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Oxygenation Instability Assessed by Oxygen Saturation Histograms during Supine vs Prone Position in Very Low Birthweight Infants Receiving Noninvasive Respiratory Support

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Objective To evaluate the effect of prone vs supine position on the oxygenation instability among very low birth weight (VLBW) infants receiving noninvasive respiratory support, as assessed by the average oxygen saturation (SpO_2) histograms.

Study design Sixty-nine histograms from 23 VLBW infants were studied prospectively. Each infant was studied during 3 consecutive 3-hour periods of alternating positions; 12 infants started the study while prone and 11 infants started supine, by random order. Histogram classification system was used to quantify oxygenation stability and time spent in different SpO_2 ranges.

Results The fraction of inspired oxygen values were similar in both positions. Unstable histograms were more common in supine vs prone position (20/34 [59%] vs 10/35 [29%]; $P = .02$, respectively). Analyzing oxygenation stability as per position change revealed that a change from prone to supine increased oxygenation instability, and supine to prone decreased instability ($P = .02$). In the supine vs prone position, percent of time spent in SpO_2 ≤80% and <90% was higher (5.0 ± 4.2 vs 2.4 ± 3.4 [$P < .001$] and 24.1 ± 13.7 vs 13.2 ± 10.0 [$P < .001$], respectively), and percent of time in SpO_2 >94% was lower (39.7 ± 26.0 vs 52.4 ± 23.4 [$P = .04$]).

Conclusions Prone positioning decreased oxygenation instability and resulted in higher oxygenation among VLBW premature infants on noninvasive respiratory support. SpO_2 histograms allow easy bedside assessment of oxygenation instability, and quantification of the time spent at different SpO_2 ranges. *(J Pediatr 2020;226:123-8)*.

Oxygenation instability and intermittent hypoxemic events are common among very low birth weight (VLBW) infants and have been associated with adverse outcomes as severe retinopathy of prematurity, bronchopulmonary dysplasia, severe intraventricular hemorrhage, and adverse 18-month neurodevelopmental outcomes.[1-4]

Different interventions, such as a change in mechanical ventilation mode and red blood cell transfusion, have been shown to influence the incidence of hypoxemic episodes in premature infants.[5,6] Prone positioning has also been found to increase average oxygen saturation (SpO_2) and decrease desaturation events.[7-11] However, this effect was not consistent in all studies, and a recent meta-analysis concluded that no particular body position is more effective in producing sustained and clinically relevant improvement during mechanical ventilation.[12-14]

SpO_2 is routinely monitored in all infants admitted to the NICU and SpO_2 histograms of the previous 1-24 hours can be easily generated by the monitor. A classification system based on the width of the histogram and the time spent in SpO_2 ≤80% can be used to describe and quantify oxygenation stability.[15] We hypothesized that oxygenation instability will improve during prone position as documented by SpO_2 histograms.

The aim of this study was to use the SpO_2 histograms to evaluate oxygenation stability among VLBW infants receiving noninvasive respiratory support, in prone vs supine positions.

Methods

Study Design and Patients

This prospective, crossover, observational study was performed in the neonatal intensive care unit of Rambam Medical Center and Bnai Zion Medical center in 2018 and 2019. Included in the study were VLBW premature infants receiving noninvasive respiratory support for respiratory distress syndrome or apnea of

FiO_2	Fraction of inspired oxygen
SpO_2	Oxygen saturation
VLBW	Very low birth weight

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prematurity, including nasal intermittent positive pressure ventilation, nasal continuous positive airway pressure, or high-flow nasal cannula (≥2 LPM) and were ≥4 days old. Excluded were infants with multiple congenital anomalies, congenital heart disease, culture-proved sepsis, hemodynamically significant patent ductus arteriosus, or grade III-IV intraventricular hemorrhage. The study was approved by the centers' institutional review board and parents gave written informed consent before recruitment.

Study Procedure

Each infant was studied for 3 consecutive time periods, serving as his or her own control. Eleven infants started the study while placed supine for 3 hours, followed by 3 hours of prone positioning, and back to supine for 3 hours; and 12 infants started in the prone position with consecutive periods of supine and then prone position. The position at study entry was randomly assigned. To avoid a bias deriving from different "prestudy" positions, all infants started the study after 3 hours of prone position.

