levels $\geq 1.75$ U/ml on day 3 was 53 percent (18 of 34) vs 22 percent (11 of 49) in patients with PCP-III. A fatality rate of 64 percent (29 of 45) was associated with elevated lavage PCP-III levels obtained 7 days after ARDS onset vs 21 percent (7 of 29) in patients with PCP levels $<1.75$ U/ml (p=0.001). When patients were analyzed according to risk factor for ARDS (ie, sepsis, trauma, other), increased fatality rates were still associated with elevated PCP-III levels obtained on day 7. Also, after stratifying for disease severity as measured by PaO$_2$/FiO$_2$ ($\geq 175$ vs $<175$) on the day of the BAL, increased fatality continued to be independently associated with elevated PCP-III levels. At 3 days after onset of ARDS, the presence of both high PCP-III levels ($\geq 1.75$ U/ml) and severely disturbed gas exchange (PaO$_2$/FiO$_2$ $<175$) was associated with fatality rates of 73 percent vs 29 percent in patients with severely disturbed gas exchange but low PCP-III levels. The relative risk associated with high PCP-III levels in patients with PaO$_2$/FiO$_2$ $<175$ was 2.6 (CI = 1.2 to 5.5) at 3 days and 3.5 (CI = 1.3 to 9.6) at 7 days. In 62 patients who had serial (two or three) lavages within 14 days of ARDS onset, PCP-III levels tended to remain constant or decrease over time in survivors (mean slope = 0.01 U/ml/day), whereas in patients who died, PCP-III increased (mean slope = 0.36 U/ml/day, p<0.10). The differences in slope between survivors and nonsurvivors were still evident after we stratified for severity as measured by PaO$_2$/FiO$_2$.

We conclude that extremely high levels of PCP-III are frequently present in BAL from patients with ARDS, and that high levels as well as levels that increase over time are associated with increased fatality. This relationship is still evident when physiologic severity as measured by oxygen requirement is taken into account. Our results suggest that PCP-III levels may be useful in assessing metabolic activity in ARDS, and sustained activity may be associated with ongoing collagen production and progressive disease.

**Fibroproliferation in Late Adult Respiratory Distress Syndrome**

**Pathophysiology, Clinical and Laboratory Manifestations, and Response to Corticosteroid Rescue Treatment**

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Adult respiratory distress syndrome (ARDS) is a dynamic disease that rapidly progresses into phases with different clinicopathologic characteristics and different therapeutic needs. Late ARDS refers to the clinical stage of ARDS when the lung attempts to repair the initial or persistent injury to the endothelial and epithelial lining of the respiratory units. Its histologic correspondent is termed fibroproliferative phase which, if unhalted, leads to extensive fibrosis. Pulmonary fibroproliferation is a stereotypic reparative reaction to tissue injury characterized by the replacement of damaged epithelial cells and the striking accumulation of mesenchymal cells and their connective tissue products in the airspaces and walls of the intra-acinar microvessels.1 Its evolution is determined by the extent of initial inflammatory reaction in the lung (alveolar denudation, basement membrane destruction, and quantity of intraalveolar exude) and by the presence of a protracted inflammatory response (with or without control of the cause of ARDS).2,3 Fibroproliferation is a diffuse process, as indicated by the findings of computed tomography, gross inspection at surgery, and microscopic analysis of biopsy specimens from different lobes.1 Regional heterogeneity, however, exists,1 and at histologic examination, focal areas of normal parenchyma are occasionally found.1

