Effect of Bronchodilators on Lung Mechanics in the Acute Respiratory Distress Syndrome (ARDS)*

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The acute respiratory distress syndrome (ARDS) is a disorder of diffuse lung injury secondary to a wide variety of clinical insults (eg, sepsis) and is manifested by impaired oxygenation, pulmonary edema, and decreased static and dynamic compliance. More recently, airflow resistance has been shown to be increased in humans with ARDS. We designed a prospective, randomized, placebo-controlled, crossover trial to determine the presence and reversibility of increased airflow resistance in ARDS. We studied eight mechanically ventilated patients with ARDS (criteria: PaO₂ ≤70 mm Hg with FIO₂ ≤0.4; diffuse bilateral infiltrates; and pulmonary artery wedge pressure ≤15 mm Hg). Each was intubated with a No. 8.0 otracheteal tube. We measured dynamic compliance (Cdyn), static compliance (Cstat), airflow resistance across the lungs (Rl), shunt fraction (Qs/Qt on FIO₂=1.0), minute ventilation (Vₑ), PaO₂/PAO₂, and dead space to tidal volume ratio (VD/VT). Patients were blindly assigned to receive either metaproterenol (1 mL 0.5% in 3 mL saline solution) or saline solution (4 mL) aerosolized over 15 min 6 h apart and in random order so that patients served as their own controls.

Metaproterenol significantly reduced Rl, peak and plateau airway pressure, and increased Cdyn. Metaproterenol tended to increase PaO₂/PAO₂, but had no effect on pulmonary shunt or dead space ventilation. We conclude that the increase in airflow resistance of ARDS is substantially reversed by aerosolized metaproterenol without affecting dead space. These data suggest that abnormalities of Rl are at least partially due to bronchospasm.

Key words: acute respiratory distress syndrome; airway resistance; lung compliance; mechanical ventilation; metaproterenol; work of breathing

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ARDS=acute respiratory distress syndrome; Cdyn=dynamic compliance; PaO₂=partial pressure of arterial oxygen; PAO₂=partial pressure of alveolar oxygen; Paw=airway pressure; PEEP=positive end-expiratory pressure; Pes=esophageal pressure; Ptr=trans pulmonary pressure; VD/VT=dead space to tidal volume ratio

Patient Selection

We studied eight patients who had ARDS and who were in the intensive care units of Vanderbilt University Medical Center. Patients who had an illness known to be associated with ARDS and who met all the following criteria were eligible for study: (1) arterial blood gases revealing a partial pressure of arterial oxygen of (PaO₂) ≤70 mm Hg while they were breathing at least 40% oxygen or a ratio of partial pressure of arterial oxygen to partial pressure of alveolar oxygen (PaO₂/PAO₂) of ≤0.8 (regardless of
the level of positive end-expiratory pressure (PEEP); (2) bilateral diffuse infiltrates on chest radiography compatible with pulmonary edema; (3) a pulmonary artery wedge pressure ≤18 mm Hg; and (4) inspiratory inflation pressure (peak dynamic pressure minus PEEP) from the ventilator manometer >90 cm H2O (tidal volume 10 mL/kg, inspiratory flow 60 L/min). Patients were excluded if they had received β-agonists of any kind or amount in the 8 h immediately preceding the study. Exclusions were made for pregnancy, age younger than 7 years, the presence of severe shock (defined as a mean arterial blood pressure of less than 60 mm Hg), or a history of obstructive airways disease (asthma or COPD). Informed consent was obtained from the patient when appropriate or the next of kin. This study was approved by the committee for the protection of human subjects at Vanderbilt University.

Randomization

Patients were studied in a prospective, randomized, placebo-controlled fashion and were crossed over to receive the alternate intervention by a computer-generated randomization schedule. Syringes numbered sequentially were filled with either 1 mL of 0.5% metaproterenol solution mixed with 3 mL of normal saline solution or 4 mL solution of normal saline solution (placebo). Depending on the order of entry into the study, patients received an aerosol of either placebo or metaproterenol (in a double-blinded fashion) given with the output of the aerosol device connected directly to the endotracheal tube. Six hours after the first aerosol dose was given, the opposite preparation was administered to the same patient.

Clinical and Routine Laboratory Data

Upon the patient's entry into the study, a clinical history was obtained and a physical examination was performed. The suspected cause, the time of the pulmonary insult (i.e., the underlying process thought to be responsible for the development of ARDS), and the time of onset of ARDS were recorded.

