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CLINICAL RESEARCH ARTICLE

Renal oxygenation measured by near-infrared spectroscopy in preterm neonates in the first week

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OBJECTIVE: To describe renal regional saturation of oxygen ($RrSO_2$) values during the first week of life for preterm neonates born at <32 weeks gestational age (GA).
METHODS: $RrSO_2$ values recorded over the first week of life using near-infrared spectroscopy were retrospectively analyzed in this two-center cohort study of preterm infants without known congenital anomalies of the kidney.
RESULTS: A cohort of 109 neonates with a median GA of 26.9 weeks and a median of 120 (IQR: 87–141) hours of continuous $RrSO_2$ monitoring were included. Separately fitted trends in $RrSO_2$ did not differ ($p = 0.52$) between sites and demonstrated a consistent decrease in $RrSO_2$ by 20 points (95% CI: 9.6–30.1) during the first 60 h of life, followed by a stabilization of $RrSO_2$ thereafter. $RrSO_2$ baseline trends increased by 2.1 (95% CI: 0.8–3.3) percentage points for each additional week GA between 24 and 32 weeks GA.
CONCLUSIONS: Despite differences in adjusted $RrSO_2$ values between sites, profiles over time are consistent, allowing for the determination of $RrSO_2$ trajectories in preterm infants. This expected pattern of $RrSO_2$ changes in the first week may help guide future investigations and interventions to identify and reduce kidney injury in the preterm neonate.

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IMPACT:

- Renal regional saturation of oxygen ($RrSO_2$) slowly decreases during the first 60 h of age in <32-week preterm neonates.
- While site differences were identified with respect to absolute values, $RrSO_2$ trends from two different centers were not different.
- Lower gestational age neonates have lower $RrSO_2$ levels during the first week.

INTRODUCTION

Premature birth continues to be a major public health problem with one in ten babies born <37 weeks. Long-term studies of 40- to 50-year-old adults born prematurely show two to three times increased risk of chronic kidney disease (CKD[1]). The etiology of this increased risk is multifactorial, but likely begins at birth and in the Neonatal Intensive Care Unit (NICU[2]). Premature neonates have reduced nephron endowment, increased nephrotoxic medication exposures, and increased acute kidney injury (AKI) compared to term neonates[3]. Unfortunately, our monitoring of kidney function in the NICU is limited to tracking urine output, which is notoriously difficult, and utilizing frequent serum creatinine checks that requires relatively large blood sampling for premature neonates[4]. A method to monitor kidney health and function non-invasively that more effectively detects sudden changes and alterations is needed to protect the limited nephrons and reduce the long-term risk of CKD.

Somatic tissue oxygenation monitoring with near-infrared spectroscopy (NIRS) is increasingly being used in neonates to detect changes in physiology that could impact clinical outcomes[5], including necrotizing enterocolitis[6,7], diagnosis of a hemodynamically significant patent ductus arteriosus[8], and neonatal encephalopathy[9]. Specifically, noninvasive measurement of renal regional saturation of oxygen ($RrSO_2$) has been feasible in preterm neonates and values less than 50 have been associated with the subsequent development of AKI[10,11]. However, normal changes in $RrSO_2$ in preterm neonates at different gestational ages (GAs) in the first week have not been well described outside of single-center studies[12–14].

To address this gap, we sought to describe $RrSO_2$ values during the first week of age for preterm neonates born at less than 32 weeks GA at two centers. We hypothesized that given rapidly changing kidney physiology and the wide range of renal development associated with varying preterm GAs[4,15–18], $RrSO_2$ would likely change significantly in the first week.

METHODS

This two-center study was conducted using existing cohorts of preterm neonates admitted to the level III NICU at UnityPoint Health-Meriter Hospital (UPHM) (Madison, WI) and the level IV NICU at Lucile Packard Children's Hospital Stanford (LPCH) (Palo Alto, CA) from 2016 to 2019. The

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Table 1. Study sample demographics.

