The Fibroproliferative Response in ARDS: Mechanisms and Clinical Significance

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Abstract

The acute respiratory distress syndrome (ARDS) continues to be a major health care problem, affecting more than 190,000 people in the US annually with a mortality of 27-45% depending on the severity of the illness and co-morbidities. Despite advances in clinical care, particularly lung protective strategies of mechanical ventilation, most survivors experience impaired health-related quality of life for years after the acute illness. While most patients survive the acute illness, a subset of ARDS survivors develops a fibroproliferative response characterized by fibroblast accumulation and deposition of collagen and other extracellular matrix components in the lung. Historically, the development of severe fibroproliferative lung disease has been associated with a poor prognosis with high mortality and/or prolonged ventilator dependence. More recent studies also support a relationship between the magnitude of the fibroproliferative response and long-term health-related quality of life. The factors that determine which patients develop fibroproliferative ARDS and the cellular mechanisms responsible for this pathological response are not well understood. This article will review our current understanding of the contribution of pulmonary dysfunction to mortality and to quality of life in survivors of ARDS, the mechanisms driving pathological fibroproliferation, and potential therapeutic approaches to prevent or attenuate fibroproliferative lung disease.

Diminished quality of life in ARDS survivors

Since the initial description of the acute respiratory distress syndrome (ARDS) by Ashbaugh and Petty in 1967, the overall mortality associated with this disorder has decreased (1-3). Multi-center randomized clinical trials have been a major driver of this improvement, fostering advances such as the use of positive end expiratory pressure (PEEP) (4), low tidal volume ventilation (5), and conservative fluid management (6). Although these interventions have resulted in improved survival and reduced time spent on mechanical ventilation, it is increasingly recognized that a substantial proportion of ARDS survivors continue to suffer from reduced health-related quality of life (HRQoL) that lasts for months to years (7-12). While recent investigations have drawn attention to extrapulmonary complications of ARDS such as depression and neuromuscular weakness, residual pulmonary dysfunction has been largely discounted as a significant contributing factor to diminished HRQoL. Indeed, the prevailing opinion among ARDS experts in the current era of lung protective mechanical ventilation is that the prevalence of persistent pulmonary impairment in ARDS survivors has decreased. However, perusal of available data suggests that pathological fibroproliferation in the lung continues to play a critical role in both short- and longer-term outcomes in ARDS patients. Understanding the clinical relevance of pro-fibrotic activity in ARDS, and predicting which patients are at risk for the development of excessive fibroproliferation will pave the way for identification of novel therapies that can target specific pathways involved in maintenance and restoration of normal lung architecture.

Persistent pulmonary dysfunction in the low tidal volume era

The most current data assessing the prevalence of pulmonary dysfunction among ARDS survivors arise from four independent cohorts in which pulmonary function tests (PFTs) were performed six months to five years after ICU discharge (7-13). These studies each demonstrated median values for forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), total lung capacity (TLC), and diffusion capacity (DLCO) that were within the normal range (i.e. > 80% predicted). For each parameter however, values in the lowest quartile were consistently below normal (8, 10, 12, 13). Notably, in one study over half of survivors had impairments in at least one of these parameters (11). Importantly, decrements in lung function changed little after the first year, and even five years after discharge, subjects in the lowest quartile of one study displayed a persistently reduced FEV_1, FVC, TLC, RV, and DLCO (9). Nevertheless, the association between these physiological abnormalities and parenchymal lung disease remains poorly defined since pulmonary function tests (PFTs) may be influenced by fibrotic lung disease as well as by neuromuscular weakness, the latter being increasingly recognized as a cause of diminished HRQoL (7).

