Conventional Mechanical Ventilation Is Associated with Bronchoalveolar Lavage-induced Activation of Polymorphonuclear Leukocytes

A Possible Mechanism to Explain the Systemic Consequences of Ventilator-induced Lung Injury in Patients with ARDS

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Background: Protective ventilatory strategies have resulted in a decreased mortality rate in acute respiratory distress syndrome, but the underlying mechanisms remain unclear. The authors hypothesized that (1) mechanical ventilation modulates activation of polymorphonuclear leukocytes (PMNs), (2) the consequent release of proteinases is correlated with a systemic inflammatory response and with multiple organ dysfunction, and (3) these deleterious effects can be minimized by a protective ventilatory strategy.

Methods: Human PMNs were incubated with bronchoalveolar lavage fluid obtained from patients at entry or 36 h after randomization to ventilation with either a conventional (control) or a lung-protective strategy. PMN oxidant production and surface expression of adhesion molecules and granule markers, including CD18, CD63, and L-selectin, were measured by flow cytometry. Extracellular elastase activity was quantified using a fluorescent substrate.

Results: Bronchoalveolar lavage obtained from both groups of patients at entry showed similar effects on PMN oxidant production and expression of surface markers. At 36 h, exposure of PMNs to bronchoalveolar lavage fluid from the control group resulted in increased PMN activation as manifested by a significant increase in oxidant production, CD18, and CD63 surface expression, and shedding of L-selectin. By contrast, these variables were unchanged at 36 h in the lung-protective group. There was a significant correlation between the changes of the variables and changes in interleukin-6 level and the number of failing organs.

Conclusions: Polymorphonuclear leukocytes can be activated by mechanical ventilation, and the consequent release of elastase was correlated with the degree of systemic inflammatory response and multiple organ failure. This result may possibly explain the decreased mortality in acute respiratory distress syndrome patients treated with a lung-protective strategy.

THE acute respiratory distress syndrome (ARDS) is an inflammatory syndrome characterized by acute neutrophilic alveolitis in association with increased alveolar-capillary permeability, bilateral pulmonary infiltrates, and severe hypoxemia. Our current understanding of the pathogenesis of ARDS suggests that the degree of inflammatory response and its sustained leukocyte activation may determine the clinical evolution of ARDS.1,2 Most patients with ARDS require mechanical ventilation to maintain adequate systemic oxygenation. Conventional respiratory support for ARDS has used large tidal volumes (VT) ranging from 10 to 14 ml/kg and minimal positive end-expiratory pressure (PEEP) to maintain adequate oxygenation at low inspiratory oxygen fraction (FiO2). While these ventilator settings are usually able to maintain oxygenation, mortality has ranged from 35 to 65%,3 with patients usually dying from progressive dysfunction of vital organs—so-called multiple organ dysfunction syndrome (MODS)—rather than from respiratory failure.3,4 A recent randomized, controlled trial showed that mortality rate could be reduced by 22% when a tidal volume of 6 ml/kg (predicted body weight) was used to ventilate patients with ARDS compared with a control group ventilated with 12 ml/kg.5 This result confirmed a large body of experimental data showing that conventional mechanical ventilation can initiate or augment pulmonary injury by a process that is indistinguishable from ARDS.7–10 One mechanism proposed to explain these results is that mechanical ventilation can augment the pulmonary inflammatory response and exacerbate the increased alveolar capillary permeability.8–11 Inflammatory mediators produced in this milieu and then released into the systemic circulation could be responsible for the development of MODS.11–14 In support of this hypothesis, we have previously shown that (1) conventional mechanical ventilation of patients with ARDS contributes to the pulmonary inflammation and systemic inflammatory response syndrome (SIRS)13 and (2) plasma concentrations of proinflammatory mediators correlate with the development of MODS.15 However, little information is currently avail-
MECHANICAL VENTILATION ACTIVATES NEUTROPHILS

MECHANICAL VENTILATION ACTIVATES NEUTROPHILS could lead to spillover of the inflammatory response not only within the lung, but also on a systemic level.