	Both sites ($n = 109$)	UnityPoint Health-Meriter Hospital ($n = 35$)	Lucile Packard Children's Hospital Stanford ($n = 74$)	p value
Estimated GA (weeks)				
Mean (SD)	27.1 (2.05)	28.5 (2.43)	26.5 (1.49)	<0.001
Median [IQR]	26.9 [25.6, 28.5]	29.0 [26.4, 30.4]	26.5 [25.6, 27.6]	<0.001
Birth weight (kg)				
Mean (SD)	0.97 (2.05)	1.13 (0.39)	0.89 (0.27)	0.002
Median [IQR]	0.89 [0.72, 1.17]	1.10 [0.82, 1.44]	0.82 [0.69, 1.06]	0.001
Apgar score				
1 min, med. [IQR]	5 [2, 6]	4 [2, 6]	5 [2, 7]	0.48
5 min, med. [IQR]	7 [6, 8]	7 [6, 8]	7 [6, 8]	0.45
Change med. [IQR]	2 [1, 4]	2 [1, 4]	2 [1, 4]	0.93
Sex				
Male, *n* (%)	57 (52%)	19 (54%)	38 (51%)	0.94
Mode of delivery				
Cesarean section, *n* (%)	70 (64%)	22 (63%)	48 (65%)	1

data on subjects from UPHM were obtained from a blinded prospective study where all neonates <32 weeks GA, and with chronologic age <48 h at the time of enrollment were eligible for inclusion in the study. Exclusion criteria were infants with known congenital anomalies of the kidney, investigator unavailability to consent parent or clinician decision that NIRS monitoring was not suitable due to clinical condition. The data on subjects from LPCH were obtained from unblinded standard clinical monitoring in all neonates <29 weeks GA. Each center received approval from their institutional review board to participate in this study. The primary study aim was to assess trends in $RrSO_2$ in the first week of life measured with continuous renal NIRS monitoring.

Both centers used the same technique for NIRS monitoring. A neonatal sensor connected to an INVOS 5100C NIRS monitor was placed on the infant's right or left flank (to measure $RrSO_2$). The sensor was placed directly over Mepitel transparent adhesive dressing to aid with skin protection. Clinicians and staff were blinded to the $RrSO_2$ values at UPHM. At LPCH the values were visible but there were no guidelines for addressing $RrSO_2$ values during the time period of the study. Sensors were kept in place until the infant was 7-days old (168 h of life (HOL)) and $RrSO_2$ values were recorded every 5–30 s.

Patient and maternal demographics and perinatal details were obtained from the electronic medical record. $RrSO_2$ data were subsequently processed to give hourly averages based on hours of life.

Statistical methods

Continuous demographic characteristics were summarized using means and standard deviations or medians and interquartile range; categorical features were described using frequencies and percentages. Distributions of continuous and categorical variables were compared between sites using χ^2 tests, *t*-tests, non-parametric (rank-sum) procedures, or multivariable regression if the characteristic was thought to be jointly influenced by several factors. Hourly readings of $RrSO_2$ over the first 168 HOL were analyzed using generalized estimating equations[19,20] for a Gaussian family, probit link function, and with autoregressive correlation structure for repeated measures over time. HOL (2–168) entered the model as a six-knot restricted cubic spline to allow for linear and non-linear behavior. Other demographic features (e.g., sex, GA, birth weight, mode of delivery) were examined to see whether they had any influence on trends. Models utilized a robust "sandwich" estimator of variance for estimation and testing of relevant effects to guard against possible misspecification of the correlation structure. A p value <0.05 was considered significant. Trends were assessed separately across centers and compared.

RESULTS

A total of 109 neonates (UPHM ($n = 35$, 32%) and LPCH ($n = 74$, 68%)) were included in the study. Demographic information for the full cohort and individual centers is listed in Table 1 along with comparisons between centers. Average GA for UPHM neonates was almost two weeks greater than those from LPCH (28.5 ± 2.43 vs. 26.5 ± 1.49, 95% CI: 1.07–2.86; $p < 0.001$), and this was associated with a 25% increase in median birth weight (95% CI: 9–44% increase; $p = 0.001$). Sex and method of delivery appeared roughly balanced between the two locations, with slightly more than half of neonates being male and just under two-thirds of births by Cesarean section delivery. There was no difference in birth weight once adjusted for GA, sex, and mode of delivery.

Recording of $RrSO_2$ took place over the first 168 HOL with occasional interruptions or delayed starts. The earliest recordings began at 2 and 5 HOL for LPCH and UPHM, respectively, with 75% of neonates from each site starting no later than 14 (LPCH) or 44 (UPHM) HOL. In addition to starting earlier, LPCH monitoring tended to have longer uninterrupted blocks of continuous measurements (median [IQR] 122 [88–145] continuous hours) compared to UPHM (115 [80–124] continuous hours).