During the 9-hour study period, the infants were handled every 3 hours, including routine care and gavage feeding. To allow a stabilization period after each care and position change, 2-hour SpO_2 histograms were recorded at the end of each 3-hour period. The position was changed and the study was stopped before the end of the 3-hour period in case of acute deterioration that required an intervention that could not have been done in the prone position, the infant was unsettled for >15 minutes as represented by an increase in basal heart rate by >20 bpm or infant cry, or a change in fraction of inspired oxygen (FiO_2) requirements of >0.3 for >15 minutes.

Respiratory support settings, minimal and maximal FiO_2 requirement, vital signs, and apneas were documented during the study. All infants were gavage fed via nasogastric tube. Length of feeds and saturation probe position were not changed during the study period. FiO_2 was manually controlled by the care team.

Measurements

SpO_2 was monitored continuously using pulse oximetry with 0.5 Hz sampling rate and normal sensitivity setting (Masimo, Irvine, California). The SpO_2 targets in our units are 90%-94%, and alarm limits are set to 89%-95% for infants on FiO_2 >0.21, and 89%-100% for infants in FiO_2 of 0.21. Two hours histograms with a 1-second real-time sampling rate were recorded from Phillips Intellivue MX550 monitors (Software Revision L.01.18). In the SpO_2 histogram, the vertical axis shows the percentage of time spent in each SpO_2 value and the horizontal axis shows SpO_2 values from 81% to 100%, 1% for each bar. Time spent in SpO_2 ≤80% is presented as a single bar, first from the left. Although the foreground bars represent time spent in each SpO_2, the background bars represent the cumulative time spent in the SpO_2 range below, that is, the percentiles.

A classification system based on the number of bars between the 10th and 90th percentiles (the width of the histogram), and the time spent in SpO_2 ≤80% was used to quantify oxygenation stability.[15] Types 1 and 2 are considered stable as the SpO_2 range (calculated by counting the bars-each represents 1%) between 10th and 90th percentile is <10% (<5% for type 1 and 5%-9% for type 2). Types 3-5 are considered unstable with SpO_2 between the 10th and 90th percentile ranges ≥10% and increasing amount of time in SpO_2 ≤80%[15] (**Figure 1**, A).

Statistical Analyses

Based on our previous study showing 80% unstable histograms among infants receiving noninvasive respiratory support and FiO_2 >0.21, and with extrapolation to our study population of more stable infants, we estimated 70% unstable histograms in the supine position with a decrease of 50% to 35% unstable histograms while prone.[15] The sample size was found to be 31 histograms in each position. The type I error was set to 5% and power was set to 80%.

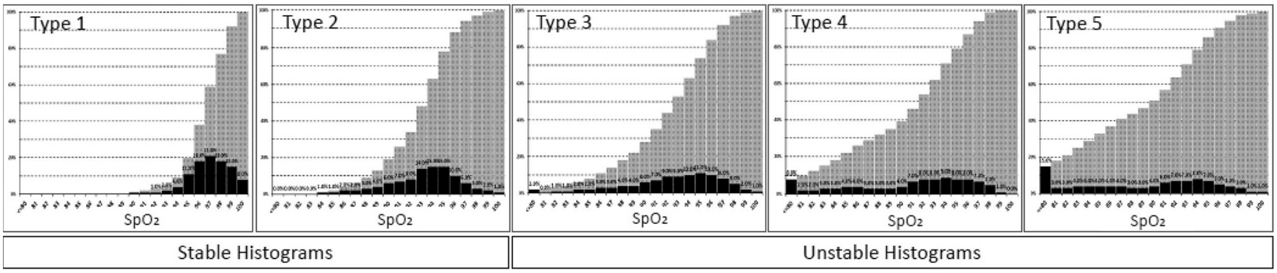
Data were statistically analyzed using SigmaPlot, version 11.0 (Systat Software Inc, San Jose, California) and Minitab, version 16.2.2 (Minitab Inc, State College, Pennsylvania). All data were tested for normal distribution (Kolmogorov-Smirnov test). Statistical analysis included descriptive statistics and comparisons of parameters between positions. For the comparison of 2 groups with normal or nonparametric distributions, we used paired and unpaired Student *t* tests for normally distributed continuous variables, and the appropriate nonparametric test (Mann-Whitney rank-sum test) when normality test failed. ANOVA and repeated measures ANOVA were used for comparison of continuous variables between >2 groups (3 positions). Paired tests (paired *t* test and repeated measures ANOVA) were used for comparison of the time spent in each saturation range following the same infants' changes in positions over time.

