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A Single-Center Observational Clinical Study on Factors Associated with Regional Cerebral Oxygen Saturation in Full-Term Newborn Infants During Birth Transition

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Hypoxic hypoperfusion injury in the brain is a cause of potential injury and even death in the growth period of newborns. Therefore, monitoring regional cerebral oxygen saturation ($CrSO_2$) during this period is particularly important. This observational clinical study from a single center aimed to investigate the factors associated with $CrSO_2$ in full-term newborn infants during birth transition.

Material/Methods: We enrolled 84 full-term newborn infants delivered by cesarean section. We started the stopwatch with the obstetrician clamping the newborns' umbilical cords and recorded the values of newborns' $CrSO_2$, pulse oxygen saturation (SpO_2), pulse rate (PR), end-tidal carbon dioxide ($EtCO_2$), and respiratory rate (RR) at 2 min, 5 min, and 10 min. We weighed the newborns before they left the operating room and used statistical methods to compare the correlation between each observation factor.

Results: Pearson correlation coefficients between $CrSO_2$ and SpO_2 measured at 2 min, 5 min, and 10 min were 0.491, 0.599, and 0.587, respectively ($P<0.01$). Pearson correlation coefficients between $CrSO_2$ and $EtCO_2$ measured at 2 min, 5 min, and 10 min were -0.304, -0.443, and -0.243, respectively ($P<0.05$). Regardless of a newborn's weight, PR, or RR, the correlation between any of those factors and the value of $CrSO_2$ measured at the corresponding time point had no significance ($P>0.05$).

Conclusions: This study showed a correlation between $CrSO_2$ and SpO_2 and $CrSO_2$ and $EtCO_2$ during birth transition of full-term infants delivered by elective cesarean section, but $CrSO_2$ had no significant correlation with neonatal weight, PR, or RR.

Keywords: Hypoxia-Ischemia, Brain • Infant, Newborn • Spectroscopy, Near-Infrared • Statistics as Topic

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Background

When a fetus changes from the intrauterine environment to the extrauterine environment, its respiratory and hemodynamic functions go through a complex physiological change, and these physiological changes are mainly caused by the establishment of spontaneous respiration and the clamping of the umbilical cord [1]. During the immediate transition period, the newborn infant is prone to hypoxia or bradycardia or both, which most often affect the brain and lead to perinatal brain damage [2-4]. Clinically, the transition from the fetus to the neonatal period (the period of birth transition) is a process that is extremely prone to large changes in oxygen metabolism [5]. Therefore, monitoring oxygen metabolism in various organs of the newborn in a continuous and noninvasive manner, especially in the brain, has potential significance to guide the timely supplementation of oxygen or respiratory support when needed [6]. Previously, the initial assessment of the basic situation of newborns in the clinical transition period was generally based on inspection, palpation, auscultation, and observation of response to stimuli. The specific assessments included activity, pulse, grimace, appearance, and respiration, which make up the Apgar score. However, this evaluation method is inadequate in clinical application because it has a high degree of observer subjectivity, which leads to differences in scores due to considerable human error. There are currently several clinical methods to monitor changes in the brain, one of the most vulnerable organs, during the transition from fetus to newborn, including trans-cranial Doppler ultrasound, monitoring of regional cerebral oxygen saturation ($CrSO_2$), and ambulatory electroencephalogram [2], of which $CrSO_2$ monitoring has been gradually promoted because of its continuity, noninvasiveness, and timely effectiveness. There has been increasing interest in continuous monitoring of $CrSO_2$ using near-infrared spectroscopy (NIRS) during immediate fetal-to-neonatal transition [2,7]. NIRS is useful in monitoring the effect of transition on the brain, the most important organ of the human body, and may help to predict the prognosis of neurological outcomes [1]. $CrSO_2$ monitoring is a noninvasive monitoring technology that uses the NIRS technology to measure the oxygen saturation of the mixed blood contained in local brain tissue, thereby assessing the oxygen metabolism of the brain tissue. Nearly 70% of the mixed blood in the monitored brain tissue comes from the small veins, nearly 20% comes from the small arteries, and nearly 10% comes from the capillaries. $CrSO_2$ monitoring has a wide range of applications, high sensitivity and specificity, and is not affected by temperature and pulsating blood flow. It can find the oxygen supply and balance demands of the measured brain area and changes in cerebral blood flow in a timely and effective manner. Therefore, it is widely increasing in use, often as a supplement to traditional monitoring. As early as 1992, Peebles et al conducted the first study on the transition period of a full-term infant using NIRS equipment and reported that with the establishment of neonatal respiration, the oxygenated hemoglobin concentration in the body increases rapidly and the deoxyhemoglobin decreases rapidly [8]. In 2000 and 2002, Isobe et al reported on the oxygen saturation of brain tissues in newborns after birth for the first time [9,10]. Recently, there have been many studies on the range of $CrSO_2$ during the fetal-to-neonatal transition period, and several observational studies on the changes of $CrSO_2$ within a few minutes after birth have been reported [10-12]. However, there are few reports in the literature about whether the monitoring indicators of traditional neonatal monitoring such as pulse oxygen saturation (SpO_2) and heart rate (HR) are correlated with $CrSO_2$. We believe it is also of great significance to explore which factors are related to the oxygen metabolism of the neonatal brain. Therefore, this observational clinical study from a single center aimed to investigate the factors associated with $CrSO_2$ in full-term newborn infants during birth transition.