Mean percent $RrSO_2$ for neonates at LPCH exhibited a non-linear relationship with time during the 168 HOL ($\chi^2_4 = 11.7$, $p = 0.019$) but with no strong association with GA ($p = 0.065$), sex ($p = 0.93$), or mode of delivery ($p = 0.52$). At UPHM, the pattern of mean percent $RrSO_2$ over time showed evidence ($\chi^2_4 = 17.0$, $p = 0.002$) of non-linear behavior and a positive association involving GA ($p = 0.034$). Sex and mode of delivery were not strongly associated with trends in the mean response ($p > 0.40$ for each). Figure 1 demonstrates these patterns for LPCH (Fig. 1a) and UPHM (Fig. 1b). Apgar score at 5 min had no association ($p = 0.856$) with $RrSO_2$ after adjusting for the other elements in the model (HOL, location, GA, mode of delivery and sex).

Trends (linear [one term] and non-linear [four components]) in percent $RrSO_2$ did not statistically differ between locations ($\chi^2_5 = 4.18$, $p = 0.524$; test of center*trend interaction). Despite a strong difference between centers in absolute values ($p = 0.001$), the mean trend for LPCH consistently remained higher than UPHM by 6.6–15.5%, with the greatest separation occurring around 50 HOL (Fig. 1). Each center showed elevated initial $RrSO_2$ values followed by a nadir reached at 60 HOL with a subsequent plateau in $RrSO_2$ values for the remaining hours. Given the statistically similar trends in $RrSO_2$ values between centers, the absolute expected change in percent $RrSO_2$ at various time points were determined (Fig. 2). The change in percent $RrSO_2$ is expected to be slightly less than 5 points in the first 2–12 HOL and 5 points from 12 to 24 HOL, with decreased changes in percent $RrSO_2$ in subsequent time intervals until reaching no change around 72 HOL, which corresponds with the plateau period previously described. The

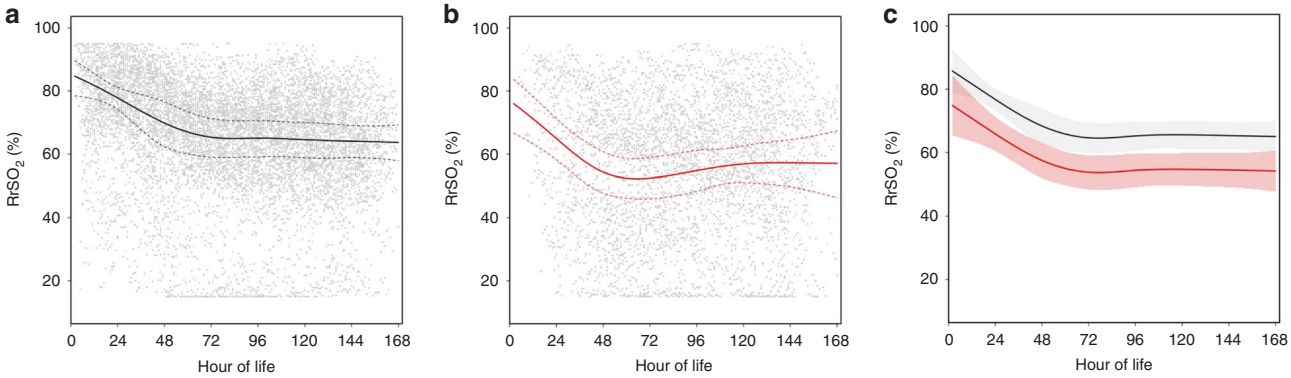

Fig. 1 $RrSO_2$ trends by center. a, b— The solid lines represent the mean $RrSO_2$ over time with pointwise 95% confidence limits for the mean at each HOL given by dashed lines; gray points are individual measurements from each neonate at the centers (**a** - Lucile Packard Children's Hospital Stanford, **b** - UnityPoint Health-Meriter Hospital). Overall common behavior $RrSO_2$ means (**c**)—each center represented with red (UnityPoint Health-Meriter Hospital) and black (Lucile Packard Children's Hospital Stanford) with shaded regions representing the 95% confidence intervals for the mean $RrSO_2$.

