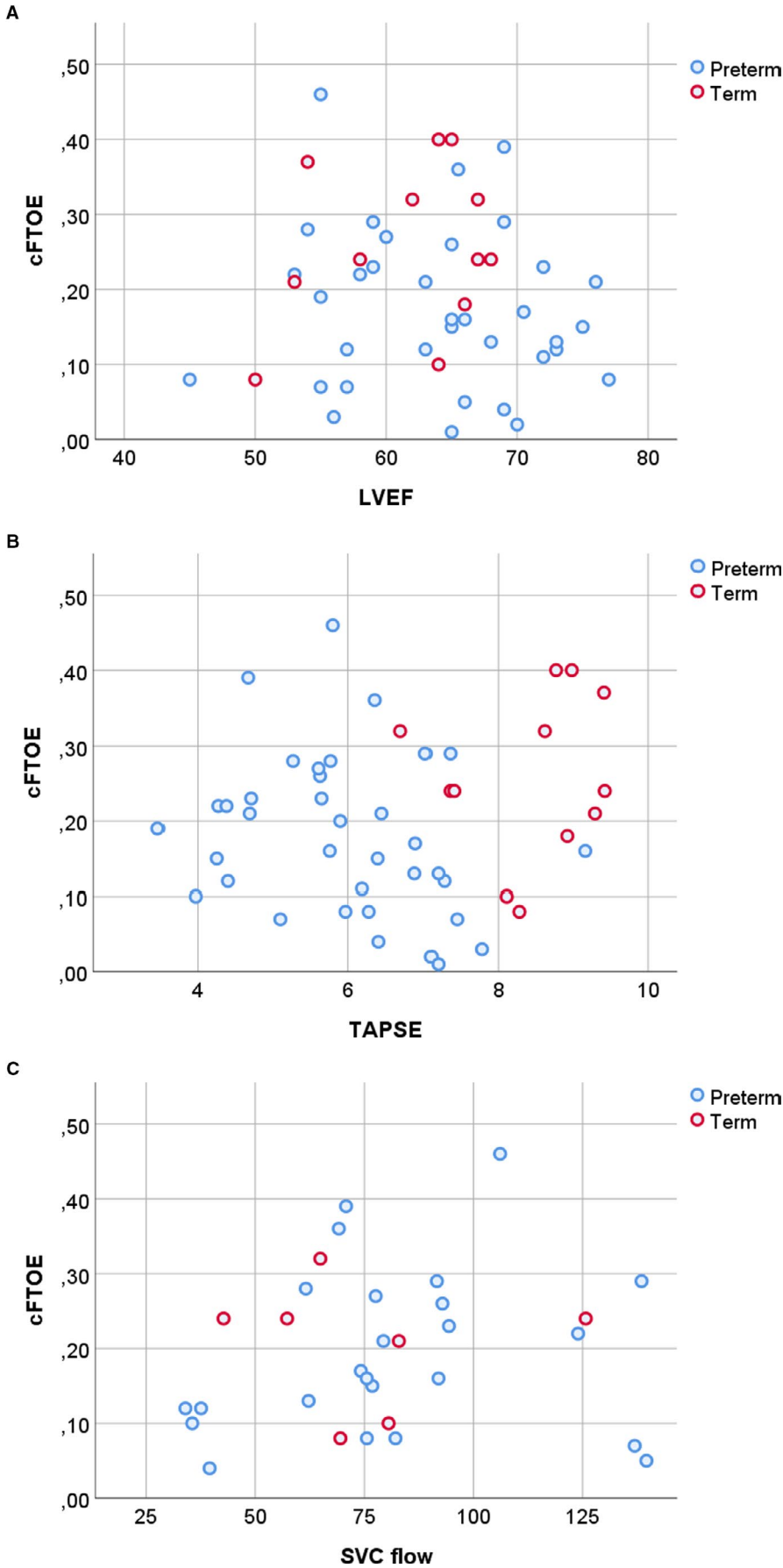
