Inhaled β2-Agonist Therapy Increases Functional Residual Capacity in Mechanically Ventilated Children With Respiratory Failure*

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Objectives: To test the hypothesis that in mechanically ventilated children with respiratory failure, aerosolized albuterol modifies functional residual capacity, lung mechanics, oxygen consumption, and hemodynamics.

Design: Prospective, self-control clinical trial.

Setting: A 24-bed PICU in a quaternary care, academic children's hospital.

Patients: 25 children (age range, 1–18 yr) undergoing mechanical ventilation to treat respiratory failure. Entry criteria included previously prescribed inhaled β2 agonists. Physiologic measurements were performed prior to and 20 minutes after administration of aerosolized albuterol solution. Functional residual capacity was determined via nitrogen washout.

Interventions: Functional residual capacity, oxygen consumption, respiratory mechanics, and vital signs were measured were measured prior to and 20 minutes after administration of aerosolized albuterol solution. Functional residual capacity was determined via nitrogen washout.

Measurement and Main Results: At baseline, functional residual capacity is only 53% of predicted. After aerosolized albuterol, functional residual capacity increased by 18.3% ($p = 0.008$). Overall, aerosolized albuterol had no effect on airway resistance. However, in patients with an endotracheal tube size of more than or equal to 4.0 mm, resistance decreased from 33 ± 3 to 25 ± 3 ($p < 0.02$). Inhaled albuterol administration had no effect on oxygen consumption despite an increase in heart rate from 116 ± 2 to 128 ± 2 beats/min ($p < 0.0001$).

Conclusions: In pediatric patients with respiratory failure, aerosolized albuterol increases functional residual capacity without a decrease in resistance. In infants and children, aerosolized albuterol might favorably enhance pulmonary mechanics and thereby represent a novel strategy for lung recruitment in children with respiratory failure. (*Pediatr Crit Care Med* 2015; 16:e189–e193)

Key Words: agonist; children; functional residual capacity; inhaled β2 agonist; respiratory failure

In children, a wide array of insults can result in respiratory failure. When lung injury is particularly severe, lung compliance and gas exchange worsen, intrapulmonary shunting becomes pronounced, and severe hypoxemia results. In the absence of therapy, this leads to progressive hypoxemia, marked increase in work of breathing and respiratory failure (1). Severe diffuse lung injury, characterized by compromise in diffusion of oxygen from the alveoli into the bloodstream where the ratio of arteriolar to alveolar oxygen is less than 200, constitutes acute respiratory distress syndrome (ARDS) (2).

Positive pressure ventilation with supplemental oxygen is the cornerstone of therapy for either respiratory failure or ARDS. Over the past several decades, consensus surrounding ventilatory strategies that optimize end-organ function, even while minimizing lung injury has emerged. The fundamental principles include provision of sufficient positive end-expiratory pressure (PEEP) to maintain functional residual capacity (FRC) above closing volumes throughout the ventilator cycle, limiting tidal volume to prevent overdistention, minimizing repeated alveolar collapse and reexpansion, and limiting radical-related injury due to high concentrations of inspired oxygen. The lung-protective strategy entails use of relatively high PEEP, low tidal volumes, and permissive hypercarbia. Studies have consistently demonstrated that low tidal volumes strategies, superimposed on an open lung strategy, decrease both mortality and lung injury (3, 4).

*See also p. 678.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

Dr. Milla lectured for Clinical Viewpoints, Inc. and Advanced Health Media, Inc. and consulted for Gilead Sciences, Inc. His institution received grant support from Kalobios Pharmaceuticals, Vertex Pharmaceuticals, and Cystic Fibrosis Foundation Therapeutics Inc. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/PCC.0000000000000448

Despite clarity surrounding the benefits of open lung strategies, optimal lung recruitment often does not occur owing, arguably, to insufficient levels of PEEP. Strategies that promote lung recruitment and act synergistically with PEEP may yield meaningful clinical benefit in the context of acute lung injury. In Pediatrics, in particular, optimal levels of PEEP may be underutilized. Thus, we explored strategies that might optimize lung recruitment even without increasing PEEP.

