Manuscript word count: 2899
Abstract word count: 248
Tables:4
Figures: 3
Suplementary tables: 2
References: 39

Diaphragm Ultrasonography to Predict Respiratory Failure in Infants with Severe Bronchiolitis

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Disclosures

FINANCIAL DISCLOSURE

This research received no specific grant from any funding agency or commercial or not-for-profit sectors.

CONFLICTS OF INTEREST

None to declare

ACKNOWLEDGMENTS

We thank all PICU staff and nurses, and of course infants and their parents for their support in the perform of this study.

Part of the material contained in this article was presented at the 2017 SECIP (Sociedad Española de Cuidados Intensivos Pediátricos) annual meeting, May 2017, San Sebastián,Spain; and in the WFPICCS (World Federation of Pediatric Intensive & Critical Care Societies) 2020 Mexico.

INTRODUCTION

Acute bronchiolitis is a leading cause of hospitalization among infants worldwide, with pediatric intensive care (PICU) admission rates of 9-13% in hospitalized previously healthy infants, and 36% in those with comorbid conditions. Among infants admitted to a PICU, about 2-5% will require conventional invasive mechanical ventilation (CMV), with a mortality rate of 1% [1–3] . Supportive treatment, non-invasive respiratory support and when needed, invasive mechanical ventilation, remain the standard of care in infants with severe bronchiolitis admitted to a PICU.

Predictive factors for PICU admission have been described in the literature[3,4]. In an attempt to increase the performance of clinical scores, some authors have advocated for the inclusion point-of-care lung parenchyma ultrasound in the evaluation of infants with bronchiolitis[5–10]. Nevertheless, the clinical assessment of the effort of breathing (EOB) is limited by subjectivity and poor specificity and it is based on experience of the clinical experience, failing by itself to predict clinical outcomes[11–15]. Objective measurements of EOB in critically ill children could be more accurate, but may be limited for routine clinical care because their invasiveness, cost, required technical expertise and necessary equipment[16].

Point-of-care ultrasound of the diaphragm (POCUS) allows for the quantification of diaphragmatic contractile activity in real time by measuring the diaphragmatic excursion (dExc), thickness and thickening fraction (dTF)[17,18]. Ultrasonographic assesment of the dTF has been described as a good indicator of changes in inspiratory muscle effort and work of breathing in adults[19–21].

The aim of the present study was to evaluate the performance of ultrasonographic indices of diaphragmatic contractile activity in infants with moderate and severe bronchiolitis supported with HFNC or NIV, and their usefullness in predicting respiratory failure and the need of mechanical ventilation in this population.

METHODS

We conducted a prospective observational study in the PICU of a public, university-affiliated Hospital in Madrid, Spain from October 2018 to March 2019. The study was setting was a 16-bed medical-surgical PICU with approximately 1,000 admissions per year. The Institutional Ethics Committee approved the study (reference number (PI-3478) and fully written informed consent was obtained from the parents of the participants before inclusion.

Patients and study protocol

Infants (<6 months old) with moderate and severe bronchiolitis (Wood Downes-Ferres scale >6) admitted to the PICU were enrolled. In compliance with the standard operating procedure in our department, the patients were placed on HFNC (AIRVO 2 Fisher & Paykel, Air flow 2 l/kg/min; with FiO2 titrated to a minimal SatO2 90%) or NIV (Servo-i, Maquet Sweeden, with a total face mask Performax XXS or XS Respironics). Treatment failure was defined according to institutional protocols (Supplementary table 1). Demographic and clinical variables, HFNC or ventilator settings and ultrasound examination were collected at admission, 24 h and 48 h of PICU admission. Patients were in semi-recumbent position troughout the study (head of bed elevated to 30 degrees). Patients with palliative situation, oncologic diseases, haemodynamic inestability, vomiting, pneumothorax and with a tracheostomy in place were excluded.

Ultrasonographic mesurements

Ultrasography was performed by two trained operators (AGZ and DRA) using a LogicF6 device (GE Helthcare) equipped with a high-resolution (6-13 MHz) linear probe and 3-5 MHz convex phased-array probe. POCUS of both hemidiaphragms (right (R) and left (L)) was performed. The dExc, speed of diaphragmatic contraction, diaphragmatic inspiratory time (dTi), diaphragmatic expiratory time (dTe) as well as the dTF (dTF = (end-inspiratory thickness -- end-expiratory thickness) / end-expiratory thickness * 100)) were measured.