Cardiac output (thermodilution), central venous pressure, pulmonary artery pressure, and pulmonary artery wedge pressure were measured with the patient supine and at end-expiration. Heart rate and systemic blood pressure was monitored in all of the patients. Mechanical ventilation was maintained throughout these measurements and all measurements in a given patient were made under the same conditions. The zero reference point for the hemodynamic measurements was the midaxillary line.

Gas exchange was assessed by measurement of arterial blood gases, PEEP requirements, minute ventilation, and respiratory rate. Standard calculations were used to measure intrapulmonary shunting, with the patient breathing 100% oxygen for 5 min and arterial and mixed venous oxygen tension and saturation being measured simultaneously. In six patients, dead space to tidal volume ratio (Vd/Vt) was measured by collecting expired gases over 5 min in a vinyl breathing bag (Douglas, Warren Collins, Braintree, Mass) and expired Pco2 was measured with a carbon dioxide analyzer (Beckman Medical Gas Analyzer LB-2, Fullerton, Calif). The dead space of the ventilator tubing (using the correction factor of 3 mL of dead space/cm H2O peak airway pressure/respiratory cycle) was subtracted from the measured tidal volume.20 The minute ventilation and dead space were determined simultaneously.

Lung Mechanics Measurements

Dynamic compliance (Cdyn) and airflow resistance (Rl) were measured at the bedside in all eight mechanically ventilated patients with ARDS using methods previously reported.21 Briefly, Cdyn and Rl were derived mathematically from four primary measurements: airflow, tidal volume, airway pressure (Paw), and midesophageal pressure.

Airflow (V), Volume (Vt), and Airway Pressure (Paw): A heated, low resistance Fleisch-type pneumotachograph (No. 2) (Hans Rudolph, Kansas City, Mo) interfaced to a pressure transducer (Validyne ± 2.0 cm H2O differential transducer model MP 45-1, Validyne, Northridge, Calif) was placed between the Y-point of the ventilator circuit and the endotracheal tube to detect flow (Fig 1). Flow signals were calibrated at the bedside with a rotameter by pressurized air. Volume was measured by integrating the flow signal and calibrated using a 3-L syringe. Tubing that linked the pressure ports with their transducers was oscilloscopically adjusted for length to assure that the primary and integrated flow signals were in phase with the pressures relevant to the measurements of interest. Airway pressure was measured using a small-caliber polyethylene catheter (internal diameter, 1.67 mm; outside diameter, 2.42 mm) with multiple side holes and an occluded end hole placed (0.5 to 1.0 cm past the end of the endotracheal tube in the trachea.

Midesophageal Pressure (Intrathoracic Pressure): A small multipurpose nasogastric-midesophageal balloon catheter (14- or 16-F outside diameter, Mallinckrodt, Glens Falls, NY) positioned in the midesophagus was used to estimate fluctuations in pleural pres-

Figure 1. Schema representation of equipment layout. Definition of abbreviations: TR=trachea; YP=Y-point of ventilator tubing; V=flow; V=volume; Rl=airflow resistance across the lungs.
The balloon of this catheter was 10 cm in length and filled with 0.5 to 1.0 mL of air to maintain appropriate minimal volume under conditions of positive pressure. Final positional adjustments were made by minimizing deflections of transpulmonary pressure during transient airway occlusion. Transpulmonary pressure (P\text{tr}) was measured by a differential transducer (model MF 45-1, Valhdyne, Northridge, Calif) as the difference between airway pressure and esophageal pressure (Paw-Pes).

**Resistance to Airflow Across the Lungs (RL) and Dynamic Compliance (Cdyn):** The flow, volume, and transpulmonary pressure signals were displayed on a dual-beam storage oscilloscope (Tektronix, Beaverton, Ore) and a four-channel strip chart recorder (Hewlett-Packard, Andover, Mass). The Pes and Paw were independently recorded on the strip chart recorder. Dynamic compliance of the lung was calculated as tidal volume divided by the difference in transpulmonary pressure measured at points of zero flow. Using a modification of the method of von Neergard and Wirz, lung resistance (average of inspiratory and expiratory resistance) was measured at midtidal volume by dividing transpulmonary pressure by flow at that point. Each patient was suctioned to clear secretions within 5 to 10 min of each measurement of lung mechanics. Within five breaths of each measurement, the patient was inflated with a volume of approximately twice the tidal volume. All measurements were made with the patient receiving the level of PEEP in clinical use prior to the study.