Neutrophils are a central component of host defense but may also cause tissue damage in many lung diseases. During the development of ARDS, neutrophils cross the alveolar-capillary endothelium, cross the interface, and transmigrate into the alveolar space; excessive accumulation and activation of neutrophils may worsen lung damage. It has been suggested that neutrophils may be further activated by the physical stress that occurs during mechanical ventilation in the treatment of ARDS. Conventional mechanical ventilation has been shown to cause hyaline membrane formation in the lung and alter alveolar-capillary permeability in a surfactant-depleted animal model of ARDS; the use of the same ventilatory strategy in neutrophil-depleted animals resulted in a marked reduction in hyaline membrane formation, and a decrease in alveolar-capillary permeability. We therefore tested the hypothesis that mechanical ventilation in humans may lead to activation of neutrophils and the release of cytotoxic products, including reactive oxygen species and proteolytic enzymes. These products could lead to further damage of the alveolar-capillary barrier and thus could lead to spillover of the inflammatory response from the lung into the systemic circulation. Minimization of the systemic spread of the inflammatory response may present a predominant mechanism for the decreased mortality in ARDS with protective ventilatory strategies.

Methods

Patient Selection

The study was carried out in 26 patients with ARDS recruited in the intensive care units of the University Hospitals of Bari (Italy) and Geneva (Switzerland). Bronchoalveolar lavage (BAL) samples obtained from these patients were the remaining material collected from a randomized trial in which a total of 37 patients were recruited. In that trial, a lung-protective strategy was found to decrease BAL fluid and blood cytokines compared with a conventional ventilatory strategy.

The protocol was approved by the Institutional Review Boards and informed consent was obtained. Patients were cared for by attending physicians who were not involved in the protocol, and all decisions regarding patient care management were made at these physician’s discretion.

Study Protocol

Protocol, inclusion, exclusion, and withdrawal criteria have been previously described. Briefly, patients were sedated, paralyzed, and ventilated (Servo 300; Siemens-Elema, Stockholm, Sweden). A volume-pressure (V-P) curve on zero end-expiratory pressure was measured. The V-P curve of the respiratory system of patients with early ARDS has a characteristic sigmoidal shape with lower (LIP) and upper (UIP) inflexion points thought to approximate the pressure required to initiate recruitment of collapsed alveoli, and the pressure at which overdistension of some lung units occurs, respectively. After the V-P curve was measured, PEEP was restored to its previous level, and BAL and plasma samples were collected 20–30 min later (entry). Patients were then randomly assigned either to a control strategy using a conventional ventilatory strategy (VT and PEEP targeted to maintain the arterial carbon dioxide tension [Paco2] between 35 and 40 mmHg and PEEP to obtain the greatest improvement in arterial oxygen saturation [SaO2] without worsening hemodynamics) or to a lung-protective strategy (VT set to obtain a value of plateau pressure [Pplat] < pressure at the UIP regardless of Paco2, and PEEP 2–3 cm H2O above the pressure at LIP). All measurements were repeated 36–40 h (36 h) after randomization.

Bronchoalveolar lavage was performed using a telescoping catheter (Ballard, Draper, UT) with two aliquots of 40–50 ml sterile isotonic saline. Lavage with a third aliquot was performed if there was less than 30–40 ml recovered fluid from the first 100 ml. The first aliquot was discarded, and the remaining BAL fluid was rapidly filtered through sterile gauze and then spun at 4°C at 400g for 15 min. The supernatant was centrifuged at 80,000g for 30 min at 4°C to remove the surfactant-rich fraction and then concentrated 10-fold on a 5,000 molecular weight cutoff filter (Amicon, Beverly, MA) under nitrogen. The concentrated supernatant was then frozen at −70°C for later analysis.