Images were obtained as previously described (17,18), with a phased-array transducer (3-5 MHz). M-mode was then used to calculate dExc - diaphragm movement toward the transducer (positive deflection on M mode) or away from the transducer (negative deflection on M mode)-, the speed of diaphragmatic contraction, and diaphragmatic inspiratory-espiratory time (dTi, dTe)(Fig 1). Three consecutive measurements were averaged.

DTF assesments were obtained at the zone of apposition of the diaphragm to the rib case, with a high-frequency linear-array probe (6-13 MHz). The ultrasonographic appearance of the diaphragm in the zone of apposition is seen as a three-layered structure composed of two parallel echogenic layers of diaphragmatic pleura and peritoneal membranes and betwen them a nonechogenic layer of muscle (Fig 1). Three subsequent inspiratory and expiratory measures of the non-echogenic layer of muscle were averaged. DTF was calculated using the M mode in the zone of apposition (Fig 1).

Statistical analysis

Data were analyzed using SPSS 24.0 toolbox (version 24, IBM, New York, USA). Normal goodness of fit was evaluated using the Kolmogorov–Smirnov test. The nonparametric data are expressed as median (Mdn) and interquartile interval [IQI 25%–75%] or the interquartile range in the case that the group only has two measures. For the nonparametric contrast of 2 unrelated samples, the Mann–Whitney U test was used. Spearman (non-parametric data) test was used for correlation analysis between variables. To analyze the association among qualitative variables, the chi-squared test was used. Statistical significance was set at $p < 0.05$.

RESULTS

Study sample

Between October 2018-March 2019, a total of 90 infants met inclusion criteria; 26 of them consented to participate and were recruited. The rest of patients were not recruited because of technical and organizational issues (lack of diafragmatic ultrasound training or lack of research personnel). Patient demograpichs and clinical characteristics are shown in Table 1. Respiratory Syncitial Virus was the main etiological agent in 24 infants (92%). The median length of PICU stay was 4 days (3-6). The initial therapy was HFNC in 14 patients (54%) and NIV in 12 patients (46%). Three patients required orotracheal intubation (11%). A total of 56 ultrasonographic evaluations were performed. At the moment of ultrasonographic evaluation respiratory support was HFNC in 31 patients and NIV in 25 patients.

Radiological involvement and Diaphragm POCUS

At admission, a chest X-ray (CXR) was performed. Any type radiological involvement was found in 19 patients (73%). Ten patients presented radiological involvement of the upper quadrants, and nine of the lower quadrants. Patients with lower radiologic involvement presented lower dExc, higher dTF, and lower diapraghm speed contraction. Among all the measures, only Left dTF and Right dExc were statiscally significant. The radiological involvement of lower quadrants upon admission was statistically correlated with escalation of respiratory support from HFNC to NIV or CMV ($\chi 2 = 5.67$ $p = 0.017$). Table 2 and Figure 2 show the relationship between lower quadrant radiological involvement and ultrasonographic parameters.

Ultrasound evaluation and need of IMV

The study sample was analyzed in two groups: a) HNFC group (i.e. patients receiving HFNC support at the time of ultrasound evaluation) and b) NIV group (i.e. patients receiving NIV at the time of ultrasound evaluation).

The POCUS measurments of both hemidiaphragms in the HFNC group are reported in Table 3 and Figure 3. No differences were observed between the subgroup that required escalation to NIV and the one that remained with HFNC.

Infants who required escalation to CMV had higher dTF, lower diaphragmatic contraction velocities, shorter expiratory times (dTe) and higher respiratory rates. Of these parameters, only left dTF, dTe and respiratory rates were statistically significant.

Regarding the NIV group, no differences were found in dExc, speed of dExc and echographic dI:E ratios between those who required CMV and those who didn't. Ultrasonographic dTF was increased in the patient on NIV requiring CMV versus those non-intubated, but this result was not estatistically significant. Results are shown in Table 4.

Diaphragm POCUS and clinical score

We found no correlation between ultrasound measurements and a clinical score used to evaluate respiratory distress in infants with bronchiolitis (Wood-Downes) (Supplementary Table 2).

Diaphragm POCUS and PICU outcomes

There were positive correlations between PICU length of stay (LOS) and the echographic dI:E ratio ($p=0.001$, $r=0.843$); and a negative correlation between PICU length of stay and dTe ($p=0.003$, $r=-0.661$). The length of HFNC support was negatively correlated with right dExc ($p=0.031$, $r=-0.524$) whereas NIV support days were correlated with left dTF ($p=0.005$, $r=0.534$), right dTF ($p=0.036$, $r=0.597$), left dExc ($p=0.028$, $r=0.516$) and right dExc ($p=0.048$, $r=0.473$).

