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ARTICLE

Response to first dose of inhaled albuterol in mechanically ventilated preterm infants

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Abstract

Background Bronchodilator responses among preterm infants are heterogeneous. Bedside measurements may identify responders.

Study design Respiratory measurements (Resistance, Compliance, FiO_2) and pulse oximetry (SpO_2) patterns were downloaded from infants <30 weeks gestational age during the first 2 months of life. Mechanically ventilated infants who received albuterol were included ($n = 33$). Measurements were compared before and after first albuterol. Secondary analyses assessed subsequent doses.

Results Median gestation and birthweight were 25 3/7 weeks and 730 g, respectively. Mean Resistance decreased post-albuterol ($p = 0.007$). Sixty-eight percent of infants were responders based on decreased Resistance. Compliance and FiO_2 did not significantly differ. Percent time in hypoxemia ($SpO_2 < 85\%$) decreased post albuterol ($p < 0.02$). In responders, Resistance changes diminished with subsequent administration (all $p = 0.01$).

Conclusions Ventilator resistance decreased in two-thirds of preterm infants, consistent with studies that utilized formal pulmonary function testing. Albuterol had a variable effect on delivered FiO_2; however, hypoxemia may be useful in evaluating albuterol response.

Introduction

Neonatal respiratory insufficiency necessitating supplemental oxygen and mechanical ventilation is required for most extremely preterm infants cared for in the neonatal intensive care unit (NICU) [1], unfortunately, these interventions may contribute to airway hyper-reactivity and chronic lung disease [2]. Airway smooth muscle is present in the preterm airways and contains neural elements responsive to cholinergic and other constrictive stimuli [3], which may precipitate airway narrowing, worsen respiratory mechanics, and lead to hypoxemia. The preterm airways also contain β2-adrenergic receptors (β2-AR) capable of agonist-stimulated bronchodilation [4]. Preterm infants at high risk for chronic lung disease show evidence of hypertrophy of airway muscle as early as 10 days of age [5]. Therefore, it is not uncommon for NICU clinicians and respiratory therapists to use inhaled β2-AR agonists, such as albuterol, to potentially relieve bronchoconstriction and wheezing, decrease airway resistance, and improve oxygenation in preterm infants with evolving and established chronic lung disease [6–10]. While systematic reviews have not shown convincing data of their efficacy in the prevention of chronic lung disease or other long-term morbidities associated with prematurity [11, 12], many preterm infants do show improvements in pulmonary function testing following inhaled β2-AR agonist therapy [4, 13–16]. Of note, some infants may never be responders in the NICU [4, 16] or have the potential to develop tolerance and become non-responders over time [13, 17].

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When individual pulmonary function testing is not available or feasible, clinicians will accordingly use physical exam and fraction of inspired oxygen (FiO_2) requirements to identify infants likely to benefit from scheduled β2-AR agonist therapy. Still, classifying responders remains a challenge without a discrete marker of treatment effect. The current bedside ventilator and monitors may have objective measures to assess β2-AR agonist responders such as airway resistance and intermittent hypoxemia. Intermittent hypoxemia (IH), a decrease in oxygenated hemoglobin (SpO_2), has been shown to correlate with responses to therapeutic blood transfusions [18, 19], and are associated with later diagnoses of chronic lung disease [20, 21], childhood asthma medication use [22], and mortality [23]. Continuous pulse oximetry monitoring provides a non-invasive modality for assessing oxygenation in the neonate and is used extensively in most NICUs [24].

The objective of this study was to utilize available bedside monitoring of intubated preterm infants to report upon respiratory and oxygenation changes (Resistance, Compliance, FiO_2, and SpO_2) following the first dose of albuterol. We hypothesized that ventilator measures of dynamic Resistance will decrease, dynamic Compliance will increase, FiO_2 will decrease, and percent time in hypoxemia will decrease after albuterol is administered. As a secondary outcome, we also investigated if changes in Resistance continue with repeated albuterol administration in first-dose responders.