Cytokine concentrations from the two groups of patients were analyzed by ELISA in Geneva and have been previously reported. The remaining samples were thawed in Toronto where this study was carried out in blinded fashion. BAL fluid from each individual patient analyzed separately and all experiments were performed in duplicate.

Study Procedures and Outcome Measures

Human Neutrophil Isolation. Neutrophils were isolated from heparinized whole blood drawn by venipuncture from normal volunteers. Isolation was performed using 3% dextran sedimentation and discontinuous plasma-Percoll (Amersham Pharmacia Biotech, Inc., Baie d’Urfe, Quebec, Canada) gradients as described previously. The separation procedure required 2 h. The neutrophils were resuspended at a cell density of 9 × 10^6 cells/ml in endotoxin-free DMEM (Life Technologies, Burlington, Ontario, Canada) and were used immediately after isolation. Neutrophil viability exceeded 97% as assessed by trypan blue exclusion.
Flow Cytometry

Oxidant and surface expression of CD18, CD63, and L-selectin were measured using flow cytometry. Neutrophils were incubated in the patient’s BAL fluid at a density of $8 \times 10^6$ cells/ml for 2 h at 37°C. For measurement of oxidant production, cells were then incubated with 5 μM dihydrorhodamine (DHR; Molecular Probes, Inc., Eugene, OR) in HEPES-buffered saline containing Ca$^{2+}$ and Mg$^{2+}$. After a 5-min incubation, neutrophils were fixed with 1% paraformaldehyde. In separate experiments, neutrophils were incubated in BAL fluid, fixed with 1% paraformaldehyde, and washed twice. Neutrophils were then labeled with mouse anti-human FITC-CD18 antibody or mouse anti-human L-selectin phycoerythrin-labeled antibodies (Serotec Ltd., Oxford, England) for 30 min and washed twice in PBS. Neutrophils were also labeled with mouse anti-human CD63 antibody (Serotec Ltd.) for 30 min, washed, and resuspended in PBS with FITC-labeled secondary antibody (1:500). After a 30-min incubation, neutrophils were washed and resuspended in PBS. Stained cells were analyzed on a FACScan (Becton Dickinson, Palo Alto, CA) using FL1 detector (488-nm excitation and 530-nm emission wavelengths). Cells were gated on the forward and right-angle light scatters to exclude debris and cell clumps. Typically, $1 \times 10^5$ cells were analyzed per condition, and the specific fluorescence was determined by subtracting the fluorescence after staining with secondary antibodies in the absence of primary antibody. Values are expressed as relative fluorescence index by dividing the linear fluorescence of the experimental groups by the values obtained from the unstimulated control cells.

Extracellular Elastase Release

Extracellular release of elastase from neutrophils was quantified by measuring the degradation of elastin in cell supernatants using an Elastase Assay Kit (EnzChek; Molecular Probes). Elastin was prepared by reductive alkylation of soluble bovine neck ligament elastin and labeled with BODIPY®-FL dye such that the conjugate’s fluorescence is quenched. Upon digestion by elastase, the fluorescence is revealed. The resulting increase in fluorescence was monitored with a fluorescence microplate reader (CytoFluor 2300; Millipore, Bedford, MA) at 530 nm.

Interleukin 6

Plasma concentration of interleukin 6 (IL-6) was measured using an enzyme-linked immunoabsorbent assay (Medgenix, Fleures, Belgium).

Statistical Analysis

To evaluate differences over time within each group, repeated-measures analysis of variance (ANOVA) by Bonferroni method was used. To evaluate differences between the two groups, the Fisher exact test for categorical variables, the t test with unequal variance for continuous variables, and the Mann-Whitney rank-sum test for ordinal variables were used.

All tests of significance were two-tailed, and $P < 0.05$ was considered as significant. Data are presented as mean ± SD.

Results

Baseline characteristics and underlying conditions responsible for ARDS in the patients included in the study are presented in table 1. Sepsis, pneumonia, and multiple trauma were the underlying conditions responsible for ARDS.