DISCUSSION

The main findings of our study were 1) that lower quadrant involvement in the admission CXR was associated with a higher need for escalation in respiratory support with diaphragmatic POCUS showing higer dTF, lower dExc and speed contraction values in these patients, 2) infants who required CMV had higher dTF, slower diaphragmatic speed contraction, shorter dTe and higer respiratory rates and 3) diaphragmatic POCUS parameters are correlated with relevant PICU outcomes such as PICU LOS and days of respiratory support.

To our knowledge, this is the first ultrasonographic study assessing diaphragmatic POCUS values in infants with moderate to severe brochiolitis requiring non-invasive respiratory support in a PICU.

Diaphragm POCUS is a non-invasive evolving technique in the ICU setting and it is accepted as a reliable tool for assessing the diaphragm function in mechanically ventilated patients[22–27]. Ultrasonographic diaphragm thickening has been described as a good index of diaphragmatic efficiency as pressure generator[20]. In adult studies, the right dTF has demonstrated a good correlation with inspiratory muscle effort and work of breathing mesurements such as esophageal or transdiaphragmatic pressure-time product (PTP) or electrical diaphragmatic activity (Edi)[19–21]. We found that in infants with moderate or severe brochiolitis with non-invasive respiratory support (HFNC, NIV) the use of ultrasonographic dTF and diaphragmatic Ti/Ttotal could reflect EOB and could help predict respiratory failure and the need for CMV.

The feasibility and reproducibility of right hemidiaphragm measurements have been shown to be superior to those of the left hemidiaphragm, and no significant difference in diaphragm thickness and contractility have been noted between the left and right hemidiaphragms in adult literature[22,23]. In our study, we found that left hemidiaphragm ultrasonography though more dificult to asses, is feasible with the probe positioned in the midaxillary line and the left apposition zone.

Although diaphragmatic dysfunction is currently a topic of interest in pediatric critical care most of the studies have been conducted in mechanically ventilated children[28–33]. These observational studies confirm the fact that, as has been shown in adults, critical illness has detrimental effects on the diaphragm of children. In these PICU population, diaphragm thickening is feasible and highly reproducible being usefull to diagnose diaphragm atrophy, which can affect up to 50% of pediatric mechanically ventilated patients (30) and is associated with longer times of NIV following extubation[31].

In spontaneously breathing adult patients, dTF has shown to be positively correlated to Vt, but this relation is inverse during pressure support breathing as in this setting Vt depends on the balance between the work provided by the patient and the ventilator[20,34].

DExc and dTF have seldomly been assessed in spontaneous breathing neonates and children[9,35,36]. In 2001, Rehan et al. described diaphragmatic dimensions (excursion, thickness, and dTF) in healthy preterm infants who did not show any signs of respiratory distress and were not receiving respiratory support[35]. The values of dTF for healthy preterm infants, with postmenstrual age of 29 to 31 weeks, were 27± 9%.

Although the diaphragm plays a fundamental role, anatomical diaphragmatic and chest wall configuration in infants (compliant chest wall and more horizontal insertion of diaphragm to chest wall) make the use of accesory inspiratory muscles and an increase respiratory rate necesary to maintain an adecuate ventilation in respiratory insufficiency. In our study, we found that patients on HFNC requiring intubation present a significantly higher RR, but found no correlation in those patients requiring escalation to NIV or intubation from NIV. Interenstingly, the patients on HFNC requiring escalation presented higher I:E ratios (higher Ti/Ttot) which resulted in a reduced their dTe, indicating an impending respiratory failure. Prolongation of Ti offers an energetically advantageous strategy of compensating an increased inspiratory resistive load and may be modulated by behavioral and cortical adaptations. At high inspiratory load close to fatigue threshold, there is a progressive decrease in Vt, Ti, Vt/Ti, and Ttot, and an increase in Ti /Ttot. When subjected to an incremental elastic load, the Ti, Ttot, and Vt are also reduced to limit the work of breathing causing a rapid shallow breathing pattern in adult population. When the diaphragm can still compensate, there is an augmentation of the dTF in order to mantain an adecuate minute ventilation and adecuate funcional residual capacity. If the mechanical load (resistive or elastic) is excessive and the diaphragm is unable to compensate there may be a decrease in Vt or Ti or both[25,37]. In our sample, infants with higher Ti/Ttotal presented a higher PICU length of stay. Our data suggest that dTF could reflect effort of breathing in infants with moderate-severe brochiolitis with non-invasive respiratory support, since patients requiring intubation and mechanical ventilation have higher dTF.