Material and Methods

This study was approved by the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (approval No. 2017 Research Project No. 54). After being introduced to the research process, 100 pregnant women signed the informed consent to participate in the study. The inclusion criteria were term pregnancy (gestational age > 37 weeks), singleton pregnancy, ASA grade I to II, and birthing by elective cesarean section with epidural block. The exclusion criteria included history of prenatal intrauterine fetal distress, history of cardiopulmonary, liver, or kidney dysfunction, and moderate to severe anemia. The patients were enrolled in the study from February to August 2017 at the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. Inclusion in the study was finalized only after the birth of the baby, as shown in **Figure 1**.

After the umbilical cord was properly cut within 2 min of birth, we excluded the newborns with weights less than 2500 g or greater than 4000 g after birth, Apgar scores ≤6 within 1 min, congenital abnormalities, and needing oxygen or mask positive pressure ventilation, vasoactive drugs, or tracheal intubation within 10 min of birth. Pregnant women with a changed method of anesthesia during surgery were also excluded. If an alarm message appeared on the brain oxygen saturation monitor, such as low signal, low perfusion, sensor off, or ambient light, we also excluded the patient.

After the pregnant woman's arrival in the operating room, she signed the informed consent, and her HR, noninvasive blood pressure (BP), and SpO_2 were monitored. When the vital signs were stable, the woman was placed in the right lateral position