To verify the results of our comparisons between the 3 positions using repeated measures ANOVA and cover for other possible treatments effects, we also ran a mixed linear model that gave the same results (linear latent growth mixture models using MPlus, version 7.2, Muthen & Muthen). Data were presented as mean ± SD for normally distributed variables, or median with IQR for variables with a nonparametric distribution. The χ^2 test or Fisher exact test were used as appropriate for comparisons of categorical variables. Statistical significance was set at a *P* value of <.05.

Results

Overall, 23 infants were included in our study (**Table**). During the study period 15 infants (66%) received nasal intermittent positive pressure ventilation support, 7 (30%) were on high-flow nasal cannula, and 1 (4%) was supported by nasal continuous positive airway pressure. Twelve infants (52%) were male. No major events were recorded and all infants completed the study. No difference was found in the number of documented apnea events in

A



B

SpO_2 range	percentage of time spent in **prone** position mean ± SD/median(IQR) N = 35	percentage of time spent in **supine** position mean ± SD/median(IQR) N = 34	*P* value
<80%	1(0.0,3.0)	3.5(2.0,6.0)	<.001*
<90%	13.2 ± 10.0	24.1 ± 13.7	<.001^
90-94%	34.0 ± 18.6	37.2 ± 15.8	.44^
>94%	52.4 ± 23.4	39.7 ± 26.0	.037^

Figure 1. A, The histogram classification system, based on the width of the histogram and the amount of time spent in SpO_2 ≤80%. Types 1 and 2 are defined as stable, and types 3-5 as unstable.[15] **B**, Time in various SpO_2 ranges in the different positions. *Mann-Whitney rank-sum test. ^*t* test.

prone position as compared with supine (median, 0 [IQR, 0-0.75] vs 0 [IQR, 0-1], respectively; *P* = .73). Sixty-nine histograms were obtained during the study period, 34 histograms in the supine position and 35 histograms while prone. Minimal and maximal FiO_2 values were similar in both positions (0.25 ± 0.04 and 0.29 ± 0.09 for prone, 0.25 ± 0.05 and 0.29 ± 0.08 for supine, respectively). Unstable histograms were more common in supine vs prone position (20/34 [59%] vs 10/35 [29%]; *P* = .02, respectively). Figure 1 describes the different histogram types—stable vs unstable—and shows the differences in time spent in different SpO_2 ranges between the 2 groups (prone vs supine). During prone positioning, oxygenation instability was significantly lower, and infants spent significantly less time in SpO_2 ≤80% and <90%, and more time in SpO_2 >94%.

During the study period, each infant had 2 position changes, and we had 46 position changes overall. Position change significantly affected oxygen stability: 6 of 13 (46%) unstable histograms became stable after position changed from supine to prone, and 6 of 16 (38%) stable histograms during prone became unstable while supine (*P* = .02). Furthermore, we found that the percentage of time spent in the lower SpO_2 levels, <80% and <90%, was higher in the supine position, and the time spent in SpO_2 >94% was higher in

Table. Characteristics of the study group

Demographic data	Mean ± SD or No. (%)	Range
Gestational age (weeks)	26.8 ± 2.7	24.1-35.4
Birth weight (g)	782 ± 220	520-1305
Age at time of study (days)	28.4 ± 15.4	4.0-57.0
Corrected gestational age at study (weeks)	30.8 ± 2.7	27.3-40.6
Weight at study day (g)	977.0 ± 268.0	575.0-1783.0
Minimal FiO_2	0.25 ± 0.04	0.21-0.40
Maximal FiO_2	0.29 ± 0.09	0.21-0.60
PEEP*	6.5 ± 0.6	6-7.5
PIP†	18.9 ± 2.5	13-22
Flow rate‡ (LPM)	2.6 ± 0.6	2-3
Past endotracheal ventilation	3/23 (13)	–
Surfactant	16/23 (70)	–

*Among infants on nasal intermittent positive pressure ventilation and nasal continuous positive airway pressure (n = 16).
†Among infants on nasal intermittent positive pressure ventilation (n = 15).
‡Among infants on high-flow nasal cannula (n = 7).