The present study showed that the use of ultrasonographic dExc was of little help to predict respiratory failure and the need of escalation of respiratory support but it was inversely correlated with length of HFNC. In our series, the mean right dExc in the HFNC group was 5.7 mm (4.9-7.6), and in the NIV group 6,6 mm (4.7-7.9) compared to 6,4± 2,1mm described in healthy children[36]. DExc is associated with inspiratory volume but does not correlate with other indexes of respiratory effort. DExc is influenced by the respiratory drive and the respiratory loads impossed by the lung and rib/abdominal cage and shouldn't be used as the sole indicator of diaphragmatic strength. It has been described that diaphragmatic shortening increases with a low respiratory workload, an adequate respiratory drive that is not limited by sedation, and when the diaphragm is healthy. In addition, dExc may vary depending on posture, exhibiting higher values when patients are supine vs seated, as well as when the abdominal and/or thoracic pressure is altered (e.g., ascites, atelectasis)[25,37].

Buonsenso et al.[9] found that infants with bronchiolitis who needed respiratory support during admission present a higher inspiratory excursion (mean right dExc was 10,38± 4mm) and describe a decrease in dTF. This diference with our findings could be related to the fact that we performed the ultrasonographic evaluation after initial stabilization, in non-strict spontaneous ventilation as our infants were already assisted on HFNC or NIV, both of which reduce the EOB[38]. The amount of continuous positive pressure generated by HFNC at 2 L/Kg/min, despite low, could have affected the dExc, as may have PEEP and pressure support (PS) during NIV. In addition, 34,6% of the infants suffering bronchiolitis in our series presented lower basal atelectasis in the CXR which could impair diafragm shape and motion, limiting also the dExc and speed contraction values and associating an increase dTF as described previously. Because of our small sample size were unable to determine a cut-off dTF percentage that could identify patients a high-risk of severe respiratory failure.

We saw no differences in dExc or dTF between patients on HFNC or NIV despite the fact that NIV should reduce the inspiratory effort and dTF. In adult patients under CMV and NIV, the dTF decreases with increasing levels of pressure support being a reliable indicator of inspiratory muscle effort in response to modifications of the support level[20]. In a recent trial, El-Mogy et al[39], concluded that stable preterm infants (30.3 ± 2.2 weeks' gestation) with mild respiratory dysfunction show comparable effects on dTF and dExc during relatively brief periods of support on nCPAP or HFNC. An explanation of our findings could be the fact that during NIV we set a relative low level of PS as the study wasn´t designed to asses the dTF variation with pressure support level modifications.

Interestingly, no correlation was found between the clinical score (Wood-Downes) and the need for CMV in infants supported with HFNC or NIV as previously described[4,12]. We found no correlation between the clinical score and echographic dTF, highlighting the subjectivity of the clinical assessment scales for infants with bronchiolitis and the need to associate more objective estimators of EOB to clinical parameters.

Our limitations include a small simple size including only three intubated patients which may limit the generalizability of the data and the lack of a control group without respiratory support. In addition, objetive measures of the inspiratory muscle effort (esophageal, diaphragmatic pressure-time product or electrical diaphragmatic activity (Edi)) were not used in our study. Additionaly we did not perform lung parenchyma POCUS. Our primary end point was the study of diapragmathic ultrasound although the assesment of lung aireation could have added more information about prognosis in our series as has been described previously[5–10]. We didin't assess the intraobserver and interobserver reproducibility of both dExc and Dtf. In order to reduce intra and inter-observer variability, we performed all protocolized measurements as described and accepted on literature[5,18], but we are aware that scanning exactly the same point in every exam in distressed infants is challenging and we cannot exclude minimal displacement that may have altered reproducibility. In order to mitigate this, the same two experienced operators performed all explorations and the recorded images of three consecutive breaths were always reviewed by them.

In conclusion, we found that in infants with moderate and severe bronchiolitis, the use of ultrasonographic dTF and diaphragmatic Ti/Ttotal could reflect the EOB and when asociated to higher RR, and lower quadrant atelectasis could help predict respiratory failure and the need of intubation and mechanical ventilation. Diaphragm POCUS may have implications for monitoring and early treatment in infants suffering respiratory distress due to bronchiolitis. Future randomized controlled trials should assess if the use of diaphragm ultrasonography impacts acute and long-term outcomes in this population.

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