Positional Effects on Lung Mechanics of Ventilated Preterm Infants with Acute and Chronic Lung Disease

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Summary. Background: The role of prone position in preterm infants has not been completely

INTRODUCTION

Prone positioning has been used to improve oxygenation in adults undergoing mechanical ventilation for severe hypoxemia and acute respiratory failure since 1974.[1–4] Several studies investigated the rationale for prone positioning and its possible role in protective ventilation.[5,6] Animal studies showed that prone position reduces ventilation induced lung injury, secondary to greater recruitment and a more homogeneous distribution of the stress applied to the parenchyma.[7–9] These mechanisms may explain the survival advantage in severely hypoxemic adult patients.[10]

As preterm infants are more exposed than adults to injury from oxygen toxicity and aggressive mechanical ventilation, prone positioning has been investigated as a potential tool for improving respiratory support in neonatal respiratory distress syndrome (RDS). A meta-analysis of data from randomized and quasi-randomized trials incorporating 133 preterm infants receiving mechanical ventilation[11] showed that prone versus supine positioning was associated with a significant improvement in oxygenation, ventilation, and thoraco-abdominal asynchrony. However, the magnitude of this change was rather small with no evidence of improvements in clinically relevant outcomes.[11]

The reason for the modest response to prone positioning in preterm newborns is likely related to the structural differences in the infant respiratory system compared

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Conflict of interest: No financial assistance was received for the study. On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Received 16 November 2013; Accepted 7 March 2014.

with the adult one, such as the incomplete growth of alveoli and bronchi, the under-developed airway cartilage, small airway and intercostal muscles,[12,13] the more compliant chest wall and the smaller effect of the gravitational force[14,15] due to the smaller geometrical distance between the dorsal and the ventral regions.

To the best of our knowledge, only two studies investigated the effect of prone positioning on pulmonary mechanics in mechanically ventilated neonates. While one found an improvement in resistance and work of breathing in the prone versus supine position during the breaths supported by the ventilator,[16] the other did not find any difference in terms of resistance but reported a significant improvement in static compliance and work of breathing in the prone versus the supine position during unsupported breaths.[17]

The difficulty in assessing lung mechanics in small preterm newborns is a major factor preventing a better understanding of the effect of prone positioning. Recently, the forced oscillation technique (FOT), a non-invasive method for the assessment of respiratory mechanical properties,[18] has been successfully applied to the study of respiratory mechanics in preterm infants during mechanical ventilation.[19] Briefly, FOT determines the mechanical properties of the respiratory system by its response to a small high-frequency ($\geq$5 Hz) oscillatory pressure superimposed on the standard breathing signal, allowing an accurate assessment of lung mechanics without interfering with the spontaneous breathing activity of the patient. In particular FOT permits to calculate resistance (Rrs) and reactance (Xrs), with the latter accounting for the elastic and inertial properties of the respiratory system.

The aims of our study were, in mechanically ventilated preterm infants: (1) to study the short term effect of supine and prone position on the mechanical properties of the respiratory system assessed by FOT; (2) to evaluate whether it is possible to identify a sub-group of infants, with acute or chronic lung disease, that benefit most from prone positioning.

MATERIALS AND METHODS

All measurements were performed in the Neonatal Intensive Care Unit of Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, University of Milan. The study was approved by the local Ethics Committee and informed parental consent was obtained for each infant.

Subjects and Protocol

Preterm infants assisted by conventional mechanical ventilation, either with RDS or with evolving bronchopulmonary dysplasia (evolving BPD, see below), were included in the study. Based on data reported in previous studies[16,20] we estimated that, to get a statistical power of 0.8, the sample size must be of six infants for the RDS group and of eight for the BPD group.

RDS was diagnosed on the basis of typical clinical and radiographic signs: tachypnea, dyspnea, cyanosis in room air together with the typical chest radiographic finding of a uniform reticulogranular pattern "ground-glass appearance" accompanied by peripheral air bronchograms.

Infants ventilated for more than 20 consecutive days at the time of measurement, who later on received the diagnosis of BPD [defined as in Ref.[21]], were defined as infants with "evolving BPD." Exclusion criteria were the presence of severe intracranial hemorrhage (III/IV) and/or malformations.