Inhaled β2 agonists have been long used by clinicians in hypoxemic, mechanically ventilated patients even in the absence of obstructive lung disease (5). Despite the ongoing clinical use of β2 agonists in mechanically ventilated patients, clear evidence surrounding either a mechanism or clinical benefit is lacking. Theoretical benefits of β2 agonist treatment include enhanced mucociliary clearance (6), optimization of lung mechanics (7), decrease work of breathing (8), and clearance of pulmonary edema (9). In vitro studies demonstrate that stimulation of the β2 receptors regulates, via cyclic adenosine monophosphate-dependent pathways, several of the key proteins and ion channels, such as epithelial sodium channels, the cystic fibrosis transmembrane conductance regulator, and the basolateral Na, K-ATPase pump, that stimulate pulmonary fluid clearance (10).

We reasoned that aerosolized albuterol in pediatric patients with acute respiratory failure increases FRC and improves lung mechanics. To test this hypothesis, we measured the effect of aerosolized albuterol on FRC and pulmonary mechanics in 25 critically ill children with respiratory failure.

PATIENTS AND METHODS

Study Design

This is a prospective study of intubated, mechanically ventilated children with respiratory failure at Lucile Packard Children's Hospital at Stanford from August 15, 2013, to April 15, 2014. Inclusion criteria include: acute respiratory failure requiring mechanical ventilation, children 0–18 years admitted to the pediatric intensive care with an active prescription for a β2-agonist therapy delivered via an inhalational route. Exclusion criteria included hemodynamic instability, fraction of inspired oxygen in excess of 60%, PEEP greater than 10 cm, or evidence of endotracheal tube (ETT) leak. The institutional review board approved the study. Informed consent was obtained from the parents or legal guardians prior to enrollment in the study.

Protocol

All clinical decisions, including ventilator mode and support strategies, were made by the primary caregivers. Immediately prior to each study, the ETT was suctioned to ensure patency and absence of leak. Racemic albuterol, as previously prescribed by the primary team, was administered via a vibrating mesh nebulizer at the humidifier, an efficient delivery method (11). Measured lung function variables included airway resistance, and FRC. Measurements were obtained prior to and 20 minutes after albuterol administration (12).

FRC Measurement Procedure

FRC was measured using an automated procedure available on the ventilator using wash in/wash out methodology (Carestation, E-COVX, General Electric, Madison, WI). The method is based on multibreath nitrogen washout, with an incremental change in F_{IO_2} of 0.1. Initially described by Olegard et al (13), subsequent studies have further validated the method both in vivo and in vitro and down to small infants (14, 15). Measurement of FRC required between 3 and 5 minutes. Ventilation and lung mechanics were not altered by measurement of FRC. The FRC values obtained were compared with predicted values based on length, age, and gender according to published studies based on multiple breath washout (16).

Study Measurements

The primary outcome measure was FRC change after inhalation of nebulized albuterol. Additional measurements of lung mechanics included airway resistance, measured as the difference between peak and plateau airway pressures by the mean inspiratory flow rate, and expressed as cm H_2O/L/s. Further validation of the airway resistance measurements was conducted in three patients using a $NICO_2$ mainstream sensor (Model 7300, Philips-Respironics, Wallingford, CT). Secondary outcome measures included heart rate and oxygen consumption as secondary outcomes. Oxygen consumption was measured using indirect calorimetry by the calorimeter module on the ventilator (Engström Carestation, GE Healthcare, Wauwatosa, WI) (17).

Statistical Analysis

The data were expressed as mean ± SE. A paired *t* test was used to compare values obtained prior to and following administration of inhaled albuterol. A *p* value of less than 0.05 was considered statistically significant. Data analysis was undertaken with Prism, version 5.0a (GraphPad Software, La Jolla, CA).

RESULTS

A total of 25 pediatric patients with acute respiratory failure requiring mechanical ventilation were enrolled in the study between August 15, 2013, and April 15, 2014. **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/PCC/A167) presents the demographic and clinical characteristics of the 25 study subjects. Of these 25 children, 60% were less than 2 years old. The majority had postoperative respiratory failure with pulmonary edema (36%). The remaining patients were diagnosed with pulmonary infections (24%), respiratory failure due to primary neurologic cause (neuromuscular disease or seizure disorder) (20%), multiple organ failure (8%), and other diagnoses in 12%. Small ETT size (≤ 3.5 mm in diameter) was used in 40% of study subjects, which is consistent with very young study population.