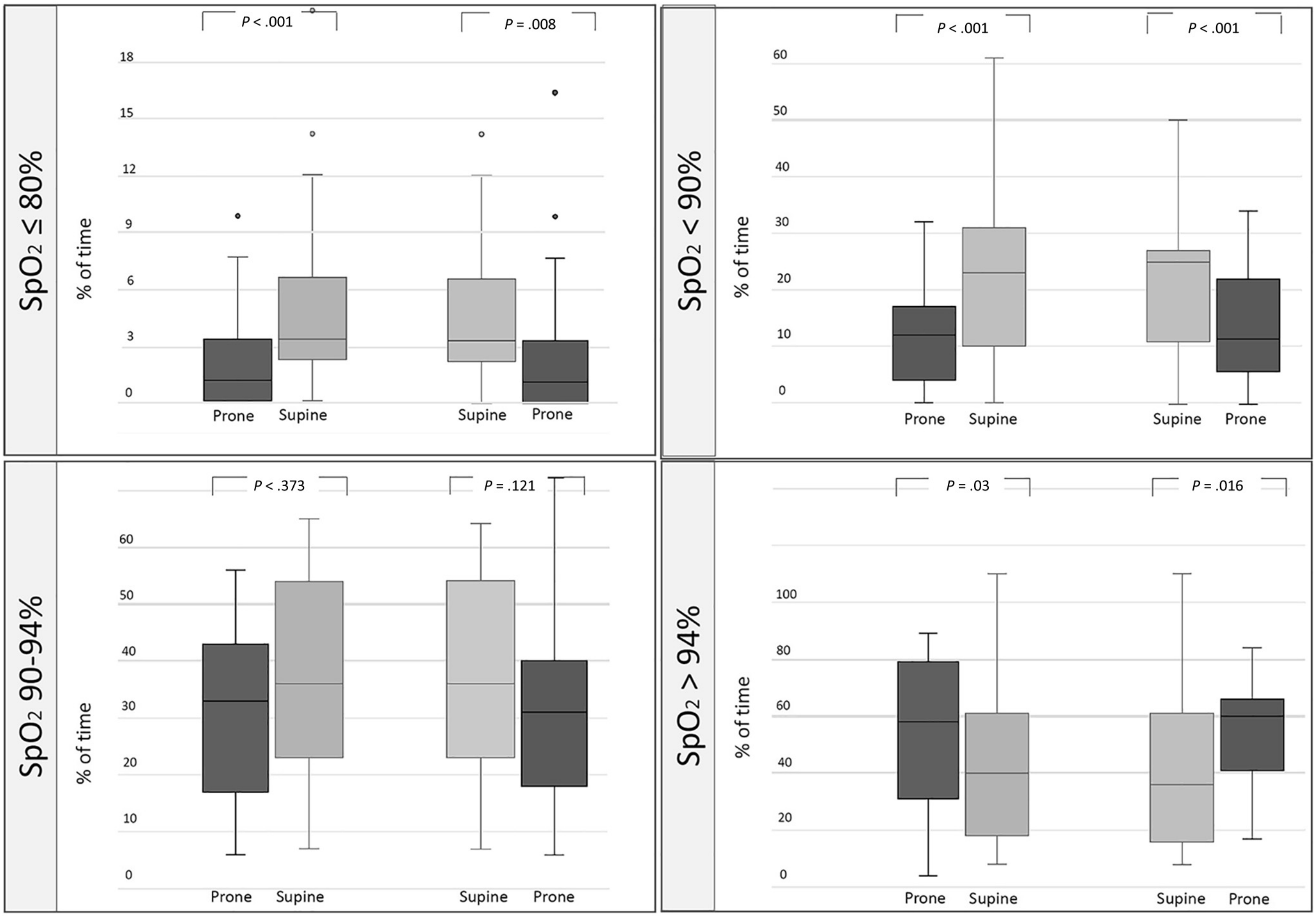


Figure 2. Percent of time spent in different SpO_2 ranges before and after a position change. Prone to supine (n = 23). Supine to prone (n = 23). Statistical analysis was done by paired *t* test. The box contains the IQR and the central line denotes the median value. The whiskers mark the minimum and maximum values calculated by 1.5 times the IQR below the first quartile and above the third quartile. The dots represent the outliers beyond these bounds.

the prone position. There were no significant differences in time spent in SpO_2 90%-94% before and after position change. Time spent in the different SpO_2 ranges before and after position change is shown in **Figure 2**.

Analyzing all 3 positions per infant, we found the same trend of increased instability during supine position, although that did not reach statistical significance ($P = .06$). Furthermore, infants who started the study while supine spent less time in SpO_2 ≤80% ($P = .012$), <90% ($P = .008$), and more time in SpO_2 >94% ($P = .002$) while placed prone. The same trend was found among infants who started the study prone, although that did not reach statistical significance (**Figure 3**).