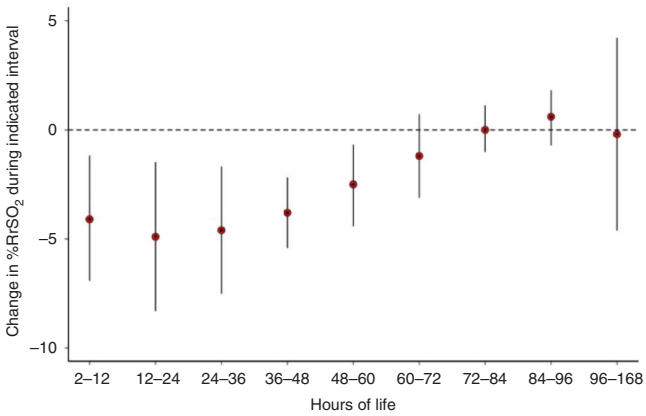

Fig. 2 Change in percent $RrSO_2$—shown over several early (2–60 HOL) and later (60–168 HOL) time intervals. Solid symbol is the average change with 95% CI as whiskers; intervals for which the 95% CI excludes zero (horizontal dashed line) are significant at the 0.05 level.

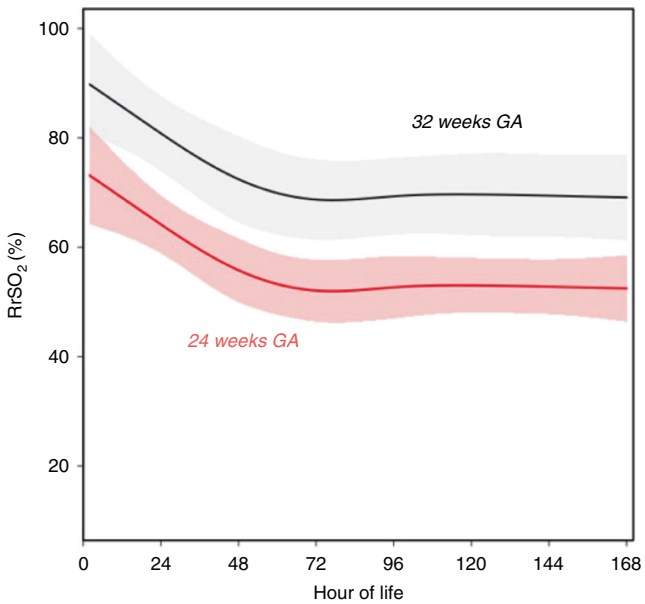

Fig. 3 Mean $RrSO_2$ by gestational age—with shaded regions representing the 95% confidence intervals for the mean $RrSO_2$.

cumulative reduction of $RrSO_2$ from 2 to 60 HOL is 20 percentage points (95% CI: 9.6–30.1; $p = 0.05$).

Stratification of $RrSO_2$ trends by GA after controlling for center, sex and mode of delivery is shown in Fig. 3. We found that the baseline $RrSO_2$ trend curve increases 2.1 percentage points (95% CI: 0.8–3.3; $p = 0.001$) for each additional week of gestation between 24 and 32 weeks.

DISCUSSION

In this two-center cohort study evaluating $RrSO_2$ trends over the first 7 days in <32-week preterm infants, we found that absolute $RrSO_2$ decreased by 20 points in the first 60 h of age followed by a plateau for the remaining days in the first week. Despite absolute center differences, both center cohorts followed a similar decreasing $RrSO_2$ trend after birth. After controlling for site, sex, and delivery method, we found that the $RrSO_2$ baseline increased by 2.1 percentage points for each additional week of gestation between 24 and 32 weeks.

The overall decrease in $RrSO_2$ seen in the first 60 HOL for these infants may be explained by expected physiologic changes in the kidney after birth. Typically, in utero kidney blood flow accounts for 3–5% of cardiac output and after birth, and increases to 10% in the first week and about 20% of cardiac output as adults[21]. The increase in tissue oxygenation due to the increased blood flow is likely offset and overcome by the increase in oxygen extraction due to a rapid increase in glomerular filtration rate (GFR) and increase in aerobic metabolism driven by an increase in ATP-dependent pumps[21]. It is likely that this increase in GFR results in increased oxygen utilization and explains the down-trending $RrSO_2$ seen in the first 60 h and this finding could be confirmed in future studies by also evaluating the fractional tissue oxygen extraction, or FTOE. The difference in oxygenation seen in the most premature neonates may be explained by decreased vascularization of the kidney, subsequently reducing oxygenation compared to less premature neonates with more advanced kidney development and vascularization. An additional factor likely to contribute to changes seen in our study is the effect of cardiac blood flow and specifically hemodynamically significant patent ductus arteriosus' that have been noted to affect renal tissue oxygenation in other studies[8,22]. In this study, we could not assess this effect as each center typically does not obtain echocardiograms until after seven days of age. While not assessed with this data, future studies could evaluate the relationship between $RrSO_2$ and the development of AKI in premature infants so that variation from our described trends could aid with AKI treatment and prevention.