Measured FRC at baseline was markedly lower than predicted, at 53% of the predicted value. Albuterol administration increased FRC by 45.6 mL (95% CI, 13–78) (a relative change of 18.3%), which was statistically significant ($p = 0.008$ by paired *t* test). This corresponded to an increase of 10.3%-predicted

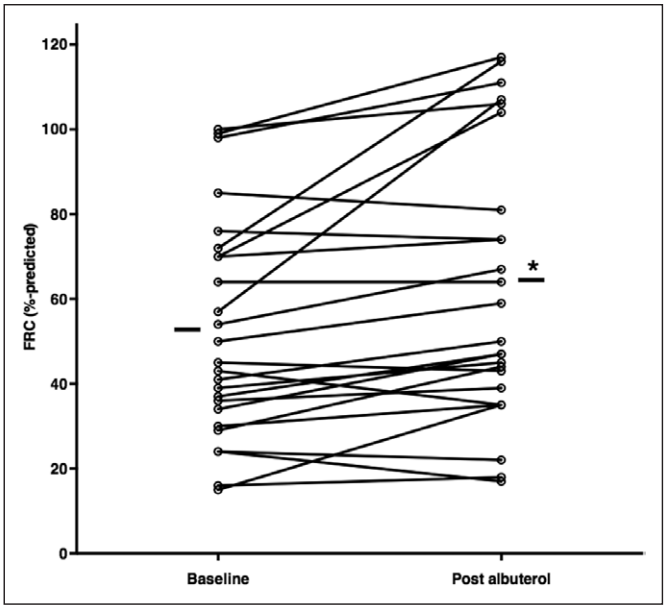

Figure 1. Functional residual capacity (FRC) percentage of predicted at baseline and postalbuterol for each patient. The *black bars* are the mean of each group. Overall, FRC increased following administration of albuterol (*$p < 0.01$, vs baseline).

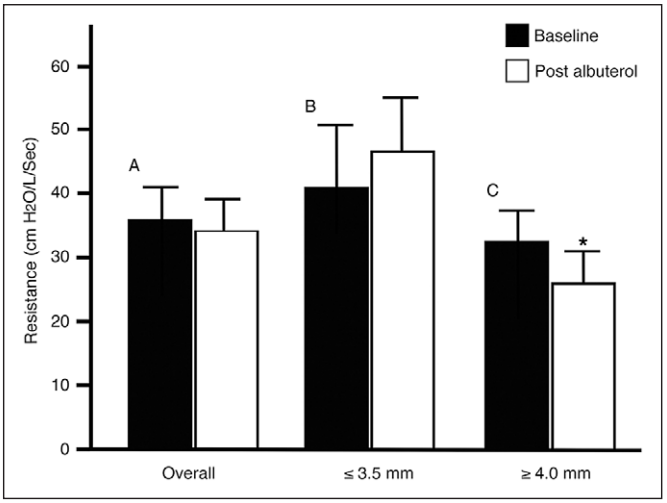

Figure 2. Airway resistance (cm H_2O/L/s) measured at baseline and after albuterol administration. **A**, Overall, albuterol had no effect on airway resistance. **B**, In patients intubated with endotracheal tube (ETT) ≥ 4.0 mm ($n = 15$ patients), albuterol caused a decrease in airway resistance of 7 cm H_2O/L/s ($p < 0.02$). **C**, In patients intubated with ETT ≤ 3.5 mm ($n = 15$ patients), albuterol had no effect on airway resistance.

