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Physiological Effect of Prone Position in Children with Severe Bronchiolitis: A Randomized Cross-Over Study (Bronchio-Dv)

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Conflict of interest:

F.B. received speaking fees and non-financial support from Maquet Critical Care. G.E.s research program is supported by a research grant from the Fonds de recherche en santé du Québec and recently conducted a feasibility study of a new ventilator, for which costs were supported by Maquet Critical Care. J.B. received travel support from, served as a speaker for, and through Neurovent Research serves as a consultant for Maquet Critical Care (Solna, Sweden) for conference attendance; served as a speaker for

The following disclosure was agreed upon by the University of Toronto, Sunnybrook Health Sciences Centre, St-Michael's Hospital, and the REBs of Sunnybrook and St-Michael's to resolve conflicts of interest: "Dr. Beck has made inventions related to neural control of mechanical ventilation that are patented. The patents are assigned to the academic institution(s) where inventions were made. The license for these patents belongs to Maquet Critical Care. Future commercial uses of this technology may provide financial benefit to Dr. Beck through royalties. Dr Beck owns 50% of Neurovent Research Inc (NVR). NVR is a research and development company that builds the equipment and catheters for research studies. NVR has a consulting agreement with Maquet Critical Care."

The others authors declare no conflict of interests.

Key words: viral bronchiolitis; prone position; work of breathing; esophageal pressure; non-invasive ventilation

Abbreviations:

EAdi: electrical activity of the diaphragm

Edi-catheter: catheter able to detect electrical activity of the diaphragm

FiO₂: inspired fraction of oxygen

LOS: length of stay

mWCAS: modified wood asthma clinical score

nCPAP: nasal Continuous Positive Airway Pressure,

NME: neuro-mechanical efficiency

pCO₂: partial pressure in carbon dioxide

PEEP: positive end expiratory pressure

SpO₂: pulse oxymetry

TcpCO₂: transcutaneous partial pressure in carbon dioxide

Objective: To assess the effect of the prone position on physiological measures including inspiratory effort, metabolic cost of breathing, and neural drive to the diaphragm as compared with the supine position in infants with severe bronchiolitis requiring non-invasive ventilation.

Study design: Fourteen infants, median [1st; 3rd quartiles] age 33 days [25; 58] were randomized to receive 7cmH₂O continuous positive airway pressure (CPAP) for 1 hour in the PP or in the SP, which was followed by cross-over to the SP and the PP for 1 hour, respectively. Flow, esophageal, airway, gastric, and transdiaphragmatic (Pdi) pressures, as well as electrical activity of the diaphragm (EAdi) were simultaneously recorded. Modified Wood's clinical asthma score (mWCAS) was also assessed.

Results: Median esophageal pressure-time product (PTPeso) per minute was significantly lower in PP than in SP (227 [156; 282] vs. 353 [249; 386] cmH₂O*s/min, p= 0.048), as were m-WCAS (p=0.033) and EAdi (p=0.006). The neuro-mechanical efficiency of the diaphragm, as assessed by Pdi to EAdi swing ratio, was significantly higher in PP than in SP (1.1 cmH₂O/ μ V [0.9; 1.3] vs. 0.7 cmH₂O/ μ V [0.6; 1.2], respectively, *P* = .022).

Conclusions: This study suggests a benefit of the PP for infants with severe bronchiolitis requiring non-invasive ventilation by significantly decreasing the inspiratory effort and the metabolic cost of breathing. Further studies are needed to evaluate the potential impact of these physiological findings in a larger population.

Trial Registration [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02602678) NCT02602678

Viral bronchiolitis is the most common lower respiratory tract illness and the leading cause of hospital admission in infants and young children (1). Viral bronchiolitis leads to small airway inflammation with edema, epithelium necrosis, and alveolar damage, that causes partial or total bronchial obstruction with hyperinflation, atelectasis, and ventilation perfusion mismatch resulting in higher work of breathing and hypoxemia (2). Between 5 and 22% of all cases require respiratory support in an intensive care unit (3,4) and management of infants with bronchiolitis remains heterogeneous (3,5). Prone positioning has been proposed in children with severe bronchiolitis but without supportive evidence (6,7). The prone position (PP) is easy to perform in small children (8) and is commonly used in neonatal and pediatric intensive care. In adults, the PP significantly decreases mortality in patients with severe acute respiratory distress syndrome and improves oxygenation (9). Moreover, the PP may improve respiratory mechanics and gas exchange in adults with chronic bronchitis (10) as in neonates (11). The PP is also able to decrease airway resistance (12) in children invasively ventilated for severe viral bronchiolitis and to decrease apnea occurrence in children with mild bronchiolitis (13). Therefore, we hypothesized that the PP may improve respiratory mechanics in children with severe bronchiolitis requiring nasal continuous positive airway pressure (nCPAP). The primary objective was to compare the effort and metabolic cost of breathing in PP and supine position (SP), and the secondary objective was to describe the physiological effects of the PP in infants with severe acute viral bronchiolitis.

METHODS:

We conducted a prospective randomized crossover physiological study in a 23-bed pediatric intensive care unit (PICU) of a tertiary university hospital (Hôpital Femme Mère Enfant, Lyon University Hospital, Bron, France). The study protocol was approved by the institutional review board (CPP SUD-EST3 – n° 2015-057B) and by the national medicines authority (ANSM–151048B-32). This clinical trial was recorded in the National Library of Medicine registry ClinicalTrials.gov (NCT 02602678).

Population

Infants younger than 6 months of age with a diagnosis of viral bronchiolitis admitted to the PICU for respiratory support were eligible if they met the following inclusion criteria: clinical and radiological diagnosis of bronchiolitis; need for respiratory support by nCPAP based on a modified Wood's clinical asthma score (m-WCAS) >4 and/or hypercapnic acidosis (pH <7.30 or pCO₂ >8kPa); written consent obtained from the parent(s) or guardian(s). Non-inclusion criteria were: chronic respiratory, neuromuscular, ear-nose-throat, or cardiac underlying disease; contraindication for placement of the esophageal probe; need for invasive ventilation (in particular when presenting more than 3 apneas per hour with heart rate <90/min or SpO₂ <90%, or altered level of consciousness); infants not affiliated to the French social security scheme (according to French regulation).

