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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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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 noninvasive ventilation.

Study design Fourteen infants, median age 33 days (IQR [first and third quartiles], 25-58) were randomized to receive 7 cmH_2O continuous positive airway pressure for 1 hour in the prone position or in the supine position, which was followed by cross-over to the supine position and the prone position for 1 hour, respectively. Flow, esophageal, airway, gastric, and transdiaphragmatic pressures, as well as electrical activity of the diaphragm were simultaneously recorded. The modified Wood clinical asthma score was also assessed.

Results Median esophageal pressure–time product per minute was significantly lower in the prone position than in the supine position (227 cmH_2O*s/minute [IQR, 156-282] cmH_2O*s/minute vs 353 cmH_2O*s/minute [IQR, 249-386 cmH_2O*s/minute]; $P = .048$), as were the modified Wood clinical asthma score ($P = .033$) and electrical activity of the diaphragm ($P = .006$). The neuromechanical efficiency of the diaphragm, as assessed by transdiaphramagtic pressure to electrical activity of the diaphragm swing ratio, was significantly higher in the prone position than in the supine position (1.1 $cmH_2O/\mu V$ [IQR, 0.9-1.3 $cmH_2O/\mu V$] vs 0.7 $cmH_2O/\mu V$ [IQR, 0.6-1.2 $cmH_2O/\mu V$], respectively; $P = .022$).

Conclusions This study suggests a benefit of the prone position for infants with severe bronchiolitis requiring noninvasive 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. *(J Pediatr 2019;205:112-9)*.

Trial registration Clinicaltrials.gov: 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 the 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 is easy to perform in small children[8] and is commonly used in neonatal and pediatric intensive care. In adults, the prone position significantly decreases mortality in patients with severe acute respiratory distress syndrome and improves oxygenation.[9] Moreover, the prone position may improve respiratory mechanics and gas exchange in adults with chronic bronchitis[10] as in neonates.[11] The prone position 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 prone position 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 the prone

EAdi	Electrical activity of the diaphragm
m-WCAS	Modified Wood asthma clinical score
nCPAP	Nasal continuous positive airway pressure
NME	Neuromechanical efficiency
PEEP	Positive end-expiratory pressure

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position and the supine position, and the secondary objective was to describe the physiological effects of the prone position in infants with severe acute viral bronchiolitis.

Methods

We conducted a prospective randomized crossover physiological study in a 23-bed pediatric intensive care unit 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 <6 months of age with a diagnosis of viral bronchiolitis admitted to the pediatric intensive care unit for respiratory support were eligible if they met the following inclusion criteria: clinical and radiologic diagnosis of bronchiolitis, need for respiratory support by nCPAP based on a modified Wood clinical asthma score (m-WCAS) of >4 and/or hypercapnic acidosis (pH <of 7.30 or partial pressure in carbon dioxide of >8 kPa), and written consent obtained from the parent(s) or guardian(s). Noninclusion criteria were chronic respiratory, neuromuscular, ear-nose-throat, or cardiac underlying disease; a contraindication for the placement of the esophageal probe; need for invasive ventilation (in particular when presenting >3 apneas per hour with heart rate of <90/minute or a pulse oximetry of <90%, or altered level of consciousness); and infants not affiliated with 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 (esophageal pressure) and 1 for gastric pressure, was inserted orally together with an orogastric catheter able to detect electrical activity of the diaphragm (EAdi; 8F, 100 cm, Maquet Critical Care, Solna, Sweden). After fixation, the correct positioning was verified by gentle manual pressure on the patient's abdomen to observe gastric pressure fluctuations without effect on the esophageal pressure tracing and negative deflection during inspiration on the esophageal pressure tracing.[14,15] The position of the catheter able to detect the EAdi 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 EAdi were recorded using the SERVO-I ventilator through a RS232 serial port continuously and simultaneously with esophageal pressure and gastric pressure using an analogical/numerical data acquisition system and transferred to a laptop (Neurovent, Inc, Toronto, Ontario, Canada). All data were analyzed offline. Only breaths with available signals for all measures (flow, airway pressure, gastric pressure, esophageal pressure, and EAdi) were analyzed. Time cursors were placed at the beginning of neural inspiration, the maximal inspiratory EAdi value, 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, inspired fraction of oxygen, transcutaneous partial pressure of carbon dioxide, 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 the supine position then the prone position, or the converse. They were placed for 1 hour in the first position with nCPAP, followed by a 15-minute washout period (in the supine position 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 noninvasive CPAP mode of the SERVO-I ventilator set at +7 cmH_2O for all infants. Airway pressure, flow, EAdi, esophageal pressure, and gastric pressure from 50 consecutive breaths during the first 5-10 minutes (initial values) and from 100 breaths during the last 50-55 minutes (end values) of each period were analyzed. The primary outcome was the mean of the esophageal pressure time product per minute over 100 breaths during the last 5 minutes of the recording.