In comparison to previous neonatal renal NIRS monitoring studies, our data has the advantage of prolonged continuous monitoring until day seven at two different sites that used similar techniques. A previous preterm study by Richter et al. intermittently evaluated $RrSO_2$ in the first 48 h after birth in 25–29-week GA infants and found a median range of 63–72% but an IQR of 48–87% suggestive of significant variability[23]. It is difficult to compare our data as many of our neonates started monitoring at 24 h but the range of values is similar between 24 and 48 h. Most recently, in a study of neonates <30 weeks, similar to our findings $RrSO_2$ declined significantly in the first 96 h and absolute values were within the range seen in our two centers[14]. In another study, McNeill et al. monitored a smaller cohort of older preterm neonates (29–33 weeks GA) from days 3–21 and found a slow decrease in renal tissue oxygenation[12]. This is different from the stable trend we observed from 60 h to 7 days of age, but our patients were of lower GA. A small cohort of preterm infants limited to a single center has also been described by Marin et al.[13] and again demonstrated similar trends over time and with GA as we have reported here. Additional studies evaluating $RrSO_2$ in term infants[24,25] describe a comparable trajectory with initial peak values of $RrSO_2$ that then nadir, although the peak $RrSO_2$ is higher in term infants than in preterm cohorts.

Although trends in $RrSO_2$ were not statistically different between the two centers, there were absolute differences that persisted, despite controlling for differences in GA and birth weight. This could be due to differences in blinding between centers that could have influenced clinicians' decisions to make clinical changes such as giving fluid boluses or blood transfusions despite neither center having a management guideline based on $RrSO_2$ values. Similarly, each center has different protocols for blood transfusions, fluid management, and other clinical needs, which without being standardized across the two centers, could influence $RrSO_2$ and is not possible to control for. Each center also has different thresholds for SpO_2 alarms (LPCH alarms at 88 and 100%; UPHM alarms at 88 and 95%). It is known that SpO_2 correlates with $RrSO_2$[26]; thus, the use of additional FiO_2 to potentially maintain a higher SpO_2 for infants at one center could have influenced the $RrSO_2$ trend. Finally, LPCH uses renal NIRS monitoring as the standard of care while the other center required obtaining consent prior to use—this difference led to fewer early time points for neonates at UPHM and may have fundamentally altered the UPHM cohort as parents who consented to the study may have had fewer sick neonates.

This study is limited by the retrospective nature and reliance on chart review for data and outcome documentation. All variables could not be controlled for and likely influenced the persistent center differences. Changes in hemoglobin levels, timing of red blood cell transfusions, blood pressure, and SpO_2 were also not acquired, limiting the ability to evaluate the effects of anemia, hypotension, and hypoxemia on $RrSO_2$ absolute values and trends. Renal fractional oxygen extraction was also not obtained. This information may confirm if changes over time and with GA are related to a relative redistribution of renal perfusion or to alterations in oxygen utilization by a maturing kidney.

CONCLUSIONS

In conclusion, this study contributes the largest number of preterm neonates with continuously monitored $RrSO_2$ over the first week of age. Although absolute differences in values existed between sites, the overall $RrSO_2$ trend was similar and initially decreased after birth, before plateauing at about 60 h of age. Future large, multicenter studies should be conducted to better evaluate center differences and confirm true normative values. Multicenter studies would also be appropriate to assess the relationship between trends in $RrSO_2$ and the development of AKI. Future critical studies are needed to evaluate whether $RrSO_2$ changes can predict AKI prior to changes in serum creatinine and urine output, and to evaluate protocols for interventions. The normative data from this study can be used to inform current clinical care as well as future studies to assess variation from the normal values, as well as clinical outcomes, with a goal to shape clinical management guidelines for AKI detection and treatment based on renal tissue oxygenation.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

M.W.H.: significant contributions to the design and conception, data analysis and interpretation, drafting the manuscript, critical revision of the manuscript and final approval. P.E.C.: analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; and final approval of the version to be published. J.E.C.: collection and interpretation of data; and final approval of the version to be published. M.R.L.: analysis of data and drafting methods/parts of results and review/approval of manuscript. V.Y.C.: significant contributions to the design and conception, data analysis and interpretation, drafting the manuscript, critical revision of the manuscript and final approval.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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