Values of ventilator settings and of arterial blood gases immediately (2 to 3 h) after randomization are presented in table 2. In the control group, PEEP levels were lower, while tidal volume and Pplat were higher than in the lung-protective-strategy group. PaO$_2$/FiO$_2$ did not differ between groups, although PaO$_2$ was higher in the control group. A significant increase in PaCO$_2$ (permissive hypercapnia) was observed in the lung-protective-strategy group.

The cell pellets obtained from the BAL fluids were analyzed for cell distribution, and there was an increased percentage of polymorphonuclear leukocytes in the control group, but not in the protective group.  

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Table 1. Patients Characteristics at the Time of Study Inclusion

<table>
<thead>
<tr>
<th>n (M/F)</th>
<th>Control</th>
<th>Lung Protective Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48 ± 17</td>
<td>45 ± 17</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Multiple trauma</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>PaO$_2$/FiO$_2$</td>
<td>117 ± 22</td>
<td>132 ± 17</td>
</tr>
<tr>
<td>APACHE II</td>
<td>16 ± 4</td>
<td>15 ± 3</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

**Pneumonia** was defined as the presence of an infiltrate on chest radiograph, plus any three of (I) purulent endotracheal aspirate, (II) known pathogens on a Gram stain, or cultured from sputum or blood, (III) temperature > 38.5°C or < 36°C, (IV) white blood cell count (WBC) > 12 × 10$^9$/ul or less than 3.5 × 10$^9$/ul, or 20% immature forms; Sepsis was defined as the presence of two or more of: (I) core temperature > 38.5°C or < 36°C, (II) WBC > 12 × 10$^9$/ul or less than 3.5 × 10$^9$/ul, or 20% immature forms, (III) one blood culture of a common pathogen, (IV) a strongly suspected site of infection from which a known pathogen was cultured, (V) gross pus in a closed space; and one or more of (I) systemic arterial hypertension for at least 2 hours (systolic blood pressure < 85 mmHg, or reduction > 40 mmHg from baseline, or need for inotropes to maintain systolic blood pressure > 85 mmHg), (II) systemic vascular resistance less than 800 dyn · s$^{-1}$ · cm$^{-5}$, (III) unexplained metabolic acidosis (base deficit > 5 mEq/l), Multple trauma was defined as the presence of fractures of two or more major long bones, an unstable pelvic fracture, or one major long bone fracture and a major pelvic fracture.

**M/F** = male/female; ARDS = acute respiratory distress syndrome; PaO$_2$ = arterial oxygen tension; FiO$_2$ = oxygen inspiratory fraction.
Neutrophil Oxygen Burst
Bronchoalveolar lavage fluid obtained from the two groups of patients at entry resulted in a similar degree of stimulation of neutrophil oxidant production as determined by oxidation of dihydrorhodamine. BAL fluid obtained from the control group 36 h after mechanical ventilation resulted in significantly increased oxidant production by neutrophils as compared with the values at entry. In contrast, incubation of neutrophils with BAL fluid obtained from the lung-protective-strategy ventilation group at 36 h did not induce any further change in oxidant production. The value of oxidant production in the lung-protective-strategy group was significantly lower ($P < 0.001$) than in the control group at 36 h (fig. 1).

Neutrophil Surface Antigen Expression
Bronchoalveolar lavage fluid obtained from both groups at entry had similar effects on the expression of neutrophil surface markers of CD18, CD63, and L-selectin. BAL fluid obtained from patients ventilated with the control strategy for 36 h resulted in significantly increased expression of CD18 and CD63 (fig. 2), and enhanced shedding of L-selectin compared with the BAL fluid obtained at entry (fig. 3). In contrast, these variables remained unchanged when neutrophils were incubated with BAL fluid obtained from the lung-protective-strategy–ventilated patients at 36 h.