To assess the clinical relevance of physiological abnormalities identified in ARDS survivors, associations between PFTs and HRQoL measured via standardized questionnaires have been explored (10, 12). Heyland and colleagues (10) observed a modest association between a lower FVC and FEV_1 and poorer scores on the physical component subtotal of the short form (SF)-36 ($\rho > 0.5$ for comparisons) as well as the St. George's Respiratory Questionnaire (SGRQ) ($\rho > 0.4$ for comparisons). Similar

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associations between FVC, FEV$_1$, DLCO, and TLC and physical function scores on the SF-36 (ρ>0.4 for comparisons) were reported by Orme and colleagues (12). In most ARDS survivor investigations however, respiratory-specific questionnaires such as the SGRQ (14) have been performed much less frequently than questionnaires that assess global health and well-being, such as the SF-36 (15) where responses may be influenced by respiratory as well as neuromuscular symptoms. Moreover, the fact that a sizable percentage of ARDS survivors have a significantly diminished six minute walk distance (8, 9, 11), further suggests that both neuromuscular impairment and pulmonary dysfunction may contribute to impairments in HRQoL. Therefore, to define the impact of residual pulmonary impairment among ARDS survivors on HRQoL, respiratory-specific assessment that confirms pulmonary pathophysiological abnormalities is necessary.

Computed tomographic (CT) scanning of the lungs of ARDS survivors often demonstrates reticular infiltrates (**Fig. 1**) that may persist for months to years after ICU discharge (9, 11, 16-18), although not all studies have observed these changes (13). Surprisingly, although the extent of reticular involvement in ARDS survivors has been associated with specific factors implicated in the pathogenesis of fibrotic lung disease, such as high airway pressures, hyperoxia, and longer duration of mechanical ventilation (16, 17), few studies have systematically examined chest CT scans in association with physiological function among ARDS survivors (9, 11, 13, 18). Published studies that have included both PFT and chest CT scans emphasize that persistent radiolographic abnormalities are generally not severe in the majority of patients and have therefore been considered to be clinically unimportant (9, 11, 13). However, most studies have not attempted to correlate chest CT scan data objectively with outcomes (including

PFTs, HRQoL measurements). Utilizing prospectively collected high resolution CT scans (HRCT), PFTs, and HRQoL data from a randomized clinical trial in patients with ARDS (19), our group recently reported that the extent of persistent reticular abnormalities on HRCT correlated with reduced, pulmonary-specific, HRQoL as assessed by SGRQ surveys obtained at 180 days (18). Notably, these HRCT abnormalities correlated with physiological features of restrictive lung disease, including low TLC, FVC, and DLCO. As in prior survivor studies, approximately 25% of ARDS survivors had physiological evidence of restrictive pulmonary physiology at 180 days. Furthermore, patients who displayed features of restrictive physiology at 180 days exhibited reticular infiltrates on HRCT 14 days after diagnosis, and their CT scans remained significantly more affected by reticulation over time compared to patients who did not develop restrictive physiology (18). These data, collected from almost 100 patients, provide additional evidence to support the concept that the lungs of a subset of ARDS survivors have persistent fibrotic changes that, in many cases, correlate with diminished HRQoL and restrictive pulmonary physiology. In future studies, systematic assessment of ARDS patients using pulmonary-specific metrics will be necessary to more precisely establish the prevalence of clinically significant pulmonary impairment.

Basic mechanisms driving fibroproliferation in ARDS

Our understanding of the basic mechanisms driving the pathological fibroproliferative response in ARDS has evolved substantially over the past two decades. ARDS is thought to develop following injury to, and disruption of, the alveolar-capillary barrier with persistent injury to the alveolar epithelium (20-22). This, in turn,

sets in motion a series of events including the exudation of plasma into the alveolar spaces, which together with impaired alveolar fluid clearance, leads to alveolar edema. Activation of the coagulation system and production of pro-inflammatory cytokines and chemokines leads to an influx of neutrophils, monocytes/macrophages and lymphocytes into the lung associated with injury to the alveolo-capillary membrane (20, 23). During the acute inflammatory phase of ARDS, unregulated release of potent cytotoxic mediators from infiltrating leukocytes including reactive oxygen and nitrogen species and proteolytic enzymes such as elastase and matrix metalloproteinases (MMPs) results in injury to pulmonary endothelial and epithelial cells and if severe, damages the scaffolding of the lung (23-26). The combination of ongoing injury and failure to repair this damage in a timely manner are major factors that contribute to the pathological fibroproliferative response (27). While the inflammatory response resolves in a timely manner in most patients, in others there is robust and persistent accumulation of macrophages, fibocytes, fibroblasts, and myofibroblasts in the alveolar compartment leading to excessive deposition of fibronectin, collagens I and III, and other components of the extracellular matrix. This is accompanied by an imbalance between profibrotic [e.g. transforming growth factor (TGF)α and β, interleukin (IL)-1β, platelet derived growth factor (PDGF), lysophosphatidic acid (LPA)] and anti-fibrotic [e.g. prostaglandin E2, keratinocyte growth factor (KGF), hepatocyte growth factor (HGF)] mediators that may drive this fibroproliferative response (28-36). As in other fibrotic disorders of the lung, the origin of the fibroblasts that accumulate in the lung in fibroproliferative ARDS remains uncertain and controversial (20, 37-40). Lung resident (interstitial) fibroblasts, the mesenchymal differentiation of lung epithelial cells and pericytes, as well as

