

## Bronchodilator Therapy in Mechanically Ventilated Patients: Patient Selection and Clinical Outcomes

Bronchodilators are among the most commonly employed drugs in the intensive care unit. Inhaled bronchodilator therapy is preferred in modern practice because of many advantages over systemic therapy.<sup>1</sup> In patients with airflow obstruction, inhaled bronchodilators improve wheezing<sup>2</sup> and hemodynamics<sup>3</sup> and reduce airway resistance and intrinsic positive end-expiratory pressure.<sup>4,5</sup> Bronchodilators also reduce the work of breathing,<sup>6</sup> and they could reduce the sensation of dyspnea while improving patient-ventilator interaction. In addition, bronchodilators could facilitate weaning in patients with limited cardiopulmonary reserve.<sup>6</sup> Combining  $\beta_2$  adrenergic and anticholinergic bronchodilators has a greater effect than therapy with either agent alone.<sup>7</sup>

Generally, use of inhaled bronchodilators in mechanically ventilated patients is quite safe. When a higher-than-recommended dose of bronchodilator is employed, the patient could develop hypokalemia<sup>8</sup> or cardiac arrhythmia.<sup>8,9</sup> Paradoxical bronchoconstriction could also occur. Moreover, the cost of bronchodilator therapy, particularly in terms of time spent by respiratory therapists for bronchodilator administration, is a major consideration.<sup>10</sup>

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The benefits of bronchodilator therapy have been studied mainly in patients with airflow obstructive disorders. Do similar benefits occur in patients without airflow obstruction? In a study in this issue of *RESPIRATORY CARE*, Chang and colleagues examined whether administration of bronchodilators influenced clinical outcomes in mechanically ventilated patients without known obstructive lung disease.<sup>11</sup> Patients who required more than 24 hours of mechanical ventilation received albuterol and/or ipratropium bromide via metered-dose inhaler. There was a trend toward longer duration of mechanical ventilation in patients who received bronchodilator therapy. However, this could be explained by a bias for bronchodilator therapy in patients who had pneumonia more frequently and lower  $P_{aO_2}$  than those who did not receive such therapy. Alternatively, patients who received mechanical ventilation for longer periods may have had a greater likelihood of receiving bronchodilator therapy. In general,

clinical outcomes did not improve with bronchodilator therapy. At the same time, bronchodilator treatment was safe and was associated with a modest increase in the cost of treatment.<sup>11</sup> This study is the first to address clinical outcomes with bronchodilator therapy in mechanically ventilated patients.

Only a few investigators have examined the role of bronchodilators in patients with no previous evidence of airflow obstruction. Gay and colleagues found a reduction in airway resistance among 13 mechanically ventilated patients, including those with and without airflow obstruction.<sup>12</sup> Other workers have noted a reduction in airway resistance in patients with acute respiratory distress syndrome.<sup>13,14</sup> In such patients bronchodilators not only reduce airway resistance, they also enhance mucociliary clearance of secretions,<sup>15</sup> and could increase clearance of alveolar edema.<sup>16</sup> Based on these physiologic effects, should we encourage widespread use of bronchodilator therapy in mechanically ventilated patients without evidence of airflow obstruction? Clearly, empirical use of bronchodilators is wasteful of limited resources and should not be encouraged. What variables should we employ to determine which mechanically ventilated patients without airflow obstruction would benefit from bronchodilator therapy?

Various predictors of disease, such as severity, previous treatment received, and baseline levels of airway resistance, were unable to predict a bronchodilator response in patients with chronic obstructive pulmonary disease.<sup>17</sup> Likewise, Wollam and colleagues could not predict which patients without evidence of airflow obstruction would respond to bronchodilators.<sup>2</sup> Monitoring the response in terms of airway pressure and resistance would be of great help in making rational decisions; however, it should be emphasized that an optimal administration technique is required to obtain a bronchodilator response.<sup>1</sup> Moreover, decisions about bronchodilator response should not be based on a single measurement; instead, several observations over 48–72 hours should be employed before deciding on the efficacy or lack thereof of bronchodilator therapy. The next obvious step is to conduct prospective placebo-controlled randomized studies to examine the effect of bronchodilators on clinical outcomes in mechanically ventilated patients. A major trial of the outcomes after inhaled bronchodilator administration in patients with acute respiratory distress syndrome is being planned by

the Acute Respiratory Distress Syndrome Network (personal communication, 2006, Leonard D Hudson, Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, Washington). Similar trials in other conditions would be needed to place bronchodilator therapy in patients without airflow obstruction on a more secure scientific foundation.

In summary, while we await further studies, the use of bronchodilators in mechanically ventilated patients without evidence of airflow obstruction need not be totally empirical. The data from Chang and colleagues<sup>11</sup> would suggest that physicians favor the use of bronchodilators in sicker patients who are expected to have a longer duration of mechanical ventilation. Obviously, prospective randomized trials are needed to confirm the benefits of bronchodilators in mechanically ventilated patients. The effects of bronchodilators on physiologic variables are well recognized. Future studies need to investigate the effects of bronchodilator administration on clinical outcomes, such as duration of mechanical ventilation, ventilator-free days, duration of intensive care unit stay, and even mortality. In addition, adverse cardiovascular and metabolic effects of bronchodilator drugs, and the occurrence of ventilator-associated pneumonia in patients who receive inhaled bronchodilators should be determined. If clinical outcomes improve after bronchodilators, the cost/benefit ratio will need to be carefully examined. In the meantime, a common sense approach that emphasizes appropriate bronchodilator administration technique and careful monitoring of the response (airway resistance, heart rate, intrinsic positive end-expiratory pressure, and oxygenation, after 15 min and 30 min of drug administration) over a brief period (48–72 h) would help to identify patients who could benefit from bronchodilator treatment, and avoid unnecessary allocation of resources to patients who did not respond. Moreover, bronchodilator therapy need not be continued until extubation if airway resistance is normal and dynamic hyperinflation is not a limiting factor to successful weaning. Such an approach should provide some rationale for the use of these drugs in these critically ill patients and restrict empirical use of bronchodilators among ventilator-supported patients who do not have evidence of airway obstruction.

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