Secondary outcomes were transdiaphragmatic pressure time product per minute, esophageal pressure time product and transdiaphragmatic pressure time product per single breath, esophageal and transdiaphragmatic inspiratory pressure swings (maximal amplitude of the inspiratory depression), EAdi at the end of the expiratory time, the difference between the minimum and the maximum EAdi values during inspiration (ΔEAdi), respiratory rate, neural inspiratory time (which corresponds to the interval between the beginning of neural inspiration and end of neural inspiration), expiratory time (which corresponds with the interval between the end of neural inspiration and the end of neural expiration), and inspiratory time to total time ratio (neural inspiratory time/neural total time). Determination of intrinsic positive end-expiratory pressure (PEEP) was attempted using deflection of the esophageal pressure at the time of flow onset from the esophageal pressure 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 esophageal pressure time product per minute in the prone position than in the supine position were considered as responders to the prone position. Post hoc analyses were performed to compare responders and nonresponders with the prone position and to characterize the impact of the prone position on EAdi during expiration and on diaphragm neuromechanical efficiency (NME) of the diaphragm defined as the ratio between transdiaphramagtic pressure swings and ΔEAdi breath by breath.

Statistical Analysis and Sample Size

Qualitative variables are reported as count and percentage, and quantitative variables are reported as median with IQR (first and third quartiles). Kolmogorov-Smirnov tests was used to assess data distribution. It was calculated that 14 infants were required for a decrease of 25% of the esophageal pressure time product per minute in the prone position as compared with the supine position, 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*(End value – Initial value) / Initial value). The nonparametric 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 $P < .05$. Statistical analysis was performed using SPSS Statistics (V22, IBM, Armonk, New York).

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; Figure 2; available at www.jpeds.com). No patient received sedative drugs before or during the study, and 2 patients had received caffeine sulfate before admission to the pediatric intensive care unit. 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. One-half of the patients received the prone position first. No adverse event was reported in the study.

Effect on Clinical Measures

The median m-WCAS was significantly lower in the prone position (3.0; IQR, 3.0-3.0) than in the supine position (3.5; IQR, 3.0-4.0; $P = .033$) and there was no significant difference in comfort between the prone and the supine position (median EDIN scale, 3.5 (IQR, 2.00-5.75) vs 5.5 (IQR, 2-7); $P = .13$). The transcutaneous partial pressure of carbon dioxide, inspired fraction of oxygen, pulse oximetry, and heart rate are reported in Table II, as relative difference over the study period; there was no significant difference in these measures between the prone and the supine position.

Effect on Physiological Measures

Median respiratory rate (66 breaths/minute [IQR, 46-78 breaths/minute] in the prone position vs 59 breaths/minute [IQR, 52-77 breaths/minute] in the supine position; $P = .40$) and respiratory cycle time durations were not different (Table III) between the 2 positions. Mean airway pressure measured at the Y-piece was similar in the prone position (6.99 cmH_2O; IQR, 6.98-7.08 cmH_2O) and supine position (7.0 cmH_2O; IQR, 6.96-7.06 cmH_2O; $P = .93$).

The median esophageal pressure time product per minute was significantly lower in the prone position (227cmH_2O*s/minute; IQR, 156-282 cmH_2O*s/minute) than in the supine position (353cmH_2O*s/minute; IQR, 249-386 cmH_2O*s/minute; $P = .048$; Figure 3), as were esophageal pressure time product per single breath (3.5 cmH_2O*s [IQR, 2.9-4.2 cmH_2O*s] vs 4.6 cmH_2O*s [IQR, 3.4-5.1 cmH_2O*s]; $P = .048$) and Swing esophageal pressure (9.3 cmH_2O; IQR, 8.3-12.8 cmH_2O] vs 14.9 cmH_2O [IQR, 11.0-16.2 cmH_2O]; $P = .035$;

Table I. Main characteristics of the population

Variables	Supine position first (n = 7)	Prone position first (n = 7)	Overall population (n = 14)
Age (d)	30 (18-39)	44 (30-63)	33 (25-58)
Weight (g)	4060 (3500-4465)	4300 (3630-4630)	4180 (3606-4525)
HFNC before nCPAP, no. (%)	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 measures 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 (h)	19 (18-75)	41 (22-60)	38 (18-69)
Duration of mechanical ventilation (h)	79 (65-119)	64 (58-87)	74 (58-98)
Invasive mechanical ventilation (no.)	0/7	0/7	0/14 (0)
LOS PICU (d)	5 (4-7)	5 (5-6)	5 (4-6)
Total LOS (d)	8 (6.5-9.5)	7 (6-9.5)	7.5 (6-10)

FiO_2, inspired fraction of oxygen; *HFNC*, high-flow nasal cannula; *LOS*, Length of stay; *PELOD*, Pediatric Logistic Organ Dysfunction; *pCO_2*, partial pressure in carbon dioxide; *PICU*, pediatric intensive care unit.
Values are median (IQR [first and third quartiles]) or counts (percent-point in group).