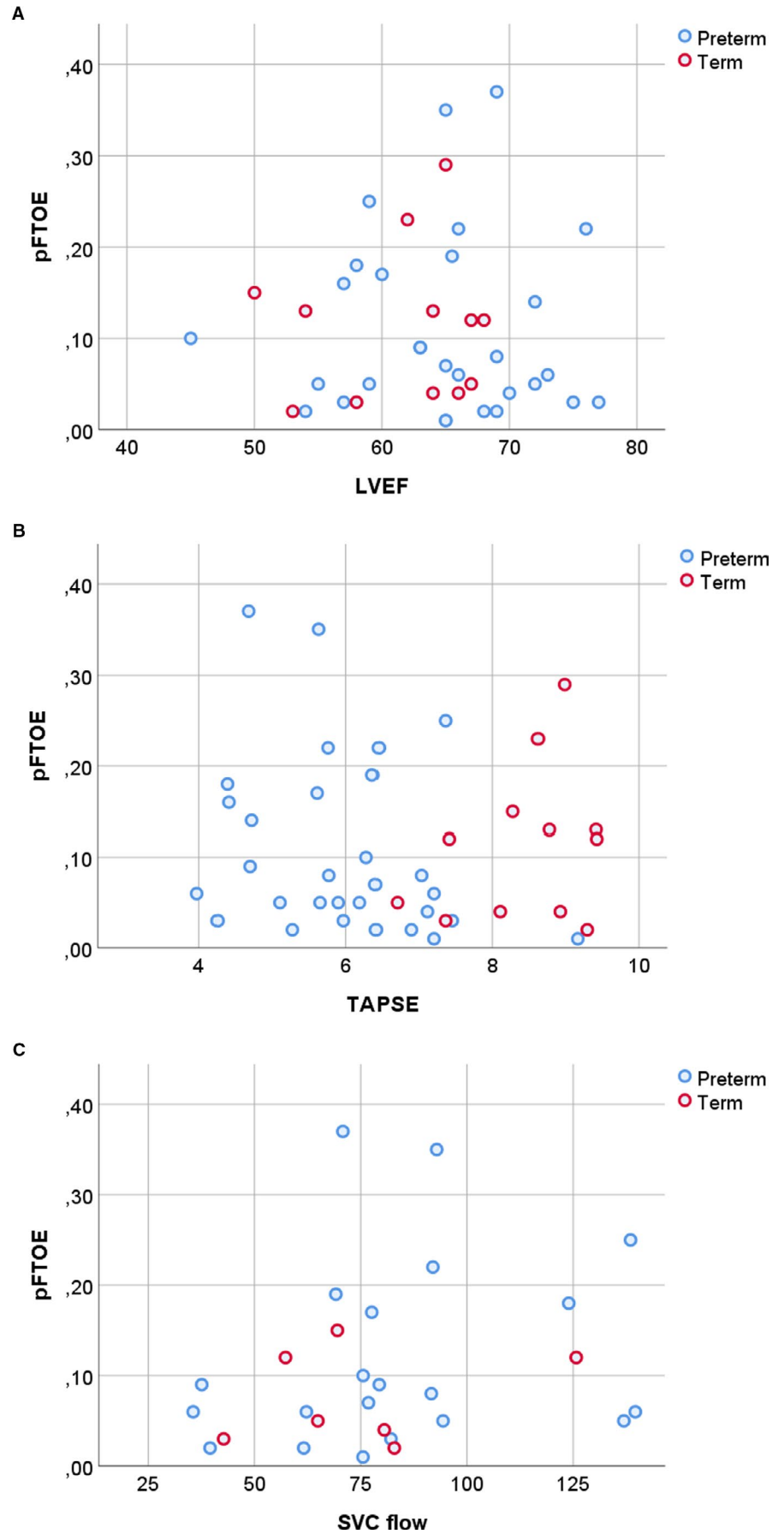