All infants were nasally intubated (endotrachal tube size 2.5–3.5 mm, Portex, Smiths Medical, St. Paul, MN) and mechanically ventilated (Babylog 8000 plus, Drager or Leoni Plus, Heinen & Lowenstein) in synchronized intermittent positive pressure (S-IPPV) mode with volume guarantee with a target tidal volume (Vt) of 5 ml/kg.

Infants were studied for 15 min periods in both the supine and prone positions in a computer-generated random sequence. At the end of the first 10 min of each period, SpO_2, heart rate (HR) and transcutaneous blood gases ($ptcO_2$ and $ptcCO_2$) were recorded. Immediately after these measurements, forced oscillations at 5 Hz were applied for the remaining 5 min while flow and pressure data were continuously recorded.

The ventilator settings were kept constant at the baseline values, FiO_2 was adjusted if needed by the attending clinician in order to maintain oxygen saturation (SpO_2) between the clinical limits (86–94%).

Experimental Set Up

Forced oscillations were delivered using a new experimental set-up described in detail elsewhere.[19] Briefly, low amplitude high-frequency (5 Hz) sinusoidal pressure oscillations ($\sim$2 cmH_2O peak-to-peak) were generated by moving the piston of a 20 ml glass syringe using a servo-controlled linear motor (P01-23 $\times$ 80 and E100-AT, Linmot, Spreitenbach, Switzerland). The syringe was connected to the inspiratory line of the mechanical ventilator close to the inlet of the endotracheal tube. Pressure (Pao) and airflow (V'ao) were measured at the airway opening by a differential pressure transducer (PXLA0075DN, Sensym, Milpitas, CA) and a mesh-type heated pneumotachograph (Hans Rudolph 8410A) coupled with a differential pressure transducer (PXLA02 $\times$ 5DN, Sensym). The measuring apparatus introduced a dead space of 1.3 ml, which is within the ATS/ERS recommendations of 2.5 ml/kg for our expected population. The accuracy of the set-up for the measurement of impedance at 5 Hz, as assessed on an in vitro model (Rrs = 103 cmH_2O^*s/l and Xrs = -67 cmH_2O^*s/l) of the infant respiratory system, was >97% for Rrs and

>99% for Xrs.[22] The reproducibility in our population, evaluated as the variability of the values computed over several breaths, was 7 cmH_2O^*s/l for both Rrs and Xrs.

Signals were sampled at 600 Hz by the same A/D-D/A board used to control the motor and recorded on the personal computer.

Since uncuffed tubes were used, the degree of leaks at baseline and after each change in posture was monitored using the ventilator and kept below its threshold.

SpO_2, HR, $ptcO_2$, and $ptcCO_2$ were measured by Philips IntelliVue X2 and Linde Medical Instruments Microgas, respectively.

Data Analysis

Taking advantage of the a priori knowledge of the frequency components of the forcing signal, respiratory system impedance (Zrs) was computed using the least squared method.[23] For each posture, the values of Rrs and Xrs at end-expiration were obtained as the average values of approximately 20 breaths free from artifacts and corrected for the contribution of the endotrachel tube.[24]

The time course of lung volume was obtained by integrating V'ao and by removing the linear drift. From this trace, Vt, respiratory rate (RR), duty cycle (Ti/Ttot), and minute ventilation ($MV = Vt \cdot RR$) were computed.

Statistical Analysis

Data were tested for normality using the Kolmogorov–Smirnov test and expressed as mean and standard deviation (SD). Differences between supine and prone positions are expressed as mean (95%CI). Significance of difference between postures was tested by two-way ANOVA for repeated measures using posture and patient's group (RDS or evolving BDP) as factors. Multiple comparison after ANOVA was performed by Holm–Sidak test. Differences were considered statistically significant for $P < 0.05$.

Pearson correlation was performed to test whether there was a statistical dependence between the posture related changes in Rrs, Xrs, $ptcCO_2$, $ptcO_2/FiO_2$, minute ventilation, baseline ventilatory settings, body weight or endotracheal tube size.

RESULTS

Eighteen neonates (Table 1) were enrolled in the study: nine infants with RDS and nine with evolving BPD. Seven out of the evolving BPD group developed severe BPD and two developed moderate BPD (as defined in Ref.[21]). In two infants with RDS and two infants with BPD it was not possible to obtain reliable measurements of $ptcCO_2$ and $ptcO_2$.