Measurements and recordings

After inclusion by an investigator, an esophageal pressure probe of 2.3 mm in diameter with 2 strain gauge pressure transducers (Gaeltec Devices Ltd, Isle of Skye, Scotland), 1 for

esophageal (Peso) and 1 for gastric (Pga) pressure, was inserted orally together with an oro-gastric catheter able to detect electrical activity of the diaphragm (Edi-catheter, 8Fr, 100cm, Maquet critical care, Solna, Sweden). After fixation, the correct positioning was verified by gentle manual pressure on the patient's abdomen to observe Pga fluctuations without effect on the Peso tracing and negative deflection during inspiration on the Peso tracing (14,15). The position of the Edi-catheter was also verified using the dedicated screen of the ventilator (SERVO-I-, Maquet critical care). The position of both catheters was verified after each position change. The bed was set at 30° inclination from the horizontal plane during the entire procedure. Airway pressure, flow, and electrical activity of the diaphragm (EAdi) were recorded using the SERVO-I ventilator through a RS232 serial port continuously and simultaneously with Peso and Pga using an analogical/numerical data acquisition system and transferred to a laptop (Neurovent.inc, Toronto, ON, Canada). All data were analyzed offline. Only breaths with available signals for all measures (flow, airway pressure, Pga, Peso, and EAdi) were analyzed. Time cursors were placed at the beginning of neural inspiration, the maximal inspiratory EAdi value (EAdi max), the end of neural inspiration, and at the end of neural expiration (Figure 1; available at www.jpeds.com), as previously described (16, 17). Heart rate, pulse oximetry (SpO₂), inspired fraction of oxygen (FiO₂), transcutaneous partial pressure of carbon dioxide (TcPCO₂), and m-WCAS, calculated by the caregiver, were collected at the beginning and at the end of each study period. Comfort was assessed by the nurse at the end of each study period using the EDIN scale as in a previous study of bronchiolitis (18).

Study design

The randomization sequence was generated by the clinical investigation center of the Hospices Civils de Lyon, France. Infants were randomized using an online data management

software (Clinsigh, Ennov, Paris, France) to receive SP then PP, or the converse. They were placed for 1 hour in the first position with nCPAP, followed by a 15-min wash-out period (in SP under spontaneous breathing with oxygen therapy but no CPAP), and then they were moved to the second position for 1 hour with resumption of nCPAP. Double circuit with heated humidifier and infant nasal masks (Fisher and Paykel Healthcare, Auckland, New Zealand) were used with the non-invasive CPAP mode of the SERVO-I ventilator set at +7 cmH₂O for all infants. Airway pressure, flow, EAdi, Peso, and Pga from 50 consecutive breaths during the first 5-10 minutes (initial values) and from 100 breaths during the last 50-55 min (end values) of each period were analyzed. The primary outcome was the mean of the esophageal pressure time product (PTPeso) per minute over 100 breaths during the last five min of the recording.

Secondary outcomes were: trans-diaphragmatic pressure time product (PTPdi) per minute, PTPeso and PTPdi per single breath, esophageal and trans-diaphragmatic inspiratory pressure swings (maximal amplitude of the inspiratory depression), EAdi at the end of the expiratory time (EAdi min), the difference between the minimum and the maximum EAdi values during inspiration (Δ EAdi), respiratory rate, neural inspiratory time (Ti; which corresponds to the interval between the beginning of neural inspiration and end of neural inspiration), expiratory time (Te; which corresponds to the interval between end of neural inspiration and end of neural expiration), and inspiratory time to total time ratio (Ti/Ttot). Determination of intrinsic positive end expiratory pressure (PEEP) was attempted using deflection of the esophageal

pressure at the time of flow onset from the P_{eso} baseline (19), and, in infants without nCPAP, on the value of the pleural pressure at the beginning of inspiration (14).

Based on the primary outcome, children with a lower PTP_{eso} per minute in PP than in SP were considered as responders to PP. Post hoc analyses were performed to compare responders and non-responders with prone position and to characterize the impact of the PP on EAdi during expiration and on diaphragm neuro-mechanical efficiency (NME) of the diaphragm defined as the ratio between P_{di} swings and Δ EAdi breath by breath.

Statistical analyses and sample size

Qualitative variables are reported as count and percentage, and quantitative variables are reported as median with interquartile range [1st; 3rd quartiles]. Kolmogorov-Smirnov tests was used to assess data distribution. It was calculated that 14 infants were required for a reduction of 25% of the PTP_{eso} per min in PP as compared with SP, assuming an alpha error of 5% and targeting a power of 90%. To take into account technical difficulties in recording physiological measures, a total of 16 patients were included. Clinical and physiological measures were expressed as absolute value and as relative difference over time ($100 \times (\text{End value} - \text{Initial value}) / \text{Initial value}$). The non-parametric Wilcoxon signed-rank test was used to compare paired samples. The Fisher exact test was used to compare qualitative variables. Differences were considered statistically significant at $p < 0.05$. Statistical analysis was performed using SPSS Statistics (V22, IBM, Armonk, NY, US).

RESULTS

Patients were enrolled between November 2015 and January 2016. Sixteen patients were included in the study and 2 patients were excluded from the analysis owing to a technical problem with the data acquisition system (no EAdi data for 1 patient and no flow data for the other). No patient received sedative drugs before or during the study, and 2 patients had received caffeine sulfate before admission to the PICU. The main characteristics of the 14 patients included in the analysis are reported in Table I. The median age of infants was 33 days [25; 58], 9 were boys (64%), and respiratory syncytial virus was found in all of them. Half of the patients received PP first. No adverse event was reported in the study.

Effect on clinical measures

The median m-WCAS was significantly lower in PP (3.0 [3.0; 3.0]) than in SP (3.5 [3.0; 4.0], $p=0.033$) and there was no significant difference in comfort between PP and SP (median EDIN scale 3.5 [2.0; 5.75] vs 5.5 [2; 7], $p=0.13$). TcPCO₂, FiO₂, SpO₂, and heart rate are reported in Table 2, as relative difference over the study period; there was no significant difference in these measures between PP and SP.

Effect on physiological measures

Median respiratory rate (66 [46; 78] in PP vs. 59 [52; 77]/min in SP, $p=0.40$) and respiratory cycle time durations were not different (Table 3) between the 2 positions. Mean airway pressure (Paw) measured at the Y-piece was similar in PP (6.99 cmH₂O [6.98; 7.08]) and SP (7.0 [6.96; 7.06], $p=0.93$).

Median PTPeso per min was significantly lower in PP (227 [156; 282] cmH₂O*s/min) than in SP (353 [249; 386], $p=0.048$; Figure 2), as were PTPeso per single breath (3.5 [2.9; 4.2] vs. 4.6 [3.4; 5.1] cmH₂O*s, $p=0.048$) and Swing Peso (9.3 [8.3; 12.8] vs. 14.9 [11.0; 16.2] cmH₂O; $p=0.035$; Table 3). PTPeso decreased over time in all infants while in PP and in 10 infants while in SP. The decrease of PTPeso and PTPdi per single breath or per minute over time as well as the magnitude of decrease in Peso and Pdi swings were significantly greater in PP than in SP (Table 3). During expiration, Pga swing was not different between prone and supine position 3.2 [2.3; 3.7] vs 3.1 [2.4; 3.5] cmH₂O, $p=0.95$. Intrinsic PEEP as determined by deflection of the esophageal pressure did not provide reliable results owing to interface air leaks. After attempting to correct for this leak in the analysis by removing breaths with flow onset before EAdi onset, the median intrinsic PEEP value was 0.9 [0.6; 1.5] cmH₂O in the prone position and 1.3 [0.9; 1.5] cmH₂O in the supine position ($p=0.25$). In infants without nCPAP it was not possible to obtain analyzable signals owing to agitation after removal of the interface.