Methods

This was a secondary analysis of responses to albuterol administration (2 puffs via a 90 mcg metered-dose inhaler (MDI) without an aerochamber spacer) in mechanically ventilated preterm infants from a cohort of infants cared for in the Level IV NICU of University of Kentucky [18, 25]. All infants <30 weeks without major congenital anomalies were approached for enrollment after parental consent. Respiratory measures (Resistance, Compliance, and FiO_2) were prospectively collected from the bedside mechanical ventilator (Draeger Babylog VN500; 4–5 min sampling rate) during the first 2 months of life. Intermittent hypoxemia measures were prospectively collected using high-resolution research pulse oximeters (Masimo Radical 7, 1 s sampling rate, 2 s averaging time). Baseline characteristics and albuterol administration were retrospectively collected from medical records and matched with cohort participants. Gestational age was based on best obstetrical dating. Small for gestational age was <10th percentile for gestational age by Fenton preterm growth charts. Chorioamnionitis was based on clinical diagnosis by obstetrical provider. Surfactant delivery was through an endotracheal tube. Patent ductus arteriosus diagnosis is based on echocardiogram findings. Institutional review board approval was obtained during the acquisition of the oxygen saturation data with waiver of consent for the current report.

Statistical analyses

For each subject, Resistance, Compliance, FiO_2, and IH measures were compared utilizing 4-h averages pre and post the first albuterol administration. To account for statistical correlation arising from these repeated measurements, paired *t* tests were utilized to test for a mean change in the given outcome type, and corresponding 95% confidence intervals are provided. Alternatively, due to the occurrence of outliers in the IH data, we present sample medians and interquartile ranges (IQRs) for changes from pre to post, and utilize the signed rank test with the change in IH as the outcome of interest. Pearson's correlations and corresponding tests were used to assess correlations between outcomes and age.

For the secondary analyses, we obtained 4-h dynamic Resistance averages pre and post the first, second, and third albuterol administrations. We utilized the change in the 4-h averages as the outcome of interest in order to account for statistical correlation at any given dose. Due to each subject contributing these measurements at three different doses, a repeated measures linear model with working unstructured covariance structure was utilized to assess and test for differences in mean dose responses.

All tests were two-sided at the 5% significance level. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Out of 218 infants screened, a total of 40 infants received albuterol while on mechanical ventilation in the first 2 months of life. Of those, 33 infants had ventilator or SpO_2 data pre/post first albuterol dose administration (28 infants had ventilator data and 28 infants had SpO_2 data, of these 23 had both). Baseline characteristics and common neonatal morbidities are presented in Table 1. The median gestational age (GA) was 25 3/7 weeks (IQR 24 2/7–26 5/7), median birth weight was 730 g (IQR 640 - 893), and 40% were female. There was no difference in baseline characteristics between responders and non-responders.

Respiratory measures

Mean respiratory measurements pre and post albuterol administration are presented in Fig. 1. Resistance decreased in 68% of infants. The mean Resistance post albuterol

Table 1 Baseline characteristics of cohort, $n = 33$.

GA at birth (weeks)	25 3/7 (24 3/7–26 5/7)	RDS (%)	100%
Birthweight (g)	730 (640–893)	Surfactant administration	100%
Day of life at albuterol dose	32 (28–40)	Oxygen on day of life 28 (%)	100%
Weight at albuterol dose	1200 (959–1344)	Oxygen at 36 weeks PMA (%)	91%
SGA (%)	18%	PEEP (cmH_2O)	8 (7–8)
Sex (% female)	40%	Respiratory rate (bpm)	25 (20–30)
Ethnicity (% White)	97%	MAP (cmH_2O)	11 (10–14)
Apgar Scores at 5 min	6 (3–6)	Inspiratory Time (seconds)	0.4 (0.35–0.5)
Chorioamnionitis	15%	PIP (cmH_2O)	25 (21–30)
ROM (>18 h)	24%	FiO_2	0.44 (0.34–0.65)
Any PDA	24%		
Moderate or Large PDA	12%		
Systemic steroids at albuterol dose	12%		
Inhaled steroids at albuterol dose	0%		
Diuretics at albuterol dose	48%		
Caffeine Therapy	100%		