emigration of bone marrow derived fibrocytes have all been implicated as potential sources of the increased lung fibroblasts (37, 40, 41).

The initial inflammatory injury to the cellular and structural elements of the lung may be amplified by damage from shear forces imparted by mechanical ventilation (42, 43) underscoring the importance of lung protective ventilation strategies to prevent ongoing epithelial injury that may drive fibroproliferation (5, 44). Severe damage to the underlying structural elements of the lung including the vasculature and the extracellular matrix scaffolding of the lung makes repair of the delicate pulmonary architecture much more difficult and predisposes to pathological fibroproliferation. Stated in another way, if the 'blueprint' specifying details of the intricate architecture of the lung is 'lost in the ruins', orderly repair is likely to fail.

One key component of the infrastructure in the lung that is damaged in ARDS is the vasculature (45, 46). Vascular lesions that have been recognized in ARDS include endothelial injury, increased microvascular permeability, thrombotic, fibroproliferative, and obliterative changes that correlate temporally with histological evidence of diffuse alveolar damage (21, 22, 46, 47). These macro and microvascular alterations must be repaired in order to restore lung function. Further, failure to repair the vasculature may contribute to the severity and persistence of lung injury (45, 46) and to disorganized repair. Indeed, there is experimental evidence that excessive or unregulated angiogenic responses, mediated by angiogenic cytokines and growth factors such as MIP-2, angiopoietin 2, and VEGF, may contribute to the initial injury and drive the fibroproliferative response (48-50). In translational studies, pulmonary levels of VEGF are decreased in the early stages of ARDS (51-53), but then subsequently increase in a

fashion that tracks with recovery from lung injury (52). Excess levels of circulating angiopoietin 2 occur early in ARDS and may contribute to the vascular leak as well as distort the microvascular architecture of the lung (54).

Evidence of fibroproliferative activity in early ARDS in translational studies

Whereas large-scale studies of pulmonary function in long-term survivors of ARDS remain sparse, ample evidence for early fibroproliferative activity in the lungs of ARDS patients has been reported for decades. Since lung biopsies are not performed in the majority of patients, investigations utilizing bronchoalveolar lavage (BAL) have provided most of the available information. Pioneering work by several groups in the 1990s demonstrated evidence of robust collagen synthesis (reflected by high levels of N-terminal peptide of type III procollagen) in the lungs of ARDS patients as early as 72 hours after the onset of disease (55-57). Interestingly, the presence of procollagen peptide III correlated with risk for fatal outcome (55, 57). Histological assessment of the lungs of ARDS patients, although limited, clearly demonstrates that fibroproliferation is present early in a substantial proportion of patients. For example, Bulpa and colleagues (58) reported that in a series of 11 immunocompetent patients who met AECC criteria for ARDS and who underwent transbronchial biopsy a median of 10 days after intubation, pathological evidence of fibroproliferation was observed in every patient. Patel and colleagues (59) reviewed the records of patients who met AECC criteria for ARDS and who underwent an open lung biopsy. Of the 57 patients who were biopsied on average 3 days after intubation (7 days after hospital admission), 23 had a pathological evidence of diffuse alveolar damage (DAD), supporting the diagnosis of