Eight infants (57%; defined as responders) had a PTPeso per min lower in PP than in SP (Figure 3, A; available at www.jpeds.com). Among them, 5 were placed first in PP and 3 in

SP ($p=0.59$). The median PTPeso per min was similar in PP between responders and non-responders (227 cmH₂O*s/min [158; 280] vs. 227 cmH₂O*s/min [159; 317], $p= 0.75$) but higher in SP in responders (379 cmH₂O*s/min [360; 389]) than in non-responders (204 cmH₂O*s/min [142; 284], $p=0.043$; Figure 2). Comparison for other variables is available in Table 4 and Table 5 (both available at www.jpeds.com).

Effects on EAdi and neuro-mechanical efficiency

EAdi max and Δ EAdi were significantly lower in PP than in SP (Table 3 and Figure 3, B [available at www.jpeds.com]). EAdi min was also significantly lower in PP (2.1 [1.6; 3.6] μ V) than in SP (3.5 [2.4; 4.4] μ V, $p=0.03$) and during all expiration time (Figure 4; available at www.jpeds.com). Diaphragm NME was significantly greater in PP 1.1 cmH₂O/ μ V [0.9; 1.3] compared with SP 0.7 cmH₂O/ μ V [0.6; 1.2], $p=0.022$.

DISCUSSION

The present study described the neural and mechanical consequences of PP in children with severe bronchiolitis and found that PP can decrease the inspiratory effort (estimated by the Peso swing) and metabolic cost of breathing (estimated by the PTPeso). Measurement of mechanical variables assessing the effort of breathing associated with neural and clinical measures provides robust and original data. These indicators, focused primarily on inspiratory effort, were lower in PP as compared with SP, and they decreased over time in both positions, but more efficiently in PP than in SP. Furthermore, the EAdi, which reflects the neural drive to the diaphragm (16,20), also decreased over time and was significantly lower in PP, and the mWCAS, described previously to standardize the scoring of accessory muscles used in bronchiolitis (18,21), was also significantly lower in PP than in SP. It is also noteworthy that the decrease in the inspiratory efforts and demand was associated with stable ventilation, with no deterioration in CO₂ measurement. All mechanical, neural, and clinical measures were consistent and showed that breathing was easier in PP than in SP as previously reported in neonates (22). Concerning the diaphragm function, there was an increase of Pdi/ Δ EAdi ratio in PP, which corresponds to an improvement of the diaphragm NME (16,23,24). Rehan et al described that in healthy term infants, the diaphragm was significantly thicker and shorter in PP than in SP.(25) They hypothesized that this thickening might be attributable to an increased diaphragmatic work in PP, which is not in agreement with the findings of the present study. We hypothesize that in children with severe bronchiolitis the improvement of NME resulted from lower airway resistance, improved lung recruitment (26), and therefore improvement of the dome shape of the diaphragm and its excursion (27). Echographic assessment of the diaphragm in bronchiolitis will be interesting to confirm this hypothesis.

Among our population, 6 infants were considered as non-responders to PP. We found that the metabolic cost of breathing was similar in PP in responders and non-responders,

although a difference was observed in the SP. Infants who respond to PP had a significantly higher value of PTPeso per min in SP than non-responders. These results suggest that PP may be particularly beneficial in infants with higher effort in SP.

All infants were ventilated using a non-invasive interface (nasal mask) and presence of air leaks was the main limitation for an accurate measurement of flow (and volume) and for the calculation of work of breathing. PTP and amplitude of pleural depression (swing) were used as an estimation of the metabolic cost of the respiratory muscles and inspiratory effort, as has been reported in several studies conducted in adults and children during non-invasive ventilation (14,28). For calculation, time cursors were placed using the EAdi signal and not the flow signal for several reasons. First, in lower obstructive lung disease, the beginning of inspiration based on flow signal may be delayed and so the PTP does not consider the part due to intrinsic PEEP (29). Second, air leaks may also influence the timing of the beginning of inspiration (and expiration). Neural time cursor may therefore vary less in these conditions and this may influence the PTP calculation herein. However, pressure swing, which is independent of time, was consistent with PTP results, suggesting that the choice of neural time did not affect the conclusions of the present study.

For expiration, the similar expiratory Pga swing described suggests no change in abdominal muscle recruitment but the tonic activity of the diaphragm (EAdi min) was lower in PP than in SP in the present study. The diaphragm may play a role to preserve lung volume and to protect against collapse during mechanical ventilation in acute respiratory distress syndrome as suggested previously (30-32). In infants, the diaphragm also remains active during expiration, which is thought to contribute to actively maintain the end expiratory lung volume (33,34). Indeed, infants younger than 1 year of age have to actively maintain their end expiratory lung volume above the relaxation volume (35,36), due to the high compliance of their chest wall. Bronchiolitis seems to be a condition in which tonic EAdi is particularly high

(33). The decrease in tonic EAdi is likely to be beneficial when considering the energetic cost and the need for the diaphragm to rest during expiration.

Respiratory conditions also improved over time in the two positions. Hough et al have demonstrated in neonates, using electrical impedance tomography (EIT), that “change” in body position leads to an improvement in ventilation distribution irrespective of the position (37). Herein, change over time appears to be greater in PP than in SP. This may be explained by the fact that children with bronchiolitis have respiratory mechanics different from neonates (for example, obstructive lung disease and air trapping with high end expiratory lung volume) (38) and part of the improvement may be due to the decrease of resistance and compliance, and not only by improvement of ventilation homogeneity. Infants were placed in SP (or lateral position) before the study, and, although the study was designed as crossover study with a 15-min washout period in SP between the 2 study periods, it is not possible to exclude an ordering effect. Furthermore, Hough et al investigated lung function improvement in children under CPAP at 2 and 4 hours after change and found that the peak was at 2 hours. We evaluated lung function after 1 hour, thus the optimal duration of PP in this population needs to be defined.

The beneficial effects of PP in bronchiolitis described here are likely to be related to the significant changes in respiratory mechanics provided by this position. PP effects oppose the main consequences of the disease, namely increased airway resistance and dynamic hyperinflation that contribute to the high effort and the ventilation-perfusion mismatch (2,14). Numa et al demonstrated that in intubated children with obstructive disease, PP decreased airway resistance (12). This was also reported in adults with chronic obstructive disease in whom PP led to a decrease of resistance and dynamic hyperinflation resulting in an improvement of work of breathing (39). In preterm infants, Gouna et al described that the thoraco-abdominal synchrony was improved in PP leading to a decrease of dynamic elevation

of end-expiratory lung volume (11). PP is also known to improve oxygenation in neonates (40) and in patients with acute respiratory distress syndrome (9,41) by homogenization of the ventilation to perfusion ratio (26,42). However, we failed to demonstrate a benefit of PP on oxygenation measures, although FiO_2 tended to be lower in the PP. This may be related to the limited duration of the investigation that could have been too short to identify such differences (43).