**Patient Protocol for Lung Mechanics Measurements:** The eight patients with ARDS selected for study had all been orally intubated with No. 8.0 (8.0 mm inside diameter) endotracheal tubes and required mechanical ventilation. We checked for leaks in the system by auscultating the neck for leaks around the endotracheal tube cuff and comparing inspiratory volume to expiratory volume with the pneumotach. Lung mechanics measurements were made at peak flow rates of 50 (actual delivered flow ranged within ±5 L/min depending on the type of ventilator). Tidal volume was determined by the primary care physician and averaged 635 ± 81 mL. The airway catheter with multiple side holes was positioned in the tracheal lumen 0.5 cm past the distal end of the endotracheal tube to eliminate the contribution of the endotracheal tube to the lung mechanics measurement. Five minutes prior to each lung mechanics measurement, each patient was given a sigh breath equal to twice the set tidal volume and was suctioned to minimize the contribution of airway secretions to airflow resistance. The PEEP settings were held constant through all measurements in a given patient. A single representative breath was frozen on the calibrated oscilloscope and photographed for data analysis. The first aerosol was then administered and the hemodynamics, lung mechanics, and blood gas measurements were repeated 30, 60, and 120 min later. Six hours after the first aerosol was given, the opposite aerosol preparation was administered following establishment of new baseline measurements. The subsequent measurements were repeated as before.

**Definitions:** Patients who met entry criteria were defined as having ARDS. The definitions of the principal causes of ARDS were modifications of those described by Pepe et al. Sepsis was defined as serious bacterial infection evidenced by two or more of the following: (1) a rectal temperature above 39°C, (2) a total leukocyte count higher than 12,000/mm³ or with more than 20% immature forms, (3) a blood culture positive for a recognized pathogen, (4) gross pus in a closed space, or (5) a positive culture from a known or strongly suspected source of systemic infection. A systemic deleterious response other than respiratory failure could be present but was not required for the diagnosis of sepsis. Pulmonary aspiration was defined as the recent aspiration of gastric contents, documented by the suctioning of such contents from the endotracheal tube regardless of their pH. Pancreatitis was defined as a syndrome consisting of severe abdominal pain, nausea, vomiting, and an elevated serum amylase level without another explanation for these findings. Shock was defined as a systemic blood pressure under 90 mm Hg that was not associated with sepsis. The category of mixed or other causes included the patients with multiple risk factors or those who had pathologic processes reported to be associated with ARDS.

**Statistics:** Data are expressed as means ± SEM. Sample size and power calculations were made prospectively with use of a standard power-function calculation. Comparisons between baseline and posttreatment values at 30, 60, and 120 min and placebo controls were made with the two-way analysis of variance for repeated measures and the Duncan multiple range test. A p value of <0.05 was considered significant.

**RESULTS**

Eight patients with ARDS from the intensive care units at Vanderbilt University Hospital were studied, including two men and six women with a mean age of 51 ± 7 years. Although two of the eight patients were smokers prior to hospitalization, neither had physical evidence, laboratory findings, or a history of previously existing lung disease. As Table 1 shows, physiologic variables were similar at the beginning of the metaproterenol and placebo portions of the trial, precluding a carryover effect and also indicative of the crossover design of the study. The mean shunt, V\text{D}/V\text{T}, PEEP level, and hemodynamic variables were similar to those we have reported previously. When measured by the ventilator manometer, the mean peak pressure at entry was 59 ± 4 cm H\text{O} at peak flow rates of 50 to 80 L/min, while the mean

<table>
<thead>
<tr>
<th>Metaproterenol (n=8)</th>
<th>Placebo (n=8)</th>
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<tbody>
<tr>
<td>Pulmonary shunting (Q*,Q)/Q*</td>
<td>0.36 ± 0.04</td>
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<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>26 ± 2</td>
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<tr>
<td>Pulmonary artery wedge pressure, mm Hg</td>
<td>14 ± 2</td>
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<tr>
<td>Positive end-expiratory pressure, cm H\text{O}</td>
<td>13 ± 2</td>
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<tr>
<td>Mean systemic blood pressure, mm Hg</td>
<td>80 ± 5</td>
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<tr>
<td>Cardiac index, L/min/m²</td>
<td>3.35 ± 0.33</td>
</tr>
<tr>
<td>Ratio of arterial to alveolar PaO₂</td>
<td>0.31 ± 0.04</td>
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*Q*,Q/Q denotes the ratio of pulmonary shunt flow to cardiac output.
peak minus plateau pressure was 13 ± 2 cm H₂O. The mean time interval between meeting our criteria for ARDS and entry into the study was 5.1 ± 1.5 hours, while the period between clinical onset of ARDS and entry was 80.5 ± 27.7 hours. The difference in these time intervals was mostly accounted for by delays in documentation of pulmonary artery wedge pressure. ARDS was attributed to sepsis in three patients, aspiration in two, shock in two, and multiple causes in one patient (sepsis plus pancreatitis).