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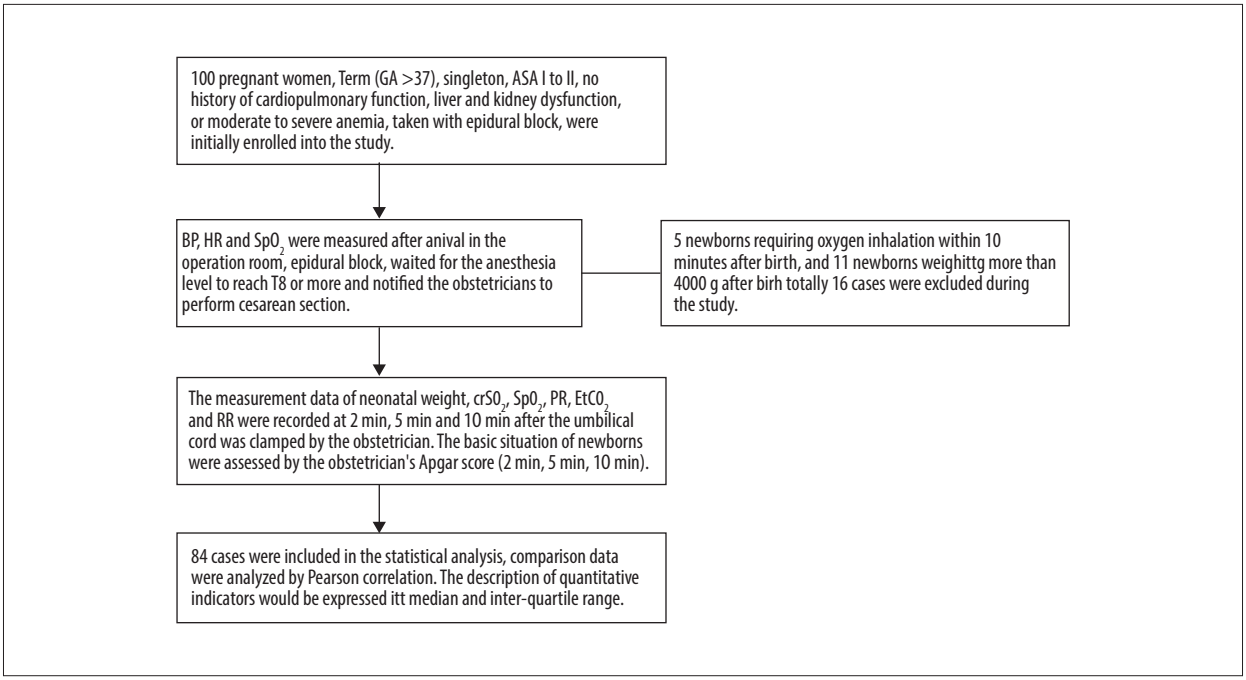

Figure 1. Flow chart of the study.

Table 1. Statistical values of neonatal monitoring indicators ($CrSO_2$, SpO_2, PR, $EtCO_2$, RR and neonatal body weight) measured at 3 time points. Values are mean±SD; n=84.

	$CrSO_2$ (%)	SpO_2 (%)	$EtCO_2$ (mmHg)	PR (/min)	RR (/min)	Weight (g)
2 min	45±17	72±10	38.1±7.9	141±15	55±18	3397±437
5 min	63±16	80±9	37.9±7.2	146±12	60±14	
10 min	75±11	88±5	34.4±6.9	144±13	60±16	

$CrSO_2$ – regional cerebral oxygen saturation; SpO_2 – pulse oxygen saturation; PR – pulse rate; $EtCO_2$ – end-tidal carbon dioxide; RR – respiratory rate.

for epidural puncture was given anesthetic drugs consisting of 2% lidocaine hydrochloride 5 mL and 0.75% ropivacaine hydrochloride 5 to 10 mL. When the anesthesia blockade level reached T8 or higher, the obstetricians were notified to perform the cesarean section. The stopwatch was started with the obstetrician clamping the newborn's umbilical cord, and the vital signs (BP, HR, and SpO_2) of the pregnant woman were recorded at this time. The obstetrician assessed the basic situation of the newborn by the Apgar score at 2 min, 5 min, and 10 min after birth, and the midwife performed sputum suction and lung expansion of the newborn. The anesthesia research assistant immediately placed the neonatal sensor of the INVOS 5100C device on the left side of the forehead of the newborn (avoiding the frontal sinuses area), fixed it with an infusion patch, placed the SpO_2 probe on the right wrist of the newborn, and prepared a breathing mask to monitor $EtCO_2$ and RR. The newborn was continuously monitored throughout the research process, during which time, the anesthesia assistant recorded the values of $CrSO_2$, SpO_2, PR, $EtCO_2$, and RR at 2 min, 5 min, and 10 min after birth. Lastly, the newborn's weight was measured before the newborn left the operating room.

Statistical Analysis

Data analysis was performed using SPSS version 21.0 (IBM Corp, Armonk, NY, USA). The description of quantitative indicators was expressed as mean±standard deviation. The data met the normality and homogeneity of variance. The correlations between the comparison data were analyzed by Pearson correlation. $P<0.05$ was considered statistically significant.