The present study has several limitations. First, it is a physiological study with a limited sample size and a short-term evaluation. This design was chosen to have no change in the modalities of nCPAP delivery and to allow the investigators to be present during the entire recording to check continuously the interface, air leaks, and position. Second, it was not possible to test the hypothesis of lower intrinsic PEEP in response to a decrease of respiratory airway resistance and dynamic hyperinflation. Third, the change in pressure signals in PP may potentially relate to a change in mediastinal pressure transmission or a positioning against the wall of the structure. Position of catheter was checked at the beginning of each recording. Furthermore, esophageal pressure measurement remains the reference for pleural pressure evaluation and has been used in several recent studies investigating in PP (44,45). Fourth, the sleeping state that may impact the neural drive and the use of accessory muscles was not recorded. In addition, all patients were already treated by nCPAP and the level of PEEP for both positions was chosen based on previous data in bronchiolitis in SP (14,46). PP further decreased the PTP_{eso} by a third in comparison with SP but it is possible that the level of nCPAP in PP, may have become higher than intrinsic PEEP in some infants, and paradoxically increased the effort of breathing based on the waterfalls theory (39). It would be interesting to compare the effects of PP to ventilatory support in itself or with other levels of PEEP.

Further studies are needed to evaluate the potential impact of these physiological findings in infants with severe bronchiolitis.

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REFERENCES

1. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The Burden of Respiratory Syncytial Virus Infection in Young Children. *N Engl J Med.* 2009; 360:588–98.
2. Meissner HC. Viral Bronchiolitis in Children. *N Engl J Med.* 2016; 374:62–72.
3. Pierce HC, Mansbach JM, Fisher ES, Macias CG, Pate BM, Piedra PA, et al. Variability of intensive care management for children with bronchiolitis. *Hosp Pediatr.* 2015; 5:175–84.
4. Gupta P, Beam BW, Rettiganti M. Temporal Trends of Respiratory Syncytial Virus-Associated Hospital and ICU Admissions Across the United States. *Pediatr Crit Care Med.* 2016; 17:e343–51.
5. Essouri S, Baudin F, Chevret L, Vincent M, Emeriaud G, Jouvét PA. Variability of Care in Infants with Severe Bronchiolitis: Less-Invasive Respiratory Management Leads to Similar Outcomes. *J Pediatr.* 2017; 188:156–162.
6. Øymar K, Skjerven HO, Mikalsen IB. Acute bronchiolitis in infants, a review. *Scand J Trauma Resusc Emerg Med.* 2014; 22:23.
7. Nagakumar P, Doull I. Current therapy for bronchiolitis. *Arch Dis Child.* BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health; 2012; 97:827–30.
8. Fineman LD, LaBrecque MA, Shih M-C, Curley MAQ. Prone positioning can be safely performed in critically ill infants and children. *Pediatr Crit Care Med.* 2006; 7:413–22.
9. Guérin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med.* 2013; 368:2159–68.
10. Mentzelopoulos SD, Roussos C, Zakyntinos SG. Prone position improves expiratory airway mechanics in severe chronic bronchitis. *Eur Respir J.* 2005; 25:259–68.
11. Gouna G, Rakza T, Kuissi E, Pennaforte T, Mur S, Storme L. Positioning effects on lung function and breathing pattern in premature newborns. *J Pediatr.* 2013; 162:1133–7.
12. Numa AH, Hammer J, Newth CJL. Effect of prone and supine positions on functional residual capacity, oxygenation, and respiratory mechanics in ventilated infants and children. *Am J Respir Crit Care Med.* 1997; 156:1185–9.
13. Poets CF, Marinaki T, Stebbens VA, O'Brien LM, Southall DP. Prone Vs. Supine Sleep Position in Bronchiolitis: Effects on Apnoea and Oxygenation. *Pediatr Res.* 1997; 42:412–2.

14. Essouri S, Durand P, Chevret L, Balu L, Devictor D, Fauroux B, et al. Optimal level of nasal continuous positive airway pressure in severe viral bronchiolitis. *Intensive Care Med.* 2011; 37:2002–7.
15. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, et al. The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med.* 2014; 189:520–31.
16. Beck J, Gottfried SB, Navalesi P, Skrobik Y, Comtois N, Rossini M, et al. Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. *Am J Respir Crit Care Med.* 2001; 164:419–24.
17. Emeriaud G, Larouche A, Ducharme-Crevier L, Massicotte E, Flechelles O, Pellerin-Leblanc A-A, et al. Evolution of inspiratory diaphragm activity in children over the course of the PICU stay. *Intensive Care Med.* 2014; 40:1718–26.
18. Milési C, Essouri S, Pouyau R, Liet J-M, Afanetti M, Portefaix A, et al. High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). *Intensive Care Med.* 2017; 43:209–16.
19. Bellani G, Coppadoro A, Patroniti N, Turella M, Arrigoni Marocco S, Grasselli G, et al. Clinical assessment of auto-positive end-expiratory pressure by diaphragmatic electrical activity during pressure support and neurally adjusted ventilatory assist. *Anesthesiology.* 2014;121:563–71.
20. Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation in respiratory failure. *Nat Med.* 1999; 5:1433–6.
21. Cambonie G, Milési C, Fournier-Favre S, Counil F, Jaber S, Picaud J-C, et al. Clinical effects of heliox administration for acute bronchiolitis in young infants. *Chest.* 2006; 129:676–82.
22. Jarus T, Bart O, Rabinovich G, Sadeh A, Bloch L, Dolfin T, et al. Effects of prone and supine positions on sleep state and stress responses in preterm infants. *Infant Behav Dev.* 2011; 34:257–63.
23. Laghi F, Shaikh HS, Morales D, Sinderby C, Jubran A, Tobin MJ. Diaphragmatic neuromechanical coupling and mechanisms of hypercapnia during inspiratory loading. *Resp Physiol Neurobi.* 2014; 198:32–41.
24. Liu L, Liu H, Yang Y, Huang Y, Liu S, Beck J, et al. Neuroventilatory efficiency and extubation readiness in critically ill patients. *Crit Care. BioMed Central;* 2012; 16:R143.
25. Rehan VK. Effects of the supine and prone position on diaphragm thickness in healthy term infants. *Archives of Disease in Childhood.* 2000; 83:234–8.
26. Lupton-Smith A, Argent A, Rimensberger P, Frerichs I, Morrow B. Prone Positioning Improves Ventilation Homogeneity in Children With Acute Respiratory Distress Syndrome. *Pediatr Crit Care Med.* 2017; 18:e229–34.