Discussion

Our study found that premature infants receiving noninvasive respiratory support demonstrated less SpO_2 instability, spent less time in the lower SpO_2 range, and more time in the higher SpO_2 range while placed prone. Using the SpO_2 histograms we were able to quantify SpO_2 instability and to document the time the infants spent in different SpO_2 levels in each position.

Different methods were used to assess the effect of body position on the oxygenation status of premature infants; among them were average SpO_2 measurements, arterial oxygen saturation, transcutaneous PaO_2, and manually recording desaturation events.[7-13,16-18] These methods yielded inconclusive results regarding the superiority of prone position on oxygenation and did not evaluate the overall oxygenation instability in the different positions.[14] SpO_2 histogram classification system, displayed by the bedside monitor, allows more insight and easily quantifies the degree of oxygenation stability, and the time spent in various SpO_2 ranges including the recommended SpO_2 range of 90%-94%, <80% and <90%, and >94%.[15,19]

Our data show that infants who are placed prone spend less time in SpO_2 <90%, and ≤80% and more time in SpO_2 >94% as compared with supine. The time spent within our neonatal intensive care unit's target range of 90%-94% was not higher during prone position as expected (**Figure 2**). Interestingly, the percent of time >94% was high, especially in the prone

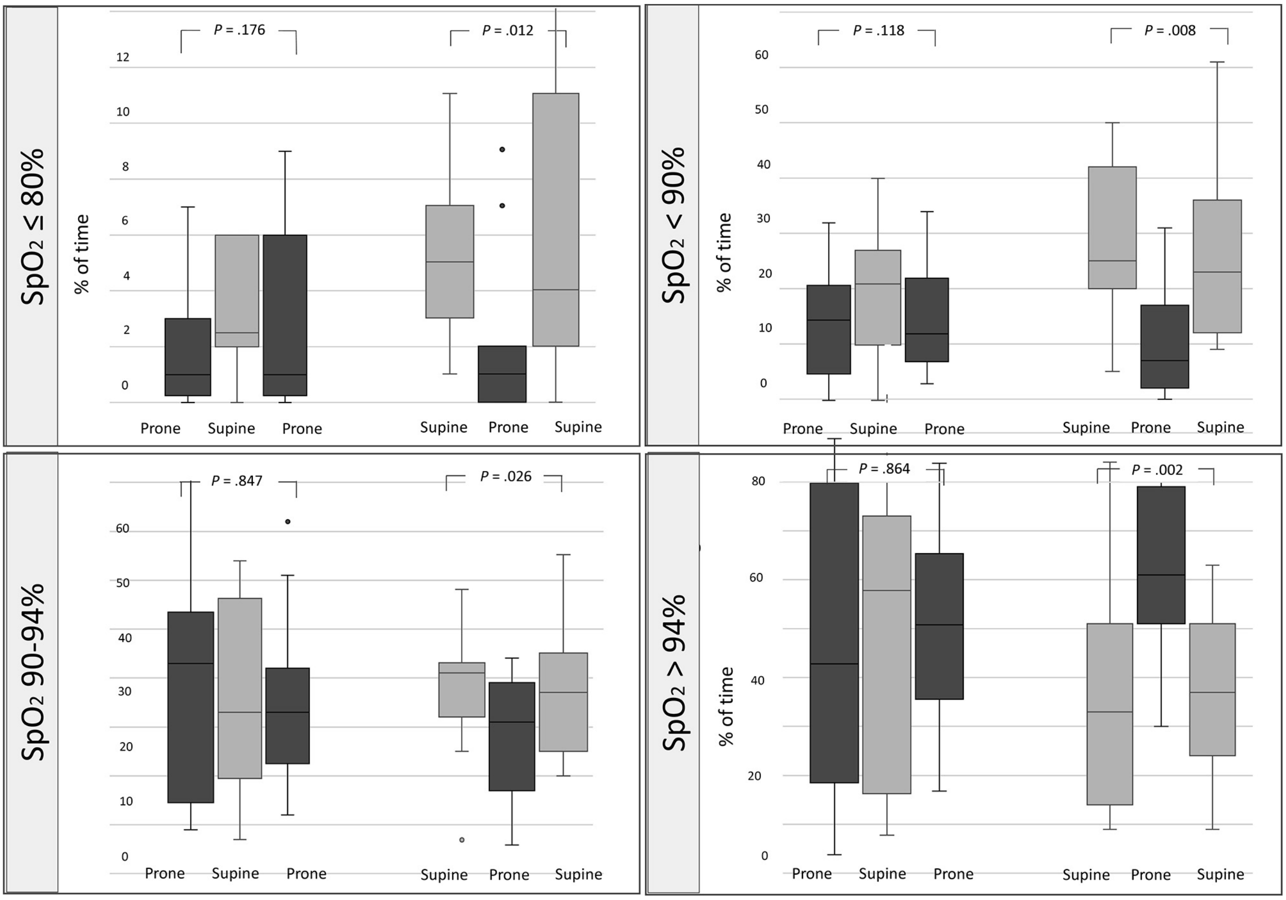


Figure 3. Percent of time spent in different SpO_2 ranges among infants who started the study prone and infants who started supine. Statistical analysis was done by repeated measures ANOVA. No statistically significant differences were found between the first and the last position in both groups. Prone to supine to prone (n = 12). Supine to prone to supine (n = 11). The box contains the IQR and the central line denotes the median value. The whiskers mark the minimum and maximum values calculated by 1.5 times the IQR below the first quartile and above the third quartile. The dots represent the outliers beyond these bounds.

position (53%). However, at certain times, part of the infants were on 0.21 FiO_2 and further weaning the FiO_2 could not be done. Nevertheless, a possible explanation for these results is the tendency of caregivers to accept higher SpO_2 to prevent hypoxemia. Van Zanten et al showed that caregivers increase FiO_2 in response to a short hypoxic episodes, but delay the titration of FiO_2 once the hypoxic episode is over, thus leading to a longer hyperoxia.[20] A similar observation was described by van der Eijk et al, showing that extremely low birth weight infants spent a total of 46% outside their neonatal intensive care unit range: 30% in SpO_2 >94% and only 16% SpO_2 <88%.[21] Moreover, when FiO_2 was controlled by automated closed-loop system, as compared with manual adjustments by the team, time in SpO_2 >93% significantly decreased and infants spent more time within the desired SpO_2 range.[22] Our findings may call for increased awareness to adjust FiO_2 when changing to prone position.