Table II. Clinical data in prone and supine position at the end of each study period

Clinical measures	Supine position	Prone position	*P* value*	Relative difference supine position (%)	Relative difference prone position (%)	*P* value*
$TcPCO_2$ (kPA)	6.5 (6.1 to 6.8)	6.9 (6.1 to 7.7)	.16	−4 (−7.9 to −2.0)	−10.4 (−16.0 to −5.6)	.24
FiO_2 (%)	30 (25 to 35)	27 (25 to 30)	.17	0 (0 to 12.5)	−1.7 (−15.6 to 0.0)	.16
SpO_2 (%)	97.5 (95 to 99)	96.5 (94 to 98)	.46	0 (−2.8 to 0)	−3 (−3.10 to 2.9)	.64
Heart rate (beats/min)	159 (146 to 164)	156 (144 to 163)	.10	−6.3 (−9.7 to −0.2)	−6.8 (−12.2 to −0.5)	.82

SpO_2, pulse oximetry; *$TcpCO_2$*, transcutaneous partial pressure in carbon dioxide.
Data are expressed as median (IQR [first and third quartiles]). Relative difference over the study period was calculated using the formula [100*(End value – Initial value)/ Initial value].
**P* value by paired nonparametric Wilcoxon signed-rank test.

Table III). The esophageal pressure time product decreased over time in all infants while in the prone position and in 10 infants while in the supine position. The decrease in the esophageal pressure time product and transdiaphragmatic pressure time product per single breath or per minute over time as well as the magnitude of decrease in esophageal pressure and transdiaphramagtic pressure swings were significantly greater in the prone position than in the supine position (Table III). During expiration, gastric pressure swing was not different between prone and supine position (3.2 cmH_2O [IQR, 2.3-3.7 cmH_2O] vs 3.1 cmH_2O [IQR, 2.4-3.5 cmH_2O]; $P = .95$). The 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 cmH_2O (IQR, 0.6-1.5 cmH_2O) in the prone position and 1.3 cmH_2O (IQR, 0.9-1.5 cmH_2O) in the supine position ($P = .25$). 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 an esophageal pressure time product per minute that was lower in the prone position than in the supine position (Figure 4, A; available at www.jpeds.com). Among them, 5 were placed first in the prone position and 3 in the supine position ($P = .59$). The median esophageal pressure time product per minute was similar in the prone position between responders and nonresponders (227 cmH_2O*s/minute [IQR, 158-280cmH$_2$O*s/minute] vs 227 cmH_2O*s/minute [IQR, 159-317cmH$_2$O*s/minute]; $P = .75$) but higher in the supine position in responders (379 cmH_2O*s/minute; IQR, 360; 389 cmH_2O*s/minute) than in nonresponders (204 cmH_2O*s/minute; IQR, 142-284cmH$_2$O*s/minute; $P = .043$; Figure 3). Comparisons for other variables are available in Tables IV and V (both available at www.jpeds.com).

Effects on EAdi and NME

The maximal inspiratory EAdi value and ΔEAdi were significantly lower in the prone position than in the supine position (Table III and Figure 4, B [available at www.jpeds.com]). The EAdi at the end of the expiratory time was also significantly lower in the prone position (2.1 µV; IQR, 1.6-3.6 µV) than in the supine position (3.5 µV; IQR, 2.4-4.4 µV; $P = .03$) and during all expiration time (Figure 5; available at www.jpeds.com). The diaphragm NME was significantly greater in the prone position (1.1 cmH_2O/µV; IQR, 0.9-1.3 cmH_2O/µV)

Table III. Physiological data in prone and supine position at the end of each study period