27. Wolfson MR, Greenspan JS, Deoras KS, Allen JL, Shaffer TH. Effect of position on the mechanical interaction between the rib cage and abdomen in preterm infants. *J Appl Physiol*. 1992; 72:1032–8.
28. Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, et al. Physiologic Effects of High-Flow Nasal Cannula in Acute Hypoxemic Respiratory Failure. *Am J Respir Crit Care Med*. 2017; 195:1207–15.
29. Brochard L. Intrinsic (or auto-) PEEP during controlled mechanical ventilation. *Intensive Care Med*. 2002; 28:1376–8.
30. Beck J, Brander L, Slutsky AS, Reilly MC, Dunn MS, Sinderby C. Non-invasive neurally adjusted ventilatory assist in rabbits with acute lung injury. *Intensive Care Med*. 2008; 34:316–23.
31. Pellegrini M, Hedenstierna G, Roneus A, Segelsjö M, Larsson A, Perchiizzi G. The Diaphragm Acts as a Brake during Expiration to Prevent Lung Collapse. *Am J Respir Crit Care Med*. 2017; 195:1608–16.
32. Brander L, Moerer O, Hedenstierna G, Beck J, Takala J, Slutsky AS, et al. Neural control of ventilation prevents both over-distension and de-recruitment of experimentally injured lungs. *Resp Physiol Neurobi*. 2017; 237:57–67.
33. Larouche A, Massicotte E, Constantin G, Ducharme-Crevier L, Essouri S, Sinderby C, et al. Tonic diaphragmatic activity in critically ill children with and without ventilatory support. *Pediatr Pulmonol*. 2015; 50:1304–12.
34. Emeriaud G, Beck J, Tucci M, Lacroix J, Sinderby C. Diaphragm Electrical Activity During Expiration in Mechanically Ventilated Infants. *Pediatr Res*. 2006; 59:705–10.
35. Stark AR, Cohlman BA, Waggener TB, Frantz ID, Kosch PC. Regulation of end-expiratory lung volume during sleep in premature infants. *J Appl Physiol*. 1987; 62:1117–23.
36. Kosch PC, Stark AR. Dynamic maintenance of end-expiratory lung volume in full-term infants. *J Appl Physiol Respir Environ Exerc Physiol*. 1984; 57:1126–33.
37. Hough J, Trojman A, Schibler A. Effect of time and body position on ventilation in premature infants. *Pediatr Res*. 2016;80:499–504.
38. Hammer J, Numa A, Newth CJL. Acute respiratory distress syndrome caused by respiratory syncytial virus. *Pediatr Pulmonol*. 1997; 23:176–83.
39. Tobin MJ, Lodato RF. PEEP, auto-PEEP, and waterfalls. *Chest*. 1989; 96:449–451.
40. Rivas-Fernandez M, Roqué i Figuls M, Diez-Izquierdo A, Escribano J, Balaguer A. Infant position in neonates receiving mechanical ventilation. *Cochrane Database Syst Rev*. 2016;(11):CD003668.
41. Guérin C. Prone position. *Current Opinion in Critical Care*. 2014; 20:92–7.

42. Guérin C, Baboi L, Richard JC. Mechanisms of the effects of prone positioning in acute respiratory distress syndrome. *Intensive Care Med.* 2014; 40:1634–42.
43. Kallet RH. A Comprehensive Review of Prone Position in ARDS. *Respir Care.* 2015; 60:1660–87.
44. Riad Z, Mezidi M, Subtil F, Louis B, Guérin C. Short-Term Effects of the Prone Positioning Maneuver on Lung and Chest Wall Mechanics in Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med.* 2018; 197:1355–8.
45. Kumaresan A, Gerber R, Mueller A, Loring SH, Talmor D. Effects of Prone Positioning on Transpulmonary Pressures and End-expiratory Volumes in Patients without Lung Disease. *Anesthesiology.* 2018; 128:1187–92.
46. Cambonie G, Milési C, Jaber S, Amsallem F, Barbotte E, Picaud JC, et al. Nasal continuous positive airway pressure decreases respiratory muscles overload in young infants with severe acute viral bronchiolitis. *Intensive Care Med.* 2008; 34:1865–72.

FIGURE LEGEND

Online Figure 1: Example of a recording

Flow, volume (Vol.), airway pressure (Paw), esophageal pressure (Peso), gastric pressure (Pga), trans-diaphragmatic pressure (Pdi), and Electrical activity of the diaphragm (EAdi) were recorded simultaneously. Neural time cursors (colored vertical bars) were placed at the beginning of neural inspiration (1), the maximal inspiratory EAdi value (EAdi max) (2), the end of neural inspiration (3), and at the end of neural expiration (4).

Figure 2: Box plot of esophageal pressure time product (PTPeso) per minute in prone and supine position in all children and in responders and non-responders.

PTPeso per min was similar in PP between responders and non-responders ($p=0.75$) but significantly higher in SP in responders than in non-responders ($p=0.043$)

Online Figure 3: Reduction of the esophageal pressure time product (PTPeso) per minute (A) and change in amplitude of electrical activity of the diaphragm (Δ EAdi) (B) in the prone position.

Online Figure 4: Electrical activity of the diaphragm during expiration

Time between the EAdi Peak and the end of expiration was divided into four equally sized quartiles (Q1, Q2, Q3, and Q4). Mean values of each expiratory quartile are presented in the prone position (PP, continuous line) and the supine position (SP, discontinuous line). Values of EAdi in PP and SP are presented at each time as median [1st; 3rd quartiles] below the figure.

Table 1: Main characteristics of the population

Variables	SP First n=7	PP First n=7	Overall Population n=14
Age (days)	30 [18; 39]	44 [30-63]	33 [25; 58]
Weight (grams)	4060 [3500; 4465]	4300 [3630; 4630]	4180 [3606; 4525]
HFNC before nCPAP (n (%))	4 (57)	5 (71)	9 (64)
PELOD 2 score	3 [3; 4]	3 [3; 4]	3 [3; 4.5]
Blood gas on admission			
pH	7.29 [7.26; 7.31]	7.30 [7.29; 7.33]	7.29 [7.27; 7.32]
pCO ₂ (kPA)	7.7 [7.6; 8.5]	7.7 [7.1; 8.5]	7.7 [7.3; 8.5]
Clinical parameters on admission			
m-WCAS	5.0 [4.5; 5.0]	4.5 [4.25; 5.5]	4.75 [4.5; 5.0]
Heart rate (beats/min)	172 [150; 175]	159 [154; 177]	166 [149; 177]
FiO ₂ (%)	30 [28; 35]	30 [25; 38]	30 [25; 35]
Time from PICU admission (min)	530 [358; 570]	624 [232; 674]	540 [282; 625]
Duration of nCPAP (hours)	19 [18; 75]	41 [22; 60]	38 [18; 69]
Duration of MV (hours)	79 [65; 119]	64 [58; 87]	74 [58; 98]
Invasive MV (n)	0/7	0/7	0/14 (0)
LOS PICU (days)	5 [4; 7]	5 [5; 6]	5 [4; 6]
Total LOS (days)	8 [6.5; 9.5]	7 [6; 9.5]	7.5 [6; 10]

Values are median [1st; 3rd quartiles] or counts (percent-point in group)

HFNC: High Flow Nasal Cannula; nCPAP: nasal Continuous Positive Airway Pressure, PELOD: Pediatric Logistic Organ Dysfunction; pCO₂: Partial pressure in carbon dioxide ; mWCAS: Modified Wood Asthma Clinical Score; FiO₂: Inspired fraction of oxygen; MV: Mechanical Ventilation; LOS: Length of stay ; PICU: Pediatric intensive care unit.