TABLE 1— Patients' Demographic Characteristics and Ventilatory Settings

	GA (week)	BW (g)	PNA (day)	Weight (g)	Gender	PEEP (cmH_2O)	PIP (cmH_2O)	Vt (ml)	FiO_2
RDS	26	940	7	760	F	5.0	23	4.3	21
	28	1,180	2	1,120	F	5.0	21	4.5	21
	27	565	1	580	M	4.5	24	3.5	25
	24	750	7	645	F	4.5	22	6.5	30
	29	1,440	1	1,360	M	4.0	20	5.2	21
	26	820	7	920	F	5.0	20	4.8	21
	25	850	7	765	M	5.0	24	6.5	30
	25	890	7	850	M	4.0	25	5.5	27
	29	1,400	5	1,355	M	5.0	24	6.5	21
Mean (std)	27 (2)	982 (297)	5 (3)	928 (289)	4F–5M	5.0 (0.4)	22 (2)	5.0 (1.1)	24 (4)
Evolving BPD	25	430	50	895	F	4.0	20	4.0	35
	23	470	32	725	F	5.0	19	5.0	25
	25	815	21	1,020	M	4.4	23	5.5	21
	24	460	28	745	F	4.0	25	4.4	35
	24	520	35	905	M	5.7	26	6.5	45
	24	650	29	915	M	5.0	22	6.0	21
	24	750	32	840	F	5.0	20	5.2	21
	24	670	27	880	M	4.0	26	5.0	35
	27	660	40	1,200	M	5.0	28	6.1	30
Mean (std)	24 (1)	603 (138)	33 (8)	903 (143)	4F–5M	4.7 (0.6)	23 (3)	5.3 (0.8)	30 (8)
All infants									
Mean (std)	25 (2)	792 (297)	19 (15)	916 (221)	8F–10M	4.7 (0.5)	23 (3)	5.3 (0.9)	27 (7)

Data are expressed as mean (SD). GA, gestational age; BW, birth weight; PNA postnatal age; PEEP, positive end expiratory pressure; PIP, positive inspiratory pressure, intended as the upper limit pressure set on ventilator; Vt, targeted tidal volume; FiO_2, fraction of inspired oxygen.

TABLE 2— Breathing Pattern and Oxygenation Parameters for Each Position

	RR (breaths/min)	Ti/Ttot (%)	Minute ventilation (ml/min)	FiO_2	$ptcO_2$ (mmHg)[1]	$ptcCO_2$ (mmHg)[1]
RDS						
Supine	55 (17)	36.8 (7)	312 (131)	24 (5)	54 (19)	61 (14)
Prone	54 (12)	36.8 (5)	305 (110)	25 (4)	55 (17)	57 (16)
Evolving BPD						
Supine	49 (5)	38.7 (6)	379 (156)	36 (13)	49 (17)	70 (12)
Prone	48 (5)	35.6 (3)	350 (122)	35 (12)	53 (13)	64 (10)

Data are expressed as mean (SD). RR, respiratory rate; Ti/Ttot, percentage of inspiratory time; FiO_2, fraction of inspired oxygen; $ptcO_2$, transcutaneous partial pressure of oxygen; $ptcCO_2$, transcutaneous partial pressure of carbon dioxide.
[1]Calculated only on seven infants.

The ventilator settings at the time of the study are also reported in Table 1. Breathing pattern and oxygenation parameters are shown in Table 2. FiO_2 was significantly higher in neonates with evolving BPD compared to the RDS group ($P = 0.02$). However, in both groups there were no statistically significant differences for any of these parameters between the two postures.

Figure 1 shows Rrs, Xrs, $ptcCO_2$, and $ptcO_2/FiO_2$ in the supine and prone position for all infants. Xrs was, on average (95%CI), −2.6 (−8.9, 3.6) cmH_2O^*s/l lower, $ptcCO_2$ was 4 (−0.1, 9.7) mmHg higher and $ptcO_2/FiO_2$ −0.1 (−0.3, 0.2) mmHg lower in the supine than in prone position (n.s.). However the statistical power that we had was not high enough to exclude that we failed in detecting differences in these parameters. The behavior of Rrs was similar in all patients: on average it was 9.8 (1.3, 18.3 as 95%CI) cmH_2O^*s/l higher in the supine compared with the prone position ($P = 0.02$).