Results

A total of 100 pregnant women who underwent elective cesarean section were included at the beginning of the study. A

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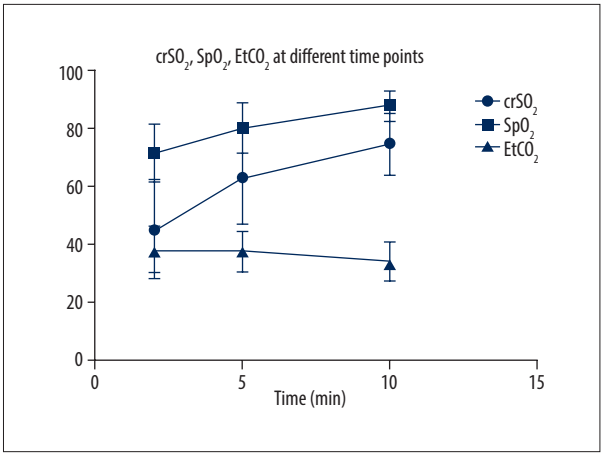

Figure 2. Dynamic changes of regional cerebral oxygen saturation ($CrSO_2$), pulse oxygen saturation (SpO_2), and end-tidal carbon dioxide ($EtCO_2$) values measured in the first 10 min after birth. The unit of $CrSO_2$ and SpO2 is percent; the unit of $EtCO_2$ is mmHg. The overall values of $CrSO_2$ and SpO_2 show an upward trend over time, and the $CrSO_2$ value increased more obviously in the first 5 min after birth. However, EtCO2 showed a downward trend.

total of 16 pregnant women were excluded during the study (including 5 cases of neonates requiring oxygen inhalation within 10 min after birth and 11 cases of newborns weighing more than 4000 g after birth). The data of 84 term newborns were included in the statistical analysis.

The average values of neonatal monitoring indicators $CrSO_2$, SpO_2, PR, $EtCO_2$, RR, and neonatal body weight were measured at 3 time points, as shown in **Table 1**.

We found that the values of $CrSO_2$ and SpO_2 measured in the first 10 min after birth in the 84 full-term infants increased over time, and the $CrSO_2$ value increased more obviously in the first 5 min after birth. However, $EtCO_2$ showed a decrease over time, as shown in **Figure 2**. The pulse rate (PR) and RR values of the neonates did not show obvious patterns during the monitoring period.

As seen in **Table 2**, the statistical results showed that $CrSO_2$ measured at 2 min, 5 min, and 10 min after birth had no significant statistical correlation with the weight of the newborns (between 2500 g and 4000 g), PR, or RR ($P>0.05$). The $CrSO_2$ and SpO_2 values of term infants measured at 2 min, 5 min, and 10 min after birth had a moderate positive correlation, with Pearson correlation coefficients of 0.491 ($P<0.01$), 0.599 ($P<0.01$), and 0.587 ($P<0.01$), respectively. The $CrSO_2$ and $EtCO_2$ values of term infants measured at 2 min, 5 min, and 10 min after birth had a weak negative correlation, a moderate negative correlation, and a weak negative correlation, respectively, with Pearson correlation coefficients of -0.404 ($P<0.01$), -0.443 ($P<0.01$), and -0.243 ($P<0.05$). The scatter plot and regression equation of the correlation analysis between $CrSO_2$ value and SpO_2 value or $EtCO_2$ value measured at 2 min, 5 min, and 10 min after birth are shown in **Figures 3 and 4**, respectively.

Discussion

The transition from fetus to newborn is a complicated process and includes changes in the respiratory system, cardiovascular system, and nervous system. Some of these changes will have long-term beneficial effects, while others will have adverse effects. The timely and effective identification of these adverse effects and the introduction of appropriate intervention are essential.

Table 2. Correlation analysis between $CrSO_2$ measured at 3 time points and neonatal body weight or SpO_2 or $EtCO_2$ or PR or RR measured at the corresponding time point (n=84). Asterisk (*, **) indicates significant differences from the $CrSO_2$ at (P<0.05, P<0.01).