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ARDS, and 18/23 (78%) were considered to be in the fibroproliferative phase of ARDS at the time of biopsy (59). The largest prospective study to date of surgical lung biopsies from ARDS patients included 100 patients hospitalized between 1996 and 2003 (60). Samples were obtained a median of 7 days after ARDS diagnosis, and 11 days after the initiation of mechanical ventilation. Fibrosis was noted in 53/100 patients, and was associated with evidence of infection in 29/53 (55%). Additional studies that used lung biopsy to study ARDS patients have demonstrated that pro-fibrotic mediators including $TGF\beta_1$ and insulin-like growth factor (IGF)-I are expressed during (and likely contribute to) the fibroproliferative response in ARDS (36, 61), thus validating the experimental studies discussed above.

Despite the widespread adoption of low tidal volume ventilator strategies (5), investigators continue to report early fibroproliferative activity in lungs of ARDS patients. For example, Marshall and colleagues reported that 24 hours after the onset of illness, N-terminal procollagen peptide III levels were significantly greater in the BAL and serum of ARDS patients than controls (62). Moreover, BAL fluid from ARDS patients induced significantly greater proliferation of cultured human lung fibroblasts than BAL fluid from controls (62). BAL fluid from ARDS patients potently induces α-smooth muscle actin expression and procollagen-1 promoter activity in cultured human lung fibroblasts via activation of the $TGF\beta$ receptors (63, 64). Importantly, $TGF\beta_1$ concentrations are markedly increased in BAL as early as 24 hours after the onset of ARDS (4, 36) and when elevated in serum, are associated with lower survival in ARDS patients with septic shock (65). Two recent studies have focused on potential cellular mediators of fibrosis, including mesenchymal cells with fibroblast like properties (*alveolar* fibroblasts or

fibrocytes) that have been isolated by BAL of ARDS patients within the first 7-14 days after diagnosis (66, 67). In both studies, the numbers of these cells in BAL fluid were greater in ARDS patients than in ventilated controls. In ARDS patients with a positive *fibroblast* culture, concentrations of BAL fluid pro-collagen I were significantly higher (66), but neither procollagen I nor other markers of fibroproliferation correlated with the *fibrocyte* number (67). However, in multivariable analyses, alveolar fibrocyte percentage was independently associated with increased mortality in patients with ARDS, accounting for potential effects of age, concomitant malignancy, and severity of illness (calculated with SOFA scores).

Identification of excessive fibroproliferation may help guide clinical decisions

Importantly, while excessive fibroproliferation is clearly detrimental, an 'appropriate' fibroproliferative response may have beneficial consequences in guiding lung repair, for example, by serving as a scaffold and providing a reservoir for nutrients and growth factors (68) for the regenerating alveolar epithelium. Thus, markers that distinguish 'appropriate' fibroproliferative activity from excessive and potentially harmful fibroproliferation are desperately needed. Indeed, identifying ARDS patients with aberrant fibroproliferative activity may prove to be helpful clinically. For example, such identification could aid in prognostic discussions with patients and their family members. Further, measurement of specific pro-fibrotic mediators may assist in predicting which patients are most likely to benefit from targeted anti-fibroproliferative therapies, and may help to monitor the clinical response of such agents. Characterization of fibroproliferative activity in acutely ill ARDS patients could involve measuring mediators

in BAL fluid, blood or urine, radiologic assessments, or combinations thereof. These results would need to be interpreted in light of the patient's history and clinical course. For example, mechanical ventilation parameters (16, 17) and specific risk factors underlying ARDS development (69) have been associated with a more protracted clinical course and subsequent fibrotic lung disease.

Bronchoscopy with BAL in the critically ill patient with ARDS is relatively safe (70), may be performed at the bedside, and provides information regarding fibroproliferative activity in the airspaces. The optimal timing to assess fibroproliferative activity in newly diagnosed ARDS is uncertain. Further, given the spectrum of illness of ARDS, not all patients may be able to tolerate bronchoscopy safely at a consistent time point. Moreover, BAL does not always provide a reproducible yield, so it is difficult to establish specific concentrations or cut points for prognostic assays that exclusively rely on BAL. For these reasons, measurement of a systemic biomarker in the bloodstream that reflects fibroproliferative activity in lungs would be preferable to identify aberrant fibroproliferation in ARDS. In idiopathic pulmonary fibrosis (IPF), systemic biomarkers have been identified that reflect disease activity and prognosis and may be predictive of response to therapy (71, 72). Many of these biomarkers have a plausible role in the pathogenesis of fibrotic disease and are therefore potential therapeutic targets. Notably, certain IPF-associated biomarkers also correlate with outcomes in ARDS, including surfactant protein-D and macrophage chemotactic protein-1 (CCL2) (73-75). Interestingly, circulating fibrocytes, which may have prognostic utility in IPF, have been identified in the blood of patients with ARDS (71). Additional investigations will be