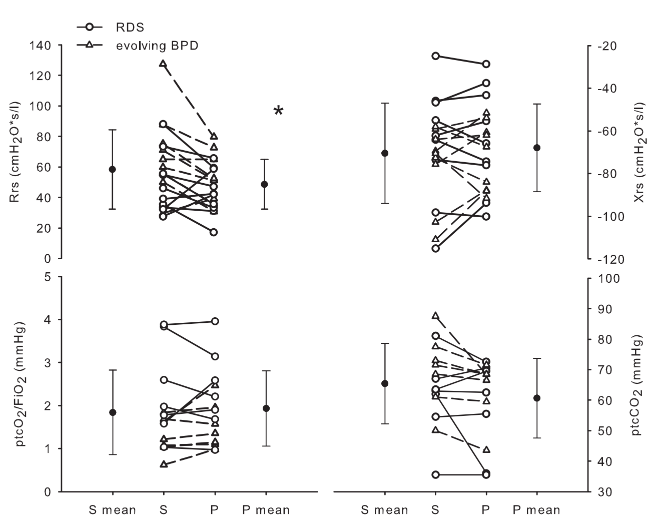

Fig. 1. Lung mechanics and gas exchange in prone versus supine position. Rrs, Xrs, $ptcO_2/FiO_2$, and $ptcCO_2$ in the supine (S) and prone (P) position. Individual data (open symbols) and mean (SD) values (closed symbols) for all patients are reported. *$P < 0.05$ between P and S.

Differences in Rrs, Xrs, $ptcCO_2$, and $ptcO_2/FiO_2$ between prone and supine position in the subgroups of infants with evolving BPD and RDS are shown in Figure 2. On average the evolving BPD group presented greater values of Rrs ($P = 0.04$) and $ptcCO_2$ (n.s.) and lower values of Xrs (n.s.) and $ptcO_2/FiO_2$ ($P = 0.04$) than the RDS group. In the evolving BPD group Rrs was, on average, 15.9 (3.6, 28.3; 95%CI) cmH_2O^*s/l lower in the prone than in the supine position changing from 69.0 ± 27.4 to 53.0 ± 16.7 cmH_2O^*s/l ($P = 0.01$), while in the RDS group it was 3.7 (−9.2, 16.5) cmH_2O^*s/l lower (n.s.) changing from 47.7 ± 20.6 to 44.0 ± 15.6 cmH_2O^*s/l (n.s.). In the evolving BPD group, $ptcO_2/FiO_2$ was on average 0.2 (−0.1, 0.5) mmHg higher in the prone position versus the supine position. The difference was not significant but the statistical power was not high enough to exclude that we failed in detecting a difference in oxygenation because of the small sample size (see discussion). There was a significant correlation between posture related changes in Xrs and Rrs ($r = -0.656$, $P = 0.003$) and between changes in $ptcO_2/FiO_2$ and $ptcCO_2$ ($r = -0.560$, $P = 0.04$), but we did not find any correlation between changes in lung mechanics, $ptcO_2$ or $ptcCO_2$ both considering the whole population or the two subgroups separately. Finally, we found no correlation between baseline ventilator settings, body size or endotracheal tube diameter and any outcome.

DISCUSSION

The main findings of this study are: (i) Rrs was decreased in the prone versus supine position in preterm infants receiving mechanical ventilation, (ii) changing posture did not affect Xrs significantly, (iii) the difference in Rrs between the supine and prone position was greater in evolving BPD than in RDS infants; (iv) we did not find any statistically significant correlation between changes in lung mechanics and transcutaneous blood gas parameters.

Both experimental protocol and set-up were well tolerated by all infants. We did not observe changes in