FIGURE 3 Scatter plot of cerebral FTOE and echocardiographic data: 3A) cerebral FTOE (%) and LVEF (%), 3B) cerebral FTOE (%) and TAPSE (mm), 3C) cerebral FTOE (%) and SVC flow (mL/kg/min)

FIGURE 4 Scatter plot of peripheral FTOE and echocardiographic data: 4A) peripheral FTOE (%) and LVEF (%), 4B) peripheral FTOE (%) and TAPSE (mm), 4C) peripheral FTOE (%) and SVC flow (mL/kg/min)



there were no correlations between cardiac function parameters and cerebral and peripheral NIRS parameters. These differences between studies may be explained by the different postnatal age in the study population.

Another influencing factor might be the postnatal age when neonates were investigated. In 2013, Sirc et al²¹ described a correlation between cerebral oxygenation and SVC flow 6 hours after birth; however, after 12 and 24 hours, there was no correlation anymore. In another study, there was also a correlation between cerebral oxygenation and LV output at a mean of 7 ± 3 hours after birth, which again could not be found on days two (29 ± 4 hours after birth) and three (53 ± 4 hours after birth).¹⁴ In contrast, Ishii et al¹³ found a correlation between cerebral oxygenation and echocardiographic parameters at 12 and 48 hours after birth in appropriate for gestational age neonates, but this significant correlation could not be shown at 3-6, 24 and 72 hours after birth. Hence, our findings with no correlation between cerebral oxygenation and LVEF, TAPSE and SVC flow at a median of 4, IQR 4-6 hours after birth are in accordance with the study by Ishii et al⁸

In regard to peripheral regional SO₂ and peripheral FTOE, we were not able to detect a significant correlation with LVEF, TAPSE and SVC flow. To our knowledge, there is only one study that has correlated peripheral blood flow measured by NIRS to echocardiographic parameters so far. Victor et al¹⁶ could not find a significant correlation between peripheral blood flow and echocardiographic parameters in 17 preterm neonates on day one after birth. This corresponds well with our findings, based on our investigation of peripheral regional SO₂ and peripheral FTOE in a larger number of neonates.

Our echocardiographic data correspond well to literature. According to the TAPSE reference values for preterm neonates published by Koestenberger et al,⁴ TAPSE data were within normal ranges in our study population. Moran et al¹⁵ assessed the SVC flow in 27 very low birth weight neonates during the first 24 hours after birth and measured a mean flow of 70.3 ± 39.5 mL/kg/min. Rather similar, Sirc et al²¹ described a mean SVC flow of 64.9 ± 19.1 mL/kg/min in 22 preterm neonates with a birth weight below 1250 g 24 hours after birth. Elsayed et al²³ published echocardiographic data of 32 haemodynamically stable preterm neonates with a mean gestational age of 30 ± 3 weeks, showing a mean LVEF of 72% (68-82 [10th percentile–90th percentile]), which is higher than the LVEF observed in the present study. The difference may be explained by the different postnatal age at the time of assessment: in the present study, neonates were measured on the first day after birth, while Elsayed et al¹⁸ assessed neonates at a mean age of 31 days after birth. There are alternative markers for left ventricular contractility described in literature. Baumgartner et al²⁴ investigated the ratio of effective arterial elastance and end-systolic chamber elastance in preterm infants during foetal to neonatal transition. However, none of the investigated parameters of cardiac function were associated with cerebral or peripheral tissue oxygenation. Therefore, it can be

speculated that any alternative parameter would reveal the same results.

This study had some limitations. Gestational age may have added some bias, but since partial correlation with correcting for gestational age did not reveal a significant correlation between echocardiographic parameters and NIRS data, we did not differentiate between preterm and term neonates to allow for a better overview. Echocardiography was always performed by the same investigator to reduce inter-individual variation. Nevertheless, intra-observer variability of up to 10% intrinsic error in echocardiographic measurements, as described in the literature,²⁵ cannot be ruled out completely. Since there is no gold standard for measuring 'tissue' oxygen saturation, accuracy of the device cannot be assessed for tissue oximetry.²⁶ Further on, different NIRS devices use different algorithms for regional SO₂ measurements, thus the absolute regional SO₂ values differ between devices and have to be compared with caution.²⁷ However, precision or test-retest variability is similar compared with pulse oximetry.²⁸

As mentioned above, the parameters of cardiac function were within normal ranges in our cohort; therefore, we can only speculate about effects of impaired cardiac function on cerebral and peripheral regional tissue oxygen saturation. Impaired cardiac function might lead to centralisation with normal cerebral tissue oxygenation and impaired peripheral tissue oxygen saturation.

Among the strengths of this study is the larger sample size compared with the published literature and the analyses of several echocardiographic parameters such as LVEF, TAPSE and SVC flow. Those parameters surrogate as markers of LV and RV systolic cardiac function. This is the first published correlation analysis between TAPSE and tissue oxygenation.

5 | CONCLUSION

In conclusion, we did not find any correlation between measures of cerebral and peripheral regional tissue oxygenation and cardiac function in cardio-circulatory stable preterm and term neonates on the first day after birth. Variations of cardiac function within normal ranges seem to have no influence on cerebral and peripheral regional tissue oxygenation in neonates. Thus, as far as regional tissue oxygenation is concerned, regional vascular resistance, microcirculation, autoregulation of the newborn and oxygen consumption seem to compensate for variations in cardiac function within normal ranges.

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CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

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