necessary to establish whether these circulating factors are indeed causally associated with pathological fibroproliferative activity in lung.

High resolution CT (HRCT) scans of the chest are routinely used to diagnose and manage patients with idiopathic interstitial pneumonias, including IPF. Related to ARDS, Gattinoni and colleagues have demonstrated the utility of standard (low resolution) CT scanning in tailoring positive end-expiratory pressure and tidal volume in ARDS patients (76). Contemporaneous work by Ichikado and colleagues has suggested an additional role for high resolution CT in *early* ARDS prognostication. These investigators retrospectively examined HRCTs obtained an average of 7 days after ARDS diagnosis, and using a previously established scoring system (77), determined that more extensive lung involvement, particularly with bronchiolectasis or bronchiectasis, was associated with increased mortality, longer time on mechanical ventilation, decreased organ failure-free days, and barotrauma (78). More recently, this same group reported that scores from HRCT scans obtained 24 hours after ARDS diagnosis were associated with clinical outcomes including ventilator- and organ failure-free days, as well as 60 and 90-day mortality (79). Higher scores in this series of patients were again driven by the occurrence of traction bronchiolectasis or bronchiectasis (79). A separate group has confirmed the utility of HRCT obtained during the acute phase of pathologically confirmed diffuse alveolar damage, and found that increased radiological lung involvement, as well as traction bronchiectasis were associated with death (80). Finally, published studies from the 2009 H1N1 epidemic indicate that HRCT is similarly useful in predicting mortality and long-term morbidity in patients with ARDS from influenza A (69, 81). Our group's recent observations complement and add to these investigations and

suggest that HRCT performed early in the course of ARDS may prognosticate functional impairment in survivors months after discharge (18). Questions that remain to be answered are how to define objectively chest HRCT radiologic patterns that most accurately reflect active fibroproliferation and the optimal time at which HRCTs will be most clinically useful.

Potential therapies for pathological fibroproliferation in ARDS

Notably, no pharmacological agents are currently available for treatment of ARDS that specifically target fibroproliferation. Based on data from research conducted in the 1990s, randomized clinical trials of corticosteroids in patients with non-resolving ARDS were conducted. In these studies, corticosteroids were administered 1 week after the onset of illness to decrease inflammation and modulate fibroproliferative activity with the goal to improve short-term outcomes (82, 83). In these investigations, no mortality benefit was observed, but shortened time on mechanical ventilation was reported in secondary analyses. Moreover, in the latter study, increased mortality was noted in ARDS patients who were treated with corticosteroids after 14 days or who had BAL pro-collagen peptide III levels below the group's median. In a subsequent study of 91 patients, early (72 hours) treatment with corticosteroids in severe ARDS was associated with a shortened duration of mechanical ventilation (84). As a whole, the available data suggest that corticosteroids do not favorably impact ARDS survival but may minimize ventilatory requirements. The use of corticosteroids in ARDS remains of unproven benefit and the source of controversy.

Other considerations for therapies to mitigate aberrant fibroproliferative activity in ARDS include agents being developed to treat pulmonary fibrosis such as tyrosine kinase inhibitors (85), peptides directed at extracellular matrix proteins and their cellular receptors (86), and molecules directed at TGF-β and the pro-fibrotic pathways regulated by this pleiotropic growth factor (**Table 1**). The rapidly increasing knowledge of TGF-β signaling pathways and how they control cell proliferation, apoptosis, inflammation, and fibrosis is being exploited to develop novel therapeutic approaches to treat human diseases such as cancer (87-89). As many of these TGF-β signaling pathways including canonical (Smad-dependent) and non-canonical (e.g. PI3 kinase, AKT, and p38 MAP kinase), also drive fibroproliferative responses (which incidentally also drive the stromal responses associated with tumors), these agents could conceivably be used in the treatment of fibroproliferative ARDS.