Physiological measures	Supine position	Prone position	*P* value*	Relative difference supine position (%)	Relative difference prone position (%)	*P* value*
Primary outcome						
Esophageal pressure time product/min (cmH_2O*s/min)	**353 (249 to 386)**	**227 (156 to 282)**	**.048**	**−29.1 (−56.4 to 11.9)**	**−53.6 (−61.5 to −25.2)**	**.013**
Secondary outcomes						
Transdiaphragmatic pressure time product/min (cmH_2O*s/min)	336 (209 to 394)	232 (204 to 324)	.084	**−20.4 (−34.6 to −5.8)**	**−40.3 (−50.8 to −12.0)**	**.022**
Esophageal pressure time product/breath (cmH_2O*s)	**4.6 (3.4 to 5.1)**	**3.5 (2.9 to 4.2)**	**.048**	**−19.7 (−45.2 to 4.6)**	**−40.5 (−52.3 to −23.3)**	**.013**
Transdiaphragmatic pressure time product/breath (cmH_2O*s)	4.5 (3.6 to 5.8)	3.9 (3.0 to 5.0)	.30	**−11.0 (−31.0 to 2.0)**	**−27.1 (−46.6 to −1.3)**	**.035**
Swing esophageal pressure (cmH_2O)	**14.9 (11.0 to 16.2)**	**9.3 (8.3 to 12.8)**	**.035**	**−27.5 (−43.9 to 8.3)**	**−41.6 (−57.7 to −25.8)**	**.008**
Swing transdiaphramagtic pressure (cmH_2O)	13.9 (10.2 to 16.9)	11.3 (9.0 to 15.2)	.096	**−17.0 (−26.8 to −4.1)**	**−40.0 (−42.0 to −10.0)**	**.011**
EAdi min (µV)	**3.5 (2.4 to 4.4)**	**2.1 (1.6 to 3.6)**	**.030**	−48.4 (−64.9 to 30.3)	−62.6 (−77.6 to −36.3)	.51
EAdi max (µV)	**22 (19 to 28)**	**16 (10 to 25)**	**.006**	**−30.2 (−49.4 to −22.4)**	**−57.7 (−68.2 to −43.0)**	**.013**
Δ EAdi (µV)	**17 (15 to 22)**	**13 (8 to 20)**	**.008**	**−30.1 (−44.9 to −15.7)**	**−57.6 (−66.3 to −39.4)**	**.016**
Neural inspiratory time (s)	0.44 (0.38 to 0.53)	0.44 (0.38 to 0.53)	.47	8.1 (−2.1 to 19.7)	16.3 (−4.7 to 29.8)	.64
Neural inspiratory time/neural total time (%)	0.45 (0.43 to 0.48)	0.47 (0.43 to 0.47)	.78	−6.3 (−9.7 to 0.1)	−1.8 (−8.6 to 2.9)	.47
Respiratory rate (/min)	59 (52 to 77)	66 (46 to 78)	.40	−11.9 (−23.5 to 3.1)	−11.3 (−20.5 to −0.9)	.55

EAdi max, maximal inspiratory EAdi value; *EAdi min*, EAdi at the end of the expiratory time; *Δ EAdi*, EAdi max – EAdi min.
Bold text indicates a statistically significant difference, $P < .05$.
Data are expressed as median (IQR [first and third quartiles]). Relative difference over the study period was calculated using the formula [100*(End value – Initial value)/ Initial value].
**P* value by paired nonparametric Wilcoxon signed-rank test.

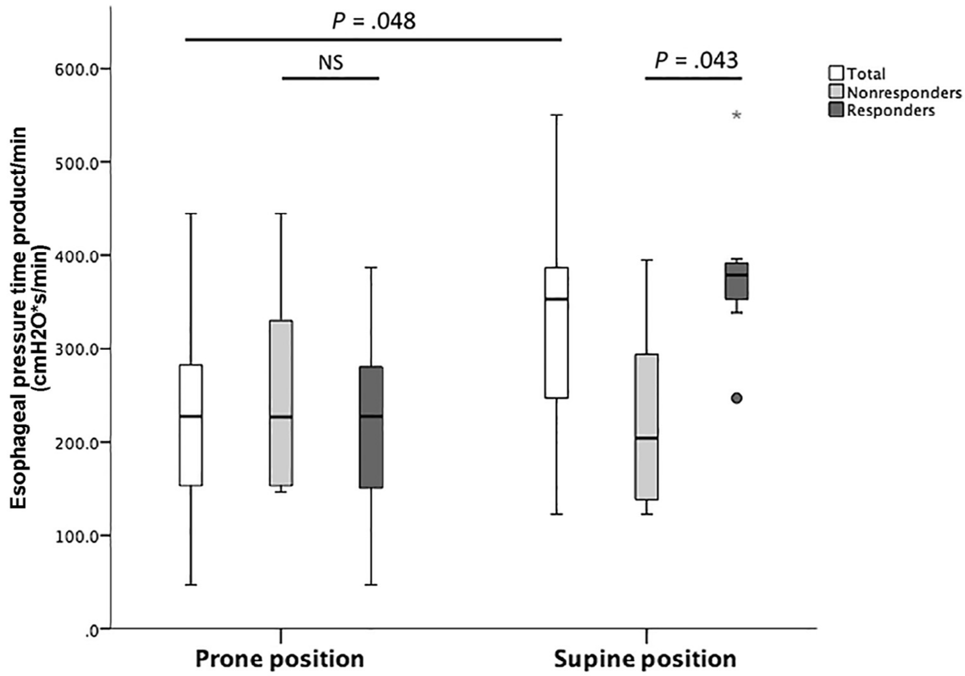

Figure 3. Box plot of esophageal pressure time product per minute in the prone and supine positions in all children and in responders and nonresponders. The esophageal pressure time product per minute was similar in the prone position between responders and nonresponders ($P = .75$) but significantly higher in the supine position in responders than in nonresponders ($P = .043$)

compared with supine position (0.7 $cmH_2O/\mu V$; IQR, 0.6-1.2 $cmH_2O/\mu V$; $P = .022$).