Table 2: Clinical data in prone and supine position at the end of each study period

Clinical Parameters	Supine Position	Prone Position	P value*	Relative difference Supine Position (%)	Relative difference Prone Position (%)	P value*
TcPCO ₂ (kPA)	6.5 [6.1; 6.8]	6.9 [6.1; 7.7]	0.16	- 4 [-7.9; -2.0]	- 10.4 [-16.0; -5.6]	0.24
FiO ₂ (%)	30 [25; 35]	27 [25; 30]	0.17	0 [0; 12.5]	-1.7 [-15.6; 0.0]	0.16
SpO ₂ (%)	97.5 [95; 99]	96.5 [94; 98]	0.46	0 [-2.8; 0]	-3 [-3.10; 2.9]	0.64
Heart Rate (beats/min)	159 [146; 164]	156[144; 163]	0.10	-6.3 [-9.7; -0.2]	-6.8 [-12.2; -0.5]	0.82

Data are expressed as median [1st; 3rd quartiles]. Relative difference over the study period was calculated using the formula (100*(End value – Initial value)/ Initial value). TcPCO₂: Transcutaneous partial pressure in carbon dioxide; FiO₂: Inspired fraction of oxygen; SpO₂: Pulse Oxymetry. * P value by paired non-parametric Wilcoxon signed-rank test.

Table 3: Physiological data in prone and supine position at the end of each study period

Physiological Parameters	Supine Position	Prone Position	P value*	Relative difference Supine Position (%)	Relative difference Prone Position (%)	P value*
Primary outcome						
PTPeso/min (cmH ₂ O*s/min)	353 [249; 386]	227 [156; 282]	0.048	-29.1 [-56.4; 11.9]	-53.6 [-61.5; -25.2]	0.013
Secondary outcomes						
PTPdi/min (cmH ₂ O*s/min)	336 [209; 394]	232 [204; 324]	0.084	-20.4 [-34.6; -5.8]	-40.3 [-50.8; -12.0]	0.022
PTPeso/breath (cmH ₂ O*s)	4.6 [3.4; 5.1]	3.5 [2.9; 4.2]	0.048	-19.7 [-45.2; 4.6]	-40.5 [-52.3; -23.3]	0.013
PTPdi/breath (cmH ₂ O*s)	4.5 [3.6; 5.8]	3.9 [3.0; 5.0]	0.30	-11.0 [-31.0; 2.0]	-27.1 [-46.6; -1.3]	0.035
Swing Peso (cmH ₂ O)	14.9 [11.0; 16.2]	9.3 [8.3; 12.8]	0.035	-27.5 [-43.9; 8.3]	-41.6 [-57.7; -25.8]	0.008
Swing Pdi (cmH ₂ O)	13.9 [10.2; 16.9]	11.3 [9.0; 15.2]	0.096	-17.0 [-26.8; -4.1]	-40.0 [-42.0; -10.0]	0.011
EAdi min (μV)	3.5 [2.4; 4.4]	2.1 [1.6; 3.6]	0.030	- 48.4 [-64.9; 30.3]	- 62.6 [-77.6; -36.3]	0.51
EAdi max (μV)	22 [19; 28]	16 [10; 25]	0.006	- 30.2 [-49.4; -22.4]	-57.7 [-68.2; -43.0]	0.013
Δ EAdi (μV)	17 [15; 22]	13 [8; 20]	0.008	-30.1 [-44.9; -15.7]	-57.6 [-66.3; -39.4]	0.016
Ti (s)	0.44 [0.38; 0.53]	0.44 [0.38; 0.53]	0.47	8.1 [-2.1; 19.7]	16.3 [-4.7; 29.8]	0.64
Ti/Ttot (%)	0.45 [0.43; 0.48]	0.47 [0.43; 0.47]	0.78	- 6.3 [-9.7; 0.1]	-1.8 [-8.6; 2.9]	0.47
Respiratory Rate (/min)	59 [52; 77]	66 [46; 78]	0.40	- 11.9 [-23.5; 3.1]	-11.3 [-20.5; -0.9]	0.55

Data are expressed as median [1st; 3rd quartiles]. Relative difference over the study period was calculated using the formula $(100 * (\text{End value} - \text{Initial value}) / \text{Initial value})$. Ti: neural inspiratory time; Te: neural expiratory time; Ttot: neural total time; EAdi: Electrical activity of the diaphragm; Δ EAdi: EAdi max - EAdi min; Peso: esophageal pressure; Pdi: Trans-diaphragmatic Pressure; PTPeso = esophageal pressure time product; PTPdi = Trans-diaphragmatic pressure time product * P value by paired non-parametric Wilcoxon signed-rank test.

Online only Table 4: Demographic and clinical data at admission between responders and non-responders

	Responders n=8	Non-responders n=6	<i>p</i> Value*
Age (days)	40 [30; 63]	24 [17; 40]	0.14
Weight (grams)	4415 [3620; 4710]	3850 [3460; 4315]	0.34
PELOD 2 score	3 [3; 5]	3 [3; 3]	0.57
pH	7.29 [7.23; 7.31]	7.30 [7.27; 7.34]	0.66
pCO ₂ (kPA)	7.65 [7.45; 8.56]	7.9 [7.32; 8.33]	0.95
mWCAS	5 [4.38; 5.1]	4.5 [4.5; 4.9]	0.66
Heart Rate (beats/min)	166 [156; 177]	161 [149; 175]	0.75
FiO ₂ (%)	33 [29; 36]	28 [25; 34]	0.41

Data are expressed as median [1st; 3rd quartiles]. PELOD: Pediatric Logistic Organ Dysfunction; pCO₂: Partial pressure in carbon dioxide ; mWCAS: modified Wood Asthma Clinical Score; FiO₂: Inspired fraction of oxygen;

* P value by independent samples mann whitney U test.

Only Online Table 5: Physiological data in prone and supine position between responders and non-responders.