			Weight	SpO_2	$EtCO_2$	PR	RR
$CrSO_2$	2 min	Pearson correlation coefficient	0.044	0.491**	-0.304**	0.079	0.205
		P value (2-tailed)	0.692	<0.0001	0.0046	0.475	0.059
		N	84	84	84	84	84
	5 min	Pearson correlation coefficient	0.09	0.599**	-0.443**	-0.022	0.216
		P value (2-tailed)	0.413	<0.0001	<0.0001	0.841	0.057
		N	84	84	84	84	84
	10 min	Pearson correlation coefficient	0.007	0.587**	-0.243*	-0.192	0.048
		P value (2-tailed)	0.953	<0.0001	0.025	0.078	0.660
		N	84	84	84	84	84

$CrSO_2$ – regional cerebral oxygen saturation; SpO_2 – pulse oxygen saturation; PR – pulse rate; $EtCO_2$ – end-tidal carbon dioxide; RR – respiratory rate.

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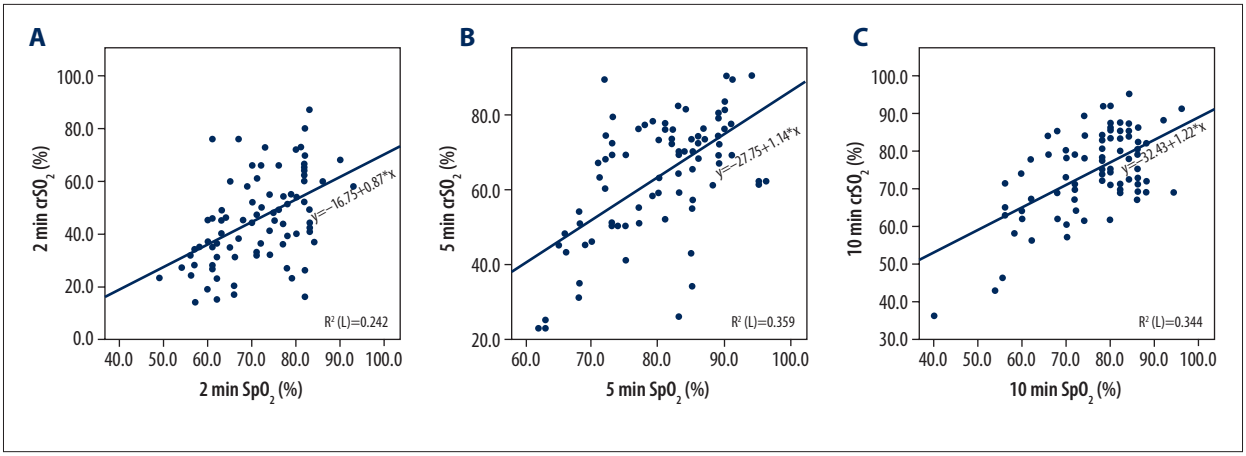

Figure 3. The scatter plots and regression equations for the correlation analysis of regional cerebral oxygen saturation ($CrSO_2$) and pulse oxygen saturation (SpO_2) values measured at 2 min, 5 min, and 10 min after birth. (**A**) The correlation analysis of $CrSO_2$ and SpO_2 at 2 min; (**B**) the correlation analysis of $CrSO_2$ and SpO_2 at 5 min; (**C**) the correlation analysis of $CrSO_2$ and SpO_2 at 10 min. The red straight line indicates linear regression. R^2 refers to the goodness of fit of the regression equation. The closer the value of R^2 is to 1, the better the regression line fits the observations; otherwise, the smaller the value of R, the worse the regression line fits the observations.

