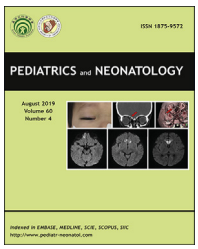
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Original Article

Effect of rewarming in oxygenation and respiratory condition after neonatal exposure to moderate therapeutic hypothermia

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Abstract *Background:* To assess changes in clinical condition and oxygenation in neonates after rewarming following moderate therapeutic hypothermia (MTH) for neonatal encephalopathy.
Methods: Retrospective study of 28 neonates receiving MTH in a tertiary neonatal intensive care unit in Israel. We compared pre-and 24 h post-rewarming arterial oxygen saturation (SaO_2) as measured by the blood gases analyzer, pulse-oximetry saturation (SpO_2), and cardio-respiratory condition.
Results: The SpO_2 declined from 96.9% (±2.9) before rewarming to 95.2% (±2.6) after rewarming ($p < 0.001$). Twelve neonates (42.9%) had clinical respiratory impairment (needing higher respiratory support or had new onset desaturations). In 16 neonates (57.1%) with no change in respiratory support after rewarming, SpO_2 decreased from 98.3 ± 1.9% to 95.6 ± 3.0% ($p < 0.001$) and SaO_2 decreased from 97.1 ± 1.7% to 96.0 ± 2.3% ($p = 0.002$). The mean SpO_2 decrease was greater than mean SaO_2 decrease (2.63 ± 1.8 and 1.1 ± 1.3 respectively, $p = 0.021$).
Conclusion: Neonates who underwent MTH showed reduction in oxygenation after rewarming either by decreasing SpO_2 or increasing FiO_2 requirements. The SpO_2 decline was larger than the SaO_2 decline. We suggest careful monitoring of neonates after rewarming.
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1. Introduction

Pulse oximetry has become essential for monitoring oxygenation in neonates. Oxygen saturation (SpO_2) has been named the "fifth" vital sign.[1] Its correlation with arterial partial pressure of oxygen (PaO_2) depends upon multiple factors, especially at which level of the slope of the oxygen-hemoglobin dissociation curve a specific SpO_2 is located.[2,3] A decrease in temperature causes a shift of the oxygen-hemoglobin dissociation curve towards the left enhancing affinity to oxygen.[4]

The use of moderate therapeutic hypothermia (MTH) became a standard of care for neuroprotection in neonates with neonatal encephalopathy.[5] Hypothermia reduces metabolic requirements, cardiac output and respiratory rate.[5,6] Thus, it would be expected that patients receiving MTH present higher SpO_2 at a given PaO_2. Conversely, during rewarming, a decrease in hemoglobin-oxygen affinity would reduce oxygen saturation.

Arterial oxygen saturation (SaO_2), as measured by the blood gases analyzer, may not reflect the actual SaO_2 in a hypothermic neonate since analyzers heat blood samples to 37 °C before measurements causing a shift back to the right to the oxygen-hemoglobin dissociation curve.

MTH is generally initiated after resuscitation in sick unstable neonates, which hinders isolating the effect of hypothermia from other factors. However, by the time of rewarming, most neonates stabilize, allowing a better assessment of the effect of temperature change on SaO_2 and SpO_2.

We sought to determine whether rewarming after MTH affects oxygenation and clinical condition.

2. Methods

We conducted a retrospective study of all neonates treated with MTH (33.5 °C) in the neonatal intensive care unit (NICU) from January 1, 2008 until September 30, 2015. Our institution is a tertiary center in Israel, treating a population with high incidence of multiparty, generally with good obstetric follow up.

Hypothermia was achieved with the Criticool device (MTRE, Yavne, Israel). The device uses a special garment wrapped around the body of the neonate. The targeted temperature is reached and maintained by feedback from the neonate's core and surface temperature. Hypothermia was initiated according to the guidelines of the Israeli Neonatal Society.[7] Rewarming was achieved by increasing temperature by 0.5 °C every hour until core temperature of 36.5 °C was reached. Respiratory support was adjusted to maintain SpO_2 targets between 90 and 95%.