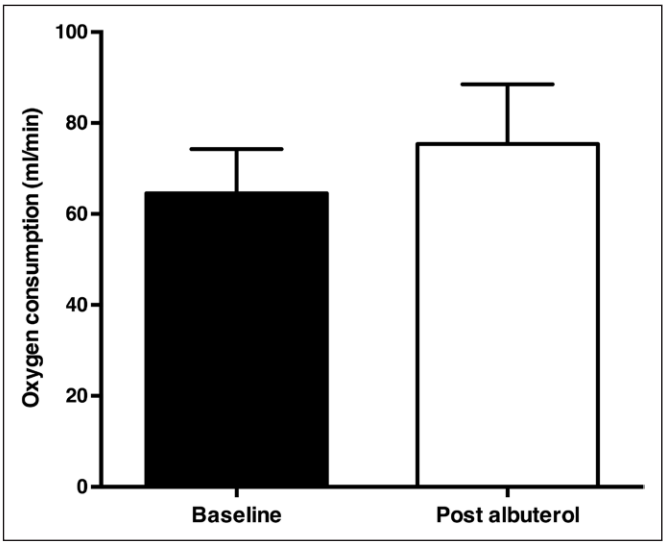

Figure 3. Oxygen consumption (mL/min), as measured by indirect calorimetry, did not change after aerosolized albuterol administration ($p = 0.08$, vs baseline).

units (95% CI, 4.2–16.4) (a relative change of 20%), which was also statistically significant ($p < 0.01$ by paired t test) (**Fig. 1**).

To better understand the physiology that underlies the increase in FRC, the change in airway resistance in response to albuterol was determined. Overall, there was no change in airway resistance after albuterol (35 ± 3 cm H_2O/L/s at baseline; 32 ± 3 cm H_2O/L/s after albuterol; $p = 0.7$; mean difference, –1.6 [95% CI, –9.4 to 6.2]).Furthermore, we analyzed the response to albuterol in children with larger and smaller ETT in place. In patients with larger ETT (diameter ≥ 4 mm), there was a significant decrease in airway resistance (from 33 ± 3 cm H_2O/L/s at baseline to 25 ± 3 cm H_2O/L/s following albuterol administration [$p < 0.002$]; mean difference, –6.5 [95% CI, –11.4 to –1.7]). In contradistinction, albuterol had no effect on airways resistance in patients with ETT of less than or equal to 3.5 mm (mean difference, 5.8; 95% CI, –13.6 to 25.3) (**Fig. 2**). The airway resistance measurements were validated using $NICO_2$ mainstream sensor for three patients, chosen randomly from each group. There was no significant difference in airway resistance measured by the $NICO_2$ mainstream sensor and the Engstrom Carestation ventilator.

Prior to albuterol administration, heart rate was 116 ± 2 beats/min. Following albuterol, heart rate increased to 128 ± 2 beats/min, evidence that albuterol had a physiologic effect on the patients. Albuterol did not cause a statistically significant increase in oxygen consumption (mean difference, 10.8 mL/min; 95% CI, –1.2 to 23; $p = 0.08$) (**Fig. 3**).

DISCUSSION

In this group of mechanically ventilated pediatric patients with respiratory failure, administration of β2 agonist treatment increased FRC. Furthermore, prior to the intervention, the measured FRC was markedly lower than the predicted FRC. Administration of aerosolized albuterol dramatically increased FRC, even in the presence of PEEP (5 cm H_2O). Despite an overall increase in FRC in all study patients, irrespective of body weight or ETT size, airway resistance decreased only in patients with ETT greater than or equal to 4.0 mm. Although albuterol caused an increased in heart rate, evidence of pharmacologic effect, oxygen consumption did not increase, arguing indirectly for safety of this therapeutic approach.

Several aspects of the present report possess significant clinical implications. First, although β2-agonist therapy is the single most widely prescribed medication in pediatric respiratory failure, the rationale for its ongoing use has not always been clear (5). From a normative perspective, the persistent use of β2-agonist therapy, even in the absence of clinical evidence to support its use might suggest clinical utility not evident in

the context of clinical trials. These data provide support for the notion that β2-agonist therapy in patients with respiratory failure can meaningfully enhance respiratory mechanics.

Similarly, the observation that measured FRC is less than predicted FRC has meaningful clinical implications. As low tidal volume ventilation strategies decrease mortality (18), achieving an optimal FRC is critically important to facilitate efficient gas exchange. Given the relatively low PEEP values classically employed in children, these data provide rationale for using higher PEEP when compliance is less than optimal, even in the presence of well preserved gas exchange. β2 agonist therapy in this patient population holds the promise of promoting lung recruitment in a manner that might be synergistic with PEEP. The observation that FRC is less than optimal, despite PEEP, is consistent with prior reports. Bikker et al (19) reported that in ICU patients without parenchymal lung disease FRC was only 66% of predicted, and 42% of predicted in patients with preexisting parenchymal lung disease, despite use of PEEP (5 cm H_2O). The present data provide rationale for the use of albuterol to optimize lung recruitment and, perhaps, potentiate the effect of PEEP while minimizing tidal volume.