Summary and conclusions

Despite major advances in the care and treatment of patients with ARDS, mortality remains unacceptably high and a significant proportion of survivors have persistent pulmonary dysfunction and reduced quality of life. Given the rapidity with which ARDS can evolve, understanding and defining the kinetics and cardinal features of the pathological fibroproliferative response is paramount since the optimal window for therapeutic intervention is most likely to either precede or coincide with the onset of fibroproliferation. Indeed, recent investigations in both ARDS and IPF underscore the difficulty of reversing already-established fibrosis (24, 83, 90-92). A better understanding of the fine balance between the physiological and pathological effects of

the various pro-fibrotic mediators might allow targeted intervention, for example, with anti-proteinases such as MMP inhibitors in an effort to prevent severe structural damage to the lung and thus tip the scales to facilitate repair to the injured lung (20). It is our hope that accurate identification of ARDS patients with aberrant fibroproliferation will facilitate the development and use of therapeutic agents that can selectively target molecules involved in the pathological fibroproliferative response (**Fig. 2**). Accurate identification of patients who will recover quickly and completely is similarly important in order to avoid exposing these individuals to potentially toxic and unnecessary therapies. Strategies that combine clinical characteristics with pathological patterns present on high resolution CT scans and fibroproliferative markers in BAL fluid or serum may help to identify individuals at risk for poor outcomes that may benefit from targeted therapies.

130 character summary sentence.

Despite lung protective ventilation, a subset of ARDS survivors develops lung fibrosis that contributes to poor quality of life.

Table 1. Molecular Targets to Limit Pathologic Fibroproliferation

Therapeutic Class	Mechanism	Molecules / Pathways
Tyrosine kinase inhibitors	Inhibit receptor signaling	TGFβ, PDGF, VEGF, FGF, Angiopoietin
Src kinase inhibitors	Inhibit profibrotic signaling downstream of receptors	TGFβ, PDGF
Histone deacetylase (HDAC) inhibitors	Prevent nuclear translocation and DNA binding of Smads	TGFβ, PDGF
Monoclonal antibodies / blocking peptides	Directly bind to growth factors or block receptor ligation binding	TGFβ, PDGF, IGF-1, FGF, Angiopoietin
Activating peptides	Inhibit synthesis of matrix proteins	Relaxins, endostatin