Neutrophil Elastase Release
We also examined whether incubation of neutrophils with the BAL fluid would increase extracellular release of elastase, a potent tissue-damaging proteolytic enzyme contained in primary granules and released by activated neutrophils.$^{19}$ BAL fluid obtained from both groups at entry had similar effects on elastase release by neutrophils. BAL fluid obtained from the control ventilatory strategy at 36 h induced a significant increase in neutrophil elastase release (fig. 4). In contrast, the level of elastase release remained low when neutrophils were incubated with BAL fluid obtained from the lung-protective-strategy patients at 36 h.

The percentage change of neutrophil elastase release stimulated by BAL obtained at 36 h and entry was correlated with the change of plasma concentration (36 h – entry) of IL-6 (fig. 5).

Several studies have reported that neutrophil elastase plays a key role in developing MSOF in patients with head injury$^{20}$ and at the early stage of acute pancreatitis.$^{21}$ We examined the relation between the number of failing organs in these ARDS patients and neutrophil elastase release (percent of baseline) stimulated by BAL fluid at 36 h, and a significant correlation was observed (fig. 6).

### Table 2. Ventilatory Parameters in the Two Groups after Randomization

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Lung Protective Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP (cm H$_2$O)</td>
<td>6.5 ± 1.7</td>
<td>14.8 ± 2.7*</td>
</tr>
<tr>
<td>FIO$_2$</td>
<td>0.9 ± 0.1</td>
<td>0.7 ± 0.1*</td>
</tr>
<tr>
<td>VT (ml/kg)</td>
<td>11.7 ± 1.0</td>
<td>7.5 ± 0.8*</td>
</tr>
<tr>
<td>Pplat (cm H$_2$O)</td>
<td>33.0 ± 3.2</td>
<td>23.6 ± 1.9*</td>
</tr>
<tr>
<td>PCO$_2$ (mmHg)</td>
<td>160 ± 53</td>
<td>151 ± 82</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.46 ± 0.04</td>
<td>7.37 ± 0.08*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

* $P < 0.001$.

PEEP = positive end-expiratory pressure; FIO$_2$ = oxygen inspiratory fraction; Pplat = end-inspiratory plateau pressure; VT = tidal volume; PCO$_2$ = arterial oxygen tension; and PaCO$_2$ = arterial carbon dioxide tension.

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Discussion

Acute respiratory distress syndrome is the most severe form of acute lung injury affecting both medical and surgical patients. It is characterized by a protein- and cell-rich pulmonary edema fluid due to increased vascular permeability in the lung. Neutrophils constitute up to 70–80% of the cells in BAL fluid of ARDS patients compared with approximately only 1–3% in normal subjects. Neutrophil-derived proteases have been suggested to be potent mediators involved in the increased lung permeability. The results of the current study demonstrate that BAL fluid obtained from patients ventilated with a conventional ventilatory strategy activates neutrophils and induces release of the proteolytic enzyme elastase to a greater extent than BAL from patients ventilated with a protective ventilatory strategy. Furthermore, the high plasma concentrations of IL-6, a pivotal inflammatory cytokine in the pathogenesis of MODS, correlates well with increased release of neu-

Fig. 2. Expression of polymorphonuclear leukocyte (PMN) surface antigens by BAL fluids. Relative fluorescence changes of CD-18 and CD-63 obtained by dividing the fluorescence of the BAL fluid–treated group by the value for the unstimulated control PMN cells. PMNs were incubated for 2 h with BAL fluids obtained from patients ventilated with either conventional strategy (control) or lung-protective strategy.

Fig. 3. Shedding of polymorphonuclear leukocyte (PMN) L-selectin by BAL fluids. Relative fluorescence changes of surface expression L-selectin obtained by dividing the fluorescence of the BAL fluid–treated group by the value for the unstimulated control PMN cells. PMNs were incubated for 2 h with BAL fluids obtained from patients ventilated with either conventional strategy (control) or lung-protective strategy.
trophil elastase. These results suggest that the activation of neutrophils and the subsequent release of proteases may be an important mechanism of ventilator-induced lung injury during conventional strategies that overdistend the lung and/or allow repeated alveolar recruitment and derecruitment. These observations may at least in part explain the decreased incidence of MODS and the improved survival observed with protective ventilatory strategies.