GA gestational age, *SGA* small for gestational age, *ROM* rupture of membranes, *PDA* patent ductus arteriosus, *RDS* respiratory distress syndrome, *PMA* postmenstrual age, *PEEP* Peak End Expiratory Pressure, *BPM* breaths per minute, *MAP* Mean Airway Pressure, *PIP* Peak Inspiratory Pressure, *FiO_2* Fraction of Inspired Oxygen. Median (interquartile range).

significantly decrease ($p = 0.007$) as shown in Fig. 1A. Compliance increased in 64% of infants. The mean Compliance increased after albuterol but was not statistically significant ($p = 0.29$) (Fig. 1B). FiO_2 increased post albuterol in 50% of infants. The overall increase in FiO_2 was not statistically significant ($p = 0.21$) (Fig. 1C). There were no statistically significant correlations found between respiratory measures and GA and postnatal age.

Intermittent hypoxemia measures

Intermittent hypoxemia measures pre and post albuterol administration are presented in Fig. 2. The percent time in hypoxemia (%time-$SpO_2 < 80$ and %time-$SpO_2 < 85$) decreased after albuterol administration in 68% of patients. Due to outliers, median change was calculated. Both %time-$SpO_2 < 80$ and %time-$SpO_2 < 85$ decreased after albuterol as presented in Fig. 2 (all $p < 0.02$). There were no statistically significant correlations found between IH measures and GA and postnatal age.

Secondary analyses

Secondary analyses were performed to assess the albuterol responses of subsequent administrations in infants who responded to initial therapy. Of the 19 responders in terms of a decrease in Resistance, 10 infants received additional albuterol doses as prescribed by their primary clinical team. All ten infants received at least three doses. Interestingly, the average response was significantly diminished with the second and third administration when compared to the first dose (all $p = 0.01$), Fig. 3. Additional doses (>3) were not included in this analysis due to small sample size as the number of infants prescribed albuterol decreased with subsequent doses.

Discussion

We observed that archived bedside monitoring shows that ventilator measures of Resistance and pulse oximetry measures of IH decreased after inhaled albuterol in the majority of ventilated preterm infants. Contrary to our original hypothesis, ventilator measures of Compliance and delivered FiO_2 did not significantly change. Although measured differently and in controlled settings, our findings of decreased Resistance following inhaled albuterol are congruent with the ~70% of individual responders reported in other studies [16, 26, 27]. While variable results of average blood oxygenation have been previously reported in multiple albuterol studies [14, 15, 26, 28, 29], we believe we are the first to quantify percent time in hypoxemia parameters (%time-$SpO_2 < 80$ and %time-$SpO_2 < 85$) in pre- and post-albuterol evaluations utilizing pulse oximeter histogram profiles.

As highlighted by Slaughter et al. in their extensive database review, there is considerable variability amongst US institutions for the indications, timing, use, and type of bronchodilators prescribed for preterm infants in the