	Responders n=8	Non-responders n=6	<i>p</i> Value*
Prone position			
Ti/Ttot (%)	0.47 [0.46; 0.47]	0.44 [0.43; 0.47]	0.76
Respiratory Rate (/min)	66 [52; 77]	62 [44; 78]	0.76
EAdi max (μV)	16 [13; 20]	19 [10; 26]	0.57
Swing Peso (cmH ₂ O)	9.2 [7.9; 12.3]	10.2 [9.2; 15.9]	0.76
Swing Pdi (cmH ₂ O)	10.5 [9.0; 14.7]	11.6 [9.4; 17.4]	0.49
PTPeso/breath (cmH ₂ O*s)	2.9 [2.8; 3.9]	3.9 [3.6; 4.2]	0.14

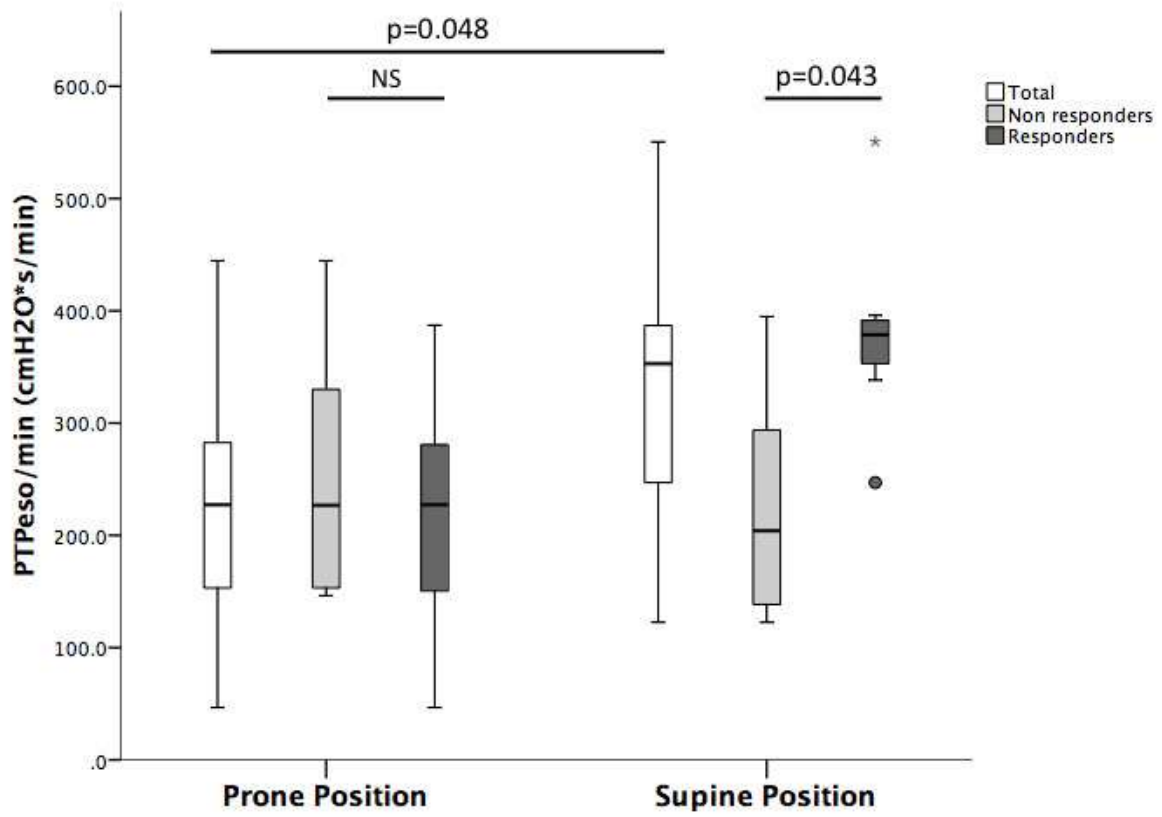
PTPdi/breath (cmH ₂ O*s)	3.4 [2.8; 4.4]	4.8 [4.1; 5.0]	0.36
PTPeso/min (cmH ₂ O*s/min)	227 [158; 280]	227 [159; 317]	0.75
PTPdi/min (cmH ₂ O*s/min)	247 [201; 321]	213 [204; 322]	1.0

Supine Position

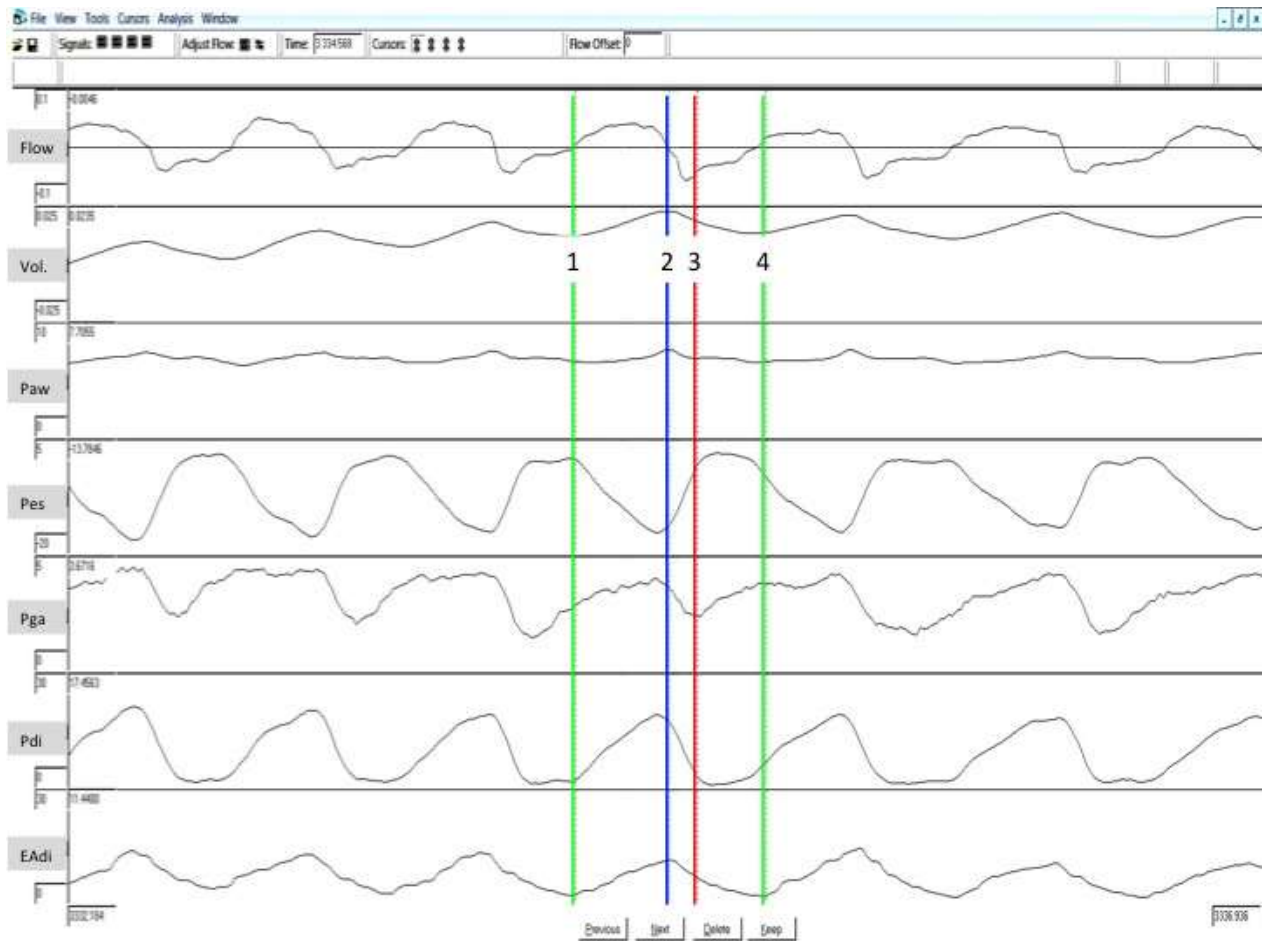
Ti/Ttot (%)	0.47 [0.46; 0.49]	0.44 [0.41; 0.45]	0.06
Respiratory Rate (/min)	61 [54; 76]	58 [49; 73]	0.66
EAdi max (μV)	25 [23; 31]	19 [18; 20]	0.11
Swing Peso (cmH ₂ O)	15.2 [14.4; 16.3]	9.2 [6.9; 15.0]	0.23
Swing Pdi (cmH ₂ O)	15.6 [12.7; 17.2]	9.4 [9.1; 14.3]	0.11
PTPeso/breath (cmH ₂ O*s)	5.0 [4.0; 6.3]	3.2 [3.0; 4.6]	0.081
PTPdi/breath (cmH ₂ O*s)	5.3 [4.2; 6.5]	3.7 [3.4; 4.5]	0.14
PTPeso/min (cmH ₂ O*s/min)	379 [360; 389]	204 [142; 284]	0.043
PTPdi/min (cmH ₂ O*s/min)	393 [326; 419]	209[172; 299]	0.029