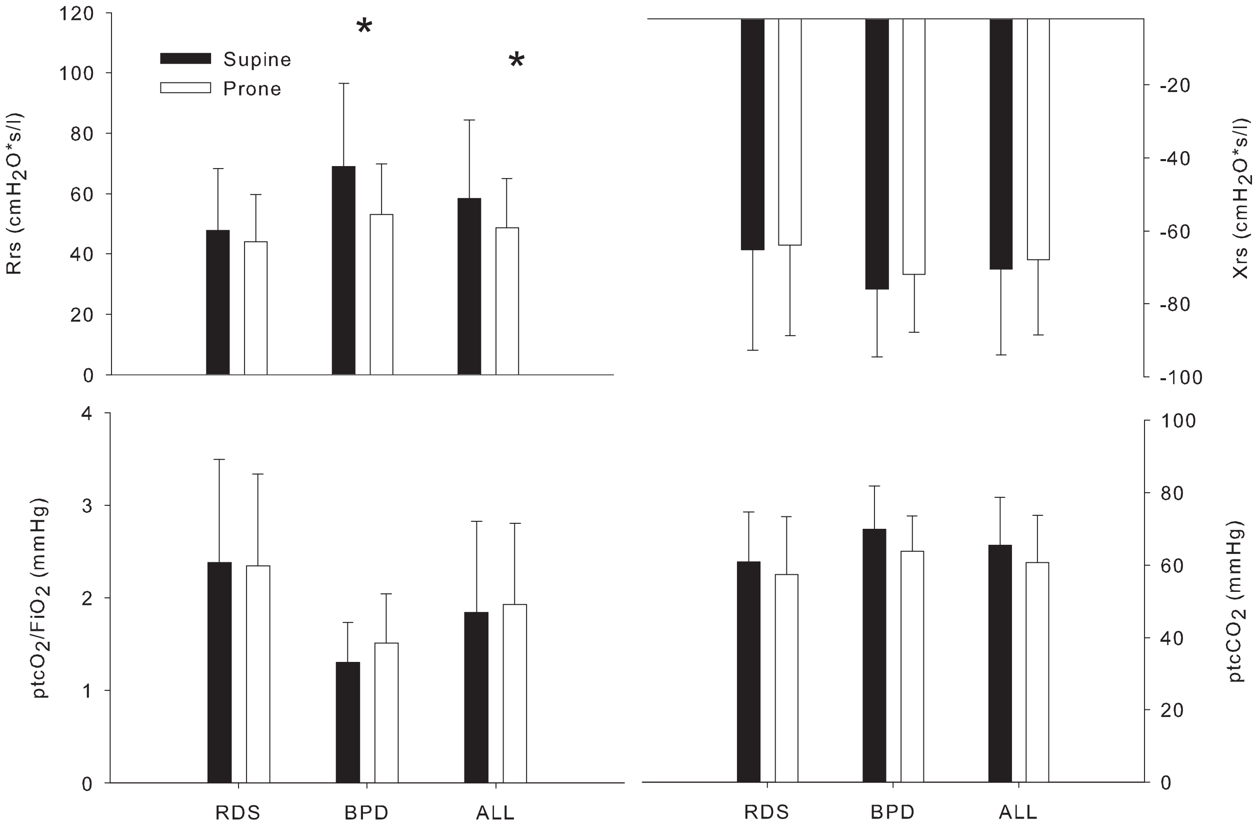

Fig. 2. Lung mechanics and gas exchange in prone and supine position in infants with RDS and BPD. Rrs, Xrs, $ptcO_2/FiO_2$, and $ptcCO_2$ in the prone (P, gray) and supine (S, black) position in the BPD group, in the RDS group and for all patients. Data are reported as mean and SD. $^*P < 0.05$ between P and S.

transcutaneous blood gasses and saturation due to the dead space added by the measuring apparatus or to the onset of oscillations. We did not experience any problem due to the change in posture including accidental extubation, bleeding or leaks. In all cases we managed to have leaks below the detection threshold of the ventilator at baseline and after changing position. Moreover, since at 5 Hz the impedance of the leak is very high compared to the impedance of the patient, possible residual leak should have had only a limited impact on the quality of the measurements.

As changes in the sleep state or movements or changes in body position may affect lung mechanics, all measurements were performed during quite sleep of the newborn. Quite sleep was defined as closed eyes, regular respiration, and absence of eye and gross body movements.

All babies were supine prior to the beginning of the study, therefore it is possible that the initial posture could have influenced the results. However, a posteriori analyses showed that there were no differences in outcomes between the babies who were randomized to begin in the supine vs. prone position.

In our study, we found only moderate changes in lung function in the prone versus the supine position, in contrast with the marked effects observed in adult patients.[1–4] This is likely due to the important structural and mechanical differences between the infant's and adult's respiratory system. In particular, in adult patients gravitational forces play an important role in determining the effect of positional changes on lung mechanics, while in infants, due to the smaller size and lower weight, it is likely that the non-dependent structures exert less compression on the dependent lung regions. This has been recently confirmed by two studies in which ventilation distribution, assessed by electrical impedance tomography, was found to be independent from gravity in infants either during spontaneous breathing, continuous positive airway pressure (CPAP) or mechanical ventilation.[14,15]

Effect of Posture on Lung Mechanics and Gas Exchange

In the present study, we found that Xrs (which is related to the elastance of the respiratory system) was not affected by changes in posture, while Rrs was significantly decreased in the prone position.