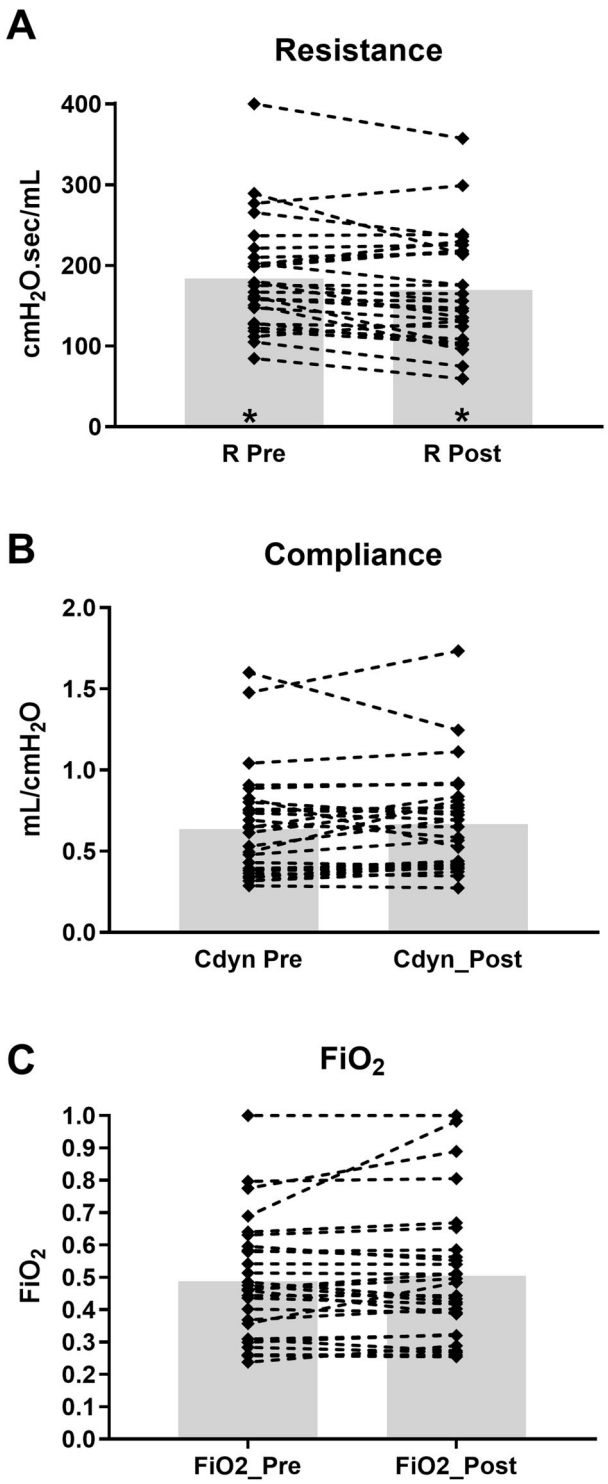

Fig. 1 Resistance decreases after albuterol. Mechanical ventilator measurements of **A** Resistance (R), **B** Compliance (Cdyn), and **C** Fraction of Inspired Oxygen (FiO_2) 4 h before (Pre) and four hours after (Post) albuterol inhalation showed a significant decrease in mean Resistance (*$p < 0.05$, two-tailed paired t test). Significant changes in Compliance and FiO_2 were not detected. Individual data points (diamonds) and group means (gray bars) are shown. $n = 28$ subjects.