Data are expressed as median [1st; 3rd quartiles]. Ti: neural inspiratory time ; Te: neural expiratory time; Ttot: neural total time; EAdi: Electrical activity of the diaphragm; Peso: esophageal pressure ; Pdi: Trans-diaphragmatic Pressure ; PTPeso = esophageal pressure time product ; PTPdi = Trans-diaphragmatic pressure time product

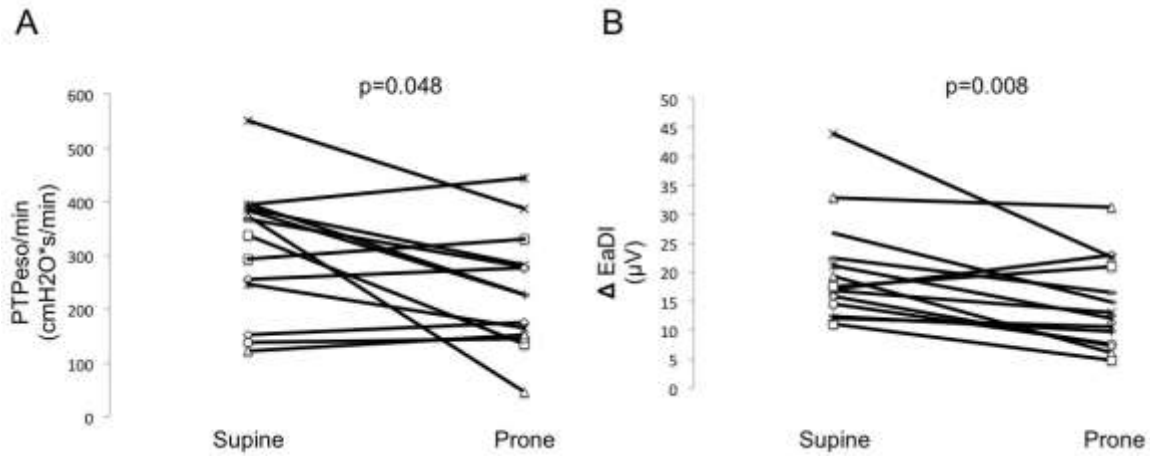
*P value by independent samples mann whitney U test.



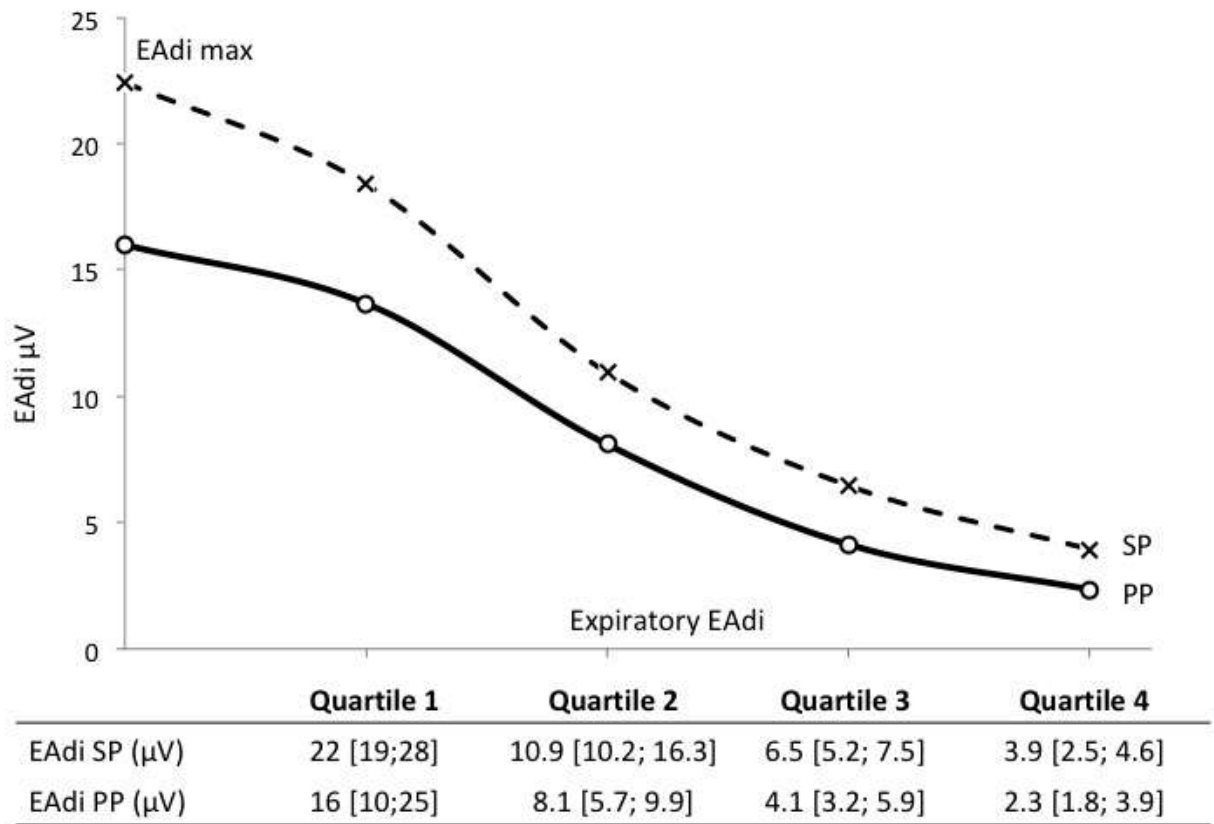
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