The effect of body position on lung mechanics that we observed is in agreement with previous studies.

Numa et al., found a significant improvement in Rrs in the prone position in infants and children with obstructive diseases.[25] Mendoza et al.[16] found no differences in dynamic compliance and a significant reduction in resistance in the prone position in a population with similar characteristics to our evolving BPD group. Schrod et al.,[26] in infants with similar characteristics to our RDS group, did not find any difference in terms of dynamic compliance. Finally, in very low birth weight infants with chronic lung disease, Mizuno and Aizawa[17] observed that before feeding the prone position resulted in a reduction in pulmonary resistance by about 20%, which is similar to what we observed in our population of infants with evolving BPD, however, in their study this difference was not statistically significant.

Differently from previous studies,[11] we did not find any change in blood gas with changing posture. When the analysis was limited to the evolving BPD group on average we observed an improvement in oxygenation (although not significant). However, we did not observe any correlation between the reduction in Rrs and changes in blood gasses. The lack of changes in blood gases with positioning may be related to the short monitoring time as changes in blood gas could have required a longer time to establish after lung mechanics had changed. Moreover, we expect that during mechanical ventilation changes in lung mechanics would not impact much on blood gasses because the resistive load is overcome by the ventilator and not by the respiratory muscles of the newborn.

Our results suggests the lack of significant alveolar recruitment/derecruitment when changing posture[27–29] and an increase of airway diameters at the level of the central airways,[30] probably due either to a slight increase in absolute lung volume in the prone position or to the effect of the weight of the lung tissue and the mediastinum on the elastic recoil forces exerted by the lung parenchyma to the external wall of the airways, or a combination of both.

Even if the reduction of Rrs in the prone position observed in the evolving BPD group was not associated to a clinical meaningful improvement of blood gasses, it could be interesting to consider this option in patients with long time constants of the respiratory system. These patients require long times for expiration and are at high risk of developing dynamic hyperinflation and high values of intrinsic PEEP (PEEPi). By reducing Rrs, prone position could reduce the time constants of the respiratory system, permitting to empty the lung in a shorter time and therefore reducing the risk of potentially harmful values of PEEPi.

Limitations of the Study

Preliminary measurements showed that major changes in lung mechanics stabilize within 1 min. However we acknowledge that we may have neglected phenomena with a longer time scale such as redistribution of fluids, adaptation of breathing pattern and changes in tissue oxygenation and CO_2 concentration. It has been recently demonstrated that breathing pattern parameters and oxygenation stabilize within 30 min of change in body position.[31] Therefore, this study design does not allow drawing conclusions about the effect of prone position for a longer time.

Another weakness of this study is that arterial blood gasses were not available, therefore, we used trascutaneous measurements (available only on 14 patients) which take longer to equilibrate and may not accurately match arterial blood gasses, especially in the older babies.

In the evolving BPD group, there is a single outlier that influences the mean difference of Rrs between prone and supine position, however, this difference is still statistically significant even without this subject. The strength of our negative results is limited by the small sample size. In fact, while the sample size has been computed to detect differences in Rrs, based on the statistical power of the tests computed on our data we cannot exclude that we failed in detecting differences in Xrs and blood gassed. With our sample size and with the observed variability in the parameters, we can conclude that, if we failed in detecting a difference between prone versus supine position, this difference is expected to be anyway below 13% for Xrs, 0.36 mmHg for ptO_2/FiO_2 and 7.0 mmHg for $ptCO_2$, with a power of 80%. Therefore, we think that, even though further studies with larger numbers of patients would clarify the role of prone positioning, the present study still provides provocative results about the effect of posture on lung mechanics in ventilated infants.

CONCLUSIONS

In conclusions, our results suggest that prone versus supine positioning does not lead to significant changes in short-term lung function assessed by FOT in mechanically ventilated infants with RDS. In patients with evolving BPD, prone positioning is associated to lower Rrs values and could have a role in the clinical management of highly obstructed patient as it reduces the time constants of the respiratory system. However, further studies are needed to confirm these data and to evaluate the effects of prone positioning in non-intubated preterm infants during spontaneous breathing or non-invasive respiratory support.

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