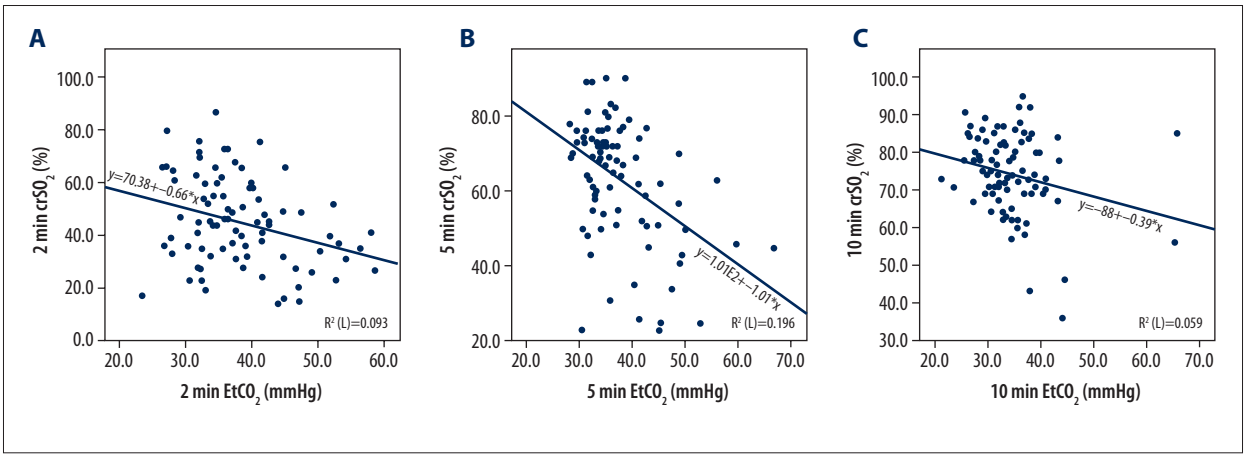

Figure 4. The scatter plots and regression equations for the correlation analysis of regional cerebral oxygen saturation ($CrSO_2$) and end-tidal carbon dioxide ($EtCO_2$) values measured at 2 min, 5 min, and 10 min after birth. (**A**) The correlation analysis of $CrSO_2$ and $EtCO_2$ at 2 min; (**B**) the correlation analysis of $CrSO_2$ and $EtCO_2$ at 5 min; (**C**) the correlation analysis of $CrSO_2$ and $EtCO_2$ at 10 min. The red straight line indicates linear regression.

The results of this study showed that there was a moderate positive correlation between $CrSO_2$ and SpO_2 values measured in term newborns within 10 min of birth ($P<0.01$) and a low to moderate negative correlation between $CrSO_2$ and $EtCO_2$ values ($P<0.05$), but $CrSO_2$ had no correlation with neonatal weight, PR, or RR value ($P>0.05$).

There have been many studies on the range of $CrSO_2$ during the fetal-to-neonatal transition period. Baik et al [13] used the NIRO 200NX device to measure the cerebral tissue oxygen saturation index (cTOI) of 230 healthy full-term newborns delivered by elective cesarean section at 15 min after birth, with results showing that the median cTOI values measured at 2 min, 5 min, 10 min, and 15 min after birth were 56% (39-75%), 66% (50-78%), 75% (62-85%), and 73% (61-84%), respectively. It is generally believed that cTOI values measured with the NIRO 300 are higher compared with the $CrSO_2$ values measured with the INVOS 5100C when regional oxygen saturation is <60%, but if regional oxygen saturation is >60%, $CrSO_2$ values are higher compared to TOI values [14]. Therefore, compared with the results of Baik et al, we found the $CrSO_2$ value measured in the present study was generally highly reliable. Our results also confirm the correlation analysis between $CrSO_2$ and other monitoring indicator of newborns.

It has been reported that $CrSO_2$ is determined not only by SpO_2, but also depends on the oxygen supply and oxygen consumption