After approval from the local institutional research board, we retrieved the relevant patients' charts using the key words: "hypothermia" or "hypoxic ischemic encephalopathy" or "asphyxia". We retrospectively collected the following data from patients' clinical records: core temperature as measured by the Criticool device, SpO_2 as measured by pulse oximetry (Nellcor bedside SpO_2, Covidien-Medtronic, Mansfield USA) and recorded by the nurse at the time of blood gases sampling and during routine vital signs measurements (every 3 h or whenever neonates' clinical status changed). If the presence of right to left shunt through the PDA was suspected, we recorded only preductal SpO_2. The SaO_2 and arterial partial pressure of carbon dioxide ($PaCO_2$) were measured as MTH patients' monitoring, in arterial blood samples (from umbilical or peripheral lines) using a blood gases analyzer (ABL 90 flex, Radiometer, Copenhagen Denmark). Since this blood gas analyzer heats blood samples to 37 °C before measurement, we also calculated the true PCO_2 of the neonate at his actual body temperature using the formula: true $PaCO_2 = PaCO_2 \cdot 10^{(0.019 \cdot (\text{temperature} - 37))}$.[8]

We also recorded heart rate, blood pressure, respiratory rate, type of respiratory support (mechanical ventilation, Nasal CPAP, high flow nasal cannula), incidence and severity of oxygen desaturations as recorded by the nursing staff. Our institutional protocol is to record all desaturations below 85% lasting at least 20 s, age in hours when MTH started, length of cooling and rewarming process, comorbidities, use of blood products, echocardiographic findings, and use of inotropic and sedative drugs from birth until 24 h after rewarming.

Statistical analysis was performed using the SPSS software (SPSS 17 IBM, Armonk, New York, USA). Results are expressed as mean ± SD, and P-values <0.05 were deemed significant. Paired Student's T test was used to compare averages of continuous variables over the 24 h that preceded rewarming with those observed during the first 24 h after rewarming. Clinical respiratory impairment was defined as new or increased respiratory support or delivered fraction of inspired oxygen (FIO_2) or new desaturation episodes with no change in ventilator support during the 24 h before and after rewarming.

3. Results

The records of 150 neonates were retrieved using the key words previously mentioned: of these neonates, 30 received MTH, all because of neonatal encephalopathy. Two of these were excluded because their deteriorating clinical condition led to a "do not resuscitate" (DNR) decision, and therefore they were not treated with invasive mechanical ventilation despite severe hypoxia before rewarming.

Demographics of the included neonates: Mean gestational age was 39.0 ± 1.3 weeks, mean weight was 3.2 ± 0.5 kg; 14 neonates were male and 14 were female. Comorbidities included: meconium aspiration (7 cases), pulmonary hypertension (3 cases) and pneumothorax (1 case). Three neonates received adult packed cells during MTH, although this occurred before the studied period (24 h before and after rewarming). Mean age at initiation of MTH was 1.6 ± 1.9 h, and duration of the rewarming process was 4.8 ± 0.9 h. The mean number of SpO_2 recordings for each neonate was 7.6 ± 1.9 and 7.3 ± 1.9 before and after rewarming, respectively.

Outcomes: As depicted in Table 1 (whole group), mean temperature rose significantly from 33.4 °C pre-warming to 36.7 °C 24 h post-warming ($p < 0.001$). SpO_2 decreased significantly by an average of 1.7% ($p < 0.001$), while there was no significant change in SaO_2. Both the ratio of SpO_2/FiO_2 and that of SaO_2/FiO_2 decreased significantly

Table 1 Average physiologic changes pre and post rewarming among 28 neonates.

	24 H before rewarming	24 H after rewarming	P value
Average Core temp	33.4 °C ± 0.2	36.7 °C ± 0.1	$p < 0.001$
Average SpO_2	96.9% ± 2.9	95.2% ± 2.6	$p < 0.001$
Average SaO_2	96.2% ± 2.5	95.7% ± 2.2	$p = 0.555$
SpO_2/FiO_2	4.48 ± 0.60	4.20 ± 0.57	$p = 0.005$
SaO_2/FiO_2	4.56 ± 0.19	4.28 ± 0.46	$p = 0.013$
Average $PaCO_2$ (Torrs) Corrected for Temperature	38.7 ± 5.0	44.7 ± 6.7	$p = 0.001$
Average pH	7.34 ± 0.06	7.37 ± 0.06	NS
Average Heart Rate	104 ± 27	134 ± 34	$p < 0.001$
Average Respiratory Rate	40.1 ± 12	45.7 ± 13	$p < 0.001$
Use of Sedative Drugs (n)	10	6	NS
Use of Inotropic Drugs (n)	0	0	NS
Average Mean arterial pressure (mm HG)	55.45 ± 8.2	52.6 ± 6.8	$p = 0.009$
Clinical Respiratory Impairment*	3	12	$p = 0.007$
Respiratory Improvement	9	2	$p = 0.019$

Table 1 depicts the results of average physiologic changes between period 1 (24 h before rewarming) and period 2 (24 h after rewarming). *Clinical respiratory impairment defined as new need of respiratory support, or an increase in FIO_2 or new desaturation episodes without a change in ventilator support.