Continuous injury to the respiratory units (endothelial and epithelial surface) is the result of persistent release of inflammatory cytokines in the lung.4 Epithelial injury provides gaps in the basement membrane for direct communication between the interstitium and the airspaces.1 Activated myofibroblasts from the interstitium migrate into the alveoli in response to chemotactic signals and attach to the luminal surface of the damaged basement membrane.1 Fibronectin and platelet-derived growth factor, which have chemotactic activity for myofibroblasts, are found elevated in the airspaces of patients with late ARDS.1 Eventually, the alveoli are obliterated by an organizing exudate composed of hypertrophied myofibroblasts and extracellular matrix.1 The complex interaction in the lung among inflammatory cytokines and fibroblasts in producing fibrosis has been described by Elias.5 Immunohistochemical studies have shown that virtually all myofibroblasts in the alveoli stain intensely for procollagen type 1, and the newly produced matrix stains intensely for cell-associated fibronectin and type 3 procollagen.6 Type III collagen (newly formed, flexible, and more susceptible to enzymatic degradation) predominates in the proliferative phase, while type I collagen (composed of thick fibrils, less responsive to treatment) is the major collagen present in the late fibrotic phase. Acute endothelial injury, as manifested by endothelial cell swelling with leakage of proteinaceous material, is more pronounced in the proliferative phase than in the exudative phase of ARDS.1 The reparative reaction at the vascular level is associated with remodeling the lumen of the small pulmonary arteries, which becomes focally obstructed by subintimal fibroproliferation and organized microthrombi. Obstruction to flow eventually stimulates adaptation of the vessels upstream with medial hypertrophy of the muscular and partially muscular arteries.1 Physiologically, progression of fibroproliferation is characterized by worsening static compliances and gas exchange (PaO$_2$/FiO$_2$), lack of alveolar recruitment by positive end-expiratory pressure (loss of the inflection point in the pressure-volume curve), increased dead space ventilation, and pulmonary hypertension.1 Clinically, it
The diffuse pulmonary injury associated with ARDS is characterized by persistent, marked neutrophilia and elevation of pyrogens (inflammatory cytokines), which favor the development of nosocomial pneumonia, extrapolmonary infections, and other complications. Corticosteroids have been used in late ARDS as a treatment intervention aimed at resolving or improving fibroproliferation. While recent, large, prospective clinical investigations have shown no benefit when short-course (<48 h), high-dose intravenous corticosteroid therapy is administered at the onset of ARDS, a beneficial effect may occur when corticosteroids are used in the late phase of ARDS. Two groups of investigators have previously reported their anecdotal experience for a total of 30 patients. We investigated the effects of corticosteroid therapy in 25 patients with late ARDS and severe fibroproliferation and attempted to identify patterns of physiologic response and variables predictive of response to treatment and outcome. Patients were receiving mechanical ventilation for an average of 15 ± 7 days and had progressive worsening in gas exchange and lung mechanics (mean lung injury score 3). All patients underwent an extensive diagnostic evaluation to rule out active infection. Thirteen had the diagnosis of fibroproliferation confirmed by open-lung biopsy. Most patients (56 percent) had fever (>38.3°C) without active site of infection, leukocytosis (88 percent), significant BAL neutrophilia (86 percent), diffuse alveolar infiltrates on chest radiograph (83 percent), and diffuse marked uptake of gallium in both lung fields (100 percent). Patients received intravenous methylprednisolone sodium succinate at a dosage of 2 to 3 mg/kg/day. The dosage was tapered after extubation and continued for a total of 6 weeks. A significant physiologic improvement, defined as a reduction in lung injury score of more than 1 point (Fig 1), and/or an improvement in PaO₂/FiO₂ ratio of >100, was seen within 7 days in 15 patients (rapid responders), within 14 days in 6 (delayed responders), and was absent in 4 (nonresponders). Survival was 86 percent in responders (combined rapid and delayed) and 25 percent in nonresponders, suggesting that outcome in ARDS is affected by resolution of fibroproliferation. Treatment