Discussion

The present study described the neural and mechanical consequences of prone positioning in children with severe bronchiolitis and found that the prone position can decrease inspiratory effort (estimated by the esophageal pressure swing) and the metabolic cost of breathing (estimated by the esophageal pressure time product). The 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 the prone position as compared with the supine position, and they decreased over time in both positions, but more efficiently in the prone position than in the supine position. Furthermore, the EAdi, which reflects the neural drive to the diaphragm,[16,20] also decreased over time and was significantly lower in the prone position. The m-WCAS, described previously to standardize the scoring of accessory muscles used in bronchiolitis,[18,21] was also significantly lower in the prone position than in the supine position. It is also noteworthy that the decrease in the inspiratory efforts and demand was associated with stable ventilation, with no deterioration in CO_2 measurement. All mechanical, neural, and clinical measures were consistent and showed that breathing was easier in the prone position than in the supine position, as previously reported in neonates.[22] Concerning diaphragm function, there was an increase of transdiaphramagtic pressure/ΔEAdi ratio in the prone position, which corresponds with 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 the prone position than in the supine position.[25] They hypothesized that this thickening might be attributable to an increased diaphragmatic work in the prone position, 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 an 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 nonresponders to the prone position. We found that the metabolic cost of breathing was similar in the prone position in responders and nonresponders, although a difference was observed in the supine position. Infants who respond to prone positioning had a significantly higher value of esophageal pressure time product per minute in the supine position than nonresponders. These results suggest that the prone position may be particularly beneficial in infants with higher effort in the supine position.

All infants were ventilated using a noninvasive 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 noninvasive 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 owing 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 gastric pressure swing described suggests no change in abdominal muscle recruitment, but the tonic activity of the diaphragm (EAdi at the end of the expiratory time) was lower in the prone position than in the supine position in the present study. The diaphragm may play a role in preserving lung volume and protecting 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 <1 year of age have to actively maintain their end-expiratory lung volume above the relaxation volume,[35,36] owing 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 2 positions. Hough et al have demonstrated in neonates using electrical impedance tomography that “change” in body position leads to an improvement in ventilation distribution, irrespective of the position.[37] Herein, change over time seems to be greater in the prone position than in the supine position. This finding may be explained by the fact that children with bronchiolitis have respiratory mechanics different from neonates (e.g., 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 the supine position (or lateral position) before the study, and, although the study was designed as crossover study with a 15-minute washout period in the supine position 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 prone positioning in this population needs to be defined.

The beneficial effects of the prone position in bronchiolitis described here are likely to be related to the significant changes in respiratory mechanics provided by this position. Prone position 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, prone positioning decreased airway resistance.[12] This phenomenon was also reported in adults with chronic obstructive disease in whom prone positioning 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 thoracoabdominal synchrony was improved in the prone position, leading to a decrease of dynamic elevation of end-expiratory lung volume.[11] The prone position 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 the prone position on oxygenation measures, although the inspired fraction of oxygen tended to be lower in the prone position. This finding 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 the prone position may potentially relate to a change in mediastinal pressure transmission or a positioning against the wall of the structure. The 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 the prone position.[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 the supine position.[14,46] Prone positioning further decreased the esophageal pressure time product by one-third in comparison with the supine position, but it is possible that the level of nCPAP in the prone position may have become higher than the 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 the prone position 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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Conflict of Interest/Funding

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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.