The decrease in time spent in SpO_2 ≤ 80% in prone position is especially significant, because time in SpO_2 ≤80% has been shown to adversely affect neurodevelopmental outcomes in extremely premature infants.[4] However, the influence of the prone position on cerebral oxygenation and blood flow among premature infants is not yet clear; therefore, the cumulative effect of oxygenation and blood flow will need to be assessed before a conclusion regarding the optimal body position among VLBW infants is made.[23-25]

Although the differences between time spent in SpO_2 ≤80%, <90%, and >94% was significantly different among infants who started the study supine, infants who started in the prone position demonstrated the same trend, although that did not reach statistical significance (**Figure 3**). This finding can be explained by the small sample size. However, a possible explanation for this observation is a protective effect of the prone position, derived from higher functional residual capacity and tidal volume demonstrated in preterm infants during prone position.[8,10,11] Because all infants started the 9-hour study after 3 hours in the prone position, infants who started the study prone practically spent 6 hours in the prone position before their position was changed to supine. Therefore, after the first position change from prone to supine, the increased oxygenation instability observed in the supine position was less significant than after only 3 hours of prone positioning.

Using electrical impedance tomography, Hough et al demonstrated a physiologic peak in lung volume 2 hours after a position change, regardless of the position itself.[26] However, in our study we consistently demonstrated superiority of prone positioning in regard to oxygenation stability; therefore, we suggest that the body position influences oxygenation, and not the position change itself.

The limitations of our study are the small sample size and the fact that the studied infants were relatively stable with low mean FiO_2 and on noninvasive support. Because of the small sample size, we could not analyze the 3 modes of noninvasive respiratory support separately. The strength of our study is the prospective design, randomization sequences of positioning, innovative assessment of oxygenation instability with SpO_2 histograms, and the inclusion of infants only on noninvasive ventilation, the respiratory support most commonly used among premature infants nowadays, which is, therefore, most clinically relevant.

In conclusion, we showed that prone position decreased oxygenation instability and resulted in higher oxygenation among VLBW premature infants on noninvasive respiratory support. Using SpO_2 histograms allows easy bedside assessment of oxygenation stability, and quantification of the time spent in different SpO_2 ranges. Future studies are needed to assess the clinical implication of SpO_2 histogram use on neonatal clinical outcomes. ■

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