Definition of Abbreviations: TGF = Transforming growth factor; PDGF = platelet derived growth factor; VEGF = vascular endothelial growth factor; FGF = fibroblast growth factor; IGF-1 = insulin-like growth factor I
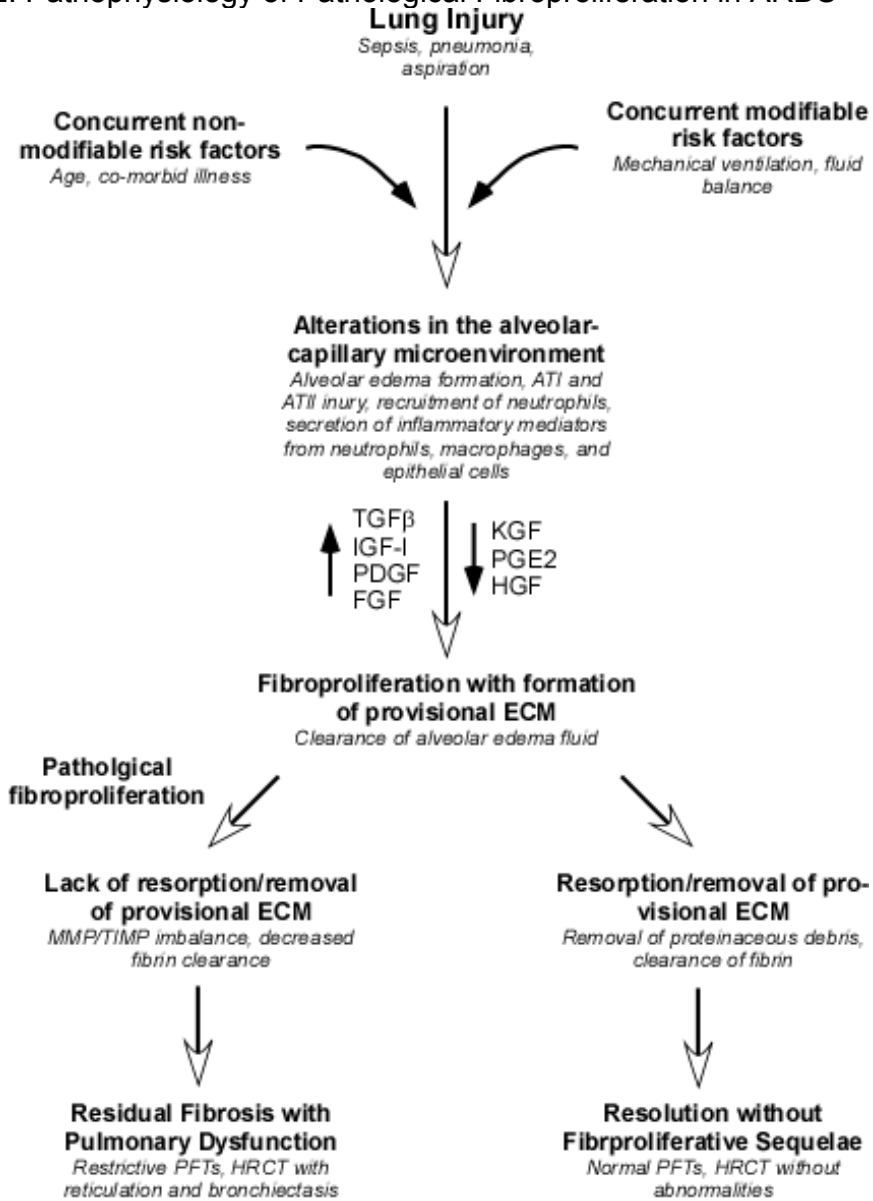
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Figure 1. High resolution chest CT scan of the base of the lungs of an ARDS survivor demonstrating persistent reticular changes in the lungs and traction bronchiectasis 18 months after the acute illness.

Figure 2. Mechanisms driving fibroproliferation in ARDS. Characteristic alterations related to lung injury evolve over time, and may be influenced by a variety of environmental and patient-specific factors. In response to alveolar-capillary injury, a provisional ECM is ultimately formed to promote repair, and proteinaceous pulmonary edema fluid is cleared from the alveolar space. The provisional ECM largely resolves after restoration of lung architecture; however, a subset of patients will not clear the provisional ECM and exhibit evidence of exuberant fibroproliferation with fibrosis lasting from months to years after their acute event. Bold lettering=major "activity" at this time point; italicized lettering=specific example within major activity

Figure 1.

Figure 2. Pathophysiology of Pathological Fibroproliferation in ARDS

Lung Injury
Sepsis, pneumonia, aspiration

Concurrent non-modifiable risk factors
Age, co-morbid illness

Concurrent modifiable risk factors
Mechanical ventilation, fluid balance

Alterations in the alveolar-capillary microenvironment
Alveolar edema formation, ATI and ATII inury, recruitment of neutrophils, secretion of inflammatory mediators from neutrophils, macrophages, and epithelial cells

TGFβ
IGF-I
PDGF
FGF

KGF
PGE2
HGF

Fibroproliferation with formation of provisional ECM
Clearance of alveolar edema fluid

Patholgical fibroproliferation

Lack of resorption/removal of provisional ECM
MMP/TIMP imbalance, decreased fibrin clearance

Resorption/removal of provisional ECM
Removal of proteinaceous debris, clearance of fibrin

Residual Fibrosis with Pulmonary Dysfunction
Restrictive PFTs, HRCT with reticulation and bronchiectasis

Resolution without Fibrproliferative Sequelae
Normal PFTs, HRCT without abnormalities

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