($p = 0.005$ and $p = 0.013$, respectively) after rewarming (Table 1). Mean heart rate, respiratory rate and $PaCO_2$ (corrected for temperature) increased significantly after rewarming. Two neonates were excluded from SpO_2/FiO_2 and SaO_2/FiO_2 analysis because they underwent extubation to non-invasive ventilation, thus precluding comparisons.

Three (11%) neonates had clinical respiratory impairment (as defined above) during the 24 h before rewarming versus 12 (43%) during the 24 h after rewarming ($p = 0.016$); among them, 9 needed higher inspired oxygen fraction (FiO_2) and 3 had new-onset desaturation, while none of these last 12 neonates had change in ventilatory support.

Among the 16 neonates who needed no change in FiO_2 and respiratory support, SpO_2 decreased in 14 cases after rewarming. Mean SpO_2 decreased from 98.3% ± 1.9—95.6% ± 3.0 ($p < 0.001$). Unlike the results for the whole group, SaO_2 also did decrease significantly (from 97.1% ± 1.7—96.0% ± 2.3 ($p = 0.002$) after rewarming. The mean SpO_2 decrease was 2.63 ± 1.8, significantly higher than the mean decrease in SaO_2 (1.1 ± 1.3), $p = 0.021$. SpO_2 increased in the two remaining neonates. No correlation was found between time at sampling after rewarming and SpO_2 (linear regression $p = 0.8$).

Although the average mean arterial pressure declined from 55.45 ± 8.2 to 52.6 ± 6.8 ($p = 0.009$) during rewarming, none of the neonates developed clinically significant hypotension (defined as requiring inotropic support).

In summary, out of 30 neonates with available outcomes after rewarming, 2 died (excluded), 26 either had clinical respiratory impairment or reduced oxygenation, and only 2 improved.

4. Discussion

While MTH has become a standard of care for HIE, subsequent rewarming may be associated with several physiologic changes.

The results of this study show that after rewarming SaO_2 and/or SPO_2 decreased in 14 out of 16 neonates whose respiratory support remained unchanged; SPO_2 increased in only 2 neonates. In the remaining 12 neonates, clinical impairment prompted changes in their respiratory support in order to avoid hypoxemia, precluding comparison of SaO_2 and/or SPO_2 after rewarming.

We propose 2 potential mechanisms for increasing SpO_2 during MTH: a shift to the left on the oxygen-hemoglobin dissociation curve, and a reduction in oxygen consumption due to lower basal metabolic needs.

***Influence of MTH on hemoglobin-oxygen affinity*:** After delivery, most neonatal hemoglobin is fetal, which has an increased oxygen affinity; thus, its dissociation curve is located at the left of adult hemoglobin. A decrease in temperature increases hemoglobin-oxygen affinity.[4] This has been shown as in case of fetal hemoglobin,[4] in agreement with the results of the current study.

For testing SaO_2, gas analyzers warm the blood samples to 37 °C in order to standardize the measurements; this actually shifts the oxygen-hemoglobin dissociation curve of hypothermic newborns rightwards back to normal. For this reason, measured SaO_2 is expected to be lower than real SaO_2 in these patients. In contrast, SpO_2 is measured in real time at patient's temperature, which explains the higher values as compared to SaO_2 during MTH, as shown in the results of the current study.

It is not clear whether the increased hemoglobin-oxygen affinity actually affects tissue oxygenation. During fetal life, when oxygen saturations are much lower, it favors oxygen uptake from the placenta and further delivery at tissue level. However, the increased hemoglobin-oxygen affinity postnatally might impair tissue oxygen delivery. Therefore, it is hard to define a target SpO_2 during MTH. Indirect markers of tissue oxygenation such as lactate or metabolic acidosis may assist the clinician.