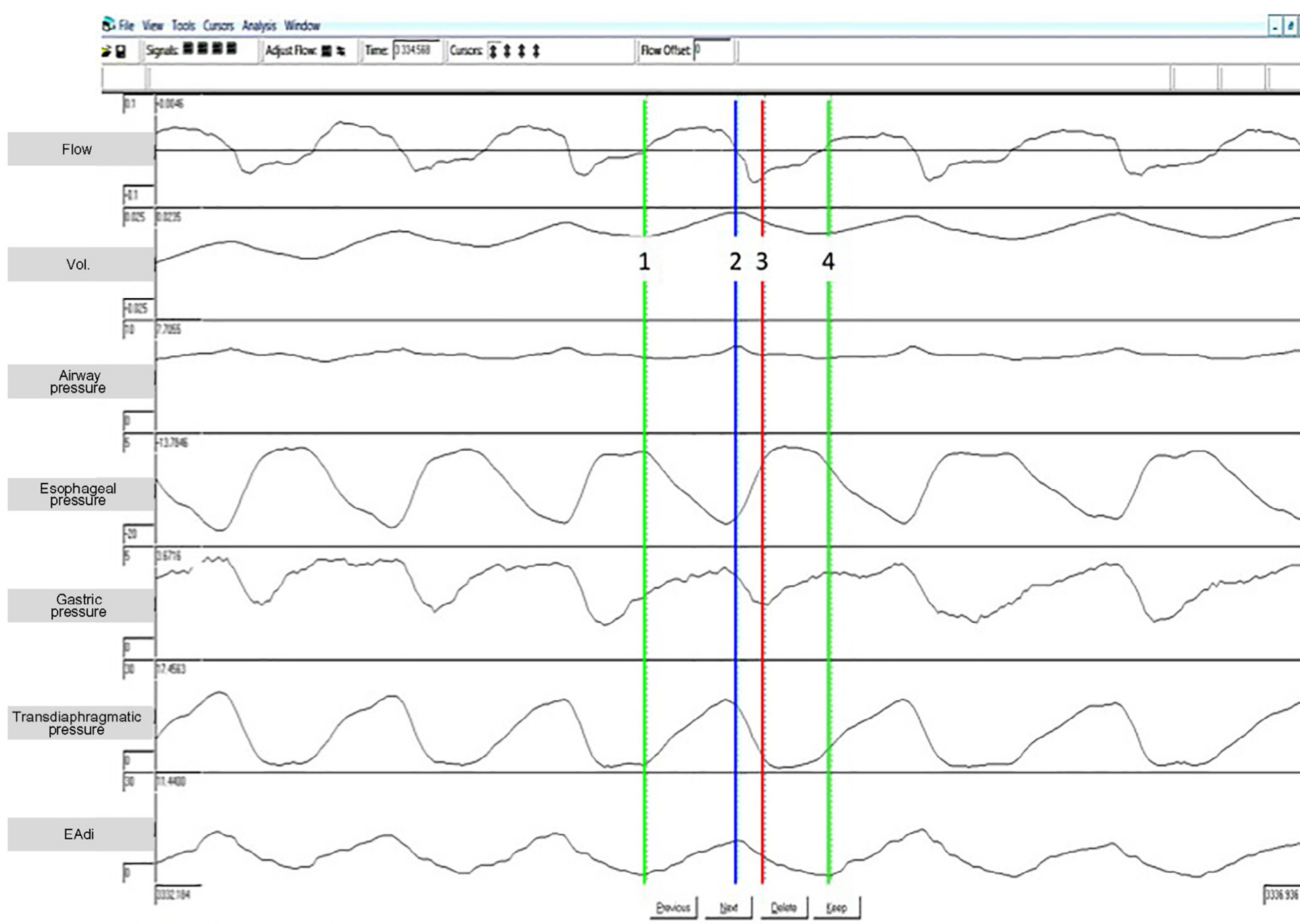


Figure 1. Example of a recording. Flow, volume (Vol.), airway pressure, esophageal pressure, gastric pressure, transdiaphragmatic pressure, and EAdi were recorded simultaneously. Neural time cursors (colored vertical bars) were placed at the beginning of neural inspiration (1), the maximal inspiratory EAdi value (2), the end of neural inspiration (3), and at the end of neural expiration (4).