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of the brain. The brain's oxygen supply is mainly affected by cerebral blood flow (CBF), and the change in CBF is affected by cardiac output and vascular resistance [15]. Therefore, the results of the present study show that the positive correlation between $CrSO_2$ and SpO_2 may have been due to the gradual increase of oxygenated hemoglobin concentration and the decrease of deoxyhemoglobin concentration in the newborn with the establishment of respiration. This is because $CrSO_2$ monitors the oxygen saturation of mixed blood in local brain tissue, with nearly 70% of the mixed blood coming from the small veins, nearly 20% coming from the arterioles, and nearly 10% coming from the capillaries, so that as SpO_2 gradually rises, $CrSO_2$ rises as well. Isobe et al [9] found evidence of a mild increase in CBF in the first 2 to 3 min after birth, followed by a decline in CBF. The underlying cause of the drop in CBF in that study is unknown. One possible explanation may be that the cerebral vascular bed constricts in response to the postnatal increase in blood oxygen content to protect the brain from excessive oxygen exposure. Another explanation might be that the increasing left-to-right shunt across the patent ductus arteriosus together with an inadequate compensatory increase in left ventricular output reduces the CBF [16,17], and $CrSO_2$ is affected by a change in CBF. The above also precisely explains why the $CrSO_2$ value showed a more obvious increasing trend in the first 5 min after birth in our present study. As Fauchere et al [12] and others have reported, $CrSO_2$ measured in full-term infants can reach a stable level at 7 to 8 min after birth, earlier than that of SpO_2 and peripheral tissue oxygen saturation, which is similar to the results of our study [18].

At the same time, our study showed a negative correlation between $CrSO_2$ and $EtCO_2$, which may have resulted from the continuous exchange between the blood and the atmosphere after the establishment of the extrauterine respiratory and circulatory system during the neonatal transition period. In other words, $CrSO_2$ gradually increased, and $EtCO_2$ gradually decreased. During a newborn's initial breaths, lung liquid is cleared and air remains in the lung at the end of expiration, providing a functional residual capacity [19]. Uniform lung aeration, establishment of functional residual capacity, and a decrease in pulmonary vascular resistance are required to commence effective pulmonary gas exchange [1]. Hypercapnia is a powerful stimulant for respiratory drive both before and after birth and could induce the large respiratory efforts observed [1]. Fetal respiratory drive is controlled by similar stimuli (hypoxia and hypercapnia), which arises from the respiratory center and mainly causes activation of the diaphragm via the phrenic nerve [20]. At the early stage of the establishment of neonatal spontaneous breathing, the excessively high CO_2 concentration in the blood in the body is expelled from the body through the gas exchange between the expanded pulmonary capillaries and the alveoli. With the continuous exchange of gas between the newborn and the outside atmosphere, the concentration of CO_2 in the blood in the body gradually decreases, and $EtCO_2$ gradually decreases until the value of $EtCO_2$ stabilizes.

Our results showed that the PR or RR in this study had no statistically significant correlation with $CrSO_2$. Because similar reports have not been published before, we consider that although PR (here, PR=heart rate) partially determines the cardiac output of newborns, hemodynamic changes caused by fluctuations in PR within a certain range will not affect the CBF of newborns because of the ability of the brain to automatically regulate; therefore, it will not affect the $CrSO_2$ of the newborn. Although RR can reflect, to a certain extent, the respiratory function of newborns when spontaneous breathing is just established, other interfering factors may have occurred during our study, such as the pain stimulation (eg, wiping, patting the soles of the feet) by the midwife, which affected measured values. Therefore, RR was not discussed in the present study, as further experimental research is needed. The results of this study showed that there is no significant correlation between the weight of full-term neonates and $CrSO_2$.

There are some limitations in the design of this study. First, the object of the study was the full-term neonate born by cesarean section. Because cesarean section includes anesthesia, this study cannot rule out whether anesthesia affected its results. If we want to completely exclude the influence of anesthesia, we need to study neonates born by vaginal delivery. Second, we have not added the blood gas analysis results of neonatal arterial blood (which can be replaced by umbilical cord blood) in exploring the relevant factors that affect brain tissue metabolism; therefore, we cannot effectively exclude some potential influencing factors, such as neonatal anemia, which could interfere with the results of the study. Third, because of social and other limiting factors, this study recorded and analyzed only the corresponding observation indicators of newborns within 10 min after birth, so it is still unknown how the observation indicators of newborns change after this period of time. We need to study this in the future.

Conclusions

In summary, this study showed a correlation between $CrSO_2$ and SpO_2 and $CrSO_2$ and $EtCO_2$ during the birth transition of full-term infants delivered by elective cesarean section, but $CrSO_2$ had no significant correlation with neonatal weight, PR, or RR.

Conflicts of Interest

None.

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