4.1. Influence of MTH on oxygen consumption

MTH reduces basal metabolic rate, decreasing oxygen consumption and CO_2 production. In vitro test of neonatal foreskin tissue during hypothermia showed a 50% decrease in oxygen consumption at 33.5 °C.[9] Furthermore, it has

been shown in vivo that cardiac output during MTH is 67% of cardiac output after rewarming.[10]

Rewarming increases metabolic demands, oxygen consumption and CO_2 production.[6] Respiratory and heart rates increase in order to improve CO_2 clearance and satisfy the increased metabolic oxygen demands, as shown in the current study.[6] Systemic and pulmonary circulations are not completely separated from each other, even in healthy neonates. There are extra- and intrapulmonary shunts of venous deoxygenated blood to systemic arterial circulation. These shunts are present in the fetus and young neonates and may play a role in the pathophysiology of bronchopulmonary dysplasia.[11,12] It has been shown in adults that an increased cardiac output, increases extra- and intrapulmonary shunts.[13] Oxygen consumption will decrease during hypothermia,[9] raising mixed venous saturation and reducing cardiac output and blood flow through these shunts. The combination of both mechanisms would increase arterial oxygenation during hypothermia in addition to the above-mentioned increase in hemoglobin-oxygen affinity. We speculate that the former mechanism could explain the increase in SaO_2 during MTH, as opposed to SpO_2 which may be affected by both.

We found that after rewarming, oxygenation decreased only in neonates who did not require increasing respiratory support and FiO_2. The expected decrease in oxygenation after rewarming was obviously masked in those neonates requiring increased FiO_2. To avoid this bias, we adjusted for delivered FiO_2 by using the ratios SpO_2/FiO_2 and SaO_2/FiO_2 for the comparisons, finding significant reductions after rewarming. Dassios et al. found trends to similar physiologic changes in mechanically ventilated newborns, although these changes did not reach statistical significance; they suggested that hypothermia may improve lung mechanics as well.[14]

Finally, although confounding factors such as blood pH and red blood cell transfusion are known to affect the shift of oxygen-hemoglobin dissociation curve, no neonate was transfused, and there were no significant changes in blood pHs during the rewarming period **(3 neonates received packed cells during MTH, as previously stated, but before the studied period).**

4.2. Clinical implications

Respiratory: The reduction of the SPO_2 found in those neonates who did not require increased respiratory support, although statistically significant, would not seem to have clinical significance. On the other hand, almost half of the neonates suffered from some degree of clinical respiratory impairment, defined by an increase in FiO_2, and/or need for respiratory support, and/or new desaturation episodes after rewarming. This impairment was transient and easily treated with noninvasive ventilation.

MTH has been reported to be associated with pulmonary hypertension.[6,15] In the current study, two neonates (7%) improved on rewarming, as evidenced by lower FiO_2 needs. Both had pulmonary hypertension during MTH with right to left shunting diagnosed either by echocardiography or by differential pre- and post-ductal saturation. We speculate that this may explain their improvement after rewarming.

In most neonates rewarming is safe, but in cases of severe respiratory disease (in addition to HIE) treated with maximal respiratory support, the clinicians should be aware of the above-mentioned possible impairments.

Further specific studies should be conducted to address this issue.

Hemodynamic: The effects of rewarming on blood pressure, as reported in the literature, are controversial.[10–16] The CoolCaP and NICHD (National Institute of Child Health and Human Development) trials reported no difference in the incidence of hypotension, need for inotropic support or volume resuscitation during cooling or rewarming.[17,18] Our data show a moderate but statistically significant decrease in blood pressure after rewarming. Like in the CoolCaP and NICHD studies, no neonate in our cohort developed clinical symptoms of hypotension during or after rewarming. Wu TW et al. found a significant increase in cardiac output throughout rewarming due to an increase in HR and lack of change in cerebral tissue oxygen saturation and extraction, which supports the relatively low clinical significance of the respiratory and hemodynamic findings of this study.[16] Nevertheless, careful monitoring is warranted in patients undergoing therapeutic hypothermia, especially in neonates with low baseline blood pressure and/or neonates treated with inotropes during and after rewarming.[19]

4.3. Limitations of the study

This retrospective study has inherent limitations of all such studies, but since MTH is the standard of care for term neonates with neonatal encephalopathy, it was ethically impossible to prospectively recruit a control group. On the other hand, the comparison before and after rewarming for each individual allowed using paired analyses. The dramatic physiologic changes characteristic of the transition period after birth, especially after hypoxia-ischemia, precluded the use of clinical data before cooling. The standardized rewarming protocol and the relative clinical stability expected by the third day of life was a more appropriate setup for the analyses. For this reason, MTH, which was the actual intervention, occurred chronologically prior to rewarming to the neonates' physiological temperature. Therefore, we assume that MTH actually improved the respiratory status rather than that the rewarming process impaired it.

5. Conclusions

After rewarming from MTH, there is a decrease in SpO_2; we speculate that this change may be attributed to both a lower hemoglobin-oxygen affinity and increased metabolic demands. Clinicians should be aware of this finding and monitor for possible impairments.

Potential benefits of increased oxygen saturation during hypothermia should be the subject of future research.

Declarations of interest

None.

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