In response to an inflammatory stimulus, there is a rapid and often massive transmigration of neutrophils from the blood across the endothelium and alveolar epithelium into the alveolar space. Neutrophils are a pivotal component of the innate immune response and essential in host defense against invading microorganisms. However, under certain pathologic conditions, such as ARDS, chronic bronchitis, asthma, and cystic fibrosis, these inflammatory cells can cause cellular injury by a number of mechanisms, including excessive production of reactive oxygen and nitrogen species and release of proteolytic enzymes.

In ARDS, the initial acute pulmonary inflammatory response may become systemic and self-propagating even after removal of the initiatory events. This can lead to diffuse endothelial injury, organ hypoperfusion (or malperfusion), and ultimately, MODS. The persistence of the inflammatory response in ARDS has been associated with poor prognosis. This concept is supported by clinical studies showing that (1) the concentration of inflammatory cytokines in the BAL and plasma on entry is higher in nonsurvivors than in survivors; (2) plasma...
concentrations of inflammatory mediators remain persistently elevated in nonsurvivors compared with survivors in whom the concentration of the mediators decreased over time; and (3) the severity of lung injury is correlated with the extent of neutrophil influx and the accumulation of neutrophil-derived cytotoxic products in the alveolar space. By way of contrast, the inflammatory response is remarkably different in an uncomplicated pneumonia in which inflammation proceeds in a more regular fashion and is resolved when inciting causes, such as bacteria, are removed. The regulatory mechanisms that limit inflammatory damage and facilitate repair of injured tissues may be lost in ARDS, and/or insults subsequent to the predisposing factors causing ARDS may continue to actively provoke the inflammatory response. Efforts to modulate this inflammatory response have met with mixed success, and thus, it is important to understand the mechanisms underlying this response.

The potential role of neutrophils as major effector cells in the generation of ventilator-induced lung injury has been clearly demonstrated by several experimental studies. In animals with intact circulating neutrophils, ventilator-induced lung injury has been clearly demonstrated by several experimental studies. In animals with intact circulating neutrophils, ventilator-induced lung injury has been clearly demonstrated by several experimental studies. By way of contrast, the inflammatory response is remarkably different in an uncomplicated pneumonia in which inflammation proceeds in a more regular fashion and is resolved when inciting causes, such as bacteria, are removed. The regulatory mechanisms that limit inflammatory damage and facilitate repair of injured tissues may be lost in ARDS, and/or insults subsequent to the predisposing factors causing ARDS may continue to actively provoke the inflammatory response. Efforts to modulate this inflammatory response have met with mixed success, and thus, it is important to understand the mechanisms underlying this response.

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We found that the release of elastase was correlated with the degree of SIRS and MODS. Such "ventilator-induced" neutrophil activation and the consequent release of elastase may represent the underlying mechanisms by which injurious ventilatory strategies spread inflammatory mediators from the lung into the systemic circulation, possibly leading to MODS. In general, the mechanisms by which mechanical ventilation induces neutrophil activation may include direct physical stress by mechanical ventilation as well as cytotoxic mediators released in the lung. In addition to optimizing ventilatory strategies, several therapies targeting inflammatory mediators have been evaluated in patients with ARDS. Our study may provide a rationale for future therapies directed at controlling the inflammatory response, perhaps with modulators directed at neutrophil function.

References

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Fig. 6. Correlation between changes of PMN elastase release and number of failing organs at 36 h. PMN elastase release was evaluated after 2 h incubation of PMNs with BAL fluid obtained from patients ventilated with either conventional strategy (control, closed circle) or lung-protective strategy (open circle).