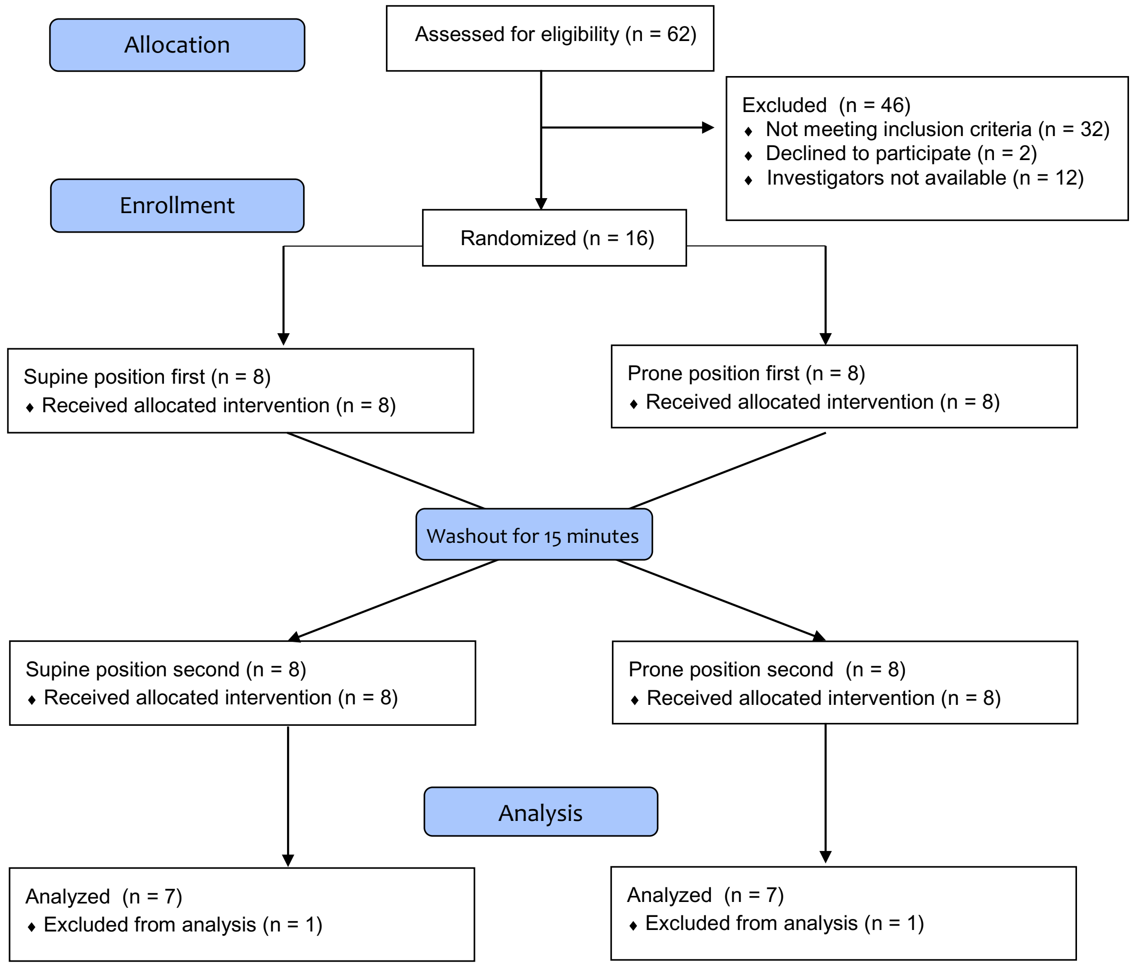


Figure 2. BRONCHIO-DV study flowchart.

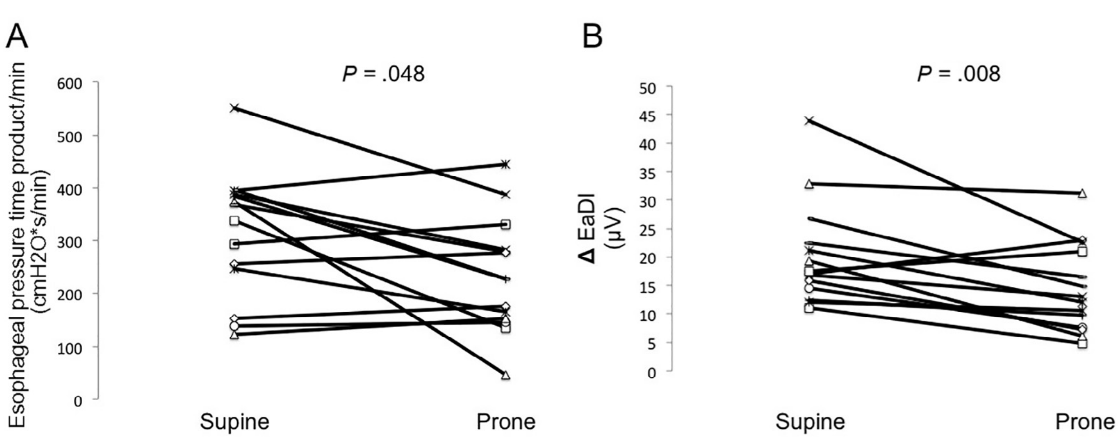
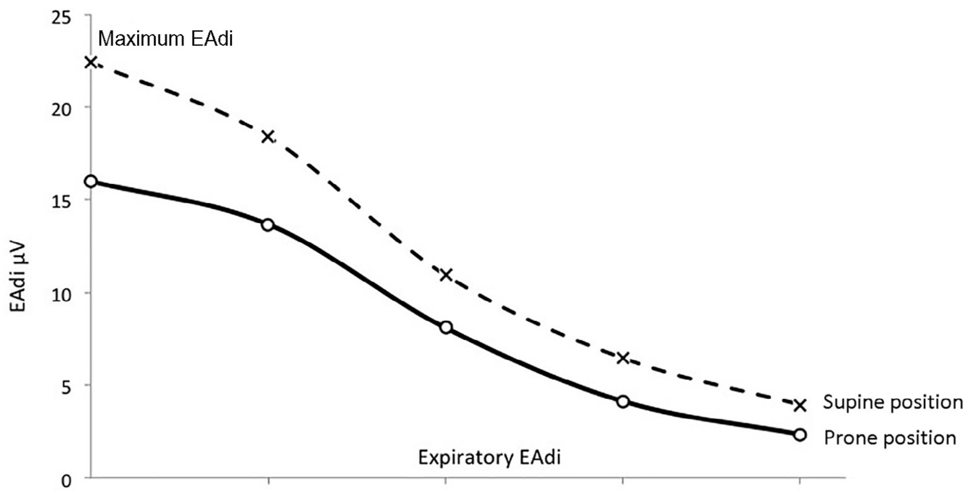


Figure 4. Reduction of the esophageal pressure time product per minute **A,** and change in amplitude of ΔEAdi **B,** in the prone position.