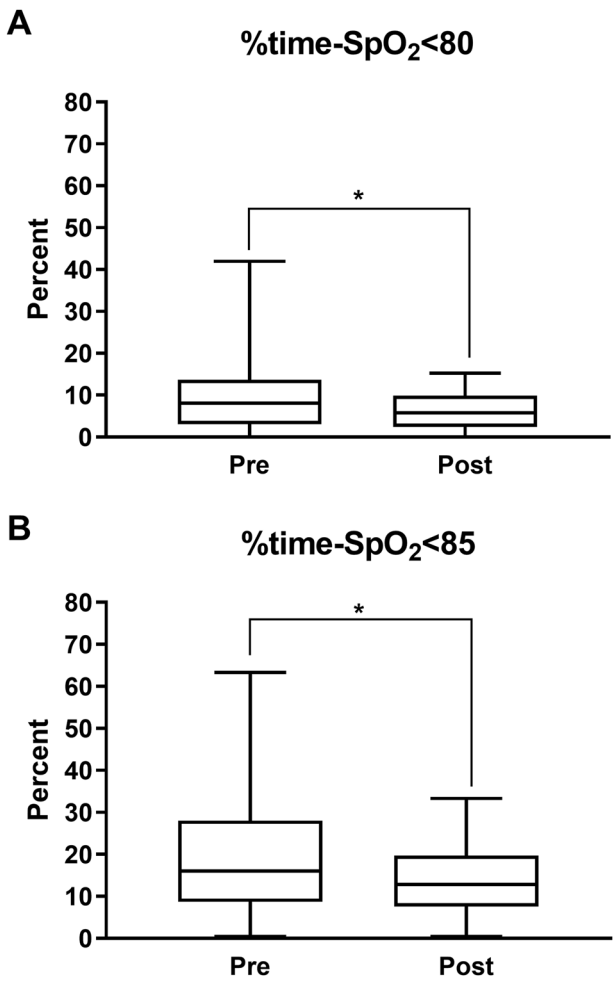

Fig. 2 Intermittent hypoxemia decreases after albuterol. Pulse oximetry histogram profiles of **A** percent time spent with $SpO_2 < 80$ (%time-$SpO_2 < 80$) and **B** percent time spent with $SpO_2 < 85$ (%time-$SpO_2 < 85$) 4 h before (Pre) and 4 h after (Post) albuterol inhalation showed a significant decrease in time spent hypoxemic (*$p < 0.05$, Signed Rank Test). Median (line) with interquartile (box) and group ranges (bars) are shown. $n = 28$ subjects.

NICU [7]. Furthermore, there are no consensus guidelines for starting or stopping these medications with a paucity of data regarding the impact of both positive and negative outcomes with longer-term use [11, 30]. While formal pulmonary function testing (PFT) in the NICU would ideally characterize the extent of neonatal lung disease and also identify β2-AR agonist responders and non-responders either by whole body infant PFT [31], breath occlusion PFT analyses of passive flow-volume curves [16], or plethysmography with helium gas dilution [32]; this requires extensive expertise, precision equipment, and in some cases patient sedation. Dynamic lung mechanics derived during spontaneous breathing may underestimate static mechanics but provide real-time analysis which can give information to assess pre/post changes [33, 34]. We believe this work is a

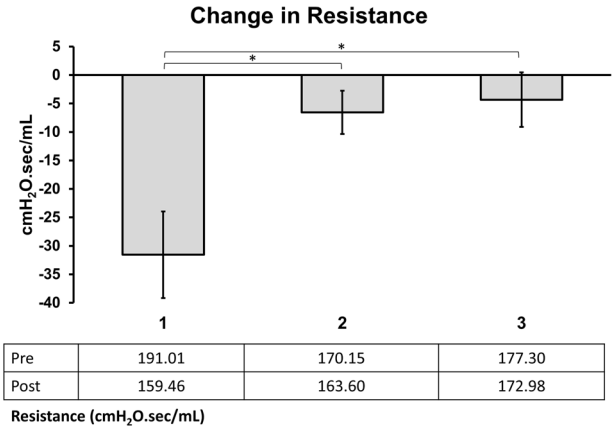

Fig. 3 Decreases in post-albuterol Resistance changes diminish with second and third dose. Mechanical ventilator measurements of changes in Resistance after albuterol show significantly decreased mean (±Std Dev) responses at Dose 2 and Dose 3 compared to Dose 1 (*$p = 0.01$, repeated measures linear model with working unstructured covariance). Raw Resistance measurements 4 h before (Pre), four hours after (Post) albuterol inhalation of first-time responders are shown. $n = 10$ subjects.

step toward early investigation of already available bedside monitoring data which could provide more objective measurements of bronchodilator responses in NICU patients than improved work of breathing, resolution of wheezing, or decrease in FiO_2.

Historically, relying upon bedside charting was not ideal [35–38]. However, next-generation mechanical ventilator interfaces and continuous pulse oximetry recordings provide high fidelity measures of respiratory parameters including actual delivered FiO_2, desaturation/IH events, and capabilities to profile time spent in hypoxemia. There were improvements in both IH measures (%time-$SpO_2 < 80$ and %time-$SpO_2 < 85$). A decrease in IH events is likely an indicator of improved and sustained aeration of previously derecruited airways and alveoli or indicative of elevated FiO_2 delivery. Indeed, while not statistically significant the FiO_2 increased in half of the study subjects following albuterol. The University of Kentucky NICU uses pulse oximetry targets of 90-95% and supplemental oxygen is titrated by the bedside nurse or respiratory therapist to maintain target range. It is possible that IH decreased with higher delivered FiO_2 after albuterol, however, FiO_2 adjustments in our clinical practice are usually driven by SpO_2 changes. This is of potential clinical significance because high-risk patterns of neonatal IH, hypoxemia, and elevated FiO_2 have been associated with short and long-term morbidities in preterm infants [39], specifically asthma and chronic lung disease [20–22]. Translational animal studies have shown that superimposed IH may further exacerbate neonatal hyperoxic airway and lung pathology [2].