Prior studies have carefully considered how β2 agonist therapy might confer clinical benefit to patients with respiratory failure. Given that lung injury can disrupt barrier function and increase both lung water and inflammation, alveolar fluid absorption, and inflammatory cell removal promote the resolution of lung injury (20, 21). Evidence from animal models, tissue culture, and ex vivo human lungs indicates that β2 agonists promote alveolar fluid clearance in lung injury and hydrostatic pulmonary edema (22). This process involves an active adenosine triphosphate-dependent transport of sodium ions out of alveolar air spaces via the apical sodium and chloride channels and basolateral Na-K-ATPases in the alveolar epithelium (9, 23). Furthermore, the long-acting β2-agonist salmeterol reduced the prevalence of high altitude pulmonary edema in a high-risk group of travelers (24). These data were translated to a randomized, controlled trial in adult patients with ARDS wherein IV albuterol decreased lung water (25). However, the results were not replicated in two relatively large, placebo-controlled randomized multicenter trials in adult patients with respiratory failure wherein mortality was increased in the treatment group relative to placebo (26, 27).

The absence of efficacy in randomized trials of IV β2 agonist therapy is not directly applicable to trials, wherein administration is via the aerosol route, especially in children. The absence of coronary artery disease in children represents a substantial physiologic difference. In the present study, a 10–20 beat/min increase in heart rate did not lead to an increase in myocardial oxygen consumption, nor any untoward myocardial or hemodynamic sequelae. In adult patients with coronary artery disease, an increase in heart rate of 10–20 beats/min in someone with relatively compromised cardiac output can be harmful. Our findings provide support for the relative safety of inhaled β2 agonist therapy in this population, as albuterol inhalation had no effect on oxygen consumption even with an increase in heart rate.

Decreased airway edema and accelerated fluid absorption may underlie the increase in lung recruitment and FRC. Maturational differences in the capacity of airway epithelium to resorb fluid may account for the improvement in younger patients, those with smaller ETTs (≤ 4.0 mm) where airway resistance did not change despite improved FRC. These data, demonstrating an absence of bronchodilation in small infants, evident by unchanged airway resistance, are consistent with previous studies demonstrating a limited capacity for bronchodilation in infants (28, 29). Although absence of airway resistance might be related to a fixed obstruction or measurement inaccuracy in the smaller ETT, all patients had ETT diameters larger than 2.5 mm, the size at which airway increases significantly (30). In addition, all patients received racemic mixtures of the (R) and (S) enantiomers of albuterol. Despite the theoretical molecular pharmacologic advantages of levalbuterol, which contains only the single active (R)-enantiomer, our interpretation of the literature is that there is no clinical advantage of levalbuterol relative to racemic albuterol.

There are significant limitations to the present study. The study was designed such that placebo treatment was not included. Furthermore, design required that control data were acquired prior to treatment data and the inability to randomize the order of data acquisition may have introduced a confounding effect. Further, the investigators were not blinded relative to treatment. To address these potential limitations, each patient served as a control, however, the lack of control would best be addressed in future trials to include a normal saline solution control group. If any interventions were prescribed between measurements, the patient was no longer eligible for the trial. A single provider performed the pulmonary mechanics testing to minimize variability. Although the results were relatively consistent across the entire study population, it is possible that results might differ substantially by disease state. This issue can be addressed in the context of a larger trial that entails a randomized, control study design.

In summary, in a prospective trial of critically ill pediatric patients with respiratory failure, aerosolized albuterol significantly increased FRC. These results suggest that delivery of β2 agonist via the aerosol route might represent a therapeutic tool that can enhance lung recruitment without increasing trauma associated with mechanical ventilation, and can be a valuable tool as a synergistic recruitment strategy. This study demonstrates the feasibility of and provides important rationale for a large-scale, randomized, controlled trial of inhaled β2 agonists in treatment in children with ARDS.

ACKNOWLEDGMENTS

We gratefully acknowledge the gracious and capable assistance of the nursing and respiratory therapy staff of Lucile Packard Children Hospital.

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