Baseline measurements were similar between treatment groups with regard to all pulmonary physiologic measurements (Table 1). There was no carry-over of metaproterenol's effects in those patients who received the metaproterenol arm first in the study (Table 1, Figs 2 and 3).

Aerosolized placebo had no effect on any of the variables measured. Aerosolized metaproterenol increased heart rate (120 ± 6 to 130 ± 10 beats/min) and mean arterial pressure (80 ± 3 to 90 ± 5 mm Hg) at 30 min compared with baseline (p < 0.05) but had no effect on cardiac index, mean pulmonary artery pressure, or mean pulmonary artery wedge pressure.

Aerosolized metaproterenol significantly increased Cdyn and reduced resistance to airflow across the lungs (Rl) at 30, 60, and 120 min compared with baseline and time-matched placebo values (p < 0.05) (Fig 2). Measured variables had returned to baseline prior to the patient's crossover to the alternate therapy. The effects on Cdyn and Rl were immediate and persisted through the 2-h period of observation. Metaproterenol tended to increase static compliance at 30 min (0.31 ± 0.008 L/cm H₂O) and 60 min (0.035 ± 0.005 L/cm H₂O) compared with baseline (0.028 ± 0.004 L/cm H₂O) but these changes did not reach statistical significance (p = 0.18 and 0.11, respectively).

When measured in the trachea, peak and plateau airway pressure were significantly reduced by metaproterenol at 30, 60, and 120 min compared with baseline and time-matched placebo values (p < 0.05) (Fig 3). The peak and plateau pressures measured by the ventilator manometer, where airway opening pressure reflects endotracheal tube and lung tissue resistance, also declined with metaproterenol (59 ± 4 cm H₂O to 57 ± 3 and 45 ± 4 cm H₂O to 42 ± 3), though the changes were less pronounced.

![Graph](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21703/ on 03/31/2017)
than when measured in the trachea. Metaproterenol tended to increase the ratio of arterial to alveolar partial pressures (PaO₂/PAO₂ on FIO₂=1.0) by 120 min (0.37 ± 0.04) compared with baseline (0.31 ± 0.04) and time-matched placebo values (0.35 ± 0.05), but this did not reach statistical significance (p=0.11). This trend was paralleled by a nonstatistically significant increase in arterial partial oxygen pressure on FIO₂=1.0 by 120 min (205±30 mm Hg to 241±28) (p=0.11). While metaproterenol tended to improve oxygenation, there was no effect on pulmonary shunting (0.36±0.04 to 0.36±0.04), minute ventilation (Vₑ) 16±3 L/min to 17±2), or (Vₑ/Vₑ) (0.74±0.03 to 0.76±0.02) at 30, 60, and 120 min following treatment (p>0.05).

DISCUSSION

Reduced lung or thoracic compliance, more specifically static compliance, is usually considered the primary disorder of lung mechanics in ARDS. The contribution of airflow resistance to lung mechanics and gas exchange abnormalities in ARDS had not been extensively studied until recently. In a previous study, we were able to show that resistance to airflow across the lung was significantly greater in 12 patients with ARDS than normal controls, 6.15 ± 0.08 vs 0.88 ± 0.08 H₂O/L/s, respectively. Although the mechanisms of the increased Rₑ are unknown, possible explanations include decreased lung volumes and/or increased airway reactivity. Processes that produce airway inflammation often lead to heightened airway resistance and reactivity; therefore, ARDS resulting from specific stimuli such as noxious gas inhalation, endotoxemia, or gastric aspiration might be complicated by airway hyperreactivity. Airway hyperreactivity has been shown to occur in animal models of septic lung injury. In the sheep endotoxin model of acute lung injury, acute endotoxemia provokes an abrupt increase in airflow resistance and a reduction in dynamic compliance, and these changes appear to be at least partially granulocyte dependent. Endotoxin also augments the responsiveness of the sheep airway to histamine. It has previously been shown in sheep that the sustained alterations in lung mechanics following endotoxin are reversible with nitroprusside and metaproterenol and that reversal does not affect the alveolar to arterial oxygen partial pressure gradient on room air. These animal experiments suggest that airway resistance can be increased by endotoxemia and may have a reversible component. Increased airflow resistance (both pulmonary tissue and airway) has been shown to be increased in patients with ARDS. Though airflow resistance has not been specifically measured in patients with sepsis without ARDS, previous studies in sepsis suggest that increased airway pressures are reversible by ibuprofen. Clinically heightened airway responsiveness has also been reported to occur in long-term survivors of ARDS when measured after recovery, suggesting the possibility that acute airway injury may also cause a permanent change in airway reactivity. Therefore, we hypothesized that airflow resistance contributes significantly to abnormalities in ARDS and could be reversed with aerosolized bronchodilator therapy.