Previous reports have emphasized improvements in Compliance following albuterol administration [14, 15, 26], whereas, others have reported no significant improvements in Compliance [16, 27, 28]. In this cohort, we did not observe a significant change in Compliance, which may be due to insufficient sample size or the manner in which real-time dynamic Compliance was measured by the mechanical ventilator without utilizing a standard single breath occlusive technique. Alternatively, one may not expect albuterol, as a bronchodilator, to change compliance measurements. That is to say, if airway narrowing was minimally contributing to extensive lobar atelectasis then a significant improvement in Compliance would not be expected after β2-AR agonist therapy.

As a planned secondary analysis, the effects of serial albuterol doses were investigated in this patient cohort. β2-AR tolerance and tachyphylaxis have been well described in the asthma literature [40, 41], but has been under-investigated in the NICU with only anecdotal descriptions [13, 42] and translational findings in newborn animal models [43]. We noted diminished changes in Resistance after the second and third albuterol doses (Fig. 3). Given the small sample size we were unable to perform statistical analyses beyond three consecutive doses. The dampened response may be due to continued bronchodilatory effects of the previous albuterol dose; however post-treatment mean Resistances remained elevated after the second and third doses when compared to the first dose. Importantly, none of the infants in this study were receiving simultaneous inhaled steroids which would align with current asthma recommendations [44]. Sample size precludes speculating on longitudinal efficacy, but given their frequent use in recent cohorts [10] these findings raise concern and further investigations of chronic β2-AR agonist therapy in the NICU population are needed. Of note, the University of Kentucky NICU does not have a NICU protocol for albuterol, prescription is at the discretion of the treating clinician.

This study has limitations as it was a single-center, retrospective study of intubated and mechanically ventilated preterm infants. Albuterol delivered by MDI to the inline ventilator inspiratory tubing is standard practice in our NICU for intubated patients, however different modes of delivery may have yielded different effects [27, 28, 45]. The treating clinical teams initially prescribed and decided to continue albuterol, which may predispose to selection bias and/or confounding-by-indication. We utilized respiratory measures (Resistance, Compliance, FiO_2) obtained from downloadable current generation mechanical ventilators compared to more standard PFT measurements. While passive ventilator measures have been reported previously [28, 46], studies comparing these passive measurements with invasive or whole body PFTs are needed. Although some may consider this a limitation that may underestimate respiratory parameters [34], we wished to focus upon

objective data that are readily available at the bedside for clinicians before and after albuterol administration. Similarly, we report upon percent time in hypoxemia rather than frequency and severity measures of IH; as percent time in hypoxemia is also readily available with most bedside monitors SpO_2 histograms.

The first dose of albuterol significantly decreased Resistance as continuously measured by mechanical ventilators in two-thirds of preterm infants, consistent with other studies that utilized more standard PFT modalities. Similarly, there was an improvement in percent time in hypoxemia after first albuterol dose administration in the majority of patients. However, albuterol had no significant effect on Compliance or FiO_2. The current practice of assessing initial albuterol response before scheduling treatment should focus on Resistance in the mechanically ventilated infant; as FiO_2 changes may be variable among preterm infants. Histogram SpO_2 patterns, routinely provided by the bedside monitors, may also be useful in evaluating albuterol responders especially while infants are on non-invasive respiratory support, and therefore do not have objective ventilator data. Although we found a diminished response with subsequent albuterol doses, the sample size precluded conclusions. Further studies to assess rapidity of β2-AR tolerance or tachyphylaxis in preterm infants with lung disease are needed.

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Author contributions TMR, MB, PJG, HB, and EGA designed the study. EGA, MB, BCP, and AP developed data collection methods, collected and archived these data. PMW and EGA analyzed the results. TMR, PMW, and EGA wrote the manuscript with all authors contributing to the final edits.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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