	Quartile 1	Quartile 2	Quartile 3	Quartile 4
EAdi supine position (µV)	22 (19-28)	10.9 (10.2-16.3)	6.5 (5.2-7.5)	3.9 (2.5-4.6)
EAdi prone position (µV)	16 (10-25)	8.1 (5.7-9.9)	4.1 (3.2-5.9)	2.3 (1.8-3.9)

Figure 5. EAdi during expiration. Time between the EAdi peak and the end of expiration was divided into four equally sized quartiles (Q1, Q2, Q3, and Q4). The mean values of each expiratory quartile are presented in the prone position (continuous line) and the supine position (discontinuous line). Values of EAdi in the prone and supine positions are presented at each time as median (IQR; first and third quartiles) below the figure.

Table IV. Demographic and clinical data at admission between responders and nonresponders

	Responders (n = 8)	Nonresponders (n = 6)	*P* value*
Age, d	40 (30-63)	24 (17-40)	.14
Weight (g)	4415 (3620-4710)	3850 (3460-4315)	.34
PELOD 2 score	3 (3-5)	3 (3-3)	.57
pH	7.29 (7.23-7.31)	7.30 (7.27-7.34)	.66
pCO_2 (kPA)	7.65 (7.45-8.56)	7.9 (7.32-8.33)	.95
m-WCAS	5 (4.38-5.10)	4.5 (4.5-4.9)	.66
Heart rate (beats/min)	166 (156-177)	161 (149-175)	.75
FiO_2 (%)	33 (29-36)	28 (25-34)	.41

FiO_2, inspired fraction of oxygen; *pCO_2*, partial pressure in carbon dioxide; *PELOD*, Pediatric Logistic Organ Dysfunction.
Data are expressed as median (IQR [first and third quartiles]).
**P* value by independent samples Mann–Whitney *U* test.

Table V. Physiological data in prone and supine position between responders and nonresponders

	Responders (n = 8)	Nonresponders (n = 6)	*P* value*
Prone position			
Neural inspiratory time/neural total time (%)	0.47 (0.46-0.47)	0.44 (0.43-0.47)	.76
Respiratory rate (/min)	66 (52-77)	62 (44-78)	.76
EAdi max (μV)	16 (13-20)	19 (10-26)	.57
Swing esophageal pressure (cmH_2O)	9.2 (7.9-12.3)	10.2 (9.2-15.9)	.76
Swing transdiaphramagtic pressure (cmH_2O)	10.5 (9.0-14.7)	11.6 (9.4-17.4)	.49
Esophageal pressure time product/breath (cmH_2O*s)	2.9 (2.8-3.9)	3.9 (3.6-4.2)	.14
Transdiaphragmatic pressure time product/breath (cmH_2O*s)	3.4 (2.8-4.4)	4.8 (4.1-5.0)	.36
Esophageal pressure time product/min (cmH_2O*s/min)	227 (158-280)	227 (159-317)	.75
Transdiaphragmatic pressure time product/min (cmH_2O*s/min)	247 (201-321)	213 (204-322)	1.0
Supine position			
Neural inspiratory time/neural total time (%)	0.47 (0.46-0.49)	0.44 (0.41-0.45)	.06
Respiratory rate (/min)	61 (54-76)	58 (49-73)	.66
EAdi max (μV)	25 (23-31)	19 (18-20)	.11
Swing esophageal pressure (cmH_2O)	15.2 (14.4-16.3)	9.2 (6.9-15.0)	.23
Swing transdiaphramagtic pressure (cmH_2O)	15.6 (12.7-17.2)	9.4 (9.1-14.3)	.11
Esophageal pressure time product/breath (cmH_2O*s)	5.0 (4.0-6.3)	3.2 (3.0-4.6)	.081
Transdiaphragmatic pressure time product/breath (cmH_2O*s)	5.3 (4.2-6.5)	3.7 (3.4-4.5)	.14
Esophageal pressure time product/min (cmH_2O*s/min)	**379** (**360-389**)	**204** (**142-284**)	**.043**
Transdiaphragmatic pressure time product/min (cmH_2O*s/min)	**393** (**326-419**)	**209** (**172-299**)	**.029**

EAdi max, maximal inspiratory EAdi value.
Bold text indicates a statistically significant difference, $P < .05$.
Data are expressed as median (IQR [first and third quartiles]).
**P* value by independent samples Mann–Whitney *U* test.