Our randomized and crossover design was successful in that the variables we measured in our patients were nearly identical at the beginning of each phase of the study. The comparability of the baseline data also indicates that there was no carryover effect in the placebo arm in those patients receiving metaproterenol first. The largest group of patients had sepsis as their underlying etiology (38%) with aspiration (25%) and shock (25%) as the second most frequent causes. All of the patients had markedly increased Rₑ and decreased Cdyn at entry and patients receiving metaproterenol experienced an immediate reduction in Rₑ and an increase in Cdyn. Peak and plateau pressures measured in the trachea were also reduced. It is also important to note that all of the airway mechanics data reported herein were obtained using airway pressure measured in the trachea. Thus, the endotracheal tube’s significant contribution to the lung mechanics measurements as shown by ourselves and others was excluded. Only two of eight patients were smokers at the time of onset of illness. None of our patients had a history of obstructive airway disease. The putum Wright stain for eosinophils was negative in each patient.

The effects of aerosolized metaproterenol on lung mechanics in this study were similar to effects we have previously observed in the sheep endotoxin model and by others who reported their findings in humans receiving intravenous salbutamol. In the sheep, sustained alterations in airflow resistance were decreased by half and Cdyn increased by 50 to 60% following metaproterenol aerosol. Data with cyclooxygenase inhibitors and thromboxane receptor antagonists suggest that part of these alterations in lung mechanics may be mediated by constrictor prostanoids. Further studies with such agents in ARDS are indicated to elucidate the mechanism of the alterations in lung mechanics.

Metaproterenol tended to improve oxygenation as measured by PaO₂/PAO₂ (p=0.11), but no effect was seen on directly measured pulmonary shunting. The disparity in the two measures of oxygenation could be attributed to improvement in ventilation/perfusion matching or to a reduction in the work of breathing and subsequent oxygen debt of the respiratory muscles as lung mechanics were improved though these were not measured directly. Despite the observed
bronchodilation, there also was no worsening of dead space in our patients, suggesting that airways connected to poorly perfused areas of lung were not recruited by bronchodilation or that bronchodilation occurred mainly in the central airways.

Another effect of bronchodilation in our patients was a reduction in peak and plateau pressures. The former was not unexpected considering the previously presented animal data. However, the reduction in plateau airway pressure was rather interesting. This finding suggests the possibility that gas exchanging lung units were recruited or that tissue forces were somehow altered. We cannot distinguish between the two with the data we collected since we did not directly measure lung volume. Micro and macro barotrauma related to high mean airway pressures in patients with ARDS contributes significantly to morbidity and mortality. Reduction in airway pressures with bronchodilation could result in a reduction in the risk of lung parenchymal trauma in mechanically ventilated patients.40

We conclude that increased resistance to airflow across the lungs is markedly increased in patients with ARDS and contributes to work of breathing. The rapid reversibility with aerosolized metaproterenol suggests that the changes are due at least in part to bronchospasm. The improvement in oxygenation (though minimal) may be due to improvement in ventilation/perfusion matching and/or to a decrease in oxygen consumption by the respiratory muscles.

However, further studies are needed to determine the long-term effects of repeated doses of bronchodilators on morbidity and mortality and the mechanisms of increased airflow resistance in ARDS before a firm recommendation can be made for their routine use in mechanically ventilated patients with ARDS. In those patients with documented bronchospasm (wheezing) or with markedly increased airflow resistance (directly measured or estimated from very high peak and plateau pressures), a trial of aerosolized bronchodilator therapy may be indicated.

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