Type III procollagen peptide (PCP-III), a byproduct of type III collagen synthesis, is a marker of fibrogenesis (see preceding article). Serum PCP-III levels are found elevated early in ARDS. Progression of fibroproliferation is associated with persistent elevation over time of PCP-III levels in serum and BAL. Mortality in late ARDS is related directly or indirectly to pulmonary fibroproliferation. Several studies have found in nonsurvivors, as opposed to survivors, evidence of progressive fibroproliferation 3 to 7 days into ARDS. Progression into fibroproliferation was characterized clinically by lack of improvement in gas exchange and PEEP requirements, worsened static compliance, increased pulmonary vascular resistance, and persistent or worsening alveolar infiltration on chest radiograph; and biologically by laboratory evidence of persistent elevation of PCP-III in the serum and bronchoalveolar lavage. Directly, pulmonary fibroproliferation can advance to extensive fibrosis, with refractory hypoxemia and/or hypercarbia, which has been described as the cause of death in 15 to 40 percent of ARDS fatalities. Indirectly, progressive fibroproliferation results in ventilator dependency and compromises pulmonary defense mechanisms, influencing the development of nosocomial pneumonia, extrapolmonary infections, and other complications.

Figure 1. Changes in lung injury score before and after administration of corticosteroid therapy. Legend: E1, E3, E7 = day 1, 3, and 7 of ARDS. –5 and –3 = 5 and 3 days before administration of corticosteroids. 0 = day treatment was started. LIS = lung injury score. (Reproduced with permission.)

![Graph showing changes in lung injury score before and after administration of corticosteroid therapy.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21692/ on 06/26/2017)
was associated with clearing of infiltrates on chest radiograph, normalization of \(^{67}\)Ga pulmonary uptake, and reduction in BAL neutrophilia (from 60 ± 6 percent to 29 ± 12 percent in 14 days).

With the exception of liver failure (p = 0.035), no physiologic variable was found at the time ARDS developed or before administration of corticosteroids that could predict the type of physiologic response or outcome. Histologic evidence of advanced fibrosis at open-lung biopsy (which was not related to the duration of mechanical ventilation) and lack of physiologic improvement with corticosteroid therapy were associated with a poor outcome. At histologic examination, the presence of preserved alveolar architecture (p = 0.045), myxoid cellular type fibrosis (p = 0.045), coexistent endoluminal bronchiolar fibrosis (p = 0.0045), and lack of arteriolar subintimal fibroproliferation (p = 0.045) separated survivors from nonsurvivors. The ICU survival rate was 86 percent in responders and 25 percent in nonresponders (p = 0.03). Only one death resulted from refractory respiratory failure.

Glucocorticosteroids are known to cause serious complications by lowering host defenses against infections and gastrointestinal bleeding. In our experience, pneumonia was a frequent complication (50 percent incidence) and was related to the pattern of response. Pneumonia was more common in nonresponders (75 percent) than in responders (38 percent). We have recognized that pulmonary infections in patients receiving corticosteroids can occur without temperature elevation. Therefore, we implemented weekly surveillance bronchoscopy with bilateral sampling, which was useful in detecting pneumonia (7 of 13 episodes) early in afibrile patients and may have contributed to decreased mortality. Recognizing the increased risk for infections, Hooper and Kearl11 routinely treated their ARDS patients receiving corticosteroids with broad spectrum antibiotics and antifungal therapy.

The potential benefits of antiinflammatory treatment include (1) halting progression to fibrosis that can lead to either death, barotrauma, or respiratory failure; and (2) decreasing the length of ventilator dependency, which creates increased risk for the development of complications (pneumonia, barotrauma, extrapulmonary infections, etc.). Mechanisms of action of corticosteroids on fibroblast replication and collagen degradation were previously described. We measured serum and BAL inflammatory cytokine levels before and after corticosteroid administration in seven patients (baseline levels similar to a control nonsurvivor group) and found survival to be associated with a significant reduction in the release of inflammatory mediators.13 We believe that by halting continuous injury,13 the reparative process in the lung can finally become effective, alveolar architecture is restored,7 gas exchange and lung mechanics improve,7-11 and pulmonary arterial pressure decreases.18

To establish the true role of corticosteroid treatment in patients with fibroproliferation and its effect on outcome, a randomized, double-blind study is necessary. This form of treatment cannot be recommended until its true efficacy has been proven.

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